ABSTRACT

The present invention provides a novel process for preparation of Fenspiride hydrochloride (Ia) comprising preparation of 4-tertiarybutoxyaminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (V) and its further cyclization in presence of a base to give Fenspiride (I), which on subsequent treatment with hydrogen chloride yields Fenspiride hydrochloride of formula (Ia) having desired purity.

We claim:

1) A process for preparation of Fenspiride hydrochloride (Ia) comprising
   a) reacting 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane in presence of a base to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III),
   b) reducing compound of formula (III) to give 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV),
   c) treating compound (IV) with a disubstituted carbonate or its derivative to give 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (V), which on subsequent reaction with a base in an organic solvent gave Fenspiride (I), further treatment of (I) with hydrochloric acid in a solvent gave Fenspiride hydrochloride of formula (Ia).

2) A process for the preparation of Fenspiride (I) comprising reaction of 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III), which on reduction gave 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV), further treatment of compound (IV) with di-tertiary butyl dicarbonate gave 4-tertiarybutoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol (Va), which on subsequent reaction with sodium tertiary butoxide, provided Fenspiride (I) having purity conforming to regulatory specifications.

3) A process according to claim 1, wherein the disubstituted carbonate is di-tertiary butyl dicarbonate, dimethyl carbonate, diethyl carbonate, dipropyl carbonate, diphenyl carbonate, dibenzyl carbonate.

4) 4-(tertiarybutoxycarbonyl)-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (Va)

5) 4-Substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (Vb, Vc, Vd Ve and Vf).

6) A process as claimed in step (a) of claim 1 and 2, wherein the base is selected from the group comprising of alkali metal carbonates or alkali metal hydroxides.

7) A process as claimed in step (b) of claim 1, wherein the reduction is carried out with zinc and hydrochloric acid or palladium on carbon or Raney nickel in an alcoholic solvent.

8) A process as claimed in step (c) of claim 1, wherein the base is an alkali metal alkoxide.

9) A process as claimed in claim 1(c) and claim 2, wherein the organic solvent is selected from the group comprising of xylene, toluene and cyclohexane.

10) A process as claimed in step (c) of claim 1 and claim 2, wherein Fenspiride (I) and Fenspiride (Ia) are isolated from ethyl acetate as solvent.

Dated this twenty-ninth day of July 2014

(Signed) _____

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To,
The Controller of Patents
The Patent Office Branch, Mumbai

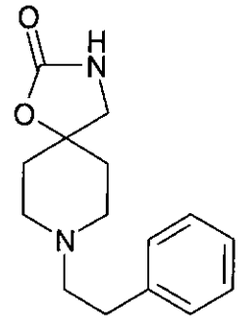
E101/32210/2014

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of a key Fenspiride intermediate, 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (V) by reaction of 4-aminomethyl-1-(2-phenylethyl)piperidine-4-ol of formula (IV) with corresponding carbonates or carbonate derivatives. Facile cyclization of Compound (V) in presence of a base provides Fenspiride (I) conforming to regulatory specification.

BACKGROUND OF THE INVENTION

Fenspiride of formula (I), chemically known as 8-(2-phenylethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one and administered as its hydrochloride salt is known to exhibit anti-inflammatory, bronchodilatory activity for treatment of diseases relating to upper and lower respiratory tract such as bronchial asthma, bronchitis, nasopharyngitis and laryngitis.



Fenspiride (I)
Fenspiride hydrochloride (Ia)

Various processes reported in the literature for the preparation of Fenspiride focus on synthesis of the oxazolidinone ring, which is a characteristic feature in the Fenspiride molecule. The process for preparation of Fenspiride (I) was first disclosed in US 3,399,192 wherein the oxazolidinone ring was synthesized by cyanation of 1-(2-phenylethyl)-4-piperidone, followed by reduction of the corresponding cyanohydrin intermediate with aluminium alanate and subsequent introduction of a carbonyl group in the resulting 1-(2-phenylethyl)-4-aminomethyl-4-hydroxy piperidine using diethyl carbonate in presence of sodium methylate. The method is suitable only for academic purpose, as it has serious industrial limitations due to the utilization of highly toxic cyanide compounds and a hazardous, moisture sensitive reagent such as aluminium alanate, which is flammable and ignites on contact with moisture or in humid conditions.

