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(54) Title: A PROCESS FOR PREPARATION OF VORTIOXETINE AND POLYMORPHS THEREOF

(57) Abstract: The present invention relates to an improved process for preparation of vortioxetine or pharmaceutically acceptable salts thereof. The present invention also relates to new process for the preparation of vortioxetine or pharmaceutically acceptable salts thereof. The present invention further relates to novel polymorphs of vortioxetine hydrobromide and process for preparation thereof.

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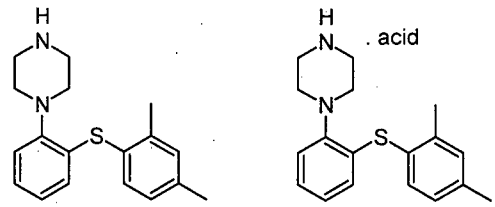
TITLE OF THE INVENTION

A PROCESS FOR PREPARATION OF VORTIOXETINE AND POLYMORPHS THEREOF

This appclaition claims the priority from our provisional Indian patent application number 3612/mum/2014 which is incorporated herein by reference.

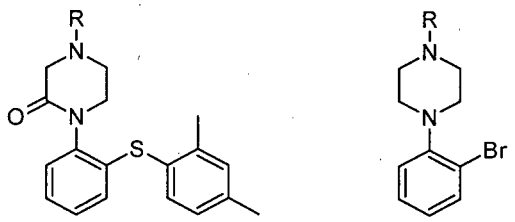
FIELD OF THE INVENTION:

The present invention relates to process for the preparation of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine compound of formula (I), its pharmaceutically acceptable salts of formula (Ia), and polymorphs thereof.



Vortioxetine (I) Vortioxetine salt (Ia)

The present invention also relates to novel intermediates 1-{2-[(2,4-dimethylphenyl)thio]phenyl}piperazin-2-one compound of formula (XIV) and 1-(2-bromophenyl) piperazine compound of formula (XV) used for the preparation of compound of formula (I) and (Ia) and process for preparation thereof.



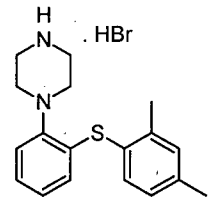
(XIV) (XV)

Wherein; R = -H, -Boc, -Benzyl etc.

The present invention also relates to novel crystalline polymorphs of hydrobromide salt of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Vortioxetine hydrobromide)

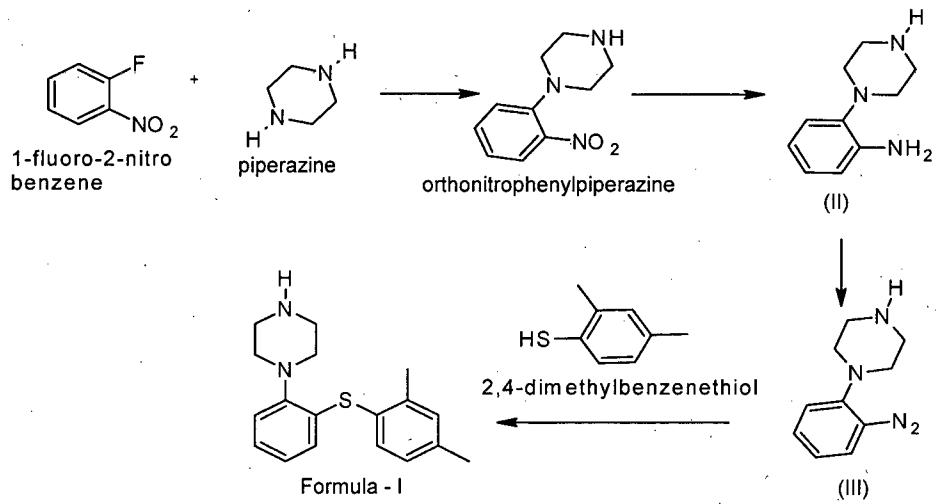
BACKGROUND OF THE INVENTION:

1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine (henceforth "Vortioxetine"), and its acid addition salts thereof have affinity to the serotonin transporter and the serotonin receptors 3 and 1A (5-HT_3 and 5-HT_{1A}). The vortioxetine hydrobromide having empirical formula $C_{18}H_{22}N_2S.HBr$ and CAS number of 960203-27-4 was approved by the USFDA and by EMA for the treatment of Major Depressive Disorder (MDD) as antidepressant drug and commercially sold under the brand name BRINTELLIX®.

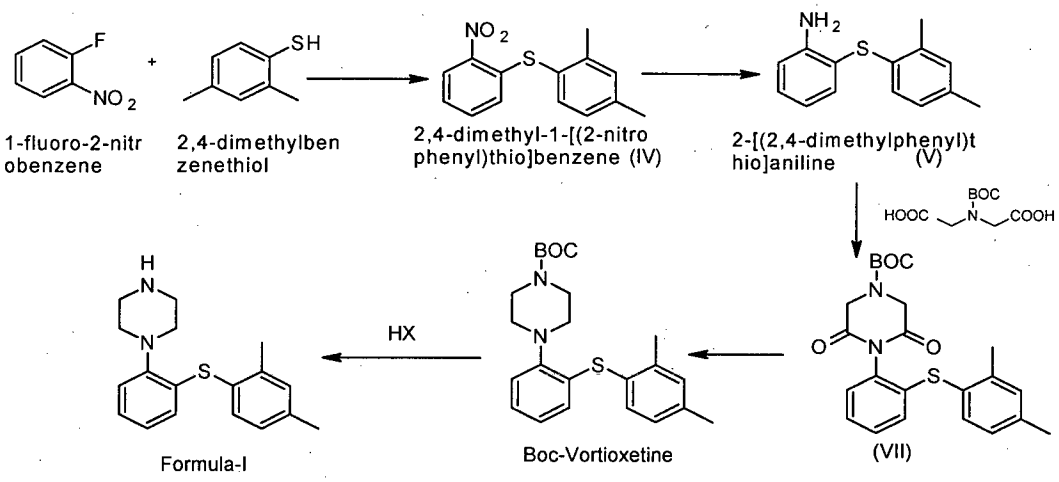


Vortioxetine.HBr

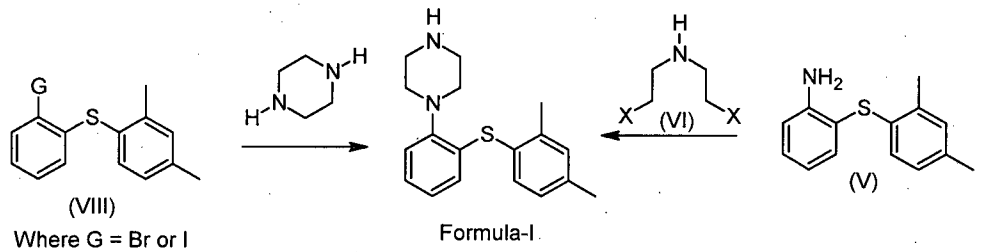
US patents 7,144,884 and 8,476,279 describes process for the preparation of vortioxetine (I) and are presented in Scheme-1 to Scheme-4



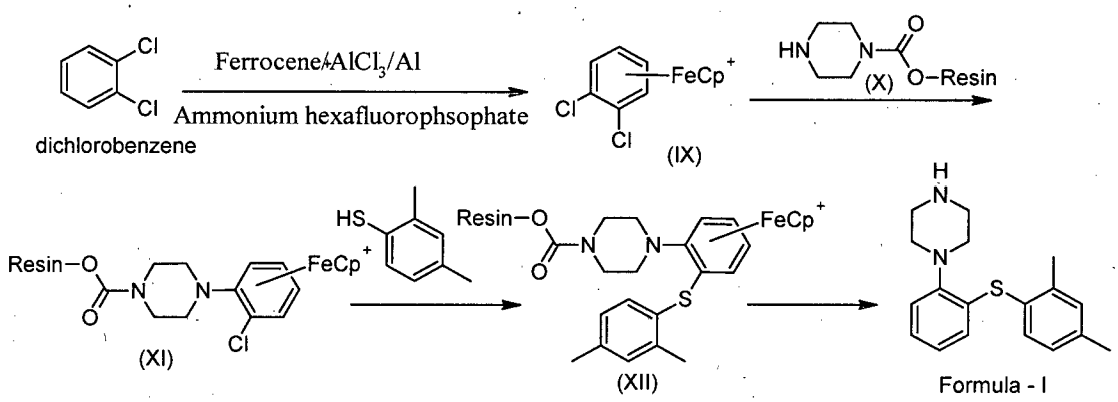
Scheme-1



Scheme-2

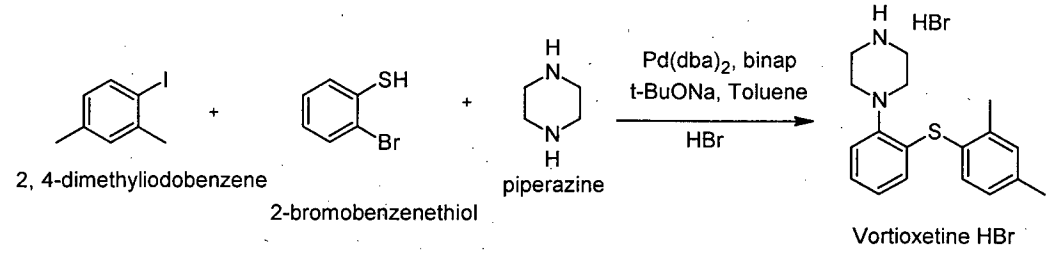


Scheme-3



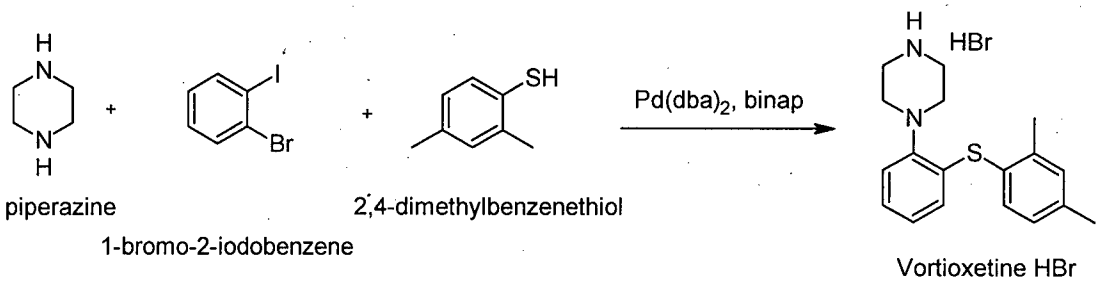
Scheme-4

Patent application WO 2013102573 discloses the synthesis of vortioxetine as shown in Scheme-5;



