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RESEARCH ARTICLE

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NOVEL SYNTHETIC APPROACHES FOR THE SYNTHESIS OF ANTIPSYCHOTIC DRUG OLANZAPINE

CHANDRA SEKHAR BVVN[$A], RAMESH KUMAR N [A], CHAKRAVARTHY A[A] AND MUKKANTI K [B]

[a] Dr Reddy's Laboratories Limited, Bachupalli, Qutubullapur, Rangareddy District-72, Andhra Pradesh, India. Fax: 91 40 4434 6285

[b] Institute of Science and Technology, JNTU, Hyderabad.

CHANDRA SEKHAR BVVN

Dr Reddy's Laboratories Limited, Bachupalli, Qutubullapur, Rangareddy District-72, Andhra Pradesh, India. Fax: 91 40 4434 6285

ABSTRACT

The present work is relatd to novel synthetic approaches for the synthesis of antipsychotic drug, Olanzapine. The present work is related to two novel approaches for the synthesis of olanzapine and an improved process for the synthesis of olanzapine. The present work is also related to identification, synthesis and characterization of process related impurities of olanzapine.

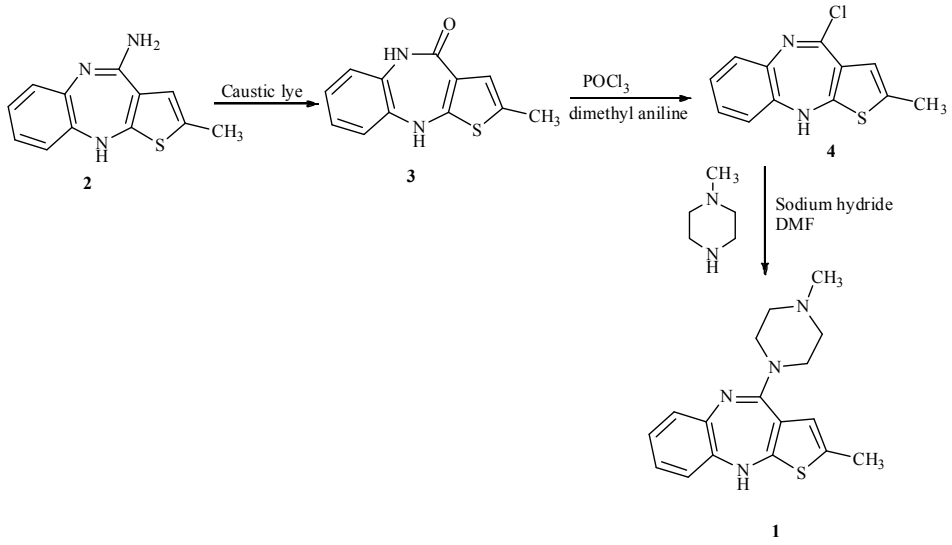
KEY WORDS

Olanzapine, compound, antipsychotic, synthesis, characterization, process.

INTRODUCTION

Olanzapine **(1)** belongs to the class of newer atypical antipsychotic drugs, bearing thieno [2,3-b][1,5]benzodiazepine moiety. These atypical antipsychotic drugs shows affinity towards the blockade of serotonin 5HT2 and dopamine D2 receptors, and used to treat schizophrenia and bipolar disorders. [1, 2, 3] Different synthetic approaches were reported in literature. [3-7] As a part of the ongoing research and development program with an objective of providing simple and commercially viable synthetic processes, the present work relates to novel synthetic approaches for the preparation of Olanzapine. The objective is also to identify and characterize the process related impurities of the novel synthetic approaches of the present work.

