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(54) **Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF DONEPEZIL

(57) **Abstract:** An improved, novel and simple industrial process for the preparation of Donepezil of formula (I) and its pharmaceutically acceptable salts manufactured by the condensation of 5,6-dimethoxy indanone of formula (III) with 1-benzyl-4-piperidine carboxaldehyde of formula (IV) to give 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine in the presence of base in organic solvents or an aqueous solvent or mixture thereof followed by the reduction carried out using at least one metal borohydride in the presence of catalytic amount of cobalt salts and suitable solvent or mixture thereof.

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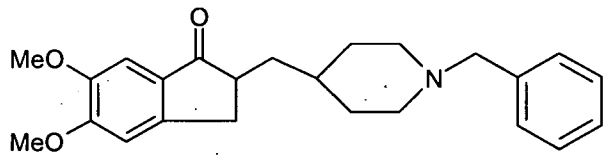
AN IMPROVED PROCESS FOR THE PREPARATION OF DONEPEZIL

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine known as donepezil and its pharmaceutically acceptable salts. The invention relates to a simplified and cost effective process, which results into substantially pure donepezil and its salts with better yields.

BACKGROUND OF THE INVENTION

Donepezil is chemically known as 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine has the formula (I).



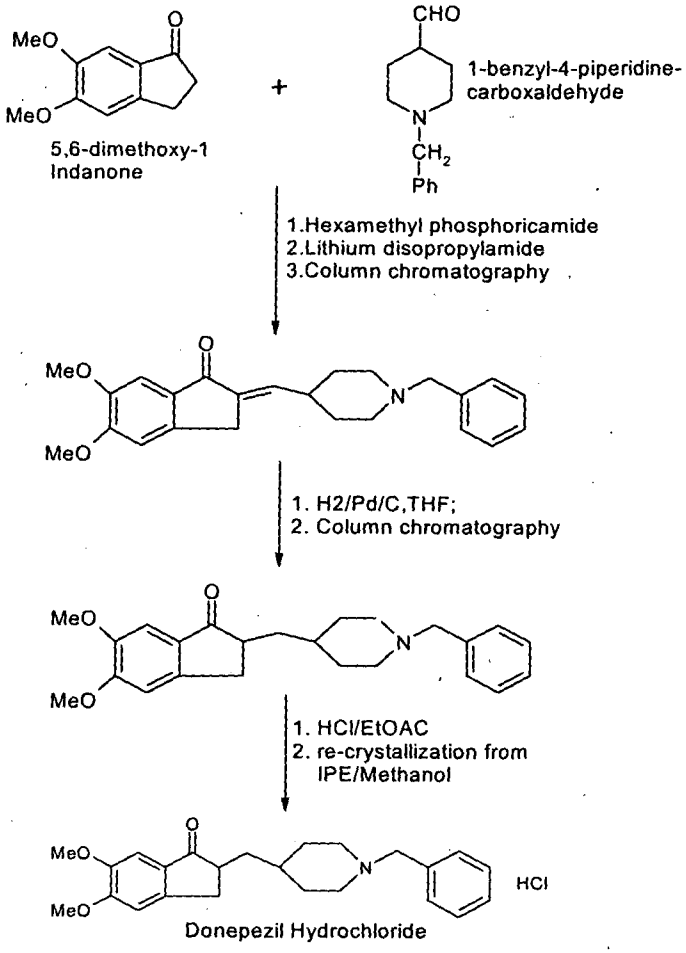
(I)

Donepezil hydrochloride, which is available in the market for the treatment of all kinds of senile dementia, in particular being useful for prevention, treatment and amelioration of Alzheimer Disease by virtue of its acetylcholinesterase inhibitory action. Donepezil's unique chemical structure makes it more specifically effective on Alzheimer disease than other drugs.

There are many processes disclosed in the prior art for producing donepezil and its pharmaceutically acceptable salts.

EP 296560 B1(Scheme-1) describes preparation of Donepezil hydrochloride by the condensation of 1- benzylpiperidine-4-carboxaldehyde with 5,6-dimethoxy-1-indanone in the presence of strong base such as lithium diisopropylamide under inert atmosphere followed by reduction with palladium carbon catalyst of the obtained compound to give the Donepezil hydrochloride with overall yield reported to be 50.8%.

Scheme-1:

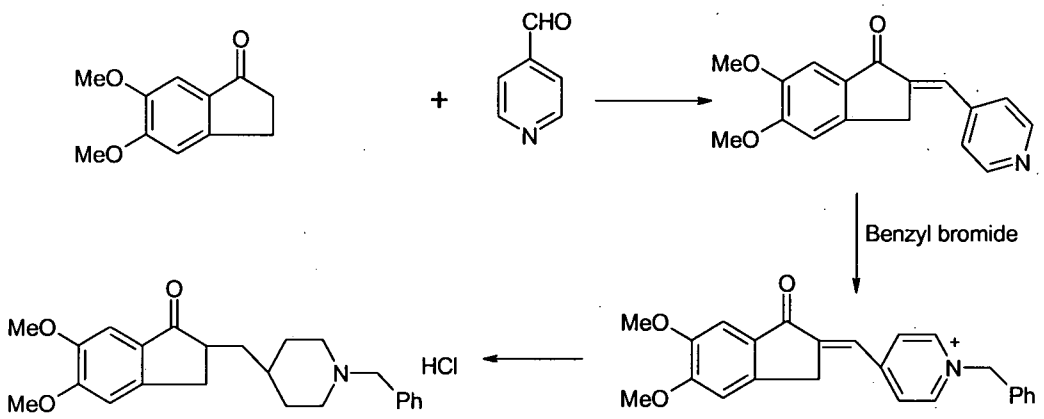


This process, however, suffers with limitations like (i) use of base lithium diisopropylamide (LDA) which requires to be produced in situ by dissolving diisopropylamine in THF followed by addition of n-butyl lithium in hexane, the later reagent being corrosive and highly flammable material. (ii) Reaction at low temperature (-78 C°), which is not industrially feasible. (iii) LDA is toxic and needs to be carefully handled. (iv) It further requires purification involving column chromatography which requires large amount of solvents, which is discarded after use or its recyclability invites purification of the recovered solvents, which substantially affect the economical viability. Furthermore, the large amounts of solvents are evaporated into the atmosphere and therefore, the column chromatography is environmentally unsafe. (v) Moreover, this process requires the use of costly metal catalyst like Pd for reduction and working under inert gas atmosphere, for which special production equipment is needed. (vi) Reaction takes place under high pressure leading to the reduction of carbonyl group to alcohol and debenzylated products and thereby demanding column purification. All these parameters make the process not only expensive but also industrially complicated.

