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Simple and efficient methods to ziprasidone, an anti-psychotic drug substance

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ABSTRACT

Two simple and efficient methods for the preparation of 5-(2-(4-(1,2-benzisothiazole-3-yl) 1-piperazinyl) ethyl)-6-chloro-1,3-dihydro-2H-indole-2-one, commonly known as ziprasidone (**1**), an anti-psychotic drug, using commercially viable reagents are reported with very good yield and quality.

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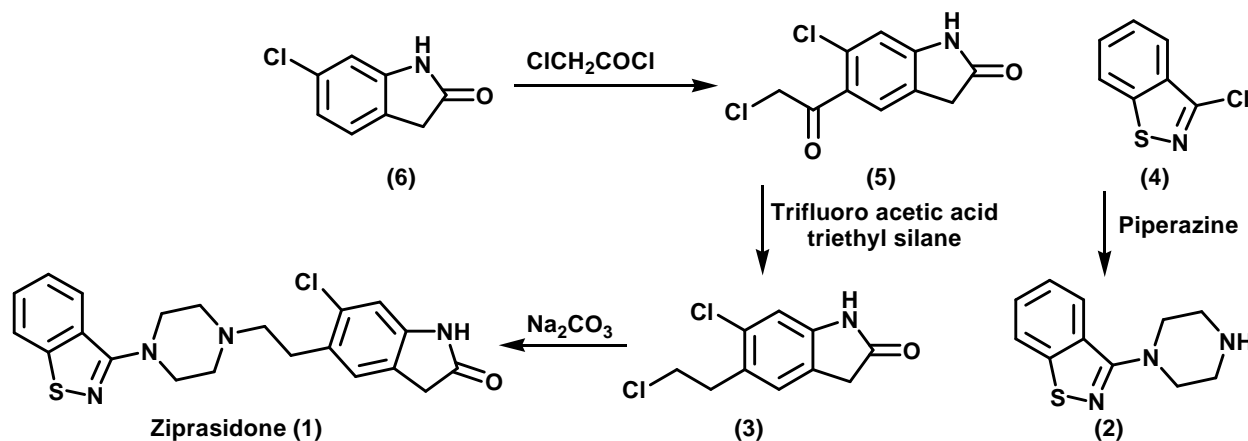
KEYWORDS

Ziprasidone;
Serotonin;
Anti-psychotic;
Drug substance;
Dopamine antagonist.

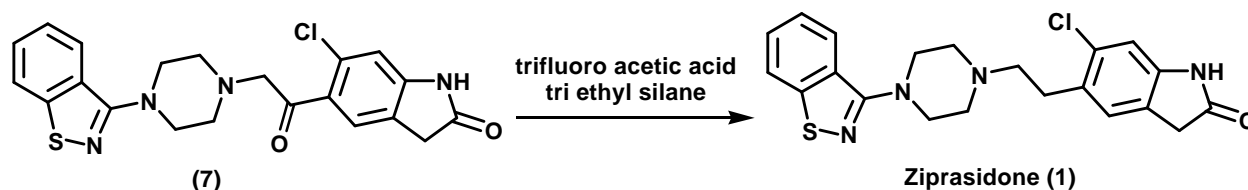
INTRODUCTION

Ziprasidone^[1,2] is a serotonin and dopamine antagonist, and is used as an anti-psychotic drug substance. Ziprasidone does not increase the weight of the patient and therefore has a distinctive advantage over other anti-psychotics, and in the market it is available as its hy-

drochloride salt. Several synthetic routes^[3-7] are available for the preparation of ziprasidone in the literature, the most commonly used synthetic route of ziprasidone (**1**) involves the condensation reaction of two advanced intermediates viz., 3-(1-piperazinyl)-1,2-benzisothiazole (**2**) and 5-(2-chloroethyl)-6-chloro oxindole (**3**) in the presence of base in aromatic hydrocarbon solvent at



Scheme 1 : Reported synthetic scheme for ziprasidone



Scheme 2 : Reported synthetic scheme for ziprasidone

reflux temperature (Scheme 1). The intermediate compound (2) was prepared by the reaction of 3-chloro-1,2-benzisothiazole (4) with excess moles of piperazine at elevated temperature. 6-Chloro oxindole (6) on Friedel-Craft reaction conditions with chloroacetyl chloride in the presence of aluminum chloride afforded 5-(2-chloroacetyl)-6-chloro oxindole (5), which was further reduced with triethyl silane in the presence of excess quantity of trifluoroacetic acid gave intermediate compound (3).

Ziprasidone was also synthesized^[8] comprising the condensation reaction of 5-(2-chloroacetyl)-6-chloro oxindole (5) with 3-(1-piperazinyl)-1,2-benzisothiazole (2) to result 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one / keto derivative of ziprasidone (7), which was reduced in the presence of triethyl silane and halo acetic acid such trifluoroacetic acid (Scheme 2).

