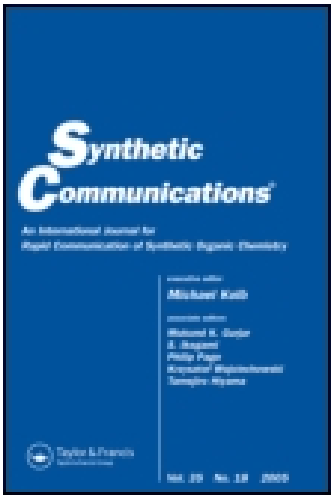

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Synthesis and Characterization of Potential Impurities of the Antimigraine Drug, Rizatriptan Benzoate

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Abstract: Rizatriptan benzoate is a recently developed antimigraine drug used for the treatment of migraines and severe headaches. In the synthesis of rizatriptan benzoate in bulk,various impurities are formed. The present work details the development of a simple and novel process for the preparation of hydrazone impurity (**6**), rizatriptan N-oxide (**7**), rizatriptan dimer (**9**), desmethyl rizatriptan (**13**), 5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine hydrochloride (**14**), N-methyl rizatriptan oxalate (**15**), and impurities.

Keywords: impurities, maxalt, migraines, rizatriptan benzoate, serotonin agonist

INTRODUCTION

Rizatriptan benzoate is described chemically as N,N-dimethyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine monobenzoate **(1).** It is used

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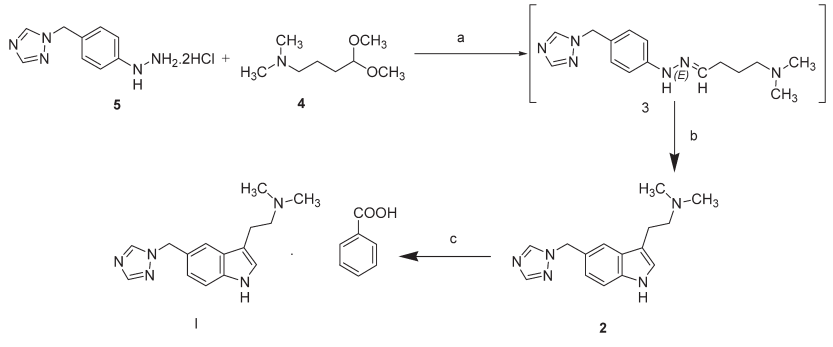
in the treatment of migraines.[1–4] Rizatriptan benzoate binds to serotonin receptors in the brain, which causes the blood vessels to narrow. By decreasing the width of blood vessels in the brain, rizatirptan relieves the pain. Rizatriptan is available as an orally disintegrating tablet with a brand name Maxalt.

The literature survey revealed various synthetic methods for rizatriptan benzoate.[5–9] It was synthesized according to the Scheme 1, with slight modifications to make it simpler and commercially viable. Reaction of 1-(4-hydrazino phenyl) methyl-1,2,4-triazole dihydrochloride **5** with 4-N,N-dimethyl amino butanal dimethyl acetal **4** in presence of 4–5% hydrochloric acid gave **3,** which undergoes cylization under reflux conditions to afford rizatriptan base **2.** Addition of benzoic acid to the base **2** gave the title compound N,N-dimethyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanaminemono benzoate **(1)**.

During the analysis of laboratory batches of rizatriptan benzoate, six impurities were detected by high performance liquid chromatography (HPLC). A literature survey revealed that the HPLC method was described for rizatriptan benzoate along with three impurities.[10] The study did not mention the synthesis and characterization of impurities. The presence of impurities in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug. Therefore, it is necessary to study the impurity profile of the API to be used in the manufacturing of a drug product. International Conference on Harmonization (ICH) guidelines recommend identifying and characterizing all impurities that are present at a level of 0.10% or more.[11,12] This became essential in the wake of stringent purity requirements from regulatory authorities. In this context, a comprehensive study was undertaken to synthesize and characterize all six impurities: hydrazone impurity (**6**),



Scheme 1. Synthesis of Rizatriptan benzoate (**1**). Reagents and conditions: (a) 4–5% HCl solution, 0 °C, 1 hr. (b) 4–5% HCl solution, reflux, 2 h, 40%. (c) Benzoic acid, isopropanol, rt, 1 h, 80%.

rizatriptan N-oxide (**7**), rizatriptan dimer (**9**), desmethyl rizatriptan (**13**), 5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine hydrochloride (**14**), and N-methyl rizatriptan oxalate (**15**) by spectroscopic and spectrometric techniques. Results are presented in this article.

