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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF 4-HYDROXY ATOMOXETINE

(57) Abstract: The present invention relates to novel process for the preparation of 4-hydroxy Atomoxetine or its pharmaceutically acceptable salts thereof. The present invention also relates to novel intermediates used in the preparation of 4-hydroxy Atomoxetine.

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NOVEL PROCESS FOR THE PREPARATION OF 4-HYDROXY ATOMOXETINE

This Patent application claims priority from Indian Patent Applications 1800/CHE/2009 filed on July 30, 2009.

FIELD OF THE INVENTION

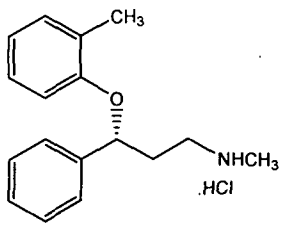
The present invention relates to novel process for the preparation of 4-hydroxy Atomoxetine or its pharmaceutically acceptable salts thereof.

The present invention also relates to novel intermediates used in the preparation of 4-hydroxy Atomoxetine.

The present invention also relates to crystalline 4-hydroxy Atomoxetine oxalate.

BACKGROUND OF THE INVENTION

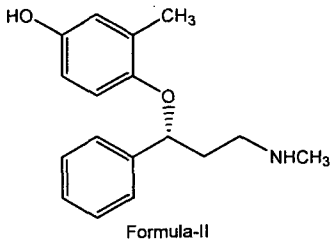
Atomoxetine, designated chemically as (-)-N-methyl-3-phenyl-3-(O-tolyloxy)-propylamine hydrochloride, is structurally represented by the compound of Formula-I and is indicated for the potential treatment of attention-deficit hyperactivity disorder (ADHD). This compound is manufactured, marketed and sold in the United States under the brand name Strattera.



Formula-I

Atomoxetine was first disclosed in US Patent No 4314081. The said patent disclosed Atomoxetine, its pharmaceutically acceptable salts, pharmaceutical composition containing them.

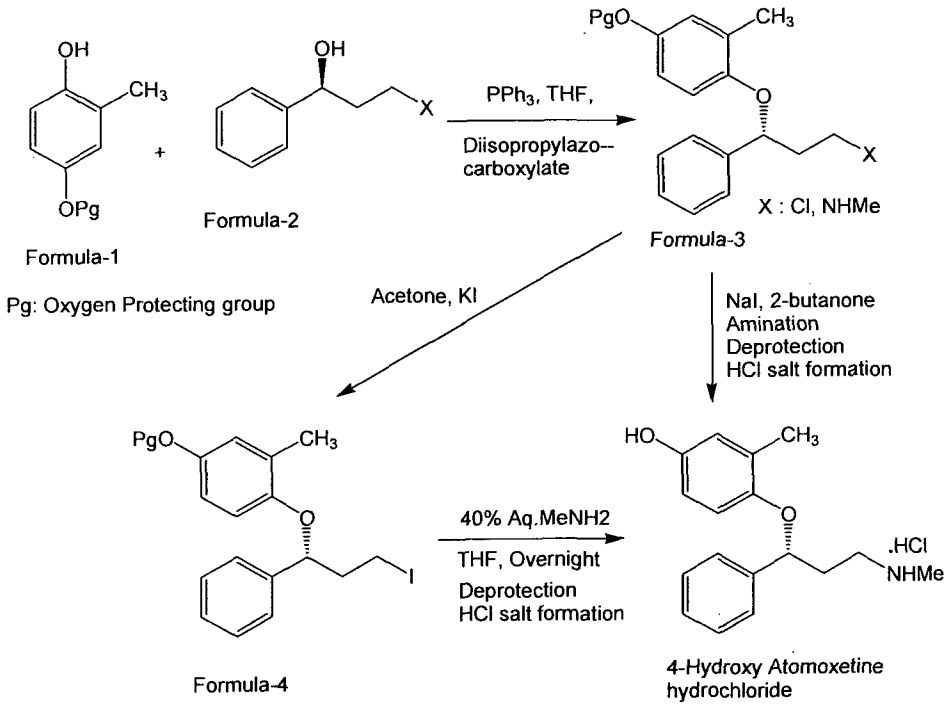
4-hydroxy Atomoxetine, chemically known as R-(-)-N-methyl-3-(2-methyl-4-hydroxyphenyl)oxy)-3-phenyl-1-aminopropane, structurally represented by Formula-II, is a metabolite of Atomoxetine.



Formula-II

4-hydroxy Atomoxetine was first disclosed in US Patent No 7384983, wherein the process involves reacting compound of Formula-1 with compound of Formula-2 in the presence of PPh3 and diisopropylazadicarboxylate in THF to give the aryl ether of Formula-3, which on iodination with (NaI in 2-butanone or KI in acetone), followed by amination with $MeNH_2$ and treatment with 0.1N HCl, afforded 4-hydroxy Atomoxetine hydrochloride.

SCHEME-I



There is a need for new synthetic methods for producing 4-hydroxy Atomoxetine, which process is cost effective, easy to practice, increase the yield and purity of the final compound.

The present invention relates to a novel process for the preparation of 4-hydroxy Atomoxetine using novel intermediates.