Scheme-1:



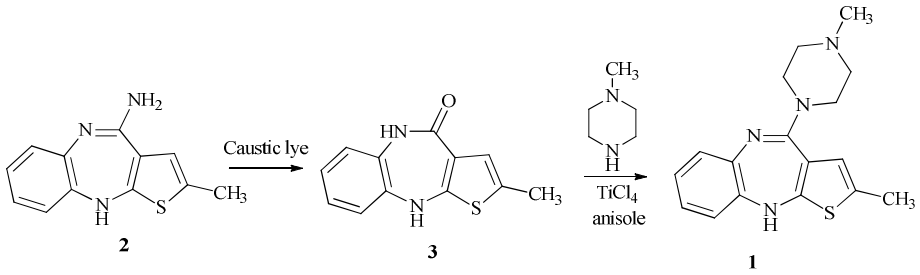
Anti-psychotic drug Olanzapine **(1)** according to scheme-1 is synthesized by:

(i) reacting10H-thieno4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine **(2)** as its hydrochloride with caustic lye at reflux for 12 hours to afford novel cyclic amide **(3)**;

(ii) treating the cyclic amide **(3)** with $POCl_3$ in the presence of dimethyl aniline to get novel imidoyl chloride intermediate **(4)**;

(iii) recating the imidoyl chloride intermediate **(4)** with N-methyl piperazine in the presence of sodium hydride in dimethyl formamide as a solvent to afford Olanzapine **(1)**.

Scheme-2:



Anti-psychotic drug Olanzapine **(1)** according to scheme-2 is synthesized by:

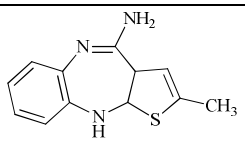
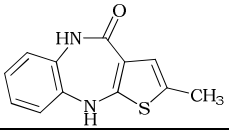
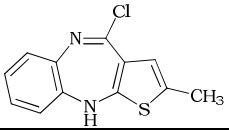
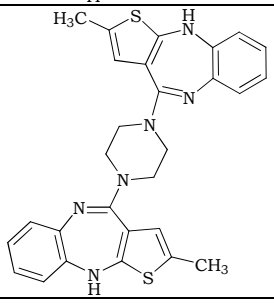
(i) reacting 10H-thieno4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine **(2)** as its hydrochloride with caustic lye at reflux for 12-14 hours to afford novel cyclic amide **(3)**;

(ii) Thus obtained cyclic amide **(3)** was converted to Olanzapine (1) directly by reacting with N-methyl piperazine in anisole and in the presence of titanium tetrachloride ($TiCl_4$) at reflux temperature to afford Olanzapine **(1)**.

During the synthesis of Olanzapine **(1)** according to the synthetic approaches of the present work, the following compounds were identified as process related impurities in Olanzapine, controlled to the limits required by ICH (International Conference on Harmonization) and were characterized. The structures of these impurities are depicted in Table 1.

Table 1

Structure of related impurities of Olanzapine (1) prepared according to present work

Compound	Structure of impurity	Chemical name
2		4-Amino-2-methyl-l0H-thieno[2,3-b][1,5]benzodiazepine hydrochloride
3		2-methyl-4-oxo-10H-thieno-[2,3-b][1,5]-benzodiazepine
4		4-chloro-2-methyl-10H-benzo[b]thieno[2,3-e][1,4]diazepine
5		Piperazine 1,4 bis-4-yl-(2-methyl)-10H-thieno-[2,3-b][1,5]-benzodiazepine

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. All the reactions were monitored by TLC and IR spectra were recorded on Perkin-Elmer model-1600 spectrophotometer. 1H-NMR spectra of the compounds were recorded on Perkin-Elmer EM-390-200 MHz spectrophotometer, using TMS as an internal standard.

10H-thieno-4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine **(2)** was prepared by a method similar to that described in US patent 5,229,382.

Synthesis of 2-methyl-5,10-dihydro-4H-benzo[b]thieno[2,3-e][1,4]diazepin-4-one (3)

General procedure: 2 (50 g; 0.188 mol) was taken in 200 ml of 30% sodium hydroxide and refluxed 10 hours. The reaction mixture was cooled to room temperature; solid was filtered and washed with plenty of water. The wet compound was taken in 1000 ml of MeOH and refluxed for 15 minutes to dissolve the solid. The solution was treated with carbon and filtered hot. The filtrate was cooled to room temperature and added 500 ml of water slowly to precipitate the solid. Stirring was continued for 60 minutes. The separated solid was filtered and washed with water. Repeated the recrystallization process for one more time and recrystallized compound was dried at 60^{O}C to yield 20 grams of **3** (Theoretical yield: 46.5%; Purity by HPLC: 99%). The obtained product was characterized as 2-methyl-5,10-dihydro-4H-benzo[b]thieno[2,3-e][1,4]diazepin-4-one **(3)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of 4-chloro-2-methyl-10H-benzo[b]thieno[2,3-e] [1,4]diazepine (4):