According to the process disclosed in EP 711756 B1(Scheme-2), 5, 6- dimethoxy-1-indanone is condensed with pyridin-4-aldehyde to give 5,6-dimethoxy-2-(pyridin-4-yl) methyleneindan-1-one,

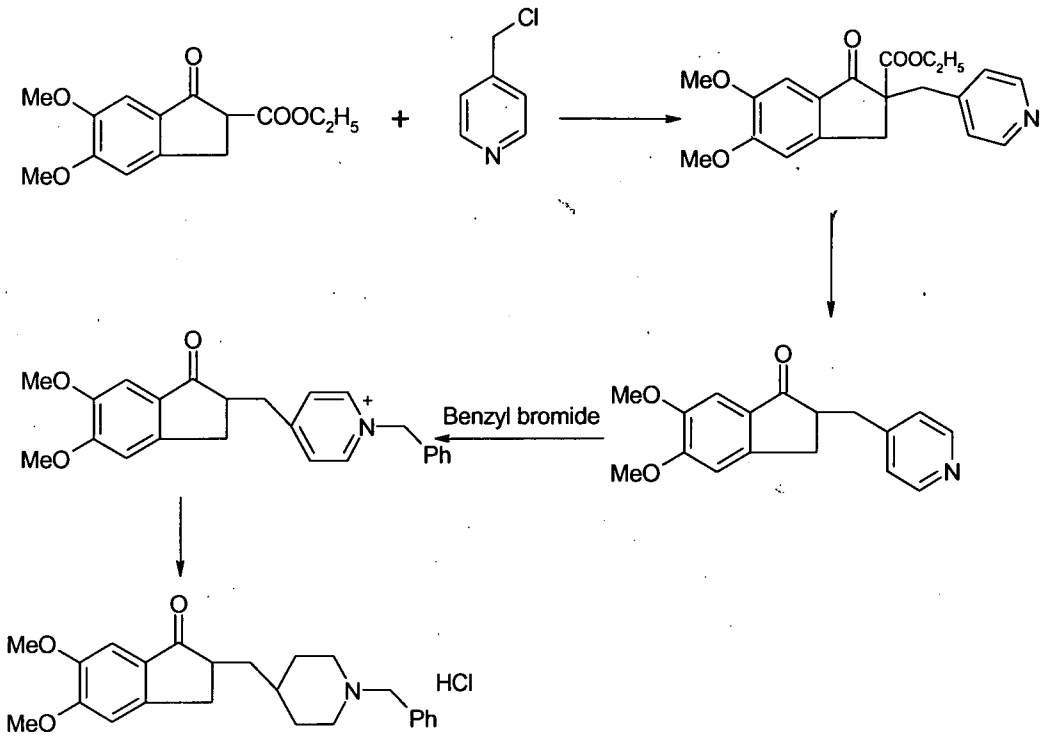
reacted with benzyl bromide to give 1-benzyl-4-(5, 6-dimethoxyindan-l-on-2-ylidene)methylpyridinium bromide and then, hydrogenated in the presence of platinum oxide catalyst in methanol solvent to yield donepezil. However, the process disclosed in EP 711756 B1 suffers with several drawbacks. The reduction of an olefinic bond and pyridinium ring in the presence of benzyl group is difficult to achieve and leads to unwanted side products including debenzylated product. Besides, the reaction time for completion of the process is too long. Reduction step employs expensive catalyst like platinum oxide and the yield of reduction in the last step is not reproducible (as described in EP 1047674 B1). Furthermore the overall yield is also not satisfactory (58.5%).

Scheme-2:



According to EP1047674B1(Scheme-3), 5,6-dimethoxy-2-ethoxycarbonyl-1- indanone is reacted with 4-pyridinylmethyl chloride to give5,6-dimethoxy-2- (4- pyridyl)methyl-2-ethoxycarbonyl-1-indanone, decarboxylated to give 5,6-dimethoxy-2- (4-pyridyl) methyl-1-indanone then, reacted with benzyl bromide to givel-benzyl-4- [(5, 6-dimethoxy-1-indanon)-2-yl] methylpyridinium bromide followed by catalytic hydrogenation to yield donepezil. The process involves introduction of alkoxy carbonyl and decarboxylation steps, thereby making the process very lengthy. The process also employs expensive catalyst such as platinum oxide and hazardous reagent such as benzyl bromide in the last step of manufacture thereby making the whole process industrially unfavorable and expensive.