US 4,028,351 discloses a method wherein the oxazolidinone moiety in Fenspiride is formed by reaction of N-(2-phenylethyl)-4-piperidone with ethyl bromoacetate in presence of activated zinc using a solvent mixture of benzene and ether to give ethyl-4-hydroxy-1-phenylethyl-4-piperidine acetate. The resultant ester on reaction with excess hydrazine hydrate in benzene gives 4-hydroxy-1-phenethyl-4-piperidineacetic acid hydrazide, which is further reacted with sodium nitrite in presence of hydrochloric acid to yield Fenspiride (I).

Although this process avoids use of hazardous cyanides, however, a lengthy reaction sequence that includes highly carcinogenic and inflammable solvents like benzene and ether, use of zinc metal, requirement of elaborate work up for removal of zinc hydroxide sludge and specific disposal procedures during effluent treatment restricts this process for commercial scale. Further, the involvement of a rearrangement reaction in the sequence and potentially hazardous intermediates such as acid hydrazides considerably reduces the yield of the desired product.

Synthetic Communication, 1994, 24(10), 1483-1487 describes a process which involves reaction of N-(2-phenylethyl)-4-piperidone with trimethylsilyl cyanide, followed by reduction of the resulting cyanohydrin derivative with lithium aluminium hydride and subsequent cyclization with triphosgene to give Fenspiride. The process utilizes hazardous reagents like trimethylsilyl cyanide, lithium aluminium hydride and triphosgene, which are extremely dangerous for utilization on a commercial scale. Trimethylsilyl cyanide is highly moisture sensitive and releases extremely toxic hydrogen cyanide gas on contact with water. Further, lithium aluminium hydride employed in the reduction step requires stringent anhydrous conditions due to its moisture sensitive nature and the possible hazard of explosion when it comes in contact with moisture.

ES 548648 discloses a process involving partial hydrogenation of 4-nitromethyl-1-(2-phenylethyl)piperidin-4-ol to give the corresponding hydroxy(hydroxylaminomethyl)piperidine intermediate, which on further reaction with phosgene, followed by hydrogenation of the resulting hydroxamic acid derivative furnishes the oxazolidinone ring of Fenspiride.

Based on the described prior art procedures, it would be evident that synthesis of the oxazolidinone ring in Fenspiride involves different carbonylation reagents like phosgene, diethyl carbonate, carbonyl diimidazole etc. While hazardous, inflammable reagents like

phosgene, diethyl carbonate create safety problems for the process, use of relatively safe carbonylating agents like carbonyl diimidazole involves a different procedural hazard involving removal of by-products like imidazole from the final product, which then requires additional unit operations in the manufacturing process leading to longer batch-cycle time and ultimately adding to the cost.

Thus, there still exists a need for a convenient, easy-to-scale up process for synthesis of Fenspiride (I) which avoids hazardous cyanation reactions, reagents like lithium aluminium hydride and employs a simple, convenient and cost-effective synthetic approach for incorporating the oxazolidinone ring in Fenspiride (I).

The present inventors have developed a process for synthesis of Fenspiride (I) in which the oxazolidinone ring is constructed by facile intramolecular cyclization of a novel intermediate, 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (V), which is synthesized by reaction of (2-phenylethyl)-4-piperidone of formula (II) with nitromethane, followed by reduction of the corresponding nitro alcohol to the corresponding amine derivative (IV) and its subsequent reaction with respective carbonates or their derivatives.

OBJECT OF THE INVENTION

An objective of the present invention is to provide Fenspiride hydrochloride of formula (Ia) having desired purity by a convenient and industrially viable process which does not involve use of toxic and hazardous reactions such as cyanation or reduction with a moisture sensitive reagent like lithium aluminium hydride.

Another object of the present invention is to provide an efficient and cost-effective process for preparation of Fenspiride hydrochloride (Ia) involving synthesis of the key intermediate 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (V) and its cyclization to yield Fenspiride (I), which on further treatment with hydrogen chloride gives Fenspiride hydrochloride (Ia).