The reported processes suffer from the formation of several impurities resulting low yield and also involves the use of corrosive, hazardous reagents such as trifluoroacetic acid and has become less attractive for commercial scale up. The major impurities are keto ziprasidone and bis piperazinyl benzisothiazole which form up to 1.0% level. To make the drug substance with the content of impurities below the ICH limits^[9], it was become mandate for more number of purifications in the final process. Therefore, to overcome these difficulties, we aimed to develop simple and efficient methods for the preparation of ziprasidone, which can be easily scaled up at commercial level. In this manuscript, we described two alternate methods for the synthesis of ziprasidone involving commonly available intermediates and less hazardous reagents.

EXPERIMENTAL

The ESI mass spectrum was recorded on 4000-Q-trap LC-Mass spectrometer. The sample introduced

into the system through HPLC by passing the column. The FT-IR spectrum was recorded on Perkin-Elmer model spectrum GX series FT-IR as KBr pellet. The ¹H NMR data were recorded at 400 MHz on Varian mercury plus 400 MHz spectrometer. The chemical shift values were reported on δ scale in ppm with respect to TMS (0.0ppm) as an internal standard.

5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one (7)

To a stirred solution of 3-(1-piperazinyl)-1,2-benzisothiazole (2), (8.9g, 0.04 mol) in cyclohexane (100.0mL), sodium carbonate (8.5g, 0.08 mol), sodium iodide (0.6g, 0.003 mol), tetrabutyl ammonium bromide (2.6g, 0.008 mol) and 5-(2-chloro acetyl)-6-chloro oxindole (5), (10.0g, 0.041 mol) were added sequentially at ambient temperature. The resulting mixture was slowly heated to reflux and stirred for reaction completion. Water (100.0mL) was added to the reaction mixture at ambient temperature and stirred to isolate the title compound. The separated solid was filtered, washed with water, methanol and dried at 60-65°C to give title compound. (15.0g, 86.0%, HPLC Purity: 98.4%). IR (cm⁻¹): 1678 (C=O), 1735 (C=O) and 3186 (amide NH); ¹H NMR (DMSO-d₆, δ ppm): 3.20-3.25, (m, 2H, CH₂), 3.25-3.40 (m, 4H, CH₂), 3.45-3.60, (m, 4H, CH₂), 3.65-3.80 (t, 2H, CH₂), 4.10 (t, 2H, CH₂), 6.85 (s, 1H, Ar-H), 7.40-7.50 (m, 2H, Ar-H), 7.55-7.60 (m, 2H, Ar-H), 8.05 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 10.75 (s, 1H, N-H); Mass: 427 (M⁺); C H N Analysis calcd. for C₂₁H₁₉ClN₄O₂S: C, 59.08; H, 4.49; N, 13.12; Found: C, 59.29; H, 4.82; N, 13.22.

6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (8)

To a stirred mixture of 5-(2-chloroethyl)-6-chloro oxindole (3), (5.0g, 0.022 moles) in tertiary butanol (50.0mL), piperazine (9.0g, 0.105 moles) was added in three different portions at reflux temperature. The reaction mass was stirred at reflux temperature for about

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6 hours to complete the reaction. Distilled off tertiary butanol completely, water (100.0mL) was added to the residual mass to dissolve and extracted with dichloromethane. The dichloromethane layer was washed with water and distilled off completely. The residual mass was triturated with hexane (30mL) to separate the solid. The separated solid was filtered off, washed with hexane (10mL) and dried at room temperature to give title compound (Yield: 4.0g, 66.0%, Purity: 95.0%). IR (cm^{-1}): 1716 (C=O), 3317 (NH) 3410 (NH); ^1H NMR (DMSO-d_6 , δ ppm): 2.30-2.50, (m, 4H, CH_2), 2.55 (s, 2H, CH_2), 2.60-2.80, (m, 6H, CH_2), 3.40-3.50 (s, 2H, CH_2), 6.85 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 10.40 (s, 1H, N-H); Mass: 280 (M^+); C H N Analysis calcd. for $\text{C}_{14}\text{H}_{18}\text{ClN}_3\text{O}$: C, 60.10; H, 6.49; N, 15.02; Found: C, 59.95; H, 6.20; N, 15.28.

