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(71) Applicant: MYLAN LABORATORIES LIMITED [IN/IN]; Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) Inventors: JAYACHANDRA, Sureshbabu; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **JEBARAJ, Rathinapandian**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **CHANDUPATLA, Shivakumar**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **KOTHAKONDA, Sudarshan Rao**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **SRINIVASARAO, Attanti Veera Venkata**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **GHANTA, Nagaraji**; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) Agents: HASAN, Afzal et al.; Hasan and Singh, Flat No. 04, Sree Nilayam Apartment, Plot No. 12, Camelot Layout (Near Chirec Public School), Kondapur, Hyderabad 500084 (IN).

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(54) Title: PROCESSES FOR THE PREPARATION OF VORTIOXETINE HYDROBROMIDE

(57) Abstract: The present invention relates to a process for the preparation of vortioxetine and its pharmaceutically acceptable salts.

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PROCESSES FOR THE PREPARATION OF VORTIOXETINE HYDROBROMIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

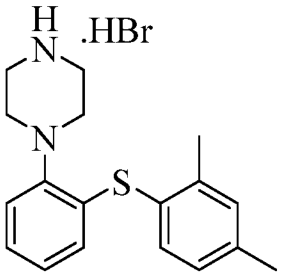
This application claims the benefit of Indian provisional patent applications No. 552/CHE/2015 filed on February 4, 2015,and 3789/CHE/2015 filed on July 22, 2015, which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of vortioxetine and its pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION

Vortioxetine hydrobromide is chemically known as 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazinehydrobromide and structurally represented as Formula-I below. Vortioxetine hydrobromide is marketedunder the trade name BRINTELLIX® by Takeda Pharmaceuticals U.S.A., Inc. and is indicated for the treatment of major depressive disorder (MDD).



Formula-I

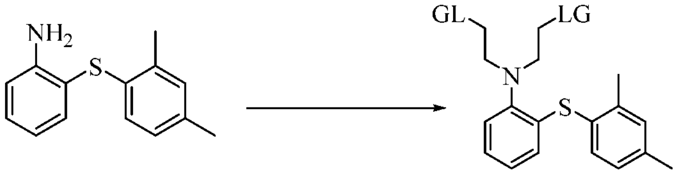
Vortioxetine is disclosed in the PCTPublication No. WO 2003029232.PCTPublication Nos. WO 2007144005, WO 2013102573, WO 2014128207, and WO 2014191548 disclose processes for the preparation of vortioxetine.

The present invention provides a process for the preparation of vortioxetine and pharmaceutically acceptable salts thereof.

SUMMARY OF THE INVENTION

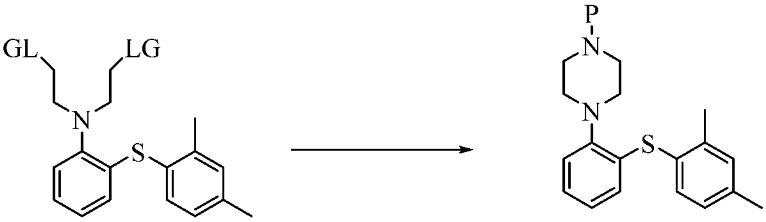
The present invention generally provides processes for the synthesis of vortioxetine or pharmaceutically acceptable salts. In all of the processes disclosed below, vortioxetine may be further converted to a pharmaceutically acceptable salt of vortioxetine.One aspect of the present invention provides a method for the preparation of formula-VI, which may include the following steps:

a) converting formula-VI into formula-IX;



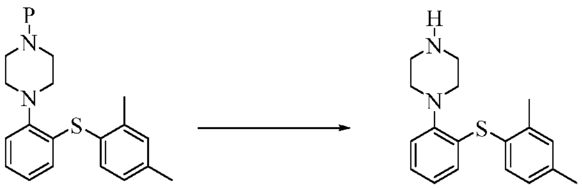
VI IX

b) converting formula-IX into formula-X; and



IX X

c) when P is not hydrogen, then converting formula-X to vortioxetine,



X II

wherein LG is a leaving group and P is a protecting group or hydrogen.

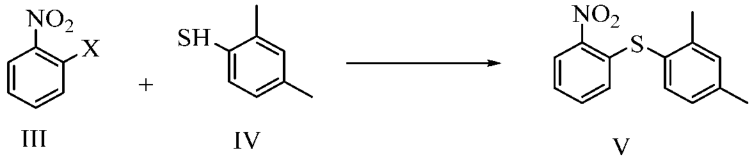
Within the context of this embodiment, formula-VI may be converted to formula-IX by reacting formula-VI with a haloacetic acid or a haloaldehyde in the presence of a reducing agent and a solvent. The haloacetic acid may be chloroacetic acid or bromoacetic acid. The haloaldehydemay be chloroacetaldehyde. The reducing agent may be selected but not limited toborane, sodium borohydride, lithiumborohydride, sodiumcyanoborohydride, sodiumtriacetoxyborohydride, borane–THF, a mixture of sodium borohydride and sulfuric acid, and mixtures thereof. The solvent may be selected from ethers and hydrocarbons. Ether solvent may be used but not limited totetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether. Hydrocarbon solvent may be used but not limited to cyclohexane, toluene and xylene.

Within the context of this embodiment, formula-IX may be converted to formula-X by reacting formula-IX with a nitrogen source in the presence of a base, a metal halide, and a solvent. The nitrogen source may be selected but not limited toammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxy benzylamine, 4-chloro benzylamine,4-bromo benzylamine, 4-nitro benzylamine, and ammonia.

The base used in this step may be selected from the group consisting of alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. The alkaline metal carbonate may be used but not limited to sodium carbonate, potassium carbonate, and cesium carbonate. The metal halide may be used but not limited tolithium bromide, sodium bromide, sodium iodide, and potassium iodide. The solvent may be selected but not limited toacetone, acetonitrile, dimethylacetamide, dimethylformamide, dimethylsulfoxide, toluene, and mixtures thereof.

Within the context of this embodiment, the process of converting formula-X to vortioxetine may be carried out in the presence of a reagent and a solvent. The reagent may be selected but not limited to 1-chloroethylchloroformate, palladium-on-carbon, and Raney nickel. The solvent may be selected from ethers, hydrocarbons and alcohols. Ether solvent may be selected but not limited totetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether. Hydrocarbon solvent may be used but not limited to cyclohexane, toluene and xylene. Alcohol solvent may be used but not limited to methanol, ethanol, propanol and isopropanol.

In another aspect, the present invention provides a process for the preparation of formula-V, that includes the step of reacting formula-III with formula-IV in the presence of a base and an alcohol solvent,

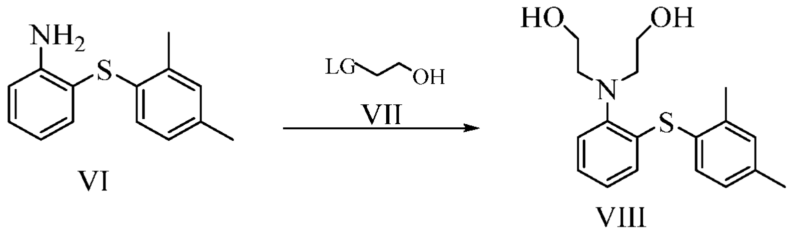


wherein X is a halo group selected from the group consisting of fluoro-, chloro-, bromo-, and iodo-.

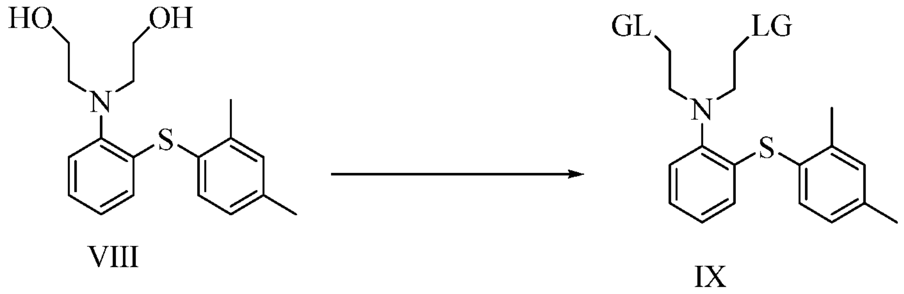
The base used in this embodiment may be an organic base or an inorganic base. The inorganic base may be selected fromalkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. The alkaline metal hydroxide may be used but not limited to sodium hydroxide and potassium hydroxide. The organic base may be used but not limited topyridine, triethylamine, and N,N-diisopropylethylamine. The alcohol solvent may be used but not limited tofrom methanol, ethanol, propanol, isopropanol, and mixtures thereof.

In another aspect, the present invention provides a process for the preparation of vortioxetine or a pharmaceutically acceptable salts thereof that includes the steps of:

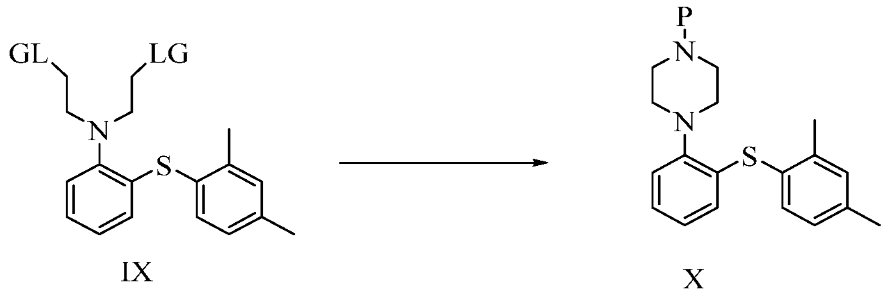
a) condensing formula-VI with formula-VII to yield a formula-VIII;



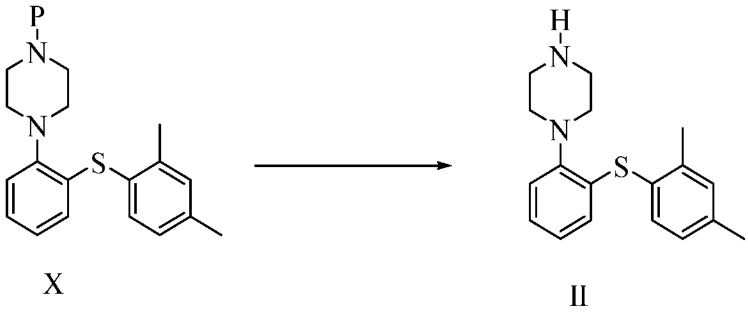
b) converting formula-VIII into formula-IX;



c) converting formula-IX into formula-X; and



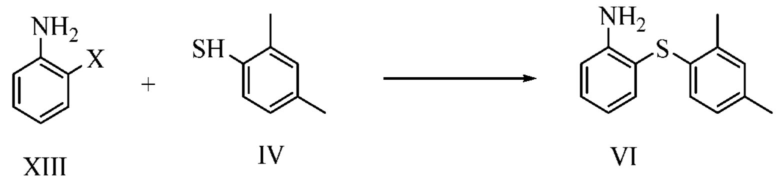
d) when P is not hydrogen, then converting formula-X to vortioxetine.