Scheme-5

US patent US 8,598,348 discloses synthesis of vortioxetine hydrobromide as shown in Scheme-6;



Scheme-6

The above synthetic Schemes for the preparation of vortioxetine have some draw backs, which limits its scope on an industrial scale and some of the drawbacks are listed below;

a) Scheme 1, 2 and 4 described in patents US 7,144,884 and US 8,476,279 for the synthesis of vortioxetine and its salts are cumbersome, lengthy, tedious to use on an industrial scale and inadvertently affecting on overall atom economy;

b) Schemes 1 to 4 described in US patents 7,144,884 and US 8,476,279 involves use of chromatographic techniques for the purification of vortioxetine, which is industrially not feasible;

c) US patents 7,144,884 and US 8,476,279 involves use of expensive pyrophoric catalyst for the reduction of nitro group and di-keto group are uneconomical;

d) Schemes 1 to 4 described in US patents 7,144,884 and US 8,476,279 provides lower yield and purity of the intermediates and final products;
e) Scheme 5 and Scheme 6 of PCT application WO2013102573 and US patent 8,598,348 respectively, involve use of palladium catalyst and ligands like BINAP, which are very costly and inadvertently increases the manufacturing cost.

Hence, there is a continuous need to develop simple, commercially advantageous and industrially viable process for the preparation of vortioxetine and its pharmaceutically acceptable salt that reduces the number of reaction steps and in turn increases overall yield of the final product.

The present invention offers an improved, efficient, economic, and production friendly process for preparation of vortioxetine and its pharmaceutically acceptable salts.

Polymorphism is a phenomenon relating to the occurrence of different crystalline forms for one molecule. There may be several different crystalline forms for the same molecule with distinct crystal structures and varying in physical properties like melting point, PXRD pattern and FTIR spectrum. These polymorphs are thus distinct solid forms which share the molecular formula of the compound from which the crystals are made up, however they may have distinct advantageous physical properties such as e.g. chemical stability, physical stability, hygroscopicity, solubility, dissolution rate, morphology or bioavailability. These polymorphic forms of the same drug substance or active pharmaceutical ingredient plays a key role in the development of the final or finished dosage form. Hence, there is a continuing need for new crystalline forms and new processes of preparing crystalline forms.

Hence, the present invention provides an improved process for the preparation of vortioxetine or its acid addition salt and a new crystalline form of vortioxetine hydrobromide thereof.

OBJECTS OF THE PRESENT INVENTION

The primary object of the present invention is to provide improved process for the preparation of vortioxetine (I) and/or its pharmaceutically acceptable salts.

Another object of the present invention is to provide new method for the preparation of vortioxetine (I) and/or its pharmaceutically acceptable salts.

Another object of the invention is to provide process for the preparation of vortioxetine and/or its pharmaceutically acceptable salts in a single pot wherein isolation of intermediates is avoided to improve atom economy and reduce the turnaround time.

Yet another object of the present invention is to provide process for preparation of vortioxetine and/or its pharmaceutically acceptable salts, wherein the said process eliminates laborious workup and extensive purifications to make the process simple cost effective, efficient and production friendly.

Yet another object of the present invention is to provide a process for preparation of vortioxetine and/or its pharmaceutically acceptable salts, which is substantially free from impurities.

Yet another object of the invention is to provide a new compound of formula (XIV), which is used as intermediate for the preparation of vortioxetine and/or its pharmaceutically acceptable salts.

Yet another object of the present invention is to provide novel crystalline forms of Vortioxetine hydrobromide (I) herein designated as Form M1 and Form M2.

BRIEF DESCRITPION OF DRAWINGS

Figure 1: X-ray powder diffraction (XRD) pattern of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene compound of formula (IV), prepared according to example 1 and 9.

Figure 2:X-ray powder diffraction (XRD) pattern of 2-[(2,4-dimethylphenyl)thio]aniline hydrochloride, prepared according to example 15.

Figure 3:X-ray powder diffraction (XRD) pattern of vortioxetine hydrobromide, prepared according to example 12.

Figure 4: X-ray powder diffraction (XRD) pattern of vortioxetine hydrobromide, prepared according to example 13.

DETAILED DESCRIPTION OF THE INVENTION

Before the present invention is described, it is to be understood that this invention is not limited to particular methodologies and materials described, as these may vary as per the person skilled in the art. It is also to be understood that the terminology used in the description is for the purpose of describing the particular embodiments only, and is not intended to limit the scope of the present invention.

Before the present invention is described, it is to be understood that unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Further, it is to be understood that the present invention is not limited to the methodologies and materials similar or equivalent to those described herein can be

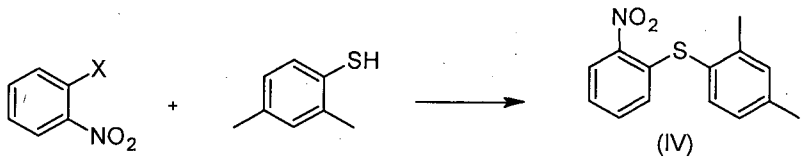
used in the practice or testing of the present invention, the preferred methods and materials are described, as these may vary within the specification indicated. Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims. Further the terms disclosed embodiments are merely exemplary methods of the invention, which may be embodied in various forms.

A term herein "reflux temperature" means the temperature at which the solvent or the solvent system refluxes or boils at atmospheric pressure.

The term "substantially free of" in reference to a composition, as used herein, means that an absent substance cannot be detected in the composition by methods known to those skilled in the art at the time of the filing of this application.

In one of the embodiments of the present invention there is provided improved process for the preparation of vortioxetine (I) and its pharmaceutically acceptable salt, said process comprising;

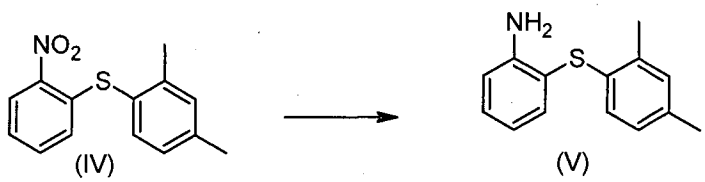
a) reacting 1-halo (or 1-pseudohalo)-2-nitrobenzene with 2,4-dimethylbenzenethiol in solvent, base and optionally in presence of catalyst to obtain 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene compound (IV);



2,4-dimethylbenzenethiol 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene

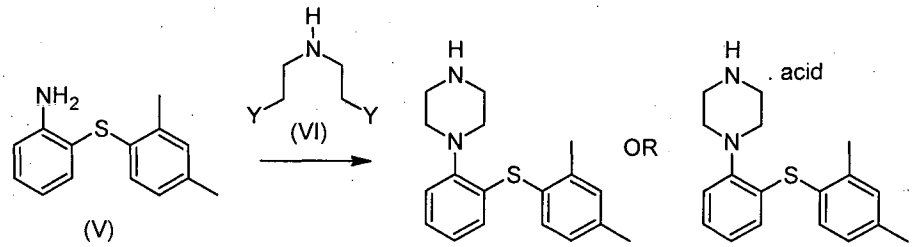
Wherein X is -Cl, -Br, -I, -F, -OTf, -OMs, or -OTs

b) reducing 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene compound (IV) to 2-[(2,4-dimethylphenyl)thio]aniline compound (V) in solvent in presence of reducing agent and catalyst;



2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene 2-[(2,4-dimethylphenyl)thio]aniline

c) reacting 2-[(2,4-dimethylphenyl)thio]aniline compound (V) or its salt with dialkyl amine compound (VI) or its acid addition salt in solvent, base and optionally in the presence of phase transfer catalyst to obtain vortioxetine (I) or its salt (Ia) and optionally purifying vortioxetine (I) or its salt (Ia);



2-[(2,4-dimethylphenyl)thio]aniline Formula-I Formula-Ia

Wherein Y is -Cl, -Br,-I,-OTf, -OMs, -OTs etc.

d) optionally converting compound of formula (I) or its salt (Ia) to the required acid addition salt and optionally purifying required vortioxetine acid addition salt (Ia).

Further, step (c) of reacting 2-[(2,4-dimethylphenyl)thio]aniline compound (V) or its salt with dialkyl amine compound (VI) or its acid addition salt can be carried out in a solvent with continuous flow of inert gas, wherein the inert gas is nitrogen, argon and the like. Preferably, the inert gas is nitrogen.

Further, the acid addition salt of Vortioxetine can be converted to its free base.

The solvent used in the steps (a), (b), (c) and (d) may be same or different; wherein the said solvent is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol, mono ethylene glycol and the like, aromatic hydrocarbons such as toluene, xylene, mesitylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane, chlorobenzene, dichlorobenzene and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether, diglyme and the like, esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; water or a mixture thereof.

Preferably, the solvent used in step (a) is water.

Preferably, the solvent used in step (b) is alcohol. More preferably, the solvent used is isopropanol.

Preferably, the solvent used in step (c) is alcohol. More preferably, the solvent used is n-butanol.

Preferably, the solvent used in step (d) is alcohol, ester, ether, ketone, water or mixtures thereof.

The steps (a), (b), (c) and (d) can be carried out at temperature range from about 0°C to 180°C or the boiling points of the solvents used. Usually the reaction may be carried out at temperature up to reflux temperature of the said solvent.

The base used in step (a) and step (c) is selected from organic or inorganic base; organic bases selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethyl amine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like.

