



Isolation and Characterization of Process Related Substances of an Antipsychotic Drug: Iloperidone

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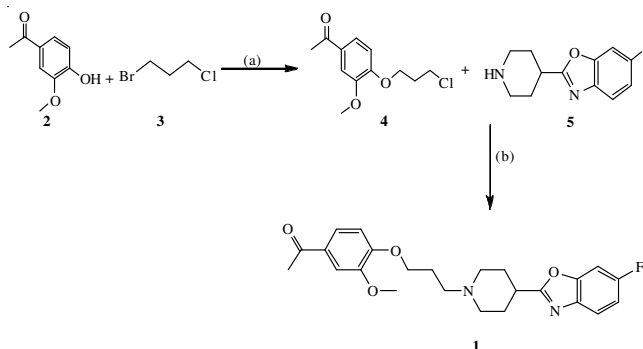
Seven unknown recurring impurities were isolated during the synthesis of Iloperidone process. All six impurities were subsequently synthesized and characterized by FTIR, MS and NMR spectral data. The structures of impurities were confirmed as 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (**4**), 1-[4-(3-hydroxypropoxy)-3-methoxy phenyl]ethanone (**7**), 1-[4-(3-bromopropoxy)-3-methoxyphenyl]ethanone (**9**), 1,1'-[4,4'-(propane-1,3-diylbis(oxy))bis(3-methoxy-4,1-phenylene)]diethanone (**10**), 1-[3-(4-acetyl-2-methoxyphenoxy)propyl]-4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-oxide (**11**) and in final other two impurities 1-(4-hydroxy-3-methoxyphenyl)ethanone (**2**) and 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole (**5**). The present work describes the formation, synthesis and characterization of these impurities.

Key Words: Iloperidone, Antipsychotic, Drug impurities, Des-Martin periodinane.

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 (α_{2c}), dopamine (D_{2A} and D_3) and serotonin (5-HT_{1A} and 5-HT₆) receptors¹. 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 antagonists².

Recently, we have described an efficient, industrial scale synthesis of iloperidone **1** (Scheme-I)³⁻⁵. 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^{6,7}.



Scheme-I: Reagents and conditions: (a) K_2CO_3 , acetonitrile, 8 h, 60-65 °C, 95 % (b). Triethyl amine, water, 14 h, 60-65 °C, 95 %

The HPLC analysis of iloperidone displayed seven impurity peaks in the range of 0.05-0.15 % levels along with the iloperidone peak. Our present work describes the synthesis and spectral characterization of process related impurities. As per the guidelines recommended by ICH, the acceptable level for a known or unknown related impurity is less than 0.15 and 0.10 %^{8,9}.

EXPERIMENTAL

All the chemicals were procured from Sigma-Aldrich, Merck and Lancaster and used as such without further purifi-

cation. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 and 75 MHz spectrometer, respectively. ^1H NMR spectra were reported using Me_4Si (δ 0.0 ppm) as internal standard. ^{13}C NMR were reported relative to CDCl_3 (δ 77.16 ppm) and $\text{DMSO}-d_6$ (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.

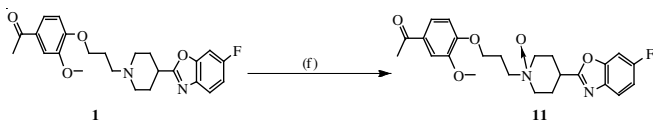
Synthesis of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4): To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl) ethanone **2** (5 g, 30 mmol), acetonitrile (20 mL) and potassium carbonate (12.5 g, 9 mmol) were charged at room temperature. Reaction temperature was raised to 75–80 °C, 1-bromo-3-chloropropane **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, 2878, 1670, 1596, 1587, 1523, 1515, 1466, 1452, 1420, 1355, 1277, 1225, 1183, 1146, 1077, 1034, 873, 806, 757, 722; ^1H NMR (300 MHz, CDCl_3) δ 2.28–2.36 (m, 2H), 2.57 (s, 3H), 3.78 (t, 2H, $J = 6.2$ Hz), 3.91 (s, 3H), 4.24 (t, 2H, $J = 6.0$ Hz), 6.92 (d, 1H, $J = 8.1$ 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, 41.08, 55.60, 65.11, 110.26, 111.23, 122.80, 130.36, 148.98, 152.20, 196.25; MS (ESI, m/z): 243 [M + H] $^+$, 265 [M + Na] $^+$. Anal. calcd. (%) for $\text{C}_{12}\text{H}_{15}\text{ClO}_3$ (242.70): C, 59.39; H, 6.23; Found (%): C, 59.28; H, 6.17.

