Indian Journal of Chemistry
Vol. 62, November 2023, pp. 1201-1207
DOI: 10.56042/ijc.v62i11.5015

A highly efficient route for synthesis of N-hydroxymethyl sumatriptan and sumatriptan dimer: Impurity C and H of anti-migraine drug sumatriptan

M R Suryawanshi*[a], R A Rane*[a], G V Babhulkar[a], P D Khobragade[a], S R Moharir[a], S A Chindhe[b] & D K Pawar[b]

[a] Department of Pharmaceutical Chemistry, BVDU Poona College of Pharmacy, Erandwane, Pune 411 038, India

[b] Chemicea Pharmaceutical Pvt Ltd, MIDC Taloja, Navi Mumbai 410 208, India

E-mail: mugdha.rs@gmail.com, rajeshrane.uict@gmail.com

Received 21 July 2023; accepted (revised) 25 October 2023

This research work describes a highly efficient route for the synthesis and characterization of the two potential sumatriptan impurities, N-hydroxymethyl sumatriptan (Impurity C) and sumatriptan dimer (Impurity H). The purity of the synthesized impurities have been confirmed using HPLC, and their structures have been identified by using MS and ^{1}H NMR spectroscopy.

Keywords: Impurities, HPLC, NMR, Migraine

Migraine is a long-lasting neurologic condition characterized by recurring bouts of nausea, discomfort, photophobia, and phonophobia, all of which can be incapacitating. It is a predominant condition that may have a remarkable impact on a patient's quality of life and ability to operate daily. The first of the triptans, sumatriptan, was approved for use in Europe in 1991 to treat migraines. Sumatriptan was approved by the FDA on December 28, 1992. It is a 5-HT receptor (type's 5-HT_{1D} and 5-HT_{1B}) agonist that selectively binds to and activates serotonin receptors in the central nervous system[1,2]. Narrowing blood vessels in the head, stopping pain signals from being sent to the brain, and blocking the release of certain natural substances that cause pain, nausea, and other migraine symptoms[3]. This might help to alleviate the pain of vascular headaches. The process for the preparation of sumatriptan described for the first time by Glaxo in the GB patent no 2162522 in 1989, is based on a Fischer indole synthesis. Impurities impacting the safety, effectiveness, and quality of pharmaceutical goods are causing increasing concern among regulatory bodies and the pharmaceutical industry. Impurities present in a drug substance in quantities beyond a particular limit must be described, recognized, and assessed both qualitatively and quantitatively, according to the Quality and Safety of The International Conference on Harmonization 2003. As per the International Conference on Harmonization (ICH) guidelines, any impurities contained in Active Pharmaceutical Ingredient should be identified and characterized at a concentration of less than 0.10% (Ref. 4).

The reported impurities (Fig. 1) in the European Pharmacopoeia are sumatriptan impurity A, sumatriptan impurity B , sumatriptan impurity C, sumatriptan impurity D, sumatriptan impurity E, sumatriptan nitroso impurity, sumatriptan dimer impurity, sumatriptan impurity H.

All of these impurities have a noteworthy influence on the quality of the therapeutic product. The synthetic route for the impurities C and H has not been reported yet; here we report the manufacturing process and establishment for these two impurities, as impurity reference substance of sumatriptan drug to control the quality of the impurity before the manufacturing process.

Experimental Section

Chemistry

All the chemicals used were procured from commercial sources such as Sigma-Aldrich, Merck and Loba Chemie and were purified prior to use. The melting points of synthesized compounds were taken on veego VMP-D digital melting point apparatus by open capillary. The reaction completion was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel F254 plates. TLC plates were visualized using iodine in a chamber or observed under UV light. Fourier transform infrared (FT-IR)

