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- (71) Applicant (for all designated States except US): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110 019 (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase - III, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN). **PRASAD, Mohan** [IN/IN]; House No. P-3/3, Phase - II, DLF Qutab Enclave, Gurgaon, Haryana 122001 (IN). **NAYYAR, Kaushal** [IN/IN]; House No. 1345, Sector - 17C, Gurgaon, Haryana 122001 (IN). **SHARMA, Namita** [IN/IN]; House No. 545, Sector - 31, Gurgaon, Haryana 122001 (IN).
- (74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).
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(54) Title: PROCESS FOR PREPARATION OF 2-(3-DIISOPROPYLAMINO-1-PHENYLPROPYL)-4-HYDROXYMETHYL-PHENOL, A METABOLITE OF TOLTERODINE

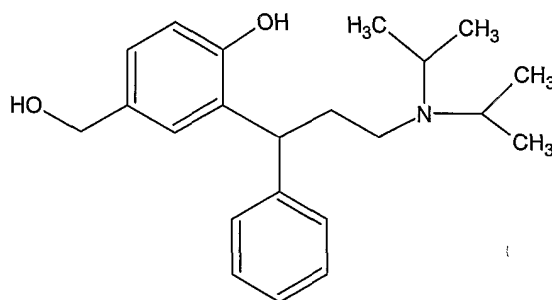
(57) Abstract: The present invention relates to processes for preparation of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol of Formula I, which is a metabolite of tolterodine.

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PROCESS FOR PREPARATION OF 2-(3-DIISOPROPYL AMINO-1-PHENYLPROPYL)-4-HYDROXYMETHYL-PHENOL, A METABOLITE OF TOLTERODINE

Field of the Invention

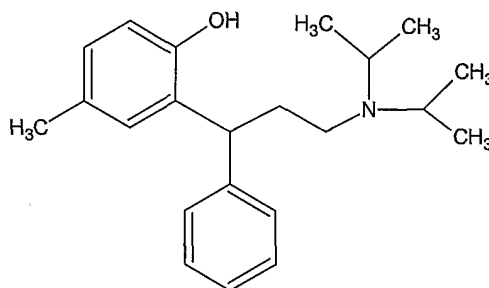
5 The present invention relates to processes for preparation of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol of Formula I, which is a metabolite of tolterodine.



FORMULA I

10 Background of the Invention

Tolterodine is N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine having Formula II. It is a potent and competitive muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and other symptoms of bladder overactivity.



FORMULA II

Tolterodine is extensively metabolized by liver following oral administration. The primary metabolic route involves the oxidation of the 4-methyl group and is mediated by the enzyme cytochrome P 4502D6 (CYP2D6) and leads to the formation of pharmacologically active 4-hydroxymethyl metabolite of Formula I. Tolterodine is

alternatively metabolized via N-dealkylation of diisopropylamino group mediated by enzyme CYP3A.

US Patent No. 5,686,464 discloses the synthesis of the above said active metabolite of tolterodine. The synthesis reported in this patent requires many steps and involves hazardous reagents. The process is not economical, not safe and time-consuming and hence not readily suitable for commercial production.

Summary of the Invention

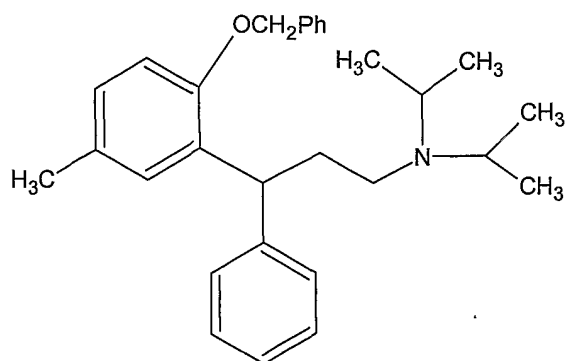
Disclosed herein are improved processes for the preparation of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol, a metabolite of tolterodine of Formula I, using easily available raw material such as tolterodine hydrobromide. The process provides simple, cost-effective and easily scalable processes for synthesis of the active metabolite.

