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Synthesis and Characterization of (3S, 4R)-4-(4-Fluorophenyl)-Piperidine-3-Methanol, a Possible Impurity in Paroxetine Hydrochloride

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ABSTRACT

(3S, 4R)-trans-4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl-piperidine is treated with methane sulfonyl chloride to convert in to mesityl derivative and then reacted with phenyl chloroformate to form carbamate derivative and finally hydrolyse to yield (3S, 4R)-4-(4-Fluuorophenyl)Piperidine-3-methanol.

Keywords: Impurity, NMR, Sesamol, Paroxetine

INTRODUCTION

Paroxetine is an antidepressant in a group of drugs called Selective Serotonin Reuptake Inhibitors (SSRIs). Paroxetine affects chemicals in the brain that may become unbalanced. Paroxetine is used to treat depression, obsessive-compulsive disorder, anxiety disorders, Post-Traumatic Stress Disorder (PTSD), and Premenstrual Dysphoric Disorder (PMDD). The Brisdelle brand of Paroxetine is used to treat hot flashes related to menopause. Brisdelle is not for treating any other conditions.

An impurity in a drug substance as defined by the International Conference on Harmonisation (ICH) Guidelines is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances [1]. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product [2]. Therefore any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties. The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Several recent books and journal reviews address this topic and guidelines are available from US and international authorities [3-10]. Most active pharmaceutical ingredients (API) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components can be generated during such a process. Those components remaining in the final API are considered as impurities. For the preparation of paroxetine Hydrochloride one of the intermediate such as (3S, 4R)-trans-4- (4-fluorophenyl)-3-hydroxymethyl-1-methyl- piperidine is required and is reacted with methane sulfonyl chloride to yield mesityl derivative and then treated with Sesamol to yield Sesamol condensed product. Sesamol condensed product is than treated with phenyl chloroformate to give carbamate intermediate and carbamate intermediate on hydrolysis yield Paroxetine. In the above reaction sequences unreacted Mesityl derivative may undergo reaction with Phenylchloroformate and after hydrolysis result in to (3S, 4R)-4-(4-Fluuorophenyl) Piperidine-3-methanol as an impurity.

(3S, 4R)-4-(4-Fluuorophenyl) Piperidine-3-methanol is also one of the degradant of Paroxetine Hydrochloride under acidic condition and with hydrogen peroxide [11]. Keeping this in mind we decided to synthesize (3S, 4R)-4-(4-Fluuorophenyl) Piperidine-3-methanol by novel route which has been disclosed in this manuscript.

EXPERIMENTAL

All the compounds were identified by examination of their spectral data and physical properties. Yields refer to the isolated yields of desired products.

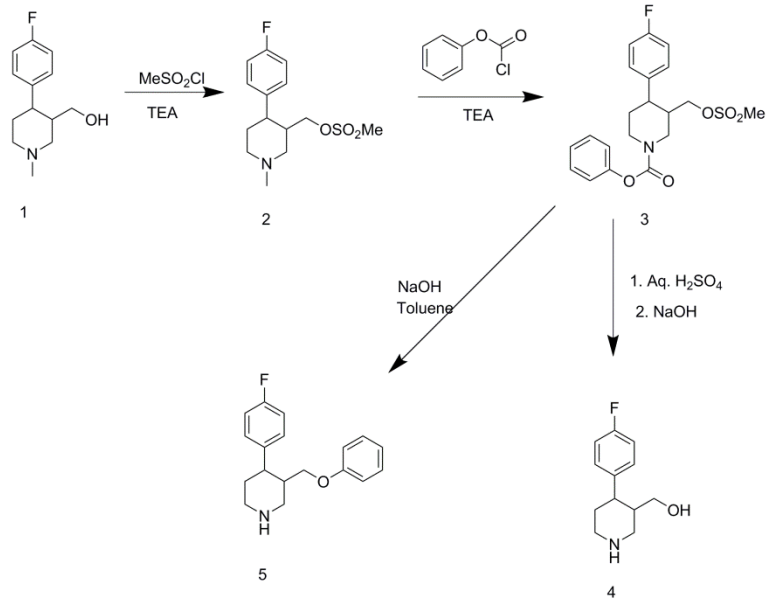
Melting points were determined on Buchi-545 melting point apparatus and are uncorrected. Progress of the reaction was monitored on TLC. IR spectra were recorded by Perkin Elmer Spectrum-1 (FTIR) using KBr discs, 1H NMR and 13C NMR was recorded in $CDCl_3$ using Avance 400 MHz Bruker spectrometer (chemical shifts (δ) in ppm) with TMS as internal standard and mass spectra were recorded on a Thermofinigan Ion Trap GCMS Polaris Q. The dry reactions were carried out under nitrogen with magnetic/mechanical stirring.

