(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 July 2009 (09.07.2009)

PCT

(10) International Publication Number
WO 2009/084038 A2

(51) International Patent Classification:
C07C 209/68 (2006.01) *C07C 215/52* (2006.01)
C07C 213/00 (2006.01)

(21) International Application Number:
PCT/IN2008/000856

(22) International Filing Date:
23 December 2008 (23.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2766/DEL/2007 28 December 2007 (28.12.2007) IN

(71) Applicant *(for all designated States except US)*: **IND-SWIFT LABORATORIES LIMITED** [IN/IN]; S.C.O. No. 850, Shivalik Enclave, NAC, Manimajra, Chandigarh 160 101 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SRINIVASAN, Chidambaram, Venkateswaran** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **AGGARWAL, Ashvin, Kumar** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **SARIN, Gurdeep, Singh** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phace-II, S.A.S. Nagar, Mohali 160 055, Punjab (IN). **WADHWA, Lalit** [IN/IN]; Ind-Swift Laboratories Limited, E-5, Industrial Area, Phase-II S.A.S Nagar, Mohali 160 055, Punjab (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2009/084038 A2

(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF *O*-DESMETHYL-VENLAFAXINE

(57) Abstract: The present invention relates to an industrially advantageous process for the preparation of *O*- desmethyl-venlafaxine, a venlafaxine metabolite, and pharmaceutically acceptable salts thereof by demethylating venlafaxine or salts using an alkali or alkaline earth metal salts of mercapto acids and their derivatives, mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids and the like or mixture thereof in presence of an organic solvent.

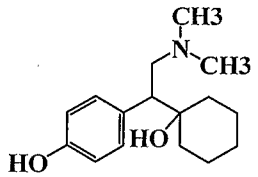
IMPROVED PROCESS FOR THE PREPARATION OF *O*-DESMETHYL-VENLAFAXINE

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of *O*-desmethyl-venlafaxine, a venlafaxine metabolite, and pharmaceutically acceptable salts thereof.

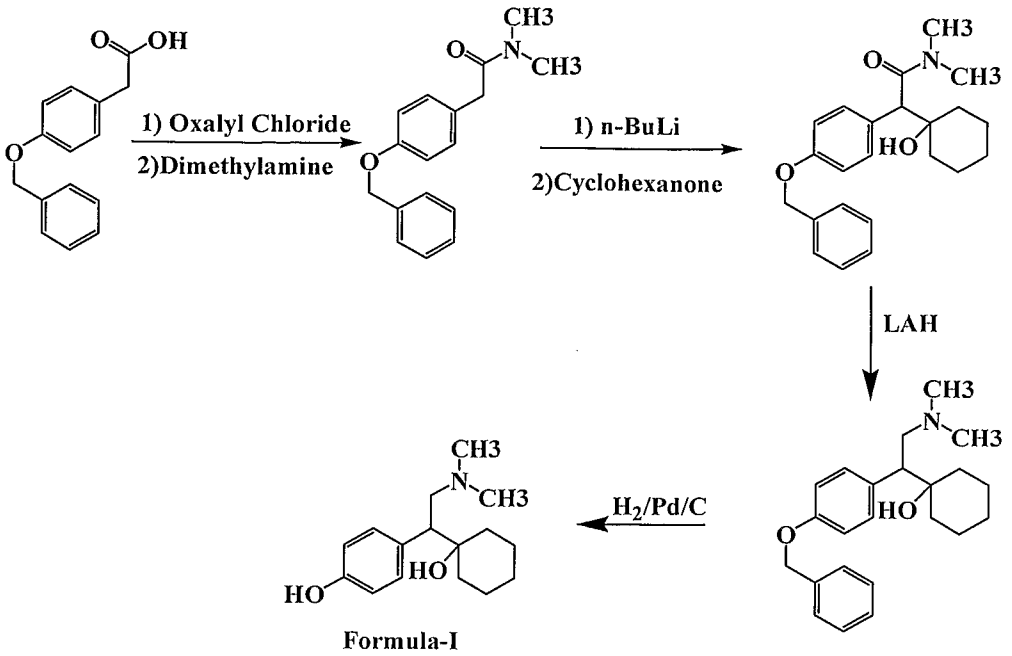
BACKGROUND OF THE INVENTION

O-Desmethyl-venlafaxine of formula I, is a major metabolite of venlafaxine and has been shown to inhibit norepinephrine and serotonin uptake and is chemically named as 1-[2-(dimethylamino)-1-(4-phenol) ethyl]-cyclohexanol.