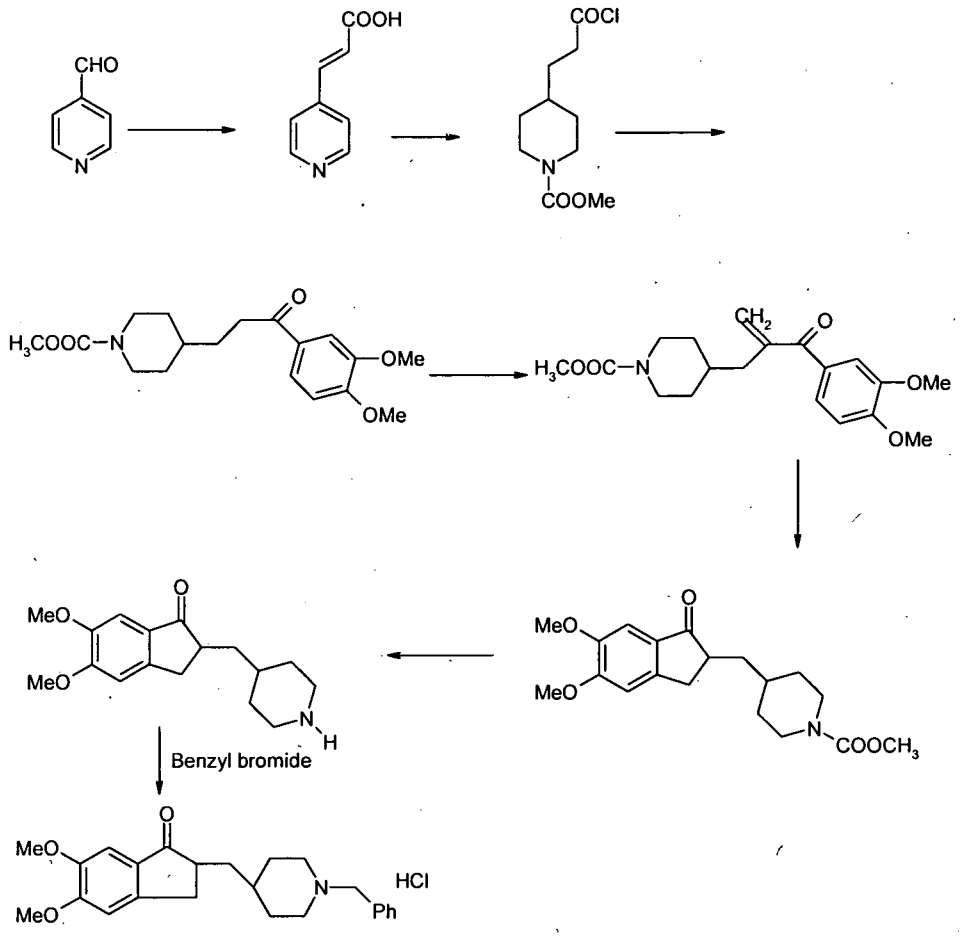
Scheme-3:



WO 97/22584 discloses the process for the preparation of Donepezil hydrochloride with overall yield 19.3%. This process is schematically represented in Scheme-4.

WO 97/22584 again involves many steps which makes the process difficult and cumbersome to carry out. Moreover, the process also uses raw materials such as methyl chlorocarbonate and tetramethyl diaminomethyl which are very expensive. The overall yield of the process is also remarkably low (19.3%). These make the overall process industrially uneconomical.

Scheme-4:



EP 1531151 A1 discloses a process for the preparation of donepezil hydrochloride, which involves the reduction of 4-[5,6-dimethoxy-1-indanone-2-ylidene) methyl] pyridine employing a noble metal catalyst or a non-oxide derivative of a noble metal catalyst in a solvent at 20 C°-100 C° and 10 - 90 psi gauge pressure followed by benzylation with benzyl bromide.

US 20040143121 describes the process for the preparation of donepezil, which involves the reduction of compound 4 - [(5, 6-dimethoxy-l-indanon-2ylidene) methyl] pyridine using platinum dioxide as catalyst, in a mixture of solvents, followed by benzylation with benzyl bromide.

EP 1608371 A1 discloses the process for the preparation of donepezil hydrochloride which comprises the two step reduction starting from 4- [(5, 6-dimethoxy-l-indanon-2- ylidene) methyl] pyridine by the preparation of intermediate 4- [(5, 6-dimethoxy-l- indanon-2-yl) methyl] pyridine followed by benzylation afforded donepezil hydrochloride.

WO 050105742 discloses process for the preparation of donepezil and its pharmaceutically acceptable salts comprises hydrogenation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]

methyl piperidine with Raney Nickel catalyst under mild condition and subsequently treating it with hydrochloric acid.

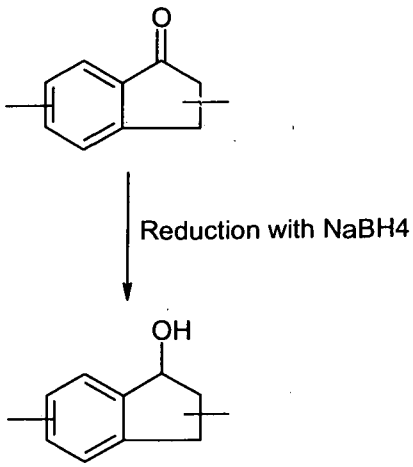
The above study of the prior art discloses that the production of donepezil involves either single stage or two stage reduction which in turn requires a strict process control and use of hazardous and flammable reagents like benzyl bromide requires special equipments. Furthermore benzyl bromide is combustible and gives off irritating or toxic fume (or gases) in fire. It also leaves an unacceptable odour in the active ingredient when being used in the last step of manufacture. Furthermore reduction in inert gas atmosphere by using noble metal catalyst or oxide derivative of noble metal catalyst will inherently require recycling because of cost factors.

There are numerous reducing agents disclosed in various references used for either selective reduction or simple reduction. In available literature, a possibility was disclosed to reduce olefins to alkanes using metal borohydride in the presence of catalytic amount of cobalt salt optionally in the presence of complexing agents. In 1979 Chung et al (J. Org. Chem. Vol. 44 no. 6 1979) reported that alcoholic $NaBH_4$-$CoCl_2$ could selectively reduce alkynes as well as mono and di-substituted alkenes. Other available references disclose selective reduction of alkenes by metal borohydride and cobalt salts are as follows:

1. Leuteneggger U. Leutengga et. al. Angrew. Chem. Int. Ed. 28: 60 (1989)
2. John O. Osby et al (J. Am. Chem. Soc.) 1986, 108, 67-72.
3. Ganem B. Chemical Reviews (1986), 86, 763-780.

The given references relate to the use of cobalt chloride and other salts in combination with borohydride and at times require ligand for reduction of double bonds preferably in α, β-unsaturated compounds, alkenes, alkyl halides, nitriles and the like. As disclosed in the given references, reduction of C=C bond requires a complexing agent. It has to be observed that none of the above references disclose the reduction of substituted indanone derivatives that too in the absence of complexing agent, which is very specific for acetylcholineesterase inhibitory action.

