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Research Article

Synthesis and Characterization of Ether-Dimer Impurity of Drug - Ranolazine Using 2, 2'- (oxybis (methylene)) Bis (Oxirane)

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Abstract

Ranolazine became the first approved member of a new family of antianginal medications in nearly 25 years when it was licensed in 2006 for the treatment of chronic angina pectoris. The exact mechanism of action of Ranolazine is unclear. Ranolazine was originally believed to work by partially inhibiting the oxidation of fatty acids. Ranolazine may lessen calcium excess in ischemic myocytes by inhibiting the late sodium current, according to more recent data. Headache, nausea, constipation, and dizziness are the most commonly reported side effects. Ranolazine is listed among the top 200 drugs by sales in the decade of the 2010s. In this study, several impurities related to Ranolazine, a piperazine derivative used as a second-line treatment for patients with stable or poorly managed chronic angina who are not responding to other medications, the synthesis of impurities produced during the bulk drug's in-house production of Ranolazine was explained. The unknown impurities were identified as2,2'-(4,4'-(oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1- diyl))bis(N-(2,6-dimethylphenyl)acetamide). The study uses a variety of spectral techniques, such as Infrared Spectroscopy (IR): A technique for determining molecular vibrations and functional groups. Atomic connectivity and structure can be thoroughly understood through nuclear magnetic resonance (NMR). The molecular weight and fragmentation patterns of compounds are ascertained through mass spectrometry (mass). Utilizing High-Performance Liquid Chromatography (HPLC), various compounds in a mixture can be separated and examined.

Keywords

Ranolazine, Impurities, Bulk Drug, Synthesis, Contaminants

1. Introduction

The chemical name for Ranolazine, which has anti-angina properties, is N-(2,6-dimethylphenyl)-2-(4-(2-hydroxy-3-(2-methoxyphen oxy)propyl)piperazin-1-yl)acetamide [1]. Angina, sometimes referred to as angina pectoris, is a sign of cardiac illness brought on by inadequate blood flow to the heart [2]. The most common cause of angina is atherosclerosis. Developed by Roche Bioscience (previously Syntex), ranolazine1-4 is a medication used to treat chronic angina that is sold by CV Therapeutics [3]. On January 27, 2006, the USFDA approved the use of the brand name Ranolazine the European Medical Agency (EMEA) subsequently gave its approval on July 9, 2008 [4]. Later, it received approval in a few other developing nations. Ranolazine is available in market in the form of 500

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mg and 1000 mg film coated tablet and the maximum daily dosage should be less than 2.0g. Over dosage of Ranolazine lead to dizziness, nausea, and vomiting [5]. The preparation and characterization data of these relatedsubstances has been necessary for the preparation of reference compounds for the quality assurance ofbulk drugs and drug formulations [6].

Chemicals known as impurities are those that are present in the API or that are created during the synthesis or development of the formulation and the API. A drug's efficacy and safety may be impacted by even trace amounts of these contaminants. The toxicological characteristics of the active drug ingredient alone do not determine a medicine's safety; its impurities also play a role. The importance of API impurity profiling is growing since impurities in APIs can affect the quality and safety of pharmaceutical products. As a result, a crucial component of medication development and regulatory evaluation is locating, separating, and measuring contaminants [7].

There are two types of impurities: (a) impurities associated with active medical ingredients, and (b) contaminants created during formulation, storage, or manufacturing [8].

A number of pharmacopeias, including the Indian Pharmacopeia, the United States Pharmacopeia, the British Pharmacopeia, and others, are progressively imposing restrictions on the authorized amounts of impurities found in formulations or active pharmaceutical ingredients (APIs) [9].

