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# An Investigation into Formation of Impurities During Synthesis of Blonanserin

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During the process development of Blonanserin (**1**), we have observed formations of unknown impurities are in the final product at enhanced levels which was identified as Des ethyl impurity, di-N-ethylpiperazine impurity, Chloro impurity and des-fluoro impurity. The present work involves detailed optimization studies directed toward the development of an efficient process for the commercial production of Blonanserin substantially free from the chloro impurity and other impurities.

**Keywords: Blonanserin, Synthesis, Impurities, Characterization.**

## INTRODUCTION

Blonanserin, (2-(4-ethyl-l-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine) is a novel anti-psychotic agent, researched and developed by the Japanese Zhu You Pharmaceutical Co Ltd. and was marketed for the first time in Japan in April 2008. Dopamine $D_2$ and serotonin 5-$HT_{2A}$ receptor antagonist properties[1-6]. It is one of the second-generation antipsychotic agents, together with risperidone and olanzapine, it is effective in the treatment of both positive and negative symptoms of schizophrenia without extra-pyramidal symtoms, but has original properties of affinity higher for the dopamine $D_2$ receptor than for the serotonin 5-$HT_{2A}$ receptor[7]. On the other hand, blonanserin is much less potent in adrenergic-$\alpha_1$, histamine $H_1$ and muscarinic $M_1$ antagonist activities[6]. Such a pharmacological profile shows that blonanserin is more specific to the dopamine $D_2$ and serotonin 5-$HT_{2A}$ receptors with fewer side effects; its excellent effects on schizophrenia have been reported in many reports[8-10]. There is a possibility that this drug gain popularity for treatment of schizophrenia throughout the world.

In the literature, references, carry out cyclization using 4-fluorobenzoylacetonitrile (**4**) and cyclooctanone in the presence of polyphosphoric acid (PPA) to get 4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-2(1*H*)-one (**3**), yield 60 %. Undergo chlorination of **3** to get 2-chloro-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (**2**), finally carry out substitution reaction with N-ethylpiperazine to get **1**. Total yield is 24.4 %.

## EXPERIMENTAL

**Preparation of 4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctane[b]pyridine-(1*H*) ketone (3)**: To a mixture of 4-fluorobenzoylacetonitrile (100 g), methane sulfonic acid (230.6 g) and water (14 mL) was heated to 65-70 °C, stirred for 3 h and added a cyclooctanone (85 g) at same temperature then heated to 110 to 115 °C stirred for 2 h, cool to room temperature then diluted with dichloromethane and water, organic layer was separated and washed organic layer with water, then distilled under vacuum solid obtained and purified with acetone to get pure compound. Yield: 120 g; 73 %.

**Preparation of 2-chloro-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (2):** To a mixture of phenyl phosphine dichloride and 73 g of **3** was heated to 155-160 °C for 4 h and TLC monitored complete the reaction and cool the reaction mass at ambient temperature then dichloromethane 700 mL and water 30 mL was added, adjusted pH 8.5 with liq ammonia then organic layer separated, washed the organic layer with water distilled under vacuum solid obtained and purified with acetone to get pure compound. Yield: 66 g; 85 %.

**Preparation of 2-(4-ethylpiperazine-1-yl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (1):** To a mixture of potassium iodide 35.7 g, N-ethylpiperazine 78 g and 65 g of **2** was heated to 165-170 °C for 8 h, cool to room temperature then water 200 mL and ethylacetate 1000 mL was added stirred reaction mass for 15 min separated organic layer then extracted with water using of hydrochloric acid solution

120 mL, layers separated product in aqueous, then adjusted pH 9 with 30 % NaOH Solution then extracted compound with ethylacetate 2 × 500 mL, combined organic layer washed with water, distilled organic layer a white crystalline compound obtained, the crude purified with isopropyl alcohol to get 71.5 g, yield 86 % obtained.