On the other hand, EP 296560 A2 in general rather discloses the use of $NaBH_4$ for the reduction of indanone to indanole group in alcohol at 0 C°. (Process J- page no. 26).



It is perceptible from the above mentioned prior art that according to the known process for the preparation of Donepezil and its pharmaceutically acceptable salts, there are more than one underlying problems associated with each of the processes. Hence, there is a long felt need to develop a new process to take care of the mentioned problems.

Thus, there is a demand for an improved process for synthesizing Donepezil and its pharmaceutically acceptable salts, which is cost effective, commercially viable with higher yields, while reducing number of process steps and avoiding harmful & expensive reagents.

The present invention discloses a process for the preparation of donepezil and its pharmaceutically acceptable salts, which solves the problems associated with the prior art and provides a simple, efficient and cost effective method for production of Donepezil and its pharmaceutically acceptable salts.

It is apparent that the prior arts mentioned above, either singly or combined together, do not disclose or motivate an ordinary person skilled in art to prepare donepezil and its pharmaceutically acceptable salts by selective reduction of olefin bond using metal borohydride and cobalt chloride salt preferably eliminating possibility of obtaining hydroxyl substituted indane and/or in the absence of complexing agents.

OBJECT OF THE INVENTION:

It is an object of the present invention to provide an improved process for the preparation of Donepezil and its pharmaceutically acceptable salts.

It is a further object of the invention to provide a process for the preparation of Donepezil and its pharmaceutically acceptable salts which gives good yields of the product and is efficient, cost-effective, industrially viable by avoiding the usage of hazardous chemicals like LDA, Palladium and use of benzyl bromide during.

It is still a further objective of the invention to provide a process for the preparation of Donepezil and its pharmaceutically acceptable salts which employs less number of reaction steps and therefore is less time consuming, easy and convenient to carry out.

It is still a further objective of the invention to provide a process for the preparation of Donepezil and its pharmaceutically acceptable salts which avoids harmful reagents used hitherto in its preparation and is safe to carry out.

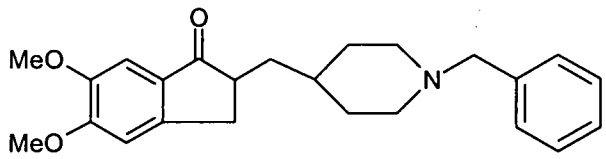
It is still a further objective of the invention to prepare substantially pure Donepezil and its pharmaceutically acceptable salts by avoiding additional steps of purification.

Still further objective of the invention is to prepare a substantially pure key intermediate of Donepezil which avoids use of LDA (Lithium diisopropyl amide) or organic base including alkali metal alkoxides.

Further object of the present invention is to provide a pharmaceutical composition containing Donepezil and its pharmaceutically acceptable salts, prepared according to instant invention.

SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of Donepezil of formula (I) and its pharmaceutically acceptable salts.

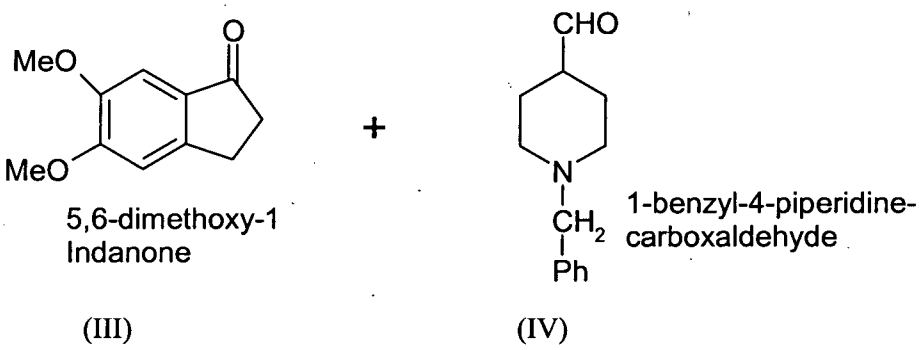


(I)

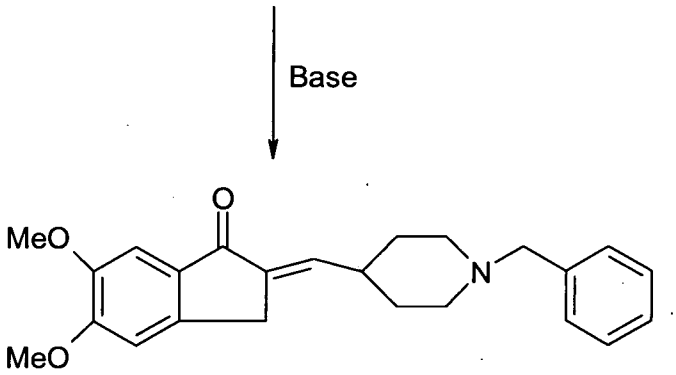
which comprises the steps of :

1. Condensation of 5,6-dimethoxy indanone of formula (III) with 1- benzyl-4-piperidine carboxaldehyde of formula (IV) to give 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl]

methyl piperidine in the presence of base in organic solvent or an aqueous solvent or mixture thereof.

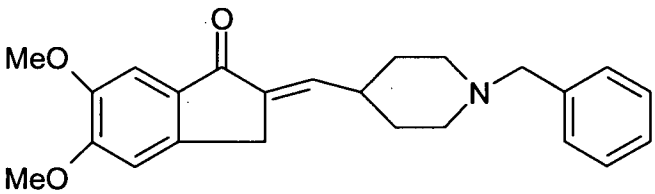


(III) (IV)

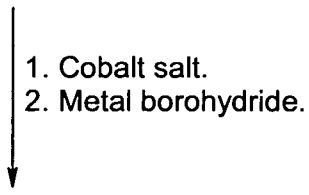


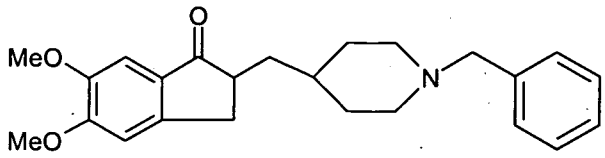
(II)

2. Reduction of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine, with metal borohydride in the presence of catalytic amount of cobalt salts in organic solvent or an aqueous solvent or mixture thereof.