SUMMARY OF THE INVENTION

The present invention relates to a novel method for synthesis of 8-(2-phenylethyl)-1-oxa-3,8-diazaspiro[4.5]decan-2-one hydrochloride of formula (Ia) having desired purity.

An aspect of the present invention relates to a process for preparation of Fenspiride hydrochloride (Ia) comprising reaction of 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III), which on reduction gives 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV), further treatment of compound (IV) with a carbonate or its derivative gives 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (V), which on subsequent reaction with a base, provides Fenspiride (I); further treatment of (I) with hydrochloric acid in a solvent yields Fenspiride hydrochloride (Ia) having purity conforming to regulatory specifications.

Another aspect of the present invention relates to a process for the preparation of Fenspiride (I) comprising reaction of 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III), which on reduction gave 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV), further treatment of compound (IV) with di-tertiary butyl dicarbonate gave 4-tertiarybutoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol (V), which on subsequent reaction with sodium tertiary butoxide, provided Fenspiride (I) having purity conforming to regulatory specifications.

The objectives of the present invention will become more apparent from the following detailed description.

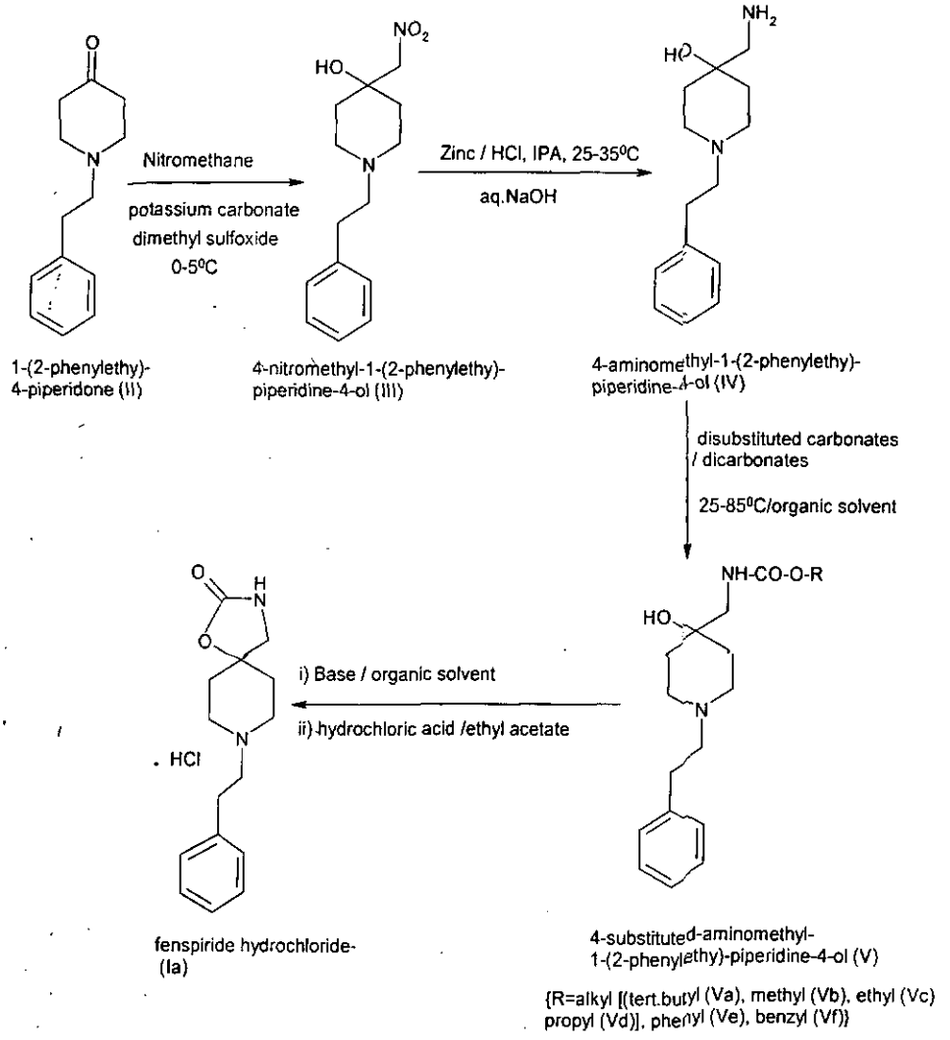
DETAILED DESCRIPTION OF THE INVENTION

Construction of oxazolidinone ring in active pharmaceutical ingredients or their intermediates has always been a challenging task for chemists and a wide range of synthetic methods have been reported in literature for its synthesis. While pursuing the development of an industrially viable and economical process for synthesis of Fenspiride, the present inventors have surprisingly found that oxazolidinone ring in the Fenspiride molecule can be easily constructed by preparation and subsequent cyclization of the key intermediate, 1-(2-phenylethyl)-4-

substituted-aminomethyl piperidin-4-ol of formula (V) wherein the substituent is selected from the group comprising of alkyloxycarbonyl, phenoxy carbonyl, benzyloxycarbonyl etc.

The process for synthesis of intermediate (V) comprises reaction of 1-(2-phenylethyl)-4-piperidone (II) with nitromethane followed by reduction of 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol (III), subsequent reaction of 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol (IV) with a reagent selected from the group comprising of disubstituted carbonates like diphenyl carbonate, dibenzyl carbonate, ditertiary butyl carbonate or their dicarbonate derivatives yielded the respective substituted-4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol; compound (V)

