Asian Journal of Chemistry; Vol. 25, No. 10 (2013), 5307-5310

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14169

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

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(*Received*: 6 June 2012; *Accepted*: 1 April 2013) AJC-13193

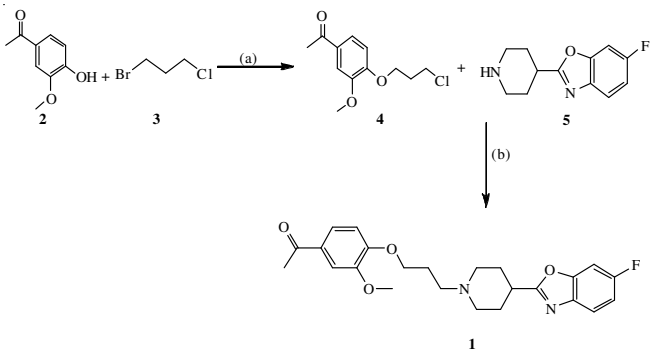
Seven unknown recurring impurities were isolated during the synthesis of Iloperidone process. All six impurities were subsequently synthesized and characterized by FTIR, MS and NMR spectral data. The structures of impurities were confirmed as 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (**4**), 1-[4-(3-hydroxypropoxy)-3-methoxy phenyl]ethanone (**7**), 1-[4-(3-bromopropoxy)-3-methoxyphenyl] ethanone (**9**), 1,1'-[4,4'-(propane-1,3-diyl*bis*(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-HT_6) receptors[1]. 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[2].

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 ºC, 95 % (b). Triehyl amine, water, 14 h, 60-65 ºC, 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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 and 75 MHz spectrometer, respectively. ^{1}H 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 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 ºC, 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 ºC 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 ºC; 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; ^{1}H 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 $C_{12}H_{15}ClO_3$ (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 ºC, 3-chloropropan-1-ol **6** (3.2 g, 33 mmol) was added drop wise at ambient temperature. After maintaining at 70-75 ºC 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 × 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 ºC; 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; ^{1}H 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 $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19; found (%): C, 64.13; H, 7.10.

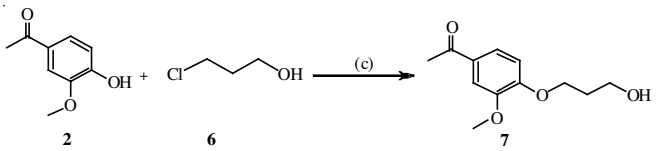
Synthesis of 1-[4-(3-bromopropoxy)-3-methoxyphenyl] ethanone (9): To a stirred solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone **2** (10 g, 60 mmol), acetonitrile (50 mL), potassium carbonate (8.3 g, 60 mmol) and 1,3-dibromopropane **8** (8.3 g, 60 mmol) were charged at room temperature. Reaction temperature was raised to 80-85 ºC 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 ºC, 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 ºC; 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; ^{1}H 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 $C_{12}H_{15}O_3Br$ (286.02): C, 50.19; H, 5.27; found (%): C, 50.14; H, 5.22.

Synthesis of 1,1'-(4, 4'-(propane-1,3-diyl*bis*(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 ºC 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 ºC, 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 ºC; 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 (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 $C_{21}H_{24}O_6$ (372.16): C, 67.73; H, 6.50; found (%): C, 50.09; H, 5.19.