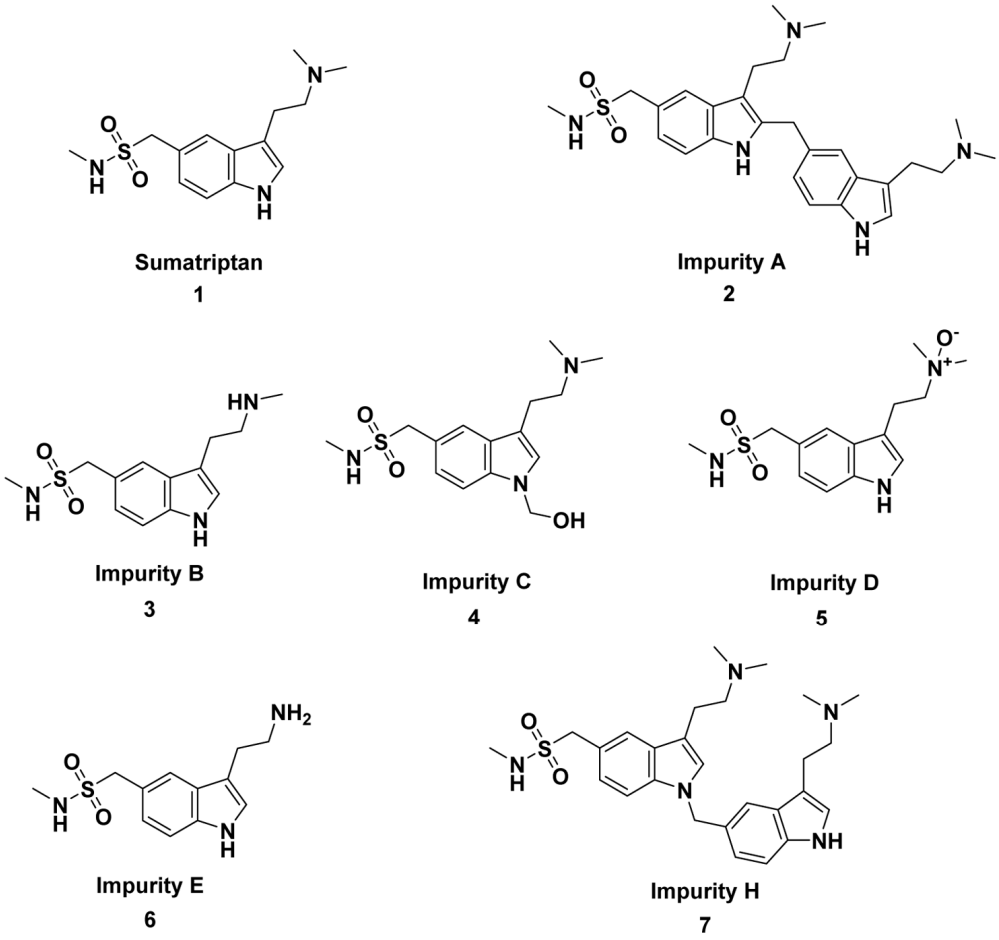


Fig. 1 — Impurities of sumatriptan

spectra were recorded in anhydrous potassium bromide (KBr) disk on Jasco FTIR 4100 and are reported in cm^{-1}. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in DMSO-d_6 using Bruker Avance (400 MHz) with Tetra Methylsilane (TMS) as an internal standard.

Synthesis of 1-azido-4-methylbenzene, 9

The solution of *p*-toluidine, **8** (5.0g, 46.6 mmol) in H_2SO_4 (20 mL) and water (30 mL) was taken in two necks round bottom flask. The reaction flask was cooled to 0 to –5°C, followed by slow addition of $NaNO_2$ (4.2g, 60.87 mmol) in water (30 mL), the reaction mixture was stirred at –5°C for 2 hr. Then slowly NaN_3 (8.2g, 0.12 mmol) was added, then the mixture was stirred for 60 minutes at –5°C. The progress of the reaction was checked by TLC. 100 mL water was added to the reaction mixture and extracted with ethyl acetate (2×100 mL), the obtained organic layer was dried over anhydrous Na_2SO_4. The solvent was then concentrated to get pure pale-yellow liquid as a compound **9** (Product yield 5.03 g, 81%) [1]. The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.71). m.p.127-128°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (3H, s), 7.38-7.40 (4H, d, J = 8.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 21.3 (1C, s), 122.2 (2C, s), 129.6 (2C, s), 136.7 (1C, s), 141.5 (1C, s); HRMS: *m/z* Calcd for **9** $C_7H_7N_3$ [M+H]: 134.0640. Found: 134.1540.