2. Materials and Methods

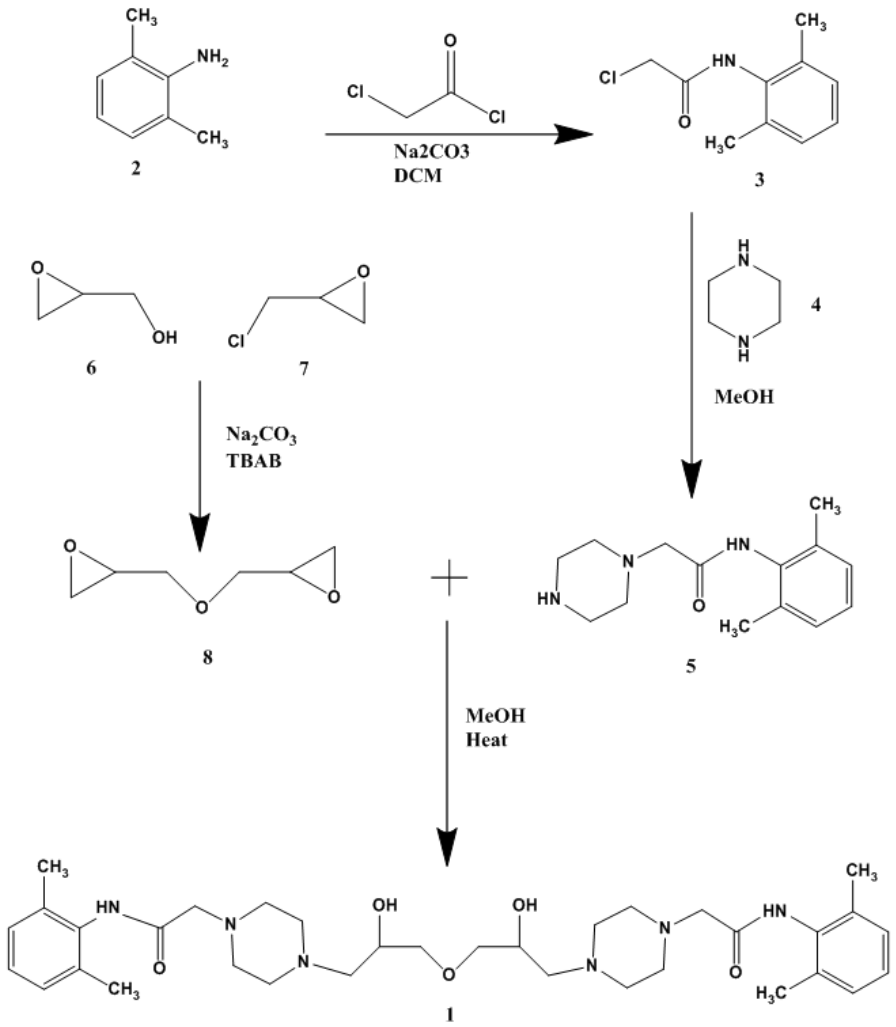

Figure 1. *Scheme; Synthesis of Ranolazine Ether Dimer.*

Reagents and conditions (3) Dichloromethane (DCM)**,** sodium carbonate (Na_2Co_3)**,** Chloroacetyl chloride, at 12 ℃ to 25 ℃ for 2 hours; (5) piperazine, methanol, reflux for four hours; (8) Tetra-n-butyl ammonium bromide (TBAB), sodium carbonate (Na_2Co_3), four hours at 40 ℃ to 50 ℃; (1) Methanol, reflux for 12 hours.

Experiment:

The Polmon melting point device was used to determine

each melting point. A Bruker 300 spectrometer was used to record the 1H-NMR and 13C-NMR spectra [6]. The internal criterion for reporting chemical shifts downfield from TMS was ppm [10]. The Perkin Elmer PE SCIEX-API 2000 mass spectrometer was used to measure the mass spectra. At 210 nm, analytical HPLC was performed using a Zorbax Eclipsse XDB, C18, 250 x 4.6 mm column. Room temperature is indicated by "RT." One of the medications used to treat this condition is ranolazine1-4 [11].

2-chloro-N-(2, 6-dimethylphenyl) acetamide (3)

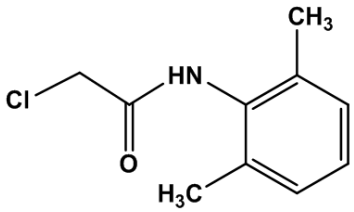

Figure 2. *Synthesis of 2-chloro-N-(2, 6-dimethylphenyl) acetamide.*

A solution of 2, 6-dimethyl aniline (2) (10 g, 0.082mol) was made in 50ml of Dichloromethane (DCM). 4.30 g (0.040 mol) of sodium carbonate (Na_2CO_3) was added to the reaction mass. After gradually adding 10.0 g (0.088 mol) of chloroacetyl chloride (2) at 12 ℃ to 25 ℃, the reaction mass was agitated for one to two hours at the same temperature. The reaction mass was monitored by thin layer chromatography (TLC). Following the addition of 100 ml of water to the reaction mixture, Dichloromethane (DCM) was vacuum-distilled at temperatures lower than 40 ℃. After a full hour of stirring, the reaction mixture was allowed to cool to room temperature. The resulting solid was filtered, cleaned with 100 milliliters of water, and dried at 60 degrees Celsius using the title chemical.