Synthesis of 1-[3-(4-acetyl-2-methoxyphenoxy)propyl]-4-(6-fluorobenzo[d]isoxazol-3-yl) piperidine 1-oxide (11): Iloperidone **1** (10 g, 23 mmol) was dissolved in methylene dichloride (100 mL) and it was cooled to 0 ºC. Dess-Martin periodinane (DMP) (10.9 g, 25 mmol) and 0.7 mL of sulfuric acid (96 %) were added to the reaction mixture and it was stirred at 0 ºC for 0.5 h. Further, temperature was raised to room temperature and stirred for 24 h, reaction progress was monitored by TLC (*n*-hexane:ethyl acetate, 7:3). After completion of reaction, reaction mass was washed with 10 % $Na_2S_2O_3$ solution (100 mL) followed by saturated $NaHCO_3$ solution (100 mL), 2 mL × 100 mL of water, 10 % NaCl solution (100 mL), dried on $MgSO_4$ (20 g), filtered the salt and evaporated solvent under vacuum at 50 ºC. Light white coloured residue was obtained, it was recrystallized from n- hexane (30 mL) to yield a white coloured solid **11** (8.8 g, 85 %) obtained. Purity 98.7 % (by HPLC), m.p. 155-157 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3083, 2958, 2878, 1655, 1606, 1584, 1509, 1467, 1419, 1348, 1273, 1223, 1182, 1143, 1121, 1032, 971, 957, 881, 857, 813, 802; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89-1.93 (m, 2H), 2.31-2.40 (m, 2H), 2.55 (s, 3H), 2.60-2.72 (m, 2H), 3.29-3.52 (m, 2H), 3.29-3.52 (m, 2H), 3.29-3.52 (m, 2H), 3.29-3.52 (m, 1H), 3.85 (s, 3H), 4.23(t, 2H, *J* = 6.0 Hz), 7.11 (d, 1H, *J* = 8.4 Hz), 7.30-7.36 (m, 1H), 7.62-7.65 (m, 1H), 7.71-7.74 (dd, *J* = 9.3 and 2.0 Hz, 1H), 8.02-8.07 (dd, *J* = 8.7 and 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.13, 24.70, 26.35, 31.49, 55.54, 63.21, 67.07, 67.82, 97.51, 110.35, 111.86, 112.67, 123.11, 123.67, 129.95, 148.63, 152.22, 160.79, 163.10, 163.69, 196.40; MS (ESI, m/z): 443 $[M + H]^+$. Anal. calcd. (%) for $C_{24}H_{27}N_2O_5F$ (442.19): C, 65.15; H, 6.15; N, 6.33; found (%): C, 65.11; H, 6.09; N, 6.29.

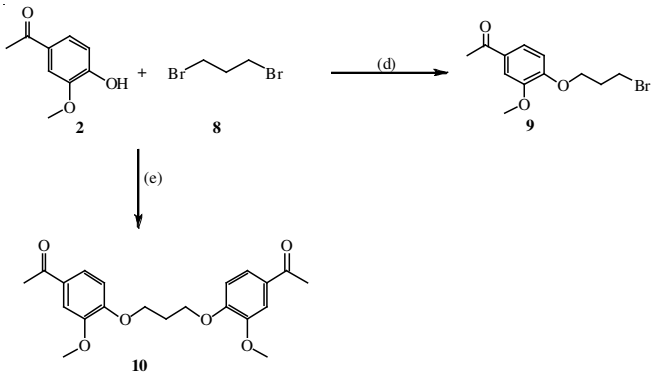
RESULTS AND DISCUSSION

During the process development of iloperidone (**1**), HPLC analysis of crude iloperidone (**1**) 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 (**1**) 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 provide a basis for initial identification. To confirm their proposed structures and complete their characterization, all five substances were individually synthesized and characterized by their respective IR, NMR and MS spectral data. The synthesis of impurity **4**, also known as iloperidone chloro impurity, it 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, it 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-dimethyl formamide 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.



Scheme-2: Synthesis of impurity **7**. Reagents and conditions: (c) K_2CO_3, N,N-dimethylformamide, 70-75 ºC, 8 h, 96 %

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** and1-(4-hydroxy-3-methoxyphenyl)ethanone **2** on condensation with1,3-dibromopropane **8** (3 mole equivalent) in presence of potassium carbonate in N,N-dimethyl formamide at ambient temperature yielded **10**, with HPLC purity 99.2 and 98.5 %, respectively. Their structures are confirmed by spectral analysis.

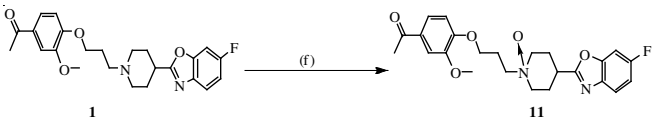


Scheme-III: Synthesis of impurities **9** and **10**. Reagents and conditions: (d) K_2CO_3, 1 mol equivalent **8**, acetonitrile, 8 h, 80-85 ºC, 90 % (e) K_2CO_3, 3 mol equivalent **8**, acetonitrile, 12 h, 80-85 ºC, 80 %

The synthesis of impurity 1-(3-(4-acetyl-2-methoxyphenoxy)propyl)-4-(6-fluorobenzo[d]isoxazol-3-yl) piperidine 1-oxide **11** from 1-(4-(3-(4-(6-fluorobenzo[d] isoxazol-3-yl)piperidin-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-fluorobenzo[d]isoxazol-3-yl)piperidin-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.



1 **11**

Scheme-IV: Synthesis of impurity **11**. Reagents and conditions: (f) Dess-Martin periodinane (DMP), sulfuric acid (96 %), methylene dichloride, 25-30 ºC, 24 h, 85 %

ACKNOWLEDGEMENTS

The authors thank the management of Mylan Laboratories Limited, Hyderabad for permission to publish this work. The authors also thank Analytical Research Department for their valuable contribution to this work.

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