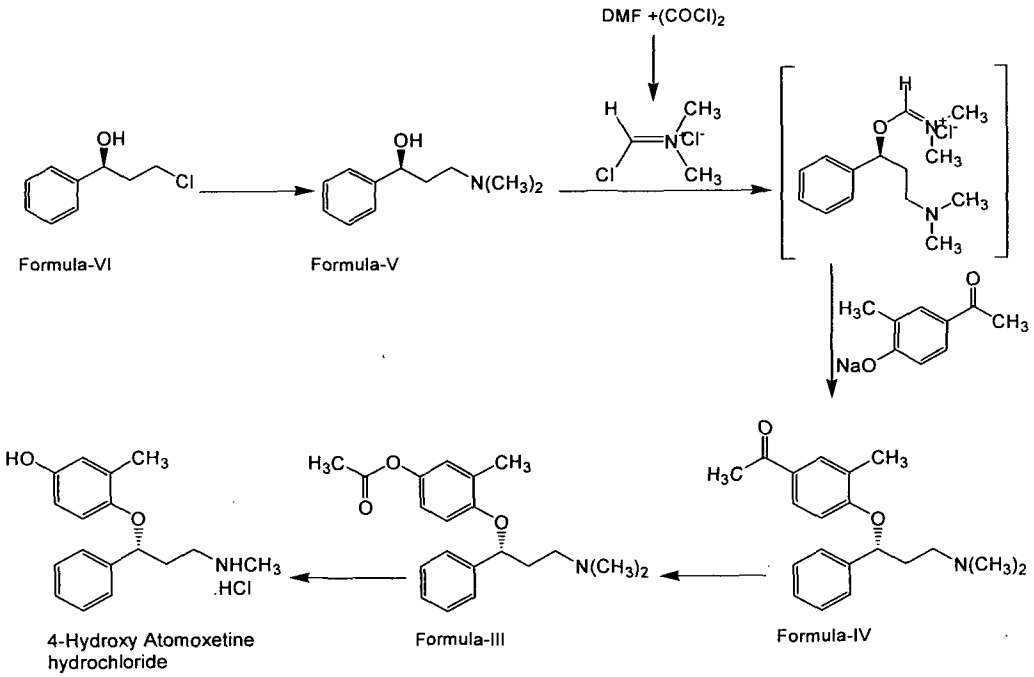
SUMMARY AND OBJECT OF THE INVENTION

The present invention relates to a novel and efficient process for the preparation of 4-hydroxy Atomoxetine or its pharmaceutically acceptable salts thereof.

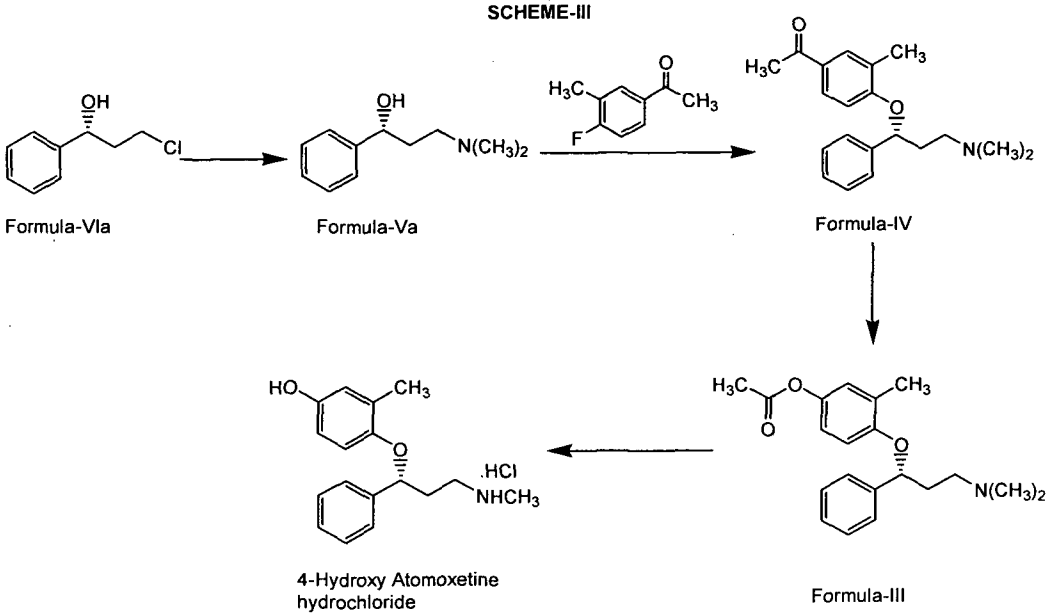
One aspect of the present invention provides a novel process for the preparation of 4-hydroxy Atomoxetine which comprises: a) reacting 3-chloro-1-phenylpropanol with dimethylamine to give N,N-dimethylamino-1-phenylpropanol, b) coupling compound obtained in step a) with 4-hydroxy-3-methyl acetophenone or 4-fluoro-3-methyl acetophenone to give N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane, c) oxidizing the compound obtained in step b) to give N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane, d) converting the compound obtained in step c) to 4-hydroxy Atomoxetine hydrochloride.

The schematic process for the preparation of 4-hydroxy Atomoxetine is as shown in scheme-II & III given below:

SCHEME-II



SCHEME-III



Formula-VIa Formula-Va Formula-IV

4-Hydroxy Atomoxetine hydrochloride Formula-III

Another aspect of the present invention provides (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane of compound of Formula-III.

In yet another aspect, the present invention provides (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane or its pharmaceutically acceptable salts of compound of Formula-IV or acid addition salt of compound of Formula-IVa.

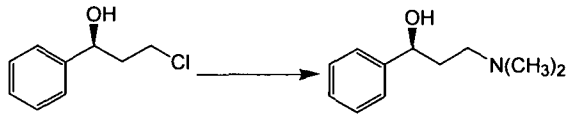
In yet another aspect, the present invention provides crystalline 4-hydroxy Atomoxetine oxalate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a novel process for the preparation of 4-hydroxy Atomoxetine which comprises reacting 3-chloro-1-phenylpropanol with dimethylamine to give N,N-dimethylamino-1-phenylpropanol, which is further reacted with 4-hydroxy-3-methyl acetophenone or 4-fluoro-3-methyl acetophenone to give N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane, which upon oxidation give N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane, followed by demethylation, hydrolysis and hydrochloride salt formation resulted in 4-hydroxy Atomoxetine hydrochloride.