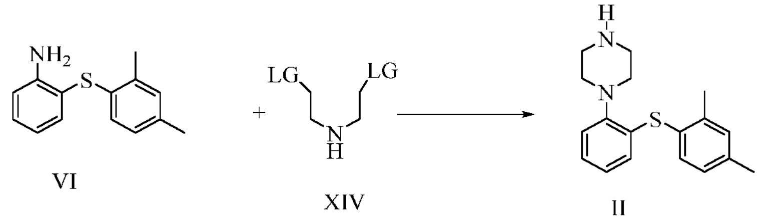
wherein LG is a leaving group and P is a protecting group or H.

In another aspect, the present invention provides a“one pot” process for the preparation of vortioxetine or a pharmaceutically acceptable salt thereof that includes the steps of:

a) reacting formula-XIII with formula-IV in the presence of a base and a catalyst to yieldformula-VI; and



b) reacting formula-VI with formula-XIV in the presence of a solvent to provide vortioxetine,

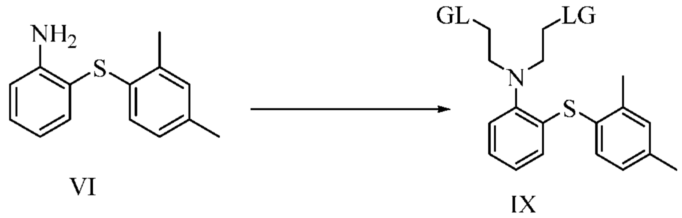


DETAILED DESCRIPTION OF THE INVENTION

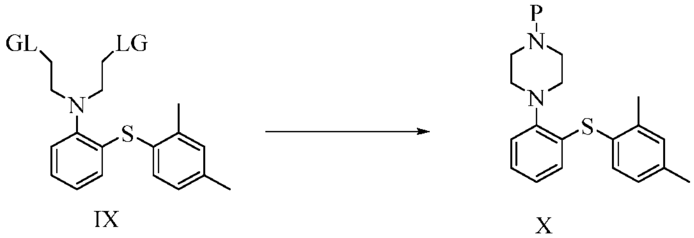
The present invention provides a process for the preparation of vortioxetine andpharmaceutically acceptable salts thereof.

One aspect of the present invention provides a process for the preparation of vortioxetine, which may be carried out by the following steps:

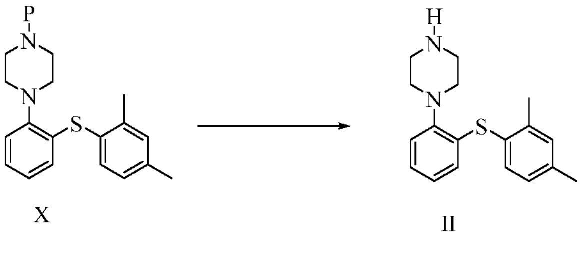
a) converting the compound of formula-VI into a compound of formula-IX;



b) converting the compound of formula-IX into a compound of formula-X;



c) deprotecting the compound of formula-Xwhen P is protecting group to yield vortioxetine (formula-II); and



d) optionally converting vortioxetine into a pharmaceutically acceptable salt.

According to this emodiment,vortioxetine may be prepared first by convertingformula-VI or the acid salt thereof,to formula-IX.

The conversion of formula-VI or the acid salt form thereof to formula-IX may be carried out by reacting with halo acetic acid or halo aldehyde in presence of reducing agent and solvent to get a compound of formula IX. Examples of suitable leaving group sources includehaloacetic acids or haloaldehydes.Example of suitable haloacetic acids include fluoroacetic acid,chloroacetic acid,bromoacetic acid, and iodoacetic acid.Examples of suitable haloaldehydes includefluoroacetaldehyde, chloroacetaldehyde, bromoacetaldehyde, and iodoacetaldehyde.In some embodiments, formula-IX is reacted with chloroacetic acid.

The solvent may be, for example, thesolvent may be selected from ethers and hydrocarbons. Ether solvent may be selected from tetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether. Hydrocarbon solvent may be used but not limited to cyclohexane, toluene and xylene.In some embodiments, tetrahydrofuran was used as the solvent for this reaction. Suitable reducing agentsinclude, for example, borane, sodium borohydride, lithiumborohydride, sodiumcyanoborohydride, sodiumtriacetoxborohydride, and borane-THFcomplex. In some embodiments, the borane-THF complex may be generated in situ by combining sodium borohydride and sulfuric acidin the presence of tetrahydrofuran. In particularly useful embodiments, the boron-THF complex is prepared in situ by combining sodium borohydride and sulfuric acid in a 200:1 molar ratio.

Within the context of the present disclosure, the “LG” moiety is aleaving group.

The term “leaving group” is well-known and understood in the art. A “leaving group” is a moiety that may be, for example, halo (e.g., fluoro, chloro, bromo, iodo), alkyl sulfonyloxy (e.g.,methanesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy), aryl sulfonyloxy (e.g., p-toluenesulfonyloxy,(4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy,(4-isopropyl-benzene)sulfonyloxy,(2,4,6-triisopropylbenzene)sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, benzenesulfonyloxy, (4-methoxy-benzene)sulfonyloxy), and alkoxy.Within the context of this embodiment, an alkoxymay be a straight or branched C_1-C_6 alkyl group. Suitable alkoxy groups include, for example,methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1,1-dimethyl ethoxy, and 1-methylpropoxy, each of which may be unsubstituted or substituted by one or more halogens.

Next, formula-IX may be converted into formula-X. Within the context of this embodiment,the “P” moiety is an amine protecting group or is hydrogen.

The conversion of formula-IX to formula-X may be carried out in the presence of a nitrogen source, a base,a metal halide,and a solvent. Within the context of this embodiment, the nitrogen source provides the nitrogen to cyclization formula-IX and form the piperazine ring of formula-X.

Suitable nitrogen sources include, for example, ammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxybenzylamine, 4-chlorobenzylamine,4-bromobenzylamine, 4-nitrobenzylamine, and ammonia. In some embodiments, 4-methoxybenzylamine or benzylamineareused as nitrogen sources.

In some embodiments of the invention, the nitrogen source may also include the protecting group. For example, cyclization of formula-IX with the nitrogen source to form the piperazine ring of formula-X may cause a side group on the nitrogen source to serve as the protecting group. For example, in some embodiments, carrying out this reaction with a 4-methoxybenzylamine nitrogen source will cause the methoxybenzyl moiety of the nitrogen source to serve as the protecting group on formula-X. In other embodiments, using ammonia as the source of nitrogen will cause P to be hydrogen atom. In that circumstance, no deprotection will be needed, as described further below.

Thebase may be, for example, an alkaline metal hydroxide, an alkaline metal bicarbonate, an alkaline metal carbonate,or analkaline alkoxide. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate, potassium bicarbonate. Examples of alkaline metal carbonatesincludesodium carbonate, potassium carbonate, and cesium carbonate.Examples of alkaline alkoxides includesodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, and potassium tert-butoxide.In some embodiments, sodium carbonate is used.

The metal halide may be, for example, lithium bromide, sodium bromide, sodium iodide,or potassium iodide.In some embodiments, lithium bromide is used as the metal halide reagent.

The solvent may be a protic or an aprotic solvent. Examples of suitable solvents include acetone, acetonitrile, dimethylacetamide, dimethylformamide, dimethylsulfoxidetoluene, and mixtures thereof.In some embodiments, acetonitrile is used.

In other embodiments, theconversion of formula-IX to formula-X may be carried out in the presence of a phase-transfer catalyst, a nitrogen source, and a solvent. Suitable phase transfer catalystsinclude, as examples,quaternary ammonium salts. For example, tetrabutylammonium bromide, tetrabutylammonium iodide, benzyltrimethylammonium chloride, benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammondium chloride, or methyltrioctylammondium chloride may be used as a phase-transfer catalyst. Suitable nitrogen sources include, for example, ammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxybenzylamine, 4-chlorobenzylamine,4-bromobenzylamine, 4-nitrobenzylamine, and ammonia. In some embodiments,benzylamineis used as the source of nitrogen. The solvent may be, for example, acetone, acetonitrile, dimetylacetamide, dimethylformamide, dimethylsulfoxide, toluene, and mixtures thereof.In some embodiments, tolueneorxylene are used as a solvent.

In some embodiments, p-toluenesulfonic acid may also be used to catalyze this reaction.

Next, formula-X may be deprotected by removal of the P group. In those instances where P is hydrogen, no deprotection need occur. Deprotection of formula-X may be carried out in the presence of a suitable reagent and a solvent. One of skill in the art will readily recognize and be familiar with appropriate reagents and conditions required for removal of a particular protecting group. For example, depending on the protecting group, suitable reagents may include, as examples,Raney nickel,or palladium-on-carbon in the presence of hydrogen source, an acid, a base, or1-chloroethylchloroformate. In some embodiments where the protecting group is a p-methoxybenzyl moiety or a benzyl moiety, 1-chloroethylchloroformatemay be used as a deprotecting agent.The solvent, again, depending on the protecting group and reagents used,may be, for example,ethers, hydrocarbons and alcohols, ether solvent may be used but not limited to totetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether. Hydrocarbon solvent may be used but not limited to cyclohexane, toluene and xylene. Alcohol solvent may be used but not limited to methanol, ethanol, propanol and isopropanolor mixtures thereof. In some embodiments, toluene or tetrahydrofuran is used as the solvent for this step.

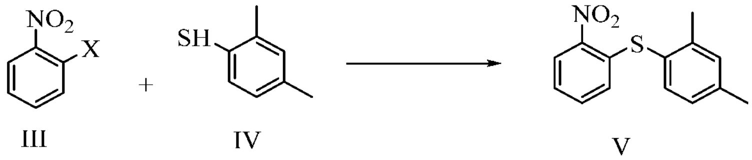
Within the context of this embodiment, vortioxetine of formula-II may be optionally converted into a pharmaceutically acceptable salt of vortioxetine. The term "pharmaceutically acceptable salt"is well-known and understood in the art and refers to salts of pharmaceutically active agents which aresuitable for use in contact with the tissues of humans and lower animals without undue adverse effects (e.g., toxicity, irritation, allergic response). Examples of pharmaceutically acceptable salts may be found inS. M. Berge, et al., J. Pharmaceutical Sciences, 66: 1-19 (1977), in which all information pertaining to the pharmaceutically acceptable salts and processes for preparation thereof are hereby incorporated by reference.