5-(2-(4-(1,2-benzisothiazole-3-yl) 1-piperazinyl) ethyl)-6-chloro-1, 3-dihydro-2H-indole-2-one (1)

Method 1

Triethyl silane (10.0g, 0.086 moles) was added slowly to the reaction mixture containing 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one (**7**), (10.0g, 0.024 moles) and methane sulfonic acid (20.0g, 0.20 moles) at below 25°C . Heated the reaction mass to $50-55^\circ\text{C}$ and stirred for reaction completion. The reaction mass cooled to $0-5^\circ\text{C}$ and stirred for 1 hour to isolate the compound. The isolated compound was filtered, washed with water (50.0mL). The wet compound further slurry washed with water (100.0mL), filtered, and dried at $60-65^\circ\text{C}$. The resultant crude ziprasidone was purified from a mixture of methanol and chloroform (Yield: 7.3 g, 76%, Purity: 99.8%).

Method 2

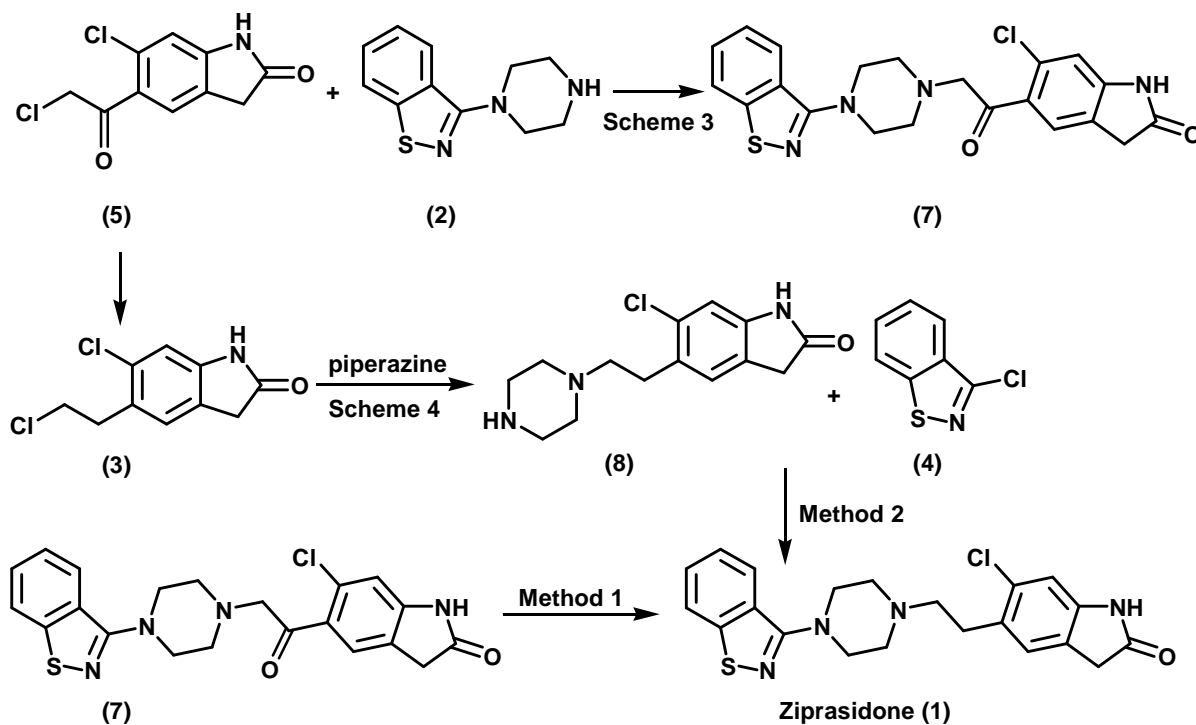
To stirred mixture of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (**8**), (3.0g, 0.010 moles), sodium carbonate (1.2g, 0.011 moles) and tertiary butanol (10mL) was added a solution of 3-chloro-1,2-benzisothiazole (4, 1.7g, 0.010 moles) in tertiary butanol (10mL). The reaction mass slowly heated to reflux and maintained for 20-22 hours for reaction completion. Tertiary butanol was concentrated under vacuum and water (50.0mL) was added and stirred for 30 minutes. The

solid was filtered, washed with water and dried at $60-65^\circ\text{C}$. The resultant crude compound was further recrystallized from a mixture of methanol and chloroform (Yield: 3.5g, 80.0%, HPLC Purity: 99.2 IR (cm^{-1}): 1714 (C=O), and 3420 (amide NH); ^1H NMR (DMSO-d_6 , δ ppm): 3.21, (m, 2H, CH_2), 3.27 (m, 2H, CH_2), 3.35, (m, 2H, CH_2), 3.54 (m, 2H, CH_2), 3.56 (d, 2H, CH_2), 3.70 (d, 2H, CH_2), δ 4.10 (d, 2H, CH_2), 6.95 (s, 1H, Ar-H), 7.15 s, 1H, Ar-H), 7.45-7.50 (d, 1H, Ar-H), 7.60-7.65 (d, 1H, Ar-H), 8,10-8.20 (m, 2H, Ar-H), 10.55 (s, 1H, N-H); Mass: 413(M^+); C H N Analysis calcd. for $\text{C}_{21}\text{H}_{21}\text{ClN}_4\text{OS}$: C, 61.08; H, 5.13; N, 13.57; Found: C, 61.29; H, 5.22; N, 13.50.