**2-(Piperazine-1-yl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (Des ethyl impurity) (8):** To a mixture of potassium iodide 5.5 g, piperazine 18.6 g and 10 g of **2** was heated to 165-170 °C for 8 h, cool to room temperature then water 30 mL and ethylacetate 150 mL was added stirred reaction mass for 15 min separated organic layer then extracted with water using of hydrochloric acid solution 18.5 mL, layers separated product in aqueous, then adjusted pH 9 with 30 % NaOH solution then extracted compound with ethylacetate 2 × 150 mL, combined organic layer washed with water, distilled organic layer a white crystalline compound obtained, the crude purified with ethanol to get yield 8.5 g. $^1$H NMR (DMSO-$d_6$) δ: 7.05-7.10 (2H, m), 7.19-7.24 (2H, m), 2.57(2H, t(5.4)), 1.37-1.44 (6H, m), 1.74-1.78 (2H, m), 2.88 (2H, t(6.2)), 6.29 (1H, s), 3.49 (4H, t(5.1)), 3.01 (4H, t(5.0)), 2.28 (1H, br,s). IR (KBr, $\nu_{max}$, cm$^{-1}$): 3416, 3330, 3261, 3068, 3045, 2922, 2849, 1606, 1590, 1543, 1507, 1470, 1449, 1411, 1293, 1273, 1245, 1218, 1192, 1154, 998, 944, 887,836, 788 *m/z*: 340 $[M + H]^+$.

**(2-(4-Ethylpiperazine-1-yl)-4-[4-(4-ethylpiperazine-1-yl)phenyl]-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine) (Di-N-ethyl piperazine impurity) (7):** Taken blonanserin filtered mother liquor 100 mL, distilled under vacuum, the residue was in column chromatography, elute the impurity with 2:98 of methanol and dichloromethane, collect the fraction distilled under vacuum 2 g of the title compound **7** obtained.

Desfluoro and Chloro impuries were prepared according to procedure of **3**, **2** and **1**.

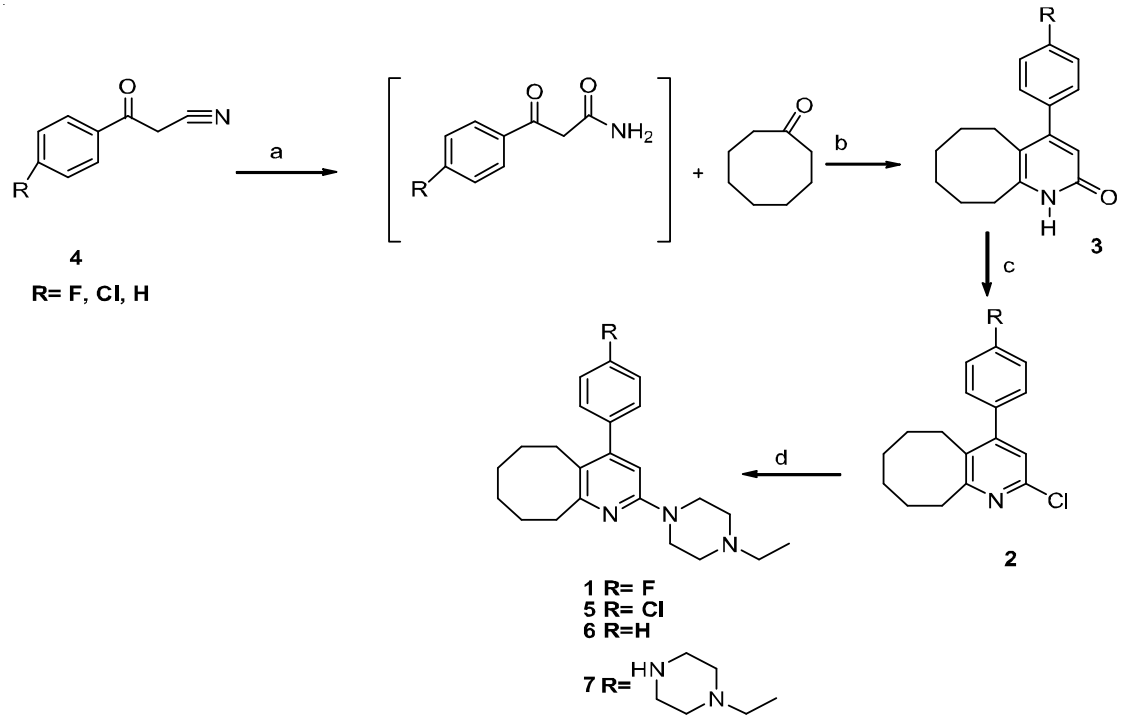
**2-(4-Ethylpiperazine-1-yl)-4-(4-chlorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (5):** $^1$H NMR (DMSO-$d_6$) δ: 7.19-7.36 (4H, d), 2.56 (2H, t), 1.37-1.42 (6H, m), 2.88 (2H, t), 6.28 (1H, s), 3.53 (4H, t), 2.56 (4H, t), 2.43-2.50 (2 H, q), 1.13 (3H, t). IR (KBr, $\nu_{max}$, cm$^{-1}$): 3074, 3040, 2950, 2920, 2844, 2832, 2814, 1600, 1585, 1541, 1493, 1468, 1444, 1408, 1260, 1241, 997, 950, 885, 844, 831, 776. *m/z* : 384 $[M + H]^+$.