Preferably, the base used in step (a) is alkali metal hydroxides. More preferably, the base used is sodium hydroxide.

The reduction step (b) can be carried out either by catalytic reduction, metallic reduction, or chemical reduction or enzymatic reduction.

The catalytic reduction of the step (b) can be carried out in presence of a catalyst selected from but not limited to palladium-carbon, palladium hydroxide-carbon, platinum oxide, rhodium on carbon, Raney nickel, nickel chloride, charcoal, graphite

and the like; in presence of hydrogen gas or hydrogen generating source such as but not limited to ammonium formate, hydrazine hydrate, hydrazine glyoxylate, glyoxylic acid, hydrazinium monoformate, sodium borohydride, lithium aluminium hydride.

Preferably, the reduction step (b) is carried out using Raney nickel in presence of hydrogen gas.

The metallic reduction in the step (b) can be carried out by using metals such as but not limited to iron, zinc, tin, and the like in presence of reagents such as acetic acid, formic acid, calcium chloride, copper sulphate, sodium hydroxide, ammonium chloride, ammonium formate, ammonium acetate, ammonium sulphate, and/or solvent.

The chemical reduction in the step (b) can be carried out using but not limited to sodium dithionate, sodium sulphide, sodium hyposulphite.

Catalyst used in step (a) and (c) is selected from metal halide like sodium iodide, potassium iodide, potassium bromide, sodium bromide and the like; acids like p-toluene sulfonic acid and the like, phase transfer catalyst including quaternary ammonium salts like tetrabutylammonium bromide (TBAB) and the like, amines like 4-Dimethylaminopyridine (DMAP) and the like.

Preferably, the catalyst used in step (a) is quaternary ammonium salts like tetrabutylammonium bromide (TBAB).

Step (c) can be carried out on solid supports like, alumina but not limited to neutral alumina, basic alumina and the like, silica gel and the like, resin and the like.

According to embodiment of the present invention, compound of formula (V) and (I) may be further converted into its pharmaceutically acceptable salts by treating with the suitable acid selected from organic acids or inorganic acids in presence of solvent.

The organic acids is selected from but not limited to maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, Cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, 8-halotheophylline; inorganic acids such as but not limited to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid; preferably hydrobromic acid.

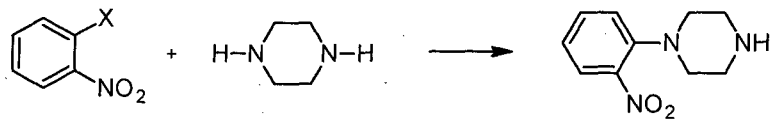
The solvent used for converting compound of formula (V) and (I) to its salt is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; water or a mixture thereof. Preferably, the solvent used is alcohol, ester, ether, ketones, water or mixtures thereof.

According to embodiment of the present invention, process for the preparation of vortioxetine (I) can be performed in a single pot by avoiding the isolation and purification of intermediates of compounds (IV) and (V) obtained in the steps (a), and (b) that improves the overall efficiency of a chemical process and reduces the burden of centrifugation, washing, drying and powder handling.

According to embodiment of the present invention, compound of formula (IV), (V), (I), and (Ia) may be further purified either by acid-base treatment, or solvent crystallization, or washing with solvent, or converting into its salts. The salts of formula (V) and (I) can be selected from organic salts like but not limited to maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylene salicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, 8-halotheophylline; and inorganic acid such as but not limited to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid.

According to another embodiment the present invention, there is provided a new method for preparation of vortioxetine (I) and its salt (Ia);
wherein the said process comprising;

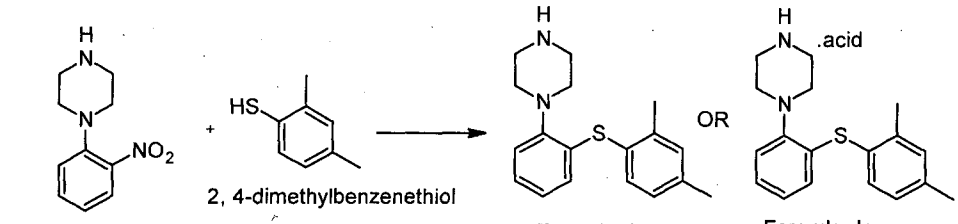
e) reacting 1-halo (or 1-pseudohalo)-2-nitrobenezene with piperazine in solvent in the presence of base and optionally in presence of catalyst to obtain *o*-nitrophenyl piperazine;



piperazine orthonitrophenylpiperazine

Wherein X is -Cl, -Br, -I, -F, -OTf, -OMs, -OTs etc.

f) reacting *o*-nitrophenylpiperazine with 2,4-dimethylbenzenethiol in solvent in the presence of catalyst, and optionally in the presence of base to obtain vortioxetine (I) or its salt of formula (Ia);



o-nitrophenylpiperazine Formula- I Formula- Ia

g) optionally converting compound of formula (I) or (Ia) to the required acid addition salt (Ia), and optionally purifying required acid addition salt (Ia).

The solvent used in step (e) and (f) may be same or different; wherein the said solvent is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; water or a mixture thereof.

The step (e), (f) and (g) can be carried out at temperature range from about0°C to 180°C or the boiling points of solvents used. Usually the reaction may be carried out at temperature up to reflux temperature of the said solvent.

The base used in step (e) and step (f) is selected from organic or inorganic base; organic bases selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethyl amine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like.

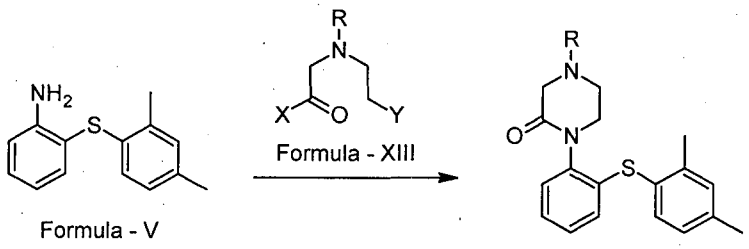
The catalyst used in step (e) and (f) is selected from but not limited to copper, Cu-halide, Cu-halide-PPh3, palladium catalysts like $Pd(OAc)_2$, Palladium-ligand, PTSA, crown ether, quaternary ammonium salts like tetrabutylammonium bromide (TBAB) and the like, amines like 4-Dimethylaminopyridine (DMAP) and the like.

According to embodiment of the present invention, process for the preparation of vortioxetine (I) can be performed in a single pot by avoiding the isolation and purification of intermediates of compounds (IV) and (V) obtained in the steps (a), and (b) that improves the overall efficiency of a chemical process and reduces the burden of centrifugation, washing, drying and powder handling.

According to embodiment of the present invention, *o*-nitrophenylpiperazine, vortioxetine (I) and its salt (Ia) may be further converted into its pharmaceutically acceptable salts, and purified as per method mentioned in first embodiment.

According to yet another embodiment there is provided a new method for preparation of vortioxetine (I) and its pharmaceutically acceptable salts (Ia);
wherein the said process comprising;

h) reacting 2-[(2, 4-dimethylphenyl) thio] aniline (V) or its salt with compound (XIII) or its salt in solvent, in the presence of base and reagent and/or catalyst to obtain compound (XIV);

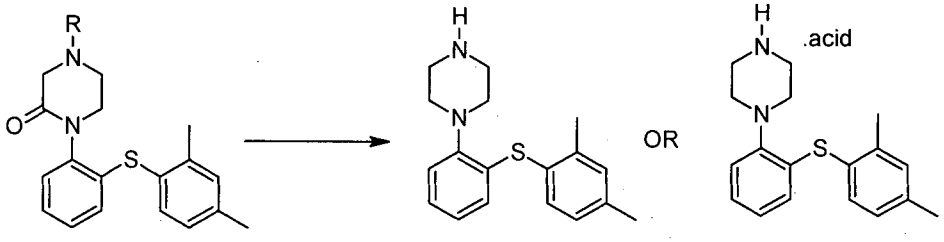


Formula - V
2-[(2,4-dimethylphenyl)thio]aniline

Formula - XIV

Wherein; X is-OH, -O-alkyl, -O-aryl, -halogen etc.,
Y is -halogen, -OTf, -OMs, and -OTs etc., and
R is-H, -Boc, -Benzyl etc.,

i) reducing compound of formula-(XIV), in solvent in the presence of reducing agent to obtain vortioxetine (I) or its salt (Ia).



Formula - XIV Formula - I Formula - Ia

The solvent used in step (h) and (i) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; water or a mixture thereof.

The base used in step (h) is selected from organic or inorganic base; the organic base is selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethyl amine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like.

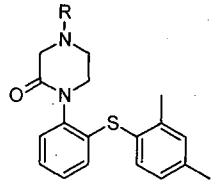
The reagent used in steps (h) are selected from but not limited to borane reagents such as boric acid, phenyl boronic acid, trimethyl borate and the like; carbodiimide reagents such as N,N'-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminoprpyl)carbodiimide (EDC) or its salt; or imidazole reagents such as 1,1'-carbonyldiimidazole (CDI) and the like, chlorinating reagents selected from but not limited to thionyl chloride, oxalyl chloride, cynuric chloride, phosphorus oxychloride and the like.

The catalyst used in step (h) of the present invention is selected from organic or inorganic catalyst or phase transfer catalyst.

The reduction step (i) can be carried out by using reducing agents such as but not limited to lithium aluminium hydride, sodium borohydride in presence of Iodine; or sodium borohydride in presence of acids, wherein acids are selected from but not limited sulfuric acid, acetic acid, trifluoroacetic acid, sodium borohydride and BF3etherate; diborane solutions like BH_3:THF, BH_3:SMe_2, vitride, sodium acyloxyborohydrides, lithium aminoborohydrides, and the like.

According to another embodiment of the present invention, compound of formula (XIV), (I) and (Ia) may be further converted into its pharmaceutically acceptable salts, and purified as per method mentioned in first embodiment.