N-(2, 6-dimethylphenyl)-2-(piperazin-1-yl) acetamide (5)

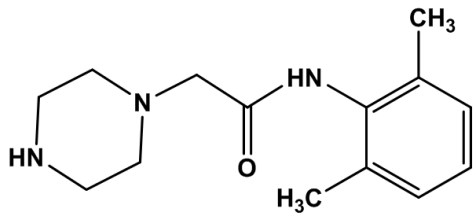

Figure 3. *Synthesis of N-(2, 6-dimethylphenyl)-2-(piperazin-1-yl) acetamide.*

The reaction mass was supplemented with piperazine (4) (13.0.6 g, 0.151 mol) after N-chloroacetyl dialkyl aniline compound (3) (10 g, 0.050 mol) was dissolved in 100 mL of methanol. For four hours, the reaction mass was heated to 60 ℃ to 70 ℃ and agitated consistently at that temperature. The reaction mass was monitored by thin layer chromatography (TLC). A vacuum was used to entirely distill methanol at temperatures below 65. After an hour of stirring, 100 mL of room temperature water was added to the reaction mixture. The separated undesirable solid was filtered and cleaned with 100 milliliters of water. To bring the pH of the filtrate down to 5.0 to 5.5, 140 mL of 44% phosphoric acid (H3PO4) solution was added, and it was agitated for 50 minutes at 25 ℃ to 30 ℃. They filtered the separated piperazine salt. Water (50 mL) was used to wash the filter, and a 20% sodium hydroxide (NaOH) solution (60 mL) was used to bring the pH down to 10.5–10.8. After being added to the reaction mixture at 28 ℃, 100 mL of Dichloromethane (DCM) was agitated for ten minutes. After separating the organic and aqueous phases, the latter was extracted using Dichloromethane (DCM) (2 x 500 mL), and the organic mixture was rinsed with 300 mL of water. A 99.8% pure title chemical was obtained by concentrating the mixed organic phase under decreased pressure after it had been dried over anhydrous sodium sulphate (Na_2SO_4).

2, 2'-(oxybis (methylene)) bis (oxirane) (8)

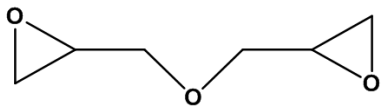

Figure 4. *Synthesis of 2, 2'-(oxybis (methylene)) bis (oxirane).*

The suspension of Tetra-n-butyl ammonium bromide (TBAB) and glycidol (6) was supplemented with sodium carbonate (Na2Co3). Epichiorohydrin (7) was gradually added to the reaction mass, which was stirred for 30 minutes at 35 ℃ to 40 ℃. The reaction mass was then swirled for 4 hours at the same temperature. Thin layer chromatography (TLC's) Observation of the reaction mass the solid was removed from the reaction mass by filtering it, diluting the solution with water, and drying the combined organic phase on anhydrous sodium sulphate (Na_2SO_4) before concentrating the mixture under reduced pressure.

2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4, 1-diyl))bis(N-(2,6-dimethylphenyl)acetamide) (1)

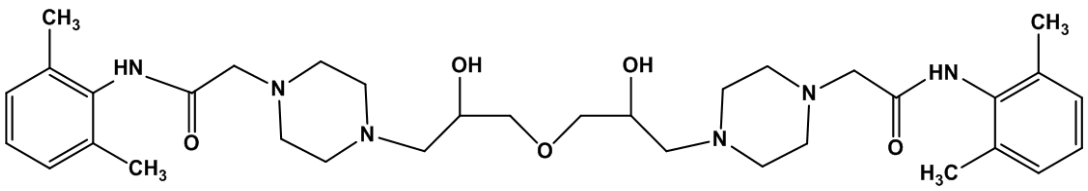

Figure 5. *Synthesis of 2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide).*