One embodiment of the present invention provides novel process for the preparation of 4-hydroxy Atomoxetine hydrochloride which comprises the steps of:

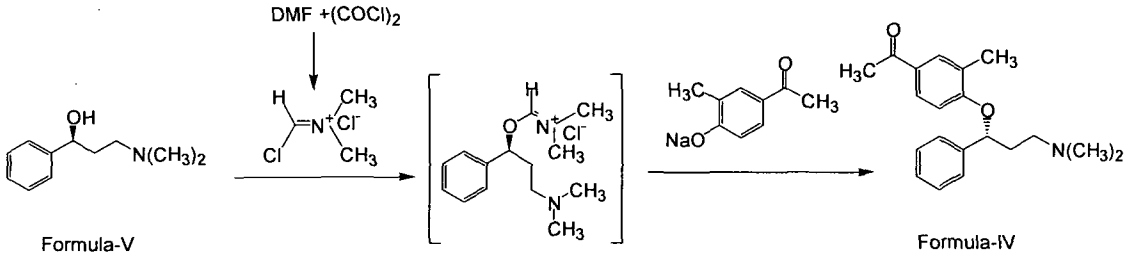
a) reacting (S)-3-chloro-1-phenylpropanol of Formula-VI with dimethylamine in a solvent optionally in the presence of a catalyst to give (S)-N,N-dimethylamino-1-phenylpropanol of Formula-V,



Formula-VI Formula-V

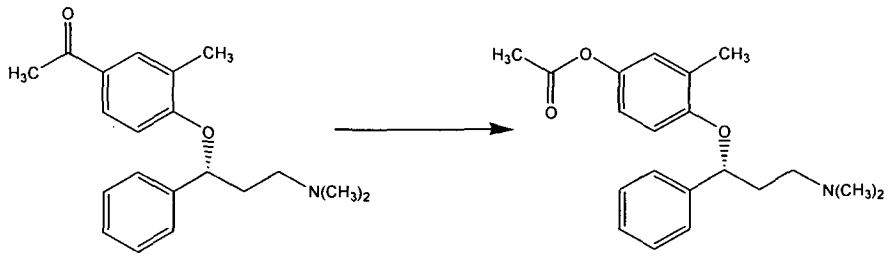
b) optionally purifying the compound of Formula-V,

c) reacting compound of Formula-V with chloromethylene-dimethyl-ammonium chloride, then coupling with sodium salt of 4-hydroxy-3-methyl acetophenone in a solvent, to give (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane of Formula-IV or its acid addition salt,



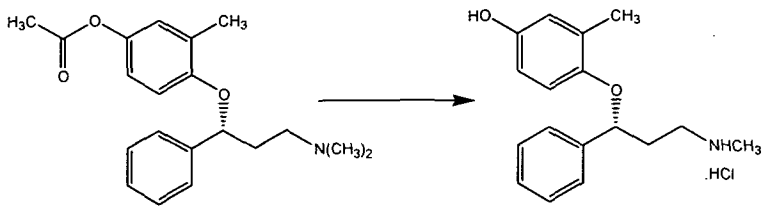
Formula-V Formula-IV

d) oxidizing compound of Formula-IV or its acid addition salt in a solvent to give (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane of Formula-III,



Formula-IV Formula-III

e) converting compound of Formula-III to 4-hydroxy Atomoxetine hydrochloride.



Formula-III 4-Hydroxy Atomoxetine hydrochloride

According to the present invention (S)-3-chloro-1-phenylpropanol of Formula-VI is dissolved in an alcohol, to this solution catalyst and dimethylamine were added and heated to reflux for about 6-8 hrs. The solvent is removed to a minimal amount, adjusted the pH of the solution to 10-13 using a base and extracted the compound in to aromatic hydrocarbon solvent and removed the solvent to obtain the compound of Formula-V. Compound of Formula-V is optionally purified by acid-base treatment, wherein the crude compound is dissolved in solvent followed by slow addition for about 20-40 min and stirred the reaction mass for about 1-3 hrs at ambient temperature. The solid thus obtained is filtered, washed with a solvent and dried at about 40-60°C to afford acid addition salt of compound of Formula-V. The acid addition salt is dissolved in water, adjusted the pH to 11 to 12 using a base, extracted the compound in to aromatic hydrocarbon solvent and isolated pure compound of Formula-V.

According to the present invention the compound of Formula-VI is dissolved in alcohol selected from methanol, ethanol, propanol, isoprapanol or butanol. The catalyst used is selected from potassium iodide or sodium iodide and the base used for adjusting the pH is sodium hydroxide. The aromatic hydrocarbon solvent is selected from toluene or xylene. The solvent used for dissolving the crude compound of Formula-V is selected from ethylacetate, acetone, methyl ethyl ketone, methyl isobutyl ketone or the mixtures thereof. The acid used in the formation of acid addition salt is selected from oxalic acid or mandelic acid.

According to the present invention chloromethylene-dimethyl-ammonium chloride is prepared by reacting dimethylformamide with oxaloyl chloride in methylenedichloride at about 0 to 5°C, to this solution is slowly added (S)-N,N-dimethylamino-1-phenylpropanol in dimethylformamide for about 1-2 hrs at 0 to 5°C. The temperature of the reaction mass is slowly raised to ambient temperature and stirred for about 1-3 hrs. Sodium salt of 4-hydroxy-3-methyl acetophenone is added for about 20-40 min and stirred the reaction for about 8-12 hrs. The reaction mass is quenched in to water and extracted in to a solvent. The solvent is removed and the residue thus obtained is dissolved in solvent, an acid is added slowly for about 20-40 min. The mixture is stirred for about 10-14 hrs at ambient temperature. The mass is then cooled to about 5-15°C and stirred for about 2 hours. The solid thus obtained is filtered to give acid addition salt of compound of Formula-IV.

