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# Industrially Scalable Synthesis of Anti-alzheimer Drug Donepezil

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This paper describes a simple, efficient and industrially scalable total synthesis of donepezil hydrochloride. The article also reported the X-ray studies of the 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one, an intermediate in the synthesis of donepezil. The crystal structure analysis of 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one shows that it crystallizes in monoclinic class under the space group P121/c1 with cell parameters, a = 17.2992(7) Å, b = 10.1999(4) Å, c = 11.9539(5) Å, β = 103.450(2)°, V = 2051.42(15) Å$^3$ and Z = 4.

**Keywords: Donepezil, Alzheimer's disease, X-ray diffraction.**

## INTRODUCTION

Alzheimer's disease, a type of dementia has no cure, over the time leads to death. It is a chronic neurodegenerative disease, commonly starts slowly and gets worse over time [1]. The symptoms of this disease are the gradual progress of absent-mindedness, trouble in language, mutism and perplexity [2]. Stepwise deterioration in remembrance and consciousness is the symptomatic course of the ailment [3]. Scientists believe that Alzheimer's disease may result from a deficiency of neurotransmitters present in brain nerves. Donepezil is an oral medication for Alzheimer's disease [4]. It belongs to cholinesterase inhibitors class of drugs with fewer side effects [5-8]. Donepezil inhibits acetylcholinesterase [9], an enzyme responsible for the destruction of acetylcholine, a neurotransmitter [10]. Research on donepezil began in 1983 with its first Phase I clinical trial in 1989 [11]. Besides, it has studied in patients with Down's syndrome, multiple sclerosis and schizophrenia.

In most of these patents, indanone was used as the starting material for the preparation of donepezil HCl. US Patent US 4,895,841 described that indanone was reacted with aldehyde by aldol condensation by using a base like LDA at -80 °C and heating the reaction mixture at room temperature to conduct dehydration which is reduced by Pd/C to yield donepezil. EP 0296560B1 discloses 1-indanon-2-yl-phosphonate with an aldehyde (Wittig reaction), which was reduced with Pd/C. US 5,606,064 discloses a process where indanone was condensed with *N*-benzyl pyridine-4-carboxaldehyde, which on treatment with benzyl bromide followed by reduction with platinum dioxide gives donepezil. US 2006/0122227A1 reported the reaction of *N*-protected 4-methyl-piperidine with 2-alkoxycarbonyl-5,6-dimethoxy-indan-1-one to yield 4-[2-alkoxycarbonyl-5,6-dimethoxy-indan-1-on-2-yl)methyl]-*N*-protected-piperidine, deprotecting the above molecule to yield 4-[2-alkoxycarbonyl-5,6-dimethoxy-indan-1-on-2-yl)methyl] piperidine which on treatment with benzyl chloride, followed by hydrolysis and decarboxylation yields donepezil. WO 97/22584 discloses the process for the preparation of donepezil. Indanone was reacted with 4-substituted piperidine derivative which on Mannich reaction followed by cyclization produces donepezil. WO 2006/070396-A1 discloses a process where Indanone was condensed with pyridine 4-carboxaldehyde, which is reacted with the peracid to make *N*-oxide followed by ring reduction using Pd/C and *N*-benzylation to yield donepezil. WO 2005/076749 A2 discloses a process where pyridine 4-carboxaldehyde was reduced with $NaBH_4$, reacted with benzyl bromide, reduction of aldehyde group to corresponding alcohol using $NaBH_4$, resulting primary alcohol was converted to primary chloride, which was reacted with 5,6-dimethoxy indanone and finally alkene reduction using $PtO_2$ yields donepezil base. WO 2007/077443 discloses a process for preparing donepezil by using condensation of aldehyde and indanone, followed by hydrogenation. This process mainly covers preparation of aldehyde by Darzen reaction. Further to our studies on active pharmaceutical ingredients and biologically active heterocycles [12-16], we report herein industrially scalable, efficient total synthesis of

donepezil hydrochloride by using safe reagents and experimental conditions. To confirm the product and to study the structural conformation details, the crystal structure of 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one, an intermediate in the synthesis of donepezil is also reported.

## EXPERIMENTAL

The melting points were ascertained on Thomas-Hoover apparatus and remain uncorrected. Infrared(KBr) spectra were recorded on Shimadzu 8300 Fourier transform infrared spectrometer. $^1$H and $^{13}$C NMR spectra (400 and 100 MHz respectively) were recorded on a Bruker AM spectrometer in DMSO solution with TMS as an internal standard. ESI mass spectra were recorded on an Agilent 6520 ESIQTOF instrument at ionization potential of 110 V. HPLC analysis was performed on Shimadzu LC-20AD using a C18, 150 mm × 4.6 mm reversed phase column with a 5 µm particle size with detection at 230 nm in water/acetonitrile/perchloric acid (75:25:0.1 v/v) and the flow rate of 1 mL/min. Thin layer chromatography (TLC) was conducted on 0.25 mm silica gel plates (60F254, Merck). Visualization was made with ultraviolet light (UV. R-340).