In the present strategy, the carbonyl group, which is an essential feature of the oxazolidine ring is introduced in the desired molecule through the meticulously selected alkoxy-carbonyl substituents. Thus, the strategy not only avoids use of hazardous carbonylation reagents for construction of oxazolidine ring, but also avoids additional purification steps for separating the side products in the conventional carbonylation reactions, as disclosed in the prior art. The side product of this facile, high-yielding cyclization of 4-substituted-aminomethyl-1-(2-phenylethyl)piperidin-4-ol (V) are compounds like tertiary butanol or other alcohols based on the substituent used, which can be easily removed from the reaction during work up. As a result of this, no additional step is required for removal of any side product. Thus, by avoiding hazardous reagents and multiple synthetic steps for the synthesis of oxazolidinone moiety, problems such as substantial quantities of associated impurities, longer reaction times are avoided, leading to Fenspiride hydrochloride (Ia) of desired purity



Scheme 1: Method embodied in the present invention for the preparation of Fenspiride hydrochloride (Ia)

In an embodiment, 1-(2-phenylethyl)-4-piperidone of formula (II) is treated with nitromethane at 0°C in an organic solvent in presence of a base, to yield 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III).

The organic solvent was selected from the group comprising of dimethyl sulfoxide, dimethyl formamide, dimethyl acetamide, and N-methyl-2-pyrrolidone, but preferably dimethyl sulfoxide. The base was selected from a group of inorganic bases comprising of sodium carbonate, potassium carbonate etc.

After completion of reaction as monitored by HPLC, the reaction was quenched with water and 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol (III) separating out was filtered and dried.

4-Nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III) was reduced by dissolving in an alcohol such as n-propanol or isopropanol, followed by addition of Zinc powder and aqueous hydrochloric acid (6N) to the mixture at 0°C and stirring at 25-35°C till completion of the reaction, based on HPLC. The reaction mixture was cooled to 5°C, treated with aqueous solution of sodium hydroxide till pH of 8-9. The mixture was extracted with an organic solvent such as dichloromethane, the organic layer was separated and concentrated to give 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (IV).

Optionally, Compound (III) can also be hydrogenated in presence of catalyst such as palladium on carbon or Raney nickel to get the desired compound of formula (IV).

