Title: A PROCESS FOR THE PREPARATION OF VENLAFAXINE HYDROCHLORIDE

Abstract: The present invention relates to a process for the preparation of Venlafaxine Hydrochloride comprising steps of i) treating 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide and super base to get l-cyano (4-methoxyphenyl)methyl cyclohexanol and ii) reducing l-[cyano (4-methoxyphenyl) methyl] cyclohexanol in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure.
Description
Title of Invention: A PROCESS FOR THE PREPARATION OF VENLAFAXINE HYDROCHLORIDE

Field of invention

The present invention relates to a process for the preparation of Venlafaxine Hydrochloride of formula (I).

Venlafaxine hydrochloride is chemically known as 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride, having molecular formula C_{17}H_{27}NO_{2}.HCl and molecular weight 313.86. The current pharmaceutical product containing this drug is being sold by Wyeth using the tradename Effexor® in the form of tablets.

Venlafaxine hydrochloride selectively inhibits the neuronal uptake of serotonin norepinephrine and to a lesser extent dopamine. Studies indicate that it has comparable or possibly slightly greater efficacy to other selective serotonin reuptake inhibitors (SSRI's). It appears to be as effective as standard antidepressants such as imipramine. Its unique chemical structure and neuro-pharmacological activity give it a broader spectrum of activity than other antidepressants.

US4535186 discloses the process for preparation of the compound of Formula (I) comprising a step of reacting p-methoxyphenyl acetonitrile with cyclohexanone in the presence of n-butyl lithium. However, this process is hazardous and commercially unfeasible due to utilization of n-butyl lithium as it is inflammable and pyrophoric substance.
WO00/32556 describes a process for the preparation of Venlafaxine comprising a step of condensation of p-methoxyphenyl acetonitrile with cyclohexanone in the presence of lithium diisopropylamide. However, this process is hazardous and commercially unfeasible due to utilization n-butyl lithium as it is corrosive and unstable substance.

CN1225356 describes a process for the preparation of Venlafaxine comprising condensing p-methoxyphenyl acetonitrile with cyclohexanone in the presence of sodium methoxide, sodium ethoxide, sodium amide, or sodium hydride in cyclohexane to obtain 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol which then reduced to 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol with sodium borohydride and boron trifluoride diethyl ether complex at reflux temperature.

WO02/18325 discloses a process for the preparation of the compound of 1-[Cyano (4-methoxyphenyl) methyl] cyclohexanol by reacting 4-methoxyphenylacetonitrile with cyclohexanone in the presence of an aqueous base and a phase transfer catalyst.

WO02/50017 discloses the reduction of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol to 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol in the presence of a nickel or cobalt catalyst.

US6350912 discloses the one-pot preparation of Venlafaxine by reduction of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol in the presence of Raney nickel to 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol, followed by conversion to Venlafaxine in yields of 15-28%.

IN194085 discloses a method for the preparation of Venlafaxine by combining p-methoxyphenyl acetonitrile with cyclohexanone and sodium hydroxide in an alcoholic solvent to produce 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol, and reducing 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol with NaBH₄ in presence of carboxylic acid in an aprotic solvent to prepare 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol.

US2005/0033088 discloses reduction of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol in the presence of palladium on charcoal catalyst in an organic acid selected from formic acid, acetic acid or propionic acid to obtain 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol. The yield of
1-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol is reported as 45-55%.

Many of the above processes have disadvantages that make them less than optimal for use on an industrial scale due to hazardous nature and huge costing of reactant materials used or low yield. Hence, there is a need in the art for processes for the preparation of Venlafaxine HCl that are suitable for use on an industrial scale and which is cost effective.

Therefore the present inventors develop a process for the preparation of Venlafaxine HCl which is not only avoid hazardous material but also shows cost effective nature at industrial scale due to continuous process of recycling at intermediate stage and avoidance of costly catalyst and reagents.