***N*-Benzyl ethyl isonipecotate (2):** Ethyl isonipecotate (**1**, 50 g, 0.31 mol) was dissolved in toluene (150 mL) in a round bottom flask, charged with potassium carbonate (60 g, 0.43 mol) and stirred for 15 min. Benzyl chloride (42 g, 0.31 mol) was charged and the reaction mass was refluxed for 4 h at 100 °C. Upon completion of the reaction as marked by TLC (hexane:ethyl acetate; 2:1), the reaction mass was cooled to room temperature and quenched with water (100 mL), stirred and the organic phase was separated. The aqueous phase was again extracted with toluene (100 mL). Combined organic phase was washed twice with saturated brine solution (50 mL). Remove toluene *in vacuo* to obtain *N*-benzyl ethyl isonipecotate (**2**, 6.97 g, 91 %) as a yellow liquid.

***N*-Benzyl piperidine alcohol (3):** Charge toluene (100 mL) in a round bottom flask along with vitride (26 g, 0.12 mol) in an inert atmosphere. *N*-Benzyl ethyl isonipecotate (**2**, 40 g, 0.16 mol) was added slowly in portions to the reaction mass. The mixture was stirred at room temperature for 2 h. After completion of the reaction the mass was quenched with chilled water. Toluene phase was separated and dried over anhydrous sodium sulfate. Toluene was removed under vacuum to get *N*-benzyl piperidine alcohol (**3**, 26.9 g, 82 %).

***N*-Benzyl piperidine-4-carboxaldehyde (4):** A round bottom flask was charged with oxalyl chloride (16.2 g, 0.12 mol), dichloromethane (150 mL) and anhydrous dimethyl sulfoxide (20 mL). Stir the reaction mixture mass in a cryo bath at -70 °C for 15 min. The resulting mixture is charged dropwise with *N*-benzyl piperidine alcohol **3** (20 g, 0.097 mol), along with triethylamine (24.6 g, 0.24 mol) and continued stirring for the next 15 min. After that, the mass is allowed to attain room temperature overnight, then diluted with dichloromethane (100 mL) and quenched with cold water. The organic layer was washed subsequently with 5 % HCl solution, brine solution, 5 % sodium bicarbonate solution and dried over sodium sulfate. Toluene was removed *in vacuo* to afford *N*-benzyl piperidine-4-carboxaldehyde (**4**, 19.2 g, 96 %).

**2-(1-Benzylpiperidin-4-ylmethyliden)-5,6-dimethoxy-indan-1-one (6):** A solution of 5,6-dimethoxy-indanone (**5**, 19 g, 0.10 mol) in methanol (8 mL) is stirred under inert atmosphere at room temperature. Slowly add NaOH flakes (12.8 g, 0.32 mol) followed by *N*-benzyl-piperidine-4-carboxaldehyde (**4**, 20.2 g, 0.10 mol) to the reaction mixture. The mixture was stirred at room temperature for 3 h and progress of the reaction was monitored by TLC (hexane:ethyl acetate; 1:1). Once the reaction is complete, the solid formed was filtered, washed with 5 % acetic acid and then with methanol and dried. The obtained solid (34 g) was taken into a round bottom flask and refluxed with DMF (50 mL). Gradually cooled to room temperature and stirred for 2 h, filtered the solid formed, wash with chilled methanol to afford a pale yellow crystalline solid **6** (32.0 g, 84 %); m.p.: 175-177 °C.

**l-Benzyl-4-[(5,6-dimethoxyl-indanon)-2-yl]methyl piperidine hydrochloride (donepezil hydrochloride) (8):** Charge 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxy-indan-1-one (**6**, 25 g, 0.066 mol) and methanol (150 mL) into SS autoclave under inert atmosphere. Charge methane sulfonic acid (8 g) to the above reaction mass and stir for 30 min. Charge activated Raney nickel (1 g). The autoclave was flushed with nitrogen gas and then applied hydrogen gas pressure (15 psi) and hydrogenated for 15 h at room temperature. After completion of the reaction, the catalyst was filtered through hyflo bed. The filtrate was neutralized with sodium carbonate (10 g) and the solid was filtered. Methanol was removed under vacuum and the residue left was charged with water (5 vol). The product was extracted with toluene (2 × 100 mL), washed with water, dried over anhydrous sodium sulfate. Toluene extract was treated with decolorizing carbon for 1 h, filtered through hyflo bed and toluene was removed under vacuum to get donepezil base as an oily product. It was dissolved in isopropyl alcohol (50 mL). Decolorizing carbon treatment is given again to isopropyl alcohol layer at 50 °C for 1 h. Carbon was filtered through hyflo bed and the clear filtrate was taken into round bottom flask. Under stirring isopropyl-HCl was added dropwise and pH was adjusted to 2-3. The temperature was raised to 70-75 °C and gradually cooled to room temperature and the product formed was filtered. The wet product was slurried with hot isopropyl alcohol, filtered and dried under vacuum to get donepezil HCl (**8**) as white crystalline solid to yield 22.8 g (85 %). m.p.: 229-231 °C. HPLC purity: 99.8 %; IR (KBr, $\nu_{max}$, cm$^{-1}$) 3588, 3371, 2925, 1683, 1592, 1501, 1455, 1315, 1266, 1217, 1119, 1039, 700; $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.48-1.5 (m, 1H), 1.82-2.10 (m, 6H), 2.63-2.68 (m, 4H), 3.28 (dd, $J$ = 8, 17.6 Hz, 1H), 3.38-3.42 (m, 2H), 3.9 (s, 3H), 3.96 (s, 3H), 4.12-4.19 (m, 2H), 6.85 (s, 1H), 7.12 (s, 1H), 7.44-7.63 (m, 3H), 10.3 (s, 1H, HCl); $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ: 206.8, 155.8, 149.6, 148.8, 131.5, 130.1, 129.2, 128.8, 128.2, 107.3, 104.4, 61.0, 56.2, 56.1, 52.4, 52.2, 44.2, 38.1, 34.0, 32.1, 29.4, 28.4; MS (ESI) *m/z* 380 [M$^+$+1].