4-Aminomethyl-1-(2-phenylethyl)-piperidin-4-ol, compound (IV), taken in a suitable solvent, and optionally in presence of base, was treated with reagents selected from group of disubstituted carbonates such as dimethyl carbonate, diethyl carbonate, dipropyl carbonate, di-tertiary-butyl carbonate, diphenyl carbonate, dibenzyl carbonate or their dicarbonate derivatives, in an organic solvent selected from the group of alcohols, ketones, ethers etc. or mixtures thereof to convert it to compound of formula (V). For example, 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (IV) was treated with di-tertiarybutyl dicarbonate at 20 to 35^{0}C, in an alcohol solvent such as methanol, ethanol, n-propanol, isopropanol etc. After completion of the reaction as monitored by HPLC, the desired product was separated to obtain the butoxycarbonyl intermediate 4-(tertiarybutoxycarbonyl)-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (Va),

Alternatively, without isolating the compound of formula (IV), the reaction mass obtained after the above-mentioned treatment of compound (III) with Zinc/HCl was basified using aqueous sodium hydroxide to pH 8 to 9 and treated with respective alkyl, phenyl or benzyl carbonate or the corresponding dicarbonate in an organic solvent or solvent mixture to obtain the intermediate (V). Particularly, in the case of tertiary butoxycarbonyl as the substituent, the basified reaction mass of intermediate (IV) was treated with di-tertiarybutyl dicarbonate. When

the reaction was complete, as monitored by HPLC, water was added to the reaction mixture followed by filtration. The filtrate was extracted with dichloromethane and the organic layer concentrated to yield a residue containing 4-tert-butoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol (Va).

The residue was dissolved in an organic solvent followed by addition of a base at 20-30°C and the mixture stirred at 40-60°C. The organic solvent was selected from the group comprising of aliphatic and aromatic hydrocarbons such as hexane, cyclohexane, xylene(s), toluene, etc., ethers such as diethyl ether, di-tert.butyl ether, di-isopropyl ether etc., but preferably toluene.

The base was selected from alkali metal alkoxides derived from methanol, ethanol, tertiary butanol and alkali metals like sodium and potassium. The base was preferably sodium tert-butoxide.

The amount of base added was between 1.2 moles and 1.7 moles per mole of compound (V). After reaction completion, the mixture was concentrated and the residue was diluted with water and ethyl acetate. Separation of the organic layer and concentration gave the product of formula (I), which was recrystallized from ethyl acetate to yield Fenspiride base of desired purity.

Fenspiride base (I) was converted to its hydrochloride salt by dissolving in dichloromethane and treated with hydrogen chloride in ethyl acetate at 25-35°C. The reaction mixture was stirred for one hour and concentrated partially. The mixture was then diluted with ethyl acetate and filtered to provide Fenspiride hydrochloride (Ia) having purity conforming to regulatory specifications.

The following examples are meant to be illustrative of the present invention. These examples exemplify the invention and are not to be construed as limiting the scope of the invention.

EXAMPLES

Example 1: Preparation of 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol (III)

1-(2-Phenylethyl)-4-piperidone (100.3g) was added to a stirred mixture of nitromethane (150 ml) and potassium carbonate (81.5gms) in dimethyl sulfoxide (200 ml) at 0^0C and stirred at the same temperature till completion of reaction. Water was added to the reaction mixture to separate out 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III), which was then filtered and washed with water and cyclohexane.

Yield: 115.6 g

%Yield: 89%; Purity: 99%

Example 2: Preparation of 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (IV)

Hydrochloric acid (6N, 500ml) was added to a mixture of 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol (III) (100.2 g) and isopropyl alcohol (500 ml) at 0°C, followed by addition of zinc powder (124.5 g) in small portions. Temperature of the reaction mass was gradually raised to 25-35°C and stirred at the same temperature till completion of the reaction. The reaction mass was cooled to 5-10°C, quenched with aqueous sodium hydroxide till the pH was 8 to 9 and extracted with dichloromethane. The organic layer was separated and concentrated to give 4-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (IV). Alternatively, the reaction mass obtained after basification could also be used as such for further reaction.

Example 3: Preparation of 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (V)

Compound (IV) (5gms) was stirred with a disubstituted carbonate (1.5 mole equivalent), in isopropyl alcohol (25ml), optionally in presence of base, till completion of the reaction. The reaction mass was concentrated or extracted with dichloromethane. The organic layer was concentrated and the residue containing the desired 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol, compound (V), was subjected to further treatment with base in toluene as solvent and heated till 50-55^{0}C till completion of reaction. The reaction mass was concentrated, followed by addition of water and ethyl acetate. Separation and concentration of the organic layer gave Fenspiride base (I) which was optionally purified by recrystallization from ethyl acetate.