(II)





(I)

Donepezil

3. Isolating highly pure donepezil and optionally converting into its pharmaceutically acceptable salt using known process in the art.

DETAILED DESCRIPTION

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

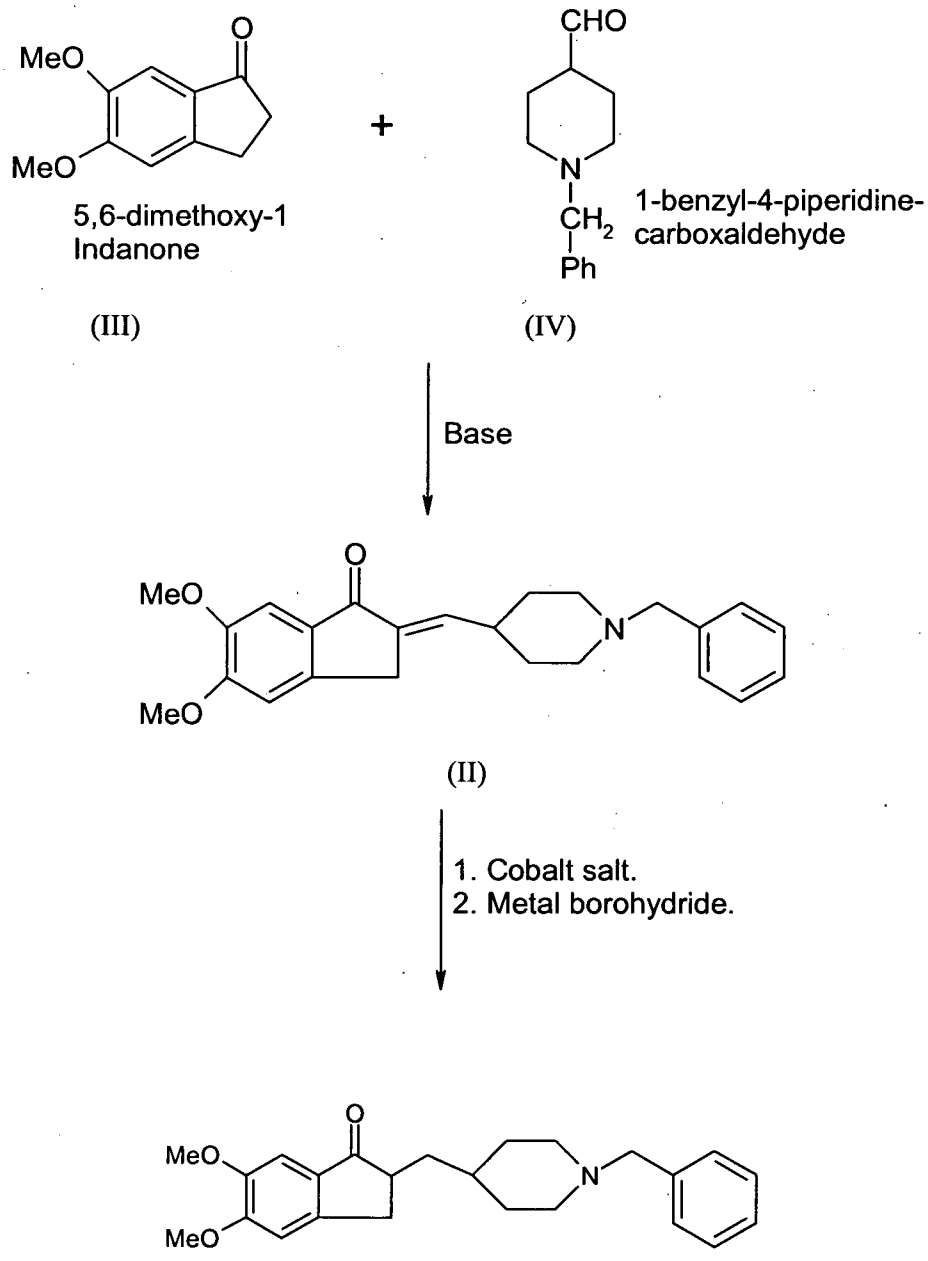
The terms "pharmaceutically acceptable salt" is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include metal complexes and salts of both inorganic and organic acids. In the present invention, the term "pharmacologically acceptable salt" include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, and phosphate, and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate, and toluenesulfonate. Further, when a certain kind of substitutent is selected, the compound of the present invention may form, e.g., alkali metal salts such as a sodium or potassium salt, alkaline earth metal salts such as a calcium or magnesium salt, organic amine salts such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine, or N,N'–dibenzylethylenediamine.

"Substantially pure" as used herein means at least 97% pure, preferably at least 99% pure, more preferably at least 99.5% pure and most preferably at least 99.9% pure.

The present invention provides an improved process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine (Donepezil) and its pharmaceutically acceptable salts, which comprises condensation of 5,6-dimethoxy indanone of formula (III) with 1- benzyl-4-

piperidine carboxaldehyde of formula (IV) to give 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine in the presence of base in organic solvents or an aqueous solvent or mixture thereof, followed by the reduction with metal borohydride in the presence of catalytic amount of cobalt salts in organic solvent or an aqueous solvent or mixture thereof. Isolating highly pure donepezil and optionally converting into its pharmaceutically acceptable salt using known process in the art. Scheme-5 illustrates an exemplary process for the preparation of Donepezil and its pharmaceutically acceptable salts in the accordance with the present invention.

Scheme-5:



(I)

Donepezil

The starting raw material of the formula (III) i.e. 5,6-dimethoxy indanone and formula (IV) i.e. 1-benzyl-4-piperidine carboxaldehyde can be obtained commercially or can be prepared using known process in art e.g., EP 296560 B1.