RESULTS AND DISCUSSION

(3S, 4R)-trans-4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl- piperidine was treated with methanesulfonyl chloride at 0-5ºC to form mesityl derivative and was characterized by spectral data. The IR spectrum of compound (2) showed disappearance of broad band at 3600 cm^{-1} for Hydroxyl group and the 1HNMR ($CDCl_3$) indicated the presence of two methyl protons at δ 2.2 and 2.75 ppm and further confirmed by mass spectrometry. Mesityl derivative further treated with phenyl chloroformate in presence of Triethyl amine to form corresponding Carbamate derivative (3) and this was characterized by NMR which was showing the absence of one of the methyl protons at δ 2.2 ppm. Carbamate derivative was subjected to Basic hydrolysis and result in to different product (5) i.e., (3S, 4R)-trans-4-(4-fluorophenyl)-3-(phenoxymethyl) piperidine. This was characterized by Mass and NMR. NMR signals showed the presence of total 9 aromatic ring proton with absence of carbamate further it was confirmed by Mass.

In another attempt Carbamate derivative was subjected to acid Hydrolysis instead of basic hydrolysis and desired product obtained (4). Structure was confirmed by its spectral data. The IR spectrum showed broad band at 3652 cm^{-1} indicating the presence of Hydroxyl group and 1H NMR showed the absence of methyl protons.

The envisaged reaction sequence is depicted in Scheme 1.



Scheme 1: The envisaged reaction sequence

Synthesis of (3S, 4R)-trans-4-((4-fluorophenyl)-1-methylpiperidine)-3-methyl methane Sulfonate (2)

To a stirred solution of Carbinol (10 mmol) in Dichloromethane (40 ml) at 0-5ºC, Triethyl amine (14 mmol) was added drop wise followed by addition of Methane sulfonyl chloride (11 mmol). The reaction was stirred for 3-4 h at 0-5ºC. Reaction was monitored by TLC (Dichloromethane: Methanol, 9:1). After completion of reaction, water was added in the reaction mixture and layer was separated and dried using sodium sulfate and solvent removed under reduced pressure.

Compound (2): Semisolid; Yield: 95%; Anal. Calcd. for $C_{14}H_{20}FNO_3S$; C, 55.80; H, 6.69; N, 4.65. Found: C, 55.91; H, 6.44; N, 4.89; IR (KBr, cm^{-1}): 3050, 1923, 1610, 1555, 1448; ^{1}H NMR (400 MHz,$CDCl_3$) δ:1.80-2.08 (m, 2H, -CH_2-), 2.20-2.27 (m, 1H, >CH-), 2.31-2.40 (m, 4H, >N-CH_3, >CH-), 2.87 (s, 3H, -SO_2CH_3), 2.94-2.98 (m, 2H, N-CH_2-), 3.09-3.14 (m, 2H, N-CH_2-), 3.78-3.95 (m, 2H, O-CH_2-), 6.98-7.19 (m, 4H, Ar-H); ^{13}C-NMR (100.622 MHz, $CDCl_3$, δ/ ppm): 34.3, 43.6, 44.2, 46.4, 56.1, 59.5, 63.2, 115.4, 128.8, 139.9, 160.2, 162.6; Mass (m/z): 302 [M+].

Synthesis of (3S, 4R)-trans-Phenyl4-(4-Fluorophenyl)-3-(((methylsulfonyl) oxy)methyl)Piperidine-1-carboxylate (Carbamate) (3)

To a stirred solution of (3S, 4R)-trans-4- (4-fluorophenyl)-3-mesyloxymethyl-1-methyl- piperidine (10 mmol) in Toluene (30 ml) at 5-10ºC, Triethylamine (3 mmol) was added dropwise followed by addition of Phenyl chloroformate (12 mmol). Temperature was raised to room temperature and stirred for 12-13 h. Reaction was monitored by TLC (Dichloromethane: Methanol, 9:1). Reaction was quenched by addition of potassium carbonate solution, after completion of reaction. Organic layer was separated and dried using Sodium sulfate, Solvent was removed under reduced pressure. Isopropyl alcohol (50 ml) was added to the crude residue and refluxed for 1 h at 75-80ºC and cooled to room temperature and filtered and washed with Isopropyl alcohol to get solid product.

