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(54) **Title**: IMPROVED PROCESS FOR THE PREPARATION OF DULOXETINE AND ITS PHARMACEUTICALLY ACCEPTABLE SALT

(57) **Abstract**: The present invention relates to an improved process for racemizing one of the enantiomers, or an enantiomerically enriched mixture, of an optically active compound (S)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine, a key intermediate used for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2- thienyl) propanamine (duloxetine) or its hydrochloride salt. Moreover, the present invention also relates to an improved process for the preparation of (*S*)-*N*-methyl-3- (1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) or its hydrochloride salt having low content of undesired R-isomer and chiral purity not less than 99%.

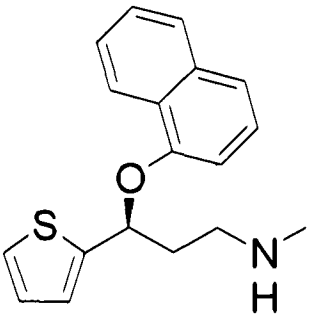
IMPROVED PROCESS FOR THE PREPARATION OF DULOXETINE AND ITS PHARMACEUTICALLY ACCEPTABLE SALT

Field of Invention

The present invention relates to an improved and environment friendly process for racemizing one of the enantiomers, or an enantiomerically enriched mixture of an optically active compound (S)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine, a key intermediate used in the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) or its hydrochloride salt. Moreover, the present invention also relates to an improved process for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) or its hydrochloride salt.

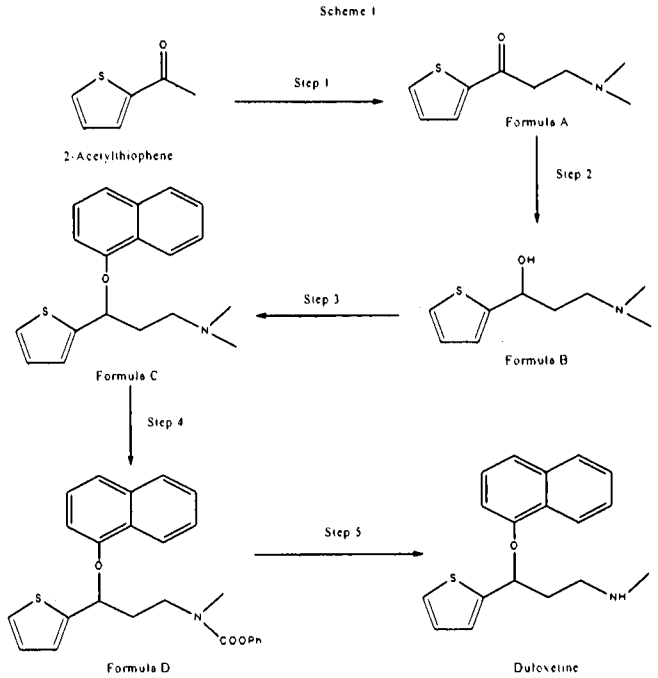
Background of the Invention

Duloxetine belongs to the class of selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors and exhibits antidepressant activity. Duloxetine selectively prevents the reuptake of 5-HT and NE *via* transporter complexes on the pre-synaptic membrane, thereby increasing the level of these neurotransmitters within the synaptic cleft. Duloxetine is chemically known as (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine and represented by Formula I:



Formula I

Duloxetine and its pharmaceutically acceptable salts are first disclosed in US Patent No. 5,023,269 and 4,956,388 as shown in Scheme 1.



In the said patent, duloxetine and its pharmaceutically acceptable salt are prepared by converting 2-acetylthiophene to 3-dimethylamino-1-(2-thienyl)-1-propanone hydrochloride of Formula A via Mannich reaction, followed by reducing the resultant to obtain the corresponding alcohol of *N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula B. The resulting alcohol *i.e.* *N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula B is then reacted with 1-fluoronaphthalene in presence of sodium hydride to form *N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine of Formula C, which undergoes demethylation to form carbamate intermediate of Formula D, which after hydrolysis yields duloxetine.

US'269 patent does not provide specific method for obtaining the optically active isomer *i.e* S-isomer of duloxetine. According to the description of US'269, optically active isomers of the racemates may be prepared from optically active precursors or by resolving the racemic mixture. For resolution of aryloxy propanamines compounds, the resolving agent disclosed are dibenzoyl-D and L-tartaric acid. Further, it has been observed that dibenzoyl-D and L-tartaric acid are poor resolving agents for resolving N, N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine compound. Further, US'269 patent is completely silent about the chiral purity of the final racemic duloxetine hydrochloride.

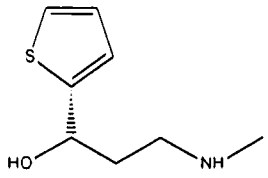
US 5,362,886 and WO2004031168 discloses chiral resolution of racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine by the use of (S)-(+) mandelic acid and (-)-2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid respectively. US'886 describes the preparation of duloxetine by the chiral resolution of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine using (*S*)-mandelic acid, followed by reaction with 1-fluoronaphthalene to obtain *N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine. The resulting *N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine is demethylated using phenyl chloroformate followed by basic hydrolysis to obtain (S)-duloxetine, which is further converted to its hydrochloride salt. The main drawback of the process disclosed in the US'886 is that the said patent nowhere discloses the racemization of undesired (*R*)-enantiomer that remains in the mother liquor. Furthermore, it has been observed that duloxetine hydrochloride prepared by the said process is found to contain R-enantiomer as an impurity in more than 0.6% even after recrystallization. Beside this, US'886 patent does not specifically disclose the enantiomeric excess of duloxetine hydrochloride prepared according to 'Preparation 2' from the (S)-(+)-N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine phosphoric acid salt, and the yield of duloxetine hydrochloride is also very poor (overall yield 33%).

WO2007045405 discloses process for the preparation of duloxetine and its pharmaceutically acceptable salt by reacting N, N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine with 1-fluoronaphthalene using 1,3-dimethyl-2-oxo-hexahydropyrimidine (DMPU) as a solvent at a temperature 70 to 120°C to form N-methyl duloxetine, which is further isolated as oxalate salt. The resulting N-methyl duloxetine oxalate undergoes hydrolysis, resolution with tartaric acid and demethylation to form duloxetine, which is further converted to its hydrochloride salt. The main drawback of the process is the use of 1,3-dimethyl-2-oxo-hexahydropyrimidine (DMPU) as a solvent, which makes the process unsuitable on commercial scale as this solvent can cause irritation to the skin, eyes and respiratory tract. The other drawback is the resolution in the final stage with costly chiral acid and consumption of the expensive 1-fluoronaphthalene compound, which not only affect the yield of the final duloxetine hydochloride, but also makes the process costly and uneconomical on large scale.