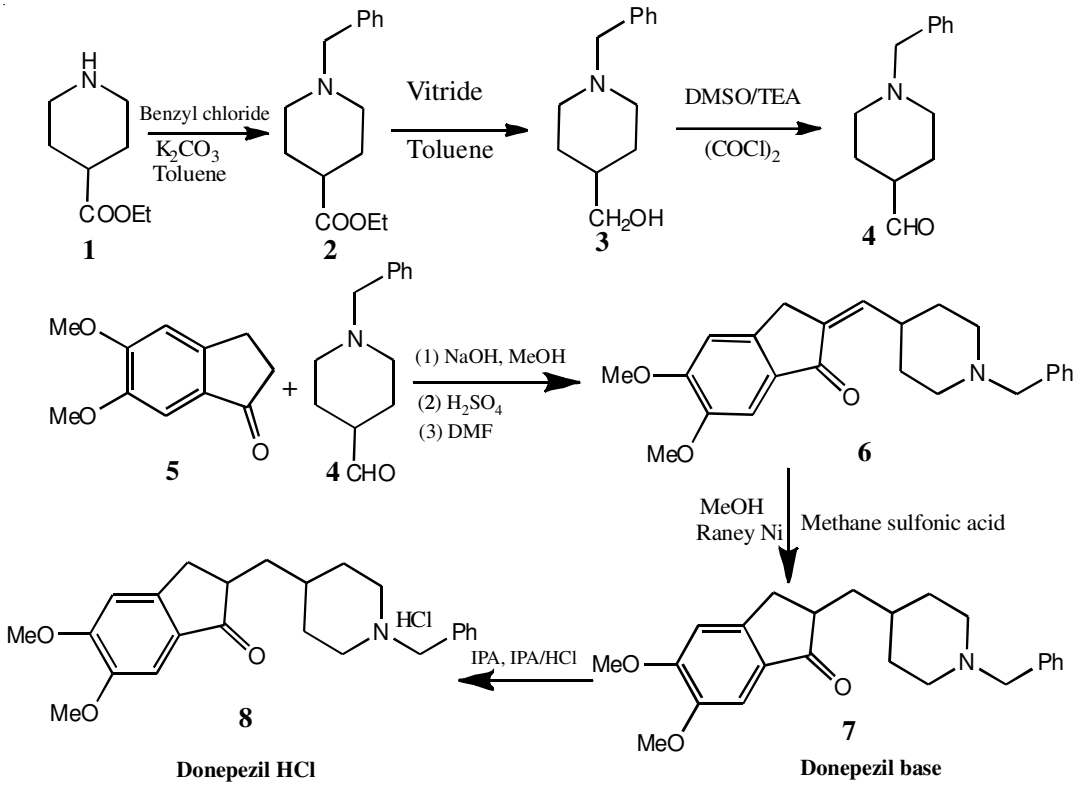
**X-ray data collection:** A specimen of $C_{24}H_{27}NO_3$ was used for the X-ray crystallographic analysis. A single crystal of the title compound with dimensions 0.10 mm × 0.10 mm × 0.01 mm was used for X-ray diffraction study. The X-ray intensity data were measured. The total exposure time was 1.44 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm [17]. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to the maximum apparent transmission was 0.868.

The structure was solved and refined using the Bruker SHELXTL Software Package [18], using the space group P121/c1, with Z = 4 for the formula unit, $C_{24}H_{27}NO_3$. The structure was deposited at the Cambridge Crystallographic Data Centre with CCDC No. 982818.

