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Research Article

SYNTHESIS AND CHARACTERIZATION OF RELATED IMPURITIES OF ELETRIPTAN HYDROBROMIDE, AN ANTIMIGRAINE AGENT

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ABSTRACT

Eletriptan hydrobromide is a known orally active antimigraine agent. Four related substances (Impurities) were observed during laboratory process development and pilot scale preparation of Eletriptan. They are desbromo eletriptan, dimer impurity of eletriptan, dehydro analogue and novel intermediate of eletriptan. The present work describes the detection, origin, synthesis, characterization and control of these related substances, thereby providing a commercial method to synthesize substantially pure eletriptan hydrobromide.

Keywords: Antimigraine agent, Eletriptan hydrobromide, synthesis, Characterization.

INTRODUCTION

Eletriptan hydrobromide is a novel, orally active, selective serotonin 5-HT1B/1D receptor agonist and is second generation anti-migraine drug, recently approved by the Food and Drug Administration for the acute treatment of migraine headache[1–4]. Control of pharmaceutical impurities is currently a critical issue in the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. Organic impurities associated with the active pharmaceutical are the unwanted chemicals which are developed during drug synthesis or formulation. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (identification and quantification) is now receiving increased attention from regulatory authorities. A number of recent articles[5] described a designed approach and guidance for the isolation and identification of process-related impurities and degradation products. In general, according to ICH guidelines on impurities in new drug products[8], identification of impurities below the 0.1 %level is not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic. In all cases, impurities should be quantified. Its presence in dosage form is limited to 0.2%due to side effects. Different side effects, such as cardiac events, asthenia, nausea, dizziness and somnolence, can develop as a consequence of a loss of the selectivity for the 5HT1B/1D receptor subtypes and selectivity for other receptors, such as dopamine and different subtypes of 5HT1 receptors [6].

A highly sensitive method for the determination of eletriptan in biological fluids (saliva and plasma) is based on HPLC analysis with gradient elution. However, to the best of our knowledge, no analytical method for the quantitative analysis of the chemical purity of eletriptan in dosage forms is yet reported in the literature. The aim of the present work is to synthesis and control of the impurities of eletriptan hydrobromide.

MATERIALS AND METHODS

Thin-layer chromatography (TLC) were run on silica gel 60 F254 precoated plates (0.25 mm, Merck, Art.5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on Perkin Elmer Spectrum FT-IR Spectrometer by using 1% potassium bromide pellet. 1H and ^{13}C NMR spectra were recorded on Bruker 300 MHz Advance NMR spectrometer at 300 MHz for 1H NMR and 75 MHz for ^{13}C NMR with TMS as an internal standard. All other reagents were purchased from Lancaster (Germany) and S.D.Fine Chemicals, Mumbai. The solvents and reagents were used without purification.

RESULTS AND DISCUSSION

For the past several years, we have been interested in designing a simple and an efficient synthesis and characterization for various bioactive target compounds, which remains a challenging area, despite impressive progress in organic synthesis.

As shown in Scheme 1 preparation of eletriptan hydrobromide 5, condensation followed by acetylating of 5-bromo-3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole **1** to obtained **2** then deactylation with potassium carbonate obtained **3** then reduction of double bond with palladium carbon to obtained **4** then followed by HBr salt and finally eletriptan hydrobromide **5** obtained

Some of the impurities and process related impurities are prepared, isolated and characterized by analytical techniques. Those impurities are namely desbromo eletriptan and dimer impurity of eletriptan.

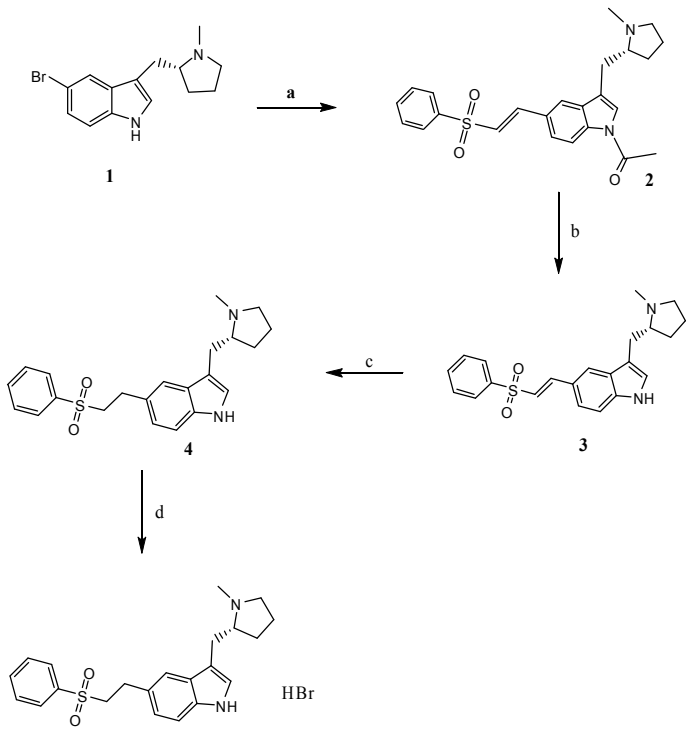
In Scheme 2 synthesis of (R)-3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole (desbromo impurity) **6** by using of Pd/C