According to the present invention the solvent used for extraction of compound of formula-IV is selected from methyltertiarybutylether, diethyl ether, diisoprpyl ether, dichloromethane, toluene or ethyl acetate. The solvent used for salt formation is selected from ethylacetate, acetone, methyl ethyl ketone, methyl isobutyl ketone or the mixtures thereof. The acid used in the formation of acid addition salt of compound of Formula-IV is oxalic acid or mandelic acid.

According to the present invention compound of Formula-IV or its acid addition salt is dissolved in a solvent and oxidizing agent is added. The reaction mass is stirred for about 6-10 hrs at ambient temperature. The organic layer is separated and isolated compound of Formula-III.

According to the present invention the solvent used for dissolution of compound of Formula IV is selected from methylenedichloride, chloroform or methyl tertiary butyl ether, diisopropylether, the oxidizing agent is selected from m-chloro perbenzoic acid or hydrogen peroxide.

According to the present invention compound of Formula-III is converted to 4-hydroxy Atomoxetine hydrochloride by demethylation, hydrolysis and salt formation, wherein the demethylation process, the compound of Formula III is dissolved in a solvent at to 50-55°C and a base is added. The temperature of the reaction mass is raised to 60-65°C and a demethylating agent is added. The temperature of the reaction mass is further raised to 80-85°C and stirred for about 2-4 hrs. The solvent is removed to afford carbamate residue.

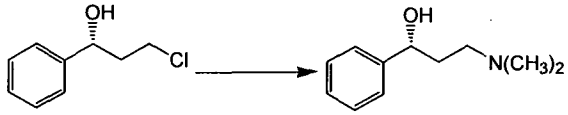
According to the present invention the carbamate residue is subjected to basic hydrolysis, wherein the residue is dissolved in a solvent, the temperature of the reaction mass is raised to 40-60°C and a base is added to the solution. The reaction mass is stirred for about 15-17 hrs at same temperature and quenched in to water. The pH of the mixture is adjusted to 2-2.4 with aqueous hydrochloric acid and the solution is washed with an organic solvent to remove impurities. Again pH is adjusted to 10-11 with ammonia solution and extracted in to a solvent and removed the solvent to get free base. The free base is dissolved in a solvent, pH is adjusted to about 1-2 with aqueous hydrochloric acid and isolated 4-hydroxy Atomoxetine hydrochloride.

According to the present invention solvents used for the dissolution of compound of Formula III is selected from toluene or xylene. The base is selected from diisopropylethylamine, triethylamine, sodium bicarbonate or potassium bicarbonate and the demethylating agent is selected from phenylchloroformate, methyl chloroformate or ethyl chloroformate.

According to the present invention solvents used for hydrolysis is selected from methanol, ethanol or dimethylsulpoxide. The base used for hydrolysis is selected from sodium hydroxide, potassium hydroxide or lithium hydroxide and the solvent for extraction of free base is ethyl acetate and for salt formation is selected from methanol, ethanol, ethylacetate or acetone or the mixtures thereof.

In another embodiment, the present invention provides a novel process for the preparation of 4-hydroxy Atomoxetine hydrochloride which comprises the steps of:

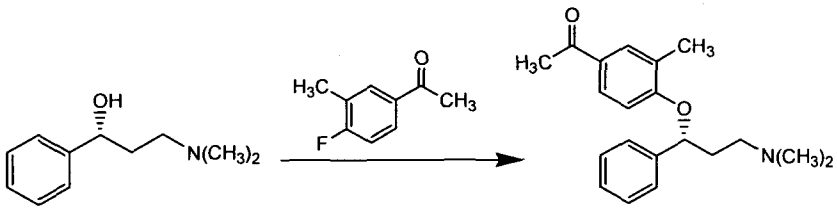
a) reacting (R)-3-chloro-1-phenylpropanol of Formula-VIa with dimethylamine in a solvent optionally in the presence of a catalyst to give (R)-N,N-dimethylamino-1-phenylpropanol of Formula-Va,



Formula-VIa Formula-Va

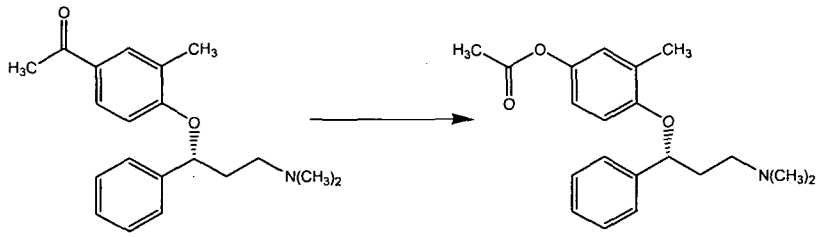
b) optionally purifying the compound of Formula-Va,

c) reacting compound of Formula-Va with 4-fluoro-3-methyl acetophenone in the presence of a base in a solvent to give compound of (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane of Formula-IV,



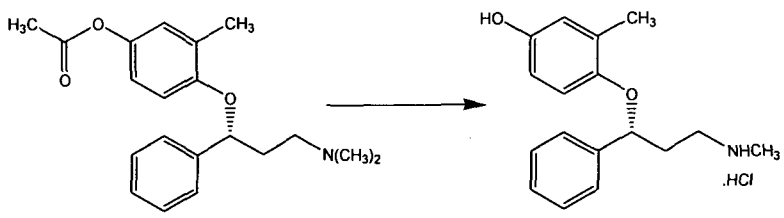
Formula-Va Formula-IV

d) oxidizing compound of Formula-IV in a solvent to give (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane of Formula-III,



Formula-IVa Formula-III

e) converting compound of Formula-III to 4-hydroxy Atomoxetine hydrochloride.



