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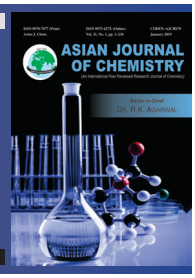

Novel and Environmentally Friendly Synthesis of Pimavanserin (5-HT2A Receptor)

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Eco-friendly synthesis of pimavanserin was developed from the key starting material 4-isobutoxy benzylamine in three different routes using water as solvent. These reactions provide an advantage of easy workup, good yields of products and uses water as the solvent. No column purification was required for the isolation of the product.

Keywords: Pimavanserin, Parkinson disease, Nuplazid, Dopamine receptor.

INTRODUCTION

Parkinson's disease is neurodegenerative disease which affects 7-10 million people worldwide every year [1]. The number of Parkinson's disease patients are increasing worldwide with the increase in the age of the worldwide population. Till April 2016, there was no approved drug available in the United States (USA) for the treatment of Parkinson's disease psychosis (PDP). Pimavanserin [2] is the first Food and Drug Administration (FDA) approved medicine in April 29th 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Pimavanserin was discovered first time in US 6756393B2 [3]. It was developed by Acadia Pharmaceuticals and marketed under the proprietary name NUPLAZID, as an oral tablet, for the treatment of Parkinson's disease psychosis. Due to the importance of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis, different synthetic routes have been reported in the literature to prepare pimavanserin [4-9]. But, several problems were observed in the synthetic processes of pimavanserine with the reported methods. The processes reported were having usage of expensive reagents, difficulty in handling in commercial scale, requires multiple purification methods which leads to lower yields.

Several literature procedures were reported by using diphenylphosphoryl azide compounds, chloroformate amino protected compounds and carbonyl diimidazole intermediates as key materials for the synthesis of pimavanserin. All the above substances were synthesized by using hazardous reagents which may lead to the formation of more byproducts in turn effect the purity and yield of pimavanserin. Hence, there is a need for the development of alternate procedures for the synthesis of pimavanserin which is industrially feasible.

Due to continuous interest in the development of API and API impurities by our laboratory [10-12], we wish to report the easy and convenient method for the synthesis of pimavanserin in this article. Thus, our efforts in achieving an environmental friendly, step-wise and one-pot synthetic process for pimavanserin *via* three different intermediates (isothiocyanate, urea and *N*-formyl) was described under green conditions.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$, DMSO-d_6 at room temperature on a Varian Mercury spectrometer plus 400 MHz using TMS as an internal standard. ^{13}C NMR spectra were obtained from a Varian Mercury plus 100 MHz spectrometer in DMSO-d_6 at room

temperature. IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on an HP 5989 A LC-MS spectrometer. TLC analyses were performed on Merck silica gel $60F_{254}$ plates.

Synthesis of 1-isobutoxy-4-(isothiocyanatomethyl)-benzene (2): A mixture of 4-isobutoxy benzylamine (10.0 g, 0.0558 mol), water (70 mL, 7.0 v) and sodium bicarbonate (18.7 g, 0.222 mol) were stirred at room temperature. The reaction mixture was cooled to 0-5 ºC and thiophosgene (12.8 g, 0.111 mol) was added at the same temperature and stirred for about 5-6 h. After completion of the starting material by TLC, 10 % sodium bicarbonate solution (20 mL, 2.0 v) was added and stirred for 5-10 min. Dichloromethane (50 mL, 5.0 v) was added to the reaction mixture and stirred for 15 min and the organic layer was separated. Organic layer was washed with water (30 mL, 3.0 v) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to get desired 1-isobutoxy-4-(isothiocyanatomethyl)benzene as an off white solid (10.5 g, 85.1 %). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.28-7.30 (d, 2H), 6.95-6.96 (d, 2H), 4.82 (s, 2H), 3.73-3.74 (d, 2H), 1.96-2.03 (m, 1H), 0.96-0.98 (d, 6H). Mass (*m/z*): 162.8 (M-58). Elemental analysis of $C_{12}H_{15}NOS$ calcd. (found) %: C 65.10 (65.12); H 6.81 (6.83); N 6.30 (6.33).