In scheme 3 prepared a novel intermediate of eletriptan , the condensations of 5-bromo-3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole **7** with phenyl vinyl sulfone, Pd (OAc), tri-O-tolyl phosphine and acetic anhydride obtained (E)-1-(3-((1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)vinyl)-1H-indol-1-yl)ethanone **8**

In scheme 4 prepared a dehydro impurity of eletriptan (E)-3-((1-methylpyrrolidin-2-yl) methyl)-5-(2-(phenylsulfonyl) vinyl)-1H-indole **9**

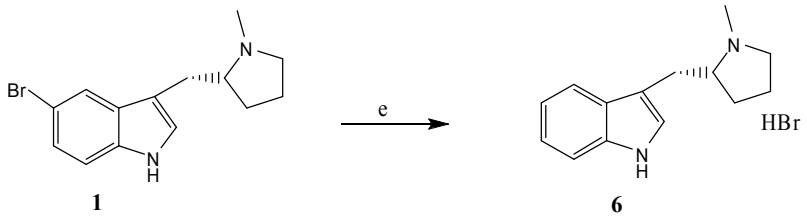
In scheme 5 a novel dimeric impurity of eletriptan hydrobromide 5, 5'-(1, 4-bis (phenylsulfonyl) butane-2, 3-diyl) bis (3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole) **10**

Scheme 1



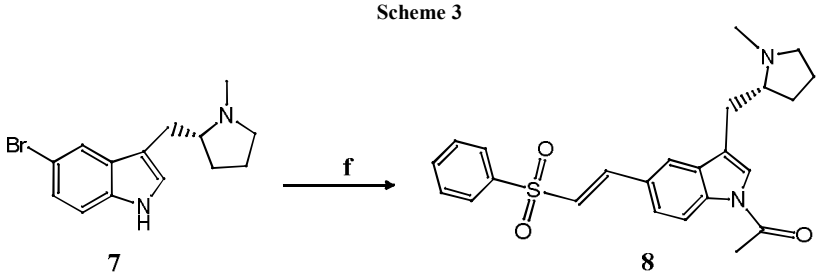
Reagents (a) Acetic anhydride, phenyl vinyl sulfone, $pd(OAc)_2$, tri-O-tolyl phosphine (b) potassium carbonate, methanol (c) pd/C, Acetone (d) HBr/ acetone.

Scheme 2

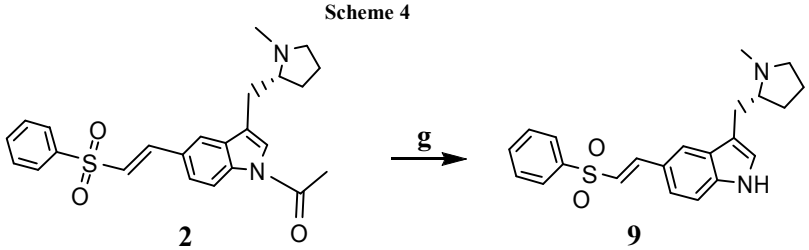


Reagents (e) Pd/C, acetone, 3.5 kg/cm^2

Scheme 3

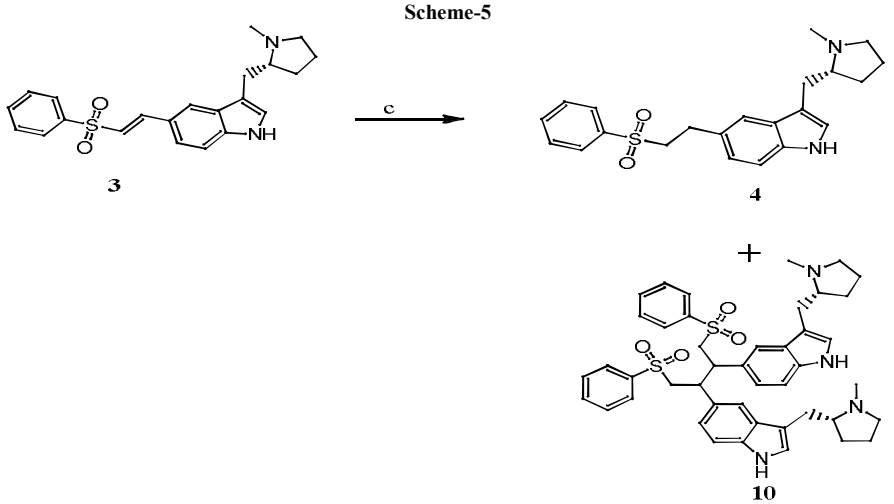


Scheme 4



Reagents (g) K_2CO_3 / Methanol/ Room temperature

Scheme-5



EXPERIMENTAL

Preparation of (R)-1-Acetyl-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole (2)