Objects of the invention

The primary object of the present invention is to provide process for the preparation of Venlafaxine hydrochloride comprising a step of treating 4-methoxyphenyl acetonitrile with cyclohexanone in the presence of alkali hydroxide and super base in suitable solvent to obtain 1-[Cyano (4-methoxyphenyl) methyl] cyclohexanol.

Another object of the present invention is to provide process for the preparation of Venlafaxine hydrochloride comprising a step of reducing 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol in the presence of catalyst, activator in suitable solvent under hydrogen pressure to obtain 1-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol.

Another object of the present invention is to provide process for the preparation of Venlafaxine HCl comprising steps of:

a) hydrogenating 1-[Cyano (4-methoxyphenyl) methyl] cyclohexanol obtained in to obtain 1-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol comprising following steps:

(i) carrying out hydrogenation lot-I of 1-[Cyano (4-methoxyphenyl) methyl] cyclohexanol in presence of catalyst, activator, alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours

(ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower layer

(iii) removing upper layer and filtering it to obtain filtrate containing 1-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol
(iv) adding lot-II of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol and alcoholic ammonia to settled lower layer

(v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours

(vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer

(vii) removing upper layer and filtering it to obtain filtrate containing 1-[1-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol

(viii) adding lot-III of 1-[1-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol and alcoholic ammonia to settled lower layer

(ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm² for 4-8 hours

(x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer

(xi) removing upper layer and filtering it to obtain filtrate containing 1-[1-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol

(xii) adding lot-IV of 1-[1-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol and alcoholic ammonia to settled lower layer

(xiii) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm² for 5-9 hours

(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer

(xv) removing upper layer and filtering it to obtain filtrate containing 1-[1-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol.

(b) combining filtrates of 1-[1-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol obtained in (iii), (vii), (xi) and (xv) and distilled out completely to obtain 1-[1-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol.

Another object of the present invention is to provide process for the preparation of Venlafaxine HCl comprising steps of:

(a) treating 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide, super base and alcoholic ammonia to obtain 1-[cyano(4-methoxyphenyl)methyl] cyclohexanol.

(b) hydrogenating 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol obtained in step (a) to obtain 1-[1-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol comprising
following steps:

(i) carrying out hydrogenation lot-I of l-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours

(ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower layer

(iii) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol

(iv) adding lot-II of l-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours

(vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer

(vii) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol

(viii) adding lot-III of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm² for 4-8 hours

(x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer

(xi) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol

(xii) adding lot-IV of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(xii) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm² for 5-9 hours

(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer

(xv) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl) -2- (amino) ethyl] cyclohexanol.

c) combining filtrates of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol obtained in (iii), (vii), (x) and (xv) and distilled out completely to obtain l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol.

d) treating l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol obtain in step (c)
with aqueous formic acid and formaldehyde to obtain Venlafaxine.

- treating Venlafaxine obtained in step (d) with alcoholic HCl to obtain Venlafaxine hydrochloride.
- purifying Venlafaxine hydrochloride obtained in step (e) with alcohol.

Another object of the present invention is to provide a process for the preparation of Venlafaxine hydrochloride in high yield and purity.

Yet another object of the present invention is to provide a process for the preparation of Venlafaxine hydrochloride, which is simple and easy to handle at production level.

Yet another object of the present invention is to provide a process for the preparation of Venlafaxine hydrochloride, which is extremely cost effective.

Summary of the invention

According to one aspect of present invention, it provides a process for the preparation of Venlafaxine hydrochloride comprising a step of treating 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide and super base.

According to another aspect of present invention, it provides a process for the preparation of Venlafaxine hydrochloride comprising a step of reducing L-[cyano (4-methoxyphenyl) methyl] cyclohexanol in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure.