Synthesis of 1-(4-fluorobenzyl)-3-(4-isobutoxy benzyl)-1-(1-methylpiperidin-4-yl)thiourea (4): A mixture of 1-isobutoxy-4-(isothiocyanato-methyl)benzene (**2**) (5.0 g, 0.0226 mol) and *N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine (6.0 g, 0.027 mol) in ethyl acetate (50 mL, 10.0 v) were stirred at 70-75 ºC for 4-5 h until the starting material disappears on TLC. Ethyl acetate was evaporated under reduced pressure and residue was purified triturated with 10 % methanol in DCM (5 mL) to get desired compound 1-(4-fluorobenzyl)-3-(4-isobutoxybenzyl)-1-(1-methyl piperidin-4-yl)thiourea (8.5 g, 84.9 %) as pale yellow solid. m.p. 136-139 ºC. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.72-7.12 (m, 8H), 5.48-5.74 (m, 2H), 4.56-4.64 (m, 4H), 3.63-3.67 (d, 2H), 3.20-3.23 (d, 2H), 2.57-2.59 (broad, m, 2H), 2.53(S, 3H), 1.96-2.15 (m, 5H), 0.95-1.01 (d, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 181.9, 162.2, 159.7, 157.5, 134.6, 131.4, 128.3, 128.1, 128.0, 114.9, 114.7, 113.9, 73.7, 55.9, 54.1, 48.0, 46.8, 44.7, 28.4, 27.7, 18.9; Mass (*m/z*): 444 (M+H). Elemental analysis of $C_{25}H_{34}N_3OSF$ calcd. (found) %: C 67.65 (67.69); H 7.71 (7.73); N 9.46 (9.47).

Synthesis of pimavanserin (5): 1-(4-Fluorobenzyl)-3-(4-isobutoxybenzyl)-1-(1-methyl piperidin-4-yl)thiourea (1.0 g, 2.256 mmol) and silver carbonate (1.2 g, 4.35 mmol) in acetonitrile (15 mL, 15.0 v) was stirred at room temperature until TLC complies (24 h). The reaction mixture was filtered to remove undissolved solids and washed the solid with acetonitrile (5 mL, 5.0 v). The acetonitrile layer was evaporated under reduced pressure to get residue, which was triturated in a mixture of water (10 mL, 10.0 v) and methanol (2 mL, 2.0 v) to get the pure compounds as yellow solid (0.91 g, 94.2%). m.p. 116-118 ºC ; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.76-7.19 (m, 8H), 4.44-4.46 (m, 1H), 4.26-4.33 (m, 5H), 3.66-3.68 (d, 2H), 2.86-2.89 (d, 2H), 2.27 (s, 3H), 2.00-2.11 (m, 3H), 1.63-1.71 (m, 4H), 0.99-1.01 (d, 6H); ^{13}C NMR (100.40 MHz, $CDCl_3$): δ 162.0, 159.6, 157.5, 157.4, 136.9, 133.0, 128.3, 128.2, 128.1, 114.7, 114.5, 114.0, 73.7, 54.8, 52.3, 45.6, 43.9, 43.05, 29.8, 27.6, 18.9; Mass (*m/z*): 428.3 (M+H).

Synthesis of of 1-(4-isobutoxybenzyl)urea (7): A mixture of 4-isobutoxy benzylamine (5.0 g, 0.0279 mol.), urea (10.0 g, 0.166 mol) and NaOH (0.99 g, 0.0247 mol) were heated to 120-130 ºC in a three- neck round bottom flask. The reaction mass was stirred for 12-15 h till the starting material of the reaction was completed by TLC. Water (50 mL, 10.0 v) was added to the reaction mixture and the pH of the reaction mass was adjusted to 7.0 by using concentrated HCl. Solid formation was observed and the solids were filtered, washed with water (20 mL, 4.0 v) and dried to get the desired compound 1-(4-isobutoxybenzyl)urea (5.0 g, 80.6 %) as off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.15-6.85 (m, 4H, arom.), 6.32-6.28 (t, 1H, -NH), 5.46 (s, 2H, $-NH_2$), 4.08-4.07 (d, 2H, $-CH_2$), 3.71-3.69 (d, 2H, $-CH_2$), 2.01-1.94 (m, 1H, -CH), 0.97-0.95 (d, 6H, $(-CH_3)_2$); ^{13}C NMR (100.40 MHz, DMSO-d_6): 158.6, 157.5, 132.6, 128.7, 114.2, 73.7, 42.3, 27.7, 19.0; Mass (*m/z*): 223.65 [M^{+} + 1]. Elemental analysis of $C_{12}H_{18}N_2O_2$ calcd. (found) %: C 64.84 (64.88); H 8.16 (8.19); N 12.60 (12.64).

