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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2008 (21.02.2008)

PCT

(10) International Publication Number
WO 2008/020452 A1

(51) International Patent Classification:
C07C 215/50 (2006.01) *C07C 269/04* (2006.01)
C07C 271/44 (2006.01)

(21) International Application Number:
PCT/IN2006/000404

(22) International Filing Date: 6 October 2006 (06.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1290/MUM/2006 17 August 2006 (17.08.2006) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, 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, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*
— *with amended claims and statement*

(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF RIVASTIGMINE

(57) Abstract: The present invention relates to an improved process for preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof comprising a step of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II).

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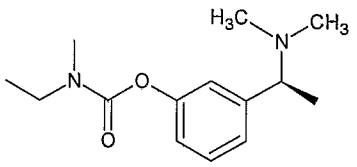
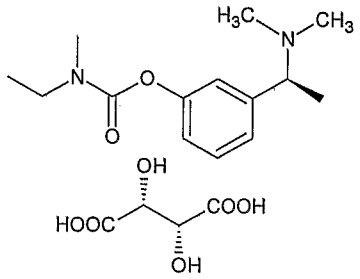
IMPROVED PROCESS FOR THE PREPARATION OF RIVASTIGMINE

Field of invention

The present invention relates to an improved process for the preparation of Ethylmethylcarbamic acid 3-[(1S)-1-(dimethylamino) ethyl] phenyl ester of formula (I) or pharmaceutically acceptable salts thereof, commonly known as Rivastigmine.



Rivastigmine
(I)



Rivastigmine tartarate
(I)-tartarate

Background of the invention

Rivastigmine is prescribed for the treatment of mild to moderate Alzheimer's disease. The tartarate salt of Rivastigmine is marketed under brand name of Exelon®. Rivastigmine is in a class of medications called cholinesterase inhibitors. It improves mental function by increasing the amount of a certain natural substance in the brain. Rivastigmine increases the amounts of a chemical called acetylcholine in the brain. Acetylcholine may be involved in memory, attention, and learning.

US patent no. 4948807 describes process for preparation of racemic Rivastigmine by reacting α-m-hydroxyphenylisopropyldimethylmine or α-m-hydroxyphenyl ethyldimethylmine with carbomyl chloride in the presence of NaH. Process for resolution of racemic Rivastigmine is described in US patent no. 5602176, which involves resolution using di-o,o'-p-toluoyl tartaric acid. The major drawback of this process is repeated recrystallization in the final step to achieve increased enantiomeric excess, which results in decreased yield with increase in processing steps.

PCT publication no. WO03/101917 describes process for preparation of Rivastigmine by condensing N-ethyl- N-methyl-4-nitrophenyl carbamate, which is obtained from 4-nitrophenyl chloroformate, with [l-(3-hydroxyphenyl) ethyl] dimethylamine, which is

obtained by demethylation of [l-(3-methoxyphenyl) ethyl] dimethylamine, in the presence of base. The process of preparation of [l-(3-hydroxyphenyl) ethyl] dimethylamine involves use of DL-methionine and 50% sulphuric acid. DL-methionine is a costly reagent and also a skin, eye and respiratory irritant.

The process described in PCT publication no. WO2004/037771 involves reductive amination of 3-methoxy acetophenone in presence of dimethylamine, titanium isopropoxide and sodium borohydride to obtain [1-(3-methoxyphenyl)ethyl]dimethylamine, which is further demethylated using hydrobromic acid to obtain 3-(1-dimethylamino)phenol. This is further resolved using (S)-(+)-camphor-10-sulfonic acid and reacted with carbamoyl chloride to obtain Rivastigmine. Titanium isopropoxide and sodium borohydride are very expensive reagents which lead to increase in overall cost of the process. Moreover hydrobromic acid is hazardous in nature and thus making it difficult to handle at commercial scale.

The process for preparation of 3-(1-dimethylamino)phenol as described in PCT publication no. WO2006/068386 involves subjecting (S)-3-(1-dimethylaminoethyl)phenol to N-methylation using formaldehyde/formic acid. Further it is subjected to O-carbamoylation to obtain Rivastigmine. It was observed by the inventors of present invention that by process described here, the product obtained did not have desired physical properties and the yield of reaction was also poor.