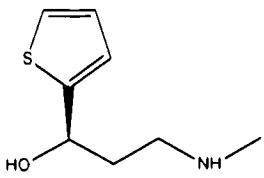
WO2007098250 and Org. Pro. Res. & Dev. 2006 (10) 905–913 provides the process for resolution of racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine and racemization of undesired *R*-enantiomer in the presence of acid in an organic solvent. The preferred acid is selected from the group consisting of hydrochloric acid and sulphuric acid. However, the examples disclosed in WO'250 require more than 20 hours during the racemization, which increases reaction cycle and hence it is unsuitable on industrial scale.

WO2006045255 discloses the resolution of the duloxetine using D-tartaric acid. Similarly, WO2004056795 discloses resolution of racemic duloxetine using various chiral acids like mandelic acid, tartaric acid, di-*p*-toluyl tartaric acid, dibenzoyl tartaric acid and camphor sulphonic acid with preference to di-*p*-toluyl tartaric acid and the conversion of the resulting salt either into free base or other addition salts like hydrochloride etc. Use of resolving agent in the final step is not very economical due to the loss of undesired (R)-isomer of duloxetine, which is not environment friendly as well as chemically unviable as the reagents, solvents etc. used for the preparation of the racemic duloxetine are waste compared to the resolution carried out at the intermediate stage *i.e.* immediately after the formation of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine. Thus, the process disclosed in WO'255 and WO'795 inturn requires enhanced raw material consumption, conversion of chiral salts into duloxetine base, its isolation and further conversion into addition salts, increases unit operations, thus makes the process industrially unsuitable.

WO2004005307 discloses a process for the preparation of duloxetine and its pharmaceutically acceptable salt by subjecting the enantiomeric mixture of (S)-(-)-3-N-methylamino-1-(2-thienyl)-1-propanol and (R)-(+)-3-N-methylamino-1-(2-thienyl)-1-propanol of Formula Ia and Ib

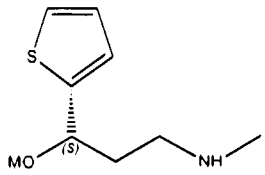


Formual Ia



Formula Ib

with (-)-2,3:4,6-di-O-isopropylidene-2-keto-l-gulonic acid to form the corresponding diasteromeric salt, liberating the enantiomerically enriched amine of Formula Ia using base, converting the said amine to enantiomerically enriched alkoxide of Formula Ic,



Ic

Formula Ic

followed by reaction with 1-halonaphthalene to form duloxetine. The main drawback of the process is the use of chiral acid (-)-2,3:4,6-di-O-isopropylidene-2-keto-l-gulonic acid as a resolving agent, which itself is sensitive to the moisture and acidic condition, and require special handling technique, thus adding the additional utility cost and skilled manpower.

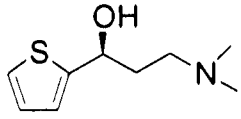
Thus, the processes disclosed in the above mentioned prior arts are not industrially feasible and cost effective to obtain duloxetine or its hydrochloride salt in high chiral purity as during the chiral resolution of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine intermediate, the desired (S)- isomer is separated from the undesired (R)- isomer and the undesired (R)-isomer is waste, as a result overall yield of the duloxetine reduces, which makes the process industrially inefficient. Beside this, the final duloxetine product prepared by most of the prior art processes show the presence of therapeutically inactive R-isomer, which result in the contamination of the final duloxetine product and in extreme cases might even be harmful to a patient being treated with a dosage form of the said API. Further, the process disclosed in the prior arts is not industrially feasible and cost effective as it requires substantial work up and treatment using multiple solvent systems for the racemization of undesired *R*-isomer. This not only lowers the yield on plant scale, but also increases the overall production cost of the final duloxetine hydrochloride.

Therefore, there is a need for a cost effective and environment friendly process for the preparation of duloxetine and its hydrochloride salt in high chiral purity, wherein isolation and purification of some intermediate is avoided, thereby involving fewer steps and to obtain the final duloxetine product containing low amount of undesired R-isomer.

Object and Summary of the Invention

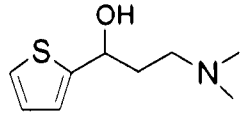
It is a principal object of the present invention to alleviate the drawbacks of the prior art processes by providing an industrially applicable, cost effective and environmental friendly process for racemization of an optically active compound (S)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine and the use of said optically active compound for producing (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) or its hydrochloride salt in high chiral purity and having low amount of undesired R-isomer.

In accordance with an embodiment, the present invention provides an improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt,



Formula III

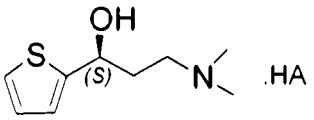
a key intermediate used for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) of Formula I or its hydrochloride salt, the process comprising the steps of resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt



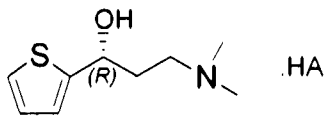
Formula II

with an optically active acid in an organic solvent to obtain diastereomeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III'

and diasteromeric salt of undesired (R)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV'



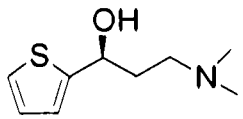
Formula III'



Formula IV'

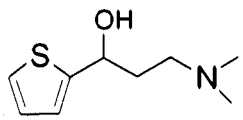
wherein HA is optically active acid, racemizing the (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with an acid in suitable solvent to form racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine and resolving the racemic *N*, *N*-dimethyl-3 -(2-thienyl)-3-hydroxypropanamine with optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

In accordance with another embodiment, the present invention provides an improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt,



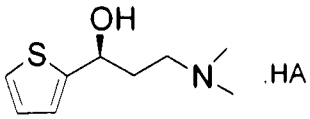
Formula III

a key intermediate used for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) of Formula I or its hydrochloride salt, the process comprising the steps of resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt

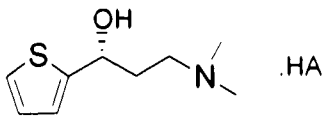


Formula II

with an optically active acid in an organic solvent to obtain diasteromeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III' and diasteromeric salt of undesired (R) -*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV'