Another object of the present invention is to provide process for the preparation of Venlafaxine HCl comprising steps of:

a) hydrogenating L-[cyano (4-methoxyphenyl) methyl] cyclohexanol obtained in to obtain L-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol comprising following steps:

(i) carrying out hydrogenation lot-l of L-[cyano (4-methoxyphenyl) methyl] cyclohexanol in presence of catalyst, activator, alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours

(ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower
(iii) removing upper layer and filtering it to obtain filtrate containing
l-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol

(iv) adding lot-II of l-[cyano (4-methoxyphenyl) methyl] cyclohexanol and alcoholic ammonia to settled lower layer

(v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours

(vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer

(vii) removing upper layer and filtering it to obtain filtrate containing
l-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol

(viii) adding lot-III of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol and alcoholic ammonia to settled lower layer

(ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm² for 4-8 hours

(x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer

(xi) removing upper layer and filtering it to obtain filtrate containing
l-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol

(xii) adding lot-IV of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol and alcoholic ammonia to settled lower layer

(xiii) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm² for 5-9 hours

(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer

(xv) removing upper layer and filtering it to obtain filtrate containing
l-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol.

(b) combining filtrates of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol obtained in (iii), (vii), (xi) and (xv) and distilled out completely to obtain
l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol.

According to another aspect of present invention, it provides a process for the preparation of Venlafaxine HCl comprising steps of:

a) treating of 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide, super base and suitable solvent to obtain
l-[cyano(4-methoxyphenyl)methyl] cyclohexanol.
b) hydrogenating 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol obtained in step (1) to obtain 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol comprising following steps:

(i) carrying out hydrogenation lot-I of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours

(ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower layer

(iii) removing upper layer and filtering it to obtain filtrate containing 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol

(iv) adding lot-II of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours

(vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer

(vii) removing upper layer and filtering it to obtain filtrate containing 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol

(viii) adding lot-III of 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm² for 4-8 hours

(x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer

(xi) removing upper layer and filtering it to obtain filtrate containing 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol

(xii) adding lot-IV of 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer

(xií) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm² for 5-9 hours

(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer

(xv) removing upper layer and filtering it to obtain filtrate containing 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol.

c) combining filtrates of 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol obtained in (iii), (vii), (x) and (xv) and distilled out completely to obtain 1-[l-(4-methoxyphenyl)-2-(amino) ethyl] cyclohexanol.
d) treating 1-[1-(4-methoxyphenyl)-2-(amino)ethyl]cyclohexanol obtained in step (c) with aqueous formic acid and formaldehyde to obtain Venlafaxine.

e) treating Venlafaxine obtained in step (d) with alcoholic HCl to obtain Venlafaxine hydrochloride.

f) purifying Venlafaxine hydrochloride obtained in step (e) with alcohol.

Detailed description of the invention

The term 'treating' as used hereinabove is meant to include but not limited to include suspending, dissolving, washing, mixing, adding, accumulating and totaling in any of the suitable solvent.

The term 'alkali hydroxide' as used hereinabove is meant to include but not limited to sodium hydroxide, potassium hydroxide and aluminum hydroxide and the like or mixture thereof.

The term 'super base' as used hereinabove is meant to include but not limited to 30% aqueous solution of sodium, potassium and aluminum cations in the ratio of 9:0.5:0.5 and hydroxide, carbonate anion in the ratio of 9:1 and the like or mixture thereof. The preferred super base is 30% aqueous solution of sodium, potassium and aluminum cations in the ratio of 9:0.5:0.5 and hydroxide, carbonate anion in the ratio of 9:1.

The term 'activator' as used hereinabove is meant to include but not limited to alkyl ammonium halide and the like. The term 'alkyl' as used hereinabove is meant to include but not limited to substituted or unsubstituted alkyl group consisting of methyl, isopropyl, ethyl, tertiary butyl and the like. The term 'halide' as used hereinabove is meant to include but not limited to chloride, bromide, iodide and the like. The preferred activator is 25% dialkyl ammonium chloride.

The term 'catalyst' as used hereinabove is meant to include but not limited to platinum dioxide, platinum and palladium and nickel on different inert supports, aluminum hydride, lithium aluminum hydride, sodium borohydride, potassium borohydride, lithium borohydride, quaternary ammonium borohydrides, and the like or mixture thereof. The preferred catalyst is Raney Ni.
The term 'alcoholic ammonia' used hereinabove is meant to include but not limited to a solution of ammonia with alcohol which is selected from group of methanol, ethanol, isopropanol and the like or mixtures thereof. The preferable alcohol is methanol.