According to the invention there is provided a new compound having a formula (XIV);



Formula - XIV

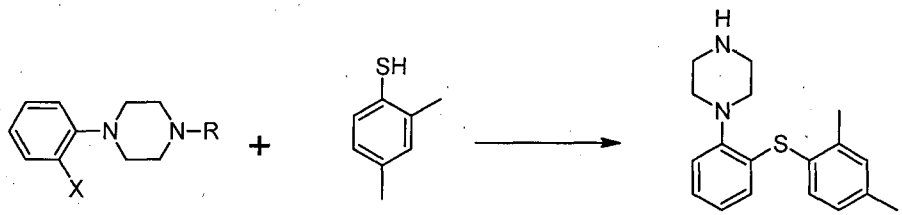
Wherein R is -H, -BOC, -Benzyl, etc.is an intermediate of vortioxetine (I) or its salt (Ia).

A process for the preparation of new compound of formula (XIV) is described in the foregoing embodiment of the present invention.

According to yet another embodiment the present invention, there is provided new method for the preparation of vortioxetine (I) or its pharmaceutically acceptable salts (Ia);

wherein the said process comprising:

j) reacting1-halo (or 1-pseudohalo)2-phenylpiperazine of formula (XV) or its acid addition salt with2, 4-dimethylbenzenethiol in a solvent and in the presence of base, and optionally in presence of catalyst to produce vortioxetine (I) or its salt (Ia);



Formula - XV 2,4-dimethylbenzenethiol Formula - I

Wherein X is -Cl, -Br, -I, -OTf, -OMs, -OTs etc.

R= -H, -Boc, -Benzyl etc.

The solvent used in step (j) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-

Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; water or a mixture thereof.

The base used in step (j) is selected from organic or inorganic base; the organic base is selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethyl amine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like.

The catalyst used in step (j) is selected from but not limited to copper, Cu-halide, Cu-halide-PPh3, palladium catalysts like $Pd(OAc)_2$, Palladium-ligand, PTSA, crown ether, quaternary ammonium salts like tetrabutylammonium bromide (TBAB) and the like, amines like 4-Dimethylaminopyridine (DMAP) and the like.

According to another embodiment of the present invention, compound of formula (XV), (I) and (Ia) may be further converted into its pharmaceutically acceptable salts, and purified as per method mentioned in first embodiment.

According to yet another embodiment of the present invention, the invention provides a novel crystalline form of vortioxetine hydrobromide, herein defined as Form M1, characterized by PXRD peaks at 2-theta (θ) = 4.50, 9.06, 11.84, 13.09, 14.22, 15.12, 15.96, 17.07, 18.15, 18.71, 19.90, 20.32, 21.28, 23.32, 23.62, 24.4, 24.93, 25.36, 27.06, 27.98 29.60, 32.53, 34.09, 35.30, 36.32±0.2 θ, with characteristic peak being at about 4.50, 9.06, 11.84, 15.96, 17.07, 18.15, 18.71, 23.32, 23.62, 24.93, 25.36+ 0.2 θ. Crystalline form of vortioxetine hydrobromide may also be characterized by PXRD pattern as depicted by Figure 3. The X-ray diffractogram was measured on Bruker Axe; DS advance Powder X-ray Diffractometer with Cu K alpha-1Radiation source having the wavelength 1.54 A°.

According to yet another embodiment of the present invention , the application provides a novel crystalline form of vortioxetine hydrobromide, herein defined as Form M2, characterized by PXRD peaks at 2-theta (θ) = 3.79, 7.60, 11.41, 13.17, 13.60, 15.12, 16.61, 17.10, 17.57, 18.34, 19.10, 20.25, 22.76, 23.17, 24.23, 27.41, 28.53±0.2, with characteristic peak being at about 3.79, 11.41, 13.17, 13.60, 17.57, 18.34, 20.25, 23.17, 27.41, 28.53±0.2θ. Crystalline form of vortioxetine hydrobromide may also be characterized by PXRD pattern as depicted by Figure 4. The X-ray diffractogram was measured on Bruker Axe, DS advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.54 A°.

The vortioxetine (I) or its salt (Ia) used in the preparation of form M1 and M2 may be obtained as per any of the above mentioned embodiment.

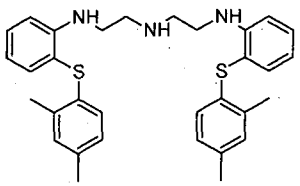
Form M1 and M2 of vortioxetine hydrobromide may be prepared from vortioxetine free base (I) or from its salt (Ia).

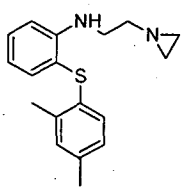
Form M1 and M2 of vortioxetine hydrobromide may be prepared from alpha, beta, gamma, delta or any other polymorphic form.

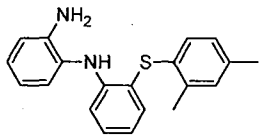
According to yet another embodiment of the present invention, the application provides a crystalline form of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (IV), characterized by PXRD peaks at 2-theta (θ)=7.51, 13.76, 14.41, 15.04, 17.80, 18.13, 22.59, 24.18, 25.66, 27.72, 31.57±0.2θ, with characteristic peak being at about 7.51, 13.76, 14.41, 15.04, 17.80, 18.13, 24.18, 25.66, 27.72±0.2θ. Crystalline form of compound (IV) may also be characterized by PXRD pattern as depicted by Figure 1. The X-ray diffractogram was measured on Bruker Axe, DS advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.54 A°.

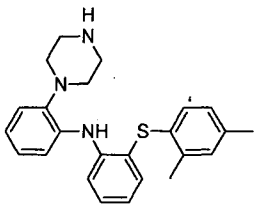
According to yet another embodiment of the present invention, the application provides a crystalline form of 2-[(2,4-dimethylphenyl)thio]aniline) hydrochloride (HCl salt of V), characterized by PXRD peaks at 2-theta (θ) = 7.11, 9.12, 11.03, 14.30, 16.60, 16.86, 17.27, 18.81, 19.62, 19.80, 20.03, 21.50, 23.12, 23.62, 23.90, 24.36, 24.70, 25.72, 30.17, 31.36, 32.16±0.2, with characteristic peak being at about 7.11, 9.12, 11.03, 14.30, 16.86, 19.62,19.80, 23.12, 23.62, 23.90, 24.36, 25.72, 30.17±0.2θ. Crystalline form of compound (V) may also be characterized by PXRD pattern as depicted by Figure 2. The X-ray diffractogram was measured on Bruker Axe; DS advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.54 A°.

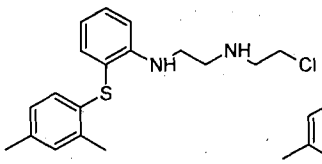
According to yet another embodiment of the present invention provides a compound (A), (B), (C), (D), (E) (F), (G), (H), (I), (J), (K), (L), (M), (N) and (O);

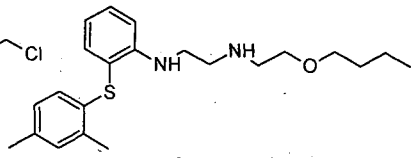

Compound - A

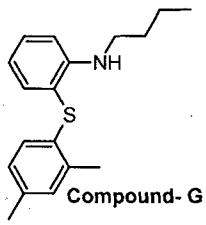

Compound - B

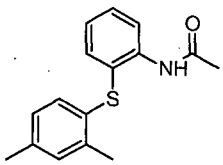

Compound-C

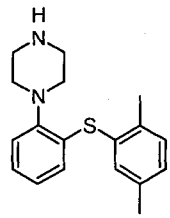

Compound-D

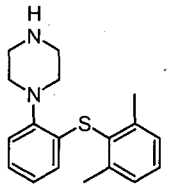

Compound - E

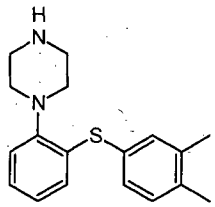

Compound - F

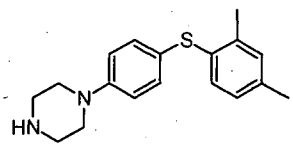

Compound- G

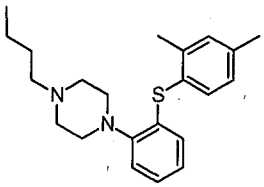

Compound- H

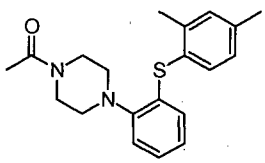

Compound - I

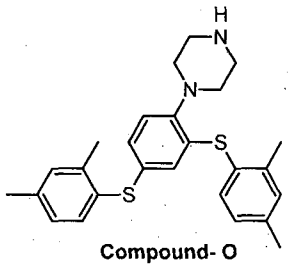

Compound - J


Compound- K


Compound- L


Compound - M


Compound- N


Compound- O

According to the present invention vortioxetine (I) or its pharmaceutically acceptable salt (Ia) prepared by foregoing process, having less than about 0.2% of compound (A), has less than about 0.2% of compound (B), has less than about 0.2% of

compound (C), having less than about 0.2% of compound (D), has less than about 0.2% of compound (E), has less than about 0.2% of compound (F), having less than about 0.2% of compound (G), has less than about 0.2% of compound (H), has less than about 0.2% of compound (I), having less than about 0.2% of compound (J), has less than about 0.2% of compound (K), has less than about 0.2% of compound (L), having less than about 0.2% of compound (M), has less than about 0.2% of compound (N), and has less than about 0.2% of compound (O) by HPLC.

BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

EXAMPLE - 1

Preparation of 2,4-dimethyl-1-[(2-nitrophenyl) thio] benzene (IV)

To the solution of 2,4-dimethylbenzenethiol (100.0 g; 0.7246 moles) and 1-fluoro-2-nitrobenzene (102.0 g; 0.7246 moles)in THF (600mL) was added KOH (5% solution in water, 800mL)at room temperature, reaction mixture was stirred at room temperature for 12 h. Product was extracted in methylene dichloride (800mL), extract was dried, filtered and evaporated to give residue, residue was crystallized in n-heptane to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene. [Yield: 160.0 g (85.0%); Purity (HPLC) = 99.95%]

EXAMPLE – 2

Preparation of2-[(2,4-dimethylphenyl)thio]aniline (V)

2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (180 g; 0.6949 moles) in IPA (1500mL) was reduced using Ra/Ni (40 g) at 63±3 °C in autoclave under 5-7 kg of hydrogen pressure for 3-5 h, catalyst was filtered through celite bed, IPA was evaporated to

obtain oil of 2-[(2,4-dimethylphenyl)thio]aniline.[Yield: 146.0 g (91.0%); Purity (HPLC) = 99.0%]

EXAMPLE – 3

Preparation of 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride[Vortioxetine Hydrochloride]

The solution of 2-[(2,4-dimethylphenyl)thio]aniline (100 g; 0.4347 moles) and bis-(2-chloroethyl)amine hydrochloride (77.6 g; 0.4347 moles) in n-butanol (500mL) was heated to reflux temperature for 24 h, cool the reaction mass to 70±2°C, anhydrous potassium carbonate (30 g; 0.2170 moles) was added and again heated the reaction mass to reflux temperature and maintained for 42 h, reaction mixture was filtered to remove undissolved solid, filtrate was evaporated to give syrup. The obtained syrup crystallized in acetone (500mL) at room temperature, solid was filtered and washed with acetone (100mL) to obtain white to off white colored crystalline solid of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (vortioxetine hydrochloride).[Yield: 70.0 g (53.8%); Purity (HPLC) = 99.0%]

EXAMPLE – 4

Preparation of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (I)

To the mixture of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (100 g; 0.2980 moles) and water (500mL),aqueous ammonia solution was added to adjust the pH to 8-9, reaction mixture was stirred for 1 h at room temperature, solid was filtered and washed with water (100mL) to obtain white to off white crystalline solid of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (vortioxetine free base).[Yield: 85.0 g (95.5%)]

EXAMPLE – 5

Preparation of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]piperazine hydrobromide (I)

To the mixture of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (100 g; 0.3344 moles) and ethyl acetate (500mL)was added aqueous hydrobromic acid at room temperature, pH of reaction mass adjusted to 1-3, obtained white solid was filtered and wash with ethyl acetate (100mL), dried the solid to obtain crystalline solid of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (vortioxetine hydrobromide). [Yield: 100.0 g (79.3%); Purity (HPLC) = 99.5%]

EXAMPLE – 6

Preparation of beta polymorphic form of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (I)

To the mixture of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (100 g; 0.3344 moles) and acetone (500 mL) was added aqueous hydrobromic acid at room temperature, pH of reaction mass adjusted to 1-3, obtained white solid was filtered and washed with acetone (100 mL), dried the solid to obtain beta polymorphic formof1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide). [Yield: 100.0 g (79.3%); Purity (HPLC) = 99.9%]

EXAMPLE – 7

Preparation of beta polymorphic form of 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (I)

To the mixture of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (100 g; 0.3344 moles) and methanol (500 mL) was added MTBE at room temperature to precipitate solid, filtered the solid and wash with MTBE (100 mL), dried the solid to obtain beta polymorphic form of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide).
[Yield: 95.0 g (95.0%); Purity (HPLC) = 99.85%]

EXAMPLE – 8

Preparation novel crystalline formM1 of 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (I)

1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (100 g; 0.3344 moles) was added in methylene dichloride (500 mL), mixture was heated to reflux temperature to get clear solution, methylene dichloride was dried under vacuum at 38±2°Coverrota-evaporator to obtain solid of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide).

[Yield: 95.0 g (95.0%); Purity (HPLC) = 99.80%, melting point; 85-90°C]

EXAMPLE –9

Preparation of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (IV)

To the solution of 2,4-dimethylbenzenethiol (10 g; 0.07246 moles) and 1-fluoro-2-nitrobenzene (10.2 g; 0.07246) in water (40mL), 5% aqueous KOH solution (80 mL) was added at room temperature, reaction mixture was stirred at room temperature for 12 h. n-heptane was added to the reaction mass, stirred for 30 minutes, solid was filtered and washed with n-heptane (50 mL) to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene. [Yield: 14.0 g (77.0%); Purity (HPLC) = 99.9%]

EXAMPLE –11

Preparation of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (IV)

To the solution of 2,4-dimethylbenzenethiol (100 g;0.7246 moles), 1-fluoro-2-nitrobenzene (102 g; 0.7246 moles) and tetrabutylammonium bromide (4g) in water (600.0 ml) was added 5% aqueous KOH solution (800mL) at room temperature, reaction mixture was stirred at room temperature for 10 h, and n-heptane was added to the stirred reaction mass. Solid was filtered and washed with n-heptane (100 mL) to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene.

[Yield: 180.0 g (96.0%); Purity (HPLC) = 99.63%]

EXAMPLE –12

Preparation of novel crystalline form M1 of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (I)

1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (10 g; 0.0334 moles)was dissolved in mixture of methanol and methylene dichloride in the ratio of 8:2 at room temperature to obtained clear solution. The obtained clear solution spray dried using spray dryer to obtain novel form (M1) of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide).

[Yield: 7.50 g (75.0%); Purity (HPLC) = 99.80%]

EXAMPLE –13

Preparation of novel crystalline form M2 of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (I)

1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (5.0 g) prepared as per example no 3 was heated in water (100.0 mL) to 83±2°C, maintained till turbid solution observed. One drop of aqueous hydrobromic acid was added to obtain clear solution. Aqueous hydrobromic acid was added till turbid solution was observed, solution was cooled to room temperature, maintained at room temperature for 30-45 min. solid was filtered, washed with water and dried under vacuum at 53±2°C to obtain novel form (M2) of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide).

[Yield: 3.5 g (70.0%); Purity (HPLC) = 99.80%]

EXAMPLE – 14

Preparation of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine (I)

Mixture of 2-[(2,4-dimethylphenyl)thio]aniline (10 g; 0.0434 moles), bis-(2-chloroethyl)amine hydrochloride (15.5g; 0.0868 moles) and basic alumina (100g)

was heated 140±2°Cfor 5-10 h, cooled the mixture to room temperature and methylene dichloride (500 ml) was added, stirred the mixture and filtered to separate the inorganic solid. Evaporated the methylene dichloride to obtain1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (I) (Vortioxetine free base).
[Yield: 5.0 g (34.24%)]

EXAMPLE – 15

Preparation of 2-[(2, 4-dimethylphenyl) thio] aniline hydrochloride

To the stirred solution of 2-[(2,4-dimethylphenyl)thio]aniline (V) benzene (25.0 g) (prepared as per example-2) in ethyl acetate (150.0 ml), aqueous solution of hydrochloric acid was added to adjust the pH in the range of 1-3, precipitated solid was filtered, washed with ethyl acetate (10 ml) and dried to obtain crystalline solid of 2-[(2, 4-dimethylphenyl) thio] aniline hydrochloride. [Yield: 25.0 g (84.7%); Purity (HPLC) = 99.05%]

EXAMPLE –16

Preparation of 2, 4-dimethyl-1-[(2-nitrophenyl) thio] benzene (IV)

To the solution of 2,4-dimethylbenzenethiol (50 g; 0.3615 moles), 1-chloro-2-nitrobenzene (57 g; 0.3615 moles) and TBAB (2 g) in water (400mL), was added 5% aqueous KOH solution (800 mL) at room temperature, reaction mixture was stirred at room temperature for 12 h. n-heptane was added to the reaction mass, stirred for 30 minutes, solid was filtered and washed with n-heptane (50 mL) to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene.
[Yield: 85.0 g (90.0%); Purity (HPLC) = 99.6%]

EXAMPLE –17

Purification of 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (I)

1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (10 g) was added to the mixture of isopropanol (100 mL) and water (20 mL), resulting mixture heated to 83±2°C and maintained till clear solution was observed, cooled the mixture to 28±2°C and maintained for 1-2 h, solid was filtered and washed with isopropanol (20 mL), solid was dried to get crystalline solid of 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride. [Yield: 9.0 g (90.0%); Purity (HPLC) = 99.9%]

EXAMPLE –18

Preparation of 2, 4-dimethyl-1-[(2-nitrophenyl) thio] benzene (IV)

To the mixture of 2,4-dimethylbenzenethiol (100 g; 0.7234 moles), 1-chloro-2-nitrobenzene (114 g; 0.7236 moles) and TBAB (1 g) in water (250 mL) was added aqueous NaOH solution (36.2 g, 0.905 moles of NaOH in 250 mL of water) at 25-35 °C, and stirred for 6 h, after completion of reaction n-heptane (200 mL) was added to the reaction mass, stirred for 30 minutes, solid was filtered and washed with n-heptane (200 mL) to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene. [Yield: 175.0 g (93.5%); Purity (HPLC) = 99.6%]

EXAMPLE –19

Preparation of 2, 4-dimethyl-1-[(2-nitrophenyl) thio] benzene (IV)

To the mixture of 2,4-dimethylbenzenethiol (10 g; 0.0723 moles), 1-chloro-2-nitrobenzene (11.4 g; 0.0723 moles) and TBAB (0.5 g) in water (50 mL) was added aqueous ammonia (10 mL) at 25-35 °C, and stirred for 6 h. after completion of reaction n-heptane (20 mL) was added to the reaction mass, stirred for 30 minutes, solid was filtered and washed with n-heptane (10 mL) to get yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene.
[Yield: 15.0 g (79.95%); Purity (HPLC) = 99.2%]

EXAMPLE –20

Purification of 2, 4-dimethyl-1-[(2-nitrophenyl) thio] benzene (IV)

The mixture of 2, 4-dimethyl-1-[(2-nitrophenyl) thio] benzene (100 g), n-heptane (500 mL) and water (500 mL) was stirred at 35-40 °C for 1 h, solid was filtered and washed with n-heptane (50 mL) to get highly pure yellow crystalline solid of 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene.