Synthesis of 1-azido-4-(bromomethyl)benzene, 10

Compound **9** (3g, 22.3 mmol) was dissolved in Dichloromethane (50 mL) and mixed well, Bromine, Br_2 (4.9g, 30.8 mmol) was slowly added to the reaction mixture and then Azobisisobutyronitrile, AIBN (280 mg, 1.7 mmol) was added with constant stirring. The reaction mixture was then refluxed for 6 hrs under an inert atmosphere. The growth of the reaction was observed by TLC. After completing the

reaction, the reaction mixture was cooled to lab temperature and filtered, the excess solvent was evaporated to get crude compound. The crude compound was purified by column chromatography (silica gel 60-120) using hexane to get brown color liquid as a compound **10** (Product yield 4.96 g, 62.30%)[5]. The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.66). m.p.137-139°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.31 (2H, s), 7.41-7.44 (4H, d, J = 8.3 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 21.3 (1C, s), 122.2 (2C, s), 129.6 (2C, s), 136.7 (1C, s), 141.5 (1C, s); HRMS: *m/z* Calcd for **10** $C_7H_6BrN_3$ [M+H]: 213.9745. Found: 213.0500.

Synthesis of 1-(3-(2-(dimethylamino)ethyl)-1*H*-indol-5-yl)-N-((2-methoxyethoxy)methyl)-Nmethylmethanesulfonamide, 11

Compound **15** (9g, 30.49 mmol) was dissolved in THF (80 mL) with continuous stirring. The reaction mixture was cooled to –10°C, and then NaH (0.9 g, 37.51 mmol) was added and stirred at 0°C for 20 minutes. Further the compound 1-(chloromethoxy)-2-methoxyethane (3.84 mL, 67.79 mmol) was added in THF solution at 0°C dropwise with continuous stirring at 0°C for 2 hours. The reaction was watched by using TLC. After completing the reaction, crushed ice (500 g) was used to quench the reaction mixture. After which the reaction mixture was extracted with ethyl acetate (3×250 mL), the combined organic layer was dried over anhyd. Na_2SO_4, evaporate the solvent under reduced pressure to get a crude compound. The crude mass was purified by column chromatography (100-200 silica gel) with 3% MeOH/DCM, to obtain pure off-white liquid (oily) as a compound **11** (Product yield 11.85 g, 65.50%). The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.78). m.p.174-176°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (6H, s), 2.67 (2H, t, J = 6.8 Hz), 2.79 (2H, t, J = 6.8 Hz), 3.08 (3H, s), 3.21 (3H, s), 3.61-3.72 (4H, t, J = 5.8 Hz), 4.53 (2H, s), 4.97 (2H, s), 6.80 (1H, d, J = 6.9 Hz), 7.09-7.10 (2H, d, J = 8.1 Hz), 7.34 (1H, t, J = 0.5 Hz) 10.71 (1H, s); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.9 (1C, s), 37.7 (1C, s), 45.0 (2C, s), 58.7-58.8 (2C, 58.7 (s), 58.8 (s)), 60.2 (1C, s), 69.8 (1C, s), 71.7-71.8 (2C, 71.7 (s), 71.7 (s)), 111.4 (1C, s), 112.7 (1C, s), 123.2 (1C, s), 123.6 (1C, s), 124.2 (1C, s), 126.8 (1C, s), 127.3 (1C, s), 136.4 (1C, s); HRMS: *m/z* Calcd for **11** $C_{18}H_{29}N_3O_4S$ [M+H]: 384.1961. Found: 384.5051.