DISCUSSIONS

In this article, we herewith disclose our work regarding the synthesis and characterization of the various potential impurities of rizatriptan benzoate.

1-(4-(2-(4-(Dimethylamino)butylidene)-hydrazino)phenyl)-methyl-1,2,4-triazole (6)

Preparation of 1-(4-(2-(4-(dimethyl amino) butylidene)-hydrazino)phenyl)-methyl-1,2,4-triazole (**6**) involves condensation of 1-(4-hydrazinophenyl)-methyl-1,2,4-triazole dihydrochloride **5** with 4-N,N-dimethylamino butanal dimethyl acetal **4** in the presence of aqueous HCl as an acid catalyst. This was an insitu intermediate in the synthesis of rizatriptan benzoate. The protonated molecular ion of **6** appeared as the base peak at 287.4 in mass spectrum. The presence of NH stretching (3430 cm^{-1}), aromatic C-H stretching (3033 cm^{-1}), aliphatic C-H stretching (2945, 2863 cm^{-1}), and C═N stretching (1613 cm^{-1}) was evident in the infrared spectrum. In the ^1H NMR spectrum, NH appeared as a singlet at 7.0δ, which disappeared on D_2O exchange. The N-CH_3 protons appeared as a singlet at 2.34 δ, and the benzylic methyl protons attached to 1,2,4-triazole appeared as a sixnglet at 5.66 δ.

N,N-Dimethyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine N-Oxide (7)

This N-oxide impurity was formed by the air oxidation of rizatriptan base during the process. rizatriptan base **2** on treatment with meta-chloroperbenzoic acid (*m*-CPBA) in dichloromethane smoothly afforded rizatriptan N-oxide in quantitative yields. The protonated molecular ion of **7** appeared as the base peak at 286.2 in mass spectrum. The IR spectrum showed the presence of aromatic C-H stretching (3042 cm^{-1}), aliphatic C-H stretching (2946, 2924 cm^{-1}), and C═N stretching (1504 cm^{-1}). In the ^1H NMR spectrum dimethyl sulfoxide (DMSO), NH appeared as a singlet at 11.3 δ, which disappeared on D_2O exchange. The N-CH_3 protons appeared as a singlet at 2.34 δ. The benzylic methyl protons attached to 1,2,4-triazole appeared as a singlet at 5.5 δ.

[3-[2-(N,N-Dimethylamino)ethyl-2-[[3-[2-(N,N-dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]methyl-1H-1,2,4-triazolebenzoate (9)

This impurity was formed by the self-condensation of two molecules of rizatriptan base with the elimination of one triazole ring, catalyzed by acid during the formation of rizatriptan base. This was further converted into benzoate salt. Preparation of this impurity involves treating rizatriptan base with dilute hydrochloric acid under reflux conditions. The protonated molecular ion of **9** appeared as the base peak at 470.5 in the mass spectrum. IR spectrum showed the presence of NH stretching (3287 cm^{-1}), aliphatic C-H stretching (2957, 2924 cm^{-1}), and aromatic C═C and C═N stretching (1599,1571 cm^{-1}) respectively. In the ^1H NMR spectrum (DMSO), two singlets appeared at 10.9 δ and 10.7 δ, corresponding to two indole NH protons, which disappeared on D_2O exchange. Two sets of two benzylic protons appeared as singlets at 5.4 δ and 4.1δ respectively. Twelve protons of N-methyl appeared as a singlet at 2.3 δ.

N-Methyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine (13)

This impurity is formed during the Fisher indole cyclization of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride **5** with 4-N,N-dimethylamino butanal dimethyl acetal **4** in the presence of aqueous HCl under reflux conditions. Preparation of this impurity involves condensation of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride **5** with sodium salt of 4-chlorobutanal bisulfite adduct **10** to afford **11**, which undergoes immediate cyclization in the presence of polyphosphoric acid isopropyl ester, to give the chloro indole derivative **12**. This was further reacted with aqueous mono methylamine solution to give the title compound **13**. The protonated molecular ion of **13** appeared as the base peak at 256.5 in mass spectrum. IR spectrum (neat) showed the presence of NH stretching (3421 cm^{-1}), aromatic C-H stretching (3042 cm^{-1}), aliphatic C-H stretching (2946, 2924 cm^{-1}), -N-H bending (1595 cm^{-1}), and aromatic C-H bending (807, 743 cm^{-1}). In the ^1H NMR spectrum (DMSO), indole NH appeared as a singlet at 10.9 δ and des-methyl NH appeared broad at 3.8 δ, which disappeared on D_2O exchange. The N-CH_3 protons appeared as a doublet at 2.4 δ. The benzylic methyl protons attached to 1,2,4-triazole appeared as a singlet at 5.43 δ.