[Yield: 98.0 g (98.0%); Purity (HPLC) = 99.9%]

EXAMPLE – 21

Preparation of 2-[(2,4-dimethylphenyl)thio]aniline (V)

2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (100 g; 0.3856 moles) in IPA (500 mL) was reduced using Ra/Ni (10 g) at 30-35 °C in autoclave under 5-7 kg of hydrogen pressure, catalyst was filtered through celite bed, filtrate was concentrated to obtain oil of 2-[(2,4-dimethylphenyl)thio]aniline (V).

[Yield: 85.0 g (96.1%); Purity (HPLC) = 99.0%]

EXAMPLE – 22

Preparation of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine [Vortioxetine (I)]

2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene (IV) (100 g; 0.3856 moles) in IPA (500 mL) was reduced using Ra/Ni (10 g) at 30-35 °C in autoclave under 5-7 kg of hydrogen pressure, catalyst was filtered through celite bed, filtrate was concentrated to obtain oil of 2-[(2,4-dimethylphenyl)thio]aniline (V).

To the obtained oil of (V), n-butanol (100 mL) and bis-(2-chloroethyl)amine hydrochloride (VI) (103.5 g; 0.5797 moles) was added, continuous flow of nitrogen gas was adjusted during heating and reaction mass was maintained at 112-116 °C, second lot of n-butanol (50 mL) was added after 50 h of maintaince, again maintained the reaction mass at same temperature for another 50 h. Temperature of reaction mass was lowered to 100 °C, third lot of n-butanol (50 mL) was added,

reaction mass was further cooled to 35-55 °C and ethyl acetate (1000 mL) was added. The obtained slurry was cooled to 25-35 °C and then was aged for 2 h, solid was filtered and washed with ethyl acetate (200 mL) to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia).

The obtained 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia) and water (1000 mL) was heated to 80-85 °C to get clear solution, the solution was cooled to 25-30 °C and agitated for 2 h, solid was filtered, washed with water (200 mL) and dried under vacuum at 55-60 °C for 5 h to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia) free from unreacted bis-(2-chloroethyl)amine hydrochloride.

The mixture of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia), isopropanol (100 mL) and water (20 mL) was heated to 80-85 °C to get clear solution, solution was cooled to 55-60 °C and ethyl acetate was added, the mixture was further cooled to 25-30 °C and aged for 2 h, , solid was filtered and washed with ethyl acetate to obtain pure crystalline solid of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia).

To the solution of pure 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrochloride (Ia) in methanol (600 mL), 10% aqueous solution of sodium hydroxide (150 mL) was added at 25-30 °C, mixture was heated to 45-50 °C and filtered to get clear solution, to this clear solution water (500 mL) was added, obtained slurry was cooled to 15-20 °C and aged for 2 h. Solid was filtered, washed with water (200 mL) and dried to obtain highly pure 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (I). [Yield: 100 g (86.9%) Purity (HPLC) = 99.9%]

EXAMPLE – 23

Preparation of 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Ia)

The mixture of 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine (100 g; 0.3350 moles) and methanol (500 mL) was heated to 45-50 °C and filtered to get clear solution, the solution was cooled to 20-25 °C, aqueous hydrobromic acid (47 mL) was added, slurry was cooled to 15-20 °C and stirred for 2 h. Solid was filtered, washed with methanol (100 mL) and dried to obtain crystalline 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (vortioxetine hydrobromide).
[Yield: 105.0 g (82.6%); Purity (HPLC) = 99.9%]

EXAMPLE –24

Purification of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Ia)

The mixture of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (10 g; 0.0264) and methanol (100 mL) was heated to 60 °C to get clear solution, solution was filtered, the filtrate was cooled to 20-25 °C and maintained for 1 h, obtained solid was filtered, washed with methanol (10 mL) and dried to obtain pure 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide. [Yield: 9.0 g (90.0%); Purity (HPLC) = 99.9%]

EXAMPLE –25

Preparation of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine (I)

To the mixture of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (10 g; 0.0264) and methanol (200 mL), 10% aqueous solution of sodium hydroxide (10 mL) was added. The mixture was heated to 60 °C, filtered to get clear solution, to the obtained solution, water (50 mL) was added at 20-25 °C and

stirred for 1 h. Solid was filtered, washed with methanol (10 mL) and dried to obtain pure crystalline solid of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine (I). [Yield: 7.0 g (90.0%); Purity (HPLC) = 99.9%]

EXAMPLE –26

Preparation of novel crystalline form M1 of 1-[2-(2, 4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Ia)

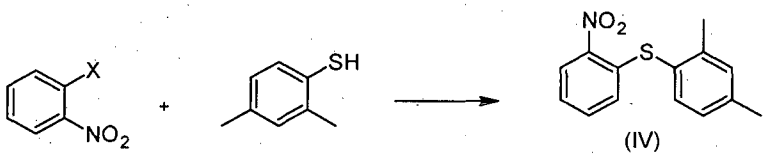
1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (10 g; 0.0264 moles) was dissolved in methylene dichloride (100 mL) at room temperature to obtained clear solution. The obtained clear solution spray dried using spray dryer to obtain M1 crystalline form of 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide (Vortioxetine hydrobromide).

[Yield: 7.50 g (75.0%); Purity (HPLC) = 99.80%]

We claim:

1. A process for preparation of Vortioxetine of formula (I) or its acid addition salt thereof, comprising:

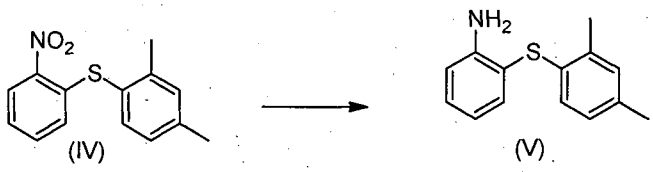
a) reacting 1-halo-2-nitrobenzene with 2,4-dimethylbenzenethiol in a solvent, a base and optionally in presence of a catalyst to obtain 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene compound (IV);



2,4-dimethylbenzenethiol (IV) 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene

wherein X is -Cl, -Br, -I, or -F.

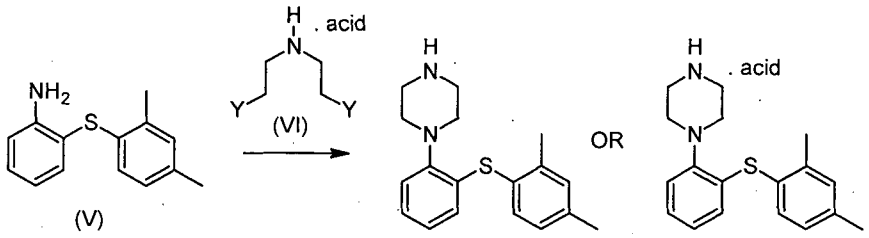
b) reducing 2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene compound (IV) to 2-[(2,4-dimethylphenyl)thio]aniline compound (V) in a solvent in presence of a reducing agent and a catalyst;



(IV) (V)

2,4-dimethyl-1-[(2-nitrophenyl)thio]benzene 2-[(2,4-dimethylphenyl)thio]aniline

c) reacting 2-[(2,4-dimethylphenyl)thio]aniline compound (V) or its salt with dialkyl amine compound (VI) or its acid addition salt in a solvent, a base to obtain vortioxetine (I) or its salt (Ia) and optionally purifying vortioxetine (I) or its salt (Ia); and



2-[(2,4-dimethylphenyl)thio]aniline Formula-I Formula-Ia

wherein Y is -Cl, -Br, or -I.

d) optionally converting compound of formula (I) or its salt (Ia) to a required acid addition salt and optionally purifying required vortioxetine acid addition salt (Ia).

2. The process as claimed in claim 1, wherein the catalyst used in step (a) is selected from metal halides such as sodium iodide, potassium iodide, potassium bromide, sodium bromide, p-toluene sulfonic acid, phase transfer catalyst like quaternary ammonium salts such as tetra-butyl ammonium bromide (TBAB), or amines such as 4-dimethylaminopyridine (DMAP); and the catalyst used in step (b) is selected from palladium-carbon, palladium hydroxide-carbon, platinum oxide, rhodium on carbon, Raney nickel, nickel chloride, charcoal, or graphite.

3. The process as claimed in claim 1, wherein the solvent used in steps (a), (b), (c) and (d) is either same or different and is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and mono ethylene glycol; aromatic hydrocarbons such as toluene, xylene and mesitylene; aliphatic hydrocarbons such as hexane and heptane; halogenated hydrocarbon such as dichloromethane, dichloroethane, chlorobenzene and dichlorobenzene; formamide such as N,N-dimethylformamide and N,N-dimethylacetamide; sulfoxides such as dimethylsulfoxide; cyclic amides such as N-Methylpyrrolidinone; nitriles such as acetonitrile; ketones such as acetone and methyl isobutyl ketone; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl

ether and diglyme; esters such as ethyl acetate, methyl acetate and isopropyl acetate; ionic liquids; water or mixture thereof.

4. The process as claimed in claim 1, wherein the base used in step (a) and (c) is selected from organic or inorganic base; organic bases selected from 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as methylamine, propyl amine, 2-propyl amine and butyl amine; secondary amines such as N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, and morpholine; tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, and trimethyl amine; inorganic bases selected from alkali metal carbonates such as potassium carbonate, sodium carbonate, and cesium carbonate; alkali metal bicarbonates such as sodium bicarbonate-and potassium bicarbonate; alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide and lithium hydroxide; metal alkoxides such as sodium methoxide, sodium ethoxide and potassium tert butoxide.

5. The process as claimed in claim 1, wherein the reducing agent used in step (b) is hydrogen gas or hydrogen generating source such as ammonium formate, hydrazine hydrate, hydrazine glyoxylate, glyoxylic acid, hydrazinium monoformate, sodium borohydride, lithium aluminium hydride.

6. The process as claimed in claim 1, wherein step (c) can also be carried out in a solvent and with continuous flow of inert gas, wherein the inert gas is selected from nitrogen or argon.

7. The process as claimed in claim 1, wherein the acid used for preparation of acid addition salts of vortioxetine (I) in step (d) is selected from maleic, fumaric,

benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, Cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, 8-halotheophylline, hydrochloric acid, hydrobromic acid, nitric acid or sulfuric acid.

