METHODS OF MANUFACTURING BENZOQUINOLINE COMPOUNDS

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ABSTRACT

The present invention relates to new methods of manufacturing benzoquinoline inhibitors of vesicular monoamine transporter 2 (VMAT2), and intermediates thereof.
METHODS OF MANUFACTURING BENZOQUINOLINE COMPOUNDS

[0001] This application claims the benefit of priority of U.S. provisional application No. 61/911,214, filed Dec. 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.


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 d6-tetrabenazine are disclosed herein.

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

\[
\text{HO} \quad \text{HO} \\
\text{or a salt thereof, comprising:}
\]

[0009] a step of reacting a compound of Formula II or a salt thereof with a compound of Formula III:

\[
\text{Y} \quad \text{R}_{15} \\
\text{in the presence of a base;}
\]

[0010] wherein:

[0011] \( \text{R}_7 \text{R}_{12} \) and \( \text{R}_{13} \) are independently selected from the group consisting of hydrogen and deuterium; and

[0012] \( \text{Y} \) is a group consisting of hydrogen and deuterium.
Y is selected from the group consisting of acetoxy, alkoxy, halogen, haloalkoxy, perhaloalkoxy, heteroalkoxy, and aryloxy, any of which may be optionally substituted.

In certain embodiments, $Y_1$ is acetoxy.

In certain embodiments, $Y_1$ is $C_1-C_4$ alkoxy.

In certain embodiments, $Y_1$ is ethoxy.

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

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

In certain embodiments, said base is an alkali metal alkoxyde.

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

In certain embodiments, $Y_1$ is ethoxy.

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

![Formula VI](image)

comprising:

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

![Formula IV](image)

![Formula V](image)

- in a solvent and in the presence of a base;

wherein:

- $R_1-R_{12}$ and $R_{12}$ 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, alkylarylsulfonate, dialkylsulfonate, dialkylsulfoxonate, alkylphosphonate, and alkylcarbonate, any of which may be optionally substituted.

In certain embodiments, $Y_2$ is iodide or methylsulfate.

In certain embodiments, $Y_2$ is iodide.

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

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

In certain embodiments, said base is potassium carbonate.

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

In certain embodiments, said solvent is acetone.

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

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

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

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

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

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

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

![Formula VII](image)

comprising:

- a first step of reacting a compound of Formula VI:

![Formula VI](image)

- 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:

R₁, R₂, and R₃ are independently selected from the group consisting of hydrogen and deuterium.

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

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

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

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

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

In certain embodiments, the volume of said acetone is between about 0.5 to about 4 times the mass of the compound of Formula VI.

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

In certain embodiments, the volume of said acetone is about 2 times the mass of the compound of Formula VI.

In certain embodiments, said quenching solvent is anhydrous solvents selected from the group consisting of water, an alcohol, and aprotic acid.

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.

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

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.

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.

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.

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

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.

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.

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

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.

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.

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

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

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

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

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

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.

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.

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

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

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

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.

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

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

\[
\begin{align*}
\text{comprising:} \\
\text{a first step of mixing the compound of Formula VII with one or more solvents; and} \\
\text{a second step of filtering the salt of the compound of Formula VII from the mixture;} \\
\text{wherein:} \\
R_{12} \text{ and } R_{14} \text{ are independently selected from the group consisting of hydrogen and deuterium.}
\end{align*}
\]

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.

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

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

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

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

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

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

\[
\begin{align*}
\text{(IX)}
\end{align*}
\]

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:

\[
\begin{align*}
\text{(VII)}
\end{align*}
\]

wherein:

- \(R_1-R_{37}\) 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, dialkylxylonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

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

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

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.

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.

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

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.

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

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

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.

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.

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

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.

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.

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

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

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

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

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

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

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

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

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 hydridides, and trialkylamines.

In certain embodiments, said base is an alkali metal carbonate.
[0122] In certain embodiments, said base is potassium carbonate.

[0123] In certain embodiments, disclosed herein is a process of preparing a compound of Formula XI:

\[ \text{(XI)} \]

comprising:

[0124] a first step of reacting a compound of Formula X or a salt thereof with a base in one or more solvents:

\[ \text{(X)} \]

[0125] a second step of adjusting the pH of the reaction mixture by addition of an acid;

[0126] a third step of adding dimethylamine or a salt thereof and a formaldehyde equivalent to the reaction mixture;

[0127] a fourth step of lowering the pH of the reaction mixture by addition of an acid;

[0128] a fifth step of raising the pH of the reaction mixture by addition of a base;

[0129] a sixth step of adding dimethylamine or a salt thereof to the reaction mixture; wherein:

[0130] \( R_{16} \) and \( R_{27} \) are independently selected from the group consisting of hydrogen and deuterium.

[0131] 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.

[0132] In certain embodiments, said base is an alkali metal hydroxide.

[0133] In certain embodiments, said dimethylamine is dimethylamine hydrochloride.

[0134] In certain embodiments, said formaldehyde equivalent is selected from the group consisting of formaldehyde, aqueous formaldehyde solution, paraformaldehyde, and trioxane.

[0135] In certain embodiments, said formaldehyde equivalent is aqueous formaldehyde solution.

[0136] 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.

[0137] In certain embodiments, a phase transfer catalyst is added during the third reaction step.

[0139] In certain embodiments, a phase transfer catalyst is tetrahydroammonium bromide.

[0140] In certain embodiments, the amount of said tetrahydroammonium bromide is about 0.1 molar equivalents relative to said compound of Formula X.

[0141] In certain embodiments, said solvent is water.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] In certain embodiments, said acid is hydrochloric acid.

[0146] In certain embodiments, the first hydrolysis step is carried out at a temperature of between about 0°C to about 100°C.

[0147] In certain embodiments, the first hydrolysis step is carried out at a temperature of between about 20°C to about 40°C.

[0148] In certain embodiments, the second pH adjustment step results in a pH of about 6 to about 8.

[0149] In certain embodiments, the second pH adjustment step results in a pH of about 6.8 to about 7.2.