To a mixture of acetonitrile (18 mL) and 5-bromo-N-methyl-pyrrolidine-1H-indole (10g) was added acetic anhydride (5.32 g) and triethylamine (5.2 g) at 25-35°C. The reaction mass was heated to 78-84°C and the stirred the reaction mass at the same temperature for about 6-7 hours. The reaction mass cooled to 25-35°C to yield N-acetyl derivative of 5-bromo-N-methyl-pyrrolidine-1H-indole. Taken another round bottom flask add a mixture of acetonitile (18 mL), tri-O-tolyl phosphine (2.4 g) and palladium acetate (480 mg) were stirred for about 1 hour at 25-35°C . Phenyl vinyl sulphone (6.3 g) and triethylamine (3.8 g) were added to the reaction mass at 25-35°C and stirred for about 15-20 minutes at 25-35°C. The temperature of the reaction mass was raised to 78-83°C and stirred at the same temperature for about 6-8 hrs. The reaction mass was collected to 25-35°C and hydrochloric acid solution (hydrochloric acid 7.6ml and water 45 ml) was slowly assed over a period of two hours. The reaction mass was stirred at 25-35°C for about two hours, filtered through hyflobed to remove unwanted salts and washed with acetonitile(30ml). The filtrate is washed with toluene (20ml × 3). The product was recovered back from toluene layer with water and hydrochloric acid was combined to the main aqueous layer. Further water (100 mL) was added to aqueous layer before precipitation with 50% sodium hydroxide solution at pH 10.5 to 11.0 at 25-35°C. The slurry was stirred at 25-30°C for one hour filtered and washed to obtain 20-22g of crude product. The crude wet material was leached in a mixture of methanol (30 mL) and water(20 mL) at 25-35°C for about 2-3 hrs. The obtained solid was filtered, washed with water and dried at 45°C for about 6-10 hrs to get 11-13 g of the title compound (**2**).

3-((1-methylpyrrolidin-2-yl) methyl)-5-(2-(phenylsulfonyl) ethyl)-1H-indole hydrobromide (Eletriptan hydrobromide) (5)

To a mixture of methanol(60 mL) and (R)-1-Acetyl-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole (10 g) was added potassium carbonate (1.2 g) in one lot at ambient temperature and stirred for about 120 min monitored reaction by TLC complies and the methanol was distilled out completely u/v at 45°C the traces of methanol were removed by distilling out acetone (10ml), resulting to residue (**3**) dissolved in acetone (40 mL) added purified water (10 mL) and methane sulphonic acid (3.4 g). Purged nitrogen gas for 10 minutes and palladium on carbon (2 g, 5% Pd/C 50% wet) was added. Maintained the reaction mass under hydrogen atmosphere for 7-10 hours at ambient temperature and filtered the catalyst, fresh palladium on carbon (1 g) was added and maintained the reaction mass under hydrogen atmosphere for 10 hours. The reaction mass was again filtered and washed with acetone-water mixture (4+1 ml). Distilled out acetone completely u/v at 45° C. Ethyl acetate (20 ml) was added at room temperature and stirred for 15 minutes. Separated the layers ethyl acetate (50 ml) was added to the aqueous layer and adjusted the pH 9-9.5 with 30% sodium hydroxide solution. Stirred the reaction mass for about 20 minutes and again separated the layers. Aqueous layer was extracted with ethyl acetate (50ml). Combined both ethyl acetate layers and washed with water (30ml). The aqueous layer was separated. Ethyl acetate layer was passed through silica gel column (8g silica gel, 100-200 mesh size) and washed the column with ethyl acetate till ethyl acetate layer is colourless. Combined all ethyl acetate elutes and distilled out ethyl acetate completely under vacuum at 45° C to get residue.

Hydrobromide salt

Methanol (10ml) was added to the above residue and stirred for about 20 minutes to get clear solution.48% aqueous hydrobromide (1.4 g) was slowly added to the reaction mass for about 30-45 minutes at 45°C and methanol was distilled off completely u/v at 40-45°C, methanol (50 ml) was added and stirred the reaction mass to get clear solution at same temperature and cool to 5°C stirred the content for 120 min and filtered the solid the title compound (**5**) obtained.