8. The process as claimed in any of the preceding claims wherein compound of formula (V) and (I) is further converted into its pharmaceutically acceptable salts by treatment with an acid in a suitable solvent.

9. The process as claimed in claim 8, wherein acid is selected from organic acids selected from maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, Cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, 8-halotheophyllineor inorganic acids, or wherein inorganic acids is selected from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid.

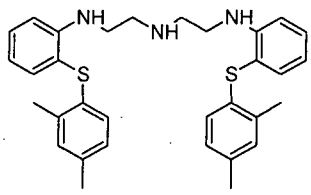
10. Crystalline vortioxetine hydrobromide Form M1 characterized by an x-ray diffraction pattern (XRD) as shown in FIG. 3.

11. A process for preparation of crystalline vortioxetine hydrobromide Form M1, comprises the steps of:

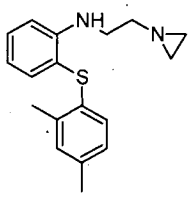
    a) dissolving vortioxetine hydrobromide in a mixture of methanol and methylene dichloride; and

b) subjecting the resulting solution to spray drying to obtain crystalline vortioxetine hydrobromide Form M1.

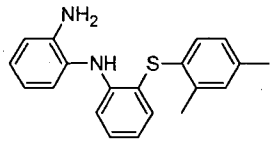
12. The process as claimed in any of the preceding claims, wherein vortioxetine (I) or its pharmaceutically acceptable salt (Ia), has less than about 0.2% of compound (A), has less than about 0.2% of compound (B), has less than about 0.2% of compound (C), having less than about 0.2% of compound (D), has less than about 0.2% of compound (E), has less than about 0.2% of compound (F), having less than about 0.2% of compound (G), has less than about 0.2% of compound (H), has less than about 0.2% of compound (I), having less than about 0.2% of compound (J), has less than about 0.2% of compound (K), has less than about 0.2% of compound (L), having less than about 0.2% of compound (M), has less than about 0.2% of compound (N), and has less than about 0.2% of compound (O) by HPLC.