The term 'alcoholic HCl' used hereinabove is meant to include but not limited to a solution of HCl with alcohol which is selected from group of methanol, ethanol, isopropanol and the like or mixtures thereof. The preferable alcohol is isopropanol.

The meaning of the term 'suitable solvent' as used hereinabove include but not limited to substituted or unsubstituted alcoholic solvent, halogenated hydrocarbon solvent, aromatic hydrocarbon solvent, ester solvent, ether solvent, cyclic ether solvent, nitrile solvent and aqueous solvent or mixture thereof. It also includes polar or nonpolar protic solvent, polar or nonpolar aprotic solvent or mixture thereof. The preferable one is mixture of methanol and water.

The term 'purifying' refers to any method known to a person skilled in the art such as purification from single solvent or combination of solvents by dissolving the compound optionally at elevated temperature and precipitating the compound by cooling the solution or removing solvent from the solution or both. It further includes methods such as solvent/antisolvent or precipitation.

Venlafaxine hydrochloride is isolated from reaction mass by conventional isolation procedure such as filtration, centrifugation, washing the wet cake and drying or by evaporation of solvent.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

Example 1

**STEP-I: Preparation of l-[cyano (4-methoxyphenyl) methyl] cyclohexanol**

4-Methoxyphenyl acetonitrile (250g) was reacted with cyclohexanone (175 g) in the presence of sodium hydroxide (80g) and super base (70g) in methanol (820ml) & water (130ml) to obtain crude material which was crystallized with toluene to form l-[Cyano(4-methoxyphenyl) methyl] cyclohexanol.

Yield: 360-375g.
HPLC Purity: 99.9%.

**STEP-II: Preparation of l-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol**

Hydrogenation in step-II was carried out in 4 parts by recycling of the catalyst.

**PART - A**

1-[cyano (4-methoxyphenyl) methyl] cyclohexanol (70g) obtained in step (I) i.e lot-1, methanolic Ammonia (490ml), catalyst (52.9 g) & activator (5.6g) was charged in reaction vessel. A hydrogen gas was purged at 8-10 kg /cm² to the mixture of reaction vessel. A hydrogen pressure was continued. Exotherm & temperature rise was observed. The temperature of reaction mixture was maintained at 30 - 32°C while maintaining hydrogen pressure for 2- 5 hrs. After completion of reaction, the reaction mixture was decanted for 30 minutes to obtain upper layer and settled lower layer. The lower settled layer was kept as it is in reaction vessel for further reaction & upper layer was siphoned out by using dip pipe. The upper layer was filtered through hyflo to remove traces of catalyst & the filtrate was kept for distillation.

**PART - B**

1-[cyano (4-methoxyphenyl) methyl] cyclohexanol (70g) obtained in step (I) i.e lot-2, methanolic Ammonia (490ml) was charged in lower settled layer obtained and kept in reaction vessel of part A. A hydrogen gas was purged at 10 kg /cm² to the mixture of reaction vessel. A hydrogen pressure was continued. Exotherm & temperature rise was observed. The temperature of reaction mixture was maintained at 30 - 32°C while maintaining hydrogen pressure for 3- 7 hrs. After completion of reaction, the reaction mixture was decanted for 30 minutes to obtain upper layer and settled lower layer. The lower settled layer was kept as it is in reaction vessel for further reaction & upper layer was siphoned out by using dip pipe. The upper layer was filtered through hyflo to remove traces of catalyst & the filtrate was kept for distillation.