Therefore there is a need to develop a process for preparation for preparation of Rivastigimine and its intermediates which is simple, cost effective, non-hazardous and commericially viable.

Object of the invention

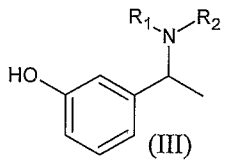
Therefore it is an object of the present invention to provide a process for the preparation of Rivastigmine of formula (I) or pharmaceutical acceptable salts thereof and its intermediates.

Yet another object of the present invention is to provide a process for the preparation of Rivastigmine of formula (I) or pharmaceutical acceptable salts thereof and its intermediates which is high yielding and has short reaction times.

Further object of the present invention is to provide a process for the preparation of Rivastigmine of formula (I) or pharmaceutical acceptable salts thereof and its intermediates which is simple, cost effective, non-hazardous and commericially viable.

Summary of the invention

In accordance with the object of the present invention, one aspect provides a process for the preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof, comprising a step of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)



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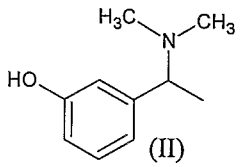
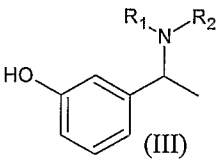


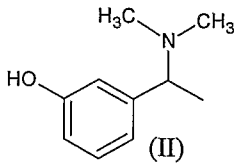
(II)

Another object of the present invention, one aspect provides a process for the preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof, comprising steps of,

(a) N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)

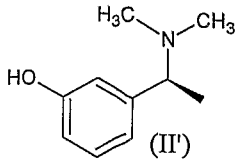


(III)



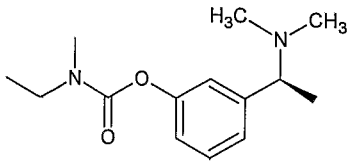
(II)

(b) optically resolving compound of formula (II) to obtain desired isomer (II')



(II')

(c) converting compound of formula (II') to Rivastigmine of formula (I) and optionally converting it to pharmaceutically acceptable salts thereof



Rivastigmine
(I)

Yet another aspect of the present invention provides a process for preparation of compound of formula (II) comprising of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent.

Further aspect of the present invention provides process for preparation of Rivastigmine or pharmaceutically acceptable salts thereof, and its intermediates which is simple, non-hazardous, high yielding, results in lesser amount of impurities, has shorter reaction duration, and is economic and commercially viable.

Detail description of the invention

The present invention provides process for preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof and its intermediates by process shown in Figure-I

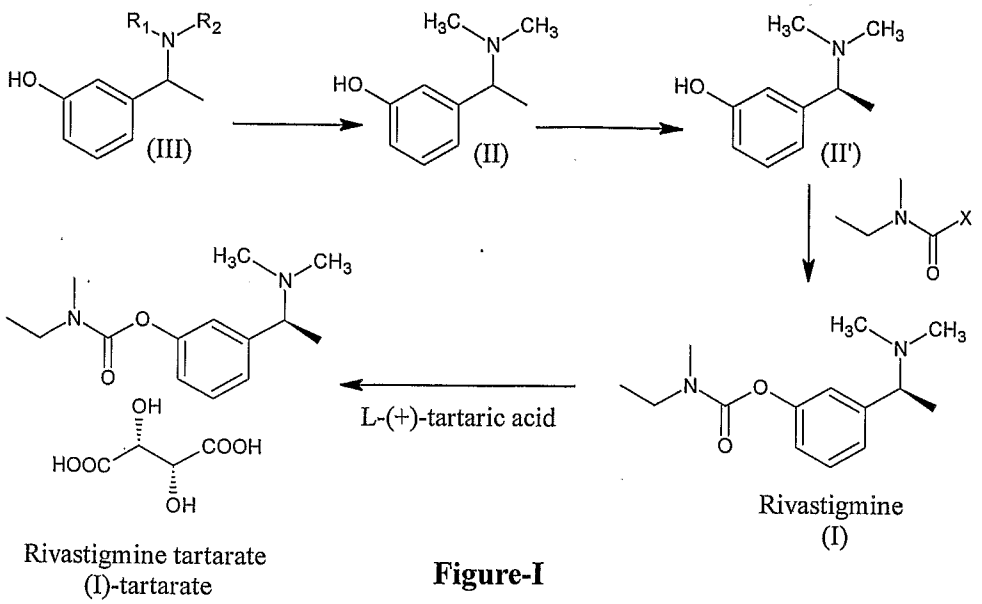


Figure-I

In accordance with the object of the present invention one of the preferred embodiment provides process for the preparation of Rivastigmine or pharmaceutically acceptable salts thereof, comprising a step of N-methylation of compound of formula (III), wherein R_1 = R_2 = H or R_1 = H and R_2 = CH_3 or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)

