INTRODUCTION

Iloperidone, also known as Fanapt, Fanapta and Zomaril, is an approved antipsychotic inhibitor in USA by the FDA for the treatment of schizophrenia. Iloperidone has been shown to act as an antagonist at all tested receptors. It was found to block the sites of noradrenalin ($\alpha_2C$), dopamine (D$_{2A}$ and D$_{3}$) and serotonin (5-HT$_{1A}$ and 5-HT$_{6}$) receptors. In addition, pharmacogenomic studies identified single nucleotide polymorphisms associated with an enhanced response to iloperidone during acute treatment of schizophrenia. It is considered an ‘atypical’ antipsychotic because it displays serotonin receptor antagonism, similar to other atypical antipsychotics. The older typical antipsychotics are primarily dopamine antagonists.

Recently, we have described an efficient, industrial scale synthesis of iloperidone 1 (Scheme-I)\(^3\). During the synthesis of 1, we came across many process related impurities and some of them were captured in our prior report. To comprehend the complete impurity profile of 1 and to compare the extent of contamination of the impurities in 1, we have decided to synthesize all the possible impurities. Impurities, 1-(4-hydroxy-3-methoxyphenyl)ethanone (2) and 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole (5) have the well-known procedure for synthesis and they are commercially available.\(^3\)

EXPERIMENTAL

All the chemicals were procured from Sigma-Aldrich, Merck and Lancaster and used as such without further purifi-
cation. $^1$H and $^13$C NMR spectra were recorded on a Bruker Avance 300 and 75 MHz spectrometer, respectively. $^1$H NMR spectra were recorded using Me$_4$Si (δ 0.00 ppm) as internal standard. $^13$C NMR spectra were reported relative to CDCl$_3$ (δ 77.16 ppm) and DMSO-d$_6$ (δ 48.5 ppm). FTIR spectra were recorded on a Perkin-Elmer Spectrum one spectrometer by using 1 % potassium bromide pellet technique and are reported in wave numbers (cm$^{-1}$). LC mass spectra were recorded on Agilent 1100 series LC-MSD-TRAP-SL system mass spectrometer. All the solvents and reagents were used without further purification.

**Synthesis of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4):** To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone 2 (5 g, 30 mmol), acetonitrile (20 mL) and potassium carbonate (12.5 g, 9 mmol) were charged at room temperature. Reaction temperature was raised to 75-80 °C, 1-bromo-3-chloropropane 3 (8.35 g, 53 mmol) in acetonitrile (20 mL) was added during 4 h dropwise at ambient temperature and maintained for 3 h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1), after completion of reaction, it was cooled to room temperature and filtered the salts. Filtrate was taken and the solvent was removed under reduced pressure below 60 °C and recrystallized from cyclohexane (30 mL) as a white crystalline solid 4 (6.93 g, 95 %) obtained. Purity 99.5 % (by HPLC), m.p. 61-63 °C; FT-IR (KBr, ν$_{max}$ cm$^{-1}$): 3072, 2964, 2933, 2842, 1663, 1670, 1596, 1587, 1523, 1515, 1466, 1452, 1420, 1355, 1277, 1225, 1183, 1146, 1077, 1034, 873, 807, 772; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.28-2.36 (36, 2H), 2.57 (s, 3H), 3.78 (t, 2H, J = 6.2 Hz), 3.91 (s, 3H), 4.23 (t, 2H, J = 8.4 Hz), 6.92 (d, 2H, J = 8.1 Hz), 7.53-7.58 (m, 1H), 7.53-7.58 (m, 1H); $^13$C NMR (75 MHz, CDCl$_3$) δ 25.82, 31.71, 45.08, 55.60, 66.38, 110.50, 111.46, 123.03, 130.65, 149.23, 152.39, 196.58; MS(ESI, m/z): 287 [M + H]$^+$

**Synthesis of 1-[4-(3-hydroxypropoxy)-3-methoxyphenyl]ethanone (6):** To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone 2 (10 g, 60 mmol), acetonitrile (50 mL), potassium carbonate (8.3 g, 60 mmol) and 1,3-dibromopropane 8 (8.3 g, 60 mmol) were charged at room temperature. Reaction temperature was raised to 80-85 °C and maintained for 8 h. The reaction progress was monitored by TLC (n-hexane:ethyl acetate, 7:3), after completion of reaction, the reaction mixture was cooled to room temperature, filtered the salts and washed with acetonitrile (10 mL). Filtrate was taken, solvent was removed under reduced pressure below 60 °C, light brown coloured residue was obtained, it was purified from column chromatography 10 % ethyl acetate in n-hexane and recrystallized from isopropyl ether (50 mL), to get a light brown coloured solid 9 (37.2 g, 90 %). Purity 99.2 % (by HPLC), m.p. 64-66 °C; FT-IR (KBr, ν$_{max}$ cm$^{-1}$): 3073, 2964, 2933, 2842, 1663, 1670, 1596, 1587, 1523, 1515, 1466, 1452, 1420, 1355, 1277, 1225, 1183, 1146, 1077, 1034, 873, 807, 772; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.28-2.36 (36, 2H), 2.57 (s, 3H), 3.78 (t, 2H, J = 6.2 Hz), 3.91 (s, 3H), 4.23 (t, 2H, J = 8.1 Hz), 6.92 (d, 2H, J = 8.1 Hz), 7.53-7.58 (m, 1H), 7.53-7.58 (m, 1H); $^13$C NMR (75 MHz, CDCl$_3$) δ 25.82, 31.71, 45.08, 55.60, 66.38, 110.50, 111.46, 123.03, 130.65, 149.23, 152.39, 196.58; MS(ESI, m/z): 287 [M + H]$^+$, 309 [M + Na]$^+$. Anal. calc. (%) for C$_{12}$H$_8$O$_2$Br (268.02): C, 50.19; H, 5.27; found (%): C, 50.14; H, 5.22.