## RESULTS AND DISCUSSION

The synthetic scheme for the synthesis of donepezil hydrochloride is as shown in **Scheme-I**. Ethyl isonipecotate (**1**) is condensed with benzyl chloride to afford *N*-benzyl ethyl isonipecotate (**2**). Potassium carbonate is used to abstract the HCl generated during the reaction course. *N*-Benzyl ethyl isonipecotate (**2**) is reduced to corresponding *N*-benzyl piperidine alcohol (**3**) using vitride as reducing agent. Vitride, also called sodium *bis*(2-methoxyethoxy)aluminum hydride is a powerful reducing agent with comparable characteristics to lithium aluminium hydride. However, it selectively reduces esters to alcohols and is freely soluble in aromatic hydrocarbons like toluene. The high solubility and non-pyrophoric qualities of this reagent are beneficial compared to lithium aluminium hydride. In contrast with lithium aluminum hydride, its solutions show better moisture stability and are superior in thermal stability as well. *N*-Benzyl piperidine alcohol (**3**) undergoes swern oxidation to provide *N*-benzyl piperidine-4-carboxaldehyde (**4**) using oxalyl chloride, dimethyl sulfoxide and triethylamine. To avoid possible side reaction, the reaction was carried out at low temperature. The reaction conditions are best suited for the oxidation of acid-sensitive alcoholic group, which might decompose under the acidic conditions of conventional methods. The reaction between 5,6-dimethoxy-indanone and *N*-benzyl-piperidine-4-carboxaldehyde ia carried out in methanolic NaOH solution to gave 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one. Sodium hydroxide is employed in the reaction as a base to avoid the use of more expensive or toxic reagents as promoters such as lithium diisopropylamide (LDA), alkali-metal alkoxide such as sodium methoxide, triethyl-amine, diisopropyl ethyl amine, pyridine, piperidine. Reduction of 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one to donepezil was carried out using Raney nickel in the presence of methane sulfonic acid in methanol medium. Methane sulfonic acid was used to convert aldol type product formed during the reaction of 5,6-dimethoxy-indanone and *N*-benzylpiperidine-4-carboxaldehyde in the presence of NaOH. Methane sulfonic acid dehydrates aldol type product into 2-(1-benzylpiperidin-4-ylmethyliden)-5,6-dimethoxyindan-1-one which undergoes reduction to donepezil. The title compound synthesized was characterized by $^1$H NMR, $^{13}$C NMR, mass spectra and elemental analyses. $^1$H NMR, $^{13}$C NMR showed all the characteristic peaks in expected region. Mass spectra indicate the peak at *m/z* 380 ($M^+$+1), which corresponds to molecular ion of donepezil base. The HPLC purity of the product was more 99.6 % by the validated method. Significant advantages of the present invention are higher purity, better yields and the industrially scalable synthesis.

**Crystal structure analysis:** Fig. 1 displays ORTEP diagram of the compound **6** at 50 % probability with atom numbering while Fig. 2. depicts the packing diagram of the title compound. Crystal data and structure refinements details are given in Table-1. The data integration using a monoclinic unit cell yielded a total of 10391 reflections to a maximum θ angle of 22.76° (0.92 Å resolution), of which 2753 were independent (average redundancy 3.774, completeness = 99.8 %, $R_{int}$ = 2.72 %, $R_{sig}$ = 3.03 %) and 1999 (72.61 %) were greater than $2\sigma(F^2)$. The final cell constants of a = 17.2992(7) Å, b = 10.1999(4)




**Scheme-I:** Scheme for the synthesis of donepezil hydrochloride

TABLE-1
X-RAY CRYSTALLOGRAPHY DATA COLLECTION AND STRUCTURE REFINEMENT

| | | | |
|---|---|---|---|
| Chemical formula | $C_{24}H_{27}NO_3$ | Independent reflections | 2753 [R(int) = 0.0272] |
| Formula weight | 377.47 | Coverage of independent reflections | 99.8 % |
| Temperature | 296(2) K | Absorption correction | Multi-scan |
| Wavelength | 0.71073 Å | Structure solution technique | Direct methods |
| Crystal system | Monoclinic | Structure solution program | SHELXS-97 (Sheldrick, 2008) |
| Space group | P121/c1 | Refinement method | Full-matrix least-squares on $F^2$ |
| Unit cell dimensions | a = 17.2992(7) Å; α = 90° | Refinement program | SHELXL-97 (Sheldrick, 2008) |
| | b = 10.1999(4) Å; β = 103.450(2)° | Function minimized | $\Sigma w(F_o^2-F_c^2)^2$ |
| | c = 11.9539(5) Å; γ = 90° | Data/restraints/parameters | 2753/0/255 |
| Volume | 2051.42(14) $Å^3$ | Goodness-of-fit on $F^2$ | 1.065 |
| Z | 4 | $\Delta/\sigma_{max}$ | 0.017 |
| Density (calculated) | 1.222 $Mg/cm^3$ | Final R indices | 1999 data; I>2σ(I); R1 = 0.0419, wR2 = 0.1099 |
| Absorption coefficient | 0.080 $mm^{-1}$ | | All data; R1 = 0.0639, wR2 = 0.1328 |
| F(000) | 808 | Weighting scheme | $w = 1/[\sigma^2(F_o^2) + (0.0778P)^2 + 0.0000P]$ where $P = (F_o^2+2F_c^2)/3$ |
| Theta range for data collection | 1.21 to 22.76° | Largest diff. peak and hole | 0.137 and-0.170 $eÅ^{-3}$ |
| Index ranges | $-18 \le h \le 18$; $-11 \le k \le 11$; $-10 \le l \le 12$ | RMS deviation from mean | 0.043 $eÅ^{-3}$ |
| Reflections collected | 10391 | | |