Formula I

O-Desmethyl-venlafaxine was first disclosed in U.S. Patent No. 4,535,186 wherein it is exemplified as a fumarate salt. The process for the preparation of *O*-desmethyl-venlafaxine includes the reaction of p-benzyloxyphenylacetic acid with dimethyl amine in the presence of oxalyl chloride to obtain 4-benzyloxy-*N,N*-dimethylbenzene acetamide which is further reacted with cyclohexanone in the presence of butyl lithium at a temperature of -70°C to yield 1-[(4-benzyloxyphenyl)[(dimethylamino) carbonyl]methyl]cyclohexanol which is then hydrogenated using lithium aluminium hydride to 1-[1-(4-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol. The resulting benzyl analogue is debenzylated using palladium on carbon as disclosed in the following scheme:



Formula-I

The above process involves the use of n-butyl lithium and lithium aluminium hydride for the preparation of *O*-desmethyl-venlafaxine, which are not advisable for use on commercial scale and are very expensive.

U.S. patent no. 6,673,838 discloses a process of preparing *O*-desmethyl-venlafaxine by demethylating venlafaxine with high molecular weight alkane, arene or arylalkyl thiolate anion such as straight or branched chain thiolate anions having 8-20 carbon atoms, mono or bicyclic arene thiolate anions having 6 to 10 carbon atoms, or mono or bicyclic arylalkyl thiolate anions having 7 to 12 carbon atom, which are very expensive and are not commercially available, hence unviable for industrial use. This patent also discloses demethylation of venlafaxine with an alkali metal salt of a trialkylborohydrides such as selectride (tri-sec-butylborohydride) or triethylborohydride. These reagents are also very costly and are difficult to use on industrial scale. Further the use of trialkylborohydrides are not advisable as these hydrides produce hazardous boron containing byproducts such as tris (1-methylpropyl)borane and tris(1-methylpropyl)boroxin which have to be oxidized using oxidizing agents viz. alkaline perborate solution, thereby increasing the cost and time cycle of the manufacturing process.

U.S. patent no. 6,342,533 discloses a process of preparing *O*-desmethyl-venlafaxine by demethylating venlafaxine with diphenylphosphide in tetrahydrofuran (generated by adding n-butyl lithium to diphenylphosphine in tetrahydrofuran below 0°C) at reflux for an overnight period.

Diphenylphosphine and n-butyl lithium are moisture sensitive, difficult to handle and are not industrial friendly. Furthermore, the method involves extraction steps using large volumes of solvent.

PCT publication no. WO 2007/071404 discloses a process of preparing *O*-desmethyl-venlafaxine by demethylating venlafaxine with metal sulfide such as sodium sulfide or potassium polysulfide in dipolar aprotic solvent such as 1-methylpyrrolidone under heating and in presence of selenium. Metal sulfide can react with acids rapidly to produce hydrogen sulfide gas, which is a highly toxic and foul smelling gas.

PCT publication no. WO 2007/120923 discloses a process of preparing substantially pure *O*-desmethyl-venlafaxine by demethylating venlafaxine with thiophenol, sodium sulfide, and a C_1-C_8 alkyl thiolate in an organic solvent with heating. This application also discloses two more methods for the preparation of *O*-desmethyl-venlafaxine, first method explains specific use of thiophenol for demethylation in non hydroxylic or non ethereal solvent in presence of a base catalyst such as alkali metal carbonate under heating and in second method didesmethylvenlafaxine is first demethylated with thiolate in high boiling point solvent followed by *N*-methylation of tridesmethyl venlafaxine to get substantially pure *O*-desmethyl-venlafaxine. This patent application discloses multi step preparation of O-desmethyl-venlafaxine which is time consuming and not suitable for large scale production.

It is well known that demethylation of *O*-methyl derivatives having tert-alcohol under acidic reaction conditions like using hydrobromic acid, aluminium triiodide, trimethylsilyliodide etc. may lead to formation of side product such as dehydrated analogues. Therefore, it is not advisable to use acidic reaction conditions to accomplish demethylation of venlafaxine. In our hands also we have observed formation of a lot of impurities when demethylation of venlafaxine was attempted using trimethylsilyliodide. The purity of resulting product does not meet the strict requirements imposed either by the pharmacopoeia or health authorities and quality directives. Thus, the preferred reaction condition to conduct demethylation of venlafaxine is basic reaction medium.

It is, therefore, desirable to solve the problems associated with the prior art and to provide an efficient process for the preparation of *O*-desmethyl-venlafaxine which improves the economics by employing easily available, less hazardous raw materials and avoiding the use of corrosive and harmful acidic reagents as well as stringent reaction conditions.