Compound (3): White Solid; Yield: 73%; m.p. 215ºC; Anal. Calcd. for $C_{20}H_{22}FNO_5S$; C, 58.96; H, 5.44; N, 3.44. Found: C, 58.74; H, 5.28; N, 3.69; IR (KBr, cm^{-1}): 3026, 1720, 1605, 1548, 1468; ^{1}H NMR (400 MHz,$CDCl_3$) δ:1.80-1.88 (m, 2H, -CH_2-), 1.92-1.94 (m, 1H, >CH-), 2.20-2.68 (m, 1H, >CH-), 2.92 (s, 3H, -SO_2CH_3), 2.97-3.09 (m, 2H, -OCH_2-), 3.85-3.89 (m, 2H, N-CH_2-), 4.03-4.44

(m, 2H, N-CH_2-), 7.05-7.42 (m, 9H, Ar-H); ^{13}C-NMR (100.622 MHz,$CDCl_3$, δ/ ppm): 37.2, 43.8, 44.9, 45.3, 58.2, 61.6, 63.3, 69.4, 115.4, 128.8, 137.7, 139.9, 151.3, 153.6, 160.2, 162.6; Mass (m/z): 408 [M+].

Synthesis of (3S, 4R)-4-(4-Fluuorophenyl) Piperidine-3-methanol (4)

Carbamate (5 mmol) and aqueous Sulfuric acid (16 ml Conc. H_2SO_4 +24 ml water) was refluxed for 24-26 h at 90-95ºC. Reaction was monitored by TLC (Dichloromethane: Methanol, 9:1). After completion of reaction, Reaction mixture was cooled to room temperature and added 50 ml water slowly. Checked pH and adjusted to 8-9 using NaOH solution and cooled to 0-5ºC. Filtered and mother liquor was extracted with Dichloromethane and dried using Sodium sulfate and solvent was removed under reduced pressure and crystallized using Isopropyl alcohol.

Compound (4): White Solid; Yield: 56%; m.p. 138ºC; Anal. Calcd. for $C_{12}H_{16}FNO$; C, 68.88; H, 7.71; N, 6.69. Found: C, 69.3; H, 7.93; N, 5.42; IR (KBr, cm^{-1}): 3652, 1658, 1593, 1537, 1453; ^{1}H NMR (400 MHz,$CDCl_3$) δ:1.69-1.77 (m, 1H, -CH_2-), 1.84-1.86 (m, 1H, -CH_2-), 1.89-1.89 (m, 1H, >CH-), 2.55-2.58 (dt, 1H, >CH-), 2.61 (t, 1H, N-CH_2-), 2.70-2.71 (dt, 1H, N-CH_2-), 3.21-3.23 (m, 1H, N-CH_2-), 3.24-3.26 (dd, 1H, -CH_2-O), 3.38-3.42 (m, 2H, >NCH_2-, -CH_2-O), 6.97-7.02 (m, 2H, Ar-H), 7.16-7.20 (m, 2H, Ar-H); ^{13}C-NMR (100.622 MHz,$CDCl_3$, δ/ ppm): 35.4, 44.7, 45.1, 47, 50.1, 63.7, 115.3, 128.7, 140.2, 160.2; Mass (m/z): 209.21 [M+].

Synthesis of (3S, 4R)-trans-4-(4-fluorophenyl)-3-(phenoxymethyl) piperidine (5)

Carbamate (5 mmol) and aqueous NaOH (8 mmol) was refluxed for 10-11 h at 90-95ºC. Reaction was monitored by TLC (Dichloromethane: Methanol, 9:1). After completion of reaction, Reaction mixture was cooled to room temperature and pH adjusted to 7. Filtered and mother liquor was extracted with Dichloromethane and dried using Sodium sulfate and solvent was removed under reduced pressure and thereafter crystallized using Isopropyl alcohol.

Compound (5): White Solid; Yield: 48%; m.p. 189ºC; Anal. Calcd. for $C_{18}H_{20}FNO$; C, 75.76; H, 7.06; N, 4.91. Found: C, 75.98; H, 7.22; N, 5.12; IR (KBr, cm^{-1}): 3118, 1602, 1554, 1503, 1447; ^{1}H NMR (400 MHz,$CDCl_3$) δ:1.76-1.83 (m, 2H, -CH_2-), 2.14 (m, 1H, >CH-), 2.2 (s, 1H, >NH), 2.63-2.77 (m, 3H, >N-CH, >N-CH, >CH-), 3.18 (d, 1H, >N-CH), 3.44-3.44 (d, 1H, >N-CH), 3.51-3.68 (m, 2H, -OCH_2),; ^{13}C-NMR (100.622 MHz,$CDCl_3$, δ/ ppm): 35.3, 42.9, 44.5, 47, 50.3, 68.4, 114.4, 115.3, 115.5, 120.6, 128.7, 128.8, 129.4, 139.9, 139.9, 158.8; Mass (m/z): 286.16 [M+].

CONCLUSION

In conclusion we have synthesized novel (3S, 4R)-4-(4-Fluuorophenyl) Piperidine-3-methanol starting from (3S, 4R)-trans-4- (4-fluorophenyl)-3-hydroxymethyl-1-methyl- piperidine under mild condition.

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