5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine Hydrochloride (14)

This impurity is formed during the synthesis of rizatriptan benzoate. Preparation of this impurity involves condensation of 1-(4-hydrazinophenyl)methyl-1,2,

4-triazole dihydrochloride **(3)** with sodium salt of 4-chloro butanal bisulfite adduct in the presence of aqueous isopropyl alcohol as a solvent medium and triethyl amine as a base under reflux conditions. The protonated molecular ion of **14** appeared as the base peak at 242 in mass spectrum. IR spectrum showed the presence of NH stretching (3400 cm^{-1}), aromatic C-H stretching (3033 cm^{-1}), aliphatic C-H stretching (2946, 2924 cm^{-1}), and aromatic C-H bending (820, 716 cm^{-1}). In the ^1H NMR spectrum (DMSO), indole NH appeared as a singlet at 11.1 δ, and free amine protons appeared as a broad singlet at 6.0 δ, which disappeared upon adding deuterium oxide. The benzylic methyl protons attached to 1,2,4-triazole appeared as a singlet at 5.43 δ.

N,N-Dimethyl-5-(1-methyl-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine Oxalate (15)

This impurity is formed during the Fisher indole cyclization of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride **(3)** with 4-N,N-dimethylamino butanal dimethyl acetal in the presence of aqueous HCl under reflux conditions. Preparation of this impurity involves N-methylation on a rizatriptan base with methyl iodide in presence of potassium ter-butoxide as a base in DMF. The protonated molecular ion of **15** appeared as the base peak at 284 in mass spectrum. IR spectrum showed the presence of aliphatic C-H stretching (3008, 2937 cm^{-1}); C═O (1639 cm^{-1}) corresponds to carboxylic acid. In the ^1H NMR spectrum (DMSO), indole N-CH_3 and six protons of tryptamine appeared as a mulitplet at 2.8 δ, and benzylic methyl protons attached to 1,2,4-triazole appeared as singlet at 5.4 δ.

CONCLUSIONS

Information on the different possible potential impurities and their synthetic routes is a prerequisite for better understanding the impurity formation pathway of the antimigraine drug rizatriptan benzoate. Keeping in view the regulatory importance of rizatriptan benzoate impurities, our efforts to synthesize and characterize them effectively prove to be valuable.

EXPERIMENTAL

Materials and Instruments

All solvents and reagents were purchased from the suppliers and used without further purification. The ^1H NMR spectra were recorded in DMSO-d_6 at 200 MHz on a Varian Gemini 200-MHz FT NMR

spectrometer. The chemical shifts were reported in parts per million (δ ppm) relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS.

1-(4-(2-(4-(Dimethylamino)butylidene)-Hydrazino)phenyl)-methyl-1,2,4-triazole (6)

To a mixture of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride **3** (20.0 g, 0.076 mol) and water (200.0 mL), concentrated hydrochloric acid solution (15.8 mL) was added slowly at 0–5°C and stirred for 30 min at 0–5°C. 4-N,N-Dimethyl aminobutanal dimethyl acetal **4** (14.7 g, 0.091 mol) was added to the reaction mixture at 0–5°C and stirred for 60 min for the reaction completion. Caustic lye (25.0 mL) was added slowly dropwise to the reaction mass up to pH 6.0–7.0. The product was extracted twice with ethyl acetate (60.0 mL). The organic phase was dried over sodium sulfate and evaporated under vacuum. The resultant solid was dried aerially to a constant weight to afford the title compound **6** (yield 15.0 g, 68.6%, purity by HPLC 97.6%).