Synthesis of 1-(1-(4-azidobenzyl)-3-(2-(dimethylamino) ethyl)-1*H*-indol-5-yl)-N-((2-methoxyethoxy)methyl)-N-methylmethanesulfonamide, 12

Compound **11** (4 g, 10.41 mmol) was dissolved in THF (110 mL) with continuous stirring in a two neck RB flask. The reaction mixture was then cooled to –10°C and addition of NaH (300 mg, 12.56 mmol) was done at –10°C and was stirred for 20 minutes. The progress of the reaction mass was observed by TLC. After completing reaction, the reaction mass was quenched with ice (500g), extracted with ethyl acetate (3×400 mL), the combined organic layer was washed with water followed by brine solution and dried over anhyd. Na_2SO_4 and remove the solvent was under reduced pressure to get crude compound. The above crude material was purified with 100-200 silica gel with 2% MeOH/DCM, to get pure off-white oily compound **12** (Product yield 4.03 g, 60.20%). The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.71). m.p.177-178°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (6H, s), 2.69 (2H, t, J = 6.8 Hz), 2.86 (2H, t, J = 6.8 Hz), 3.08 (3H, s), 3.21 (3H, s), 3.61-3.72 (4H, t, J = 5.8 Hz), 4.50 (2H, s), 4.97 (2H, s), 5.18 (2H, s), 6.99-7.04 (2H, d, J = 8.0 Hz), 7.21 (1H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.2 Hz), 7.65-7.70 (3H, d, J = 1.6 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.9 (1C, s), 37.7 (1C, s), 45.0 (2C, s), 50.0 (1C, s), 58.7-58.8 (2C, 58.7 (s), 58.8 (s)), 60.2 (1C, s), 66.2 (1C, s), 70.7 (1C, s), 71.7 (1C, s), 109.3 (1C, s), 118.0 (1C, s), 122.0 (1C, s), 122.2 (2C, s), 123.6 (1C, s), 124.2 (1C, s), 126.8 (1C, s), 127.3 (1C, s), 129.4 (2C, s), 136.5-136.8 (3C, 136.6 (s), 136.7 (s), 136.7 (s); HRMS: *m/z* Calcd for **12** $C_{25}H_{34}N_6O_4S$ [M+H]: 515.2362. Found: 515.6450.

Synthesis of 1-(1-(4-azidobenzyl)-3-(2-(dimethylamino) ethyl)-1*H*-indol-5-yl)-N-methylmethanesulfonamide, 13

Compound **12** (3 g, 0.582 mmol) was cooled to –20°C. Further, addition of pre-cooled 5N HCL was carried out with continuous stirring at –20°C for 3 hr., the reaction was monitored using TLC. After completion of the reaction, the reaction mass was quenched with ice (250g), extracted with 3% MeOH and DCM (3×500 mL), the combined organic layer was washed with water, brine solution, and dried over anhyd. Na_2SO_4, remove the solvent by reduced pressure to get crude material. The above crude material was purified by column chromatography

(100-200 silica gel) with 5% MeOH + DCM, to get pure oily compound **13** (Product yield 3.25 g, 98%). The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.67). m.p.197-199°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (6H, s), 2.69 (2H, t, J = 6.8 Hz), 2.86 (2H, t, J = 6.8 Hz), 2.95 (3H, s), 4.52 (2H, s), 5.18 (2H, s), 6.99-7.04 (2H, d, J = 8.0 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.34 (1H, s), 7.43 (2H, d, J = 8.2 Hz), 7.65-7.69 (3H, d, J = 8.2 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.9 (1C, s), 29.2 (1C, s), 45.0 (2C, s), 50.0 (1C, s), 58.9 (1C, s), 60.2 (1C, s), 109.3 (1C, s), 118.0 (1C, s), 122.0 (1C, s), 122.2 (2C, s), 123.6 (1C, s), 124.2 (1C, s), 126.8 (1C, s), 127.3 (1C, s), 129.4 (2C, s), 136.5-136.8 (3C, 136.6 (s), 136.7 (s), 136.7 (s)); HRMS: *m/z* Calcd for **13** $C_{21}H_{26}N_6O_2S$ [M+H]: 426.1838. Found: 426.5390.