[0150] In certain embodiments, the second pH adjustment step is carried out at a temperature of between about 10°C to about 60°C.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] In certain embodiments, the third addition step is carried out at a temperature of between about 10°C to about 60°C.

[0155] In certain embodiments, the third addition step is carried out at a temperature of between about 25°C to about 35°C.

[0156] In certain embodiments, the reaction temperature is maintained for about 1 to about 24 hours after third addition step.

[0157] In certain embodiments, the reaction temperature is maintained for about 9 to about 15 hours after third addition step.

[0158] In certain embodiments, the reaction temperature is maintained for about 12 hours after third addition step.

[0159] In certain embodiments, the fourth pH adjustment step results in a pH of less than 3.

[0160] In certain embodiments, the fourth pH adjustment step results in a pH of less than 1.
In certain embodiments, the fourth pH adjustment step is carried out at a temperature of between about 10°C. to about 60°C.

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

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

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

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

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

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.

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.

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

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

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

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

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

The compounds as disclosed herein may also contain less prevalent isotopes for other elements, including, but not limited to, 13C or 15C for carbon, 32S, 34S, or 36S for sulfur, 15N for nitrogen, and 17O or 18O for oxygen.

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.

As used herein, the terms below have the meanings indicated.

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

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.

When ranges of values are disclosed, and the notation "from n1 to n2" or "n1-n2" is used, where n1 and n2 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.

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.

The term "(S)" or "(R)" when used to describe a given position in a molecule such as R, R, or the symbol "D," when used to represent a given position in a drawing of a molecular structure, means that the species 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.

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.

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.

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.

The terms "3S,11bS enantiomer" or the term "3R, 11bR enantiomer" refers to either of the δ6-tetabenazine stereoisomers having the structural formulas shown below:
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-tetrazenine), or all of the foregoing may be intended to be described.

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:

[0189] 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.

[0190] 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, nonyl 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 (—CH2—). Unless otherwise specified, the term “alkyl” may include “alkylene” groups.

[0191] 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-ethylamethylamino and the like.

[0192] The term “amino,” as used herein, alone or in combination, refers to RNR', wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, ary1, 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.

[0193] 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.

[0194] The term “halo,” or “halogen,” as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[0195] 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.

[0196] 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, pentfluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluorodiethyl, difluoropropyl, dichloroethyl and dichloromethyl. “Haloalkylene” refers to a haloalkyl group attached to two or more positions. Examples include fluoromethylene (—CFH—), difluoromethylene (—CF2—), chloromethylene (—CHCl—) and the like.
The term “perhaloalkoxy” refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

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.

The terms “sulfonate,” “sulfonic acid,” and “sulfonic” as used herein, alone or in combination, refer to the \(-\text{SO}_2\text{H}\) group and its anion or the \(-\text{SO}_3^-\) — group.

The terms “sulfate,” “sulfuric acid,” and “sulfuric,” as used herein, alone or in combination, refer to the \(\text{HOSi(=O)}\) \(_2\text{O}^-\) group and its mono-o- or dianion or the \(-\text{SO}_3^-\) — group.

The terms “phosphate,” “phosphoric acid,” and “phosphoric,” as used herein, alone or in combination, refer to the \(\text{PO}(=\text{O})\) \(_2\text{H}^-\) group and its mono-, di-, or trianion or the \(-\text{PO}_4^{3-}\) — group.

The terms “carbonate,” as used herein, alone or in combination, refer to the \(-\text{OC}(=\text{O})\text{O}^-\) — group.

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 to synaptic vesicles.

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.

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 irreversibly 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.

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 disorders such as oppositional defiant disorder.

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 base addition salts. For a more complete discussion of the preparation and selection of salts, refer to “Handbook of Pharmaceutical Salts, Properties, and Use,” Stahl and Wermuth, Ed., (Wiley-VCH and VHCA, Zurich, 2002) and Berge et al., J. Pharm. Sci. 1977, 66, 1-19.

Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acetylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, \((+)-\text{camphoric acid, camphorsulfonic acid,} \((+)-\text{(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactic acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-gluconuronic acid, L-glutamic acid, \(\alpha\)-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, \((+)-\text{lactic acid,} \((+)-\text{DL-lactic acid, lactobionic acid, lauric acid, maleic acid,} \((+)-\text{L-malic acid, malonic acid,} \((+)-\text{DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, neotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phos- phoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid,} \((+)-\text{L-tartaric acid, thio- cyanic acid, p-toluene sulfonic acid, undecylenic acid, and valeric acid.}

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, disopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, TH-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinalidine, quinoline, isouquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-aminohexylhydroxymethyl)-1,3-propanediol, and tromethamine.

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, N.Y., 2002; Vol. 126).

General Synthetic Methods for Preparing Compounds

[0211] 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.

[0212] The compounds as disclosed herein can be prepared by methods known to one of skill in the art and routine modifications thereof, and/or the 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., 2000, (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; U.S. Pat. No. 2,830,993; U.S. Pat. No. 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.

[0213] The following schemes can be used to practice the present invention. Any position shown as hydrogen may optionally be replaced with deuterium.
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 phosphorus 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.

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 $R_{17}$-$R_{12}$, compound 1 with the corresponding deuterium substitutions can be used. To introduce deuterium at $R_{17}$, compound 2 with the corresponding deuterium substitution can be used. To introduce deuterium at one or more positions of $R_{17}$-$R_{12}$, compound 4 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of $R_{17}$-$R_{12}$, compound 7 with the corresponding deuterium substitutions can be used.

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

[0218] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 1, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions of R_{16} or R_{18}, compound 10 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R_{26} or R_{27}, compound 11 with the corresponding deuterium substitutions can be used.

[0219] Deuterium can also be incorporated to various positions having an exchangeable proton, via proton-deuterium equilibrium exchange.