The N-methylation of compound of formula (III) is carried out using paraformaldehye in the presence of Raney Nickel and hydrogen in a suitable solvent. Suitable solvent can be selected from group comprising of alcohols, esters, chlorinated hydrocarbons or mixtures thereof, examples of which include but are not limited to methanol, ethanol, isopropanol, ethylacetate, methylacetate, butylacetate, chloroform, methylene dichloride, ethylene dichloride and the like or mixtures thereof.

The reaction is carried out at temperature range of about ambient temperature to about reflux temperature of the solvent, more preferably at 25°C to 80°C. The duration of the reaction is about 2 hours to about 10 hours, preferably 3 hours to 6 hours. The hydrogen pressure is maintained between 5 kg/cm^2 and 15 kg/cm^2, preferably 10 kg/cm^2.

After completion of the reaction the product is isolated by normal work up procedures. The crude product thus obtained can be further purified by crystallization from solvent selected from aromatic hydrocarbons, ethers or mixtures thereof for example toluene, petroleum ether and the like or mixtures thereof. Compound of formula (II) obtained by the process of present invention has purity greater than about 95%, preferably 97% and more preferably 98%. The yield of reaction is greater than about 80%, preferably 83% and more preferably 85%.

Another preferred embodiment of the present invention provides process for the preparation of Rivastigmine or pharmaceutically acceptable salts thereof, comprising steps of,

(a) N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)

(b) optically resolving compound of formula (II) to obtain desired isomer (II')

(c) converting compound of formula (II') to Rivastigmine of formula (I) and optionally converting it to pharmaceutically acceptable salts thereof

Yet another embodiment of the present invention provides process for preparation of compound of formula (II) comprising of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent.

Compound of formula (III) is prepared by reductive amination of 3-hydroxy acetophenone in the presence of methyl amine.

The compound of formula (II) thus obtained can be further resolved by process known *perse* or by any method known to person skilled in art. Preferably compound of formula (II) is resolved using d-camphorsulphonic acid in ethanol to obtain desired isomer of formula (II'). Compound of formula (II') is converted to Rivastigmine or a

pharmaceutically acceptable salt thereof by methods know to person skilled in art or any method well-known in the prior art.

In a preferred embodiment compound of formula (II') is further subjected to O-carbamoylation in the presence of base to obtain Rivastigmine of formula (I). Rivastigmine can be optionally converted to desired pharmaceutically acceptable salt, preferably tartarate salt by conventional methods.

The process of the present invention is illustrated by the following examples and should not be construed so as to limit the scope of the invention in any manner.

Examples:

Example 1: Preparation of α-m-hydroxy phenylethyldimethylamine

N-methylation was carried out on α-m-hydroxy phenylethylamine (25g) with Paraformaldehyde (33g) in presence of Raney Nickel (30g) in methanol (500ml) at 80°C and 10kg /cm^2 of hydrogen pressure in an autoclave. After 3-4 hours the product was isolated by removing Raney nickel and concentrating the filtrate. The product was further purified by dissolving the crude product in Toluene (50ml) and is crystallized by slow addition of Petroleum ether (150ml). Pure α-m-hydroxy phenylethyldimethylamine is isolated (25g, Yield: 83%, purity 98%) by filtration.

Characterization data:

^{1}H-NMR (DMSO): 9.25(1H, s), 7.05(1H, t), 6.60(3H, m), 3.08(1H, q), 2.05(6H, s), 1.19(3H, d)

13C-NMR (DMSO): 158.0, 146.7, 129.8, 118.7, 114.8, 114.5, 65.8, 43.6, 20.9.