**2-(4-Ethylpiperazine-1-yl)-4-phenyl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (6):** $^1$H NMR (DMSO-$d_6$) δ: 7.24-7.27 (3H, m), 7.32-7.42 (2H, m), 2.55-2.60 (2H, m), 1.38-1.43 (6H, m), 1.75-1.80 (2H, m), 2.89 (2H, t), 6.33 (1H, s), 3.53 (4H, t), 2.55-2.60 (4H, m), 2.43-2.50 (2H, q), 1.13 (3H, t). IR (KBr, $\nu_{max}$, cm$^{-1}$): 3077, 3055, 3026, 2942, 2923, 2849, 2826, 1585, 1546, 1493, 1456, 1450, 1410, 1264, 1245, 1167, 1127, 1000, 925, 886, 833, 769, 703. *m/z*: 350 $[M + H]^+$.

## RESULTS AND DISCUSSION

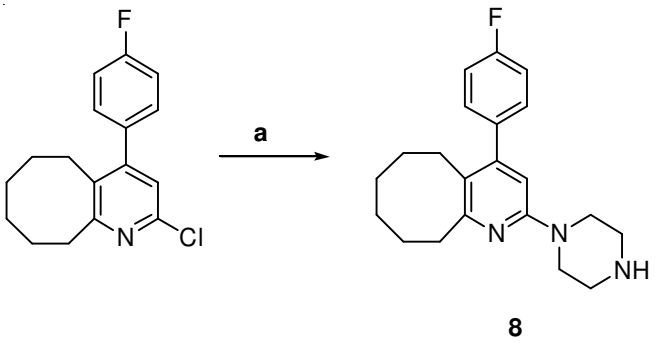
4-Fluorobenzoyl acetonitrile (**4**) is treated with methane sulphonic acid and water at 70 °C to form *in situ* 3-(4-fluorophenyl)-3-oxopropanamide which is further treated with cyclooctanone to obtain 4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocyclooctane[b]pyridine-(1*H*)ketone (**3**), intermediate **2** was prepared by using of **3** and phenyl phosphine dichloride finally condensation of intermediate **2** with N-ethyl piperazine in the presence of potassium iodide to give Blonanserin (**1**) (**Scheme-I**).

During our preliminary optimization studies, we have observed four major impurity in the final product and the molecular weights of these impurities were identified by LC-MS




**Reaction conditions:**(a) Methane sulfonic acid, water b) 110 to 115°C, MDC, Acetone c) phenyl phosphine dichloride d) N-ethyl piperazine, KI, ethyl acetate

**Scheme-I:** Commercial synthesis of Blonanserin




**8**

**Reaction conditions:** (a) piperazine, KI, ethyl acetate

**Scheme-II**

analysis as 339, 461, 383 & 385 and 349 were identified as Des ethyl impurity, di-N-ethylpiperazine impurity, chloro impurity and des-fluoro impurity respectively. The structure was further confirmed through synthesis/isolation from mother liquor, characterization and HPLC spike studies. The content of compounds **5**, **6**, **7** and **8** in the final product varied depending upon the various process parameters and the control of these impurities could be accomplished by employing appropriate controls in the process and temperature in the process. Detailed investigation and careful mapping of the impurities at all the stages indicated that the impurity was formed during the penultimate

A key portion of the development of a commercial synthesis is the identification of all impurities in the drug substance and later intermediates. From the outset, identification of the unknown impurity had proven problematic. No samples of Blonanserin with > 0.05 % of the impurity were available, but we were unable to draw a structure to fit this mass, without a structure it is impossible to determine the source of an impurity in a complex synthetic route; the mass expected for earlier steps cannot be predicted. Given the possibility of a higher dose requiring the lower qualification threshold, identification was again attempted. Improved isolation equipment and NMR techniques resulted in the successful identification of the impurity.

Des ethyl impurity (**8**) was formed a small amount of ethyl piperazine present in N-ethylpiperazine, that impurity was prepared by using of piperazine in the presence of potassium iodide to get des ethyl impurity (**Scheme-II**), Di-N-ethyl-piperazine (**7**) impurity was formed by using excess of N-ethyl-piperazine and carryover of chloro and desfluoro instead of fluoro in 4-fluorobenzoyl acetonitrile, that two impurities chloro impurity **5** and desfluoro impurity **6** was formed up to final stage (**Scheme-I**).

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