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Der Pharma Chemica, 2012, 4 (1):347-351
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

A cost effective and large-scale synthesis of Zolmitriptan: An anti-migrane drug

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ABSTRACT

An improved process for the preparation of pure Zolmitriptan described via an in situ preparation of hydrazine followed by indole cyclisation of Oxazolidine derivative. In this article which we have provided improved reaction conditions, which ex-cluded the usage of column chromatography, and an overall yield of 60% with 99.9% HPLC purity has been achieved.

Key words: Zolmitriptan, anti-migraine, indole, Oxazolidine.

INTRODUCTION

Zolmitriptan [1-5] chemically known as (S)-4-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone, and is a selective 5 HT1- receptor agonist. The 5 HT1- receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5 HT1- receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, [6] cluster headache and headache associated with vascular disorders, [7] herein after referred to collectively as migraine. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to maximum of 15 mg per day.

The first reported by Burroughs Wellcome Co., synthesis of Zolmitriptan involved the isolated hydrazine HCl derivative (**3)** with column chromatography then followed by Fisher Indole reaction [8, 9] between the hydrazine [10] and acetal [11, 12] derivative (**4)** to get Zolmitriptan(**5**). Our approach was aimed to provide a commercially viable [13, 14] process for producing pure Zolmitriptan (**5**).

The present invention provides a process for producing pure Zolmitriptan (**5**) employing novel reaction conditions as well as without using column.

MATERIALS AND METHODS

The ^{1}H NMR spectra were recorded on a Gemini 200 MHz FT NMR spectrometer with chemical shifts reported in ppm relative to TMS. The IR spectra were recorded in the solid state as KBr discs using a Perkin Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP8000 and AB-4000 Q-trap LC-MS/MS instruments. Elemental analysis for CHN was performed on a Perkin Elmer model 2400 CHNS/O analyzer at Dr. Reddy's Laboratories Ltd., Hyderabad.

Preparation of (S)-N, N-Dimethyl-2-[5-[2-oxo-l,3-oxazolidinylmethyI]-lH- indoI-3- yljethyl amine [Zolmitriptan (crude)](5)

(S)-4-(4-Aminobenzyl)-l,3-oxazolidine-2-one**(1)** (80 g, 0.4166 moles) was charged to a cooled solution of water (480 mL) and concentrated hydrochloric acid (500 mL) at 5°C to 0°C. To this a solution of sodium nitrite (31.8 g, 0.4614 moles) dissolved in DM water (160 mL) was slowly added at -5 to 0°C. The reaction mass was maintained for 1 hr at -5 to 0°C. The above cold diazonium solution was added at -15 to -10°C, to a pre-cooled solution of stannous chloride (383.76 g, 1.7006 moles) in conc. hydrochloric acid (480 mL). The temperature of the reaction mass was slowly raised to room temperature and maintained for 4 hrs at 25-30°C. Then to this reaction mass was added DMwater (1600 mL), cooled and pH of the reaction mass was adjusted to 1.7-1.85 with 50% sodium hydroxide solution. After pH adjustment, temperature was raised to 25-30°C. If the pH of the reaction mass retains 1.7-1.85, (if not re-adjust to 1.7-1.85), then heat to 96 -103°C maintained for 30 minutes, then added slowly (N,N-dimethyl) aminobutyraldehyde diethyl acetal (4) (117.92 g, 0.7313 mole) to the reaction mass and maintained for 3-4 hrs at 96 -103°C.The progress of the reaction was monitored by TLC till the disappearance of hydrazine was observed. The reaction mixture was cooled to 25-30°C, then filtered through high flow bed, collect the stannous chloride cake into fresh RBF add 800 mL of DM water heat the cake to 70-75°C maintain for one hour at 70-75°C, filter through high flow bed subsequently washed with 80 mL hot DM water. Combined all the filtrate, adjust the pH to 6.9 - 7.0 with sodium hydroxide solution a trace solids were appeared, filtered through high flow bed. The filtrate collected was washed twice with dichloromethane (2X400 mL) to the filtrate, adjusted pH to 10.5 - 11.0 with sodium hydroxide solution extracted with Ethyl acetate (2000 mL), organic layer separated, the aqueous layer again extracted with ethyl acetate (400 mL) and the total organic layers were combined, washed with saturated aqueous sodium chloride solution, organic layer concentrated under reduced pressure below 40°C. To get residue, to that residue add isopropyl alcohol (160 mL), heated to 70-75°C maintain for one hour, then cooled to 25-30°C. To this n-heptane (104 mL) was added at 25-35°C and maintained for 90 minutes. The crystals precipitated was filtered under nitrogen atmosphere and washed with a mixture of Isopropyl alcohol & n-heptane (1:1) (160 mL). The wet material was suck dried for 10 minutes under nitrogen atmosphere and dried under reduced pressure at 45-50°C for 24 hrs.