Mass(Methanol) : 166.2 (M+1)

Example 2: Preparation of α-m-hydroxy phenylethyldimethylamine

N-methylation was carried out on α-m-hydroxy phenylethylmethylamine (25g) with Paraformaldehyde (15g) in presence of Raney Nickel (30g) in methanol(500ml) at 80°C and 10kg /cm^2 of hydrogen pressure in an autoclave. After 3-4 hours the product was isolated by removing Raney nickel and concentrating the filtrate. The product was further

purified by dissolving the crude product in Toluene (50ml) and is crystallized by slow addition of Petroleum ether (150ml). Pure α-m-hydroxy phenylethyldimethylamine is isolated (23g, Yield: 85%, purity 98%) by filtration.

Characterization data:

^{1}H-NMR (DMSO): 9.25(1H, s), 7.05(1H, t), 6.60(3H, m), 3.08(1H, q), 2.05(6H, s), 1.19(3H, d)

13C-NMR (DMSO): 158.0, 146.7, 129.8, 118.7, 114.8, 114.5, 65.8, 43.6, 20.9.

Mass(Methanol) : 166.2 (M+1)

Example 3: Preparation of dl-α-m-Hydroxyphenylethylmethylamine:

A solution of 33 % Methyl amine in Ethanol (170 ml) and 3-hydroxy acetophenone (25.0 g) in Methanol (1000 ml) was charged to an autoclave. To the above solution Raney Ni (2.5 g) was added and the mixture was hydrogenated at 40-80°C for 8-16 hrs. After the completion of the reaction, the reaction mixture was passed through celite bed and then the solvent was distilled out under vacuum. Cyclohexane was added to the residue and then stirred for 15-30 min. at ambient temperature. The solid material was filtered and dried in hot air oven at 50-60°C for 5-6 hrs. (Yield 18-25g).

Example 4: Preparation of α-m-hydroxy phenylethyldimethylamine

N-methylation was carried out on α-m-hydroxy phenylethylmethylamine (25g) with Paraformaldehyde (15g) in presence of Raney Nickel (30g) in methanol (500ml) at 80°C and 10kg /cm^2 of hydrogen pressure in an autoclave. After 3-4 hours the product was isolated by removing Raney nickel and concentrating the filtrate. The product was further purified by dissolving the crude product in Toluene (50ml) and is crystallized by slow addition of Petroleum ether (150ml). Pure α-m-hydroxy phenylethyldimethylamine is isolated (23g, Yield: 85%, purity 98%) by filtration.

Characterization data:

^{1}H-NMR (DMSO): 9.25(1H, s), 7.05(1H, t), 6.60(3H, m), 3.08(1H, q), 2.05(6H, s), 1.19(3H, d)

13C-NMR (DMSO): 158.0, 146.7, 129.8, 118.7, 114.8, 114.5, 65.8, 43.6, 20.9.

Mass(Methanol) : 166.2 (M+1)

Example 5: Resolution of dl-α-m-Hydroxyphenylethylmethylamine:

Racemic dl-α-m-Hydroxyphenylethylmethylamine (20 g) dissolved in Ethanol (300 ml) was added d-camphorsulphonic acid (33 g), and the reaction mixture was heated to 40-80°C for 10-60 mins, and then Ethanol was distilled out completely under vacuum, the same operation was repeated twice with Ethanol (100ml X 2). Residual mass was added Ethyl acetate (250 ml) and distilled out. The residual mass was added *i*-Propanol (60 ml) and stirred for 2-3 days at 0-25°C. The precipitated solid was filtered (10-20 g).

The camphorsulfonate thus obtained was dissolved in Sod. Carbonate soln and then extracted with Ethyl acetate (2x 25ml). Combined organic layer was distilled out and Cyclohexane (50ml) was added to the residual mass and stirred for 10-30 mins. The solid material was then filtered and dried under vacuum at 40-80°C (5-10g) (m.p. 171°C $[\alpha]_D$ -68.0°; c= 5.0 in C_5H_5N)