The reaction mass was increased by adding 2, 2'-(oxybis (methylene)) bis (oxirane) (8) (10.0.6 g, 0.0768 mol) after N-(2, 6-dimethylphenyl)-2-(piperazin-1-yl) acetamide (5) (47g, 0.1922 mol) was dissolved in 300 mL of methanol. The reaction mass was vigorously agitated for 17 hours at 60 ℃ to 70 ℃. 20% MeOH/DCM was used in thin layer chromatography (TLC) to monitor the reaction mass. A vacuum was used to entirely distill methanol at temperatures below 65. In the resulting reaction mixture, component 8 was refined with 99% purity using column chromatography (DCM: Methanol). IR (KBr, cm–1): 1252 and 1025 (Ether, C-O-C) & 1126 (C-N), 3547 (Alcohol, OH), 2925 (Ali, CH), 1518 (Aromatic, C═C), 1252 (C-O-C, Aryl ethers), 3012 (Aromatic, =CH), 2820 (Ali, CH), 1676 (Amide, C=O). δH 9.01 (s, 1H, N-H), 6.5-7.0 (m, 3H, Ar-H), 5.2 (s, 1H, OH), 2.3 (s, 1H, Ar CH), 3.6 (s, 3H, CH3), 2.8 (s, 2H, CH_2), and 13C NMR (500 MHz, DMSO–d6): 17.5, 17.4, 17.5, 17.5, 17.5 55.3, 57.0, 57.1, 63.2, 63.6, 66.2, 66.3, 95.2, 95.1, 127.0, 127.2, 128.6, 128.8, 130.5, 130.5, 137.0, 137.1, 168.2, 168.3 M/S (m/z): 624.8 (M+1)

3. Results and Discussion

The impurity ranolazine ether dimer was produced (Scheme). It is prepared via the following steps: Williamson ether synthesis, piperazine condensation reaction, N-alkyl linkage creation, and chloroacetyl chloride condensation reaction. During in-house testing, it was discovered that ranolazine has ether dimer impurities ranging from 0.1% to 0.5%. These ether dimer impurities were created following their identification using mass detection by LC-MS and subsequent confirmation by HPLC. For the analytical technique validation of ranolazine bulk drug, these contaminants must be synthesized in pure form. A thorough investigation was then conducted to get these pollutants ready.

IR INTERPRETATION OF RANOLAZINE ETHER DIMER
Batch Number: GS-RAZ-02133
Molecular. Weight: 624.8
Molecular. Formula: C34H52N6O5

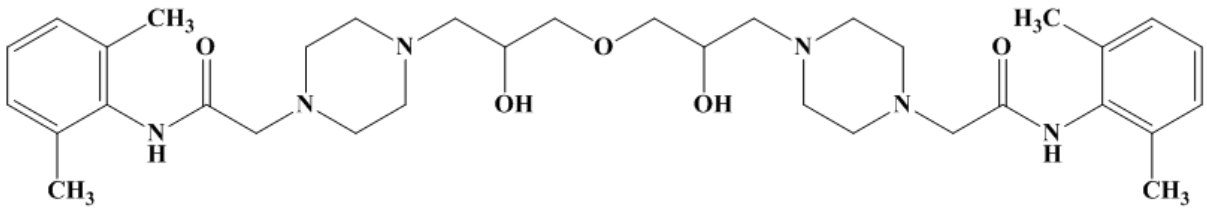

Figure 6. *2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide) (1).*

Ranolazine Ether Dimer:
2,2'-(4,4'-(3,3'-oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide); Pharmaceutical Standards, Intermediates, Fine Chemicals

Table 1. *Functional group and quantitied frequencies.*

S. No	Wave number (cm^{-1})	Group	Stretch
1	1494.7	Aromatic Ring System	C-C=C
2	1666.1	Amide Linkage	HN-C=O
3	2817.9	Alkyl Group	H-C-H
4	3280.1	Primary Hydroxy Group	C-OH

The signals of the IR spectrum and their interpretation are consistent with the structural formula.

HNMR INTERPRETATION OF RANOLAZINE ETHER DIMER
Batch Number: GS-RAZ-02133
Molecular. Weight: 624.8
Molecular. Formula: C34H52N6O5

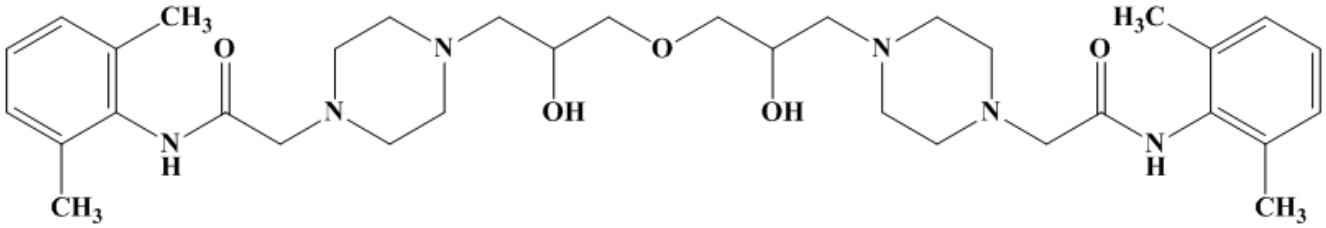

Figure 7. *2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide) (1).*

Ranolazine Ether Dimer: 2,2'-(4,4'-(3,3'-oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide); Pharmaceutical Standards, Intermediates, Fine Chemicals