Example 4: Preparation of 4-tertiarybutoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol (Va)

Di-tertiarybutyl dicarbonate (100.7 g) was gradually added to the reaction mass from Example 2 and the resulting mixture was stirred at 25-35^{0}C till completion of the reaction based on HPLC. Water was added to the reaction mass, filtered, the filtrate was extracted with dichloromethane (500ml). The organic layer was separated and concentrated to give 4-tert.butoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (Va).

Example 5: Preparation of Fenspiride base (I)

Sodium tert-butoxide (51.3g) was gradually added to a mixture of compound (V; 120.2gms) and toluene (500 ml) with stirring and the reaction mass heated to 50-55^{0}C till completion of reaction. The reaction mass was concentrated, followed by addition of water and ethyl acetate. Separation and concentration of the organic layer gave Fenspiride base (I) which was optionally purified by recrystallization from ethyl acetate.

Example 6: Preparation of Fenspiride hydrochloride (Ia)

About 10% solution of hydrogen chloride in ethyl acetate (200 ml) was gradually added to the solution of Fenspiride base (65.7 g) in dichloromethane (390 ml) at room temperature. After completion of the reaction, as monitored by TLC, the reaction mass was concentrated, which was followed by addition of ethyl acetate to the residue. Filtration and drying of the resulting solid yielded Fenspiride hydrochloride (Ia).

Yield: 73.8 g

%Yield: 98%; Purity: > 99.8%

We claim:

1) A process for preparation of Fenspiride hydrochloride (Ia) comprising
   a) reacting 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane in presence of a base to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III),
   b) reducing compound of formula (III) to give 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV),
   c) treating compound (IV) with a disubstituted carbonate or its derivative to give 4-substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol (V), which on subsequent reaction with a base in an organic solvent gave Fenspiride (I), further treatment of (I) with hydrochloric acid in a solvent gave Fenspiride hydrochloride of formula (Ia).

2) A process for the preparation of Fenspiride (I) comprising reaction of 1-(2-phenylethyl)-4-piperidone of formula (II) with nitromethane to give 4-nitromethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (III), which on reduction gave 4-aminomethyl-1-(2-phenylethyl)-piperidine-4-ol of formula (IV), further treatment of compound (IV) with di-tertiary butyl dicarbonate gave 4-tertiarybutoxycarbonylaminomethyl-1-(2-phenylethyl)-piperidin-4-ol (Va), which on subsequent reaction with sodium tertiary butoxide, provided Fenspiride (I) having purity conforming to regulatory specifications.

3) A process according to claim 1, wherein the disubstituted carbonate is di-tertiary butyl dicarbonate, dimethyl carbonate, diethyl carbonate, dipropyl carbonate, diphenyl carbonate, dibenzyl carbonate.

4) 4-(tertiarybutoxycarbonyl)-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (Va)

5) 4-Substituted-aminomethyl-1-(2-phenylethyl)-piperidin-4-ol of formula (Vb, Vc, Vd Ve and Vf).

6) A process as claimed in step (a) of claim 1 and 2, wherein the base is selected from the group comprising of alkali metal carbonates or alkali metal hydroxides.

7) A process as claimed in step (b) of claim 1, wherein the reduction is carried out with zinc and hydrochloric acid or palladium on carbon or Raney nickel in an alcoholic solvent.

8) A process as claimed in step (c) of claim 1, wherein the base is an alkali metal alkoxide.

9) A process as claimed in claim 1(c) and claim 2, wherein the organic solvent is selected from the group comprising of xylene, toluene and cyclohexane.

10) A process as claimed in step (c) of claim 1 and claim 2, wherein Fenspiride (I) and Fenspiride (Ia) are isolated from ethyl acetate as solvent.

Dated this twenty-ninth day of July 2014

(Signed) _____

Sunil G. Bhat
Associate Director, Intellectual Property
Emcure Pharmaceuticals Ltd.

To,
The Controller of Patents
The Patent Office Branch, Mumbai