Synthesis of 1-[4-(3-hydroxypropoxy)-3-methoxyphenyl]ethanone (7): To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone **2** (5 g, 30 mmol), N,N -dimethyl formamide (25 mL) and potassium carbonate (12.5 g, 9 mmol) were charged at room temperature. Reaction temperature was raised to 70–75 °C, 3-chloropropan-1-ol **6** (3.2 g, 33 mmol) was added drop wise at ambient temperature. After maintaining at 70–75 °C for 3 h, progress of the reaction was monitored by TLC (methylene dichloride: methanol, 4:1) reaction mixture was cooled to room temperature. Reaction mass was quenched into water (50 mL) and ethyl acetate (100 mL), further pH was adjusted to 6.5 by using acetic acid (10 mL). Two layers, were separated, organic layer was washed with water twice (50 mL \times 2 mL) and washed with 10 % sodium chloride (50 mL). Organic layer was taken and ethyl acetate was completely distilled off an oily residue was obtained, it was recrystallized from isopropyl ether (50 mL), light pink coloured solid **7** (6.47 g, 96 %) was obtained. Purity 99.16 % (by HPLC), m.p. 79–81 °C; FT-IR (KBr, ν_{max} , cm^{-1}): 3011, 2955, 2923, 2842, 1663, 1590, 1552, 1501, 1470, 1422, 1349, 1262, 1211, 1175, 1143, 1075, 1043, 852, 806, 762, 721; ^1H NMR (300 MHz, CDCl_3) δ 2.13–2.18 (m, 2H), 2.55 (s, 3H), 3.78 (t, 2H, $J = 6.2$ Hz), 3.91 (s, 3H), 4.25 (t, 2H, $J = 6.0$ Hz), 4.39 (t, 1H, $J = 6.8$ Hz),

6.92 (d, 1H, $J = 8.1$ 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, 65.11, 110.26, 111.23, 122.80, 130.36, 148.98, 152.20, 196.25; MS(ESI, m/z): 225 [M + H] $^+$, 247 [M + Na] $^+$. Anal. calcd. (%) for $\text{C}_{12}\text{H}_{16}\text{O}_4$ (224.25): C, 64.27; H, 7.19; found (%): C, 64.13; H, 7.10.

Synthesis of 1-[4-(3-bromopropoxy)-3-methoxyphenyl]ethanone (9): 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** (15.56 g, 90 %). Purity 99.2 % (by HPLC), m.p. 64–66 °C; FT-IR (KBr, ν_{max} , cm^{-1}): 3073, 3008, 2958, 2932, 2841, 1669, 1595, 1586, 1521, 1466, 1448, 1419, 1383, 1350, 1274, 1224, 1182, 1145, 1039, 1022, 873, 807; ^1H NMR (300 MHz, CDCl_3) δ 2.36–2.45 (m, 2H), 2.57 (s, 3H), 3.63 (t, 2H, $J = 6.3$ Hz), 3.91 (s, 3H), 4.23 (t, 2H, $J = 5.9$ Hz), 6.92 (d, 1H, $J = 8.4$ Hz), 7.53–7.58 (m, 1H), 7.53–7.58 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 26.08, 29.70, 31.99, 55.88, 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. calcd. (%) for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{Br}$ (286.02): C, 50.19; H, 5.27; found (%): C, 50.14; H, 5.22.

Synthesis of 1,1'-(4,4'-(propane-1,3-diylbis(oxy))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 monitoring 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; ^1H NMR (300 MHz, CDCl_3) δ 2.38–2.46 (m, 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 26.05, 28.81, 55.84, 65.26, 110.36, 111.33, 123.04, 130.47, 149.15, 152.48, 196.61; MS(ESI, m/z): 373 [M + H] $^+$, 395 [M + Na] $^+$. Anal. calcd. (%) for $\text{C}_{21}\text{H}_{24}\text{O}_6$ (372.16): C, 67.73; H, 6.50; found (%): C, 50.09; H, 5.19.



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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