[0220] 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

[0221]

![Chemical Structure](image)

Step 1

[0222]

![Chemical Structure](image)

Optimization of Reaction Conditions

[0223] General Procedure:

[0224] Dopamine hydrochloride is suspended in ethyl formate at 25-30°C. The suspension was cooled to 10-15°C and sodium tert-butoxide 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 wherein 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, CDCl₃), 8.87 (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

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

[0225]

![Chemical Structure](image)

Representative Example

Step 1

[0226] d₆-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride

![Chemical Structure](image)
Step 1

Optimization of Reaction Conditions

**General Procedure:**

N-(2-(3,4-dihydroxy-phenyl)-ethyl)-formamide is charged with solvent, base, phase transfer catalyst if any, and d₄-methyl iodide (CD₂I₂) 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 vol) and water (4.0 vol). The layers are separated and the organic layer is washed twice with 5% aqueous NaOH solution (2x4.0 vol) followed by water (4.0 vol). The organic layer is distilled under reduced pressure to give crude d₄-N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide.

**TABLE 2**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (6 vol) 38-42°C, 36 hours</td>
<td>50 g</td>
<td>80.6%</td>
<td>93.9%</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (6 vol) 38-42°C, 36 hours</td>
<td>21 g</td>
<td>75%</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) 2-Methyl-tetrandrofuran (8 vol) Tetraethylammonium bromide (0.05 eq) 38-42°C, 36 hours</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**TABLE 3**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 g</td>
<td>K₂CO₃ (3 eq) CH₄I (3 eq) Acetone (8 vol) 18-crown-6 (0.05 eq) 38-42°C, 12 hours</td>
<td>116 g</td>
<td>~100%</td>
<td>92.4%</td>
</tr>
<tr>
<td>2</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (8 vol) 38-35°C, 36 hours</td>
<td>47.6 g</td>
<td>82.4%</td>
<td>90.9%</td>
</tr>
<tr>
<td>3</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.6 eq) Acetone (8 vol) 38-35°C, 36 hours</td>
<td>48 g</td>
<td>83.0%</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

**TABLE 4**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (8 vol) 28-35°C, 36 hours</td>
<td>44.3 g</td>
<td>76.7%</td>
<td>94.2%</td>
</tr>
<tr>
<td>2</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (8 vol) 28-35°C, 36 hours</td>
<td>47.6 g</td>
<td>82.4%</td>
<td>90.9%</td>
</tr>
<tr>
<td>3</td>
<td>50 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.6 eq) Acetone (8 vol) 28-35°C, 36 hours</td>
<td>48 g</td>
<td>83.0%</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

**TABLE 5**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (8 vol) 28-35°C, 36 hours</td>
<td>198.9 g</td>
<td>83.7%</td>
<td>93.1%</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>K₂CO₃ (3 eq) CH₄I (2.2 eq) Acetone (8 vol) 28-40°C, 36 hours</td>
<td>21 g</td>
<td>72.9%</td>
<td>95.8%</td>
</tr>
</tbody>
</table>

**TABLE 6**

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Phase Transfer Catalyst (eq)</th>
<th>CH₄I Base (eq)</th>
<th>Solvent/ Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 g</td>
<td>Tetraethylammonium bromide (0.05)</td>
<td>3 K₂CO₃ (3.0) Acetone 35-45°C, 45 hours</td>
<td>Worked well</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 g</td>
<td>Tetraethylammonium bromide (0.08)</td>
<td>3 K₂CO₃ (3.0) Acetone 35-45°C, 45 hours</td>
<td>Worked well</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10 g</td>
<td>None</td>
<td>2.2 C₆H₅CO₃ (2.0) Acetone 35-45°C, 20 hours</td>
<td>1.5% Formamidine methylation, 5% monomethylated phenol remaining</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 6-continued

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

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Phase Transfer Catalyst (eq)</th>
<th>CH3I Base (eq)</th>
<th>Solvent/Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>10 g</td>
<td>None</td>
<td>2.5 CH3CO3 (2.0)</td>
<td>Acetone 35-45°C, 20 hours</td>
<td>2% Formamide methylation, 3% monomethylated phenol remaindering</td>
</tr>
<tr>
<td>5</td>
<td>10 g</td>
<td>Tetrabutylammonium bromide (0.05)</td>
<td>2.2 K2CO3 (3.0)</td>
<td>Acetone 35-45°C, 20 hours</td>
<td>Worked well</td>
</tr>
<tr>
<td>6</td>
<td>10 g</td>
<td>Tetrabutylammonium bromide (0.05)</td>
<td>2.5 K2CO3 (3.0)</td>
<td>Acetone 35-45°C, 20 hours</td>
<td>Worked well</td>
</tr>
</tbody>
</table>

TABLE 7

Optimization of reaction conditions by varying phase transfer catalyst

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) 28-42°C, 36 hours</td>
<td>28 g</td>
<td>82.3%</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) 28-42°C, 36 hours</td>
<td>24 g</td>
<td>81%</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>25 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium iodide (0.05) 28-42°C, 36 hours</td>
<td>23 g</td>
<td>79.8%</td>
<td>83.4%</td>
</tr>
</tbody>
</table>

TABLE 8

Optimization of reaction conditions by varying phase transfer catalyst quantity

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.05) 28-42°C, 36 hours</td>
<td>50 g</td>
<td>86.6%</td>
<td>93.9%</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) Tetrabutylammonium bromide (0.05) 28-40°C, 36 hours</td>
<td>22 g</td>
<td>76.3%</td>
<td>90.78%</td>
</tr>
<tr>
<td>3</td>
<td>25 g</td>
<td>K2CO3 (3 eq) CH3I (2.2 eq) Acetone (8 vol) Without tetrabutylammonium bromide 28-42°C, 36 hours</td>
<td>21 g</td>
<td>72.9%</td>
<td>95.85%</td>
</tr>
</tbody>
</table>

Optimization of Reaction Conditions

[0230] N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide (190 g, 1.049 mol, 1.00 eq) was charged with solvent (1.52 L, 8.0 vol) followed by K2CO3 (434 g, 3.149 mol, 3.00 eq) at 25-30°C. CD3I (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 (2×760 mL, 2×4.0 vol) followed by water (760 mL, 4.0 vol). The organic layer was distilled under reduced pressure to give 158 g crude d,N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide.