To the dried material were added 800 mL of DM water into a round bottom flask and stirred for one hours. The slurry thus obtained was filtered and washed with 160 mL DM water and suck dried for 10 minutes under nitrogen atmosphere. The wet material was dissolved in 400 mL Iso-

propyl alcohol at 50°C, charcoalised and filtered mass through Hyflow bed followed by washing with 160 mL Isopropyl alcohol to the Hyflow bed. The filtrate was concentrated under reduced pressure to 180 mL and cooled to 25-30°C. Then n-heptane 104 mL was added maintain for 60-90 minutes at 15-20°C, filtered under nitrogen atmosphere and washed with mixture of Iso-propyl alcohol & n-heptane (1:1) (200 mL). The wet material suck dried for 10 minutes under nitrogen atmosphere and dried under reduced pressure at 45-50°C for 10 hrs. Dry wt: 56-70g.

Spectroscopic data: DSC: 138.38°C, IR(KBr) (cm^{-1}): 3351 (NH) ,2925,2859 (Aliphatic(S) –C-H),1737 (-C=O), 1479,1409 (Aliphatic(B) –C-H),1259 (-C-O),1096 (-C-N) and 778 (Aromatic –C-H).

^{1}H NMR (500 MHz, DMSO-d_6, δppm): 7.79 (s, 1H, NH), 4.22 (t, Ha, CH), 4.03 (m, Hb, CH), 4.03 (m, 1H, CH), 2.89 (dd, Ha, CH), 2.76 (d, Hb, CH), 6.92 (dd, 1H, Ar-H), 7.25 (d, 1H, Ar-H) 7.36 (s, 1H, Ar-H) , 10.71 (s, 1H, NH), 7.11 (d, 1H, CH), 2.80 (t, 2H, CH), 2.51 (m, 2H, CH),2.21 (s,3H, CH), 2.21 (s,3H, CH).

^{13} C NMR (125 MHz, DMSO-d_6, δ ppm) : 158.7, 68.1, 53.2, 40.6, 125.8, 122.5, 111.2, 118.8, 127.5, 135.2, 22.7, 112.4, 23.1, 59.9, 45.1, 45.1.

Mass: 287 (M^{+1}), m/z=243,58; C H N O Analysis calcd. for $C_{16}H_{21}N_3O_2$: C 64.26(64.11); H 8.28(8.34); N 12.02(12.00); $[\alpha]_D^{22}$ -4.79° (C=0.5% in Methanol).