**Synthesis of 1,1'-(4,4'-propane-1,3-diybis(oxoxy))bis(3-methoxy-4, 1-phenylene) diethanone (10):** To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone 2 (20 g, 120 mmol), acetonitrile (100 mL), potassium carbonate (50.56 g, 361 mmol) and 1,3-dibromopropane 8 (72.9 g, 361 mmol) were charged at room temperature. Reaction temperature was raised to 80-85 °C and maintained for 12 h. The reaction progress was monitored by TLC (n-hexane:ethyl acetate, 7:3), after completion of reaction, it was cooled to room temperature, filtered the salts and washed with acetonitrile (20 mL). Filtrate was taken and the solvent was removed under reduced pressure below 60 °C, light white coloured residue was obtained, it was purified from column chromatography 10 % ethyl acetate in n-hexane and recrystallized from methylene dichloride:n-hexane (40:80 mL), as a white coloured solid 10 (35.8 g, 80 %) was obtained. Purity 98.5 % (by HPLC), m.p. 116-118 °C; FT-IR (KBr, ν$_{max}$ cm$^{-1}$): 3081, 2958, 2938, 1671, 1586, 1513, 1462, 1450, 1417, 1345, 1273, 1220, 1147, 1050, 1031, 1022, 875, 807, 795; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.38-2.46 (52, 2H), 2.56 (s, 6H), 3.91 (s, 6H), 4.32 (t, 4H, J = 6.2 Hz), 6.94 (d, 2H, J = 8.1 Hz), 7.53-7.56 (m, 2H), 7.53-7.56 (m, 2H); $^13$C NMR (75 MHz, CDCl$_3$) δ 25.82, 31.71, 45.08, 55.60, 66.38, 110.50, 111.46, 123.03, 130.65, 149.23, 152.39, 196.58; MS(ESI, m/z): 287 [M + H]$^+$, 309 [M + Na]$^+$. Anal. calc. (%) for C$_{12}$H$_8$O$_2$Br (268.02): C, 50.19; H, 5.27; found (%): C, 50.14; H, 5.22.
**RESULTS AND DISCUSSION**

During the process development of iloperidone (I), HPLC analysis of crude iloperidone (I) revealed seven impurities ranging from 0.01-0.15 %, according to ICH (International Chemical Harmonium) guidelines, the amount of acceptable level for known and unknown compounds in a final drug candidate must be less than 0.15 and 0.10 %, respectively. In order to meet the stringent regulatory requirements, the impurities needed to be identified and characterized. Hence, samples of iloperidone (I) were initially analyzed by LCMS to provide parent ions of m/z 221, 225, 167, 443, 243, 373 and 287 for the seven impurities and thus proposed a basis for initial identification. To confirm their proposed structures and complete their characterization, all five substances were individually synthesized using NMR and MS spectral data. The synthesis of impurity 4, also known as iloperidone chloro impurity, is one of the key raw materials for pharma stage. Its synthesis from 1-(4-hydroxy-3-methoxyphenyl)ethanone 2 and 1-bromo-3-chloropropane 3 in the presence of potassium carbonate in acetonitrile at ambient temperature is described in **Scheme-I**. The HPLC purity of compound 4 is 99.5 % it was characterized by spectral analysis. The synthesis of impurity 7, also known as iloperidone hydroxy impurity, is synthesized from condensation of 1-(4-hydroxy-3-methoxyphenyl) ethanone 2 with 3-chloropropan-1-ol 6 in the presence of potassium carbonate in N,N-dimethylformamide at ambient temperature conditions afforded the impurity 7 in good yield and 99 % HPLC purity is described in **Scheme-II**. The structure of 7 was confirmed by spectral analysis. Synthetic scheme for impurities 9 and 10 showed in **Scheme-III**. Compounds 9 and 10 also known as iloperidone bromo and dimer impurities, they are synthesized from 1-(4-hydroxy-3-methoxyphenyl)ethanone 2 and 1,3-dibromopropane 8 (1 mol equivalent) to give impurity 9 and (1-(4-hydroxy-3-methoxyphenyl)ethanone 2 on condensation with 1,3-dibromopropane 8 (3 mole equivalent) in presence of potassium carbonate in N,N-dimethylformamide at ambient temperature yielded 10, with HPLC purity 99.2 and 98.5 %, respectively. Their structures are confirmed by spectral analysis.

The synthesis of impurity 1-(3-(4-acetyl-2-methoxyphenoxy)propyl)-4-(6-fluorobenz[d]isoxazol-3-yl)piperidine 1-oxide 11 from 1-(3-(4-(6-fluorobenz[d]isoxazol-3-yl)piperidine-1-yl)propoxy)-3-methoxyphenyl)ethanone 1 and Dess-Martin periodinane (DMP) by using sulfuric acid (96 %) in methylene dichloride. It is N-oxidation of 1-(4-(3-(4-(6-fluorobenz[d]isoxazol-3-yl)piperidine-1-yl)propoxy)-3-methoxyphenyl)ethanone and it is further purified by crystallization in n-hexane with good purity 98.7 % by HPLC and yield is 85 % (**Scheme-IV**). The structure was confirmed by spectral analysis. Mass spectrum showed mass at m/z 443 (M + H)⁺.

**Conclusion**

We have identified, synthesized and characterized seven process related substances in the protocol of the synthesis of antipsychotic drug iloperidone 1, which can provide high throughputs and high quality product in each stage.
Scheme-IV: Synthesis of impurity 11. Reagents and conditions: (f) Dess-Martin periodinane (DMP), sulfuric acid (96 %), methylene dichloride, 25-30 °C, 24 h, 85 %

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