Preparation of a pharmaceutically acceptable salt of an active pharmaceutical agentis well known in the art. For example, the salts can be prepared in situ during the final isolation and purification of the compounds taught herein or separately by reacting a free base moiety on the active pharmaceutical agent with a suitable reagent.For example, a free base moiety on vortioxetine can be reacted with a suitable acid to obtain a pharmaceutically acceptable salt of vortioxetine.

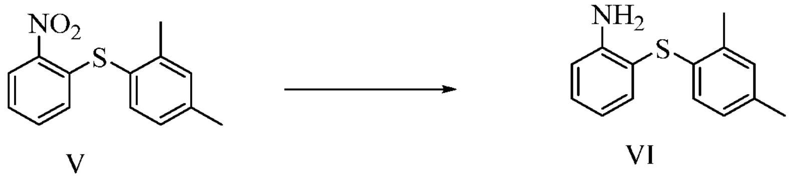
Examples of suitable acids include, for example, inorganic acids or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid. Suitable organic acids include, for example, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid,and malonic acid. Apharmaceutically acceptable salt of the active pharmaceutical agent may alternatively be prepared by other methods well-known in the art,for example, ion exchange.Additional examples of suitable pharmaceutically acceptable salts of the active pharmaceutical agent which may be formed include, for example,adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, (R,S)-malate, (S)-malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, phthalate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. In certain embodiments, a particularly useful pharmaceutically acceptable salt of vortioxetine is the hydrobromide salt.

One embodiment of the present invention provides a process for the preparation of formula-VI, which may be carried out by the following steps:

a) reacting a compound of formula-III with a compound of formula-IV in the presence of a base and an alcohol solvent to get a compound of formula-V; and



b) reducing the compound of formula-V into a compound of formula-VI.



Within the context of this embodiment, the "X" moiety is a halogen (for example, fluoro, chloro, bromo, or iodo).

As shown above, formula-VI may be prepared by reactingformula-III with formula-IV. This may be carried out in the presence of a base and an alcohol solvent. Within the context of this embodiment, the alcohol solvent may be, for example, methanol, ethanol, propanol, isopropanol, or mixtures thereof. In some embodiments, the solvent used is isopropyl alcohol.In some embodiments, the solvent used is a mixture of water and isopropyl alcohol.

The base used in this reaction may be inorganic or organic. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of suitable alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxidesinclude sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Within the context of this embodiment of the invention, any organic base is suitable for this step. For example, pyridine, triethylamine,or N,N-diisopropylethylamine may be used.In some embodiments, the base used in the reaction of formula-III with formula-IV is potassium hydroxide, triethylamine, or N,N-diisopropylethylamine. One of skill in the art will readily recognize numerous inorganic and organic bases that are suitable for carrying out this step of the process.

As a next step in the formation of vortioxetine or pharmaceutically acceptable salts thereof, formula-V may bereduced to formula-VI. This step may be carried out, for example, by catalytic reduction in the presence of a suitable hydrogen source (e.g., hydrogen gas). Examples of catalysts include Raney nickel, platinum (IV) oxide, and palladium-on-carbon.

The reduction reaction may be carried out in the presence of suitable solvent. One of skill in the art will be familiar with suitable reaction conditions for carrying out the reduction with a particular reagent or set of reagents. For example, catalytic reductions may be performed in the presence of methanol. Other solvents that may be used include, for example, ethanol, isopropyl alcohol, water, ormixtures thereof.

In some particularly useful embodiments, the reduction of formula-V to formula-VI is carried out in the presence of Raney nickel, methanol, and hydrogen gas.

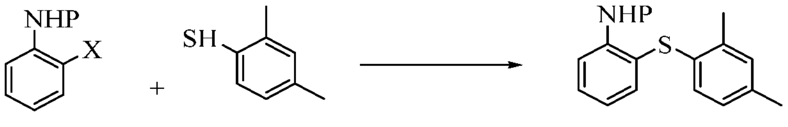
In other embodiments, formula-V may benon-catalytically reduced to formula-VIin the presence of iron powder, water, and ammonium chloride.

In some embodiments of the present invention, formula-VI maybe converted into its acid salt form, which describes an acid salt of the compound. Conversion of formula-VI may increase the purity of the product formed which in turn may increase yields and purity of subsequent products of subsequent reactions, including the final vortioxetine product. Methods for converting compounds into their acid salt forms are well known in the art, and may be carried out, for example, by reacting a free base moietyon the compound with a suitable reagent.

For example, a free base moiety on formula-VI can be reacted with a suitable acid to obtain a pharmaceutically acceptable salt of formula-VI.Examples of suitable acids include, for example, inorganic acids or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid. Suitable organic acids include, for example, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid,and malonic acid. Apharmaceutically acceptable salt may alternatively be prepared by other methods well-known in the art,for example, ion exchange.Additional examples of suitable saltsinclude, for example,adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, (R,S)-malate, (S)-malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, phthalate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. In certain embodiments, the acid is an inorganic acid (e.g., hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid,orperchloric acid). In certain other embodiments, the acid is hydrochloric acid or hydrobromic acid.

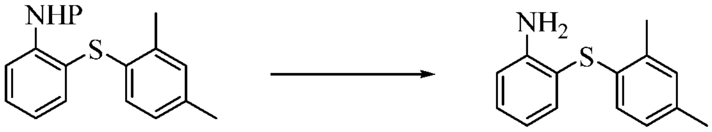
A further aspect of the present invention provides a method for the preparation of formula-VI, which may include the following steps:

a) reacting a compound of formula-IIIa with a compound of formula-IV to get a compound of formula-Va;and



IIIa IV Va

b) optionallydeprotecting the compound of formula-Va wherein P is a protecting group, to yield a compound of formula-VI.



Va VI.

Within the context of this embodiment, the “X” moiety is a halogen (for example, fluoro, chloro, bromo, or iodo). The “P” moiety is an amine protecting group or is hydrogen, as discussed further herein below.

The term “amine protecting group”is well known and understood in the art. Examples of suitable amine protecting groups, as well as suitable conditions for protecting and deprotecting, can be found in prior art, such as J. F. W. McOmie, “Protective Groups in Organic Chemistry”, Plenum Press, London and New York 1973; T. W. Greene and P. G. M. Wuts, “Protective Groups in Organic Synthesis”, Third edition, Wiley, New York 1999; “The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981; in “Methoden der organischenChemie”, Houben-Weyl, 4th edition, Vol. 15/1, Georg ThiemeVerlag, Stuttgart 1974; H.-D. Jakubke and H. Jescheit, “Aminosauren, Peptide, Proteine”, VerlagChemie, Weinheim, Deerfield Beach, and Basel 1982; and Jochen Lehmann, “Chemie der Kohlenhydrate: Monosaccharide und Derivate”, Georg ThiemeVerlag, Stuttgart 1974.

Amine protecting groups include, for example, $-R^P$, $=R^Q$, $-C(O)R^0$, $-C(O)OR^0$,$-S(O)_2R^0$, and 2-nitrophenylsulfenyl, wherein

R^P is a $-C(R^{P1})_3$, wherein each R^{P1} is hydrogen or optionally substituted aryl, provided that at least one R^{P1} is not hydrogen;

R^Q is $=C(H)-R^0$; and

R^0 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} haloalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein each alkyl, aryl, and heteroaryl group is optionally substituted.

“Optionally substituted” as used herein means the reference group is substituted by one or more groups (e.g., 1 to 5, or 1 to 3, or 1 to 2 groups or 1 group) that are each independently halo, alkyl, alkoxy, nitro, cyano, tri(C_{1-3}alkyl)silyl (e.g., trimethylsilyl).

Particular examples of amine protecting groups include, carbonyls (e.g., methyl carbamate, 9-fluorenylmethyoxycarbonyl (Fmoc), trichloroethoxycarbonyl (Troc), tert-butyloxycarbonyl (BOC), 2-trimethylsilylethyloxycarbonyl (Teoc), allyloxycarbonyl (Alloc), p-methoxybenzyl carbonyl (Moz), and carboxybenzyl (Cbz)), sulfonyls (e.g., p-toluenesufonyl (Ts), trimethylsilylethanesulfoyl (Ses), tert-butylsulfonyl (Bus), 4-methoxyphenylsulfonyl, 4-nitrobenzenesulfonyl (nosyl)), trityl (trt), benzyl (Bn), 3,4-dimethyoxybenzyl (Dmpm), p-methoxybenzyl (PMB),p-methoxyphenyl (PMP), acetyl (Ac), formyl, trifluoroacetyl (Tfa), benzoyl (Bz), or 2-nitrophenylsulfenyl (Nps).

The term "alkenyl" as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl, and 3,7-dimethylocta-2,6-dienyl.

The term "alkoxy" as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term "alkyl" as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms, unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term "aryl," as used herein, means a monocyclic (i.e., phenyl), bicyclic, or tricyclic ring fused or bridged system containing at least one phenyl ring. Non-phenyl rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated, may contain one or more heteroatoms, each selected from N, S, and O, and may be optionally substituted with one or two oxo and/or thia groups. Examples of aryl groups include phenyl, napthyl, anthracenyl, and fluorenyl.

The term "arylalkyl" as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, fluorenylmethyl and 2-naphth-2-ylethyl.

The term "halo" or "halogen" as used herein, means -Cl, -Br, -I or -F.

The term "haloalkyl" as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, perfluorononyl, and 2-chloro-3-fluoropentyl.

The term "heteroaryl," as used herein, means a monocyclic, bicyclic, or tricyclic ring system containing at least one heteroaromatic ring. Any additional rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated or may be aromatic rings, and each may optionally contain one or more heteroatoms, each selected from N, S, and O. Representative examples of monocyclic and bicyclicheteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl,triazinyl. benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiadiazolyl, benzothiazolyl, cinnolinyl, dihydroquinolinyl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, and tetrahydroquinolin-yl.

The term "heteroarylalkyl" as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heteroarylalkyl include, but are not limited to, furylmethyl, imidazolylmethyl, pyridinylethyl, pyridinylmethyl, pyrimidinylmethyl, and thienylmethyl.

The term "oxo" as used herein means a =O group.The term "thia" as used herein means a =S group.

As shown above, the present invention encompasses the reaction of formula-IIIawith formula-IV to produce formula-Va. This reaction may be carried out in the presence of a base, a catalyst, and a solvent. The base may be inorganic or organic.Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of suitable alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxidesinclude sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide,and potassium tert-butoxide. Examples of suitable organic basesincludeethylamine, methylamine, imidazole, pyridine, trimethylamine, and N, N-diisopropylethylamine. In some embodiments, potassium tert-butoxide is used as the base.