Synthesis of 1-(1-(4-aminobenzyl)-3-(2-(dimethylamino) ethyl)-1*H*-indol-5-yl)-N-methylmethanesulfonamide, 14

Compound **13** (3 g, 0.703 mmol) was dissolved in dioxane/methanol/water (30 mL) with vigorous stirring, further HCL (1.75 g, 48.01 mmol) and Sn Powder (1.43 g, 12.04 mmol) was added to the reaction mixture with continuous stirring and was subjected to reflux for 6 hr. Reaction growth was observed using TLC. After completion of the reaction, the reaction mixture was filtered and thoroughly washed with 3% MeOH and DCM, after which 100 mL of water was added to the filtrate. The organic layer was separated using a separating funnel and was dried over anhyd. Na_2SO_4 and the excess solvent was evaporated under vacuum to get pure semisolid compound **14** (Product yield 3.53 g, 94%) [6]. The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.66). m.p.193-195°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (6H, s), 2.69 (2H, t, J = 6.8 Hz), 2.86 (2H, t, J = 6.8 Hz), 2.95 (3H, s), 4.52 (2H, s), 4.91 (2H, s), 5.11 (2H, s), 6.69 (2H, d, J = 8.2 Hz), 6.85 (2H, d, J = 6.8 Hz), 6.99 (1H, d, J = 8.2 Hz), 7.04 (1H, t, J = 0.5 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.33 (1H, s), 7.69 (1H, d, J = 1.6 Hz); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.9 (1C, s), 29.2 (1C, s), 45.0 (2C, s), 50.0 (1C, s), 58.9 (1C, s), 60.2 (1C, s), 109.3 (1C, s), 114.3 (2C, s), 118.0 (1C, s), 122.0 (1C, s), 123.6 (1C, s), 124.2 (1C, s), 126.8 (1C, s), 127.3 (1C, s), 129.4 (2C, s), 136.6 (1C, s), 136.7 (1C, s), 148.4 (1C, s); HRMS: *m/z* Calcd for **14** $C_{21}H_{28}N_4O_2S$ [M+H]: 401.1933. Found: 401.5410.

Synthesis of 1-(3-(2-(dimethylamino)ethyl)-1-((3-(2-(dimethylamino)ethyl)-1*H*-indol-5-yl)methyl)-1*H*-indol-5-yl)-N-methylmethanesulfonamide, 7

Compound **14** (3 g, 7.47 mmol) was dissolved in 50 mL water with continuous stirring, H_2SO_4 (40 mL) was added to the reaction mixture, further it cooled to –20°C and a slow addition of $NaNO_2$ (869.4 mg, 12.6 mmol) in water (10 mL) with vigorous stirring of the reaction mixture at –20°C for 6 hrs was carried out. Then drop-wise addition of $SnCl_2$ (9.04 g, 40 mmol) in water over a period of 20 minutes was done. The reaction was stirred at the same temperature for 30 minutes, and then the temperature was slowly rise to 0°C and stirred for 2 hr. The progress of the reaction was monitored by TLC. After completion of the conversion to get compound 1-(3-(2-(dimethylamino) ethyl)-1-(4-hydrazineylbenzyl)-1H-indol-5-yl)-N-methylmethane sulfonamide hydrochloride, then adjust the *p*H 1.7 to 1.9 using 50% NaOH solution, then added 5,5-dimethoxy-N,N-dimethylpentan-1-amine (2.16 g, 12 mmol), then heated to 130°C for 10 hr. The progress of the reaction was monitored by TLC, after completion of reaction to get compound **7**, compound (E)-1-(1-(4-(2-(4-(dimethylamino)butylidene) hydrazineyl)benzyl)-3-(2 (dimethylamino)ethyl)-1H-indol-5-yl)-N-methylmethanesulfonamide was heated to 110°C for 6 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction for in MeOH (40 mL) in 250 mL RB flask then Pd/Cl (2.4g) was added, the reaction was monitored by TLC. Then reaction mixture was cooled to 0°C, and was basified (*p*H = 10-11) using aq. Ammonia. The reaction mixture was further extracted with 3% MeOH in DCM (3×250 mL), the obtained organic layers were combined and was washed with water, brine solution and dried over anhyd. Na_2SO_4. The excess solvent was evaporated through reduced pressure to get crude material. The above crude compound was purified by column chromatography (100-200 silica gels) with 6% MeOH in DCM with 5 mL ammonia solution. To get a pure pale yellow solid compound as **7** (Product yield: 4.60 g, 74.30%). The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.78). m.p.204-207°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.19-2.21 (12H, s), 2.52-2.54 (8H, t, J = 6.8 Hz), 2.74-2.82 (4H, t, J = 6.8 Hz), 4.33 (2H, s), 5.37 (2H, s), 6.76-6.77 (1H, d, J = 8.0 Hz), 6.95-6.97 (1H, d, J = 8.0 Hz), 7.01-7.12 (2H, t, J = 8.2 Hz), 7.22-7.24 (1H, d, J = 8.0 Hz), 7.32 (1H, s), 7.46-7.50 (3H, d,