RESULTS AND DISCUSSION

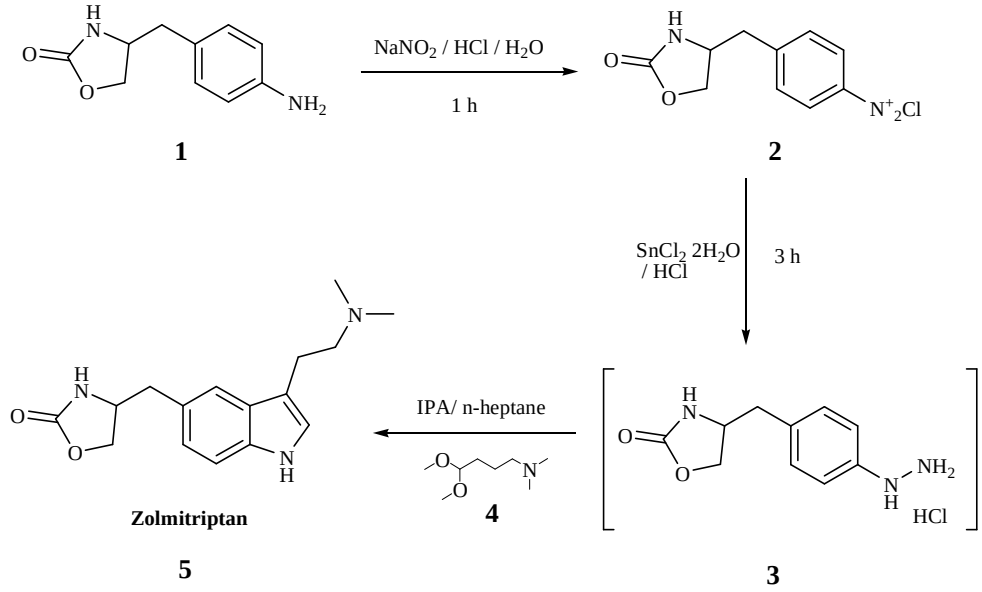
As mentioned in (scheme1), our approach began with (5)-4-(4-amino benzyl)Oxazolidine-2-one (**1**) is diazotization of(1) using aqueous sodium nitrite and concentrated HCl at -5 to 0°C gave the desired diazonium chloride salt(2). Reduction of (**2**) using stannous chloride di-hydride and concentrated HCl followed by adjustment of pH of the reaction mass to 1.7-1.85 with 55% sodium hydroxide solution afforded the hydrazine hydrochloride salt(3). The compound (3) was reflux with 4-4-dimethoxy-N,N-dimethylbutane-1-amine(4)to gave Zolmitriptan(5), in high yield. It was observed that the Zolmitriptan crude high yield were obtained only when the pH of the reaction mixture was 1.7 to 1.85 (Table-1), Recrystallisation of this crude material from IPA/n-heptane gives Zolmitriptan (5) Table-2. Different solvent ratios such as IPA/ n-heptane to purify the crude Zolmitriptan, by increasing the ratio of isopropyl alcohol yield of Zolmitriptan(5) decreased, ratio of 60:40 IPA/ n-heptane were explored to obtained highly pure Zolmitriptan(5).

Table 1. Optimization of pH of reaction mass at hydrazine hydrochloride salt (3)

Experiment	pH of reaction mass at hydrazine hydrochloride salt(3)	Amount of compound (1) g	Zolmitriptan (5) g	Purity by HPLC (%)	Observation
1	1.2	10	6.5	97.17	Unknown impurities
2	1.7	10	11	99.59	Desired product obtained
3	1.85	10	11	99.59	Desired product obtained
4	2.2	10	3.5	98.11	Reaction not completed

Table 2. Optimization of Isopropyl alcohol/n-heptane during Recrystallisation of zolmitriptan yield (%) Vs Purity by HPLC

Experiment	Isopropyl alcohol (%)	n-heptane (%)	Total Volumes of solvent	Zolmitriptan(5) crude g	Obtained Pure Zolmitriptan Yield (%)	Purity by HPLC (%)
1	100	0	2.0	10.0	3.1	99.96
2	**60**	**40**	**3.3**	**10.0**	**9.0**	**99.96**
3	60	40	4.5	10.0	6.0	99.74
4	60	40	5.0	10.0	6.0	99.77
5	70	30	3.3	10.0	6.8	99.67
6	70	30	4.5	10.0	5.5	99.49
7	75	25	2.0	10.0	6.5	99.66



1 **2** **3** **4** **5**

Scheme 1. Synthesis of Zolmitriptan

CONCLUSION

In conclusion, we have developed an improved process this is an economical and high yielding process for the industrial production of Zolmitriptan using cheaply available reagents and starting materials.

Acknowledgement
The authors are thankful to the management of Dr. Reddy's Laboratories Limited and the colleagues of analytical research and development is highly appreciated.

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