Suitable catalysts include, for example, bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$), tris(dibenzylideneacetone)palladium(0)($Pd(dba)_3$),palladium(II) acetate ($Pd(OAc)_2$),copper, cuprous bromide, cuprous iodide,(±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP), and combinations thereof.In some embodiments, a combination of bis(dibenzylideneacetone)palladium(0) and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene were found to be particularly effective.

Suitable solvents include, for example, acetone, acetonitrile, dimetylacetamide, toluene, xylene, and mixtures thereof.In some embodiments, toluene, or xyleneis used as the solvent.

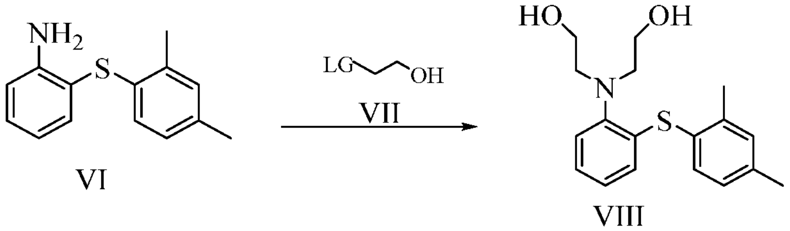
Next, formula-Va may be deprotected. Again, one of skill in the art will be familiar with and knowledgeable regarding suitable deprotection conditions for the variety of protecting groups that may be used in the context of the present invention. For example, many protecting groups may be removed by hydrogenolysis or through the use of an acid or a base.

Within the context of this embodiment, formula-VI may be optionally converted into its acid salt form, as previously described. Conversion of formula-VI may increase the purity of the product formed which in turn may increase yields and purity of subsequent products of subsequent reactions, including the final vortioxetine product.

Within the context of this embodiment, formula-VI or the acid salt form thereof may be used as an intermediate in the synthesis of vortioxetine or pharmaceutically acceptable salts thereof.

The present disclosure also encompasses an additional process for the preparation of vortioxetine, which may be carried out by the following steps:

a) condensing a compound of formula-VI with a compound of formula-VII to a compound of obtain formula-VIII;



VI

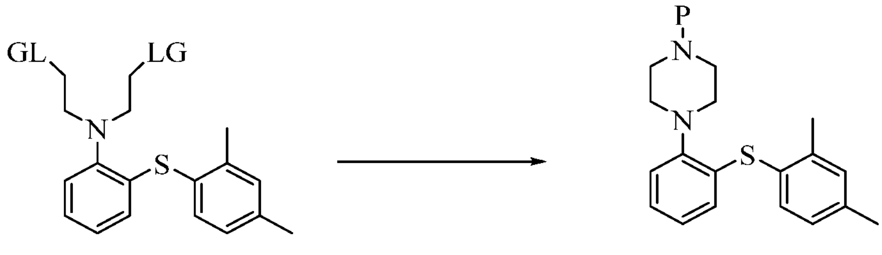
VIII

b) converting the compound of formula-VIII into a compound of formula-IX;

VIII

IX

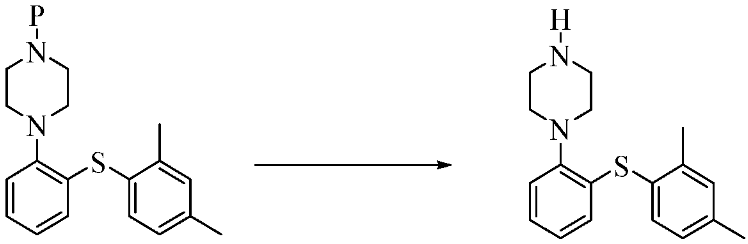
c) converting the compound of formula-IX into a compound of formula-X;



IX

X

d) deprotecting the compound of formula-X to produce vortioxetine; and



X

II

e) optionally converting vortioxetine of formula-II into a pharmaceutically acceptable salt of vortioxetine.

As shown in this process, formula-VI may initially be condensed with formula-VIIto obtain formula-VIII.Herein, formula-VI may be in free base or acid salt formas described above.The "LG" moiety on formula-VII is a leaving group, as defined previously. In some embodiments, formula-VII is 2-bromoethanol or 2-chloroethanol such that the leaving group on formula-VII is a bromo- or chloro- group, respectively.

The condensation of formula-VI with formula-VII may be carried out in the presence of a base.The base may be an organic or aninorganic base. Examples of suitable organic basesinclude pyridine, triethylamine, imidazole, and N,N-diisopropylethylamine. In some embodiments, N,N-diisopropylethylamineis used as an organic base. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.Examples of alkaline metal hydroxides include sodium hydroxide andpotassium hydroxide. Examples of suitable alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide.In some embodiments, sodium carbonate is used as an inorganic base.

Solventsuseful in this step include polar organic acids, for example,tetrahydrofuran, ethyl acetate, acetone, acetonitrile, toluene, butyronitrile,N-methyl pyrrolidone, N,N-dimethylformamide,dimethyl sulfoxide, and mixtures thereof.

Next, formula-VIII may be convertedintoformula-IX by replacing each hydroxyl group on formula-VIII with a leaving group ("LG"). The "LG" moiety on formula-IXmay be the same or different than the "LG" moiety on formula-VII as discussed above. The conversion of formula-VIII into formula-IX may be carried out by reacting formula-VIII with a reagent in presence of a base and a solvent. One of skill in the art will recognize and be familiar with a variety of suitable leaving groups and suitable reagents and solvents for carrying out the substitution of the hydroxy groups for a leaving group.

The following examples provide certain embodiments through exemplary specific leaving groups and reactants. The scope of the invention, however, is not limited by these examples and may include the use of other leaving groups and corresponding suitable conditions for use of those leaving groups.

Within the context of one embodiment, the leaving group may be an alkyl sulfonyloxy group, for example, a mesyloxy group,or anaryl sulfonyloxygroup, for example, a tosyloxy group. Suitable reagents for replacing the hydroxyl moieties with a mesyloxy or toxyloxy leaving group include mesylchlorideandtosylchloride, respectively.

When the leaving group is an alkyl sufonyloxy or an aryl sunfonyloxymoiety, the reaction may be carried out in the presence of a base and a solvent. The base may be organic or inorganic. Examples of inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.Examples of suitable alkaline metal hydroxides include sodium hydroxide andpotassium hydroxide. Examples of suitable alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of organic basesinclude pyridine, methylamine, imidazole, trimethylamine, and N,N-diisopropylethylamine.Suitable solvents that may be useful in this embodiment include dichloromethane, acetone and dimethyl acetamide, dimethyl formamide, acetonitrile,tetrahydrofuran, and mixtures thereof.

Inanother embodiment, the leaving group maybe a triflate or a chloride moiety. For example, the hydroxyl groups of formula-VIII may be replaced with a triflate by reacting formula-VIII withtrifilicanhydride. Each hydroxyl group of formula-VIII may be replaced with a chloride moiety by reacting formula-IX with, for example, phosphorousoxychloride, phosphorous pentachloride,orthionyl chloride.When the leaving group is a triflate or halide, the reaction maybe carried out in presence of suitable solvent. Suitable solventsinclude, for example, dichloromethane, toluene, acetone and dimethylacetamide, dimethyl formamide, acetonitrile, tetrahydrofuran, and mixtures thereof.

Next, formula-IX may be converted into formula-X. Within the context of this embodiment,the "P" moiety is an amine protecting group or is hydrogen.

The conversion of formula-IX to formula-X may be carried out in the presence of a nitrogen source, a base,a metal halide,and a solvent. Within the context of this embodiment, the nitrogen source provides the nitrogen to cyclization formula-IX and form the piperazine ring of formula-X.

Suitable nitrogen sources include, for example, ammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxybenzylamine, 4-chlorobenzylamine, 4-bromobenzylamine, 4-nitrobenzylamine, and ammonia. In some embodiments, 4-methoxybenzylamine or benzylamineare used as nitrogen sources.

In some embodiments of the invention, the nitrogen source may also include the protecting group. For example, cyclization of formula-IX with the nitrogen source to form the piperazine ring of formula-X may cause a side group on the nitrogen source to serve as the protecting group. For example, in some embodiments, carrying out this reaction with a 4-methoxybenzylamine nitrogen source will cause the methoxybenzyl moiety of the nitrogen source to serve as the protecting group on formula-X. In other embodiments, using ammonia as the source of nitrogen will cause P to be hydrogen atom. In that circumstance, no deprotection will be needed, as described further below.

Thebase may be, for example, an alkaline metal hydroxide, an alkaline metal bicarbonate, an alkaline metal carbonate,or an alkaline alkoxide. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate, potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, and potassium tert-butoxide. In some embodiments, sodium carbonate is used.

The metal halide may be, for example, lithium bromide, sodium bromide, sodium iodide, or potassium iodide. In some embodiments, lithium bromide is used as the metal halide reagent.

The solvent may be a protic or an aprotic solvent. Examples of suitable solvents include acetone, acetonitrile, dimethylacetamide, dimethylformamide, dimethylsulfoxide, ethyl acetate, toluene, and mixtures thereof. In some embodiments, acetonitrile is used.

In other embodiments, the conversion of formula-IX to formula-X may be carried out in the presence of a phase-transfer catalyst, a nitrogen source, and a solvent. Suitable phase transfer catalystsinclude, as examples,quaternary ammonium salts. For example, tetrabutylammonium bromide, tetrabutylammonium iodide, benzyltrimethylammonium chloride, benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammondium chloride, or methyltrioctylammondium chloride may be used as a phase-transfer catalyst. Suitable nitrogen sources include, for example, ammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxybenzylamine, 4-chlorobenzylamine,4-bromobenzylamine, 4-nitrobenzylamine, and ammonia. In some embodiments,benzylamineis used as the source of nitrogen. The solvent may be, for example, acetone, acetonitrile, dimetylacetamide, dimethylformamide, dimethylsulfoxide, ethyl acetate, toluene, and mixtures thereof. In some embodiments, toluene or xylene are used as a solvent.

In some embodiments, p-toluenesulfonic acid may also be used to catalyze this reaction.

Next, formula-X may be deprotected by removal of the P group. In those instances where P is hydrogen, no deprotection need occur. Deprotection of formula-X may be carried out in the presence of a suitable reagent and a solvent. One of skill in the art will readily recognize and be familiar with appropriate reagents and conditions required for removal of a particular protecting group. For example, depending on the protecting group, suitable reagents may include, as examples, Raney nickel,or palladium-on-carbon in the presence of hydrogen source, an acid, a base, or 1-chloroethylchloroformate. In some embodiments where the protecting group is a p-methoxybenzyl moiety or a benzyl moiety, 1-chloroethyl chloroformate may be used as a deprotecting agent. The solvent, again, depending on the protecting group and reagents used, may be, for example, ethers, hydrocarbons and alcohols. Ether solvent used but not limited to tetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether. Hydrocarbon solvent may be used but not limited cyclohexane, toluene and xylene. Alcohol solvent may be used but not limited to methanol, ethanol, propanol and isopropanol or mixtures thereof. In some embodiments, toluene or tetrahydrofuran is used as the solvent for this step.