Formula-III 4-Hydroxy Atomoxetine hydrochloride

According to the present invention (R)-3-chloro-1-phenylpropanol of Formula-VIa is dissolved in an alcohol, to this solution catalyst and dimethylamine were added and heated to reflux for about 6-8 hrs. The solvent is removed to a minimal amount, adjusted the pH of the solution to 10-13 using a base and extracted the compound in to aromatic hydrocarbon solvent and removed the solvent to obtain the compound of Formula-Va. Compound of Formula-Va is optionally purified by acid-base treatment, wherein the crude compound is dissolved in solvent followed by slow addition for about 20-40 min and stirred the reaction mass for about 1-3 hrs at ambient temperature. The solid thus obtained is filtered, washed with a solvent and dried at about 40-60°C to afford acid addition salt of compound of Formula-Va. The acid addition salt is dissolved in water, adjusted the pH to 11 to 12 using a base, extracted the compound in to aromatic hydrocarbon solvent and isolated pure compound of Formula-Va.

According to the present invention the compound of Formula-VIa is dissolved in alcoholic solvent selected from methanol, ethanol, propanol, isoprapanol or butanol. The catalyst used is selected from potassium iodide or sodium iodide and the base used for adjusting the pH is sodium hydroxide. The aromatic hydrocarbon solvent is selected from toluene or xylene. The solvent used for dissolving the crude compound of Formula-Va is selected from ethylacetate, acetone, methyl ethyl ketone, methyl isobutyl ketone or the mixtures thereof. The acid used in the formation of acid addition salt is selected from oxalic acid or mandelic acid.

According to the present invention compound of Formula Va is dissolved in dimethylacetamide, base is added followed by 4-fluoro-3-methyl acetophenone at about 5-20°C, stirred at 25-35°C for about 12 hrs. The pH of the reaction mass is adjusted to 3-5 with acetic acid, quenched into water and washed with organic solvent, again adjusted the pH of the reaction mass to 8-11 with ammonium hydroxide solution and extracted into a solvent. The solvent is removed to afford compound of Formula-IV.

According to the present invention the solvent used for dissolution of compound of Formula-Va is selected from dimethylacetamide, dimethylformamide, toluene, xylene, methyltertiary butyl ether or tetrahydrofuran and the base used is sodium hydride.

According to the present invention compound of Formula-IV is dissolved in a solvent and an oxidizing agent is added. The reaction mass is stirred for about 6-10 hrs at ambient temperature. The organic layer is separated and isolated compound of Formula-III.

According to the present invention the solvent used for dissolution of compound of Formula IV is selected from methylenedichloride, chloroform, methyl tertiary butyl ether or diisopropylether, the oxidizing agent is selected from m-chloro perbenzoic acid or hydrogen peroxide.

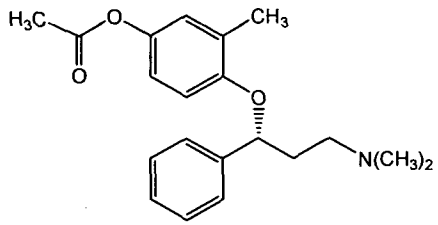
According to the present invention compound of Formula-III is converted to 4-hydroxy Atomoxetine hydrochloride by demethylation, hydrolysis and salt formation, wherein the demethylation process, the compound of Formula III is dissolved in a solvent at to 50-55°C and a base is added. The temperature of the reaction mass is raised to 60-65°C and a demethylating agent is added. The temperature of the reaction mass is further raised to 80-85°C and stirred for about 2-4 hrs. The solvent is removed to afford carbamate residue.

According to the present invention the carbamate residue is subjected to basic hydrolysis, wherein the residue is dissolved in a solvent, the temperature of the reaction mass is raised to 40-60°C and a base is added to the solution. The reaction mass is stirred for about 15-17 hrs at same temperature and quenched in to water. The pH of the mixture is adjusted to 2-2.4 with aqueous hydrochloric acid and the solution is washed with an organic solvent to remove impurities. Again pH is adjusted to 10-11 with ammonia solution and extracted in to a solvent and removed the solvent to get free base. The free base is dissolved in a solvent, pH is adjusted to about 1-2 with aqueous hydrochloric acid and isolated 4-hydroxy Atomoxetine hydrochloride.

According to the present invention solvents used for the dissolution in demthylation is selected from toluene or xylene. The base is selected from diisopropyl ethylamine, triethylamine, sodium bicarbonate or potassium bicarbonate and the demethylating agent is selected from phenylchloroformate, methyl chloroformate or ethyl chloroformate.

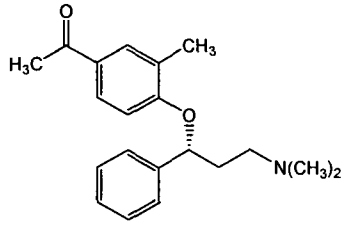
According to the present invention solvents used for hydrolysis is selected from methanol, ethanol or dimethylsulpoxide. The base used for hydrolysis is selected from sodium hydroxide, potassium hydroxide or lithium hydroxide and the solvent for extraction of free base is ethyl acetate and for salt formation is selected from methanol, ethanol, ethylacetate or acetone or the mixtures thereof.

In yet another embodiment the present invention provides a novel compound of Formula-III.