Step 2

[0231] 

Representative Example

Step 1

d,N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide

General Procedure:

[0233] N-(2-(3,4-dimethoxy-phenyl)-ethyl)-formamide is charged with solvent and POCl3 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 stirred for 1 hour followed by addition of an anti-solvent if applicable. In some cases, d,N-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride precipitates in the form of a salt directly from the reaction mixture. In others, d,N-6,7-dimethoxy-3,4-dihydroisoquinoline is isolated after acid-base workup.
### TABLE 9

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93 g</td>
<td>POCl₃ (1 eq)</td>
<td>None</td>
<td>49 g</td>
<td>57.6%</td>
<td>90.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetonitrile (10 vol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80-85°C, 2 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>200 g</td>
<td>POCl₃ (1 eq)</td>
<td>None</td>
<td>112 g</td>
<td>61.5%</td>
<td>84.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-95°C, 1 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Optimization of reaction conditions by varying the solvent**

Quenching solvent and anti solvent (reaction solvent toluene)

3 20 g POCl₃ (1 eq) MTBE* (4 vol) (0-30°C, 12 hours, seeded with product) None sticky mass — —

4 20 g POCl₃ (1 eq) DCM* (2 vol) (0-30°C, 12 hours, seeded with product) None sticky mass — —

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

---

### TABLE 10

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48 g</td>
<td>POCl₃ (1.8 eq)</td>
<td>Ethanol (3.8 eq)</td>
<td>20.2 g</td>
<td>46%</td>
<td>91.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-95°C, 1 hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48 g</td>
<td>POCl₃ (distilled, 1.8 eq)</td>
<td>Ethanol (3.8 eq)</td>
<td>35 g</td>
<td>76%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-95°C, 1 hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50 g</td>
<td>POCl₃ (1 eq)</td>
<td>Ethyl Acetate (2 vol)</td>
<td>120 g</td>
<td>67%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-95°C, 1 hour</td>
<td>Ethyl Acetate/ HCl (2 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20 g</td>
<td>POCl₃ (distilled, 1.8 eq)</td>
<td>Ethanol (2.4 eq)</td>
<td>20.1 g</td>
<td>73.5%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-45°C, 1 hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50 g</td>
<td>POCl₃ (distilled, 1.8 eq)</td>
<td>Ethanol (3.8 eq)</td>
<td>20.1 g</td>
<td>73.5%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toluene (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-95°C, 1 hour</td>
<td>Ethanol (3.8 eq)</td>
<td>20.1 g</td>
<td>73.5%</td>
<td>—</td>
</tr>
</tbody>
</table>

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

6 28 g POCl₃ (1.8 eq) Toluene (2 vol) Ethanol (3.8 eq) MTBE* (4 vol) 24 g >100% Isolated by acid-base workup 80-85°C, 1 hour, seeded with product

7 25 g POCl₃ (1.8 eq) Toluene (2 vol) IPA* (3.8 eq) MTBE* (4 vol) 14.5 g 53.2% 80.2% (black solid)

8 25 g POCl₃ (1.8 eq) Toluene (2 vol) 1-Butanol (3.8 eq) MTBE* (4 vol) 20.1 g 73.5% 80.1% (black solid)

9 25 g POCl₃ (1.8 eq) Toluene (2 vol) 1-Prepanol (3.8 eq) MTBE* (4 vol) 20.1 g 73.5% 80.1% (black solid)

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

---

### TABLE 11

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 g</td>
<td>POCl₃ (1.8 eq)</td>
<td>Ethanol (3.8 eq)</td>
<td>110 g</td>
<td>93.3%</td>
<td>(hygroscopic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetonitrile (2 vol)</td>
<td>MTBE* (4 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80-85°C, 1 hour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 11-continued

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

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>IPA* (3.8 eq) MTBE* (4 vol)</td>
<td>17 g</td>
<td>62.4%</td>
</tr>
<tr>
<td>3</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-Butanol (3.8 eq) MTBE* (4 vol)</td>
<td>17.3 g</td>
<td>63.8%</td>
</tr>
<tr>
<td>5</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>Solid not isolated MTBE* (4 vol)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-Propanol (3.8 eq) MTBE* (4 vol)</td>
<td>17 g</td>
<td>62.4%</td>
</tr>
<tr>
<td>7</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-Pentanol (3.8 eq) MTBE* (4 vol)</td>
<td>13.4 g</td>
<td>49.2%</td>
</tr>
<tr>
<td>8</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>2-methyl propanol (3.8 eq) MTBE* (4 vol)</td>
<td>12.77 g</td>
<td>46.9%</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol Ethyl acetate (4 vol)</td>
<td>13.3 g</td>
<td>48.8%</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol Isopropyl acetate (4 vol)</td>
<td>14.83 g</td>
<td>54.5%</td>
</tr>
<tr>
<td>3</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol 2-methyl-THF* (4 vol)</td>
<td>14.2 g</td>
<td>52.2%</td>
</tr>
<tr>
<td>4</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol Ethyl acetate HICl (4 vol)</td>
<td>13.0 g</td>
<td>47.7%</td>
</tr>
<tr>
<td>5</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol MTBE* (4 vol)</td>
<td>18.3 g</td>
<td>67.2%</td>
</tr>
<tr>
<td>6</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol MTBE* (8 vol)</td>
<td>17.5 g</td>
<td>64.3%</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol Ethyl acetate (4 vol)</td>
<td>14.7 g</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>28 g</td>
<td>Acetonitrile (2 vol)</td>
<td>1-butanol MTBE* (4 vol)</td>
<td>21.3 g</td>
<td>70%</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 g</td>
<td>Ethanol MTBE* (4 vol)</td>
<td>Solid not isolated MTBE* (8 vol)</td>
<td>10.5 g</td>
<td>38.5%</td>
</tr>
<tr>
<td>2</td>
<td>25 g</td>
<td>Acetonitrile (3.8 eq)</td>
<td>1-butanol MTBE* (8 vol)</td>
<td>38.5%</td>
<td></td>
</tr>
</tbody>
</table>