Reference example 1: Preparation of S-(-)-Rivastigmine

300ml of tetrahydrofuran (THF) are placed in a 0.51-three-neck flask and sodium hydride as a 60% dispersion in oil (11.3g) is added slowly under inert conditions (Ar or N_2) and stirring. A suspension develops, to which α-m-hydroxy phenylethyldimethylamine (46.5g, 0.281mol) is added at room temperature. A solution of the phenolate forms, to which 35.7g (0.281mol) of carbamoylchloride are added dropwise over 10 minutes while slightly cooling down to 15°C. The reaction is slightly exothermic. The rate of dropping is kept such that the temperature of the reaction mixture does not exceed 30°C. After all the agent is added, the cooling system is put aside and the reaction mixture is mixed for 2 hours at room temperature. Thereafter, THF is evaporated in a rotary vacuum evaporator. The evaporation residue is partitioned between 200 ml 1N NaOH and 500 ml of ether. The organic layer is separated and the aqueous fraction is shaken with additional 2x 200 ml of ether. The combined ether layers are shaken out with lx 100 ml water and lx 50 ml brine. The organic fraction is dried over anhydrous sodium sulfate. The solvent is evaporated and the crude product is vacuum distilled.

b. p. =135-140°C at 13 Pa

45.6 g of a colorless viscous oil are obtained, i.e. a 80.5% yield. Content GC 99.6%

Reference example 2: Preparation of Rivastigmine hydrogentartrate

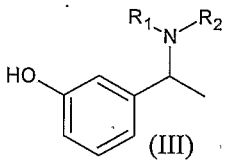
45.6g of S-(-)-rivastigmine and 27.4g of L- (+)-tartaric acid are dissolved in 125ml of anhydrous ethanol at 60-70°C under stirring. At this temperature, 630ml of ethylacetate are gradually added to the solution. The solution is left to cool down to room temperature and to crystallize at +5°C for at least 12 hours. The precipitated white crystalline product is sucked off, washed with 100ml of ethylacetate, and vacuum dried at 40°C. 67.5g of the desired product with m.p.=125-126°C (i.e. 92.6 % of the theoretical yield). $([a]_D$ = +5.5; c=5, ethanol).

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

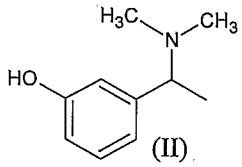
CLAIMS

1. A process for the preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof, comprising steps of,

(a) N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)

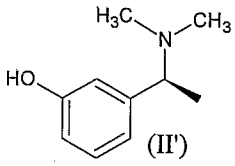


(III)



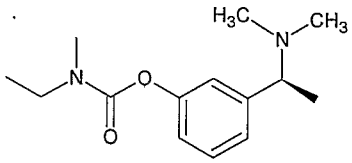
(II)

(b) optically resolving compound of formula (II) to obtain desired isomer (II')



(II')

(c) converting compound of formula (II') to Rivastigmine of formula (I) and optionally converting it to pharmaceutically acceptable salts thereof



Rivastigmine
(I)

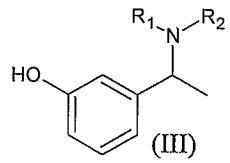
2. The process as claimed in claim 1, wherein suitable solvent is selected from group comprising of alcohols, esters, chlorinated hydrocarbons or mixtures thereof

3. The process as claimed in claim 2, wherein said suitable solvent is selected from group comprising of methanol, ethanol, isopropanol, ethylacetate, methylacetate, butylacetate, chloroform, methylene dichloride, ethylene dichloride or mixtures thereof.

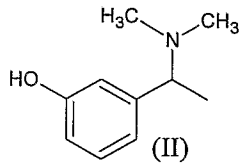
4. The process as claimed in claim 1, wherein reaction is carried out at hydrogen pressure maintained between 5 kg/cm^2 and 15 kg/cm^2

5. The process as claimed in claim 1, wherein said resolution in step (b) is carried out using d-camphorsulphonic acid.

6. A process for the preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof, comprising a step of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)



(III)



(II)

7. A process for preparation of compound of formula (II) comprising of N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent.

8. The process as claimed in claim 5 and 6, wherein suitable solvent is selected from group comprising of alcohols, esters, chlorinated hydrocarbons or mixtures thereof

9. The process as claimed in claim 7, wherein said suitable solvent is selected from group comprising of methanol, ethanol, isopropanol, ethylacetate, methylacetate, butylacetate, chloroform, methylene dichloride, ethylene dichloride or mixtures thereof.