IR (KBr, cm^{-1}): 3430 (N-H), 3033 (Ar-H), 2945, 2863 (Ali-H), 1613 (C=N). ^{1}H NMR (DMSO, δ ppm): 9.7 (s, 1H), 8.6 (s, 1H), 8.0 (s, 1H), 7.0–7.2 (m, 4H), 6.8 (d, 1H), 5.2 (s, 2H), 2.2 (m, 4H), 2.0 (s, 6H), 1.6 (m, 2H). Mass: 287.4 ($M^+ + 1$).

N,N-Dimethyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine N-Oxide (7)

A mixture of rizatriptan base **2** (17 g, 0.062 mol), dichloromethane (100.0 mL), and *meta*-chloro per benzoic acid (10.86 g, 0.062 mol) was stirred for 3–4 h for reaction completion. The mixture was placed in an ice-water bath, and a saturated solution of sodium sulfite (25.0 mL) was added. The reaction mixture was stirred at room temperature for 15 min. Starch/iodine paper test showed the absence of peroxide. The organic and aqueous layers were separated. The organic layer was concentrated under vacuum at 40°C to get the residue. The residue was chromatographed on silica gel eluting with CH_2Cl_2/methanol/NH_3 (30:8:1) to afford the title compound **7** (yield 10.0 g, 55.5%, purity by HPLC 97.0%).

IR (KBr, cm^{-1}): 3358 (N-H), 3042 (Ar-H), 2946, 2924 (Ali-H), 1504 (C=N). ^{1}H NMR (DMSO, δ ppm): 11.3 (s, 1H), 8.6 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 7.3 (d, 1H), 7.2 (s, 1H), 7.0 (d, 1H), 5.4 (s, 2H), 3.4 (m, 4H) 3.2 (d, 6H). Mass: 286.2 ($M^+ + 1$).

[3-[2-(N,N-Dimethylamino)ethyl-2-[[3-[2-(N,N-dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]methyl-1H-1,2,4-triazolebenzoate (9)

A solution of rizatriptan base **2** (67.0 g, 0.248 mol), water (670.0 mL), and HCl (88.0 mL) was added, and the reaction mixture was refluxed for 4 h. The pH of the aqueous layer was adjusted to 10–11 using caustic lye (60.0 mL). The product was extracted twice with ethyl acetate (200.0 mL) and dried over sodium sulfate. The organic layer was concentrated under vacuum at 40°C to get the residue. The residue was chromatographed on silica gel eluting with CH_2Cl_2/Methanol/NH_3 (30:8:1) to give it as a yellow oil (16.0 g, 13.7%). The benzoate salt was prepared by addition of a solution of benzoic acid (4.16 g, 0.034 mol) in acetone (10.0 mL) to a solution of the yellow oil (16.0 g, 0.034 mol) in acetone (10.0 mL). The precipitated solid was filtered, washed with acetone (5.0 mL), and dried to a constant weight at 40–50°C to yield dimer of rizatriptan benzoate **9** (yield 16.0 g, 79.3%, purity by HPLC 96.5%).

IR (KBr, cm^{-1}): 3287 (N-H), 2957, 2924 (Ali C-H), 1599, 1571 (Ar C═C, C═N), 725 (Ar C-H). ^{1}H NMR (DMSO, δ ppm): 10.9 (s, 1H, Ar N-H), 10.7 (s, 1H, Ar N-H), 8.6 (s, 1H Ar C-H), 8.0 (m, 5H, Ar C-H), 7.6 (m, 2H, Ar C-H), 7.5 (m, 3H, Ar C-H), 7.4 (m, 2H), 7.1 (s, 1H, Ar C-H), 6.9 (m, 2H, Ar C-H), 5.4 (s, 2H, Ali CH_2), 4.1 (s, 2H), 2.8 (m, 4H), 2.6 (m, 2H, CH_2), 2.3 (s, 12H, CH_3). Mass: 486 ($M^+ + 1$).

N-Methyl-5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine (15)

Stage 1

To a mixture of sodium bicarbonate (19.2 g) and water (100.0 mL), 1-(4-hydrazinophenyl) methyl-1,2,4-triazole dihydrochloride **3** (20.0 g, 0.076 mol) was added at room temperature. The reaction mass was cooled to 0–5°C, and sodium salt of 4-chloro butanal bisulfate adduct **10** (17.6 g, 0.839 mol) was added. The reaction mass was stirred for 60 min for the completion of the reaction. To the reaction mass, ethyl acetate (100.0 mL) was added and stirred for 15 min. The organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate (50.0 mL), combined with the total organic layer, dried over sodium sulfate, and evaporated under vacuum. The resultant solid was dried aerially to a constant weight to afford 1-(4-(2-(4-chlorobutylidene)-hydrazino)phenyl)-methyl-1,2,4-triazole 11 (yield 15.2 g, 71.7%). IR (KBr, cm^{-1}): 3430 (N-H), 3033 (Ar-H), 2945, 2863 (Ali-H), 1613 (C═C, C═N). Mass: 209 ($M^+ - 69$).