*MTBE = Methyl tert-butyl ether; 2-methyl-THF = 2-methyltetrahydrofuran (4 vol).
TABLE 14-continued

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-50°C, 2 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MTBE = Methyl tert-butyl ether;**

TABLE 15

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch</th>
<th>Reaction Conditions</th>
<th>Quenching/ Anti-Solvent</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 50 g</td>
<td>POCl3 (0.5 eq) Acetonitrile (2 vol) 80-85°C, 2 hours</td>
<td>1-butanol (3 eq) MTBE* (4 vol)</td>
<td>12 hours</td>
<td>Product obtained as a gummy solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 50 g</td>
<td>POCl3 (1.0 eq) Acetonitrile (2 vol) 80-85°C, 2 hours</td>
<td>1-butanol (3 eq) MTBE* (4 vol)</td>
<td>12 hours</td>
<td>Product obtained as a gummy solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 25 g</td>
<td>POCl3 (1.8 eq) Acetonitrile (2 vol) 80-85°C, 2 hours</td>
<td>1-butanol (3 eq) MTBE* (4 vol)</td>
<td>12 hours</td>
<td>Product obtained as a gummy solid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Representative Example

Step 2

d$_6$-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride

[0234] 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 refluxed 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$_3$), $\delta$ 14.456 (br s, 1H), 9.105-0.133 (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 (M+)².

Step 3

Optional purification of d$_6$-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride

[0235] To increase the purity of d$_6$-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride various purification procedures were attempted.

TABLE 16

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 5 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol (3 vol) 60-65°C, 1 hour</td>
<td>Cooled and filtered at 25-30°C</td>
<td>2.1 g</td>
<td>42%</td>
<td>94.5%</td>
</tr>
<tr>
<td>2 5 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol (8 vol) 75-80°C, 16 hour</td>
<td>Cooled and filtered at 25-30°C</td>
<td>1.4 g</td>
<td>28.0%</td>
<td>89.0%</td>
</tr>
<tr>
<td>3 5 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Propanol (8 vol) 95-100°C, 16 hour</td>
<td>Cooled and filtered at 25-30°C</td>
<td>1.02 g</td>
<td>20.4%</td>
<td>84.8%</td>
</tr>
<tr>
<td>4 5 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Butanol (8 vol) 115-120°C, 16 hour</td>
<td>Cooled and filtered at 25-30°C</td>
<td>0.85 g</td>
<td>17.0%</td>
<td>76.0%</td>
</tr>
<tr>
<td>5 5 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 1-Pentanol (8 vol) 135-140°C, 16 hour</td>
<td>Cooled and filtered at 25-30°C</td>
<td>1.19 g</td>
<td>23.8%</td>
<td>85.7%</td>
</tr>
</tbody>
</table>

TABLE 17

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetone (3 vol)</td>
<td>Stirred at 25-30°C C, for 2 hour, then filtered and dried</td>
<td>1.75 g</td>
<td>83.3%</td>
<td>93.3%</td>
</tr>
<tr>
<td>2 2 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Acetonitrile (2 vol)</td>
<td>Stirred at 25-30°C C, for 2 hour, then filtered and dried</td>
<td>1.21 g</td>
<td>60%</td>
<td>94.5%</td>
</tr>
<tr>
<td>3 2 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Ethanol/acetonitrile/acetone (1:1:8) (3 vol)</td>
<td>Stirred at 25-30°C C, for 2 hour, then filtered and dried</td>
<td>1.35 g</td>
<td>67.5%</td>
<td>—</td>
</tr>
<tr>
<td>4 2 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methanol/ethyl acetate (5:95) (3 vol)</td>
<td>Stirred at 25-30°C C, for 2 hour, then filtered and dried</td>
<td>1.78 g</td>
<td>89%</td>
<td>—</td>
</tr>
</tbody>
</table>
TABLE 17-continued

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>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</td>
<td>1.34 g</td>
<td>67%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>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</td>
<td>1.46 g</td>
<td>73%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>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</td>
<td>0.55 g</td>
<td>55%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>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</td>
<td>4.8 g</td>
<td>96.0%</td>
<td>93.5%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>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</td>
<td>4.87 g</td>
<td>97.4%</td>
<td>79.1%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>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</td>
<td>4.31 g</td>
<td>86.2%</td>
<td>94.1%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>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</td>
<td>1.63 g</td>
<td>32.6%</td>
<td>90.9%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5 g, 6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) Methyl tert-butyl ether (6 vol) 50-65°C 1-butanol (12 vol) Stirred at 28-32°C for 16 hours, then filtered and dried</td>
<td>3.4 g</td>
<td>68%</td>
<td>91.7%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>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</td>
<td>1.138 g</td>
<td>92%</td>
<td>99.0%</td>
<td></td>
</tr>
</tbody>
</table>

EXAMPLE 3

(RR, SS)-1,3,4,6,7,11b-Hexahydro-9,10-di(methoxy-d₃)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one ((+/-)-d₃-Tetrabenazine)

Step 1

Representative Example

Step 1

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

**[0240]** General Procedure:

**[0241]** 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide is charged to a suspension containing 6,7-dimethoxy-3,4-dihydroisoquinoline (hydrochloride or free base, 1.00 eq) and solvent. If 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-tetrabenazine is the desired product.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 g</td>
<td>6,7-Dimethoxy-3,4- dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (0.75 eq) Methanol/water (1:1) (6 vol) K2CO3 (1 eq) 45-50° C., 90 hour</td>
<td>20.3 g</td>
<td>40.7%</td>
<td>98.8%</td>
</tr>
<tr>
<td>2</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4- dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (0.75 eq) Ethanol (6 vol) 75-80° C., 48 hour</td>
<td>1.4 g</td>
<td>8.3%</td>
<td>97.8%</td>
</tr>
<tr>
<td>3</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4- dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (0.75 eq) Ethanol (6 vol) 75-80° C., 48 hour</td>
<td>1.4 g</td>
<td>8.3%</td>
<td>98.1%</td>
</tr>
</tbody>
</table>