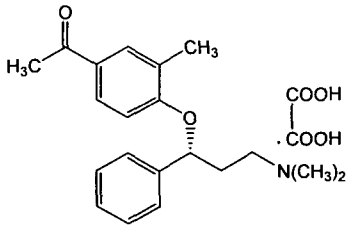
Formula-III

In yet another embodiment, the present invention provides a novel compound of Formula-IV or its acid addition salts.



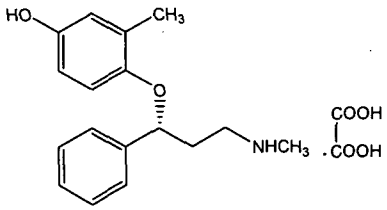
Formula-IV

In yet another embodiment, the present invention provides a novel compound of Formula-IVa.



Formula-IVa

In yet another embodiment, the present invention provides crystalline 4-hydroxy Atomoxetine oxalate.



The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention in any way.

EXPERIMENTAL SECTION

Example –1: Preparation of (S)-N, N-dimethylamino-1-phenylpropanol

(S)-3-chloro-1-phenylpropanol (100gms;0.58moles), ethanol (500 ml), potassium iodide(10gms), 40% dimethylamine solution (500ml) were taken in a round bottom flask and heated to 55 to 60°C and maintained for about 7hours. Ethanol was distilled under vacuum at below 60°C up to inside volume of 300ml. The pH of the solution was adjusted to about 11 to 12 using 100ml of 20% sodium hydroxide solution and extracted with toluene (250ml). The toluene layer was washed with brine solution (100ml) and distilled off completely under vacuum. The residue was dissolved in ethyl acetate (300ml) and acetone (300 ml) and cooled the reaction mass to 20 to 25°C. To the reaction mass was added oxalic acid slowly over a period of 30minutes. The reaction mass was stirred for 2hours at 20 to 25°C. The solid obtained is filtered, washed with ethyl acetate and dried at 50 to 55°C to afford (S)-N, N-dimethylamino-1-phenylpropanol oxalate.

Dry wt – 130gms

The above Oxalate salt was taken into purified water (300ml) and toluene (400ml) and adjusted the pH to 11 to 12 with sodium hydroxide solution, separated the layers and aqueous layer was extracted with toluene (150ml). All the toluene layers were combined, washed with 200ml of brine solution and distilled under vacuum completely at below 60°C to afford (S)-N,N-dimethylamino-1-phenylpropanol weight = 80gm.

SOR= -24.734°(C=1 chloroform)

Example –2: Preparation of (R)-N, N-dimethylamino-1-phenylpropanol

(R)-3-chloro-1-phenylpropanol (100gms;0.58moles), ethanol (500 ml), potassium iodide(10gms), 40% dimethylamine solution (500ml) were taken in a round bottom flask and heated to 55 to 60°C and maintained for about 7hours. Ethanol was distilled under vacuum at below 60°C up to inside volume of 300ml. The pH of the solution was adjusted to about 11 to 12 using 100ml of 20% sodium hydroxide solution and extracted with toluene (250ml). The toluene layer was washed with brine solution (100ml) and distilled off completely under vacuum. The residue was dissolved in ethyl acetate (300ml) and acetone (300 ml) and cooled the reaction mass to 20 to 25°C. To the reaction mass was added oxalic acid slowly over a period of 30minutes. The reaction mass was stirred for 2hours at 20 to 25°C. The solid obtained is filtered, washed with ethyl acetate and dried at 50 to 55°C to afford (R)-N, N-dimethylamino-1-phenylpropanol oxalate.

Dry wt – 130gms

The above Oxalate salt was taken into purified water (300ml) and toluene (400ml) and adjusted the pH to 11 to 12 with sodium hydroxide solution, separated the layers and aqueous layer was extracted with toluene (150ml). All the toluene layers were combined, washed with 200ml of brine solution and distilled under vacuum completely at below 60°C to afford (R)-N,N-dimethylamino-1-phenylpropanol weight = 80gm.

SOR= -24.734°(C=1 chloroform)

Example–3: Preparation of (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane oxalate

Mixture of dimethylformamide (39.6gms; 0.54mole) and methylenedichloride (150ml) were taken into a round bottom flask and cooled to 0 to 5°C. Oxaloyl chloride (60.5gms; 0.47mole) was added slowly at 0 to 5°C under nitrogen atmosphere, and maintained for about 60min. (S)-N, N-dimethylamino-1-phenylpropanol (75gms; 0.41moles) (obtained from example–1) solution in dimethyl formamide as added slowly to the iminium intermediate formed above over a period of 90min. The temperature of the reaction mass was raised slowly to about 25–35°C and maintained for about two hours. Sodium salt of 4-hydroxy, 3-methyl acetophenone (216gms; 1.25moles) was added slowly to the reaction mass over a period of 30minutes and maintained the reaction mass for 10hrs. The reaction mass was quenched into purified water (500ml) at a temperature of about 10 to 15°C. Methyl tertiary butyl ether (500ml) was added and maintained for about 30minutes. Allowed the reaction mass to settle and separated the organic layer. The aqueous layer was extracted with methyl tertiary butyl ether (300ml). All the organic layers were combined and washed with 10% sodium hydroxide solution (2X225ml). The organic layer was washed with purified water (225ml) and finally with 225ml of 10% sodium chloride solution. Methyl tertiary butyl ether layer was distilled off completely under vacuum at below 60°C. To the residue added acetone (150ml) and ethyl acetate (375ml) and stirred for about 30minutes. Oxalic acid (28.2gms) was added slowly over a period of 30minutes. The resultant mass was stirred for about 12hours at a temperature of about 25 to 35°C. The reaction mass cooled to about 10 to 15°C and maintained for about 2hours. The resultant solid was filtered and washed with ethyl acetate. The solid was dried at 40 to 45°C for 6hours to afford (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane oxalate.