**PART - C**

1-[cyano (4-methoxyphenyl) methyl] cyclohexanol (70g) obtained in step (I) i.e lot-3, methanolic Ammonia (490ml) was charged in lower settled layer obtained and kept in reaction vessel of part B. A hydrogen gas was purged at 13-15 kg /cm² to the mixture of reaction vessel. A hydrogen pressure was continued. Exotherm & temperature rise was observed. The temperature of reaction mixture was maintained at 34-35 °C while maintaining hydrogen pressure for 4-8 hrs. After completion of reaction, the reaction mixture was decanted for 30 minutes to obtain upper layer and
settled lower layer. The lower settled layer was kept as it is in reaction vessel for further reaction & upper layer was siphoned out by using dip pipe. The upper layer was filtered through hyflo to remove traces of catalyst & the filtrate was kept for distillation.

[190] PART - D

[191] 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol (70g) obtained in step (I) i.e lot-4, methanolic Ammonia (490ml) was charged in lower settled layer obtained and kept in reaction vessel of part C. A hydrogen gas was purged at 18 kg/cm² to the mixture of reaction vessel. A hydrogen pressure was continued. Exotherm & temperature rise was observed. The temperature of reaction mixture was maintained at 34-35 ⁰C while maintaining hydrogen pressure for 5-9hrs. After completion of reaction, the reaction mixture was decanted for 30 minutes to obtain upper layer and settled lower layer. The lower settled layer was kept as it is in reaction vessel for further reaction & upper layer was siphoned out by using dip pipe. The upper layer was filtered through hyflo to remove traces of catalyst & the filtrate was kept for distillation.

[193]  The filtrate of part A, B, C and D which are kept for distillation were combined and distilled out completely to obtain 1-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol.

[195] STEP-III: Preparation of Venlafaxine HCl

[197] The distilled mass of 1-[l-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol obtained in step -II was treated with aqueous formic acid (469g) then extracted by dichloromethane (540 ml) for removal of impurities and then treated with formaldehyde (237 g) for methylation to obtain crude Venlafaxine which was isolated by extraction with Toluene (1100 ml) followed treatment with isopropanolic HCl (300ml) to obtain Venlafaxine HCl which was purified with isopropanol (1555 ml).

[198] Yield: 200-23Og.
[199] HPLC purity: 99.8%.
[200]
Claims

[Claim 1] 1. A process for the preparation of Venlafaxine HCl comprising steps of:
   a) treating of 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide, super base and alcoholic ammonia to obtain l-[Cyano(4-methoxyphenyl)methyl] cyclohexanol;
   b) hydrogenating l-[cyano (4-methoxyphenyl) methyl] cyclohexanol obtained in step (1) to obtain l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol comprising following steps:
      (i) carrying out hydrogenation lot-I of l-[Cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours;
      (ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower layer;
      (iii) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol;
      (iv) adding lot-II of l-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
      (v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours;
      (vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer;
      (vii) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol;
      (viii) adding lot-III of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
      (ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm² for 4-8 hours;
      (x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer;
      (xi) removing upper layer and filtering it to obtain filtrate containing l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol;
      (xii) adding lot-IV of l-[l-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
(xiii) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm² for 5-9 hours;
(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer;
(xv) removing upper layer and filtering it to obtain filtrate containing 1-[1-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol;
c) combining filtrates of 1-[1-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol obtained in (iii), (vii), (xi) and (xv) and distilled out completely to obtain 1-[1-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol;
d) treating 1-[1-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol obtained in step (e) with aqueous formic acid and formaldehyde to obtain Venlafaxine;
e) treating Venlafaxine obtained in step (d) with alcoholic HCl to obtain Venlafaxine hydrochloride;

purifying Venlafaxine hydrochloride obtained in step (e) with alcohol.

[Claim 2] 2. A process for the preparation of Venlafaxine HCl comprising a step of treating of 4-methoxyphenyl acetonitrile with cyclohexanone in presence of alkali hydroxide, super base and alcoholic ammonia to obtain 1- [Cyano (4-methoxyphenyl)methyl] cyclohexanol.