The present invention provides an industrially advantageous process of making *O*-desmethyl-venlafaxine in high yield and purity by demethylation of venlafaxine using mild reaction conditions and less hazardous reagents. The process of present invention is convenient to operate on a commercial scale and gives the desired product in good yield and quality.

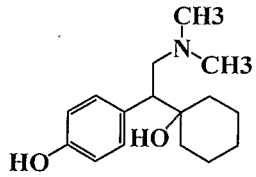
OBJECT OF THE INVENTION

The principal and foremost object of the present invention is to provide an improved process for the preparation of *O*-desmethyl-venlafaxine in good yield and quality which is efficient, industrially advantageous and convenient to operate on industrial scale.

Another object of the present invention is to provide a process for the preparation of *O*-desmethyl-venlafaxine by employing mild reaction conditions.

SUMMARY OF THE INVENTION

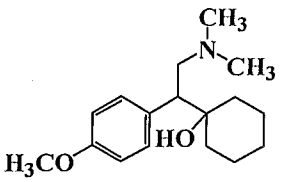
Accordingly, the present invention provides an improved process for the preparation of *O*-desmethyl-venlafaxine of Formula I,



Formula I

or pharmaceutically acceptable salts thereof which comprises the step of:

(a) demethylating venlafaxine of Formula II,



Formula II

or its salts using alkali or alkaline earth metal salts of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids or mixture thereof in presence of organic solvent;

(b) isolating *O*-desmethyl-venlafaxine of Formula I from the reaction mass; and

(c) optionally, converting *O*-desmethyl-venlafaxine of Formula I in to pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. shows a powdered X-ray diffraction pattern (PXRD) of *O*-desmethyl venlafaxine.

Figure 2. shows a differential scanning calorimetric thermogram (DSC) of *O*-desmethyl-venlafaxine.

Figure 3. shows an infra-red spectrum (IR) of *O*-desmethyl-venlafaxine.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved process for the preparation of *O*-desmethyl-venlafaxine of Formula I or pharmaceutically acceptable salts thereof by demethylation of venlafaxine of Formula II or its salt using mild demethylating reagents like alkali and alkaline earth metal salts of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates, thioacids and the like. Preferably thioacetic acid is employed.

The starting material, venlafaxine or its salts may be procured from the market or may be prepared in accordance with procedures known in the art such as described in U.S. Pat. Nos. 4,535,186, and 5,043,466 and PCT publication no. WO 2007/049302.

The salts of the starting material, venlafaxine can be formed conventionally by reaction of the free base with an equivalent amount of corresponding acid. The acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids.

In accordance with the present invention, demethylation of venlafaxine or its salt is performed using alkali or alkaline earth metal salts of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids which are readily available and industrially viable. The formation of side products is minimized by using alkali and alkaline earth metal salts of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids hence the final product is obtained in good yield and purity. The appropriate alkali and alkaline earth metal salts of mercapto acids and

their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids can be selected from mercapto acids such as thioglycolic acid, aromatic mercapto acids; mercaptoacetates such as methyl mercaptoacetates; mercaptoamides such as mercaptoacetamides; mercapto alcohols such as 2-mercaptoethanol; thioacids such as thioacetic acid, xanthates such as potassium or sodium xanthates; heterocyclic mercaptans such as 2-mercaptobenzoxazole, 2-mercaptobenzthiazole; and the like or mixture thereof. Most preferably salt of thioglycolic acid is employed in demethylation of venlafaxine.

In the preferred embodiment of the present invention, alkali and alkaline earth metal salts of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids is taken as 2-10 mole equivalents, more preferably 3- 7 mole equivalents and most preferably 4- 6 mole equivalents.

Generally, the demethylation reaction involves the addition of alkali or alkaline metal salt of mercapto acids and their derivatives such as ester, amide etc., mercapto alcohols, heterocyclic mercaptans, xanthates and thioacids to the venlafaxine base or salt thereof in the presence of organic solvent. The reaction is performed at a temperature of from about ambient temperature to about 220°C, more preferably from about 50°C to about 210°C, and most preferably from about 150°C to about 200°C. The reaction mass is stirred for few minutes to few hours, preferably the reaction mass is stirred for a period of about 10-80 hours at 130-200 °C. More preferably the reaction mass is stirred for a period of about 10-50 hours at 150-190°C and most preferably the reaction mass is stirred for a period of about 12-48 hours at 150-180°C. The solvent employed for the demethylation includes but not limited to halogenated solvents such as dichloroethane, aliphatic esters such as butyl acetate, aliphatic amides such as *N',N'*-dimethylacetamide, *N',N'*-dimethylformamide, *N*-methyl-2-pyrrolidone; aliphatic ketones such as methyl isobutylketone; aromatic hydrocarbons such as toluene; diol such as ethylene glycol, methylene glycol, PEG600 and the like and mixtures thereof. Preferably the solvent employed is selected from *N*-methyl-2-pyrrolidone or *N',N'*-dimethylacetamide. It is advantageous when the quantity of solvent taken is about three to seventeen times with respect to the starting material more preferably quantity of solvent taken is about five to fifteen times.