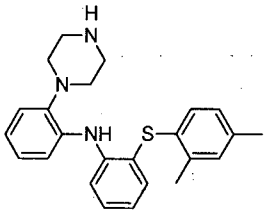
Compound - A



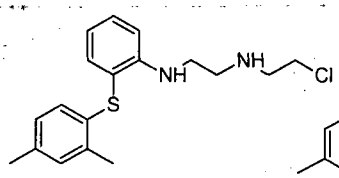
Compound - B



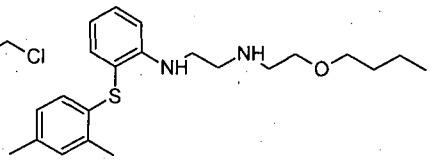
Compound-C



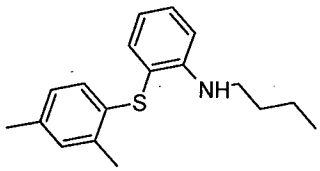
Compound-D



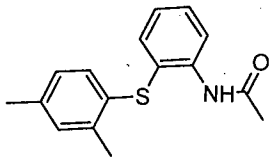
Compound - E



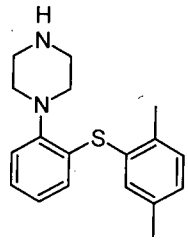
Compound - F



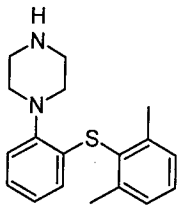
Compound- G



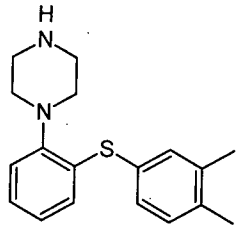
Compound- H



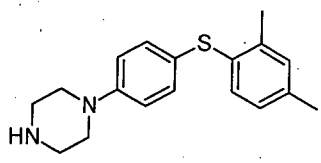
Compound - I



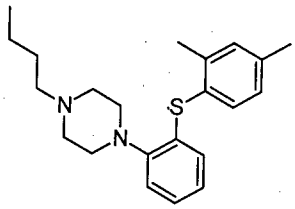
Compound - J



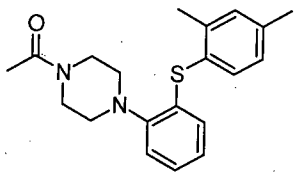
Compound- K



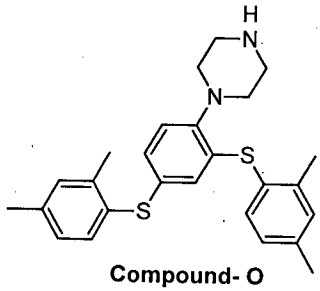
Compound- L



Compound - M



Compound- N



Compound- O

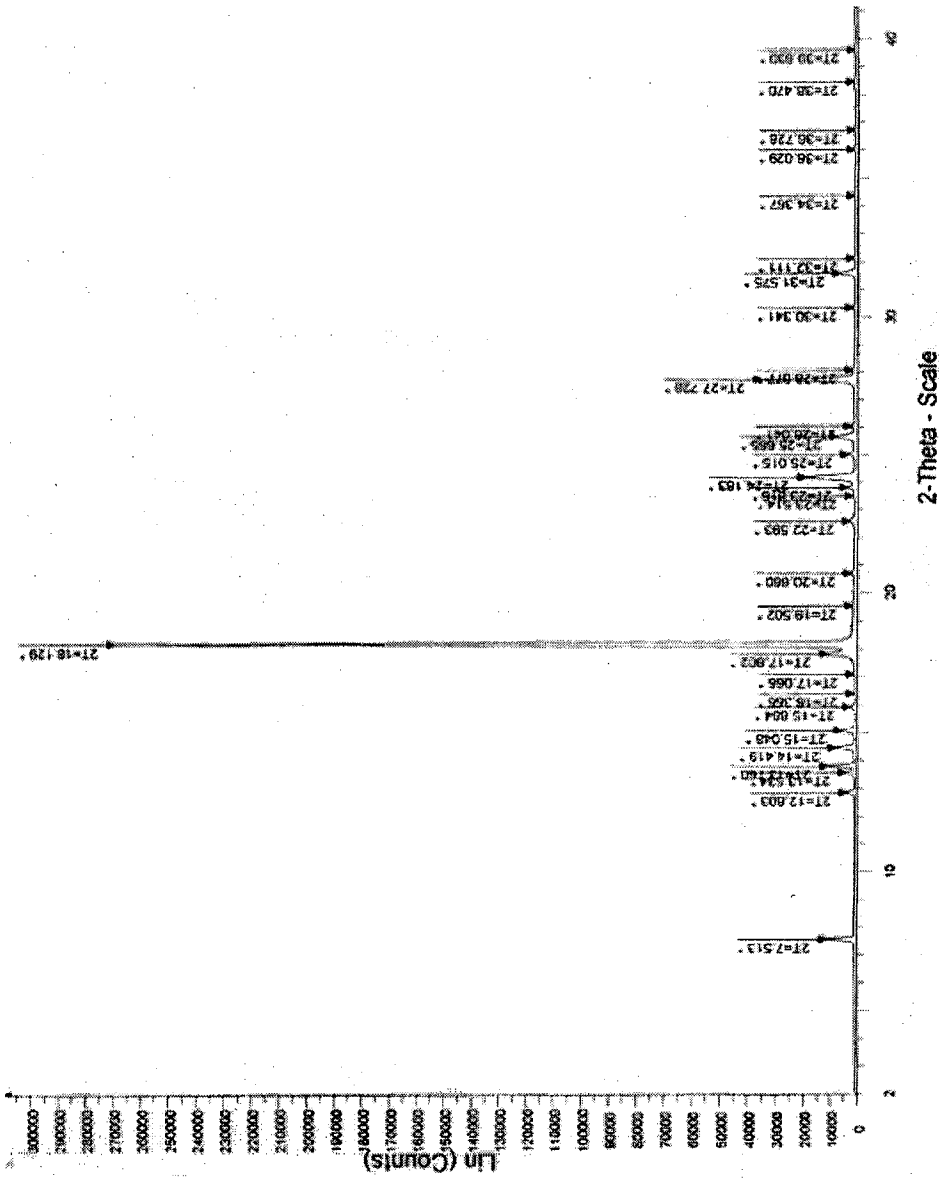


Figure-1

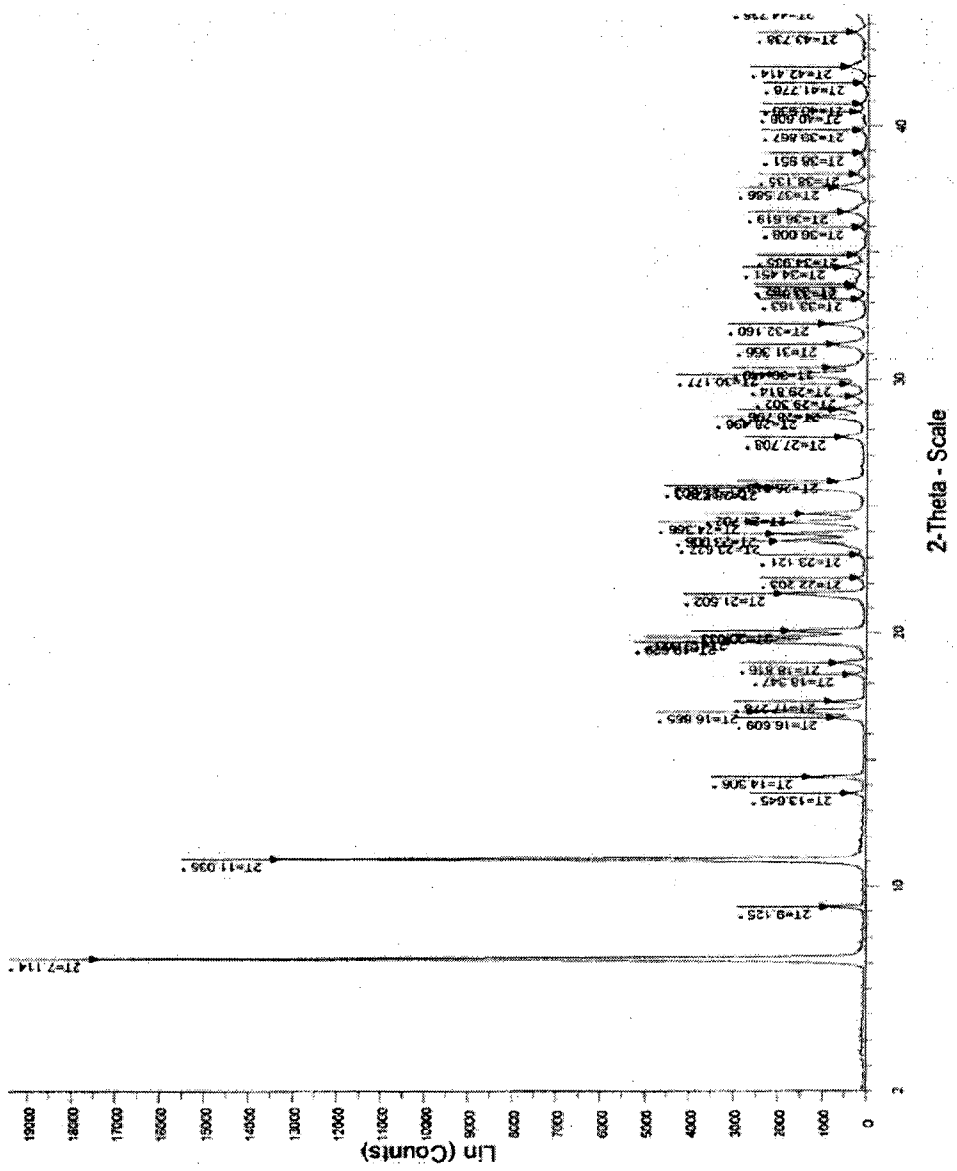

Lin (Counts)
2-Theta - Scale
2T=7.114
2T=9.125
2T=11.036
2T=13.645
2T=14.306
2T=16.609
2T=16.865
2T=18.347
2T=18.816
2T=21.502
2T=22.305
2T=23.121
2T=24.366
2T=27.708
2T=29.814
2T=30.177
2T=31.366
2T=32.160
2T=33.163
2T=34.451
2T=36.008
2T=36.619
2T=37.586
2T=38.651
2T=39.467
2T=40.608
2T=41.776
2T=42.414
2T=43.736

Figure-2

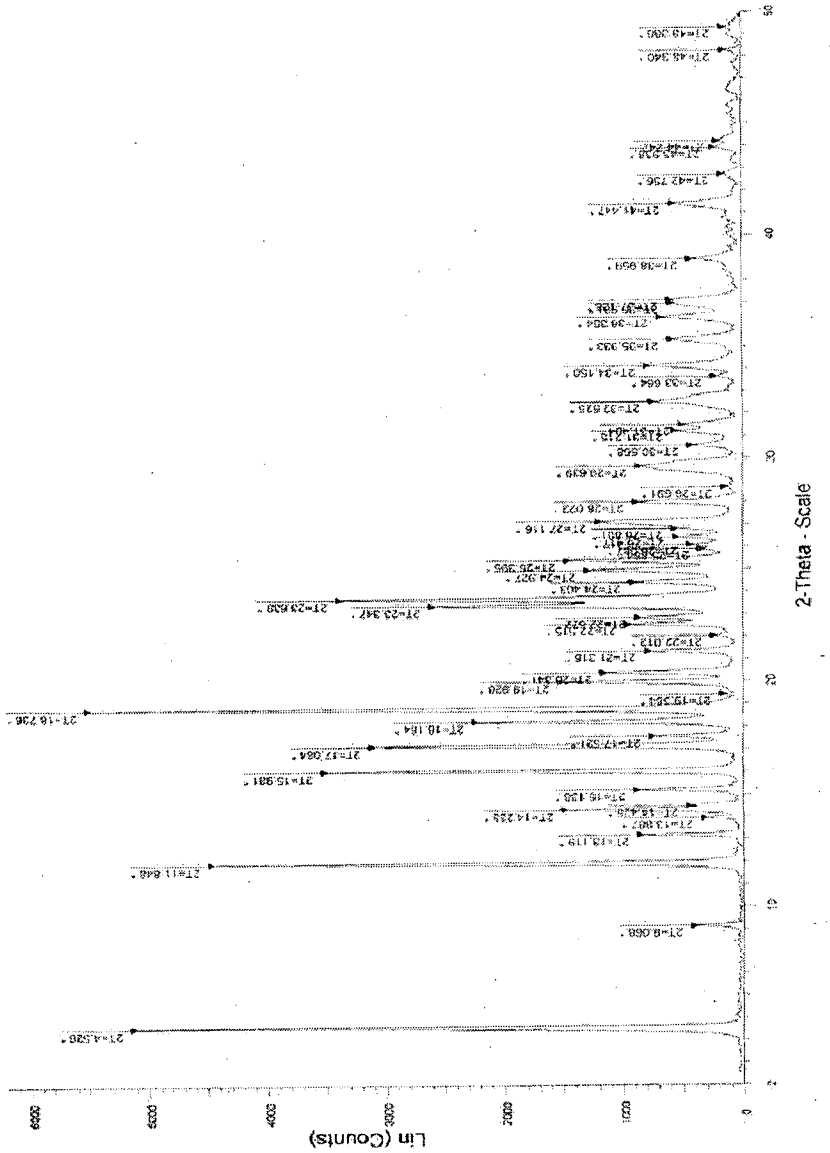


Figure-3

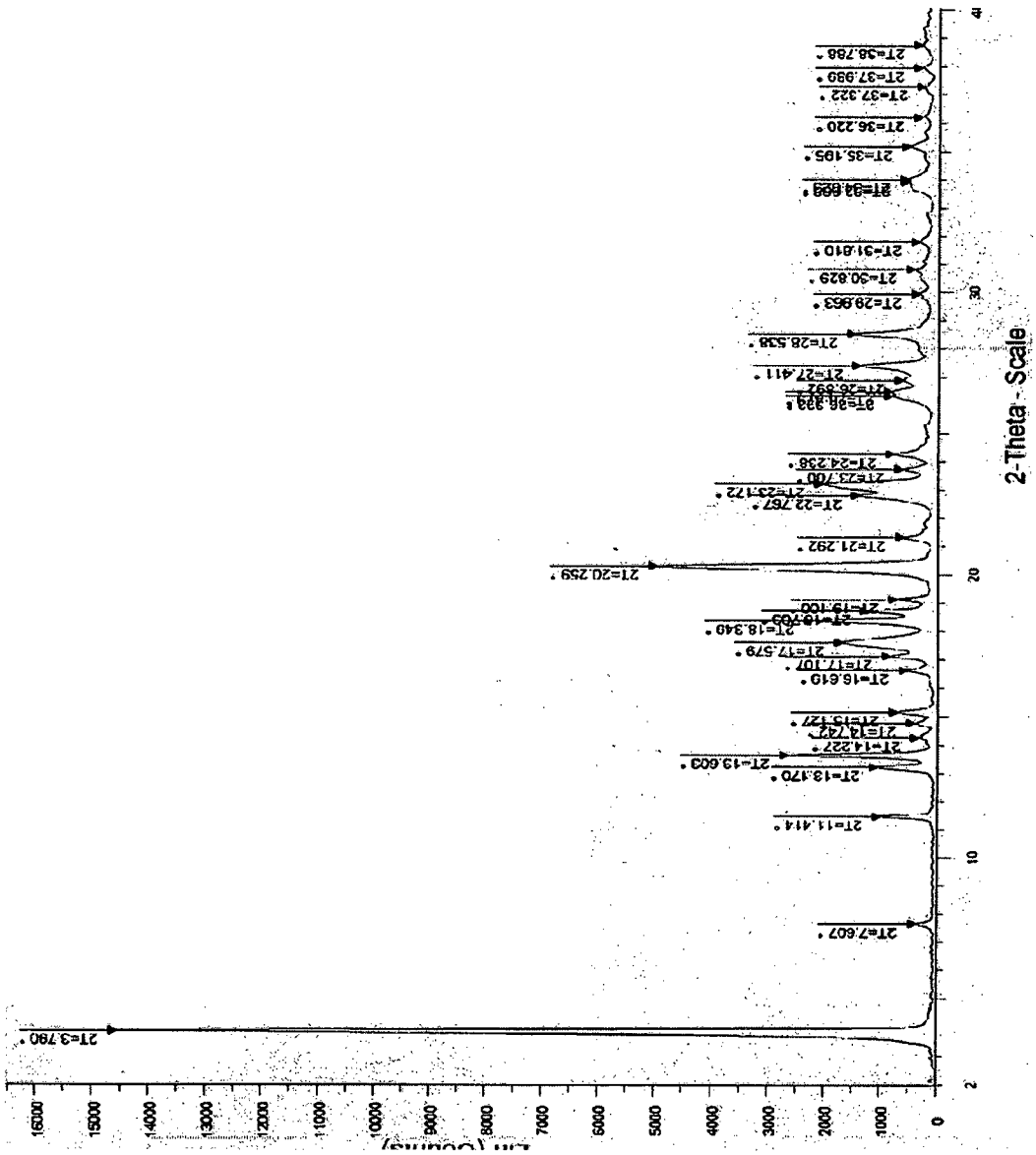

2T=3.780
2T=7.607
2T=11.414
2T=13.170
2T=13.603
2T=14.227
2T=15.127
2T=16.610
2T=17.579
2T=18.340
2T=19.100
2T=20.259
2T=21.292
2T=22.767
2T=24.238
2T=27.411
2T=28.538
2T=29.863
2T=30.829
2T=31.810
2T=35.195
2T=36.220
2T=37.322
2T=37.989
2T=38.786
2-Theta - Scale

Figure-4