Table 1 — HPLC data for sumatriptan impurity H

Peak	Retention time (min)	Height a.u.	Area a.u. (min)	Area (%)
1	7.316	176170	8405	0.923
2	9.724	18908148	1002575	99.077
Total		19084318	1010980	100.000

Table 2 — HPLC data for sumatriptan impurity C

Peak	Retention time (min)	Area a.u. (min)	Height a.u.	Area (%)
1	9.665	16062	2146	0.076
2	10.228	20988741	1153215	99.924
Total		21004803	1155361	100.00

J = 1.6 Hz), 10.74 (1H, s); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.8-22.9 (2C, 22.9 (s), 22.9 (s)), 29.2 (1C, s), 45.0-45.0 (4C, 45.0 (s), 45.0 (s)), 50.0 (1C, s), 58.9 (1C, s), 60.2-60.3 (2C, 60.2 (s), 60.2 (s)), 109.3 (1C, s), 111.4 (1C, s), 112.7 (1C, s), 118.0 (1C, s), 122.0 (1C, s), 123.2 (1C, s), 123.6 (1C, s), 124.2 (1C, s), 126.8 (1C, s), 127.3-127.3 (2C, 127.3 (s), 127.3 (s)), 127.4 (1C, s), 129.4 (1C, s), 136.4 (1C, s), 136.7 (1C, s), 138.3 (1C, s); HRMS: *m/z* Calcd for **7** $C_{27}H_{37}N_5O_2S$ [M+H]: 496.2668. Found: 496.10 HPLC purity: 99.077% (Table 1).