The reaction completion can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC) for the presence or absence of starting material. The reaction is generally conducted until, ideally, not more than 1% of the starting material remains.

After completion of the reaction, the solvent is removed by suitable techniques like evaporation or distillation under vacuum.

Alkali or alkaline metal salts of above described demethylating agent employed in the process of present invention can be used as such for the reaction or can be generated *insitu* in the reaction mixture for demethylation of venlafaxine. For this purpose demethylating agent is dissolved in a suitable solvent in the presence of source of alkali or alkali metal ion and stirred at ambient temperature to form their alkali or alkali metal salts. The solvent used for the generation of the alkali or alkaline metal salts of the demethylating agent are same as employed for the demethylation reaction (as described above). Source of alkali or alkali metal ion include but not limited to alkali or alkali metal hydroxides, carbonates, bicarbonates or hydride, alkoxide thereof. Preferably the source of alkali or alkali metal ion is sodium hydride.

The demethylation reaction can be performed in the presence or absence of phase transfer catalyst. The phase transfer catalyst employed can be selected from amongst, but not limited to tetraalkylammonium or phosphonium halide such as tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium hydrogen sulphate, crown ethers like 15-crown-5, 18-crown-6, and the like. Preferably the catalyst employed is tetrabutylammonium bromide.

O-Desmethyl-venlafaxine prepared by the process of present invention can be isolated from the reaction mass by any suitable technique known in the art. Preferably the isolation of *O*-desmethyl-venlafaxine from reaction mass can further be performed in two ways.

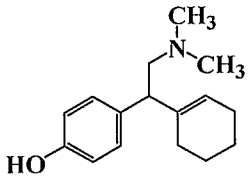
According to one aspect of the present invention, the pH of the reaction mass, after solvent removal, is adjusted to 8-10 with organic or mineral acid such as hydrochloric acid, sulphuric acid or acetic acid. The pH is preferably adjusted to 8.5-9.2 with concentrated hydrochloric acid. The precipitated solid is further stirred for few minutes to few hours, preferably 1 hour at a temperature of below 20°C and isolated.

According to yet another aspect of the present invention, the pH of the reaction mass is adjusted to 1-2 with organic or mineral acid. The pH is preferably adjusted to 1.2-1.4 with dilute hydrochloric acid. The aqueous layer is washed with organic solvents and treated with adsorbent to assist in impurity removal; it is effective to treat the substrate with active charcoal. Organic solvent include halogenated solvent such as dichloromethane; ester such as ethylacetate or hydrocarbon solvent

such as cyclohexane and the like or mixture thereof. After charcoalization, the pH of the aqueous layer is adjusted to 8-10 with suitable base at a temperature of below 20 °C, preferably 10-15 °C. Base used can be organic or inorganic base. Inorganic base include alkali metal bicarbonates, carbonates or hydroxides thereof. Organic base include amine base such as triethylamine and the like. Preferably saturated aqueous potassium carbonate solution is used. The precipitated solid is further stirred for a period of 1 hour at a temperature of below 20 °C, preferably 10-15 °C and then isolated.

The precipitated product obtained by either of the two processes can be isolated by the methods known in prior art preferably by filtration. However, other equivalent separation or isolation procedures could, also be used. The wet solid is then washed with demineralized water to give pure *O*-desmethyl-venlafaxine.

It is generally observed that under acidic conditions, *O*-desmethyl-venlafaxine is dehydrated to give 4-(1-cyclohex-1-enyl-2-dimethylamino-ethyl)-phenol of formula III,



Fórmula III

as an impurity. But in our hands, following the procedure reported in the present invention, the product is found to be free from the above impurity or having impurity up to an amount less than 1%, preferably less than 0.5%, most preferably less than 0.1%.

According to yet another aspect of the present invention, the *O*-desmethyl-venlafaxine so formed can optionally be purified with a suitable solvent to give *O*-desmethyl-venlafaxine in purity above 99% by HPLC. The solvent employed can be selected from, but is not limited to alcohol, esters, halogenated solvents, nitriles, ketones, aromatic hydrocarbon or mixtures thereof; preferably the solvent employed is selected from isopropyl alcohol, ethyl acetate or mixtures thereof.