Administration of the active metabolite of tolterodine to patients would appear to have some advantage over administration of tolterodine, since only one active principle (compound) has to be handled by the patient. This should normally result in less variation in efficacy and fewer side effects for patients. This should also substantially reduce the risk of interaction with other drugs. The active metabolite of tolterodine should therefore be more effective in the treatment of urinary urge inconstitence.

Detailed Description of the Invention

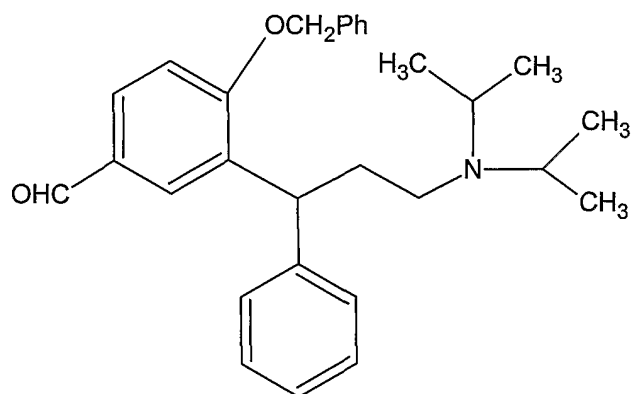
In one aspect is provided a process for the preparation of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol, a metabolite of tolterodine, wherein the process includes

- a) reacting tolterodine or a salt thereof with a benzylating agent to produce a compound of Formula III,



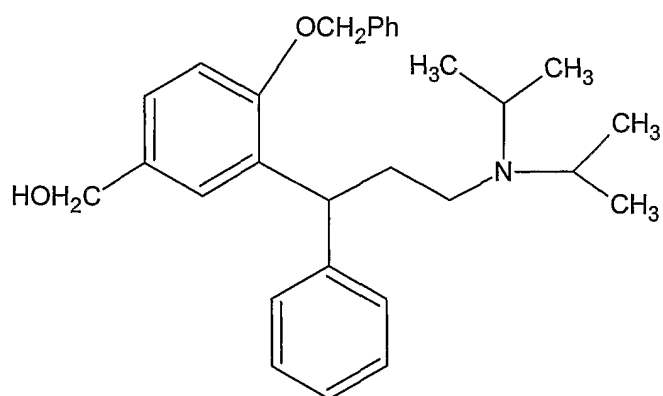
FORMULA III

- b) oxidizing the compound of Formula III to produce a compound of Formula IV or a salt thereof,



FORMULA IV

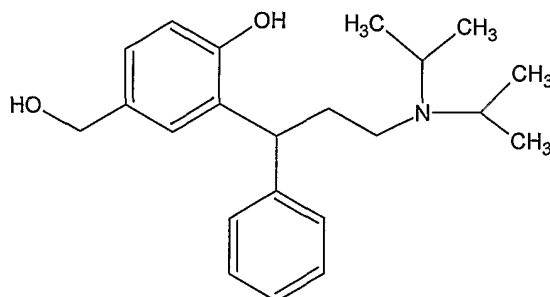
- 5 c) reducing the product of Formula IV to produce a compound of Formula V or a salt thereof, and



FORMULA V

- d) debenzylating the compound of Formula V to produce the compound of Formula I or a salt thereof.

Optionally, and desirably at this point, any non-pharmaceutically acceptable salt can be converted to a pharmaceutically acceptable salt by methods known to those in the art.



FORMULA I

5

The process of benzylation at step a) of first aspect includes reacting tolterodine or a pharmaceutically acceptable salt thereof of Formula II with a benzylation agent to get a compound [3-(2-benzyloxy-5-methyl-phenyl)-3-phenyl-propyl]-diisopropylamine of Formula III. The benzylation step can be performed in an organic solvent comprising alcohols and non-alcoholic solvents or mixtures thereof. The reaction can be performed in the presence of a base and worked-up after completion to afford the intermediate compound of Formula III.