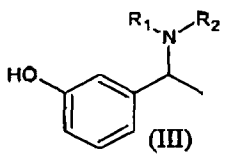
10. Use of compound of formula (II) in the process for preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof

AMENDED CLAIMS

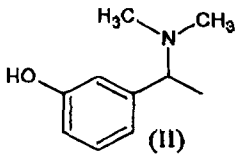
received by the International bureau on 05 December 2007 (05.12.07).

1. A process for the preparation of Rivastigmine of formula (I) or pharmaceutically acceptable salts thereof, said process comprising steps of,

(a) N-methylation of compound of formula (III), wherein $R_1 = R_2 = H$ or $R_1 = H$ and $R_2 = CH_3$ or an acid addition salt thereof, using paraformaldehyde in the presence of Raney Nickel and hydrogen in a suitable solvent to obtain compound of formula (II)

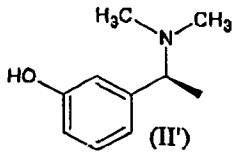


(III)



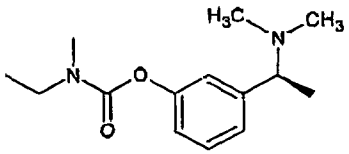
(II)

(b) optically resolving compound of formula (II) to obtain desired isomer (II')



(II')

(c) converting compound of formula (II') to Rivastigmine of formula (I) and optionally converting it to pharmaceutically acceptable salts thereof



Rivastigmine
(I)

2. The process as claimed in claim 1, wherein suitable solvent is selected from group comprising of alcohols, esters, chlorinated hydrocarbons or mixtures thereof.

3. The process as claimed in claim 2, wherein said suitable solvent is selected from group comprising of methanol, ethanol, isopropanol, ethylacetate, methylacetate, butylacetate, chloroform, methylene dichloride, ethylene dichloride or mixtures thereof.

STATEMENT UNDER ARTICLE 19 (1)

Present invention relates to process for preparation of Rivastigmine or its salt by N-methylation of compound III using paraformaldehyde and Raney Nickel catalyst to form α -m-hydroxy-phenylethyldimethylamine, resolving it to desired isomer and converting to Rivastigmine.

D1 (2006/048720) teaches method of preparation of substituted phenyl carbamate and its salt. The process comprises reacting 3-hydroxy acetophenone with ammonia in presence of Raney Nickel catalyst and alcohol solvent to give 3-1-aminoethyl phenol. It is then converted to dimethyl phenol (formula V) which is subsequently converted to rivastigmine. Unlike D1 where Raney nickel is used as catalyst for reductive amination, present invention uses Raney nickel as catalyst with paraformaldehye in the step of N-methylation and use of paraformaldehye which is available as white crystalline powder promotes production in industrial scale and is non-cumbersome.

D2 (WO 03/101917) is acknowledged in present specification. Its starting material is [1-(3-methoxyphenyl)ethyl]dimethylamine which is further demethylated to obtain [1-(3-hydroxyphenyl)ethyl]dimethylamine using DL-methionine. Thus, N-methylated product is starting material and no process for carrying out N-methylation is disclosed. Contrarily present invention is includes process of N-methylation using paraformaldehye and Raney nickel as catalyst and does not use DL methionine.

D3 (US 4948807) acknowledged in present specification, uses repeated re-crystallization in final step resulting in decreasing yield of product unlike present invention. D3 is product patent and discloses only final step of condensation to obtain Racemic Rivastigmine. It does not mention preparation of dimethylamine compound which is starting material for the condensation step, whereas, in present invention

dimethylamine intermediate of Rivastigmine is prepared, which is simple, cost-effective, non-hazardous and commercially viable.

D4 (WO 2004/037771) teaches reacting optically active phenol (formula III), optionally its alkali salt, with carbamoyl halide (formula VII) to form compound of formula II which is converted to rivastigmine by reacting with tartaric acid. The solvent includes tetrahydrofuran, 1-2-dimethoxyethan. D4 teaches carrying out reductive methylation of methoxy acetophenone using dimethylamine in presence of reducing agent. This process directly gives N,N-dimethylated product. Contrarily present invention uses amine as starting material and is further N-methylated in presence of paraformaldehyde and Raney nickel catalyst.