O-Desmethyl-venlafaxine, so formed by the process of the present invention, is characterized by at least one of Karl Fisher or TGA, powdered X-Ray diffraction (PXRD), Infra-red spectroscopy (IR) or differential scanning calorimetry (DSC).

O-Desmethyl-venlafaxine as prepared by the process of present invention is having about less than 0.7% moisture by weight as measured by Karl Fisher or Thermogravimetric analysis (TGA). Preferably, the moisture content is less than 0.5% by weight, most preferably less than 0.1% by weight. O-Desmethyl-venlafaxine so synthesized displays X-ray powder diffraction pattern as shown in Fig.1. It further displays differential scanning calorimetric thermogram (DSC) as shown in Fig.2 with the onset temperature at 228 °C. O-Desmethyl-venlafaxine is further characterized by an infra-red analysis and peaks are same as shown in Fig.3.

X-ray diffraction of O-desmethyl-venlafaxine is measured on a PANalytical X'Pert Pro diffractometer with Cu radiation and expressed in terms of two-theta, d-spacings and relative intensities. One ordinarily skilled in the art understands that experimental differences may arise due to differences in instrumentation, sample preparation or other factors.

All infrared measurements are made on Perkin Elmer Spectrum 100 spectrometer using KBr pellets having the characteristic absorption bands expressed in reciprocal centimeter. DSC was conducted using a Metler Toledo DSC 823^e a sample weight of about 4-5 mg.

O-Desmethyl-venlafaxine so formed can be optionally converted to its pharmaceutically acceptable acid addition salt by suspending the free base of *O*-desmethyl-venlafaxine along with the corresponding acid in a suitable solvent for a time sufficient to convert to its pharmaceutically acceptable acid addition salt. Pharmaceutically acceptable acid addition salt includes inorganic or organic salt, selected from, but are not limited to, hydrochloric, hydrobromic, fumaric, maleic, succinic, tartarate, sulfuric, phosphoric, tartaric, acetic, and citric acid. Preferably *O*-desmethyl-venlafaxine is isolated as corresponding succinate salt.

The order of adding or mixing the reactant used in the process of present invention does not matter and does not change the composition of the product formed.

Although, the following examples illustrate the practice of the present invention in some of its embodiments, the examples should not be construed as limiting the scope of the invention. Other embodiments will be apparent to one skilled in the art from consideration of the specification and examples. It is intended that the specification, including the examples, is considered exemplary only, with the scope and spirit of the invention being indicated by the claims which follow.

EXAMPLES:

Example -1: Preparation of *O*-desmethyl-venlafaxine

To a solution of thioglycolic acid (2.66 g, 0.028 mol) in *N*-methyl-2-pyrrolidone (30 ml), sodium hydride (1.47 g, 0.059 mol, 60% dispersion in mineral oil) was added at 25-40 °C. The reaction mixture was stirred for 30 minutes, and then venlafaxine (2.0 g, 0.007 mol) was added and stirred at 160-165 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under vacuum to give residue which was diluted with demineralized water (40 ml) and pH of the reaction mass was adjusted to 9.1 with hydrochloric acid. The precipitated solid was stirred for 30 minutes at 10-15 °C and filtered. The wet solid was washed with demineralized water (2x10 ml) followed by purification with isopropyl alcohol to obtain 0.85 g (yield 45%) of title compound as off white powder having purity 99.45% by HPLC.

Example -2: Preparation of *O*-desmethyl-venlafaxine

To a solution of thioglyconamide (2.63 g, 0.028 mol) in *N*-methyl-2- pyrrolidone (30 ml), sodium hydride (1.47 g, 0.059 mol, 60% dispersion in mineral oil) was added in lots. The reaction mass was allowed to stir for 30 minutes and venlafaxine (2.0 g, 0.007 mol) was added at 25-30 °C. The reaction mixture was stirred at 165-170 °C for 48 hours and the progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under vacuum to give residue which was diluted with demineralized water (40 ml). The pH of the reaction mass was adjusted to 9.1 with concentrated hydrochloric acid. The precipitated solid was stirred for 30 minutes at 10-15 °C, filtered and washed with demineralized water (3x15 ml) to obtain 1.14 g (yield 60%) of title compound as off white powder.