TABLE-2
ATOMIC COORDINATES AND EQUIVALENT ISOTROPIC ATOMIC DISPLACEMENT PARAMETERS ($Å^2$)

| | x/a | y/b | z/c | U/eq | | x/a | y/b | z/c | U/eq |
|---|---|---|---|---|---|---|---|---|---|
| O1 | 0.80970(9) | 0.96545(15) | 0.90332(13) | 0.0709(5) | C11 | 0.42967(14) | 0.2812(2) | 0.7135(2) | 0.0671(7) |
| O2 | 0.85014(9) | 0.74549(14) | 0.99827(13) | 0.0671(5) | C12 | 0.49180(13) | 0.2431(2) | 0.65040(19) | 0.0559(6) |
| O3 | 0.14335(10) | 0.68052(15) | 0.90971(14) | 0.0774(5) | C13 | 0.53612(15) | 0.1313(2) | 0.6767(2) | 0.0717(7) |
| N1 | 0.38696(10) | 0.17040(16) | 0.74707(16) | 0.0581(5) | C14 | 0.59466(16) | 0.0997(3) | 0.6210(3) | 0.0856(8) |
| C1 | 0.78256(15) | 0.0888(2) | 0.8523(2) | 0.0845(8) | C15 | 0.61010(18) | 0.1808(3) | 0.5380(3) | 0.0896(9) |
| C2 | 0.88274(13) | 0.9243(2) | 0.89556(18) | 0.0531(6) | C16 | 0.87004(15) | 0.6247(2) | 0.0567(2) | 0.0908(9) |
| C3 | 0.93340(13) | 0.99287(19) | 0.84446(17) | 0.0539(6) | C17 | 0.90516(13) | 0.8008(2) | 0.94790(17) | 0.0520(6) |
| C4 | 0.00684(13) | 0.9388(2) | 0.84261(16) | 0.0499(6) | C18 | 0.97730(13) | 0.74782(19) | 0.94465(18) | 0.0530(6) |
| C5 | 0.07146(12) | 0.9965(2) | 0.79333(18) | 0.0591(6) | C19 | 0.02796(12) | 0.81810(19) | 0.89136(17) | 0.0488(6) |
| C6 | 0.13671(13) | 0.89541(19) | 0.82202(17) | 0.0537(6) | C20 | 0.29760(13) | 0.9855(2) | 0.6828(2) | 0.0658(7) |
| C7 | 0.21032(14) | 0.9061(2) | 0.80991(19) | 0.0624(6) | C21 | 0.33807(13) | 0.1044(2) | 0.6465(2) | 0.0657(7) |
| C8 | 0.24634(12) | 0.0222(2) | 0.76545(19) | 0.0595(6) | C22 | 0.50814(15) | 0.3231(2) | 0.5664(2) | 0.0769(8) |
| C9 | 0.29677(14) | 0.1001(2) | 0.8650(2) | 0.0655(7) | C23 | 0.56729(19) | 0.2923(3) | 0.5113(2) | 0.0926(9) |
| C10 | 0.33723(13) | 0.2145(2) | 0.8230(2) | 0.0666(7) | C24 | 0.10728(14) | 0.7825(2) | 0.87862(18) | 0.0559(6) |

U(eq) is defined as one-third of the trace of the orthogonalized $U_{ij}$ tensor

TABLE-3
BOND LENGTHS (Å)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| O1-C2 | 1.355(2) | O1-C1 | 1.429(3) | C10-H10A | 0.97 | C10-H10B | 0.97 |
| O2-C17 | 1.361(2) | O2-C16 | 1.419(2) | C11-C12 | 1.501(3) | C11-H11A | 0.97 |
| O3-C24 | 1.226(2) | N1-C11 | 1.456(3) | C11-H11B | 0.97 | C12-C22 | 1.373(3) |
| N1-C21 | 1.463(3) | N1-C10 | 1.460(3) | C12-C13 | 1.369(3) | C13-C14 | 1.373(3) |
| C1-H1A | 0.96 | C1-H1B | 0.96 | C13-H13 | 0.93 | C14-C15 | 1.365(4) |
| C1-H1C | 0.96 | C2-C3 | 1.371(3) | C14-H14 | 0.93 | C15-C23 | 1.355(4) |
| C2-C17 | 1.419(3) | C3-C4 | 1.390(3) | C15-H15 | 0.93 | C16-H16A | 0.96 |
| C3-H3 | 0.93 | C4-C19 | 1.375(3) | C16-H16B | 0.96 | C16-H16C | 0.96 |
| C4-C5 | 1.500(3) | C5-C6 | 1.509(3) | C17-C18 | 1.369(3) | C18-C19 | 1.396(3) |
| C5-H5A | 0.97 | C5-H5B | 0.97 | C18-H18 | 0.93 | C19-C24 | 1.461(3) |
| C6-C7 | 1.319(3) | C6-C24 | 1.484(3) | C20-C21 | 1.514(3) | C20-H20A | 0.97 |
| C7-C8 | 1.492(3) | C7-H7 | 0.93 | C20-H20B | 0.97 | C21-H21A | 0.97 |
| C8-C20 | 1.520(3) | C8-C9 | 1.525(3) | C21-H21B | 0.97 | C22-C23 | 1.376(3) |
| C8-H8 | 0.98 | C9-C10 | 1.505(3) | C22-H22 | 0.93 | C23-H23 | 0.93 |
| C9-H9A | 0.97 | C9-H9B | 0.97 | – | – | – | – |