The alternative method of manufacturing 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II) has already been disclosed in EP 296560 B1 and JP-11171861.

In a first embodiment, present invention provides an improved process for the preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II) by the condensation comprises the steps mentioned below:

1. Addition of base in appropriate solvent or mixture thereof, followed by the addition of 5,6-dimethoxy-1-indanone (III) & 1- benzyl-4-piperidine carboxaldehyde (IV) in stepwise manner.

2. The obtained reaction mixture of step 1 is heated to reflux temperature and maintained till the reaction is complete.

3. Isolating the product of formula (II) wherein it may involve one or more steps like optionally distilling out the solvent or cooling the reaction mixture, and optionally purifying from appropriate organic solvent or an aqueous solvent or mixture thereof. The product obtained may be further dried to achieve the desired product.

The solvent used in the above reaction steps may be either organic or aqueous solvent, which is selected from the group comprising of dimethoxyethane, 1,3-dioxalane, ethylacetate, water, acetonitrile, tetrahydrofuran; dimethylformamide; diemthylacetamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such as benzene, toluene, xylene, etc. , halogenated hydrocarbons such as

dichloromethane, chloroform, carbon tetrachloride, dichloroethylene etc. ,ketones such as acetone, methyl ethyl ketone, ethyl isobutyl ketone, etc. , ethers such isopropyl ether, methyl tertiary butyl

ether, diethyl ether or petroleum ether, or carboxylates such ethyl acetate, or a mixtures thereof preferably tetrahydrofuran.

Purification can be carried out using solvent selected from the group comprising of C1-C4 alcohol, ester, ether, carboxylates, halogenated hydrocarbons, aromatic hydrocarbons, water or a mixtures thereof.

Base may be selected from the group comprising of alkali metal or alkaline earth metal hydroxide such as sodium hydroxide, potassium hydroxide, cerium hydroxide. Sodium hydroxide is particularly preferred base.

In another embodiment, the present invention further comprises a novel and improved method of reduction of compound of formula (II), which is faster, easier and results in substantially pure with improved yield of donepezil and its pharmaceutically acceptable salts. It is also more convenient for scale up at plant level, since it does not require any special equipment.

The said process comprising the steps mentioned below:

1. Reduction of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II) with metal borohydride in the presence of catalytic amount of cobalt salts in an appropriate solvent.

2. The reduction is usually carried out in any suitable conditions of temperature, and time sufficient to promote substantial reduction of the compound of formula (II).
3. When reduction is substantially complete the reaction mixture is extracted and optionally purified using organic solvent to obtain donepezil base.

4. donepezil base can be optionally converted into its pharmaceutically acceptable salts and can be optionally purified with organic solvents and mixture thereof. The product obtained may be further dried to achieve the desired product.

The reducing agents employed for reduction are metal borohydrides, which includes but is not limited to sodium borohydride, potassium borohydride, lithium borohydride, zinc borohydride, rubidium borohydride, as well as cesium borohydride, any of these alone or in admixture.

The preferred metal borohydrides for the present invention are sodium and potassium borohydride. Most preferred is sodium borohydride.

The cobalt salts used for catalysis are potentially suitable cobalt component for incorporating cobalt, which include but are not limited to, cobalt nitrate hexahydrate, hydrated cobalt nitrate, cobalt chloride, hydrated cobalt chloride, cobalt chloride hexahydrate, cobalt chloride hydrate, cobalt acetate tetrahydrate, cobalt acetylacetonate, cobalt acetylacetonate hydrate, cobalt carbonate hydrate, cobalt perchlorate hexahydrate, hydrated cobalt sulfate, cobalt sulfate hydrate, and the like and combinations thereof.

The preferred cobalt component for incorporating cobalt, preferably impregnating cobalt is hydrated cobalt chloride.

The most preferred cobalt component for incorporating cobalt, preferably impregnating cobalt is cobalt chloride hexahydrate. The required catalytic amount of cobalt salt for reduction is in the range of 0.0001 mole to 1.0 mole.

The reaction conditions under which the compound formula (II), the alkali metal borohydride, and the cobalt salts are employed, in general can be any suitable conditions of temperature, and time sufficient to promote substantial reduction of the compound formula (II). The temperature should be a temperature effective to provide a suitable reaction time and an exemplary temperature range is from about -40° C to 50° C, preferred temperature ranges from 0° C to 30° C more preferred temperature ranges from 10° C to 30° C. The reaction time may vary, depending upon temperature, as well as specific reactants, but exemplary time can be expected to be generally in the range of about 0.1 to 20 hours.

Examples of the suitable solvents employed for the reduction of formula (II) include any organic or an aqueous solvent or a mixture of solvents, which are inert. Example of such solvent without limitation includes water, alcohols such as methanol ,ethanol, propanol, isopropanol; acetonitrile, tetrahydrofuran; dimethylformamide; diemthylacetamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons such as benzene, toluene, xylene, etc., halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, dichloroethylene etc. ,ketones such as acetone, methyl ethyl ketone, ethyl isobutyl ketone, etc. , ethers such isopropyl ether, methyl tertiary butyl ether, diethyl ether or petroleum ether, or carboxylates such ethyl acetate.

The preferred solvents as per present invention for reduction are THF: water/ THF: methanol/ DMF: Methanol. The most preferred solvents are THF: Methanol. The ratio of solvent system can vary from 0.1: 1 to 30:1.

Extraction and further purification can be done with any process known in the art like; acid-base purification, distillation of the solvent, carbon treatment, etc. This may involve one or more organic solvents. Examples of such solvents without limitation includes alcohols such as methanol, ethanol, propanol, isopropanol; dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether or petroleum ether, etc.

The product obtained may be further dried to achieve the desired product. For example product may be dried in tray drier, dried under vacuum and/ or in a fluid bed drier.