**[0242]** Tables 19 and 20—In-Process HPLC Results

**[0243]** The diastereomer impurity is the (RS, SR) diastereomer of d-tetrabenazine. 

**[0244]** TABLE 19-continued Optimization of the reaction by varying the solvent

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4- dihydro isoquinoline free base (1 eq) 2-acetyl-N,N,N,N-</td>
<td>6.8 g</td>
<td>40.8%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>

**[0245]** TABLE 20-continued Optimization of the reaction by varying the solvent

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 g</td>
<td>6,7-Dimethoxy-3,4- dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (1:1) (6 vol) K2CO3 (1 eq) 45-50° C., 63 hour</td>
<td>8.3 g</td>
<td>74.5%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>

**[0246]** *SM = Starting material; [6,7-Dimethoxy-3,4-dihydroisoquinoline]. The diastereomer impurity is the (RS, SR) diastereomer of d-tetrabenazine.

**[0247]** TABLE 21 Optimization of the reaction by varying the reaction temperature

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
</table>
| 1        | 8 g        | 6,7-Dimethoxy-3,4- dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (1:1) (6 vol) K2CO3 (1 eq) 45-50° C., 63 hour | 8.3 g | 74.5% | 99.1% | 0.04% The diastereomer impurity is the (RS, SR) diastereomer of d-tetrabenazine.

**[0248]** TABLE 22 Optimization of the reaction by varying the reaction temperature

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
</table>
| 2        | 10 g       | 6,7-Dimethoxy-3,4- dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (1:1) (6 vol) K2CO3 (1 eq) 45-50° C., 63 hour | 8.3 g | 74.5% | 99.1% | 0.04% The diastereomer impurity is the (RS, SR) diastereomer of d-tetrabenazine.

**[0249]** TABLE 23 Optimization of the reaction by varying the reaction temperature

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
</table>
| 3        | 10 g       | 6,7-Dimethoxy-3,4- dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-N,N,N,N-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (1:1) (6 vol) K2CO3 (1 eq) 45-50° C., 63 hour | 8.3 g | 74.5% | 99.1% | 0.04% The diastereomer impurity is the (RS, SR) diastereomer of d-tetrabenazine.
### TABLE 21-continued

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8 g</td>
<td>6,7-Dimethoxy-3,4-</td>
<td>8.5 g</td>
<td>76.7%</td>
<td>99.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dihydroquinoline</td>
<td></td>
<td></td>
<td>0.04%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrochloride (1 eq)</td>
<td></td>
<td></td>
<td>Diastereomer impurity*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-acetyl-N,N,N,A-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>tetramethyl-1-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentaammine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>iodide (1.08 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methanol/water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1:1) (6 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>K$_2$CO$_3$ (1 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 g</td>
<td>6,7-Dimethoxy-3,4-</td>
<td>8.3 g</td>
<td>75%</td>
<td>99.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dihydroquinoline</td>
<td></td>
<td>0.1%</td>
<td>Diastereomer impurity*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrochloride (1 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-acetyl-N,N,N,N,A-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>tetramethyl-1-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentaammine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>iodide (1.08 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methanol/water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1:1) (6 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>K$_2$CO$_3$ (1 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>65-70° C, 63 hour</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 24

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 g</td>
<td>6,7-Dimethoxy-3,4-</td>
<td>8.3 g</td>
<td>76.9%</td>
<td>98.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dihydroquinoline</td>
<td></td>
<td></td>
<td>0.09%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrochloride (1 eq)</td>
<td></td>
<td></td>
<td>undesired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-acetyl-N,N,N,A-</td>
<td></td>
<td></td>
<td>isomer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tetramethyl-1-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentaammine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>iodide (1.08 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methanol/water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1:3) (6 vol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>K$_2$CO$_3$ (1 eq)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45-50° C, 63 hour</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### [0243] Tables 22 and 23—In-Process HPLC Results

<table>
<thead>
<tr>
<th>Ex. 3 - Methanol:Water (1:1) 65-70° C.</th>
<th>Ex. 2 - Methanol:Water (1:1) 45-50° C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours</td>
<td>SM*</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>15 h</td>
<td>0.8%</td>
</tr>
<tr>
<td>23 h</td>
<td>33.1%</td>
</tr>
<tr>
<td>39 h</td>
<td>14.3%</td>
</tr>
<tr>
<td>47 h</td>
<td>17.9%</td>
</tr>
<tr>
<td>Crude</td>
<td>88.6%</td>
</tr>
<tr>
<td>After</td>
<td>91.6%</td>
</tr>
<tr>
<td>EA</td>
<td>—</td>
</tr>
<tr>
<td>Final</td>
<td></td>
</tr>
</tbody>
</table>

*SM = Starting material; [6,7-Dimethoxy-3,4-dihydro isoquinoline]. The diastereomer impurity is the (RS, SR) diastereomer of d$_4$-tetrabenazine.

### [0244] Tables 25 and 26—In-Process HPLC Results

<table>
<thead>
<tr>
<th>Ex. 1 - Methanol:Water (1:3) 45-50° C.</th>
<th>Ex. 2 - Methanol:Water (3:1) 45-50° C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours</td>
<td>SM*</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>24 h</td>
<td>—</td>
</tr>
<tr>
<td>48 h</td>
<td>—</td>
</tr>
<tr>
<td>63 h</td>
<td>—</td>
</tr>
<tr>
<td>Crude</td>
<td>—</td>
</tr>
<tr>
<td>After</td>
<td>—</td>
</tr>
<tr>
<td>EA</td>
<td>—</td>
</tr>
<tr>
<td>Final</td>
<td>—</td>
</tr>
</tbody>
</table>

*SM = Starting material; [6,7-Dimethoxy-3,4-dihydro isoquinoline]. EA = Ethyl Acetate; The diastereomer impurity is the (RS, SR) diastereomer of d$_4$-tetrabenazine.
### Ex. 3 - Methanol: Water (4:1) 45-50° C.