The organic solvents can include alcohols selected from primary, secondary or tertiary alkanols, for example, methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol and t-butanol. The non-alcoholic organic solvents can include ketones, ethers, esters, polar aprotic solvents, aromatic hydrocarbons or mixtures thereof for example. Ketones may be selected from acetone, ethyl methyl ketone, methyl isobutyl ketone and diisobutyl ketone for example. Ethers may be selected from tetrahydrofuran, 1,4-dioxane, diisopropyl ether and diethyl ether for example. Esters may be selected from methyl acetate, ethyl formate, ethyl acetate and n-butyl acetate for example. Polar aprotic solvents may be selected from N,N-dimethylformamide, N,N-dimethylacetamide and dimethylsulphoxide for example. Aromatic hydrocarbons may be selected from toluene, xylene, ethyl benzene and benzene for example. In some embodiments, organic solvents may be selected from methanol, ethanol, acetone, ethyl acetate and mixtures thereof. For example, a mixture of methanol and acetone can be used.

25

Benzylating agent can be selected from benzyl chloride, substituted benzyl chlorides such as p-chlorobenzyl chloride, p-nitrobenzyl chloride, o-chlorobenzyl chloride, o-nitrobenzyl chloride, benzyl alcohol, dibenzyl ether and p-chlorophenyl benzyl ether for example. In some embodiments, benzyl chloride can be used.

5 Base used in the reaction can include hydrides, alkoxides, hydroxides or carbonates of alkali or alkaline earth metals, or mixtures thereof for example. Hydrides can be selected from sodium hydride, potassium hydride, or calcium hydride for example. Alkoxides can be selected from sodium methoxide, sodium ethoxide, potassium t-butoxide or potassium isopropoxide for example. Hydroxides of alkali metals can be selected from
10 sodium hydroxide or potassium hydroxide for example. Carbonates of alkali metals can be selected from sodium carbonate potassium carbonate or lithium carbonate for example. In particular examples, potassium carbonate can be used.

 The oxidation of the benzyl derivative, [3-(2-benzyloxy-5-methyl-phenyl)-3-phenyl-propyl]-diisopropyl amine of Formula III in step b) can be performed in the
15 presence of an organic solvent optionally containing water. The reaction can be carried out for about 1 to about 10 hours, followed by a suitable work-up to afford the intermediate 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl]-benzaldehyde of Formula IV.

 Organic solvent may be selected from dimethylformamide, chloroform,
20 acetonitrile, tetrahydrofuran, toluene, dimethylsulphoxide, dimethylacetamide or mixtures thereof for example.

 Oxidizing agents used are conventional and may be selected from ruthenium chloride/sodium periodate, fuming nitric acid, peracids, Dess-Martin reagent, chromium 4-oxide, nickel peroxide, sodium dichromate, manganese dioxide, potassium permanganate,
25 activated silver oxide, pyridinium chlorochromate, ceric ammonium nitrate, ceric ammonium citrate for example. Sodium persulphate and/or potassium persulphate in the presence of copper (II) sulphate may also be used as oxidizing agent. In some embodiments sodium persulphate can be used.

 The reduction of 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl]-
30 benzaldehyde of Formula IV in step c) can be performed with conventional reducing agents in the presence of an organic solvent. The reaction can be carried out for about 1 to

about 10 hours followed by suitable work up to get reduced intermediate product, [4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol of Formula V.

The reducing agent may be selected from sodium borohydride, potassium borohydride, Vitride®, tetralkylammonium borohydride, calcium borohydride, zinc borohydride, sodium cyanoborohydride, and lithium aluminium hydride for example. In some embodiments, sodium borohydride can be used.

Organic solvent used in step c) may be selected from alkanols, ethers and acetonitrile or mixtures thereof for example. The alkanols and ethers may be the same as suggested in step a).