Å, c = 11.9539(5) Å, β = 103.450(2)°, volume = 2051.42(14) $Å^3$, are based upon the refinement of the XYZ-centroids of 2468 reflections above 20 σ(I) with $4.67° < 2\theta < 40.69°$. The final anisotropic full matrix least-squares refinement on $F^2$ with 255 variables converged at R1 = 4.19 %, for the observed data and wR2 = 13.28 % for all data. The goodness-of-fit was 1.065.

TABLE-4
BOND ANGLES (°)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C2-O1-C1 | 117.56(17) | C17-O2-C16 | 117.61(18) | C12-C11-H11A | 108.8 | N1-C11-H11B | 108.8 |
| C11-N1-C21 | 111.35(18) | C11-N1-C10 | 110.03(17) | C12-C11-H11B | 108.8 | H11A-C11-H11B | 107.7 |
| C21-N1-C10 | 109.94(17) | O1-C1-H1A | 109.5 | C22-C12-C13 | 117.6(2) | C22-C12-C11 | 120.5(2) |
| O1-C1-H1B | 109.5 | H1A-C1-H1B | 109.5 | C13-C12-C11 | 121.9(2) | C12-C13-C14 | 121.4(2) |
| O1-C1-H1C | 109.5 | H1A-C1-H1C | 109.5 | C12-C13-H13 | 119.3 | C14-C13-H13 | 119.3 |
| H1B-C1-H1C | 109.5 | O1-C2-C3 | 125.1(2) | C13-C14-C15 | 120.1(3) | C13-C14-H14 | 120.0 |
| O1-C2-C17 | 114.10(19) | C3-C2-C17 | 120.8(2) | C15-C14-H14 | 120.0 | C23-C15-C14 | 119.4(3) |
| C2-C3-C4 | 119.1(2) | C2-C3-H3 | 120.5 | C23-C15-H15 | 120.3 | C14-C15-H15 | 120.3 |
| C4-C3-H3 | 120.5 | C19-C4-C3 | 120.15(19) | O2-C16-H16A | 109.5 | O2-C16-H16B | 109.5 |
| C19-C4-C5 | 111.67(19) | C3-C4-C5 | 128.17(19) | H16A-C16-H16B | 109.5 | O2-C16-H16C | 109.5 |
| C4-C5-C6 | 103.23(17) | C4-C5-H5A | 111.1 | H16A-C16-H16C | 109.5 | H16B-C16-H16C | 109.5 |
| C6-C5-H5A | 111.1 | C4-C5-H5B | 111.1 | O2-C17-C18 | 125.8(2) | O2-C17-C2 | 114.5(2) |
| C6-C5-H5B | 111.1 | H5A-C5-H5B | 109.1 | C18-C17-C2 | 119.7(2) | C17-C18-C19 | 118.9(2) |
| C7-C6-C24 | 123.8(2) | C7-C6-C5 | 127.52(19) | C17-C18-H18 | 120.5 | C19-C18-H18 | 120.5 |
| C24-C6-C5 | 108.43(19) | C6-C7-C8 | 126.7(2) | C4-C19-C18 | 121.4(2) | C4-C19-C24 | 109.97(19) |
| C6-C7-H7 | 116.6 | C8-C7-H7 | 116.6 | C18-C19-C24 | 128.7(2) | C21-C20-C8 | 111.55(18) |
| C7-C8-C20 | 113.02(18) | C7-C8-C9 | 110.26(19) | C21-C20-H20A | 109.3 | C8-C20-H20A | 109.3 |
| C20-C8-C9 | 108.74(17) | C7-C8-H8 | 108.2 | C21-C20-H20B | 109.3 | C8-C20-H20B | 109.3 |
| C20-C8-H8 | 108.2 | C9-C8-H8 | 108.2 | H20A-C20-H20B | 108.0 | N1-C21-C20 | 110.54(19) |
| C10-C9-C8 | 111.72(19) | C10-C9-H9A | 109.3 | N1-C21-H21A | 109.5 | C20-C21-H21A | 109.5 |
| C8-C9-H9A | 109.3 | C10-C9-H9B | 109.3 | N1-C21-H21B | 109.5 | C20-C21-H21B | 109.5 |
| C8-C9-H9B | 109.3 | H9A-C9-H9B | 107.9 | H21A-C21-H21B | 108.1 | C12-C22-C23 | 121.2(2) |
| N1-C10-C9 | 110.83(18) | N1-C10-H10A | 109.5 | C12-C22-H22 | 119.4 | C23-C22-H22 | 119.4 |
| C9-C10-H10A | 109.5 | N1-C10-H10B | 109.5 | C15-C23-C22 | 120.3(3) | C15-C23-H23 | 119.8 |
| C9-C10-H10B | 109.5 | H10A-C10-H10B | 108.1 | C22-C23-H23 | 119.8 | O3-C24-C19 | 127.1(2) |
| N1-C11-C12 | 113.97(18) | N1-C11-H11A | 108.8 | O3-C24-C6 | 126.3(2) | C19-C24-C6 | 106.56(19) |