Synthesis of pimavanserin from compund 7: A mixture of 1-(4-isobutoxybenzyl)urea (1.0 g, 4.5 mmol) and *N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine (**3**) (1.0 g, 4.5 mmol) were heated to 120-130 ºC until the TLC complies (12 h). Water (10 mL, 10.0 v) was added to the reaction mass after cooling it to room temperature and extracted with ethyl acetate (10 mL, 10.0 v). Ethyl acetate layer was evaporated under reduced pressure to get solid compound which was triturated using 10 % methanol in ethyl acetate (10 mL) to get pimavanserin (1.3 g, 83.1 %).

Synthesis of *N*-(4-isobutoxybenzyl)formamide (9): 4-Isobutoxy benzylamine acetate (10.0 g, 0.0558 mol) was stirred in water (30 mL, 3.0 v) at room temperature. The pH of the reaction mass was adjusted to 11-12 with aqueous ammonia solution. The product was extracted using toluene (50 mL, 5.0 v). Formic acid (2.3 g) was added to the toluene layer and it was refluxed for 4-5 h using dean-stark apparatus. After the completion of starting material using TLC, solvent was removed under reduced pressure and the crude residue was extracted with hexane to get *N*-(4-isobutoxy-benzyl)formamide as an off-white solid (10.0 g, 75.05 %). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.39 (broad, 1H, -NH), 8.09 (s, 1H, -COH), 7.17-6.85 (m, 4H, arom.), 4.21-4.20 (d, 2H, $-CH_2$), 3.72-3.70 (d, 2H, $-CH_2$), 2.01-1.95 (m, 1H, -CH), 0.97-0.95 (d, 6H, $(-CH_3)_2$); ^{13}C NMR (DMSO-d_6): δ 164.6, 160.8, 157.8, 131.4, 130.8, 128.6, 128.3, 114.4, 114.3, 73.7, 43.9, 40.1, 27.6, 18.9. Mass (*m/z*): 206.5 (M-H)

Synthesis of pimavanserin from compound 9: *N*-(4-isobutoxybenzyl)formamide (2.0 g, 0.0096 mol) was stirred in DCM (20 mL, 10.0 v) at room temperature in a three neck round bottom flask. To this triethyl amine (3.9 g, 0.0385 mol) was added at room temperature. The reaction was cooled to 0-5 °C, and then triphosgene (1.98 g, 0.0066 mol.) was added in lot wise to above reaction mixture at 0-5 °C. After complete addition of triphosgene, the reaction mass was warmed to room temperature and stirred for 2-3 h till the completion of the starting material. Wash the reaction mixture with water (10 mL, 5.0 v) and dried over anhydrous Na_2SO_4. The organic layer was transferred into another round bottom flask under inert

atmosphere and cooled to -65 to -60 ºC. Dimethyl sulfoxide (DMSO) (0.82 g, 0.0105 mol) and trifluoromethanesulfonic anhydride (0.1 mL, 0.0045 mol) were added to the reaction mixture at -65 to -60 ºC. Reaction mixture was stirred for 10-15 min at the same temperature. Then (*N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine)) (2.1 g) in DCM (10.0 v) was added at -65 to -60 ºC. Reaction mixture was warmed to room temperature and stirred for 2-3 h. The reaction mixture was washed with water (10 mL, 5.0 v) and dried the organic layer over Na_2SO_4. The solvent was evaporated under reduced pressure and residue was triturated with acetone to give pimavanserin (3.2 g, 77.7 %) as yellow solid.