Debenzylation of [4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol of Formula V in step d) can be performed using a noble metal catalyst in an organic solvent. The debenzylation reaction can be effected in presence of hydrogen gas. A compound capable of generating hydrogen gas can also be used during this reaction as source of hydrogen. The reaction temperature is kept between 0 to 100°C. The desired product 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenol of Formula I can be isolated by suitable aqueous basic work-up.

Organic solvent used in debenzylation at step d) can be selected from alkanols, ethers, aromatic hydrocarbons or mixtures thereof for example. The alkanols may be selected from methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol, t-butano for example. Ethers may be selected from tetrahydrofuran, diethyl ether, 1,4-dioxane and diisopropyl ether for example. Aromatic hydrocarbon may be selected from toluene, xylene and ethyl benzene for example.

The noble metal catalyst used in the step of debenzylation can be selected from palladium on carbon, palladium acetate, platinum oxide, platinum black, platinum oxide adsorbed on carbon, rhodium on carbon, ruthenium and its salts adsorbed on solid support for example. The compound capable of generating hydrogen gas can be selected from ammonium formate, formic acid, alkali metal formates such as sodium formate, potassium formate for example. When such compounds are used as source of hydrogen, the reaction can be carried out at atmospheric pressure and at a lower temperature.

The suitable aqueous basic work-up can involve dissolving the residue in an organic solvent and washing with a base. Any organic solvent may be used for extraction and such solvent are known to a person of ordinary skill in the art and can include

water-immiscible and partially-miscible solvents, such as alkanols, ethers, aromatic hydrocarbon and mixtures thereof. Base may include sodium or potassium carbonate for example.

5 A second aspect provides a compound of Formula IV or a salt, hydrate, solvate or polymorph thereof.

A third aspect provides a compound of Formula V or a salt, hydrate, solvate or polymorph thereof.

10 While the present invention has been described in terms of some specific embodiments, certain modification and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Example 1: Preparation of Tolterodine Metabolite, 2-(3-Diisopropylamino-1-Phenyl-Propyl)-4-Hydroxy Methyl-Phenol

Step A: Preparation of [3-(2-Benzyloxy-5-Methyl-Phenyl)-3-Phenyl-Propyl]-Diisopropylamine

15 To the mixture of methanol (65 ml) and acetone (65 ml), tolterodine hydrobromide (15.3 g, 0.0376 mole) was added. To the above reaction mixture potassium carbonate (11.5 g, 0.0833 mole), sodium iodide (2.7 g, 0.018 mole) and (5.25 g, 0.0415 mole) of benzyl chloride were added at ambient temperature. Reaction mixture was then refluxed for 3.25 hours. The solvent was distilled out completely under vacuum and to the solid
20 residue water (200 ml) was added, followed by the extraction with diethyl ether (3 x 100 ml). Combined organic layer was washed with water (100 ml) followed by sodium carbonate (100 ml, 33% aqueous solution). Solvent was removed under high vacuum to produce 14.1 g of title compound.

25 **Step B: Preparation of 4-Benzyloxy-3-(3-Diisopropylamino-1-Phenyl-Propyl)-Benzaldehyde**

To the [3-(2-benzyloxy-5-methyl-phenyl)-3-phenyl-propyl]-diisopropyl amine (14 g, 0.0336 mole), acetonitrile (300 ml) and water (300 ml) were added at room temperature. To this of copper sulfate (9.17 g, 0.0367 mole) and of sodium persulfate (24.18 g, 0.101 mole) were added and the reaction mixture was refluxed (78 – 80°C) for 4 hours. The
30 reaction mixture was cooled to room temperature and was extracted with dichloromethane (2 x 200 ml). Combined organic layer was washed with water (200 ml) followed by brine

(2 x 200 ml). Dichloromethane was removed under vacuum to produce 9.94 g of title compound as liquid.