Within the context of this embodiment, vortioxetine of formula-II may be optionally converted into a pharmaceutically acceptable salt of vortioxetine. The term "pharmaceutically acceptable salt"is well-known and understood in the art and refers to salts of pharmaceutically active agents which aresuitable for use in contact with the tissues of humans and lower animals without undue adverse effects (e.g., toxicity, irritation, allergic response). Examples of pharmaceutically acceptable salts may be found inS. M. Berge, et al., J. Pharmaceutical Sciences, 66: 1-19 (1977), in which all information pertaining to the pharmaceutically acceptable salts and processes for preparation thereof are hereby incorporated by reference.

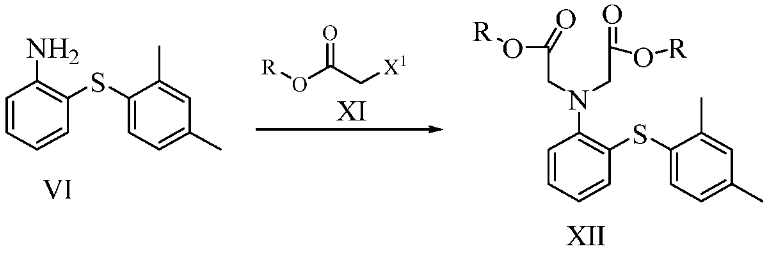
Preparation of a pharmaceutically acceptable salt of an active pharmaceutical agentis well known in the art. For example, the salts can be prepared in situ during the final isolation and purification of the compounds taught herein or separately by reacting a free base moiety on the active pharmaceutical agent with a suitable reagent.For example, a free base moiety on vortioxetine can be reacted with a suitable acid to obtain a pharmaceutically acceptable salt of vortioxetine.

Examples of suitable acids include, for example, inorganic acids or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid. Suitable organic acids include, for example, acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid,and malonic acid. Apharmaceutically acceptable salt of the active pharmaceutical agent may alternatively be prepared by other methods well-known in the art,for example, ion exchange.Additional examples of suitable pharmaceutically acceptable salts of the active pharmaceutical agent which may be formed include, for example,adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, (R,S)-malate, (S)-malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, phthalate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts. In certain embodiments, a particularly useful pharmaceutically acceptable salt of vortioxetine is the hydrobromide salt.

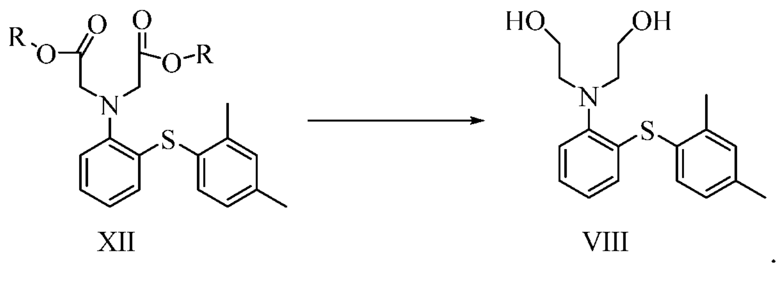
Vortioxetine produced by the processes herein may be converted into vortioxetine hydrobromide salt by processes, for example,disclosed in U.S. Patent Nos. 8,722,684 and 9,133,144. The processes disclosed for conversion of vortioxetine to the hydrobromide salt are hereby incorporated by reference. Specifically, salts of vortioxetine may be prepared by dissolving the free base in an appropriate solvent, adding the relevant acid, followed by precipitation. Precipitation may be accomplished either by the addition of a second solvent, and/or evaporation, and/or cooling, as described more fully hereinbelow.

Another aspect of the present invention provides a method for preparing formula-VIII. Within the context of this aspect, formula-VIII may be prepared by the following steps:

a) reacting a compound of formula-VI with a compound of formula-XI to yielda compound of formula-XII; and



b) converting the compound of formula-XII into a compound of formula-VIII.



According to this embodiment, formula-VI may be reacted with formula-XIto yield formula-XII. The "R" moiety is a C_1-C_4 alkyl and the "X^1" moiety is ahalogen.

In this embodiment, his reaction may be carried out in the presence of a base and a solvent. The base may be inorganic or organic. Examples of inorganic bases include alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.Alkaline metal hydroxides may be for example, sodium hydroxide or potassium hydroxide. Alkaline metal bicarbonates may be, for example, sodium bicarbonate, or potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of suitable alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of suitable organic bases include pyridine, methylamine, ethylamine, triethylamine, imidazole, and N,N-diisopropylethylamine.

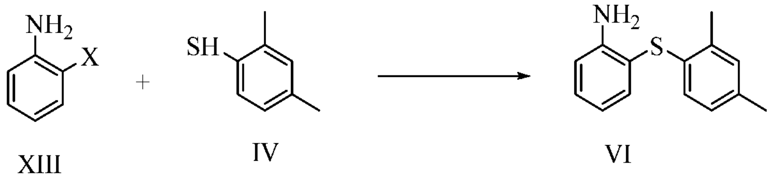
The solvent used in this step may be protic or aprotic. Examples of usefulprotic solventsinclude methanol, ethanol, isopropyl alcohol, n-butanol, tert-butanol, and mixtures thereof. Suitable aprotic solvents include, as examples, tetrahydrofuran, ethylacetate, acetone, acetonitrile, butyronitrile, N-methyl pyrrolidone, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof.

Next, formula-XII may be converted into formula-VIII. This may be carried out in the presence of a reducing agent. Examples of suitablereducing agentsinclude lithium aluminum hydride, sodium hydride,diisobutylaluminum hydride (DIBAL-H),orsodium bis(2-methoxyethyoxy)aluminumhydride (vitride).

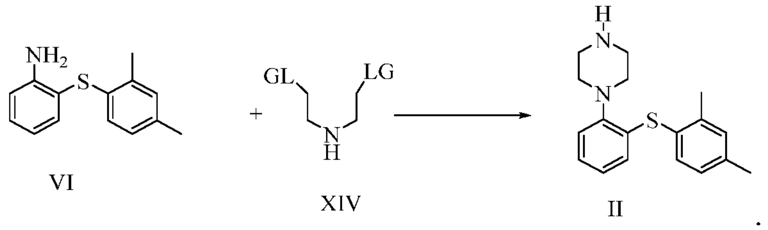
Within the context of the present invention, formula-VIII may be prepared as an intermediate in the synthesis of vortioxetine or pharmaceutically acceptable salts thereof.

Another aspect of the present inventionprovides a “one pot” process for the preparation of vortioxetine that may be carried out in a single reaction vessel without isolation of any intermediates. This process may include the following steps:

a) condensinga compound of formula-XIII with a compound of formula-IVto geta compound of formula-VI; and



b) reactingthe compound of formula-VI with a compound of formula-XIV to produce vortioxetine.

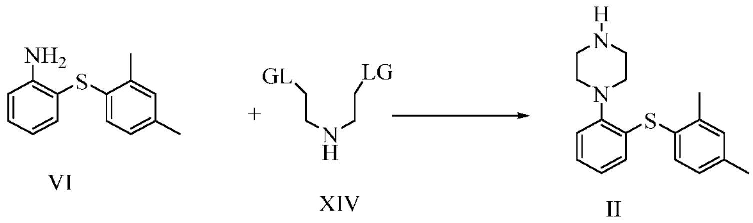


According to this embodiment, formula-XIII may be reacted with formula-IV to yield formula-VI. This reaction may be carried out in the presence of a catalyst, a base, and a solvent.The base may be inorganic or organic. Examples of inorganic bases include alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of suitable alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of suitable alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate.Examples of suitable alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of suitable organic bases includemethylamine, ethylamine, imidazole, pyridine, triethylamine, and N,N-diisopropylethylamine.In some embodiments, potassium tert-butoxideis used.

Suitable catalysts include, for example, bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$), tris(dibenzylideneacetone)palladium(0)($Pd(dba)_3$),palladium(II) acetate ($Pd(OAC)_2$),copper, cuprous bromide, cuprous iodide,(±)-2,2’-bis(diphenylphosphino)-1,1’-binaphtalene (rac-BINAP), and combinations thereof.In some embodiments, a combination of bis(dibenzylideneacetone)palladium(0) and (±)-2,2’-bis(diphenylphosphino)-1,1’-binaphtalene is used.

The solvent useful in this step may be, for example, methanol, ethanol, propanol, isopropanol, n-butanol, or mixtures thereof.In some embodiments,o-xylene is the solvent. The obtained compound 2-(2,4-dimethyl-phenyl-sulfanyl) aniline of formula VI is reacted with a compound of formula XIV or its acid addition salt; wherein "LG" moiety is a leaving group, as previously disclosed and defined above. In some particularly useful embodiments, a 2-chloroethyl or bromo leaving group is used to get vortioxetine.

Another aspect of the present invention provides a process for the preparation of vortioxetine or a pharmaceutically acceptable salts thereof which may be accomplished by reacting a 2-(2,4-dimethyl-phenyl-sulfanyl) aniline or acid addition salt with a compound of formula-XIV or an acid addition salt thereof.



In one embodiment, formula-VI or an acid addition salt thereof may be reacted with a compound of formula-XIV or an acid addition salt thereof in presence of catalyst and solvent. Within the context of the present embodiment, LG is leaving group. The catalyst used for this reaction may be, for example, p-toluenesulfonic acid. Suitable solvent include, for example, acetone, acetonitrile, dimethylacetamide, xylene, toluene, methanol, ethanol, propanol, isopropanol, n-butanol, or mixtures thereof.

The following examples merely illustrate certain embodiments of the processes disclosed herein and are not intended to limit the scope of the disclosure in any way.

EXAMPLES:

Example 1: Preparation of formula-V from 1-fluoro-2-nitrobenzene (formula-III) and formula-IV

In a flask, a mixture of potassium hydroxide (14.912g, 0.2657mol) in isopropyl alcohol(125mL)was prepared and the reaction mass was stirred at 25°C. To this,2,4-

dimethylbenzenethiol (formula-IV, 24.5g, 0.1772 mol) and 1-fluro-2-nitrobenzene(formula-III, 25g, 0.1772 mol) were slowly added and the reaction mass was stirred for 60-90 minutes at 25-35°C. After completion of the reaction, the reaction mass was cooled to 0-5°C,stirred for 2-3 hours at 0-5 °C, then filtered. The obtained solid was washed with chilled isopropyl alcohol, further washed with water, and dried at 50-55°C to yield(2,4-dimethylphenyl)(2-nitrophenyl)sulfane.