Example -3: Preparation of *O*-desmethyl-venlafaxine

To a solution of thioglycolic acid (13.3 g, 0.144 mol) in *N*-methyl-2-pyrrolidone (150 ml), sodium hydride (7.36 g, 0.306 mol, 60% dispersion in mineral oil) was added at 25-40 °C. The reaction mixture was stirred for 30 minutes, then venlafaxine (10.0 g, 0.036 mol) was added and the reaction mass was stirred at 160-165 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under vacuum to give residue which was diluted with demineralized water (200 ml) and the pH of the reaction mass was adjusted to 1.3 with aqueous 5N-hydrochloric acid. The aqueous layer was washed with dichloromethane (2x40 ml) and treated with activated carbon. After charcoalization the pH of the aqueous layer was adjusted

to 8.7 with saturated aqueous potassium carbonate solution at 10-15 °C. The precipitated solid was stirred for 30 minutes at 15-20 °C and filtered. The wet solid was washed with demineralized water (3x40 ml) and recrystallized with isopropyl alcohol (40 ml) to obtain 6.95 g (yield 73.47 %) of title compound as white powder having purity 98.87% by HPLC.

Example -4: Preparation of *O*-desmethyl-venlafaxine

To a stirred solution of thioglycolic acid (2.66 g, 0.028 mol) in *N',N'*-dimethyl acetamide (30 ml), sodium hydride (1.47 g, 0.059 mol, 60% dispersion in mineral oil) was added at 20-40 °C. The reaction mixture was stirred for 30 minutes, then venlafaxine (2.0 g, 0.007 mol) was added and the reaction mass was stirred at 160-165 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under vacuum to give residue which was diluted with demineralized water (40 ml) and pH of the reaction mass was adjusted to 8.8 with hydrochloric acid. The precipitated solid was stirred for 30 minutes at 10-15 °C and filtered. The wet solid was washed with demineralized water to obtain 1.31 g (yield 68.9%) of title compound as off white powder.

Example -5: Preparation of *O*-desmethyl-venlafaxine

To a solution of thioacetic acid (10.9 g, 0.143 mol) in *N*-methyl-2-pyrrolidone (150 ml), sodium hydride (12.3 g, 0.308 mol, ~60% dispersion in mineral oil) was added in lots at 25-40 °C. The reaction mixture was stirred at 25-40 °C for 30 minutes, venlafaxine base (10 g, 0.036 mol) was added and the reaction mass was heated to 160-180 °C for 24 hours. The progress of the reaction was monitored by HPLC. After completion of reaction, the solvent was removed under vacuum to give a residue which was diluted with demineralized water (150 ml). The pH of the reaction mass was adjusted to 1.3 with aqueous hydrochloric acid. The aqueous layer was washed with dichloromethane (40 ml x 3) and treated with activated carbon. After charcoalization, the pH of the aqueous layer was adjusted to 8.7 with aqueous potassium carbonate solution at 10-20 °C. The precipitated solid was stirred for 1hour at 10-20 °C and filtered. The wet solid was washed with demineralized water (50 ml x 2) and recrystallized with isopropyl alcohol (50 ml) to obtain 7 g (yield 74%) of title compound as white powder having purity 99.95% by HPLC.

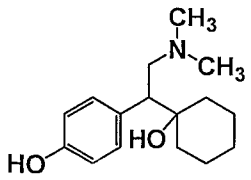
Example -6: Preparation of *O*-desmethyl-venlafaxine

To a solution of venlafaxine (10 g, 0.036 mol) in *N*-methyl-2-pyrrolidone(150 ml), a sodium salt of thioglycolic acid (16.46g) was added at 25-40 °C. The reaction mixture was heated at 160-180 °C.

The progress of the reaction was monitored by HPLC. After the completion of reaction, the solvent was removed under vacuum to give a residue which was diluted with demineralized water (150 ml). The pH of the reaction mass was adjusted to 1.3 with aqueous hydrochloric acid. The aqueous layer was washed with dichloromethane (45 ml x 2) and treated with activated carbon. After charcoalization the pH of the aqueous layer was adjusted to 8.8 with aqueous potassium carbonate solution at 10-20 °C. The precipitated solid was stirred for 1 hour at 10-20 °C and filtered. The wet solid was washed with demineralized water (40 ml x 2) and recrystallized with isopropyl alcohol (50 ml) to give 7.1 g (yield 74.7%) of title compound as white powder having purity 99.37 % by HPLC.