General procedure: A mixture of **3** (5.0 g; 0.022 mol), 150 mL of toluene and 13.9 mL (0.11 mol) of N, N-dimethylaniline was stirred at 25-35°C. 10 ml (0.108 mol) of $POCl_3$ was added slowly to the above reaction mixture at 25-35°C. The resultant reaction mixture was refluxed at 100°C for 4-5 hours. After completion of the reaction, the resultant reaction mixture is evaporated to give the desired **(4).** The obtained product was characterized as 4-chloro-2-methyl-10H-benzo[b]thieno[2,3-e] [1,4]diazepine **(4)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of Olanzapine (1) by using (3):

General procedure: 3 (2.4 g; 0.01 mol) was suspended in N-methyl piperazine (10 mL). Titanium chloride (1.2 mL; 0.011 mol) in dry anisole (5 mL) was added and the resultant reaction mixture maintained at reflux till the completion of reaction. After conventional work up procedure gave the desired **(1).** The obtained product was characterized as Olanzapine **(1)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of Olanzapine (1) by using (4):

General procedure: 0.55 g (60%, 0.0137 mol) of sodium hydride was dissolved in 10 mL of DMF at 25-35°C and the mixture was cooled to 0°C. 5.0 mL (0.045 mol) of N-methyl piperazine was slowly added to the reaction mixture at 0-5°C. Then a solution of (5.0 g; 0.02 mol) of **4** in 20 mL of DMF was added to the above reaction mixture at 0-5°C. The reaction mixture was maintained at the same temperature till the completion of reaction. After conventional work up procedure gave the desired **(1).** The obtained product was characterized as Olanzapine **(1)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of 4-Amino-2-methyl-l0H-thieno[2,3-b][1,5]benzodiazepine (2):

General procedure: 6.6 gm of sulphur (0.206 mol) and 9.75 mL (0.136 mol) of propionaldehyde were charged in to round bottom flask containing 22.5 mL of dimethyl formamide at 0-5°C. The reaction mass was cooled to 0-5°C. 9.6 mL of triethylamine (0.0689 mol) was added slowly at 0-5°C in 45-60 minutes. The reaction mixture temperature was increased to 15-20°C. Added a solution of 7.5 mL (0.11 mol) of malononitrile in 15.0 mL of DMF to the reaction mixture at 15-20°C in 3-4 hours.

The mixture was maintained at 15-20°C for 2-4 hours. After completion of the reaction, 72.5 mL of water was charged and the reaction mixture was cooled to 0-5°C. The resultant reaction mass was slowly transferred into another round bottom flask containing chilled water with stirring. The reaction mass was stirred for 10-15 min, the obtained solid was collected by filtration, washed with 73.0 mL of water and suck dried for 30 minutes. The obtained wet compound was taken in 61.5 mL of methanol and stirred for 45 minutes. The undissolved solid from the reaction mass was filtered. The filtrate obtained was subjected to distillation completely under vacuum at below 50°C. The reaction mass was cooled to 20-35°C and 54.5 mL of water was charged to reaction mass at 20-35°C. The reaction mass was stirred for 20-35 min at 20-35°C. The obtained product was filtered, washed with 7.5 mL of water and dried at 60°C to give 11.1 gm of 2-amino-5-methylthiophene-3-carbonitrile.