TABLE-5
ANISOTROPIC ATOMIC DISPLACEMENT PARAMETERS ($Å^2$)

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O1 | 0.0642(11) | 0.0714(11) | 0.0806(11) | 0.0155(9) | 0.0243(9) | 0.0088(9) |
| O2 | 0.0657(11) | 0.0637(10) | 0.0755(11) | 0.0154(8) | 0.0241(9) | -0.0070(8) |
| O3 | 0.0773(11) | 0.0498(10) | 0.1101(14) | 0.0082(9) | 0.0319(10) | 0.0062(9) |
| N1 | 0.0582(11) | 0.0478(10) | 0.0736(13) | -0.0045(9) | 0.0260(10) | -0.0055(9) |
| C1 | 0.0764(18) | 0.0802(18) | 0.097(2) | 0.0175(15) | 0.0209(15) | 0.0217(15) |
| C2 | 0.0538(14) | 0.0538(13) | 0.0510(13) | -0.0003(11) | 0.0109(11) | -0.0020(12) |
| C3 | 0.0621(15) | 0.0480(13) | 0.0499(13) | 0.0058(10) | 0.0095(11) | -0.0010(12) |
| C4 | 0.0592(14) | 0.0478(13) | 0.0418(13) | -0.0008(10) | 0.0100(11) | -0.0087(11) |
| C5 | 0.0674(15) | 0.0541(13) | 0.0562(14) | 0.0057(11) | 0.0151(12) | -0.0078(12) |
| C6 | 0.0584(15) | 0.0479(13) | 0.0568(14) | -0.0036(10) | 0.0173(12) | -0.0062(12) |
| C7 | 0.0657(16) | 0.0533(14) | 0.0695(16) | -0.0022(11) | 0.0187(13) | -0.0005(12) |
| C8 | 0.0551(14) | 0.0549(13) | 0.0722(16) | 0.0015(12) | 0.0223(12) | -0.0021(12) |
| C9 | 0.0721(16) | 0.0571(14) | 0.0744(16) | -0.0057(12) | 0.0317(13) | -0.0016(12) |
| C10 | 0.0680(16) | 0.0546(14) | 0.0833(17) | -0.0074(12) | 0.0300(14) | -0.0022(12) |
| C11 | 0.0636(15) | 0.0479(13) | 0.0941(19) | 0.0028(12) | 0.0276(14) | -0.0029(12) |
| C12 | 0.0550(14) | 0.0453(13) | 0.0689(16) | 0.0020(11) | 0.0175(12) | -0.0071(11) |
| C13 | 0.0792(17) | 0.0617(15) | 0.0839(18) | 0.0101(13) | 0.0384(15) | 0.0088(14) |
| C14 | 0.084(2) | 0.0667(17) | 0.114(2) | -0.0051(16) | 0.0389(18) | 0.0058(15) |
| C15 | 0.094(2) | 0.083(2) | 0.109(2) | -0.0298(18) | 0.0571(19) | -0.0238(18) |
| C16 | 0.0821(18) | 0.0882(19) | 0.106(2) | 0.0472(17) | 0.0286(16) | -0.0051(15) |
| C17 | 0.0564(14) | 0.0504(13) | 0.0485(13) | -0.0005(10) | 0.0109(11) | -0.0119(12) |
| C18 | 0.0636(15) | 0.0395(11) | 0.0547(14) | 0.0006(10) | 0.0116(12) | -0.0057(11) |
| C19 | 0.0540(14) | 0.0419(12) | 0.0499(13) | -0.0051(10) | 0.0108(11) | -0.0074(11) |
| C20 | 0.0635(14) | 0.0662(15) | 0.0705(16) | -0.0104(12) | 0.0215(13) | -0.0107(12) |
| C21 | 0.0634(15) | 0.0685(15) | 0.0701(16) | -0.0022(13) | 0.0257(13) | -0.0073(12) |
| C22 | 0.0761(18) | 0.0646(15) | 0.094(2) | 0.0145(15) | 0.0270(16) | -0.0049(14) |
| C23 | 0.115(2) | 0.087(2) | 0.089(2) | 0.0053(16) | 0.0512(19) | -0.0184(19) |
| C24 | 0.0645(16) | 0.0434(13) | 0.0597(14) | -0.0049(11) | 0.0144(12) | -0.0058(12) |

The anisotropic atomic displacement factor exponent takes the form: $-2\sigma^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

The largest peak in the final difference electron density synthesis was 0.137 $e^-/Å^3$ and the biggest hole was-0.170 $e^-/Å^3$ with an RMS deviation of 0.043 $e^-/Å^3$. The calculated density was 1.222 $g/cm^3$ and F(000), 808 $e^-$ based on the final model. Positional coordinates of all the atoms, anisotropic atomic displacement and hydrogen atomic coordinates along with