<table>
<thead>
<tr>
<th>Hours</th>
<th>SM*</th>
<th>Product</th>
<th>Diastereomer*</th>
<th>SM*</th>
<th>Product</th>
<th>Diastereomer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>48 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>63 h</td>
<td>—</td>
<td>17.75%</td>
<td>2.57%</td>
<td>—</td>
<td>17.75%</td>
<td>2.57%</td>
</tr>
<tr>
<td>Crude</td>
<td>—</td>
<td>97.97%</td>
<td>0.50%</td>
<td>—</td>
<td>97.97%</td>
<td>0.50%</td>
</tr>
<tr>
<td>After EA*</td>
<td>—</td>
<td>98.15%</td>
<td>0.35%</td>
<td>—</td>
<td>98.15%</td>
<td>0.35%</td>
</tr>
<tr>
<td>treatment</td>
<td>—</td>
<td>99.28%</td>
<td>0.03%</td>
<td>—</td>
<td>99.28%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Product</td>
<td>7.58</td>
<td>7.58</td>
<td></td>
<td>54.4</td>
<td>54.4</td>
<td></td>
</tr>
</tbody>
</table>

### Ex. 4 - Methanol, 45-50° C.

<table>
<thead>
<tr>
<th>Hours</th>
<th>SM*</th>
<th>Product</th>
<th>Diastereomer*</th>
<th>SM*</th>
<th>Product</th>
<th>Diastereomer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>48 h</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>63 h</td>
<td>—</td>
<td>17.75%</td>
<td>2.57%</td>
<td>—</td>
<td>17.75%</td>
<td>2.57%</td>
</tr>
<tr>
<td>Crude</td>
<td>—</td>
<td>97.97%</td>
<td>0.50%</td>
<td>—</td>
<td>97.97%</td>
<td>0.50%</td>
</tr>
<tr>
<td>After EA*</td>
<td>—</td>
<td>98.15%</td>
<td>0.35%</td>
<td>—</td>
<td>98.15%</td>
<td>0.35%</td>
</tr>
<tr>
<td>treatment</td>
<td>—</td>
<td>99.28%</td>
<td>0.03%</td>
<td>—</td>
<td>99.28%</td>
<td>0.03%</td>
</tr>
<tr>
<td>Product</td>
<td>7.58</td>
<td>7.58</td>
<td></td>
<td>54.4</td>
<td>54.4</td>
<td></td>
</tr>
</tbody>
</table>

*SM = Starting material; 6,7-Dimethoxy-3,4-dihydroisoquinoline; EA = Ethyl Acetate; The diastereomer impurity is the (RS,SR) diastereomer of d6-tetrabenazine.

### TABLE 27

Optimization of the reaction by varying the reaction time

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>8.5 g</td>
<td>61%</td>
<td>92.2%</td>
</tr>
<tr>
<td>2</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>9.4 g</td>
<td>97.4%</td>
<td>99.6%</td>
</tr>
<tr>
<td>3</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>9.2 g</td>
<td>96%</td>
<td>98.3%</td>
</tr>
</tbody>
</table>

*SM = Starting material; 6,7-Dimethoxy-3,4-dihydroisoquinoline; EA = Ethyl Acetate; The diastereomer impurity is the (RS,SR) diastereomer of d6-tetrabenazine.

### TABLE 30

Comparison of d6-6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride and d6-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>HPLC Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>9.4 g</td>
<td>67.4%</td>
<td>96.5%</td>
</tr>
<tr>
<td>2</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>9.96 g</td>
<td>72.0%</td>
<td>99.9%</td>
</tr>
<tr>
<td>3</td>
<td>10 g</td>
<td>6,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (1 eq) 2-acetyl-1,11,11-tetramethyl-1-pentanaminium iodide (1.08 eq) Methanol/water (3:1) (6 vol)</td>
<td>9.4 g</td>
<td>68.3%</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

*SM = Starting material; 6,7-Dimethoxy-3,4-dihydroisoquinoline; EA = Ethyl Acetate; The diastereomer impurity is the (RS,SR) diastereomer of d6-tetrabenazine.
### Table 30-continued

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Batch Size</th>
<th>Reaction Conditions</th>
<th>Product Quantity</th>
<th>Product Yield</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>125 g</td>
<td>Methanol/water (3:1) (6 vol)</td>
<td>125.7 g</td>
<td>72.7%</td>
<td>99.64%</td>
</tr>
</tbody>
</table>

**Representative Example**

**Step 2**

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

**[0246]** The 2-acetyl-N,N,N,4-tetramethyl-1-pentanaminium iodide from step 1 (146 g) was charged to a suspension containing d₆-6,7-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 K₂CO₃ (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%). ^1H NMR (300 MHz, CDCl₃), 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-6,7)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one

**[0247]** Crude (RR,SS)-1,3,4,6,7,11b-Hexahydro-9,10-di(methoxy-6,7)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one from step 2 (90 g) 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 warm 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%). ^1H NMR (300 MHz, CDCl₃), 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

[0248]

2-Acetyl-4-methylpentanoic acid ethyl ester

[0250] To a solution of ethyl acetooacetate (500 g, 3.842 mol, 1.00 eq) in DMF (1.5 L, 5.0 vol), KI (63.7 g, 0.384 mol, 0.10 eq), tetrabutylammonium bromide (136 g, 0.422 mol, 0.11 eq) and K₂CO₃ (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 (2×2.0 L, 2×4.0 vol) and the combined organic layers were washed with water (2×1.5 L, 2×3.0 vol). The organic layer was evaporated under reduced pressure to obtain crude 2-acetyl-4-methylpentanoic acid ethyl ester.

Step 2

[0251]

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

[0252] 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 (2×2.56 L, 2×4.0 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, 1.30 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 reaction 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 adjusted 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 (2×2.56 L, 2×4.0 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 (2×2.56 L, 2×4.0 vol and 1×1.28 L, 1×2.0 vol) and the combined organic layers were washed sequentially with purified water (2×1.92 L, 2×3.0 vol) and 10% ammonium chloride solution (2×3.2 L, 2×5.0 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%).