72 mL of DMSO, 12.0 gm (0.085 mol) of 2-fluoronitrobenzene, 37.68 gm (0.273 mol) of potassium carbonate and 12.0 gm (0.086 mol) of 2-amino-5-methylthiophene-3-carbonitrile were charged in to a round bottom flask. The mixture was heated to 65°C and maintained for 9 hours. The reaction mixture was cooled to 40°C, 14.9 mL of water was slowly added at temperature below 45°C. The reaction mass was stirred for 45 minutes, filtered the material and spin dried for 30-40 minutes. The resultant wet compound was purified by using 53.0 mL of methanol and dried at 65°C to afford 15.0 gm of the 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile.

70.0 mL of 1,4-Dioxane, 15.0 gm (0.058 mol) of 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile and 2.15 gm of Raney Nickel were mixed with 5.0 mL of 1,4-Dioxane by applying vacuum into a vessel. The reaction mixture was maintained under hydrogen pressure below 4 Kg/cm2 at 70°C for 3 hours. The reaction mixture was cooled to 35°C. After completion of the reaction, the reaction mixture was filtered, washed with 4.0 mL of 1,4-Dioxane and distill off the solvent 1,4-dioxane under vacuum at below 70°C. The residue was cooled to 40-50°C then 19.0 mL of isopropyl alcohol and 6.2 mL of HCl were added to the residue. The mixture was heated to reflux and maintained at reflux temperature for 12 hours. Then cooled to 0-5°C and maintained for 1 hour at 0-5°C. The obtained product was filtered, washed with 4.0 mL of isopropyl alcohol and dried at 60°C for 3 hours to get crude **(2)** as its hydrochloride. The crude **(2)** as its hydrochloride was purified from a mixture of methanol and chloroform to give 5.8 gm of pure **(2)** as its hydrochloride. The obtained product was characterized as **(2)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of Piperazine 1,4 bis-4-yl-(2-methyl)-10H-thieno-[2,3-b][1,5]-benzodiazepine (5):

General procedure: A mixture of 10 g (0.0377 mol) of **2** as its hydrochloride, 4.8 g (0.0565 mol) of piperazine, 10 mL of DMSO and 40 mL of toluene were heated to reflux and maintained at reflux for 40 minutes. The reaction mixture was cooled to 25-35°C, filtered the insoluble solids from the reaction mixture under reduced pressure. The resultant solid was purified three times from methanol to get 1.2 g of pure **(5)**. The obtained product was characterized as dimer impurity of Olanzapine **(5)** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

The characterization data of compounds 1-5 are presented in Table 2.

Table 2
Characterization data for compounds 1-5

Compound No.	IR (cm^{-1})	M^+ (m/z)	^1H NMR (ppm)
1	3236 (N-H stretching); 3051 (aromatic C-H stretching); 1285 and 1221 (C-N stretching)	313	2.21 [s, 3H, CH3 attached to thiophene moiety], 2.27 (s, 3H, CH3 attached to nitrogen group), 6.34 (s, 1H, CH), 6.60-6.90 (m, 4H, Ar-H), 7.60(s, 1H, NH)
2	3299 & 3184 (primary N-H stretching)	229	2.25 [s, 3H, CH3 attached to thiophene moiety], 6.82 (s, 1H, CH), 6.87-6.99 (m, 4H, Ar-H), 2.5 (s,2H, NH2).
3	1632 (amide carbonyl stretching); 3626 (amide–NH stretching); 3282 (N-H stretching)	230	2.2 [s, 3H] corresponds to methyl group attached to aromatic thiophne moiety.; 6.58 (s, 1H, CH); 6.77-6.88 (m, 4H, Ar-H); 6.9 (s,1H, NH)
4	3282 (N-H stretching); 3036 (aromatic C-H stretching); 749 (C-Cl stretching)	249	2.36 [s, 3H] corresponds to methyl group attached to aromatic thiophene moiety.; 6.8 (s, 1H, CH); 6.86-7.20 (m, 4H, Ar-H); 3.39 (s,1H, NH)
5	3292 (N-H stretching)	511	2.27-2.29 [s, 6H, CH3 attached to thiophene moiety], 2.5-3.42 [m, 8H, CH2), 6.42 (s, 2H, aromatic CH), 6.68-6.87 (m, 8H, Ar-H), 7.65 (s,2H, NH).

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