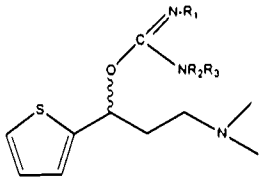


Formula III'



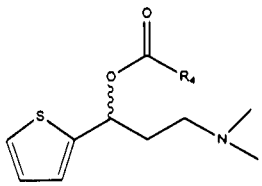
Formula IV'

wherein HA is an optically active acid, treating the (R)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with a coupling agent in a suitable solvent to form an isourea ether of Formula V



Formula V

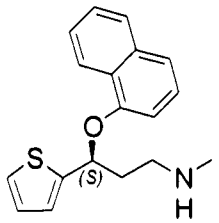
wherein R_1 and R_2 independently represent an optionally substituted alkyl, cycloalkyl, aralkyl or aryl radical; and R_3 in addition to these radicals, can also be a hydrogen, converting the resultant isourea ether of Formula V with the carboxylic acid in an aprotic solvent to obtain corresponding ester of Formula VI,



Formula VI

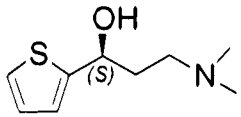
wherein R_4 represents hydrogen or an optionally substituted saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals or an optionally substituted araliphatic or aromatic hydrocarbon radicals and hydrolysis of the corresponding ester of Formula VI in presence of base using protic solvent, to obtain racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine, followed by resolving the racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine with an optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

In accordance with yet another embodiment, the present invention provides an improved process for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) of Formula I or its hydrochloride salt,



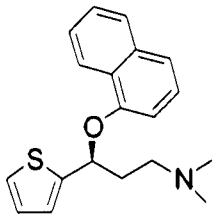
Formula I

the process comprising the steps of reacting desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt;



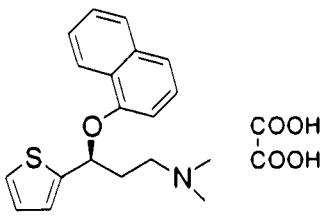
Formula III

with 1-fluoronaphthalene in presence of base and a solvent at temperature ranging from 35 to 55°C to obtain (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII;



Formula VII

treating the resultant (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII with oxalic acid in an organic solvent to obtain (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VIII,



Formula VIII

demethylating (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate of Formula VIII using chloroformate preferably phenyl chloroformate in presence of a base followed by hydrolysis of the resultant carbamate compound using

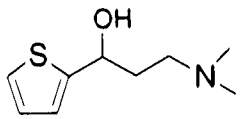
alkali metal hydoxide in presence of hydrocarbon solvent to obtain duloxetine of Formula I *in situ* and converting the resulting duloxetine base to its hydrochloride salt, optionally purifying the crude duloxetine hydrochloride to obtain pure duloxetine hydrochloride.

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

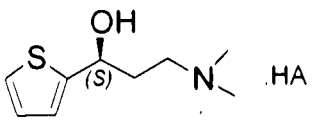
In accordance with an embodiment, the present invention provides an improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt, a key intermediate used for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) of Formula I or its hydrochloride salt, the process comprising the steps of;

(a) resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt

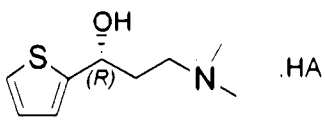


Formula II

with an optically active acid to obtain diasteromeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III' and diasteromeric salt of undesired (R) -*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV,'



Formula III'



Formula IV'

wherein HA is an optically active acid;

(b) racemizing (R)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with an acid in a suitable solvent to form racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine, resolving the racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine with an optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

The optically active acid used herein is selected from the group comprising of mandelic acid, tartaric acid, camphor sulphonic acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid and the like. The solvent employed during the resolution is selected from a group comprising of alcohol such as methanol, ethanol, n-propanol, isopropanol n-butanol, isobutanol and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, and the like; ethers such as diethyl ether, methyl tertiary butyl ether, tetrahydrofuran, dioxane and the like; esters such as ethyl acetate, isopropyl acetate, butyl acetate and the like; or mixture thereof. The resolution takes place at a temperature between 40-100°C, preferably 45 to 90°C, more preferably between 70-80°C for 1-4 h, preferably 1-2 h.

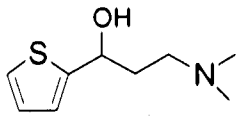
According to the present invention, the desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt is separated and the resulting mother liquor enriched with (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt is racemized using organic or inorganic acid or its mixture thereof. Preferably, the organic acid is selected from group comprising of formic acid, acetic acid, *p*-toluene sulphonic acid, trifluoroacetic acid, camphorsulphonic acid and the like. Preferably, the inorganic acid is selected from the group comprising of hydrochloric acid, hydrobromic acid, perchloric acid, phosphoric acid, sulphamic acid, nitric acid, boron trifluoride, potassium hydrogen sulphate and the like. A mixture of organic and inorganic acid such as hydrobromic acid in acetic acid can also be used.

The solvents used for racemization are selected from the group comprising of chlorinated hydrocarbons, alicyclic hydrocarbons, amides, sulphoxide, nitriles and the like or mixture thereof. Preferably the solvent is selected from chloroform, dichloromethane, cyclohexane, dimethylformamide, dimethylacetamide,

dimethylsulphoxide, acetonitrile, propionitrile and the like or mixture thereof. The racemization takes place at a temperature between 20-100°C, preferably 20 to 60°C, more preferably between 20-30°C for 4-10h, preferably 6-8h. Preferably the reaction temperature and reaction time depends upon the type of solvent chosen for the racemization.

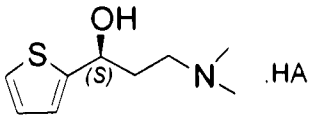
In accordance with another embodiment of the present invention, there is provided an improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt, a key intermediate used for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) of Formula I or its pharmaceutically acceptable salt, the process comprising the steps of:

(a) resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt

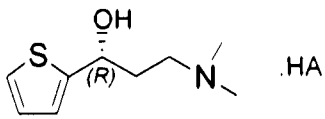


Formula II

with an optically active acid to obtain diasteromeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III' and diasteromeric salt of undesired (R) -*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV'



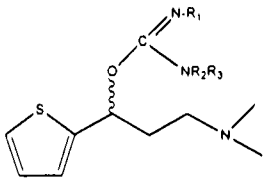
Formula III'



Formula IV'

wherein HA is an optically active acid

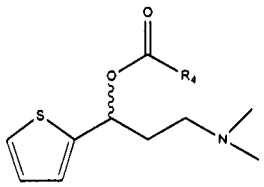
(b) treating (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with a coupling agent in suitable solvent to form an isourea ether of Formula V,