Example 2: Preparation of formula-V from 1-fluoro-2-nitrobenzene (formula-III) and formula-IV

In a flask, a mixture of N,N-disiopropylethylamine (27.48g, 0.2126mol)in isopropyl alcohol(125 mL) was prepared and the reaction mass was stirred at 25°C.To this,2,4-dimethylbenzenethiol(formula-IV, 24.5g, 0.1772 mol) and 1-fluro-2-nitrobenzene(formula-III, 25g, 0.1772 mol) were slowly added and the reaction mass was stirred untilcomplete consumption of the starting material. The reaction mass was cooledto 0-5°C,stirred for 2-3 hours at 0-5°C, then filtered. The obtained solid was washed with chilled isopropyl alcohol, further washed with water,then dried at 50-55°C to yield (2,4-dimethylphenyl)(2-nitrophenyl)sulfane.

Example 3: Preparation of formula-V from 1-fluoro-2-nitrobenzene (formula-III) and formula-IV

In a flask, a mixture of triethylamine (21.5g, 0.2126molin isopropyl alcohol(125mL)was prepared and the reaction mass was stirred at 25°C. To this,2,4-dimethylbenzenethiol(formula-IV, 24.5g, 0.1772 mol) and1-fluro-2-nitrobenzene(formula-III, 25g, 0.1772 mol) were slowly added and stirred the reaction mass till complete consumption of the starting material.The reaction mass was cooled to 0-5°C, stirred for 2-3 hours at 0-5°C, then filtered. The obtained s was washed with chilled isopropyl alcohol, further washed with water,then dried at 50-55°C to yield(2,4-dimethylphenyl)(2-nitrophenyl)sulfane.

Example 4: Preparation of formula-V from 1-cloro-2-nitrobenzene (formula-III) and formula-IV

In a flask, a mixture of potassium hydroxide (15.22g, 0.2712mol) in isopropyl alcohol(125mL)was prepared and the reaction mass was stirred at 25°C. To this, 2,4-

dimethylbenzenethiol(formula-IV, 25 g, 0.1808mol) and 1-chloro-2-nitrobenzene(formula-III, 34.2g, 0.2170mol) was slowly added and the reaction temperature was raised to50-55 °C. The reaction mass was then stirred for 120-180 minutes at 50-55°C. After completion of the reaction, the reaction mass was cooled to 0-5°C and stirred for 2-3 hours at 0-5°C. The solution was filtered and the obtained solid was washed with chilled isopropyl alcohol, further washed with water, then dried at 50-55 °C to yield (2,4-dimethylphenyl)(2-nitrophenyl)sulfane.

Example 5: Preparation of formula-V from 1-cloro-2-nitrobenzene (formula-III) and formula-IV

In a flask, a mixture of potassium hydroxide (13.4g, 0.2388mol) in dimethylformamide(125 mL)was prepared and the reaction mass was stirred at 25°C. To this formula-IV (22g, 0.1590 mol) and 1-chloro-2-nitrobenzene(formula-III, 25g, 0.15869 mol) were slowly added and the reaction mass was stirred at 30-35°C. After completion of the reaction, water was added and stirred for 1-2 hours at 30-35°C. The solution was filtered and the obtained solid was washed with water and dried at 50-55°C to yield formula-V.

Example 6: Preparation of formula-VI from formula-V

A mixture of formula-V (60g, 0.2313 mol), Raney nickel (9.0 g), and methanol (480mL) was prepared in a hydrogenated vessel. Hydrogen gas was then introduced to the vessel up to 7 kg/cm^2. The reaction suspension was heated to 45-50 °C for 5 hours. After completion of the reaction, the reaction mass was filtered. The filtrate was concentrated under vacuum at 45-50°Cto yield formula-VI.

Example 7: Preparation of formula-VI from formula-V

A mixture of formula-V (60g, 0.2313 mol), Raney nickel (9.0 g), and methanol (480mL)was prepared in a hydrogenated vessel. Hydrogen gas was then introduced to the vessel up to 7 kg/Cm^2. The reaction suspension was heated to 45-50 °C for 5 hours. After completion of the reaction, the reaction mass was filtered. The filtrate was concentrated under vacuum at 45-50°C to yield formula-VI (52 g, 98%yield).The obtained formula-VI was dissolved in toluene (520mL) and hydrobromic acid (38 mL) was slowly added. The reaction mix was stirred the reaction mass for 60-90 minutes then filtered to obtain a product which was washed with toluene. The hydrobromic acid salt of formula-VI was converted into free base by using an aqueous sodium hydroxide solution(20%, 55 mL) to yield formula-VI as liquid.

Example 8: Preparation of formula-VI from formula-V

Amixture of formula-V (25g, 0.09639 mol), iron powder (21.5g, 0.385 mol), and water (250mL)wasprepared and the reaction mass was stirred at 25°C. To this,15 mL ammonium chloride solution(3.0 g, 0.0559 mol) dissolved in 15 mL of water)was slowly added. The temperature of the reaction mass was raised to 70-75°C and the reaction mass was stirred for 5-6 hours at 70-75 °C.After completion of the reaction, the reaction mass was cooledto 25-35°C and toluene (150mL)was added. The reaction mass was stirred for 30 minutes, then filtered through HYFLO to obtain the product,which was then washed with toluene. The organic layer was separated, washed with water, and then concentrated under vacuum at 50-55°C to yieldformula-VI.

Example 9: Preparation of formula-Va from formula-IIIa and formula-IV

A mixture of bis(dibenzyldieneacetone)palladium (0.668 g, 0.00116 mol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (0.728 g, 0.00116 mol), and toluene (175 mL) was prepared. The reaction mass was stirred at 25°C under nitrogen atmosphere. Formula-IV (17.6 g, 0.1273 mol) and2-bromoaniline (formula-IIIa, 20 g, 0.116 mol) were added and the reaction mass was stirred for 15 minutes at 25-35 °C. Potassium tert-butoxide (15.65 g, 0.1395 mol) was added and the reaction temperature was raised to 110-120 °C and stirred for 2-3 hours. After completion of the reaction, the reaction mass was cooled to 5-10°C and water was added. The reaction mass was filtered, washed with toluene, and the organic layer was separated. Hydrochloric acid (10 mL) was slowly added to the organic layer and the solution was stirred for 45-60 minutes. The solution was filtered to obtain the final product(the hydrochloric salt of formula-VI)which was washed with toluene. The hydrochloric acid salt was converted into free base using sodium hydroxide solution to yield formula-Vaas liquid.

Example 10: Preparation of formula-VIII from formula-VI and 2-chloroethanol

Sodium carbonate (13.86 g, 0.1308 mol),formula-VI (10 g, 0.0436 m), and 2-chloroethanol (formula-VII, 45.3mL)were combined in a flask. The reaction mass was heated to 115±5°C and stirred at same temperature overnight. The reaction mass was then cooled to 25-30°C.The resulted reaction mass was filtered, washed with toluene (30mL), and the filtrate was concentrated under vacuum. To this residue, a mixture of toluene (60mL) and water (40mL) were added and the pH was adjusted to 7.0-8.0 using sodium carbonate solution. The reaction mass was stirred and the aqueous and organic layers were separated. The organic layer was washed with water (3x 30 mL), further washed with sodium chloride solution (5% in 50mL water), and concentrated by distillation to get a crude product (formula-VIII). The obtained crude product was dissolved in acetone (50mL)and aqueous hydrobromic acid (48%, 6.1 mL)was slowly added. The reaction mass was stirred for 2-3 hours then cooled to 5-10 °C and stirred for an additional 2 hours. The solution was filtered to obtain the final product (hydrobromic acid salt of formula-VIII, which was washed with chilled acetone (30mL).

The hydrobromic acid salt of formula-VIII was converted into free base using an aqueous sodium hydroxide solution (10%)to get formula-VIII as a solid.

Example 11: Preparation of formula-VIII from formula-VI and 2-chloroethanol

Sodium carbonate (7.34 g, 0.1526 mol), formula-VI (10 g, 0.0436 mol), and 2-chloroethanol (45 mL) were combined in a flask. The reaction mass was heated to 115±5 °C and stirred at this temperature for 12-15 hours before cooling the reaction mass to 25-30°C.Ethyl acetate (100 mL)was added and the solution was washed with an aqueous sodium chloride solution (5%, 100 mL).The organic and aqueous layers were separated. The pH of the aqueous layer was adjusted to 7.0-7.5 with aqueous potassium carbonate solution, if necessary, followed by addition of ethylacetate and separation of the organic and aqueous layers. The organic layer was combined with the ethyl acetate organic layer obtained previously, and the combined layers were concentrated by distillation to get a crude product. The crude product was dissolved in toluene(100 mL),hydrobromic acid (48%, 100 mL) was added at 25-30°C,and the solution was stirred for 2-3 hours.The solution was filtered and the obtained product (the hydrobromic salt of formula-VIII)was washed with toluene. The hydrobromic acid salt of formula-VIII was converted into the free base using sodium hydroxide solution to yieldformula-VIII.

Example 12: Preparation of formula-IX,where LG = methanesulfonyl,from formula-VIII

Formula-VIII (10.0 g, 0.0315 mol), triethylamine (11.13 g, 0.1102 mol), and dichloromethane (50 mL) were combined in a flask.Methanesulfonylchloride (10.82 g, 7.3 mL)in 10 mL methylene dichloride) was slowly added at 0-5°C over 30-45 minutes.The reaction mass was stirred for 45-60 minutes at 5-10°C. After completion of the reaction, water (50 mL) was added slowly into the reaction mixtureandthe organic and aqueous layers were separated. The organic layer was washed with 5% aqueous $NaHCO_3$ solution and concentrated under vacuum to yieldformula-IX whereinLG is a methanesulfonylmoiety.

Example 13: Preparation offormula-IX, where LG = Cl,from formula-VIII

A solution of formula-VIII (10.0g, 0.0315 mol) in dichloromethane (50mL)was prepared in a flask. Thionylchloride (8.2g, 0.0693 mol, 5 mL) was slowly added at 0-5°C over 30-45minutes. The reaction temperature was raised to 30-35°C and stirred for 60-120minutes at 30-35°C. After completion of the reaction, the reaction mass was quenched into chilled water (50 mL) stirred. The aqueous and organic layers were separated and the organic layer was washed with 5% aqueous $NaHCO_3$ solution and concentrated under vacuum to yield formula-IX whereinLG is Cl.

Example 14: Preparation offormula-IX, where LG = Clfrom formula-VIII

Phosphorous pentachloride (5.9 g, 0.0283 mol) and dichloromethane (30 mL) were combined in a flask and formula-VIII (3.0 g, 0.00945 mol) was added. The resulting reaction mixture was dissolved in dichloromethane (15 mL) at 0-5°C for 30 minutes and the temperature of the reaction mixture was raised to 30-35°C and stirred for 45-60 minutes at 30-35°C. After completion of the reaction, water (15 mL) was added slowly into the reaction mixture and the organic and aqueous layers were separated.The organic layer was washed with 5% aqueous $NaHCO_3$ solution and concentrated under vacuum to yieldformula-IX whereinLG is Cl.