[Claim 3] 3. A process for the preparation of Venlafaxine HCl comprising a step of hydrogenating 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol to obtain 1-[1-(4-methoxyphenyl)-2- (amino) ethyl] cyclohexanol comprising following steps:
(i) carrying out hydrogenation lot-I of 1-[Cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) in presence of catalyst, activator and alcoholic ammonia under hydrogen pressure of 8-10 kg/cm² for 2-5 hours;
(ii) decanting the reaction mass of step (i) to obtain upper layer and settled lower layer;
(iii) removing upper layer and filtering it to obtain filtrate containing 1-[1-(4-methoxyphenyl) - 2- (amino) ethyl] cyclohexanol;
(iv) adding lot-II of 1-[cyano (4-methoxyphenyl) methyl] cyclohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
(v) reducing a mixture of step (iv) under hydrogen pressure of 9-11 kg/cm² for 3-7 hours;
(vi) decanting the reaction mass of step (v) obtained after reduction to obtain upper layer and settled lower layer;
(vii) removing upper layer and filtering it to obtain filtrate containing \( l-[l-(4\text{-methoxyphenyl}) - 2\text{- (amino) ethyl}] \) cyclohexanol;
(viii) adding lot-III of \( l-[l-(4\text{-methoxyphenyl})-2\text{- (amino) ethyl}] \) cy-clohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
(ix) reducing a mixture of step (viii) under hydrogen pressure of 12-16 kg/cm\(^2\) for 4-8 hours;
(x) decanting the reaction mass of step (ix) obtained after reduction to obtain upper layer and settled lower layer;
(xi) removing upper layer and filtering it to obtain filtrate containing \( l-[l-(4\text{-methoxyphenyl}) - 2\text{- (amino) ethyl}] \) cyclohexanol;
(xii) adding lot-IV of \( l-[l-(4\text{-methoxyphenyl})-2\text{- (amino) ethyl}] \) cy-clohexanol prepared in step (a) and alcoholic ammonia to settled lower layer;
(xiii) reducing a mixture of step (xii) under hydrogen pressure of 16-19 kg/cm\(^2\) for 5-9 hours;
(xiv) decanting the reaction mass of step (xiii) obtained after reduction to obtain upper layer and settled lower layer;
(xv) removing upper layer and filtering it to obtain filtrate containing \( l-[l-(4\text{-methoxyphenyl}) - 2\text{- (amino) ethyl}] \) cyclohexanol combining filtrates of \( l-[l-(4\text{-methoxyphenyl})-2\text{- (amino) ethyl}] \) cy-clohexanol obtained in (iii), (vii), (x) and (xv) and distilled out completely to obtain \( l-[l-(4\text{-methoxyphenyl})-2\text{- (amino) ethyl}] \) cy-clohexanol.

[Claim 4] 4. The process according to claim 1 or 2, wherein alkali hydroxide used is sodium hydroxide, potassium hydroxide, aluminum hydroxide or mixture thereof.

[Claim 5] 5. The process according to claim 1 or 2, wherein super base used is 30% aqueous solution of sodium, potassium and aluminum cations in the ratio of 9:0.5:0.5 and hydroxide, carbonate anion in the ratio of 9:1 or mixture thereof.

[Claim 6] 6. The process according to claim 1 or 3, wherein activator used is alkyl ammonium halide.

[Claim 7] 7. The process according to claim 6, wherein activator used is 25% dialkyl ammonium chloride.

[Claim 8] 8. The process according to claim 1 or 3, wherein catalyst used is platinum dioxide, platinum and palladium and nickel on different inert supports, aluminum hydride, lithium aluminum hydride, sodium
borohydride, potassium borohydride, lithium borohydride, quaternary ammonium borohydrides or mixture thereof.

[Claim 9] 9. The process according to claim 8, wherein catalyst used is Raney Ni.

[Claim 10] 10. The process according to claim 1 or 2 or 3, wherein alcoholic ammonia used is prepared from solvent selected from methanol, ethanol, isopropanol or mixture thereof.

[Claim 11] 11. The process according to claim 1 or 3, wherein alcoholic HCl used is prepared from solvent selected from methanol, ethanol, isopropanol or mixture thereof.