WE CLAIM

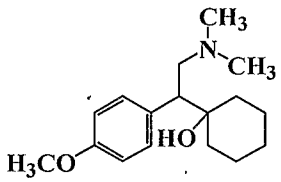
1). A process for preparing *O*-desmethyl-venlafaxine of formula I,



Formula I

or pharmaceutically acceptable salts thereof, comprising the steps of:

(a) demethylating venlafaxine of formula II,



Formula II

or its salts using an alkali and alkaline earth metal salts of mercapto acids and their derivatives, mercaptoalcohols, heteroçyclic mercaptans, xanthates and thioacids and the like or mixture thereof in presence of an organic solvent;

(b) isolating *O*-desmethyl-venlafaxine of formula I from the reaction mass; and

(c) optionally, converting *O*-desmethyl-venlafaxine of formula I to pharmaceutically acceptable salts thereof.

2). The process according to claim 1, wherein in step a) mercapto acids and their derivatives include thioglycolic acid, aromatic mecapto acids, mercaptoacetates such as methyl mercaptoacetates, mercaptoamides such as mercaptoacetamides and the like.

3). The process according to claim 1, wherein in step a) mercaptoalcohols include 2-mercaptoethanol and the like.

4). The process according to claim 1, wherein in step a) heterocyclic mercaptans include 2-mercaptobenzoxazole, 2-mercaptobenzthiazole and the like.

5). The process according to claim 1, wherein in step a) alkali or alkali metal salt of xanthates include potassium or sodium xanthates and the like.

6). The process according to claim 1, wherein in step a) thioacids include thioacetic acid and the like.

7). The process according to claim 1, wherein in step a) alkali or alkaline metal salt of thioacetic acid is used.

8). The process according to claim 1, wherein in step a) alkali or alkaline metal salt of thioglycolic acid or thioglyconamide is used.

9). The process according to claim 1, wherein in step a) the solvent include halogenated solvents, aliphatic esters, amides, aliphatic ketones, aromatic hydrocarbons, diols or mixtures thereof.

10). The process according to claim 1, wherein in step a) the solvent is dichloroethane, butyl acetate, *N',N'*-dimethylacetamide, *N',N'*-dimethylformamide, *N*-methyl-2-pyrrolidone, methyl isobutylketone, toluene, ethylene glycol, methylene glycol, PEG600 and the like or mixture thereof.

11). The process according to claim 1, wherein in step a) the solvent is *N',N'*-dimethylacetamide, *N*-methyl-2-pyrrolidone or mixture thereof.

12). The process according to claim 1, wherein demethylation reaction is performed at a temperature of ambient temperature to about 220 °C.

13). The process according to claim 1, wherein demethylation reaction is preferably performed at a temperature of from 50 °C to 210 °C.

14). The process according to claim 1, wherein demethylation reaction is preferably performed at a temperature of from 150 °C to 200 °C.

15). The process according to claim 1, wherein in step b) isolation of the *O*-desmethyl-venlafaxine comprises:

(a) adjusting the pH of the reaction mixture to 8-10 with a suitable acid; and

(b) isolating the precipitated solid.

16). The process according to claim 15, wherein in step a) suitable acid include organic or mineral acid such as hydrochloric acid, sulphuric acid or acetic acid and the like.

17). The process according to claim 1, wherein in step b) isolation of the *O*-desmethyl-venlafaxine comprises:

(a) adjusting the pH of the reaction mixture to 1-2 with a suitable acid;

(b) optionally, washing the reaction mixture with organic solvent;

(c) adjusting the pH of the reaction mixture to 8-10 with suitable base; and

(d) isolating the precipitated solid.

18). The process according to claim 17, wherein in step a) suitable acid include organic or mineral acid such as hydrochloric acid, sulphuric acid or acetic acid and the like.

19). The process according to claim 17, wherein in step b) organic solvent include halogenated solvent such as dichloromethane; ester such as ethyl acetate or hydrocarbon solvent such as cyclohexane and the like or mixture thereof.

20). The process according to claim 17, wherein in step c) suitable base is inorganic base which include alkali metal bicarbonates, carbonates or hydroxides thereof such as potassium carbonate or organic base which include trialkylamine such as triethylamine and the like.