Step C: Preparation of [4-Benzyloxy-3-(3-Diisopropylamino-1-Phenyl-Propyl)-Phenyl]-Methanol

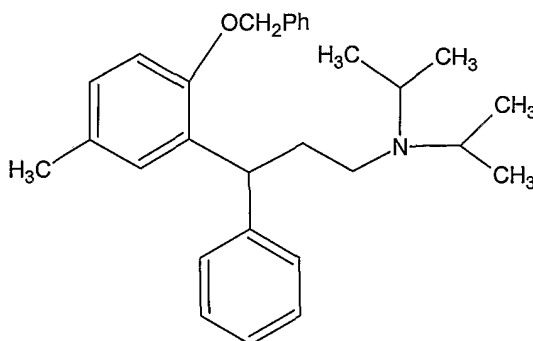
5 To 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl]-benzaldehyde (9 g, 0.021 mole) of Formula IV in methanol (90 ml) were added sodium borohydride (1.59 g, 0.042 mole). The reaction mixture was refluxed for 3 hours and the solution cooled to room temperature followed by adding water (90 ml). Methanol was removed under vacuum and the aqueous layer was extracted with 2 x 90 ml chloroform. The chloroform was
10 evaporated under vacuum which resulted in crude title compound (8 g).

Step D: Preparation of 2-(3-Diisopropylamino-1-Phenyl-Propyl)-4-Hydroxy Methyl-Phenol (Formula I)

[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (8g) of Formula V was dissolved in methanol (80 ml), and to it 10% Palladium on Carbon (0.8 g,
15 50% wet) was added. The mixture was hydrogenated at 40 – 50 psi hydrogen pressure using Paar hydrogenator. The reaction mixture was filtered through celite bed and the solvent was distilled out completely under vacuum. The residue was dissolved in dichloromethane (50 ml) and washed with aqueous sodium carbonate solution (5%, 2 x 50 ml). The residue was finally washed with water (50 ml) and the solvent was distilled out
20 completely under vacuum to produce of title compound (2.5 g).

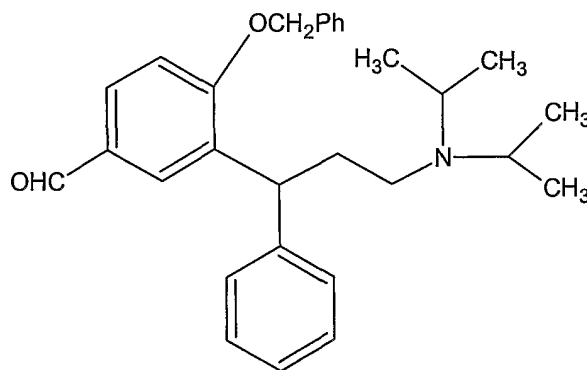
We claim:

- 1 1. A process for the preparation of 2-(3-diisopropylamino-1-phenylpropyl)-4-
2 hydroxymethyl-phenol, a metabolite of tolterodine, wherein the process comprises:
3 a) reacting tolterodine or a salt thereof with a benzylating agent to produce a
4 compound of Formula III;



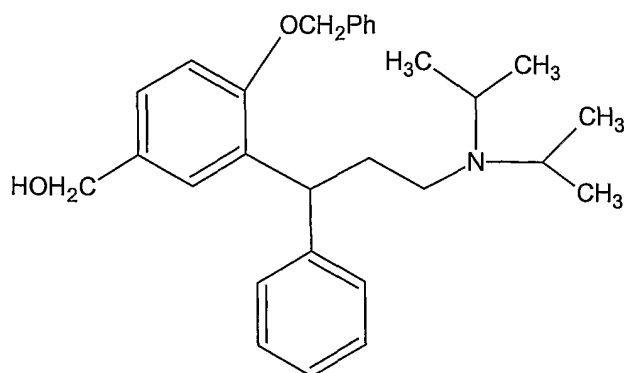
FORMULA III

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8 b) oxidizing the compound of Formula III to produce a compound of
9 Formula IV or a salt thereof;