Example 15: Preparation offormula-IX, where LG = Cl,from formula-VI

Chloroacetic acid (37.0 g 0.3924 mol), formula-VI (5 g, 0.0218 mol), and tetrahydrofuran (7.5 mL) were combined in a flask. The reaction mass was stirred for 10-15 minutes at 20-25°C. Borane–THF complex solution (1M, 131 mL, 0.1308mol) was slowly added at 20-25°C and stirred for 4-5 hours at 25-30°C. After completion of the reaction, methanol was slowly added at 20-25°Cand the reaction mass was stirred for 60 minutes. The resulted reaction mass was concentrated under vacuum at 30-35°C. Water (150 mL) and dichloromethane (50 mL) were added and the pH was adjusted to 7-8 using aqueous sodium carbonate solution. The organic and aqueous layers were separated and the organic layer was washed with water then concentrated under vacuum at 30-35°C to yield formula-IX wherein LG is Cl.

Example 16: Preparation offormula-IX, where LG = Cl, from formula-VI

Chloroacetic acid (15.45 g, 0.1635 mol), formula-VI (2.5g, 0.0109 mol), and tetrahydrofuran (40 mL)were combined and the reaction mass was stirred for 10-15 minutes at 20-25°C.The reaction mass was then cooled to 0-5°C and sodium borohydride(2.75g, 0.07275mol)was slowly added at 0-5 °C. Sulfuric acid was slowly added to the reaction mass at 0-5°C and the reaction mass was stirred for 15-30 minutes at 0-5 °C. The temperature of the reaction mass was raised to 20-25°C and stirred for 60-120 minutes. After completion of the reaction, the reaction mass was cooled to 0-5°C and to this, methanol(5 mL) and hydrochloric acid (37%, 8 mL) were slowly added at 0-5°C.The reaction temperature was raised to 25-30 °C and stirred for 60 minutes at 25-30°C.The resulted reaction mass was concentrated under vacuum at 30-35°C.Water (75 mL) and dichloromethane (25 mL) were added and the pH was adjusted to 7-8 using aqueous sodium carbonate solution.The organic and aqueous layers were separated and the organic layer was concentrated under vacuum at 30- 35°C to yield formula-IX wherein LG is Cl.

Example 17: **Preparation of PMB-protected formula-Xfrom formula-IX**

Lithium bromide (3.3 g, 0.0379mol),formula-IX (where LG is Cl, 6.8g, 0.0191mol), 4-methoxybenzylamine (3.1g 0.0225mol), sodium carbonate (6.0g, 0.0566mol), and acetonitrile (34 mL)were combined in a flask.The reaction mass was heated to reflux. After completion of the reaction, the reaction mass was cooled, filtered, and washed with acetonitrile. The obtained wet material was combined with water to form a slurry. The slurry was filtered and the obtained solid was washed with water. The obtained wet material was dissolved in acetone (34 mL) at 50-55 °C for 30 minutes, then water (14 mL) was slowly added at same temperature. The solution was cooled to 25-30°C, then further cooled to 0-5 °C. The solution was stirred at 0-5°C for 3 hours, filtered, and washed with a mixture of water and acetone (1:1)to yield PMB-protected formula-X.

Example 18: **Preparation of Bn-protected formula-X from formula-IX**

Benzylamine (0.48 g 0.0045 mol) and formula-IX (where LG = Cl, 2.0 g, 0.0056 mol) were combined in a flask. A catalytic amount of p-toluenesulfonic acidand toluene were added and the resulted solution was heated to reflux and maintained at reflux for 10-15 hours. After completion of the reaction, the reaction mass was concentrated under vacuum and the obtained residue was diluted with ethyl acetate and washed with 10% aqueous sodium carbonate solution.The layers were separated, and the organic layer was washed with an aqueous sodium chloride solution (5%, 21 mL)and concentrated by vacuum to yield Bn-protected formula-X.

Example 19: **Preparation of vortioxetinehydrobromide from formula-X**

A solution ofPMB-protected formula-X(100g, 0.2388mol) in tetrahydrofuran (200mL)was cooled to 0-5°C.Liquid 1-chloroethylchloroformate (41g, 0.2867mol) was added at 0-5°C for 30 minutes.The reaction temperature was raised to 30-35°C and stirred for 2-3hours at 30-35 °C. The reaction mass was concentrated under vacuum and to this, methanol (300mL)was added and the temperature of the reaction mass was raised to 60-65 °C. The reaction mass was then stirred for 5-6 hours and concentrated to get a residue. The residue was further treated with acetone (500 mL),aqueous hydrochloric acid(27mL),and water (50mL). The reaction mass was then stirred for 30 minutes at 50-55°C and then cooled to 0-5°C.Thereaction mass was filtered and the obtained solid was washed with chilled acetone to get vortioxetine hydrochloride (70 g, 83% yield and 99.9% purity).The vortioxetine hydrochloride is converted into the free base form of vortioxetine using dichloromethane (400 mL) and sodium hydroxide (7%, 320 mL) solution. The aqueous and organic layers were separated and the organic layer was washed with water and filter through HYFLO. The organic layer was then concentrated under vacuum at 40-45°C to get vortioxetine. To the obtained vortioxetine, acetone(500mL) and aqueous hydrobromic acid (48%, 40mL) were added and the reaction mass was heated to 50-55 °C for about 60 minutes before cooling the solution to 25-30°C. The reaction mass was stirred for 60 minutes then further cooled to 0-5 °C and stirred for 2 hoursmore at 0-5°C. Thereaction mass was filtered and the obtained solid was washed with chilledacetone and dried under vacuum at 55°C to yield vortioxetine hydrobromide.

Example 20: **Preparation of vortioxetine hydrobromide from formula-X**

A solution of PMB-protected formula-X (5.0 g, 0.01196 mol) in toluene (17.5 mL) was cooled to 0-5°C. Liquid1-chloroethylchloroformate (2.1 g, 0.01468 mol) was added at 0-5°C over 30 minutes.The reaction temperature was raised to 30-35°C and the reaction mass was stirred for 2-3 hours. The reaction mass was then concentrated under vacuum and to this, methanol (25 mL) was added. The temperature of the reaction mass was raised to 60-65°C, stirred for 5-6 hours, and concentrated to get a residue. The residue was further treated with toluene (25 mL), aqueous hydrochloric acid (1.3 mL), and water (2.5 mL), and the reaction mass was stirred for 30 minutes at 50-55°C. The reaction mass was then cooled to 0-5°C then filtered. The obtained solid was washed with chilled toluene to get vortioxetine hydrochloride (3.4g, 81% yield). The hydrochloride salt of vortioxetine was converted into the free base form of vortioxetine using dichloromethane (20 mL) and aqueous sodium hydroxide (7%, 16 mL) solution. The organic and aqueous layers were separated and the organic layer was washed with water and filtered through HYFLO. The organic layer was then concentrated under vacuum at 40-45°C to get vortioxetine. To the obtained vortioxetine, toluene (15 mL) and aqueous hydrobromic acid (48%, 2.0 mL) were added and the reaction mass was heated to 60-65°C for about 60 minutes then cooled to 25-30°C and stirred for 60 minutes. The solution was filtered and the obtained solid was washed with toluene and dried under vacuum at 55°C to yield vortioxetine hydrobromide.

Example 21: Preparation of vortioxetine hydrobromide from formula-IX

Formula-IX (where in LG is a methanesulfonylmoiety, 5 g, 0.0105 mol), ammonium formate (1.98 g 0.0315 mol), lithium bromide (1.82 g, 0.021 mol), and potassium carbonate (4.35 g, 0.0315 mol) were combined in a flask.Acetonitrile (25 mL) was added and the resulting suspension was refluxed. After completion of the reaction, the reaction mass was cooled, filtered, and washed with acetonitrile. The obtained filtrate was concentrated under vacuum and the residue was dissolved in toluene and heated to 60°C. Aqueous hydrobromic acid (48%, 1.67 mL) was slowly added and the reaction mass was maintained for 30 minutes at 60°C. The reaction mass was cooled to room temperature and stirred for 60 minutes. The reaction mass was filtered and the obtained solid was washed with toluene to yield vortioxetine hydrobromide.

Example 22: Preparation of vortioxetine hydrobromide ("onepot" process)

A mixture of bis(dibenzyldieneacetone) palladium (0.16712 g, 0.00029 mol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene(0.180 g, 0.00029 mol), and *o*-xylene(50 mL)were combined in a flask. The reaction mass was stirred at 25°C under nitrogen atmosphere and 2-bromoaniline (formula-XIII, 5 g, 0.029 mol) and 2,4-dimethylthiophenol (formula-IV, 4.42 g, 0.03194 mol) were added. The reaction mass was stirred for 15 minutes at 25-35°C before adding potassium tert-butoxide (4.9 g, 0.0436 mol). Thetemperature of the reaction mass was raised to 110-120 °C and stirred for 2-3 hours. After completion of the reaction, the reaction mass was cooled to 25-30°C. Bis(2-chloroethyl)amine hydrochloride (formula-XIV, 10.36 g, 0.058 mol) was then added and the reaction mass was stirred for 15-30 minutes. The reaction temperature was raised to 110-130 °C and stirred for 15-20 hours. After completion of the reaction, the reaction mass was cooled to 5-10°C and water (50 mL) was added. The reaction mass was stirred for 15 minutes before filtering and separating the organic and aqueous layers. The organic layer was adjusted to a pH of 9-10 with a 10% sodium hydroxide solution,stirred for 15 minutes, and the organic and aqueous layers were separated. The organic layer was concentrated by distillation at 60-65 °C under vacuum and the resulting residue was dissolved in toluene. The solution was heated to 60 °C and aqueous hydrobromic acid (48%, 5 mL)was slowly added. The reaction mass was maintained for 30 minutes at 60°, then cooled to room temperature and stirred for 60 minutes.The reaction mass was filtered and the resulting solid was washed with toluene to yield vortioxetine hydrobromide.