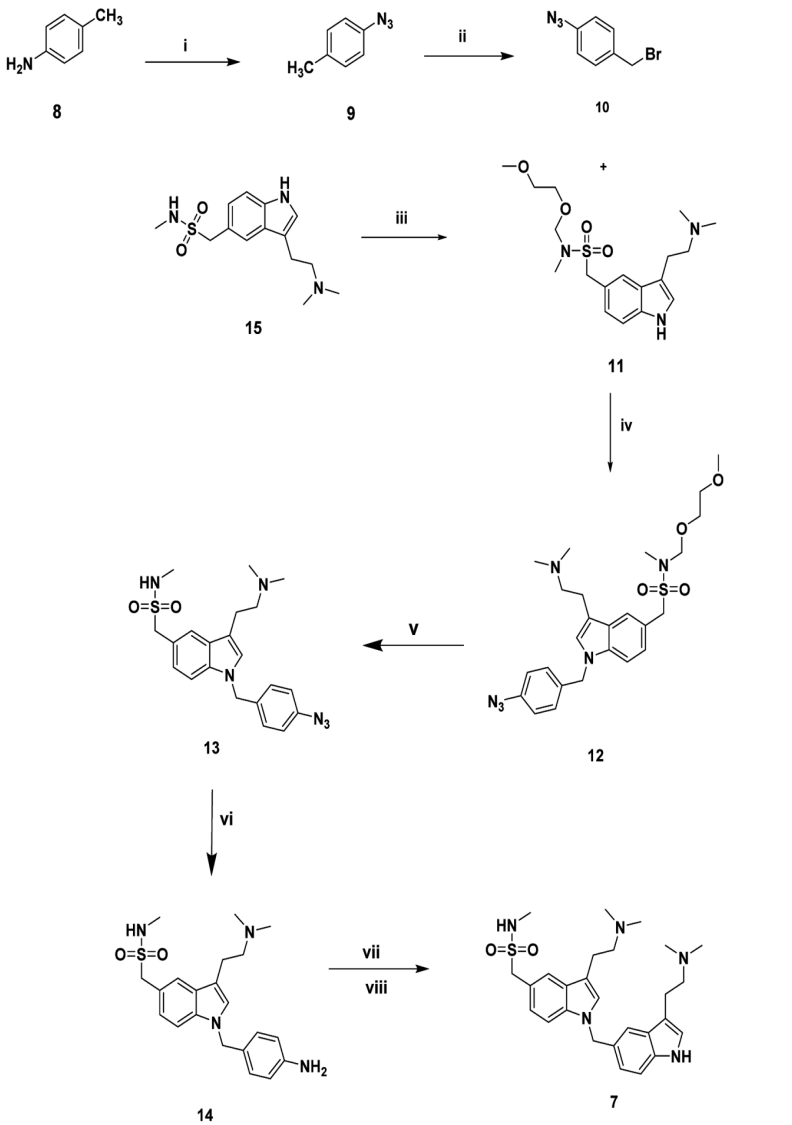
Synthesis of 1-(3-(2-(dimethylamino)ethyl)-1-(hydroxymethyl)-1*H*-indol-5-yl)-N-methylmethanesulfonamide, 4

Compound **15** (7g, 23.0 mmol) was dissolved in 50 mL methanol with continuous stirring and solution of $NaBH_4$ in H_2O (2.23g in 30 mL water) was prepared and added in the reaction mixture. Further addition of 45% HCHO solution (30 mL) in methanol (18 mL) at –5°C. Then reaction mixture was vigorously stirred at lab temperature for 16 hrs. The reaction was observed by TLC. 500 mg of activated charcoal was added and the solution was stirred for 10 min. The solution was then filtered with whatman filter paper and further ethyl acetate was used to extract the product, the obtained organic layer was dried over anhyd. Na_2SO_4,the resulting solution was then concentrated under reduced pressure to get product **4**. Purified by column chromatography using 6% MeOH/DCM (Product yield 6.29 g, 78.72%). The reaction was monitored by TLC, silica gel; petroleum hexane: ethyl acetate = 9:1 V/V (R_f 0.78). m.p.177-178°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (6H, s), 2.47-2.53 (4H, t, J = 6.8 Hz), 2.78-2.81 (3H, s), 4.37 (2H, s), 5.43-5.45 (2H, s), 6.31-6.34 (1H, s), 6.79-6.81 (1H, t, J = 8.0 Hz), 7.13-7.15 (1H, d, J = 8.0), 7.23 (1H, s), 7.47 (1H, d, J = 1.8 Hz), 7.52 (1H, s); ^{13}C NMR (400 MHz, DMSO-d_6): δ 22.9 (1C, s), 29.2 (1C, s), 45.0 (2C, s), 58.9 (1C, s), 60.2 (1C, s), 65.3 (1C, s), 109.3 (1C, s), 118.0 (1C, s), 123.6 (1C, s), 124.2 (1C, s), 125.1 (1C, s), 126.8 (1C, s), 127.3 (1C, s), 135.2 (1C, s); HRMS: *m/z* Calcd for **4** $C_{15}H_{23}N_3O_3S$ [M+H]: 326.1460. Found: 326.30. HPLC purity: 99.924% (Table 2).