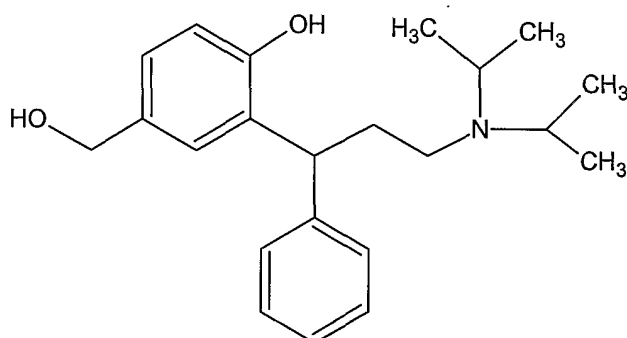
FORMULA IV

- 13 c) reducing the product of Formula IV to produce a compound of Formula V or
 14 a salt thereof; and



FORMULA V

- 16 d) debenzylating the compound of Formula V to produce the compound of
 17 Formula I or a salt thereof.



FORMULA I

- 18
- 1 2. The process according to claim 1, wherein the benzylation step is performed in an
 2 organic solvent.
 - 1 3. The process according to claim 2, wherein the organic solvent is selected from the
 2 group consisting of alcohols and non-alcoholic solvents or mixtures thereof.
 - 1 4. The process according to claim 3 wherein the alcohols are selected from the group
 2 consisting of primary, secondary or tertiary alkanol or mixtures thereof.
 - 1 5. The process according to claim 4 wherein the primary alkanol is selected from the
 2 group consisting of methanol, ethanol, n-propyl alcohol, n-butanol or mixtures
 3 thereof.
 - 1 6. The process according to claim 4 wherein the secondary alkanol is selected from
 2 the group consisting of iso-propyl alcohol, iso-butanol or mixtures thereof.

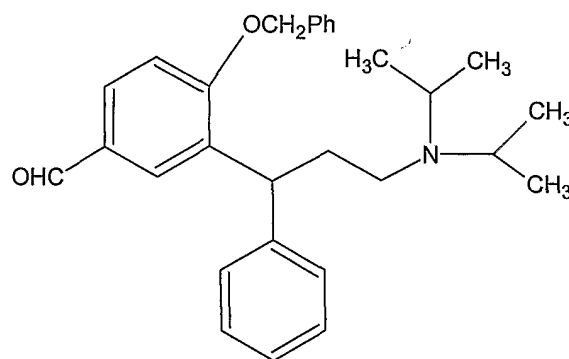
- 1 7. The process according to claim 4 wherein the tertiary alkanol is t-butanol.
- 1 8. The process according to claim 3 wherein the non-alcoholic solvents are selected
2 from the group consisting of ketones, ethers, esters, polar aprotic solvents,
3 aromatic hydrocarbons or mixtures thereof.
- 1 9. The process according to claim 8 wherein ketones are selected from the group
2 consisting of acetone, ethyl methyl ketone, methyl iso-butyl ketone, diisobutyl
3 ketone or mixtures thereof.
- 1 10. The process according to claim 8 wherein ethers are selected from the group
2 consisting of tetrahydrofuran, 1,4-dioxane, diisopropyl ether, diethyl ether or
3 mixtures thereof.
- 1 11. The process according to claim 8 wherein esters are selected from the group
2 consisting of methyl acetate, ethyl formate, ethyl acetate, n-butyl acetate or
3 mixtures thereof.
- 1 12. The process according to claim 8 wherein polar aprotic solvents are selected from
2 the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide,
3 dimethylsulphoxide or mixtures thereof.
- 1 13. The process according to claim 8 wherein aromatic hydrocarbons are selected from
2 the group consisting of toluene, xylene, ethyl benzene, benzene or mixtures
3 thereof.
- 1 14. The process according to claim 2 wherein the organic solvent is preferably selected
2 from the group consisting of methanol, ethanol, acetone, ethyl acetate or mixtures
3 thereof.
- 1 15. The process according to claim 2 wherein the organic solvent is a mixture of
2 methanol and acetone.
- 1 16. The process according to claim 1 wherein the benzoylating agent is selected from
2 the group consisting of benzyl chloride, substituted benzyl chlorides or mixtures
3 thereof.
- 1 17. The process according to claim 16 wherein the substituted benzyl chlorides are
2 selected from the group consisting of p-chlorobenzyl chloride, p-nitrobenzyl
3 chloride, o-chlorobenzyl chloride, o-nitrobenzyl chloride, benzyl alcohol, dibenzyl
4 ether, p-chlorophenyl benzyl ether or mixtures thereof.