Example 23: Preparation of vortioxetine hydrobromide ("onepot" process)

A mixture of bis(dibenzyldieneacetone) palladium (0.16712 g, 0.00029 mol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene(0.180 g, 0.00029 mol), and *o*-xylene (50 mL) were combined in a flask. The reaction mass was stirred at 25°C under nitrogen atmosphere followed by the addition of 2-bromoaniline (formula-XIII, 5 g, 0.029 mol) and formula-IV (4.42 g, 0.03194 mol). The reaction mass was stirred for 15 minutes at 25-35 °C followed by the addition of potassium tert-butoxide (4.9 g, 0.0436 mol). The reaction temperature was raised to 110-120 °C and stirred for 2-3 hours. After completion of the reaction, the reaction mass was cooled to 25-30 °C and bis(2-chloroethyl)amine hydrochloride (formula-XIV, 10.36 g, 0.058 mol) and catalytic amount of p-toluenesulfonic acid were added. The reaction mass was stirred for 15-30 minutes before raising the reaction temperature to 110-130 °C and stirring for 15-20 hours. After completion of the reaction, the reaction mass was cooled to 5-10°C and water was added followed by stirring for 15 minutes. The reaction mass was filtered and the organic and aqueous layers were separated. The organic layer was adjusted to a pH of 9-10 with 10% sodium hydroxide solution, the reaction mass was stirred for 15 minutes, and the aqueous and organic layers were separated. The organic layer was concentrated by distillation at 60-65 °C under vacuum, the resulting residue was dissolved in toluene, and the solution was heated to 60°C.Aqueous hydrobromic acid (48%, 5 mL) was slowly added and the reaction mass was maintained for 30 minutes at 60 °C. The reaction mixture was cooled to room temperature and stirred for 60 minutes. The reaction mixture was filtered and the resulting solid was washed with toluene to yield vortioxetine hydrobromide.

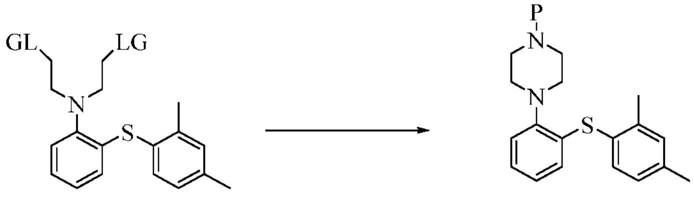
We claim:

1. A process for the preparation of vortioxetine or a pharmaceutically acceptable salt thereof comprising the steps of:

   a) converting formula-VI into formula-IX;

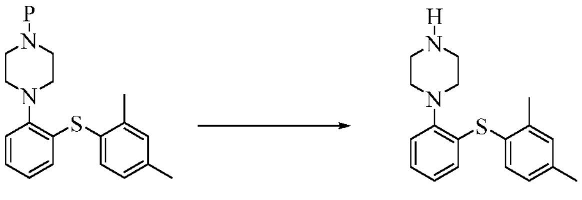
VI IX

   b) converting formula-IX into formula-X;



IX X

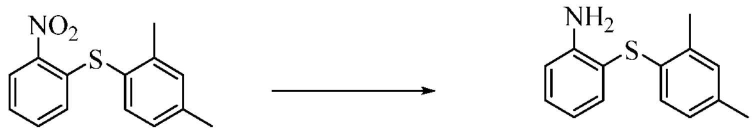
   c) when P is not hydrogen, then converting formula-X to vortioxetine,



X II

wherein LG is a leaving group and P is a protecting group or hydrogen.

2. The process according to claim 1, wherein formula-VI is prepared by reducing the compound of formula-V.



V VI

3. The process according to claim 1, wherein the LG group is a halo group.

4. The process according to claim 1, wherein formula-VI is converted to formula-IX by reacting formula-VI with a haloacetic acid or a haloaldehyde in the presence of a reducing agent and a solvent.

5. The process according to claim 4, wherein the haloacetic acid is selected from the group consisting of chloroacetic acid and bromoacetic acid.

6. The process according to claim 4, wherein the haloaldehyde is chloroacetaldehyde.

7. The process according to claim 4, wherein the reducing agent is selected from the group consisting of borane, sodium borohydride, lithiumborohydride, sodiumcyanoborohydride, sodiumtriacetoxyborohydride, borane–THF, a mixture of sodium borohydride and sulfuric acid, and mixtures thereof.

8. The process according to claim 4, wherein the solvent is selected from ethers and hydrocarbon solvents.

9. The process according to claim 8, wherein ether solvent is selected from tetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether.

10. The process according to claim 9, wherein hydrocarbon solvent selected from cyclohexane, toluene and xylene.

11. The process according to claim 1, wherein formula-IX is converted to formula-X by reacting formula-IX with a nitrogen source in the presence of a base, a metal halide, and a solvent.

12. The process according to claim 11, wherein the nitrogen source is selected from the group consisting of ammonium formate, ammonium acetate, aminopyridine, dimethylaminopyridine, methylamine, ethylamine, N,N-diisopropylethylamine, benzylamine, 4-methoxy benzylamine, 4-chloro benzylamine,4-bromo benzylamine, 4-nitro benzylamine, and ammonia.

13. The process according to claim 11, wherein the base is selected from the group consisting of alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.

14. The process according to claim 11, wherein the alkaline metal carbonate is selected fromthe group consisting of sodium carbonate, potassium carbonate, and cesium carbonate.

15. The process according to claim 11, wherein the metal halide is selected from lithium bromide, sodium bromide, sodium iodide, and potassium iodide.

16. The process according to claim 11, wherein the solvent is selected from the group consisting of acetone, acetonitrile, dimethylacetamide, dimethylformamide, dimethylsulfoxide, toluene, and mixtures thereof.

17. The process according to claim 1, wherein P is a protecting group and the conversion offormula-X to vortioxetine is carried out in the presence of a reagent and a solvent.

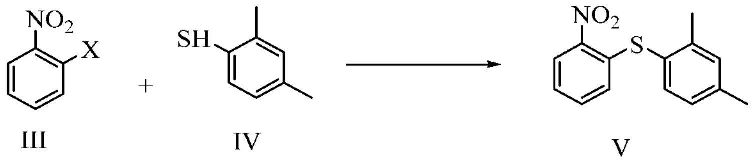
18. The process according to claim 17, wherein the reagent is selected from the group consisting of 1-chloroethylchloroformate, palladium-on-carbon, and Raney nickel.

19. The process according to claim 17, wherein the solvent is selected from ethers, hydrocarbons and alcohol solvent.

20. The process according to claim 19, wherein ether solvent is selected from tetrahydrofuran, diethyl ether, 1, 4-dioxane, methyl tert-butyl ether.

21. The process according to claim 19, wherein alcohol solvent is selected from methanol, ethanol, isopropyl alcohol, butanol, and mixtures thereof.

22. The process according to claim 2, wherein formula-V is prepared by reacting formula-III with formula-IV in the presence of a base and an alcohol solvent,



wherein X is a halo group selected from the group consisting of fluoro-, chloro-, bromo-, and iodo-.

23. The process according to claim 22, wherein the base is an organic base oran inorganic base.

24. The process according to claim 23, wherein the inorganic base is selected from the group consisting of alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.

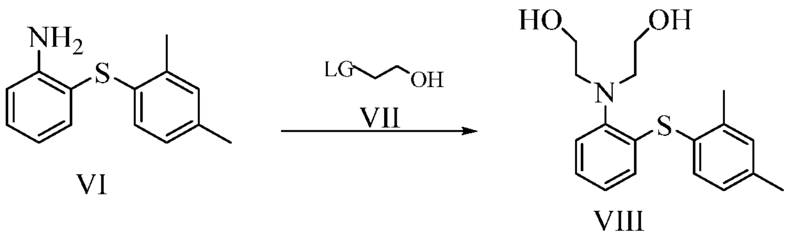
25. The process according to claim 24, wherein the alkaline metal hydroxide is selected from the group consisting of sodium hydroxide and potassium hydroxide.

26. The process according to claim 23, wherein the organic base is selected from the group consisting of pyridine, triethylamine, and N,N-diisopropylethylamine.

27. The process according to claim 22, wherein the alcohol solvent is selected from methanol, ethanol, propanol, isopropanol, and mixtures thereof.

28. A process for the preparation of vortioxetine or a pharmaceutically acceptable salts thereof comprising the steps of:

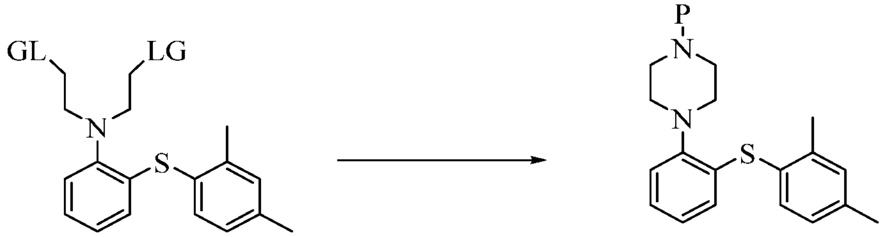
    a) condensing formula-VI with formula-VII to yield a formula-VIII;



    b) converting formula-VIII into formula-IX;

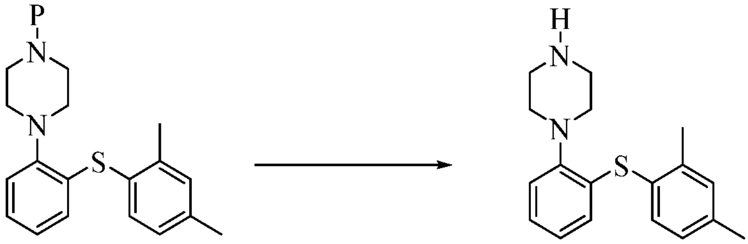
VIII IX

c) converting formula-IX into formula-X;



IX X

d) when P is not hydrogen, then converting formula-X to vortioxetine.



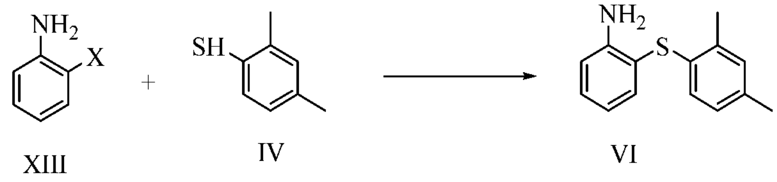
X II

wherein LG is a leaving group and P is a protecting group or H.

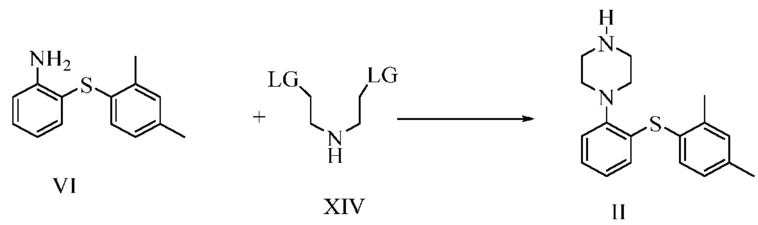
29. The process according to claims 1 or 28, wherein P is H.

30. A process for the preparation of vortioxetine or a pharmaceutically acceptable salt thereof comprising the steps of:

a) reacting formula-XIII with formula-IV in the presence of a base and a catalyst to yield formula-VI; and



b) reacting formula-VI with formula-XIV in the presence of a solvent to provide vortioxetine



wherein formula-VI is not isolated.