D5 (WO 2006/68386), acknowledged in present specification teaches preparation of rivastigmine, subjecting compound of formula VII to N-methylation to obtain compound of formula VIII and subjecting it to O-carbomoylation to obtain acid addition salt or compound of formula I. The N-methylation is performed by formaldehyde. Incorporation of this N-methylation step in the process of D4 would not lead to present invention since D5 does not teach or motivate use of paraformaldehye as methylating agent and Raney Nickel as catalyst.

To establish the surprising effect of present process by use of paraformaldehye as methylating agent and Raney Nickel as catalyst further experiments were carried out when N-methylation using formaldehyde/formic acid yielded 60% and purity of about 70 to 80% and the reaction time of about 10 to 14 hours. Whereas, N-methylation with paraformaldehye as methylating agent and Raney Nickel as catalyst the yield of 85%, purity of about 98-99.2% and reaction time about 7 hours was achieved.

Claim 1 is amended for further clarification which may be regarded as amendment with Statement Under Article 19.

The amended claims annexed hereto may kindly be taken as amended claims under Article 19 of the PCT.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2006/000404

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C215/50 C07C271/44 C07C269/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/048720 A1 (EMCURE PHARMACEUTICALS LTD [IN]; GHARPURE MILIND MORESHWAR [IN]; BHAWA) 11 May 2006 (2006-05-11) page 11 - page 12, line 17; claim 15	1-10
X	WO 03/101917 A (SUN PHARMACEUTICAL IND LTD [IN]; PATEL HETALKUMAR VIRENDRABHAI [IN]; T) 11 December 2003 (2003-12-11) cited in the application	10
A	page 11; claims 1,20; example 1	1-9
X	US 4 948 807 A (ROSIN MARTA W [IL] ET AL) 14 August 1990 (1990-08-14) cited in the application	10
A	column 6, line 30 - line 50; claim 1	1-9

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 July 2007	09/07/2007

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2006/000404

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037771 A (ZENTIVA A S [CZ]; STEPANKOVA HANA [CZ]; HAJICEK JOSEF [CZ]; SIMEK STAN) 6 May 2004 (2004-05-06) cited in the application	10
Y	page 8; claims 1-4	1-9
Y	WO 2006/068386 A (DONG KOOK PHARM CO LTD [KR]; CHA KYUNG HOI [KR]; LIM DAE SUNG [KR]; LE) 29 June 2006 (2006-06-29) cited in the application	1-9
A	claims 1-4	10
A	US 5 602 176 A (ENZ ALBERT [CH]) 11 February 1997 (1997-02-11) claim 1	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2006/000404

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2006048720	A1	11-05-2006	NONE		
WO 03101917	A	11-12-2003	AU	2003263574 A1	19-12-2003
			US	2006293518 A1	28-12-2006
US 4948807	A	14-08-1990	AU	595504 B2	05-04-1990
			AU	5428486 A	11-09-1986
			CA	1284501 C	28-05-1991
			CY	1748 A	03-06-1994
			DE	3675408 D1	13-12-1990
			DE	19875046 I1	04-09-2003
			DK	99186 A	06-09-1986
			EP	0193926 A2	10-09-1986
			ES	8801193 A1	01-03-1988
			FI	860914 A	06-09-1986
			GR	860586 A1	07-07-1986
			HK	130293 A	03-12-1993
			HU	41718 A2	28-05-1987
			IE	58838 B1	17-11-1993
			IL	74497 A	09-02-1990
			JP	1629293 C	20-12-1991
			JP	2055416 B	27-11-1990
			JP	61225158 A	06-10-1986
			LU	90312 A9	06-01-1999
			NL	980031 I1	04-01-1999
			NZ	215348 A	26-04-1990
			PH	23325 A	14-07-1989
			PL	146301 B1	31-01-1989
			PT	82127 A	01-04-1986
			ZA	8601653 A	28-10-1987
WO 2004037771	A	06-05-2004	AU	2003277795 A1	13-05-2004
			CZ	20023555 A3	14-01-2004
			EP	1556338 A1	27-07-2005
			US	2006122417 A1	08-06-2006
WO 2006068386	A	29-06-2006	KR	20060072326 A	28-06-2006
US 5602176	A	11-02-1997	NONE		