- 1 18. The process according to claim 16 wherein the benzoylating agent is benzyl
2 chloride.
- 1 19. The process according to claim 1 wherein step a) is carried out in presence of a
2 base.
- 1 20. The process according to claim 19 wherein base used is selected from the group
2 consisting of hydrides, alkoxides, hydroxides or carbonates of alkali or alkaline
3 earth metals, or mixtures thereof.
- 1 21. The process according to claim 20 wherein the hydrides are selected from the
2 group consisting of sodium hydride, potassium hydride, calcium hydride or
3 mixtures thereof.
- 1 22. The process according to claim 20 wherein the alkoxides are selected from the
2 group consisting of sodium methoxide, sodium ethoxide, potassium t-butoxide,
3 potassium isopropoxide or mixtures thereof.
- 1 23. The process according to claim 20 wherein hydroxides are selected from the group
2 consisting of sodium hydroxide, potassium hydroxide or mixtures thereof.
- 1 24. The process according to claim 20 wherein carbonates are selected from the group
2 consisting of sodium carbonate, potassium carbonate, lithium carbonate or mixture
3 thereof.
- 1 25. The process according to claim 24 wherein potassium carbonate is used.
- 1 26. The process according to claim 1 wherein step b) is performed in an organic
2 solvent optionally containing water.
- 1 27. The process according to claim 26 wherein the organic solvent is selected from
2 dimethylformamide, chloroform, acetonitrile, tetrahydrofuran, toluene,
3 dimethylsulphoxide, dimethylacetamide or mixtures thereof.
- 1 28. The process according to claim 1 wherein oxidation in step b) is carried out using
2 an oxidizing agent selected from the group consisting of ruthenium chloride /
3 sodium periodate, fuming nitric acid, peracids, Dess-Martin reagent, chromium 4-
4 oxide, nickel peroxide, sodium dichromate, manganese dioxide, potassium
5 permanganate, activated silver oxide, pyridinium chlorochromate, ceric ammonium
6 nitrate or ceric ammonium citrate.

- 1 29. The process according to claim 28 wherein sodium persulphate and/or potassium
2 persulphate in the presence of copper (II) sulphate is used as an oxidizing agent.
- 1 30. The process according to claim 28 wherein sodium persulphate is the oxidizing
2 agent.
- 1 31. The process according to claim 1 wherein step c) is performed in an organic
2 solvent.
- 1 32. The process according to claim 31 wherein the organic solvent is selected from the
2 group consisting of alkanols, ethers, acetonitrile or mixtures thereof.
- 1 33. The process according to claim 32 wherein the alkanols are selected from the
2 group consisting of primary, secondary or tertiary alkanol or mixtures thereof.
- 1 34. The process according to claim 33 wherein the primary alkanol is selected from
2 the group consisting of methanol, ethanol, n-propyl alcohol, n-butanol or mixtures
3 thereof.
- 1 35. The process according to claim 33 wherein the secondary alkanol is selected from
2 the group consisting of iso-propyl alcohol, iso-butanol or mixtures thereof.
- 1 36. The process according to claim 33 wherein the tertiary alkanol is t-butanol.
- 1 37. The process according to claim 32 wherein ethers are selected from the group
2 consisting of tetrahydrofuran, 1,4-dioxane, diisopropyl ether, diethyl ether or
3 mixtures thereof.
- 1 38. The process according to claim 1 wherein reduction in step c) is carried out using a
2 reducing agent selected from the group consisting of sodium borohydride,
3 potassium borohydride, Vitride®, tetralkylammonium borohydride, calcium
4 borohydride, zinc borohydride, sodium cyanoborohydride, lithium aluminium
5 hydride or mixtures thereof.
- 1 39. The process according to claim 38 wherein reducing agent is sodium borohydride.
- 1 40. The process according to claim 1 wherein debenzylation of compound of
2 Formula V, is performed by using a noble metal catalyst.
- 1 41. The process according to claim 40 wherein the noble metal catalyst is selected
2 from the group consisting of palladium on carbon, palladium acetate, platinum