Stage 2

A mixture of 1-(4-(2-(4-chloro butylidene)-hydrazino)phenyl)-methyl-1,2,4-triazole **11** (10.0 g, 0.036 mol) and polyphosphoric isopropyl ester (40.0 g) in chloroform (100.0 mL) was added, heated to 55–60°C, and maintained for 6 h for reaction completion. The reaction mass was cooled to 25–35°C, and water (60.0 mL) was added. The organic and aqueous layers were separated. The Aqueous layer was extracted with chloroform (60.0 mL). Combined organic layers were washed twice with 5% sodium bicarbonate solution (60.0 mL) and evaporated. To the resultant residue **12,** methanol (100.0 mL) was added, followed by KI (7.5 g) and aqueous methylamine solution (50.0 mL). The reaction mass was heated to 50–60°C and maintained for 5 h until reaction completion. To the reaction mixture, water (50.0 mL) was added and extracted twice with ethyl acetate (50.0 mL). The total organic fractions were dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/Methanol/NH_3 (30:8:1) to afford the title compound **13** (yield 10.0 g, 55.5%, purity by HPLC 95.7%).

IR (KBr, cm^{-1}): 3421 (N-H), 3042 (Ar-H), 2946, 2924 (Ali-H), 1595.1 (-N^+-H, bending), 1433,1363 (Ali C-H bending), 807,743 (aromatic C-H bending). ^{1}H NMR (DMSO, δ ppm): 10.9 (s, 1H, Ar N-H), 8.60 (s, 1H) 7.95 (s, 1H) 7.55 (s, 1H), 7.30 (d, 1H), 7.18 (s, 1H) 7.03 (d, 1H), 5.43 (s, 2H), 3.8 (br-s, 1H), 2H (m, 2.86), 2H (m, 2.66), 2.4 (d, 3H, N-CH_3). Mass: 256.5 ($M^+ + 1$).

5-(1H-1,2,4-Triazol-1-yl-methyl)-1H-indole-3-ethanamine Hydrochloride (14)

To mixture of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride **3** (10.0 g, 0386 mol) and 50% aqueous isopropyl alcohol (100.0 mL), sodium salt of 4-chloro butanal bisulfate adduct **10** (12.0 g, 0.057 mol) was added. The pH of the reaction mass was adjusted to 3.5 with triethyl amine (12.0 mL). The reaction mass was heated to 75–80°C and maintained for 2 h for reaction completion. The reaction mass was cooled to 25–35°C and evaporated under reduced pressure at 50–60°C. The residue was dissolved in water (100.0 mL) and filtered through a Celite® bed. The product was extracted twice with dichloromethane (50.0 mL) and evaporated under reduced pressure. The crude product was dissolved in isopropyl alcohol (20.0 mL), and HCl in isopropyl alcohol (20.0 mL) was added at room temperature. The precipitated solid was filtered, washed with isopropyl alcohol (10.0 mL), and dried to a constant weight at 40–50°C to yield 5-(1H-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine hydrochloride **14** (5.0 g, 47%, purity by HPLC 96.8%).

IR (KBr, cm^{-1}): 3400 (N-H), 3033 (Ar C-H), 1556.1 (-N^+-H, bending), 1430, 1382 (Ali C-H bending), 820, 716 (aromatic C-H bending). ^{1}H NMR (DMSO, δ ppm): 11.1 (s, 1H), 9.0 (s, 1H), 8.3 (s, 1H), 7.55 (s, 1H), 7.40 (d, 1H), 7.20 (d, H), 7.17 (s, 1H), 6.0 (br-s, 2H), 5.43 (s, 2H), 2.86 (m, 2H), 2.66 (s, 2H). Mass: 242 ($M^+ + 1$).