RESULTS AND DISCUSSION

Initially, we have chosen 4-isobutoxy benzylamine (**1**) as a key starting material for the synthesis of pimavanserin. The initial reaction was reaction of 4-isobutoxy benzylamine (**1**) with thiophosgene using sodium bicarbonate in water. The reaction was stirred at 0-5 ºC for 5-6 h to yield corresponding 1-isobutoxy-4-(isothiocyanatomethyl)benzene (**2**) in good yield. The next step is reaction of compound **2** with *N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine (**3**). This reaction was performed using ethanol as solvent in refluxing conditions for 1-2 h to get respective thiourea derivative *i.e*. 1-(4-fluorobenzyl)-3-(4-isobutoxybenzyl)-1-(1-methylpiperidin-4-yl)thiourea (**4**) (**Scheme-I**). To improve the reaction yield various solvents were employed *i.e*. methanol, acetonitrile, isopropyl alcohol, DMF, toluene, acetone, ethyl acetate for synthesis of compound **4**. Among all the solvents, ethyl acetate gave good yields for the reaction in terms of the reaction time and yield (Table-1).

TABLE-1
SCREENING OF SOLVENT FOR THE SYNTHESIS OF 1-(4-FLUOROBENZYL)-3-(4-ISOBUTOXYBENZYL)-1-(1-METHYL PIPERIDIN-4-YL)THIOUREA (**4**)

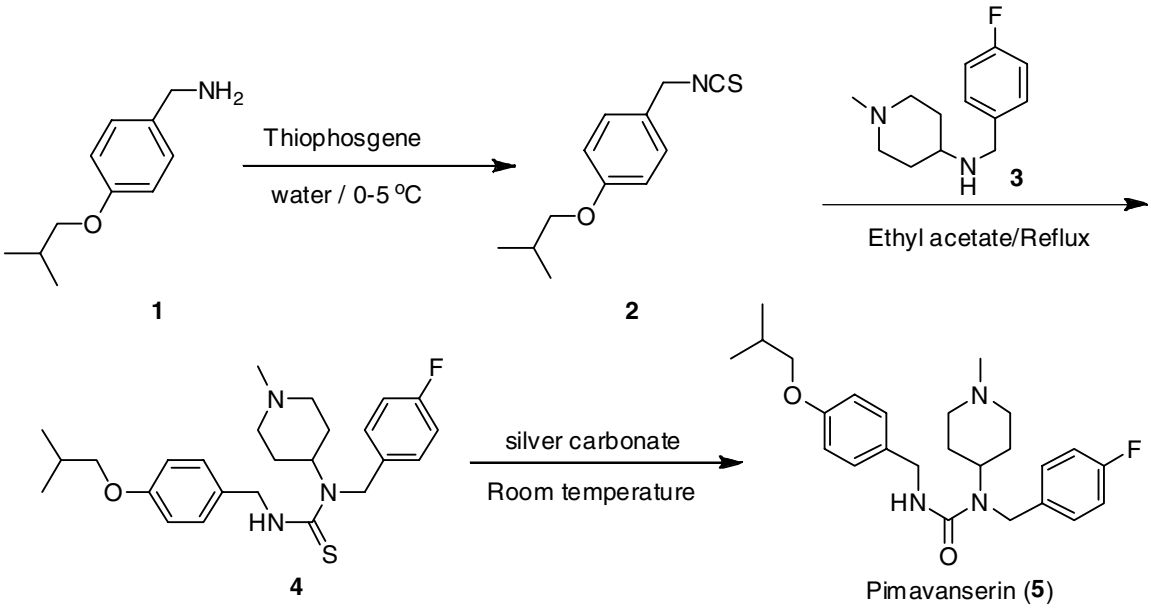
S. No.	Solvent	Reaction	Time (h)	Yield (%)
1	Ethyl acetate	Reflux	5	85
2	Acetonitrile	Reflux	5	75
3	DMF	80-85 °C	10	65
4	Acetone	Reflux	8	77
5	Methanol	Reflux	8	70
6	Isopropyl alcohol	Reflux	8	69
7	Toluene	80-85 °C	10	65

Oxidation was performed on compound **4** using different oxidizing agents. Compound **4** was oxidized with several oxidizing agents like silver carbonate, oxone, H_2O_2, DMSO at room temperature for 24 h. In all the reagents, silver carbonate was effective to give the title compound pimavanserin (**5**) in excellent yield (94.2%) (Table-2). The structure of compound was established by its spectral data (*i.e.* IR, ^{1}H NMR, ^{13}C NMR and mass).