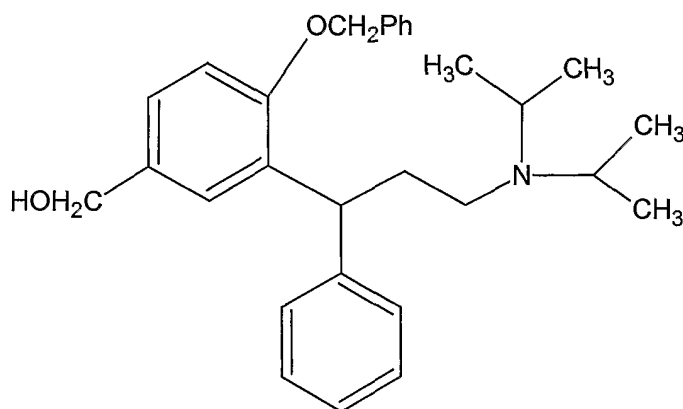
- 3 oxide, platinum black, platinum oxide adsorbed on carbon, rhodium on carbon,
4 ruthenium and its salts adsorbed on solid support.
- 1 42. The process according to claim 1 wherein debenzylation of compound of Formula
2 V, is performed in the presence of an organic solvent.
- 1 43. The process according to claim 42 wherein organic solvent is selected from the
2 group consisting of alkanols, ethers, aromatic hydrocarbons or mixtures thereof.
- 1 44. The process according to claim 43 wherein alkanols are selected from the group
2 consisting of methanol, ethanol, n-propyl alcohol, iso-propyl alcohol, isobutanol,
3 n-butanol, t-butanol or mixtures thereof.
- 1 45. The process according to claim 43 wherein ethers are selected from the group
2 consisting of tetrahydrofuran, diethyl ether, 1,4-dioxane, diisopropyl ether or
3 mixture thereof.
- 1 46. The process according to claim 43 wherein aromatic hydrocarbons are selected
2 from the group consisting of toluene, xylene, ethyl benzene or mixtures thereof.
- 1 47. The process according to claim 1 wherein debenzylation of compound of
2 Formula V, is performed in the presence of hydrogen gas or a compound capable
3 of generating hydrogen gas.
- 1 48. The process according to claim 47 wherein the compound capable of generating
2 hydrogen gas is selected from the group consisting of ammonium formate, formic
3 acid, alkali metal formates such as sodium formate, potassium formate.
- 1 49. The process according to claim 47, wherein the compound capable of generating
2 hydrogen gas is used in the process which can be carried out at atmospheric
3 pressure and at a lower temperature.
- 1 50. The process according to claim 1 wherein debenzylation of compound of
2 Formula V, is performed to get the metabolite of tolterodine of Formula I after
3 aqueous basic work-up.
- 1 51. The process according to claim 50 wherein the aqueous basic work-up comprises
2 dissolving the residue in an organic solvent and washing with a base.
- 1 52. The process according to claim 51 wherein the organic solvent comprises
2 water-immiscible or partially-miscible solvents.

- 1 53. The process according to claim 51 wherein the base is selected from the group
2 consisting of sodium carbonate or potassium carbonate.
- 1 54. The process according to claim 51 wherein the base used is sodium carbonate.
- 1 55. The process of claim 1, further comprising converting a salt of the compound of
2 Formula I to a pharmaceutically acceptable salt.
- 1 56. The compound of formula IV or a salt, hydrate, solvate or polymorph thereof.



FORMULA IV

- 1 57. The compound of formula V or a salt, hydrate, solvate or polymorph thereof.



FORMULA V