[0253] 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.

What is claimed is:

1. A process of preparing a compound of Formula 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:

![Scheme](attachment:image.png)

in the presence of a base;
wherein:
R₇-R₁₂ and R₁₅ are independently selected from the group consisting of hydrogen and deuterium; and
Y₁ is selected from the group consisting of acetoxyl, alkoxy, haloalkoxy, perhaloalkoxy, heteroarylalkoxy, and aryloxy, any of which may be optionally substituted.

2. (canceled)

3. The process of claim 1 wherein Y₁ is ethoxy and said base is sodium tert-butoxide.

4-9. (canceled)

10. A process of preparing a compound of Formula VI:

![Scheme](attachment:image.png)

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

![Scheme](attachment:image.png)

in a solvent and in the presence of a base;
wherein:
R₅-R₁₂ and R₁₅ are independently selected from the group consisting of hydrogen and deuterium; and
Y₂ is selected from the group consisting of halogen, alkyl sulfate, alkyl sulfonate, haloalkyl sulfonate, aryl sulfonate, alkylaryl sulfonate, dialkylxoxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

11. (canceled)

12. The process of claim 10 wherein Y₂ is iodide and said base is potassium carbonate.

13-16. (canceled)

17. The process of claim 10 wherein said solvent is acetone.

18. (canceled)

19. The process of claim 17 wherein the volume of said solvent is between about 6 to about 10 times the mass of the compound of Formula IV.

20. (canceled)

21. The process of claim 10 wherein said reaction step is carried out in the presence of a phase transfer catalyst selected from the group consisting of tetrabutylammonium bromide, tetrabutylammonium iodide, and 18-crown-6.

22. (canceled)

23. The process of claim 21 wherein said phase transfer catalyst is tetrabutylammonium bromide.

24. A process of preparing a solid salt of a compound of Formula VII:

![Scheme](attachment:image.png)

comprising:
a first step of reacting a compound of Formula VI:

![Scheme](attachment:image.png)

with a dehydrating agent in a reaction solvent;
a second step of adding a quenching solvent and an anti-solvent to the reaction mixture; and
a third step of isolating the salt of the compound of Formula VII from the reaction mixture;
wherein:
R₅-R₁₂ and R₁₅ 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 phosphorous oxychloride.
27. (canceled)
28. The process of claim 26 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. (canceled)
30. (canceled)
31. The process of claim 24 wherein said reaction solvent is acetonitrile.
32. (canceled)
33. The process of claim 31 wherein the volume of said acetonitrile is between about 1.5 to about 2.5 times the mass of the compound of Formula VI.
34-36. (canceled)
37. The process of claim 24 wherein said quenching solvent is 1-butanol.
38-39. (canceled)
40. The process of claim 37 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.
41-43. (canceled)
44. The process of claim 24 wherein said antisolvent is methyl tert-butyl ether.
45. (canceled)
46. The process of claim 44 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.
47-50. (canceled)
51. The process of claim 24 wherein said first reaction step is held at a temperature of between about 80°C. to about 85°C.
52-55. (canceled)
56. The process of claim 24 wherein second reaction step is carried out at between about 25°C. to about 35°C.
57-58. (canceled)
59. A process of purifying a hydrochloride salt of a compound of Formula VII:

\[
\text{comprising:}
\]

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

\(X\) is selected from the group consisting of halogen, alkyl sulfone, alkyl sulfinate, alkylsulfinate, perhaloalkyl sulfoximate, aryl sulfoximate, alkylaryl sulfoximate, dialkyl oxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

60. (canceled)
61. The process of claim 59 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.

63-64. (canceled)
65. The process of claim 59 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:

\[
\text{comprising:}
\]
a step of reacting a compound of Formula VII or a salt thereof with a compound of Formula VIII in one or more solvents:

\[
\text{wherein:}
\]
\(R_1-R_{27}\) are independently selected from the group consisting of hydrogen and deuterium; and

\(X\) is selected from the group consisting of halogen, alkyl sulfone, alkyl sulfinate, alkylsulfinate, perhaloalkyl sulfoximate, aryl sulfoximate, alkylaryl sulfoximate, dialkyl oxonium, alkylphosphate, and alkylcarbonate, any of which may be optionally substituted.

67. (canceled)
68. The process of claim 66 wherein said solvent is a mixture of methanol and water.
69. (canceled)
70. The process of claim 68 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. (canceled)
73. The process of claim 71 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. (canceled)

75. The process of claim 66 wherein said solvent is a mixture of ethanol and water.

76. (canceled)

77. The process of claim 75 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. (canceled)

80. The process of claim 78 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.

81-83. (canceled)

84. The process of claim 66 wherein said reaction step is held at a temperature of between about 40°C to about 60°C.

85-86. (canceled)

87. The process of claim 84 wherein said reaction step is carried out for about 24 to about 72 hours.

88. (canceled)

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.

90-91. (canceled)

92. The process of claim 89 wherein said base is potassium carbonate.

93. A process of preparing a compound of Formula XI:

![Diagram of Formula XI]

comprising:

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

![Diagram of Formula 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:

R₁₋₇ 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 potassium hydroxide.

95-98. (canceled)

99. The process of claim 93 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 hydrochloric acid.

101. (canceled)

102. The process of claim 93 wherein a phase transfer catalyst tetrabutylammonium bromide is added during the third reaction step.

103-104. (canceled)

105. The process of claim 93 wherein said solvent is water.

106. The process of claim 93 wherein 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.

107-109. (canceled)

110. The process of claim 93 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.

112-114. (canceled)

115. The process of claim 93 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.

116-117. (canceled)

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. (canceled)

120. The process of claim 118 wherein the reaction temperature is maintained for about 9 to about 15 hours after third addition step.

121-122. (canceled)

123. The process of claim 93 wherein the fourth pH adjustment step results in a pH of less than 1.

124-126. (canceled)

127. The process of claim 93 wherein the fifth pH adjustment step results in a pH of about 12 to about 13.

128-130. (canceled)

131. The process of claim 93 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.

132-137. (canceled)