Results and Discussion

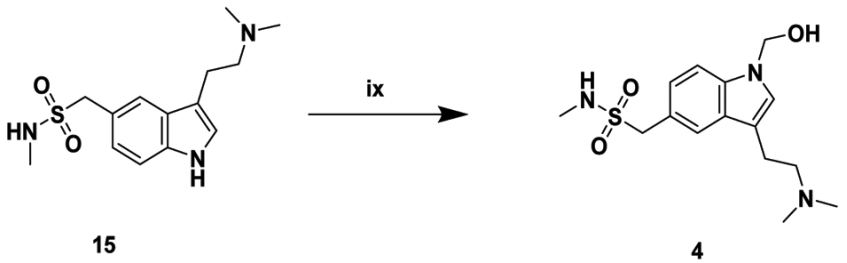
The preparation method for the Antimigraine drug sumatriptan was reported by Chen Y *et al*. *via* the Fischer indole synthesis method in 2008. The preparation of sumatriptan impurity H involves, firstly the synthesis of compound **10** and compound **11**. The toluidine **8** when react with sodium nitrite in sulphuric acid and then sodium azide was added to form 4-azidotoluene as **9**, which on treated with bromine and Azobisisobutyronitrile in dicloromethane to get compound **10**. Compound **11** was formed due to a reaction between the compound **15** with 1-(chloromethoxy)-2-methoxyethane in the presence of sodium hydride and dichloromethane. The coupling occurs between **10** and **11** to form a product **12**. Then **12** was acidified with hydrochloric acid at –20°C to get compound **13**, which on treated with hydrochloric acid in Sn to form a compound **14**. Then **14** were treated with sodium nitrite in sulphuric acid and stannous chloride, form intermediate product. Then refluxing for 10 hrs at 130°C to get finale compound **7** *i.e*. Impurity H (Scheme 1).

The synthesis of sumatriptan impurity C **4** involves the following steps; When Compound **15** was reacted with methanol in formaldehyde followed by reduction with sodium borohydride to get the final product **4** as sumatriptan impurity C (Scheme 2).



Reaction conditions: (i) $NANO_2/H_2SO_4$, NaN_3, 0 to –5°C; (ii) Br_2/AIBN, DCM; (iii) NaH/THF, 1-(chloromethoxy)-2 methoxyethane; (iv) NaH/THF, –10°C; (v) 5N HCl, –20°C; (vi) Sn/HCl; (vii) $NaNO_2/H_2SO_4$, $SnCl_2$; (viii) 130°C/10 h

Scheme 1 — Synthesis of sumatriptan impurity H



Reaction conditions: (ix) 35% HCHO, $NaBH_4$/MeOH/RT/16 h

Scheme 2 — Synthesis of sumatriptan impurity C

Conclusion

We have successfully synthesized and characterized the two impurities N-Hydroxymethyl sumatriptan (Impurity C) and sumatriptan dimer (Impurity H) of sumatriptan drug. This study helps to get easy and high-yielding accessibility to these key impurities which can strongly help to improve the quality of final sumatriptan drug products.

Acknowledgement

The authors acknowledge Dr. A. P. Pawar, Principal, Poona College of Pharmacy for his support and encouragement.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776

References

1 Awolade P, Cele N, Kerru N, Gummidi L, Oluwakemi E & Singh P, *Eur J Med Chem,* 187 (2020) 111921. DOI: 10.1016/j.ejmech.2019.111921

2 Chheda J N, Huber G W & Dumesic J A, *Angew Chemie Int Ed*, 46 (2007) 7164. DOI: 10.1002/anie.200604274

3 Dechant K L & Clissold S P, *Drugs,* 43 (1992) 776-98. DOI: 10.2165/00003495-199243050-00010.

4 Jakate A, Boinpally R, Butler M, Lu K, McGeeney D & Periclou A, *Headache: J Head and Face Pain,* 60 (2020) 1340-1350. DOI: 10.1111/head.14095

5 Mojzych, M.. *Molbank*, 2005 (1), M 404 https://doi.org/10.3390/M404.

6 Pietrobon D & Moskowitz M A, *Pathophysiology of Migraine*, 75 (2013) 365. https://doi.org/10.1146/annurev-physiol-030212-183717.