Dry wt – 57.5gms of HPLC purity – 99.10%

SOR= -12.206°(C=1 chloroform).

^{1}H NMR (DMSO-d6) : 2.23-2.37 (m,s, 5H), 2.44 (s,3H), 2.74(s,6H), 3.12-3.20 (m, 2H), 5.59-5.63 (m, 1H), 6.82(d,1H,ArH), 7.29-7.43(m, 5H,ArH), 7.62-7.66(dd,2H,ArH), 7.75(d,1H,ArH), 8.10-10.20 (brs, 2H).

Example–4: Preparation of (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane

4-fluoro-3-methyl acetophenone (46.5gms) was slowly added to sodium hydride (2.5gms) and (R)-N,N-dimethylamino-1-phenylpropanol (Obtained example-2) (50gms) in dimethylacetamide at 10 to 15°C. The reaction mass was raised slowly to a temperature of about 25 to 35°C and maintained for 12hours. The pH of the reaction mass was adjusted to 4 to 5 using acetic acid. The resultant mass was quenched into purified water and washed with toluene (50ml). Again pH was adjusted to 9 to 10 using ammonia hydroxide solution and the resultant mass was extracted with toluene (1x500ml & 1x250ml). The toluene layers were combined washed with 100ml of purified water, finally with 10% sodium chloride solution and distilled off toluene under vacuum completely at below 55°C to afford (R)-N,N-dimethyl-3-(2-methyl-4-acetylphenyl)oxy)-3-phenyl-1-aminopropane.

Wt – 62gms

Example–5: Preparation of (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane

To a solution of (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane oxalate (25gms;0.06mole) or its free base (Obtained examples-3 & 4 respectively) in methylene dichloride (250ml) was added acetic acid (3.9gm) and m-CPBA(30gms) at 25 – 35°C. The reaction mass was maintained for about 8 hours at 25 to 35°C. Again m-CPBA (70%; 15gm) was added and maintained for about 6hrs at 25 to 35°C. Again m-CPBA (70%; 15gm) was added and maintained for about 6hrs at 25 to 35°C. 10% sodium bisulfite solution (250ml) was added and filtered the salts. Methylene dichloride layer was separated and distilled completely under vacuum at below 40°C. To the residue was added methyl tertiary butyl ether (200ml) and the solution was washed with 20% potassium carbonate solution (3X100ml) followed by brine solution(100ml). The organic layer was distilled under vacuum at below 50°C to afford N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane.

Residue wt: 17gms, Purity – 91.0%

^{1}H NMR ($CDCl_3$) : 1.94-2.23 (m, s,11H), 2.29 (s,3H), 2.44 (t, 2H), 5.15-5.19 (m, 1H), 6.57(d,1H,ArH), 6.63-6.66(dd, 1H,ArH), 6.83(d,1H,ArH), 7.23-7.33(m,5H,ArH).

Example–6: Preparation of 4-hydroxy Atomoxetine Hydrochloride

In a round bottom flask taken a solution of (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane (30gms; 0.09moles) (Obtained from example-5) in toluene and raised the temperature to 50 to 55°C. Diisopropyl ethylamine (20gms) was added and further raised the temperature to about 60 to 65°C. Phenyl chloroformate (20gms) was added at 60 to 65°C and

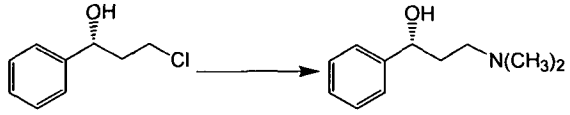
raised the temperature to 80 to 85°C. The reaction mass was maintained at 80 to 85°C for about 3 hours.. The reaction mass was washed initially with 5% sodium bicarbonate solution(120ml) followed by washing with 0.5N hydrochloric acid solution(60ml) and 5% sodium bicarbonate solution(120ml). The organic layer was distilled completely under reduced pressure to afford the carbamate residue Wt- 41gms.

The above residue was dissolved in dimethyl sulfoxide (390ml) and raised the temperature to 50 to 55°C. 4N sodium hydroxide solution (160ml) was added and maintained for 16hours at 50 to 55°C. The reaction mass was quenched into purified water (300ml) and washed with toluene (60ml). The pH was adjusted to 2.2 with CP HCl solution and washed the Reaction mass with with ethyl acetate. Again adjusted the pH to 10.0 with ammonia solution and extracted with ethyl acetate. The ethyl acetate layers were combined and distilled off completely under vacuum at below 50°C. To the residue was added acetone (40ml) and ethyl acetate (100ml). To the reaction mass was added Oxalic acid (8.6gms) slowly over a period of 10minutes. The reaction mass was maintained for 2hours and filtered. The residue was washed with ethyl acetate (20ml), followed by n-Hexane (10ml) and dried under vacuum at 40 to 45°C for 10hours to afford 4-hydroxy Atomoxetine oxalate salt wt – 18.6gms

The 4-hydroxy Atomoxetine oxalate salt obtained above (15gms) was taken into purified water (30ml) and adjusted the pH to 10 with ammonia solution. The reaction mass was extracted with ethyl acetate (50ml). To the ethyl acetate layer was added water (30ml) and adjusted the pH to 1.0 with CP HCl solution. The aqueous layer was separated and distilled the organic layer completely under vacuum at below 50°C. The residue was added ethyl acetate (30ml) and maintained for 2hrs. The solid obtained was filtered and washed with ethyl acetate (10ml) and dried the product under vacuum at 40 – 45°C to afford 4-hydroxy Atomoxetine hydrochloride Wt – 9.0gms