N,N-Dimethyl-5-(1-methyl-1,2,4-triazol-1-yl-methyl)-1H-indole-3-ethanamine oxalate (15)

To a solution of rizatriptan base **2** (17.0 g, 0.063 mol) in THF (100.0 ml) potassium tert butoxide (14.2 g, 0.126 mol) was added at room temperature. Methyl iodide (6.1 mL, 0.094 mol) was added dropwise at room temperature, and the reaction mass was maintained for 2 h. Water (150.0 mL) was added to the reaction mixture. The product was extracted twice with dichloromethane (100.0 mL) and evaporated. The oxalate salt was prepared by addition of a solution of oxalic acid (4.4 g, 0.035 mol) in isopropyl alcohol (10.0 mL) to the residue in isopropyl alcohol (20.0 mL). The precipitated solid was filtered, washed with isopropyl alcohol (5.0 mL), and dried to a constant weight at 40–50°C to afford the title compound **15** (yield 11.3 g, 48.0%, purity by HPLC 97.5%). IR (KBr, cm^{-1}): 3008, 2937 (Ali C-H), 1639 (C═O), 1466, 1404 (Ali C-H, bending), 1137 (-C-N).^{1}H NMR (DMSO, δ ppm): 8.60 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 7.30 (d, 1H), 7.18 (s, 1H), 7.03 (d, 1H), 5.40 (s, 2H), 3.30 (m, 2H) 3.0 (m, 2H) 2.8 (s, 9H). Mass: 284 ($M^+ + 1$).

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REFERENCES

1. Wolf, H. G. The pathophysiology of headache. *Int. J Neurol.* **1963**, *3* (1), 287.
2. Lance, J. W. In *Mechanism and Management of Headache*; 2nd edn.; Butterworth: London, 1973.
3. Fozard, J. The animal pharmacology of drugs in the treatment of migraine. *J. Pharm. Pharmacol* **1975**, *27*, 297–321.
4. Lance, J. W. 5-Hydroxytryptamine and its role in migraine. *Eur. Neurol.* **1991**, *31* (5), 279–281.
5. Rabasseda, X.; Mealy, N.; Castaner, J. Synthesis of MK-0462. *Drugs of Future* **1995**, *20* (7), 676–679.
6. Remuzon, P.; Dunny, C.; Jacquet, J. P.; Soumeillant, M.; Bouzard, D. 4-Hydroxy-2-methyl-3(2H)-isothiazolone-1,1-dioxide as protecting group of 4-(N-methylaminousulfonyl) methylphenylhydrazine during fischer indole synthesis. *Tetrahedron Lett.* **1995**, *36* (35), 6227–6230.

7. Chen, C.-Y.; Senanayake, C. H.; Billy, T. J.; Larsen, R. D.; Verhoeven, T. R.; Redider, P. J. *J.Org.Chem.* **1994**, *59*, 3738.
8. Street, L. J.; Baker, R.; Davey, W.; Guiblin, A. R.; Jelly, R. A.; Reeve, A. J.; Routledge, H.; Sternfled, F.; Watt, A. P.; Beer, M. S.; Middlemiss, D. N; Noble, A. J.; Stanton, J. A.; Scholey, K.; Hargreaves, R. J; Sohal, B.; Graham, M. I.; Matassa, G. Synthesis and serotonergic activity of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyamine and anologues. Potent agonists for 5-HT1D receptors. *J. Med. Chem.* **1995**, *38*, 1799.
9. Baker, R.; Hadham, M.; Matassa, V. G.; Pelham, F.; Street, L. J.; Harlow. Triazole containing indole derivatives. US Patent. 5,298,520, 1994.
10. Mallikarjuna, R. B; Sangaraju, S. Srinivasu, M. K; Madhavan, P.; Lalitha Devi, M.; Rajendrakumar, P.; Chandrasekhar, K. B; Arpita, Ch.; Satya Balaji, T. Development of validation of a specific stability indicating high performance liquid chromatographic method for rizatriptan benzonate. *J. Pharm. Biomed. Anal.* **2006**, *41*, 1146–1152.
11. ICH Guidelines, Q_3A (R) Impurities in New Drug Substances, The quality guidelines for Active Pharmaceutical Ingredients related to impurities according to the International Conference of Horminization. February 2002.
12. ICH Guidelines, Q_3B (R) Impurities in New Drug Products, The quality guidelines for Active Pharmaceutical Ingredients related to impurities according to the International Conference of Horminization. February 2002.