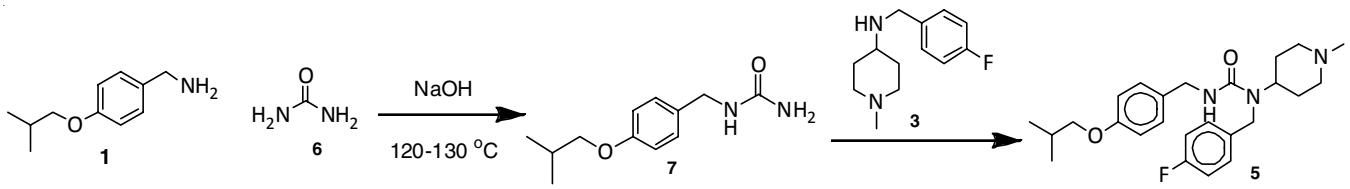
TABLE-2
SYNTHESIS OF COMPOUND **5** FROM COMPOUND **4** USING VARIOUS OXIDIZING AGENTS

S. No.	Oxidizing agent	Reaction time (h)	Yield (%)
1	H_2O_2	24	72
2	DMSO/HCl	24	75
3	Oxone	24	78
4	Silver carbonate	24	94

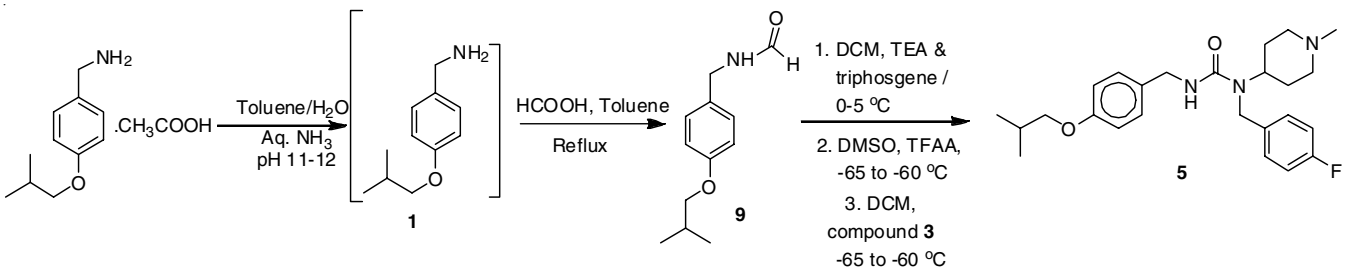
In another method shown in **Scheme-II**, 4-isobutoxy benzylamine (**1**), urea (**6**) and sodium hydroxide were heated



Scheme-I: Synthesis of pimavanserin (**5**) from isothiocyanate



Scheme-II: Synthesis of pimavanserin (**5**) from urea intermediate



Scheme-III: Synthesis of pimavanserin (5) from formamide intermediate

to 135-140 ºC for 12-15 h with continuous stirring. After completion of the reaction the reaction mass was checked by TLC and pH adjusted with HCl solution up to 7. The resulting solid was washed with water to yield the corresponding intermediate compound 1-(4-isobutoxybenzyl)urea (**7**). Further treatment of 1-(4-isobutoxybenzyl)urea with *N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine (**3**) was refluxed for 12 h at 120-130 ºC followed by ethyl acetate extraction to get target compound pimavanserin (**5**) as yellow solid in good yields.

In an alternate method shown in **Scheme-III**, 4-isobutoxy benzylamine **(1)** formic acid and toluene were refluxed for 4-5 h at 110 ºC using Dean-Stark apparatus. After completion of the reaction, the reaction mass was extracted with hexane and dried to get intermediate *N*-(4-isobutoxybenzyl)formamide **(9)**. Further, formamide intermediate **9** was stirred with *N*-(4-fluorobenzyl)-1-methylpiperidin-4-amine **(3)** in DCM at room temperature for 2-3 h to get final compound **5**.

Conclusion

In summary, a novel and environmentally friendly synthesis of pimavanserin (5-HT2A receptor) *via* three efficient intermediates (isothiocyanate, urea and *N*-formyl) under green conditions using water as solvent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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