Additionally donepezil can be optionally converted into its pharmaceutically acceptable salt using know process in art. The solvent used for the preparation of pharmaceutically acceptable salt can be one or more organic solvents. Examples of such solvents without limitation includes alcohols such as methanol, ethanol, propanol, isopropanol; dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether or petroleum ether, etc. It can be further purified or re-crystallized from the same or different solvent or solvents mixtures mentioned above if required.

Further it has been surprisingly found that during condensation of formula III with Formula IV in presence of base and solvents as described herein above the purity of the intermediate compound of formula II and yield is improved in comparison to the reaction carried out in the presence of alkoxide (prepared insitu or otherwise) as reported in JP 11171861. It has been further discovered that this improvement in purity is because of the absence of Impurity A, which is detected at about 0.51 RRT detected by HPLC method with following condition:

Col: SS col.(0.25meter x 4.6mm) (lxd) with octadecylsilyl silica gel (5um)
Mobile phase: ACN(25): Potassium dihydrogen phosphate buffer (pH: 3.6 with phosphoric acid (75) at 234nm. which is unavoidable and could not be removed from the formula II even after purification or by resubjecting the impure formula II (obtained by following JP 11171861) to the condition as described in JP11171861.

Donepezil and its pharmaceutically acceptable salt prepared according to present invention can be administered either orally as powders, granules, tablets, capsules or syrup, or parenterally as an injection, or as an external preparation or drop, or as a suppository.

The pharmaceutical compositions of Donepezil and its pharmaceutically acceptable salts prepared according to present invention may comprise one or more pharmaceutically acceptable excipients selected from carrier / diluent, disintegrant, binder, film forming agent, lubricant, opacifiers, plasticizers, stabilizers, colouring agent, anti-tacking agent, organoleptic additives such as flavoring agent, sweetener or coloring agent and others known to the skilled person in the art.

Diluent / Carrier may be selected from anhydrous lactose, lactose monohydrate, dicalcium phosphate dihydrate, microcrystalline cellulose, modified lactose, starch, starch derivatives, mannitol, spray dried Mannitol, Ran Explo-C® (Microcrystalline cellulose, Colloidal silicon dioxide, Crospovidone), Ran Explo-S® (Microcrystalline cellulose, Colloidal silicon dioxide and Sodium starch glycollate) and the like known to the skilled person in the art.

Disintegrant may be selected from croscarmellose sodium, sodium starch glycolate, starch, pregelatinized starch, partially pregelatinized starch, sodium carboxymethyl cellulose, microcrystalline cellulose, cross-linked polyvinylpyrrolidone, Low – substituted hydroxy propyl cellulose and the like known to the skilled person in the art.

Binder may be selected from hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carbomers, dextrin, ethyl cellulose, methylcellulose, shellac, zein, gelatin, polymethacrylates, polyvinyl pyrrolidone, starch, pregelatinized starch, sodium alginate, gums, synthetic resins and the like known to the skilled person in the art..

Lubricant / glidant may be selected from talc, metallic stearates such as magnesium stearate, calcium stearate, zinc stearate; sodium stearyl fumarate, colloidal silicon dioxide, finely divided silicon dioxide, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl monostearate, glyceryl behenate, polyethylene glycols, starch, sodium stearyl fumarate, mineral oil, magnesium trisilicate; or mixtures thereof.

The sweetener may be selected from aspartame, saccharin sodium, acesulfame potassium, dried invert sugar, dextrose, glucose, fructose, galactose, levulose, maltose, neotame, sucralose or mixture thereof.

The flavoring agent may be selected from cherry, black current, pineapple, orange, strawberry, banana, vanilla, mint, menthol, citric acid, fumaric acid, tartaric acid, and their mixture thereof.

Film forming agent may be selected from hydroxypropyl methylcellulose (hypromellose), polyvinylpyrrolidone, gelatin, hydroxypropyl cellulose, polyethylene oxide, hydroxyethyl cellulose, sodium alginate and and the like known to the skilled person in the art.. The film forming agent may be used in seal coat, drug coat, separating coat, film coat and such like.

The invention will now be described in connection with certain preferred embodiments in the following examples. The invention may not be so construed so as to limit it only to these particular embodiments. Thus, the following examples, which include preferred aspects, will only serve to illustrate the practice of this invention.

Example-1

Preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II).

6.5 gm of sodium hydroxide was added to 50 ml of tetrahydrofuran at room temperature. The mixture was stirred at room temperature for 30 minutes and then 5.0 gm of 5,6-dimethoxy-1-indanone & 6.5 gm of 1-benzyl-4-piperidine carboxaldehyde were added thereto. The mixture was heated to reflux and stirred at reflux temperature (65 C°- 70 C°) for 3 hours. The tetrahydrofuran was completely distilled off from resulting mass under vacuum below 50 C°. Isopropyl alcohol was added to the residue at 45 C°- 50 C°and the content were then cooled to 25 C°- 30 C° and stirred for 1 hour at 25 C°- 30 C. Solution is further cooled to 0-5°C and stirred for 3 hours at 0-5°C. The separated solid was filtered off under suction, washed with chilled isopropyl alcohol (25 ml) and dried the material at 30 C°- 35 C° for 5 hours to afford 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II) (weight: 8.0 gm) and purity is 97.04%.

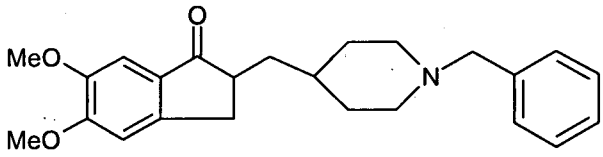
Example-2

Preparation of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl] methyl piperidine hydrochloride (Donepezil hydrochloride).