Formula V

wherein R_1 and R_2 independently represent an optionally substituted alkyl, cycloalkyl, aralkyl or aryl radical; and R_3 in addition to these radicals, can also additionally be hydrogen;

(c) converting the resultant isourea ether of Formula V with a carboxylic acid to obtain corresponding ester of Formula VI,



Formula VI

wherein R_4 represent hydrogen or an optionally substituted saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals or an optionally substituted araliphatic or aromatic hydrocarbon radicals, and

(d) hydrolysis of the corresponding ester of Formula VI in presence of base using protic solvent, to obtain racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine, followed by resolving the racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine with an optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

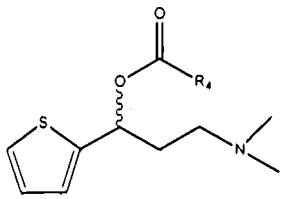
The optically active acid used for resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt is selected from the group comprising of mandelic acid, tartaric acid, camphor sulphonic acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid and the like. The suitable solvent employed during the resolution is selected from a group comprising of alcohols such as methanol, ethanol, n-propanol, isopropanol n-butanol, isobutanol and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, and the like; ethers such as diethyl ether, methyl tertiary butyl ether, tetrahydrofuran, dioxane and the like; esters such as ethyl acetate, isopropyl acetate, butyl acetate and the like; or mixture thereof. The

resolution takes place at a temperature between 40-100°C, preferably 45 to 90°C, more preferably between 70-80°C for 1-4 h, preferably 1-2 h.

The resulting mother liquor enriched with (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt is treated with a coupling agent which is selected from a group comprising of *N,N'*-dicyclohexylcarbodimide, *N,N'*-diisopropylcarbodiimide, N,N'-di-tert-butylcarbodiimide, 1,3-di-p-tolylcarbodiimide, bis(3-chloro-2-methyl phenyl)carbodiimide, bis (o-tolylcarbodiimide), 1-*tert*-butyl-3-ethylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, bis(2,6-diisopropylphenyl)carbodiimide, bis(2,6-diethylphenyl)carbodiimide, N-cyclohexyl-N'-isopropylcarbodiimide, N-methyl-N'-phenylcarbodiimide, 1-cyclohexyl-3-(2-(4-morpholinyl)ethyl)carbodiimide, N,N'-dicyclohexyl-N-methylcarbodiimidium iodide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and the like. The reaction optionally takes place in presence of catalyst selected from metal chloride preferably copper (I) and copper (II) halide, titanium (IV) alcoholates, titanium (IV) halides, zinc halide, tin halide, iron halide, boron halide, chromium chloride and the like, preferably copper (I) or copper (II) halide.

The solvent used for coupling reaction is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene and the like; chlorinated hydrocarbons such as chloroform, dichloromethane, chlorobenzene and the like; esters such as ethyl acetate, propyl acetate and the like; ethers such as methyl tertiary butyl ether, tetrahydrofuran, 1,4-dioxane and the like; amides such as dimethyl formamide, dimethylacetamide and the like; sulphoxide such as dimethylsulphoxide and the like, nitriles such as acetonitrile, propionitrile and the like or mixture thereof. The reaction is carried out under inert atmosphere at temperature 0-200°C, preferably 20-100°C for 15-25 h, preferably 20-22 h.

The resulting isourea ether of Formula V is then reacted with the carboxylic acid in an aprotic solvent to obtain corresponding ester of Formula VI;



Formula VI

wherein R_4 represent hydrogen or an optionally substituted saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals or an optionally substituted araliphatic or aromatic hydrocarbon radicals.

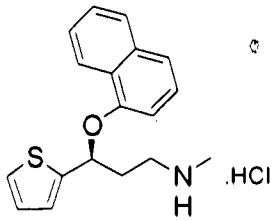
The carboxylic acid is selected from the group comprising of formic acid, acetic acid, benzoic acid, methane sulphonic acid, *p*-toluene sulphonic acid and the like. The aprotic solvent used for esterification is selected from, aliphatic hydrocarbons such as hexane, cyclohexane and the like; aromatic hydrocarbons such as toluene, xylene and the like; chlorinated hydrocarbons such as chloroform, dichloromethane and the like; esters such as ethyl aceate, propyl acetate, butyl acetate and the like; ethers such as tetrahydrofuran or dioxane and the like; amides such as dimethyl formamide and the like; sulphoxide such as dimethylsulphoxide and the like, nitriles such as acetonitrile, propionitrile and the like or mixture thereof.

The resulting ester of Formula VI undergoes hydrolysis to obtain racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II in presence of a base and optionally in a solvent. The base is selected from the group comprising of an alkali metal or alkaline earth metal hydroxide, bicarbonates, carbonate and the like, wherein alkali metal or alkaline earth metal is selected from a group comprising of lithium, sodium, potassium, magnesium, calcium, barium and the like. The solvent used herein is selected from protic solvents such as methanol, ethanol, propanol, butanol and the like.

According to the process described above, the racemic *N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine compound of Formula II is further resolved using optically active acid to give the diasteriomerically enriched salt of the optically pure acid. This salt is filtered and separated from the undesired (R) isomer to obtain

enantiomerically pure (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

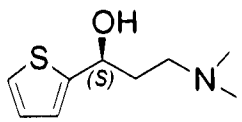
In accordance with yet another embodiment, the present invention also provides an improved process for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) of Formula I or its hydrochloride salt



Formula I

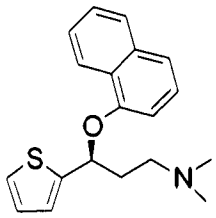
the process comprising the steps of

(a) reacting desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt



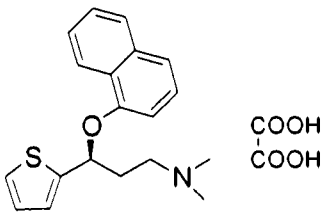
Formula III

with 1-fluoronaphthalene in presence of a base and a solvent at temperature ranging from 35 to 55°C to obtain (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII;



Formula VII

(b) treating (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII with oxalic acid to obtain oxalate salt of Formula VIII;



Formula VIII

(c) demethylating (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate of Formula VIII using chloroformate preferably phenyl chloroformate in presence of a base followed by hydrolysis of the resultant carbamate compound using alkali metal hydoxide in presence of hydrocarbon solvent to obtain duloxetine of Formula I *in situ*;

(d) converting the resulting duloxetine base to its hydrochloride salt and;

(e) optionally purifying the crude duloxetine hydrochloride to obtain pure duloxetine hydrochloride.