RESULTS AND DISCUSSION

The first alternate method (Scheme 3), involves the reaction of 3-(1-piperazinyl)-1,2-benzisothiazole (**2**) with 5-(2-chloro acetyl) -6-chloro oxindole (**5**) at refluxing temperature in presence of cyclohexane, sodium carbonate and catalytic amounts of sodium iodide and tetrabutyl ammonium to yield 5-(2-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one / keto derivative of ziprasidone (**7**). The IR spectrum of (**7**) showed characteristic two CO absorption peaks at 1732cm^{-1} , 1716cm^{-1} and one broad amide NH peak at 3437cm^{-1} . The ^1H NMR spectrum displayed six aromatic protons at δ 8.05-8.10 (2s, 2H), δ 7.65 (s, 1H), δ 7.45 (t, 1H), δ 7.55 (t, 1H), 6.90 (1, 1H) along with the amide NH at δ 10.75 and 12 methylene protons displayed as multiple peaks at δ 3.20-3.95ppm. The mass spectrum displayed a protonated molecular ion peak at m/z 427.0 (M^+). This spectral data is inconformity with the structure of (**7**).

The resulted keto ziprasidone was subjected to reduction in the presence of triethyl silane and methane sulfonic acid to provide the ziprasidone (**1**) with good purity and yield. The safety profile of methane sulfonic acid is much better than trifluoroacetic acid. It was also observed that the commercial price of methane sulfonic acid is two folds lesser than trifluoroacetic acid. These unique properties of methane sulfonic acid were motivated us to utilize as one of the reagent for the instant reaction. Furthermore, the use of methane sulfonic acid with combination of triethyl silane for the reduction of carbonyl group is not reported in the literature to the



best of our knowledge. The IR spectrum of **1** showed characteristic sharp amide CO absorption peak at 1714cm^{-1} and one broad amide NH peak at 3420cm^{-1} . The ^1H NMR spectrum displayed six aromatic protons at δ 8.10-8.20 (m, 2H), δ 7.60-7.65 (d, 1H), δ 7.45-7.50 (d, 1H), δ 7.15 (s, 1H), 6.95 (s, 1H). The exchangeable proton observed at δ 10.55 (s, 1NH) and this was further confirmed by recording the deuterated proton spectra wherein disappearance of amide NH signal at δ 10.55 observed. The 12 methylene protons displayed at δ 4.10 (d, 2H), δ 3.70 (d, 2H), 3.56 (d, 2H), 3.54 (m, 2H), 3.35 (d, 2H), 3.27 (d, 2H and 3.21 (m, 2H). The mass spectrum displayed a protonated molecular ion peak at m/z 413.0 (M^+).

The second alternate method (Scheme 4) comprises the reaction of 5-(2-chloroethyl)-6-chlorooxindole (**3**) with excess moles of piperazine afforded 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (**8**), which is a new intermediate for the preparation of ziprasidone to the best of our knowledge. The compound (**8**) is reported as one of the metabolite for the ziprasidone^[9-11] in the literature; however there is no experimental procedure is reported. The authors of this manuscript were prepared compound (**8**) involving the simple reagents and utilized for the preparation of ziprasidone. The IR spectrum of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole

(**8**) showed characteristic sharp carbonyl and two sharp NH absorptions at 1716cm^{-1} , 3317cm^{-1} and 3410cm^{-1} respectively. The ^1H NMR spectrum displayed amide NH signal at δ 10.35-10.45, two aromatic protons at δ 6.80ppm and 7.20ppm respectively. The signals corresponding to 14 methylene protons were observed in the up field region at δ 3.40-3.45, (s, 2H), δ 2.65-2.75 (m, 6H) and 2.30-2.45 (m, 6H). The positive mode mass spectrum displayed a protonated molecular ion peak at m/z 280 (M^+) with chlorine isotopic abundance. This spectral data is inconformity with the structure of 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (**8**). The piperazinyl oxindole derivative (**8**) was coupled with 3-chloro-1, 2-benzisothiazole (**4**) to afford the targeted compound ziprasidone in a satisfactory yield and purity. The structure of ziprasidone (**1**) obtained in the above alternate routes was confirmed by comparison with an authentic sample of ziprasidone.

CONCLUSION

In conclusion, we have provided two simple and efficient methods for the preparation of 5-(2-(4-(1, 2-benzisothiazol-3-yl) 1-piperazinyl) ethyl) -6-chloro-1, 3-dihydro-2H-indole-2-one, commonly known as ziprasidone (**1**).

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