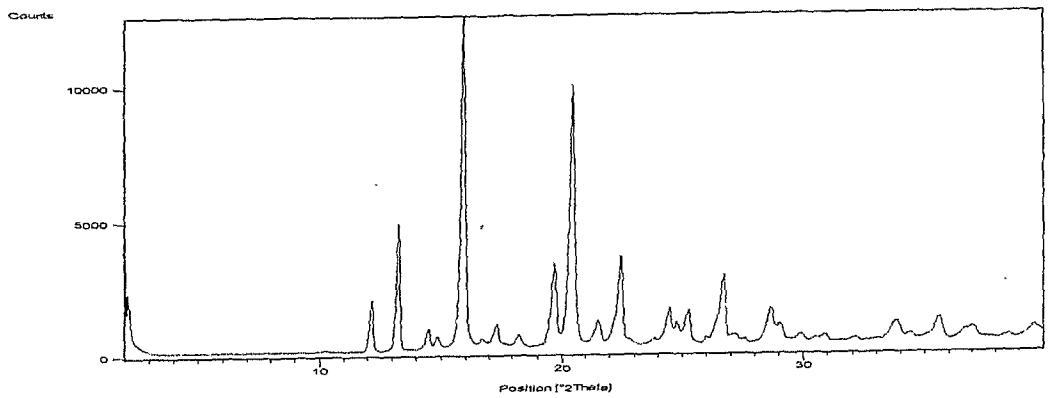


Fig. 1

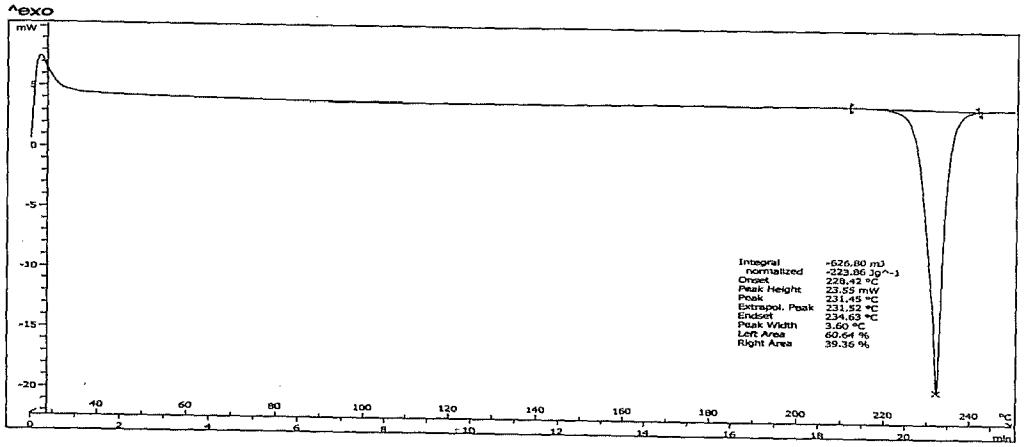

^exo
mW
5
0
-5
-10
-15
-20
40
60
80
100
120
140
160
180
200
220
240
°C
0
2
4
6
8
10
12
14
16
18
20
min
Integral -626.80 mJ
normalized -323.86 Jg^-1
Onset 228.42 °C
Peak Height 23.55 mW
Peak 231.45 °C
Extrapol. Peak 231.52 °C
Endset 234.63 °C
Peak Width 3.60 °C
Left Area 60.64 %
Right Area 39.36 %

Fig. 2

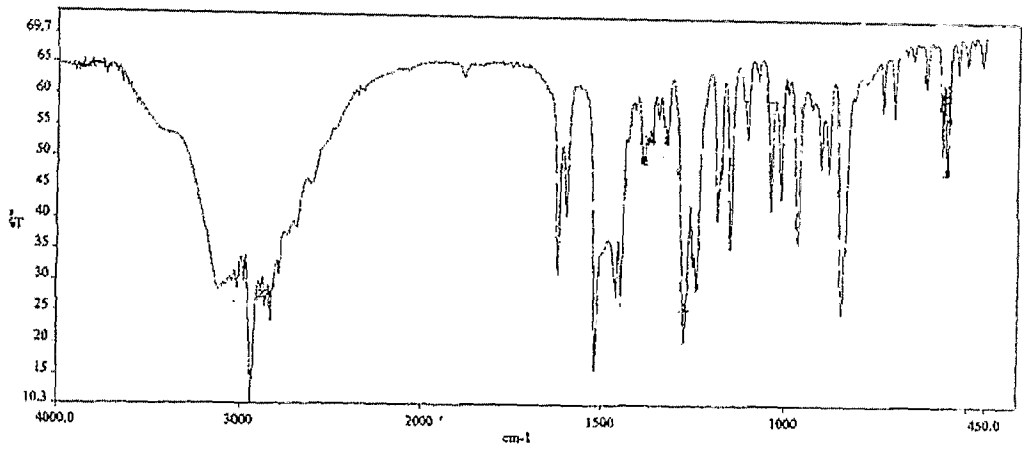

69.7
65
60
55
50
45
40
35
30
25
20
15
10.3
%T
4000.0
3000
2000
1500
1000
450.0
cm-1

Fig. 3