Preparation of (R)-3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole (6) Added Pd/C (5g) to a mixture of 5-bromo-N-methyl-pyrrolidine (5g) and acetone (50ml) purge hydrogen gas pressure of 5 kg/cm^2 about 10 hours monitored by TLC then filtered reaction mass and distilled solvent under vacuum the crude product isolated with hexane solid was filtered the title compound (6) obtained. **^{1}HNMR:** 7.38(d,1H), 7.08-7.13(m, 1H), 6.99-7.05(m, 1H), 7.59(d, 1H), 7.30(d, 1H), 2.92 3.00(dd, 1H), 3.34-3.39(m, 1H), 3.62(br, 1H), 1.71-2.07(m, 2H), 1.71-2.07(m, 2H), 3.073.10(br, 1H), 3.62(br, 1H), 2.87(s, 2.87), 9.58(br, 1H), 11.00(s, 1H).**^{13}CNMR:** 136.15, 111.5(CH), 121.16(CH), 118.51, 118.21 (CH), 126.71, 123.84 (CH), 108.91, **IR (KBr):** 3241, 3041, 2752, 1667, 1616, 1578, 1547, 1457, 1426, 13266, 1339, 1242, 1007, 918, 898, 846, 821, 767, 746, 683. **MS:** m/z 215

Preparation of (E)-3-((1-methylpyrrolidin-2-yl) methyl)-5-(2-(phenylsulfonyl) vinyl)-1H-indole (9). To a mixture of methanol(60 mL) and (R)-1-Acetyl-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole (10 g) was added potassium carbonate (1.2 g) in one lot at ambient temperature and stirred for about 120 min monitored reaction by TLC complies and the methanol was distilled out completely u/v at 45°C the title compound (**9**)obtained. **^{1}HNMR:** 7.34(d, 1H), 7.45-7.49(dd, 1H), 7.62-7.77(m, 1H), 7.2(d, 1H), 2.07-2.15(q, 1H), 2.48-2.55(m, 1H), 3.01-3.07(dd, 1H), 1.43-1.71(m, 2H),), 1.43-1.71(m, 2H), 2.35-2.39(m, 1H), 2.93-2.99(m, 1H), 2.35(s, 3H), 7.39(d, 1H), 7.62-7.77(m, 1H), 7.92-7.94(m, 2H), 11.10(br, 1H). **^{13}CNMR:** **137.68,111.96(CH),121.87(CH),122.77,121.12(CH),127.86, 124.38 (CH), 113.69, 28.97, 66.03 (CH), 30.78(CH_2), 21.55 (CH_2), 56.88 (CH_2), 40.46 (CH_3), 144.53 (CH), 141.66, 126.85 (CH), 129.47 (CH), 137.68 (CH). IR (KBr):** 3558, 3389, 3227, 3045, 2952, 2849, 2790, 1597, 1580, 1446, 1359, 1333, 1288, 1178, 1141, 1083, 854, 801, 752, 733, 687. **MS:** m/z 383, 381

Preparation of 5, 5'-(1, 4-bis (phenylsulfonyl) butane-2, 3-diyl) bis (3-((1-methylpyrrolidin-2-yl) methyl)-1H-indole) (10). To a mixture of (E)-3-((1-methylpyrrolidin-2-yl) methyl)-5-(2-(phenylsulfonyl) vinyl)-1H-indole (**3**) (5 g) and acetone (50 mL) was added Pd/C (10 gm) purge hydrogen gas pressure of 5 kg/cm^2 at 45°C about 48 hours monitored by TLC then filtered reaction mass and distilled solvent under vacuum the crude product separated by column chromatography eluted with ethyl acetate and methanol ratio of (9:1), then distilled under vacuum the title compound (**10**)obtained. **^{1}HNMR:** 7.05-7.25(m, 2H), 6.83(d, 1H),7.05-7.25(m, 1H), 7.35-7.57(m, 2H),7.05-7.25(m, 2H), 2.88-2.96(m, 4H), 2.28-2.47(m, 2H), 1.40-1.59(m, 4H), 1.40-1.59(m, 4H), 2.06-2.11(m, 2H), 2.88 2.96(m, 2H), 2.28-2.47(m, 6H), 4.03-4.16(m, 2H), 4.66-4.71(m, 1H), 4.03-4.16(m, 1H), 3.61-3.64(m, 2H) 8.00(d, 2H), 7.70-7.76(m, 2H), 7.35-7.57(m, 2H), 7.70-7.76(m, 2H), 7.35-7.57(m, 1H), 7.70-7.76(m, 1H), 10.74-10.81(br, 2H)**. IR(KBr):**3384,3060,2926,2852,2786,1626,1586,1479,1447,1304,1149,1085,1044,888,800,740,688,637**. MS:** m/z 763

CONCLUSION

In summary, we have developed a method for preparation of eletriptan hydrobromide and to control the impurities, these impurities were synthesized, evaluated and characterized by NMR, IR and Mass spectrographic techniques.

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