The reaction of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt with 1-fluoronaphthalene takes place in presence of a base, wherein the base is selected from organic or inorganic. The organic base is selected from diethylamine, triethylamine, pyridine and the like. The inorganic base is selected from the group comprising of alkali metal or alkaline earth metal hydroxide, hydride, carbonate and the like, wherein alkali metal or alkaline earth metal is selected from a group comprising of lithium, sodium, potassium, magnesium, calcium, barium and the like. The solvent used in the reaction is selected from the group comprising of amides such as dimethylformamide, dimethyl acetamide; sulphoxide such as dimethylsulphoxide and the like; esters such as ethyl acetate, propyl acetate, butyl acetate and the like or mixture thereof.

The reaction of (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III with 1-fluoronaphthalene takes place at temperature ranging from 35 to 55°C, preferably between 45-55°C without the use of potassium salt preferably potassium benzoate as disclosed in the US5362886 patent which not only controls the racemization, but also reduces the formation of undesired R-isomer, to obtain (*S*)-*N*,*N*'-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII, in higher purity.

The resulting (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII is converted into (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate salt of Formula VIII using organic solvent, wherein the organic solvent is selected from esters such as ethyl acetate, propyl acetate, butyl acetate, isopropyl acetate and the like, chlorinated hydrocarbons such as chloroform, dichloromethane and the like or mixture thereof. The reaction takes place at temperature ranging from 20-80°C, preferably between 25-30°C for 4-7 h more preferably 5-6 h.

Alternatively, the preparation of (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate salt of Formula VIII is carried out without isolating intermediate compound (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII, thereby reduces a step during the synthesis of duloxetine hydrochloride.

The resulting (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate salt of Formula VIII undergoes demethylation *via* carbamate formation by treatment with chloroformate, preferably phenyl chloroformate using diisopropylamine as a base to obtain carbamate intermediate, which *in situ* is subjected to hydrolysis with an alkali metal hydoxide such as lithium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide barium hydroxide, cesium hydroxide and the like in an hydrocarbon solvents, preferably aromatic hydrocarbons selected from the group comprising of toluene, xylene, and the like, preferably in toluene to obtain duloxetine base, as an oily residue.

The resulting duloxetine base is further converted to duloxetine hydrochloride, free from the acidic impurity by treating the duloxetine free base with solvent preferably ethyl aceate followed by addition of concentrated hydrochloric acid. The resulting solid was washed with ethyl acetate till the pH of the filtrate becomes neutral (pH 6 to 7). Washing with excess of ethyl aceate of the crude duloxetine hydrochloride not only removes the residual hydrochloride, which adhere

on the surface of duloxetine hydrochloride molecules but also enhances the purity and stability of the final duloxetine hydrochloride.

The resulting crude duloxetine hydrochloride is then optionally purified by treating the resultant with ester solvent, preferably ethyl acetate followed by addition of water to obtain pure duloxetine hydrochloride.

The racemic *N,N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II used as starting material is prepared from 2-acetyl thiophene by the methods known in the prior arts.

In conclusion, the present invention provides a safe, environment and industrial friendly and commercially viable process for the production of duloxetine hydrochloride having low content of undesired R-isomer and chiral purity not less than 99%.

The following examples are provided only to exemplify, but not to limit the scope of the invention.

Example 1

Preparation of *N,N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine

150 g of 3-dimethylamino-1-(2-thienyl)-1-propanone hydrochloride was taken in 300 ml methanol. To the resulting mixture, 300 ml water and sodium hydroxide solution (27.3g in 45ml water) was added and stirred for few minutes. To the resulting mixture, 15.5 g of sodium borohydride was added. The reaction mass was heated at 35-40°C under stirring for 2 hour. After completion of reaction, methanol was distilled off and the reaction mass was cooled to room temperature. Dichloromethane was added and the reaction mass was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with water. The organic layer was distilled under vacuum to obtain the title compound.

Yield: 90-95%.

Example 2

Preparation of (S)-(-)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine mandelate

N,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine obtained from Example 1 was taken in 315 ml of ethanol and 60 ml of methyl tertiary butyl ether at room temperature and 77g of *S*-(+)-mandelic acid was added. The reaction mixture was heated at 70-80°C under stirring for 1 hr. The reaction mass was cooled to 15-20°C under stirring for 2h and the resulting solid was filtered, washed with methyl tertiary butyl ether and dried under vacuum. To the resulting solid, 180 ml ethanol and 45 ml methyl tertiary butyl ether was added and heated to 70-75°C under stirring for 1 h. Cool the resulting solution to 15-20°C and stirred for 2h. The solid precipitated was filtered, washed with methyl tertiary butyl ether and dried under vacuum at 40-45°C for 7-8h to obtain title compound in about 99% ee.

Yield: 33-35%;

Example 3

Preparation of racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine *via* racemization of undesired enantiomer of N, N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine

5.0g of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine(*R*:*S*/75:25) was dissolved in 5 ml of dichloromethane. 50ml of 20% phosphoric acid was added to the resulting solution at room temperature. The reaction mixture was allowed to stir at same temperature for 6-8h. The progress of reaction was monitored by HPLC. After the completion of reaction, aqueous layer was basified to pH 10.5 with aqueous ammonia. The aqueous layer was extracted with dichloromethane (2 x10 ml) and the organic layer was mixed. The solvent was distilled to obtain racemic alcohol (R:S) (50: 50)

Yield: 90% .

Example 4

Preparation of racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine *via* racemization of undesired enantiomer of N, N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine

5.0g of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine (*R*:*S*/80:20) was dissolved in 40 ml of dichloromethane. 10 ml of 20% concentrated hydrochloric acid was added to the resulting solution at room temperature. The reaction mixture was allowed to stir at same temperature for 6h. The progress of reaction was monitored by HPLC. After the completion of reaction, dichloromethane was added to the aqueous layer and was basified with sodium hydroxide solution till pH 9-9.5. The two layers were separated and the organic layer was distilled to obtain racemic alcohol (R:S) (50: 50)

Yield: 90% .