TABLE-6
HYDROGEN ATOMIC COORDINATES AND ISOTROPIC ATOMIC DISPLACEMENT PARAMETERS (Å$^2$)

| | x/a | y/b | z/c | U/eq | | x/a | y/b | z/c | U/eq |
|---|---|---|---|---|---|---|---|---|---|
| H1A | -0.1808 | 0.1564 | 0.8863 | 0.127 | H13 | 0.5264 | 0.0756 | 0.7334 | 0.086 |
| H1B | -0.2690 | 0.1077 | 0.8653 | 0.127 | H14 | 0.6238 | 0.0230 | 0.6399 | 0.103 |
| H1C | -0.2207 | 0.0851 | 0.7711 | 0.127 | H15 | 0.6497 | 0.1596 | 0.5001 | 0.108 |
| H3 | -0.0812 | 0.0744 | 0.8115 | 0.065 | H16A | -0.1202 | -0.4403 | 1.0035 | 0.136 |
| H5A | 0.0891 | 0.0802 | 0.8288 | 0.071 | H16B | -0.1731 | -0.4033 | 1.0890 | 0.136 |
| H5B | 0.0537 | 0.0085 | 0.7108 | 0.071 | H16C | -0.0830 | -0.3641 | 1.1172 | 0.136 |
| H7 | 0.2432 | -0.1662 | 0.8313 | 0.075 | H18 | -0.0077 | -0.3337 | 0.9774 | 0.064 |
| H8 | 0.2032 | 0.0788 | 0.7246 | 0.071 | H20A | 0.3376 | -0.0774 | 0.7196 | 0.079 |
| H9A | 0.2632 | 0.1320 | 0.9138 | 0.079 | H20B | 0.2647 | -0.0559 | 0.6152 | 0.079 |
| H9B | 0.3366 | 0.0429 | 0.9109 | 0.079 | H21A | 0.3712 | 0.0776 | 0.5954 | 0.079 |
| H10A | 0.2975 | 0.2752 | 0.7820 | 0.08 | H21B | 0.2982 | 0.1648 | 0.6050 | 0.079 |
| H10B | 0.3698 | 0.2603 | 0.8884 | 0.08 | H22 | 0.4787 | 0.3993 | 0.5464 | 0.092 |
| H11A | 0.4550 | 0.3297 | 0.7820 | 0.08 | H23 | 0.5779 | 0.3484 | 0.4554 | 0.111 |
| H11B | 0.3917 | 0.3392 | 0.6650 | 0.08 | – | – | – | – | – |

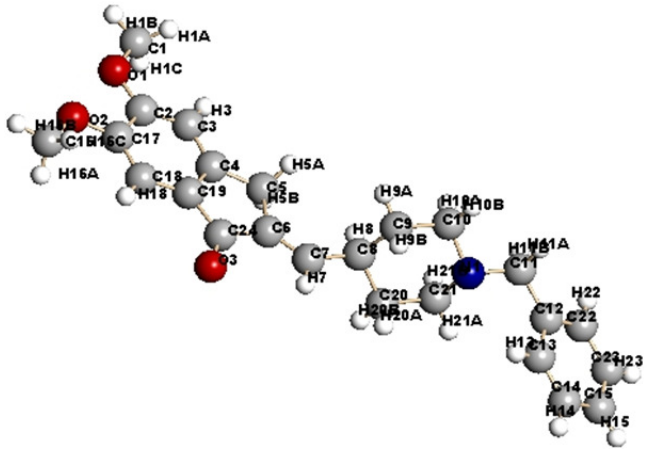



Fig. 1. ORTEP diagram of the compound **6** at 50 % probability with atom numbering

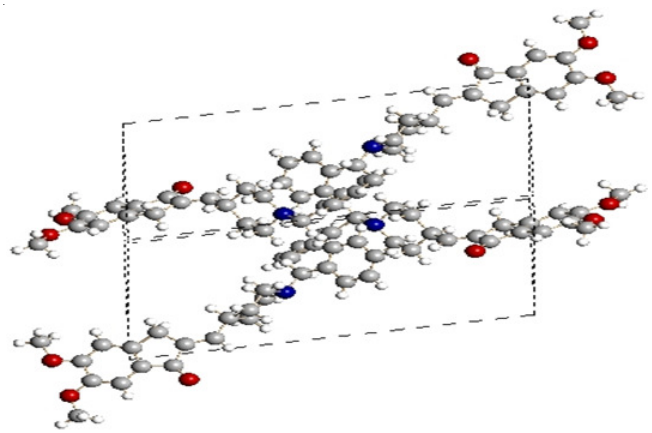


Fig. 2. Packing diagram of the title compound

isotropic atomic displacement parameters are accounted in Tables 2-6 respectively and attached as supporting information.

## Conclusion

Based on a thorough study of patents and research papers on donepezil hydrochloride, an efficient, industrially scalable method for donepezil hydrochloride has developed. Modern analytical techniques are adopted to characterize and title compound and HPLC purity of the product was more than 99.8 %. The structure of intermediate compound **6** was confirmed by the single crystal X-ray studies.

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