7.0 gm of 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II) was added in 154.0 ml of tetrahydrofuran and stirred at 25 C°- 30 C° for 10 minutes, followed by addition of 0.882 gm of cobalt chloride hexahydrate at 25 C°- 30 C°. The mixture was cooled to 15 C°- 20 C° & stirred at same temperature for 10 minutes and then 42.0 ml of methanol was added thereto at 15 C°- 20 C°. 1.4 gm of sodium borohydride in small portions was added to the reaction mixture at 15 C°- 20 C° within 30 minutes with stirring. After the addition was over, the reaction mixture was stirred at 15 C°- 20 C° for about 1 hour. The methylene chloride (100 ml) was added to the reaction mixture at 15 C°- 20 C° and stirred for 15 minutes at 25 C°- 30 C° and then organic phase was separated. The aqueous phase was extracted with 50.0 ml of methylene chloride, and the organic phase was combined with each other. The combined organic phase was washed with water and distilled out solvent completely under the vacuum below 40 C° from the organic phase. The resulting residue was mixed with 7.0 ml of methanol and 56.0 ml of ethyl acetate and stirred for 15 minutes at 25 C°- 30 C°, followed by addition of 2.5 gm of conc. Hydrochloric acid at 25 C°- 30 C° within 30 minutes. The resulting mixture was stirred for 3 hours at 25 C°- 30 C°and then cooled to 0 C°- 5 C°. It was further stirred for 2 hours at same temperature and the separated solid was filtered with suction at 0 C°- 5 C°, washed bed with chilled ethyl acetate (10 ml) and dried the material at 40 C°- 45 C° in vacuum drier to get donepezil hydrochloride (weight 6.4 gm) HPLC purity : 99.27%. Further it was recrystallized from methanol/ TBME to obtain highly pure donepezil hydrochloride (weight 5.44 gm).

We Claim:

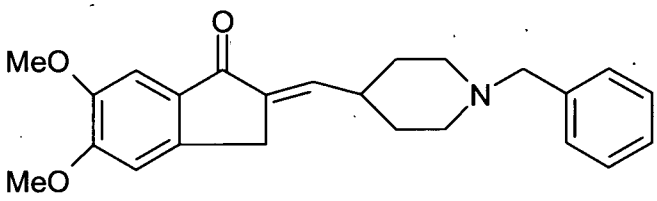
1. A process for the preparation of donepezil of formula (I) or pharmaceutically acceptable salts thereof,



(I)

Comprising:

a. reducing 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine (II)

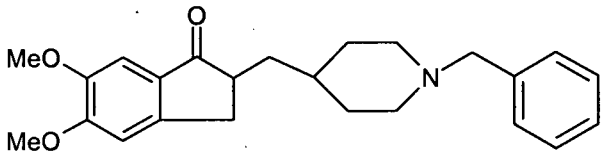


(II)

with metal borohydride in the presence of catalytic amount of cobalt salt in an organic solvents or an aqueous solvent or a mixture thereof: and

b. optionally converting formula(I) to its pharmaceutically acceptable salt .

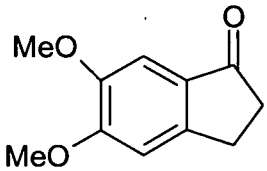
2. A process for the preparation of donepezil of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

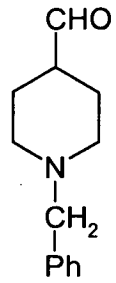
the process comprising:

(a) condensing 5,6-dimethoxy indanone of formula (III)



(III)

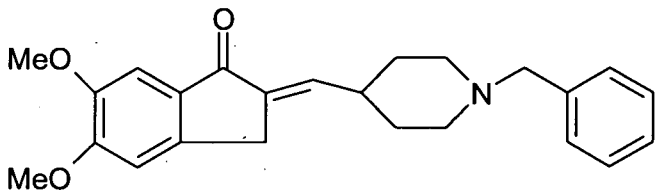
with a 1- benzyl-4-piperidine carboxaldehyde of formula (IV)



(IV)

to obtain 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine in the presence of alkali or alkaline earth metal hydroxide in organic solvent selected from the group comprising of dimethoxyethane, 1,3-dioxalane, ethylacetate, acetonitrile, tetrahydrofuran; dimethylformamide; diemthylacetamide; dimethylsulfoxide; dioxane; aromatic hydrocarbons, halogenated, carboxylates or an aqueous solvent or mixture thereof.

(b) reducing 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-ylidenyl] methyl piperidine of formula (II)



(II)

with metal borohydride in the presence of catalytic amount of cobalt salt in an organic solvents or an aqueous solvent or mixture thereof: and

(c) optionally converting formula (I) to its pharmaceutically acceptable salt.

3. The process according to claim 2, wherein the alkali metal hydroxide is sodium hydroxide and solvent used in step (a) is THF.

4. The process according to claim 1 or 2 , wherein metal borohydride is selected from the group comprising of sodium borohydride, potassium borohydride, lithium borohydride, zinc borohydride, rubidium borohydride, cesium borohydride or in admixture.

5. The process according to claim 4, wherein the metal borohydride is sodium borohydride.

6. The process according to claim 1 or 2, wherein the cobalt salt is selected from the group comprising of cobalt nitrate hexahydrate, hydrated cobalt nitrate, cobalt chloride, hydrated cobalt chloride, cobalt chloride hexahydrate, cobalt chloride hydrate, cobalt acetate tetrahydrate, cobalt acetylacetonate, cobalt acetylacetonate hydrate, cobalt carbonate hydrate, cobalt perchlorate hexahydrate, hydrated cobalt sulfate, cobalt sulfate hydrate or combinations thereof.

7. The process according to claim 6, wherein the cobalt salt is cobalt chloride hexahydrate.

8. The process according to claim 1 or 2, wherein the solvent used in reduction is selected from the group comprising of water, alcohols, acetonitrile, tetrahydrofuran, dimethylformamide, diemthylacetamide, dimethylsulfoxide, dioxane, aromatic hydrocarbons, halogenated hydrocarbons, ketones, ethers, carboxylates or a mixture thereof.

9. The process according to claim 8, wherein the solvent is THF/ Methanol mixture.

10. A pharmaceutical composition of donepezil and its pharmaceutically acceptable salts prepared according to claim 1 or 2 with at least one pharmaceutically acceptable excipient.

11. A process for the preparation of donepezil and its pharmaceutically acceptable slats, substantially as herein described, particularly with reference to the foregoing examples.