Example 5

Preparation of racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine *via* racemization of undesired enantiomer of N, N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine

5.0g of *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine mandelate salt (*R*:*S*/80:20) was taken in 50 ml water. To the resulting mixture 10 ml of concentrated hydrochloric acid was added and the resulting solution was stirred at room temperature. The reaction mixture was allowed to stir at same temperature for 8h. The progress of reaction was monitored by HPLC. After the completion of reaction, to the resulting mixture, dichloromethane was added and was basified with sodium hydroxide solution till pH 9-9.5. The two layers were separated and the organic layer was distilled under vacuum to obtain to obtain racemic alcohol (R:S) (50:50).

Example 6

Preparation of racemic *N, N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine via racemization of undesired enantiomer of N, N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine

0.2 gm of N, N-dimethyl-3-(2-thienyl)-3-hydroxypropanamine (R:S/75:25) was taken in anhydrous dioxane. To the resulting mixture 0.5 gm (1.2mol) of dicyclohexylcarbodimide and 50 mg copper chloride (0.18 mol) was added and heated at 50°C for 48h. To the resulting mixture, 1.37 gm of formic acid (2.8 mol) was added at room temperature and stirred for 30 minutes. The resulting mixture was heated to reflux for 20h and allowed to cool. Dicyclohexylurea was filtered off and the resulting filtrate was distilled off to obtain ester. The resulting oily ester was taken in methanol and 5 ml of 10% sodium hydroxide solution was added. After completion of the reaction, solvent was distilled off and the desired product was extracted from dichloromethane. Solvent was distilled off to obtain racemic alcohol. (R:S) (54:46).

Example 7

Preparation of *N,N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine

150 g of 3-dimethylamino-1-(2-thienyl)-1-propanone hydrochloride was taken in a mixture of 300 ml methanol and 300 ml water. To the resulting mixture, sodium hydroxide solution (27.3g in 45ml water) was added and stirred for few minutes. To the resulting mixture, 15.5 g of sodium borohydride was added. The reaction mass was heated at 35-40°C under stirring for 2 hour. After completion of reaction, methanol was distilled off and the reaction mass was cooled to room temperature. Dichloromethane was added and the reaction mass was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with water. The organic layer was distilled under vacuum to obtain title compound which is used as such in Example 8.

Example 8

Preparation of (S)-(-)-*N,N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine mandelate

N,N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine obtained from Example 7 was taken in 315 ml of ethanol and 60 ml methyl tertiary butyl ether at room temperature and 77g of S-(+)-mandelic acid was added. The reaction mixture was heated at 70-80°C under stirring for 1 hr. The reaction mass was cooled to 15-20°C under stirring for 2 hr and the resulting solid was filtered, washed with methyl tertiary butyl ether and dried under vacuum. To the resulting solid, 180 ml ethanol and 45 ml methyl tertiary butyl ether was added and heated to 70-75°C under stirring for 1 hr. The resulting solution was cooled to 15-20°C and stirred for 2 hr. The resulting solid was filtered, washed with methyl tertiary butyl ether and dried under vacuum at 40-45°C for 7-8 hr to obtain title compound in about 99% ee.

Yield: 33-35%;

Example 9

Preparation of (*S*)-*N,N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

200 g of N,N-Dimethyl-3-hydroxy-3-(2-thienyl) propanamine mandelate was mixed with 250 ml water and 500ml dichloromethane. The pH of the reaction mixture was adjusted between 11-12 using 30% sodium hydroxide solutions. The reaction mixture was stirred at 20-25°C for 30 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (100 ml). The organic layers were combined and washed with water. The organic layer was concentrated under vacuum. The resulting mass was taken in 450ml dimethylsulphoxide and was stirred at room temperature. To this, 28.4 g sodium hydride was added and the mixture was stirred. To the resulting mass, 103.6 g of 1- fluoronaphthalene was added and the reaction mass was stirred at 48-50°C for 14-16 hours. After completion of the reaction, the reaction mass was cooled to room temperature. The resulting mass was transfer to another flask containing water at temperature 5-10°C. The pH of the resulting mixture was adjusted to 5-6 using acetic acid and cyclohexane was added under stirring at 10-15°C. The layers were separated and to the aqueous layer, toluene was added, pH was adjusted between 10-11.0 using 30% sodium hydroxide solution. The resulting mass was stirred at room temperature for few minutes. The organic layer was separated and aqueous layer was extracted with toluene. The organic layers were combined and

distilled out. The resulting reaction mass was taken in 1400ml ethyl acetate at room temperature and 71.0 g oxalic acid was added. The reaction mass was stirred for 5hr at room temperature. The resulting solid was filtered and washed with ethyl acetate and dried under vacuum at 50-55°C for 4hr to obtain title compound.

Yield: 90-92%

Example 10

Preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine hydrochloride (crude Duloxetine hydrochloride)

50 g of (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate was taken in 200 ml toluene and 100 ml water at room temperature. The pH of the resulting mixture was adjusted between 11-12 using 30% sodium hydroxide solution. The resulting mass was heated at 40-45°C for 1 hour. The reaction mass was cooled to room temperature, filtered and washed with toluene. The layers were separated and the aqueous layer was extracted with toluene. The organic layer is combined, wash with water and distilled under vacuum at 50-55°C. To the resulting oily residue, 200 ml toluene and 8.g diisopropyl ethylamine was added at room temperature. The resulting mixture was cooled at 15-20°C and 23.2 g of phenyl chloroformate was added. The reaction mass was stirred for 2 hr, sodium bicarbonate solution (1%) was added and the resulting mixture was heated at 40-45°C for 1 hr. The resulting mixture was cooled to room temperature and the layers were separated. The organic layer was first washed with 0.5 N HCl solutions and then with 1% $NaHCO_3$ solution. Finally the organic layers was combined and washed with water. To the resulting organic layer, 32.9 g potassium hydroxide was added and heated at 80-85°C for 7 hr. The resulting mixture was cooled to room temperature and water was added under stirring. The organic layers were separated, and wash the aqueous layer with toluene. The organic layers were combined and filter through hyflo. The resulting filtrate was washed with water till pH 8-9 and the layers were separated. The organic layer was washed with water and distilled under vacuum to obtain oily residue. The resulting oily mass was taken in 500 ml ethyl acetate, cool to 0-5°C and concentrated hydrochloric acid was added, stirred for 1-2 hr as a result solid

precipitate off. The resulting solid was filtered, washed with ethyl acetate and dried under vacuum 40-45°C for 12-13 hr to obtain title compound.

Yield: 62-66%; Chiral purity: 99.5%.