2. Novel process for the preparation of 4-hydroxy Atomoxetine which comprises the steps of:

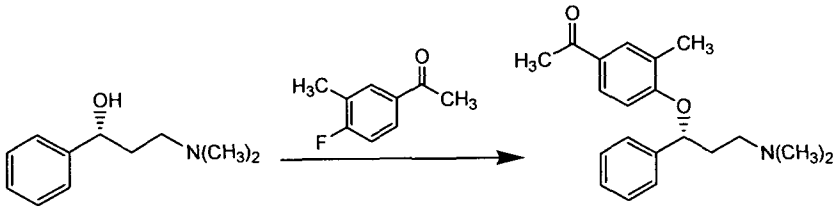
a) reacting (R)-3-chloro-1-phenylpropanol of Formula-VIa with dimethylamine in a solvent in the presence of a catalyst to give (R)-N,N-dimethylamino-1-phenylpropanol of Formula-Va,



Formula-VIa Formula-Va

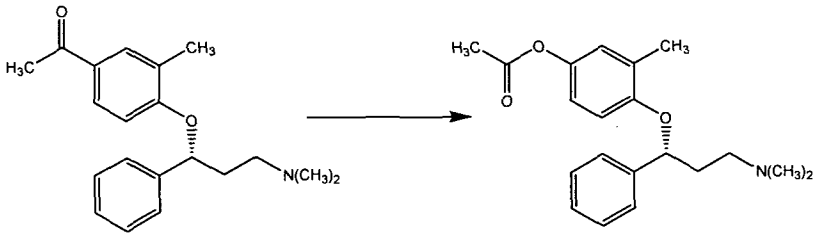
b) optionally purifying the compound of Formula-Va,

c) reacting compound of Formula-Va with 4-fluoro-3-methyl acetophenone in the presence of a base in a solvent to give compound of (R)-N,N-dimethyl-3-(2-methyl-(4-acetylphenyl)oxy)-3-phenyl-1-aminopropane of Formula-IV,



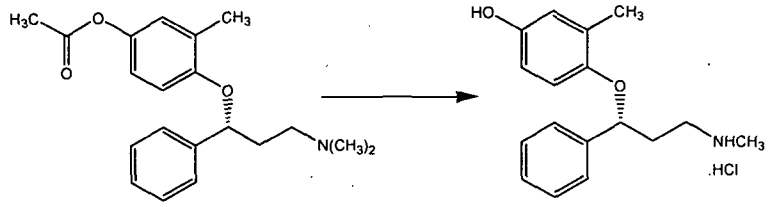
Formula-Va Formula-IV

d) oxidizing compound of Formula-IV in a solvent to give (R)-N,N-dimethyl-3-(2-methyl-(4-acetoxyphenyl)oxy)-3-phenyl-1-aminopropane of Formula-III,



Formula-IVa Formula-III

e) converting compound of Formula-III to 4-hydroxy Atomoxetine hydrochloride.



Formula-III

4-Hydroxy Atomoxetine hydrochloride

3. The process according to claim 1&2, where in said solvent used in step a) is selected from alcohol such as methanol, ethanol, propanol, isopropanol or butanol and the catalyst used is potassium iodide or sodium iodide.

4. The process according to claim 1&2, where in said purification in step b) is carried out by acid-base treatment.

5. The process according to claim 1&2, where in said solvent used in step c) is selected from dimethylformamide or dimethylacetamide.

6. The process according to claim 2, where in said base used in step c) is selected from sodium hydride.

7. The process according to claim 1&2, where in said oxidizing agent used in step d) is selected from m-chloro perbenzoic acid or hydrogen peroxide and the solvent is selected from methylenedichloride, chloroform, methyl tertiary butyl ether or diisopropylether.

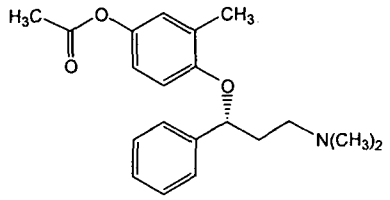
8. The process according to claim 1&2, where in said conversion of compound of Formula-III to 4-hydroxy Atomoxetine hydrochloride in step e) involves demethylation, hydrolysis and salt formation.

9. The process according to claim 8, where in said reagent used for demethylation is selected from phenylchloroformate, methyl chloroformate or ethyl chloroformate and the solvent is selected from toluene or xylene.

10. The process according to claim 8, where in said base used for hydrolysis is selected from sodium hydroxide, potassium hydroxide or lithium hydroxide and the solvent is selected from methanol, ethanol or dimethylsulpoxide.

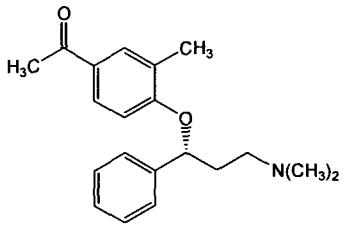
11. The process according to claim 8, where in said hydrochloric acid used for salt formation is aqueous hydrochloric acid and the solvent is selected from methanol, ethanol, ethylacetate, acetone or the mixtures thereof.

12. Novel compound of Formula-III or its salt.



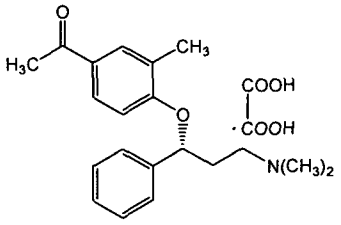
Formula-III

13. Novel compound of Formula-IV or its salt.



Formula-IV

14. Novel compound of Formula-IVa.



Formula-IVa

15. Crystalline 4-hydroxy Atomoxetine oxalate.