Example 11

Purification of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine hydrochloride (pure duloxetine hydrochloride)

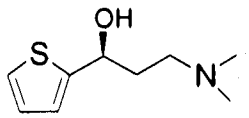
100 g crude duloxetine hydrochloride was taken in 300 ml ethyl acetate and heated to 60-65°C under stirring followed by addition of 20 ml water. The reaction mass was stirred for few minutes, then cooled to room temperature and 700 ml ethyl acetate was added within 1hr hr to precipitate the solid. The resulting solid was stirred for 2 hr at room temperature, filtered, washed with ethyl acetate and dried under vacuum oven at 40-45oC for 12-13 hr to obtain pure title compound.

Yield: 85-90% Chiral purity: 99.8%.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modification and variations would present themselves to those skilled in the art without departing from the scope and sprit of this invention.

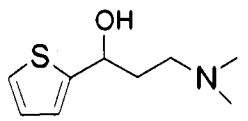
We claim:

1. An improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt, a key intermediate used in the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine (duloxetine) of Formula I or hydrochloride salt the process comprising the steps of:



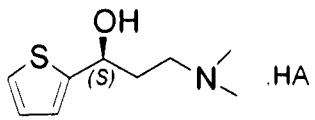
Formula III

(a) resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt

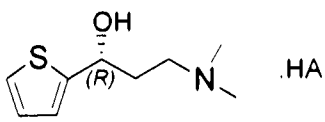


Formula II

with an optically active acid in an organic solvent to obtain diasteromeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III' and diasteromeric salt of undesired (R)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV'



Formula III'



Formula IV'

wherein HA is an optically active acid;

(b) racemizing the (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with an acid in a suitable solvent to form racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine; and

(c) resolving the racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine with an optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

2. The process according to claim 1(a), wherein the optically active acid is selected from the group comprising of mandelic acid, tartaric acid, camphor sulphonic acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid.

3. The process according to claim 1(a), wherein the organic solvent is selected from the group comprising of alcohols, ketones, ethers, esters and mixture thereof.

4. The process according to claim 3, wherein the organic solvent is selected from the group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, methyl ethyl ketones, methyl isobutyl ketones, methyl tertiary butyl ether, tetrahydrofuran, dioxane, ethyl acetate, isopropyl acetate, butyl acetate or mixture thereof.

5. The process according to claim 1(a), wherein the resolution takes place at a temperature between 40-100°C for 1-4 h.

6. The process according to claim 1(b), wherein the racemization of (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt is performed in presence of an acid in a suitable solvent.

7. The process according to claim 6, wherein the acid is selected from the group comprising of organic or inorganic acid or mixture thereof.

8. The process according to claim 7, wherein the organic acid is selected from the group comprising of formic acid, acetic acid, *p*-toluene sulphonic acid, trifluoroacetic acid, camphorsulphonic acid.

9. The process according to claim 7, wherein the inorganic acid is selected from the group comprising of hydrobromic acid, hydrochloric acid, perchloric acid, phosphoric acid, sulphamic acid, nitric acid, boron trifluoride, potassium hydrogen sulphate.

10. The process according to claim 7, wherein the mixture of organic and inorganic is hydrobromic acid along with acetic acid.

11. The process according to claim 6, wherein the solvent is selected from the group comprising of chlorinated hydrocarbons, alicyclic hydrocarbons, amides, sulphoxide, nitriles, water or mixture thereof.

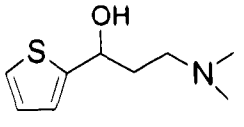
12. The process according to claim 11, wherein the solvent is selected from chloroform, dichloromethane, cyclohexane, dimethylacetamide, dimethylformamide, dimethylsulphoxide, acetonitrile, propionitrile or mixture thereof.

13. The process according to claim 1(b), wherein the racemization is carried out at temperature ranging from 20 to 100°C.

14. The process according to claim 1(b), wherein the racemization is carried out for 4 to 10 hr.

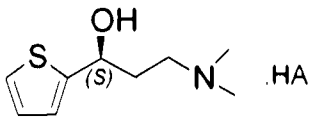
15. An improved process for producing (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III or its salt, a key intermediate used in the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine) of Formula I or its hydrochloride salt, the process comprising the steps of;

(a) resolving *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula II or its salt

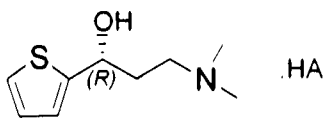


Formula II

with an optically active acid in an organic solvent to obtain diasteromeric salt of desired (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula III' and diasteromeric salt of undesired (R) -*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine salt of Formula IV'



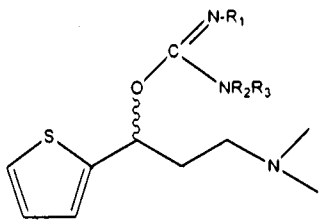
Formula III'



Formula IV'

wherein HA is an optically active acid;

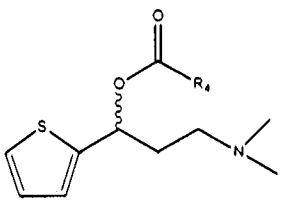
(b) treating (R)-*N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine or its salt with a coupling agent in a suitable solvent to form an isourea ether of Formula V



Formula V

wherein R_1 and R_2 independently represent an optionally substituted alkyl, cycloalkyl, aralkyl or aryl radical; and R_3 in addition to these radicals, can also be hydrogen;

(c) treating the resulting isourea ether of Formula V with the carboxylic acid in an aprotic solvent to obtain corresponding ester of Formula VI;



Formula VI

wherein R_4 represent hydrogen or an optionally substituted saturated or unsaturated aliphatic or cycloaliphatic hydrocarbon radicals or an optionally substituted araliphatic or aromatic hydrocarbon radicals; and

(d) hydrolyzing the corresponding ester of Formula VI in presence of a base using protic solvent followed by resolving the racemic *N*, *N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine with an optically active acid to precipitate (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt.

16. The process according to claim 15(a), wherein the optically active acid is selected from the group comprising of mandelic acid, tartaric acid, camphor sulphonic acid, dibenzoyl tartaric acid, di-*p*-toluoyl tartaric acid.

17. The process according to claim 15(a), wherein solvent is selected from the group comprising of alcohols, ketones, ethers, esters and mixture thereof.

18. The process according to claim 17, wherein the solvent is selected from the group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, methyl ethyl ketone, methyl isobutyl ketone, methyl tertiary butyl ether, tetrahydrofuran, dioxane, ethyl acetate, isopropyl acetate, butyl acetate or mixture thereof.

19. The process according to claim 15(a), wherein the resolution takes place at a temperature between 40-100°C for 1-4 h.

20. The process according to claim 15(b), wherein the coupling agent is selected from the group comprising of *N,N'*-dicyclohexylcarbodimide, *N,N'*-diisopropylcarbodiimide, N,N-di-tert-butylcarbodiimide, 1,3-di-p-tolylcarbodiimide, bis(3-chloro-2-methyl phenyl)carbodiimide, bis (o-tolylcarbodiimide), 1-*tert*-butyl-3-ethylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, bis(2,6-diisopropylphenyl)carbodiimide, bis(2,6-diethylphenyl)carbodiimide, N-cyclohexyl-N'-isopropylcarbodiimide, N-methyl-N'-phenylcarbodiimide, 1-cyclohexyl-3-(2-(4-

morpholinyl)ethyl)carbodiimide, N,N'-dicyclohexyl-N-methylcarbodiimidium iodide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).

21. The process according to claim 15(b), wherein the solvent used for coupling is selected from the group comprising of, aromatic hydrocarbons, chlorinated hydrocarbons, esters, ethers, amides, sulphoxide, nitriles or mixture thereof.

22. The process according to claim 21, wherein the solvent is selected from the group comprising of toluene, xylene, chloroform, dichloromethane, ethyl aceate, propyl acetate, tetrahydrofuran, 1,4-dioxane, dimethyl formamide, dimethylacetamide, dimethylsulphoxide, acetonitrile, propionitrile or mixture thereof.

23. The process according to claim 15(b), wherein the coupling is carried out at temperature ranging from 0 to 200°C.

24. The process according to claim 23, wherein the coupling is carried out at temperature ranging from 20 to 100°C.

25. The process according to claim 15(c), wherein the carboxylic acid is selected from the group comprising of formic acid, acetic acid, benzoic acid, methane sulphonic acid and *p*-toluenesulphonic acid.

26. The process according to claim 15(c), wherein the aprotic solvent is selected from the group comprising of aliphatic hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, esters, ethers, amides, sulphoxide, nitriles or mixture thereof.

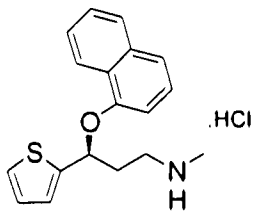
27. The process according to claim 26, wherein the solvent is selected from hexane, cyclohexane, toluene, xylene, chloroform, dichloromethane, ethyl acetate, propyl acetate, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, dimethylsulphoxide, acetonitrile, propionitrile or mixture thereof.

28. The process according to claim 15(d), wherein the base used for hydrolysis is selected from the group comprising of alkali metal or alkaline earth metal hydroxide, carbonate, bicarbonates.

29. The process according to claim 28, wherein the alkali metal or alkaline earth metal is selected from a group comprising of lithium, sodium, potassium, magnesium, calcium and barium.

30. The process according to claim 15(d), wherein the protic solvent is selected from the group comprising of methanol, ethanol, propanol, butanol or mixture thereof.

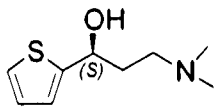
31. An improved process for the preparation of (*S*)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (duloxetine hydrochloride) of Formula I having low content of undesired R-isomer and chiral purity not less than 99%,



Formula I

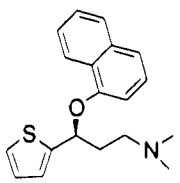
the process comprising the steps of:

(a) reacting the (S)-*N*,*N*-dimethyl-3-(2-thienyl)-3-hydroxypropanamine of Formula III or its salt, obtained from claim 1 or claim 14;



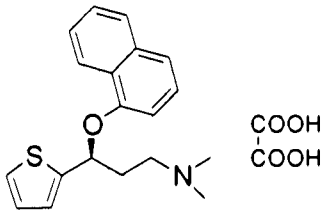
Formula III

with 1-fluoronaphthalene in presence of a base and solvent at temperature ranging from 35 to 55°C to obtain (*S*)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine of Formula VII;



Formula VII

(b) treating the resultant (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine of Formula VII with oxalic acid in an organic solvent to obtain (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate salt of Formula VIII;



Formula VIII

(c) demethylating (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate of Formula VIII using phenyl chloroformate in presence of a base followed by hydrolysis of the resultant carbamate compound using alkali metal hydoxide in presence of aromatic hydrocarbon to obtain duloxetine of Formula I *in situ;*

(d) converting the resulting duloxetine base to its hydrochloride salt; and

(e) optionally purifying the crude duloxetine hydrochloride to obtain pure duloxetine hydrochloride.

32. The process according to claim 31(a), wherein the base is selected from organic or inorganic.

33. The process according to claim 32, wherein the organic base is selected from the group comprising of diethylamine, triethylamine, diisopropylethylamine and pyridine.

34. The process according to claim 32, wherein the inorganic base is selected from the group comprising of alkali metal or alkaline earth metal hydroxide, carbonate and bicarbonate.

35. The process according to claim 34, wherein the alkali metal or alkaline earth metal is selected from a group comprising of lithium, sodium, potassium, magnesium, calcium and barium.

36. The process according to claim 31(a), wherein the solvent is selected from the group comprising of amides, sulphoxide, esters or mixture thereof.

37. The process according to claim 36, wherein the solvent is selected from the group comprising of dimethylformamide, dimethylacetamide, dimethylsulphoxide, ethyl acetate, propyl acetate, butyl acetate or mixture thereof.

38. The process according to claim 31(b), wherein the oxalate salt of Formula VIII is prepared in an organic solvent selected from the group comprising of esters, chlorinated solvents or mixture thereof.

39. The process according to claim 38, wherein the solvent is selected from the group comprising of ethyl acetate, propyl acetate, butyl acetate, isopropyl acetate, chloroform, dichloromethane or mixture thereof.

40. The process according the claim 31(c), wherein the demethylation of (*S*)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate of Formula VIII take in presence of base selected from diisopropylamine.

41. The process according to claim 31(c), wherein the hydrolysis of the carbamate compound is carried out in the presence of alkali metal hydoxide selected from the group comprising of sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, barium hydroxide and cesium hydroxide.

42. The process according to claim 31(c), wherein hydrolysis of the resultant carbamate compound is carried out in aromatic hydrocarbon selected from toluene or xylene.

43. The process according to claim 31(d), wherein the duloxetine hydrochloride is obtained by treating duloxetine free base with concentrated hydrochloric acid.

44. The process according to claim 31(e) the resulting crude duloxetine hydrochloride is optionally purified using ethyl acetate and water as solvent to obtain pure duloxetine hydrochloride.