HNMR 400.1500024 MHz SOLVENT USED: DMSO (d6) δ PPM

δ 1.23-1.34 ppm (4H, s, -4CH), δ 2.17-2.19 ppm (12H, s, -4ArCH3),

δ 2.27-2.37 ppm (5H, m, -5CH), δ 2.50-2.67 ppm (10H, m, -10CH),

δ 3.10 ppm (4H, s, -4CH), δ 3.16-3.17 ppm (1H, d, -CH),

δ 3.30-3.32 ppm (2H, m, -2CH), δ 3.37-3.41 ppm (2H, m, -2CH)

δ 3.75 ppm (2H, s, -2OH), δ 4.56 ppm (2H, s, -2CH),

δ 7.06 ppm (6H, s, -6ArCH), δ 9.15 ppm (2H, s, -2CONH),

MASS INTERPRETATION OF RANOLAZINE ETHER DIMER

Batch Number: GS-RAZ-02133

Molecular. Weight: 624.8

Molecular. Formula: C34H52N6O5

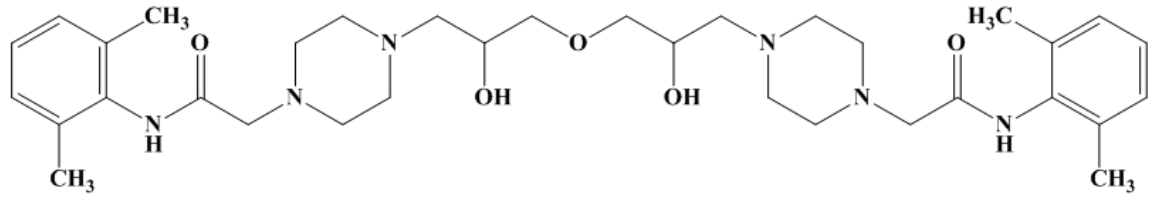

Figure 8. *2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide) (1).*

Ranolazine-Ether-Dimer; 2,2'-(4,4'-(3,3'-oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide); Pharmaceutical Standards, Intermediates, Fine Chemicals

Table 2. *Ranolazine-Ether-Dimer mass value.*

m/z (molecular mass)	Fragments (mass value)
625.87 (+ve mode)	[M+1]
623.24 (-ve mode)	[M-1]

The molecular mass of *RANOLAZINE ETHER DIMER* (624.8) has been confirmed with fragments appears [M+1] 625.87 in positive mode and [M-1] 623.24 in negative mode. The signals of the mass spectrum and their interpretation are consistent with the structural formula.

HPLC INTERPRETATION OF RANOLAZINE ETHER DIMER

Batch Number: GS-RAZ-02133

Molecular. Weight: 624.8

Molecular. Formula: C34H52N6O5

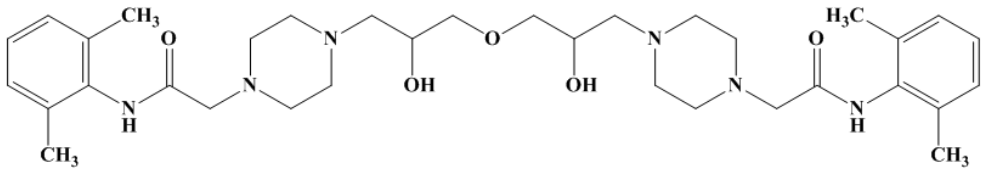

Figure 9. *2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide) (1).*

Table 3. 235 NM, 4 NM RESULTS.

Name	Retention Time	Area	Area %	Height	Relative RT
GS-RAZ-02133	9.267	50350682	98.12	3079880	1.00
Peak @ 9.840 Minutes	9.840	397287	0.77	39652	0.922
Peak @ 13.860 Minutes	13.860	235776	0.46	11916	0.778
Peak @ 14.667 Minutes	14.667	334266	0.65	16465	0.740

Chromatographic purity (HPLC): 98.12 %

4. Conclusion

For Ranolazine quality control, our current study shows a straightforward method for producing a high-quality Ranolazine impurity reference. An impurity of Ranolazine (ether dimer) is 2,2'-((oxybis(2-hydroxypropane-3,1-diyl))bis(piperazine-4,1-diyl))bis(N-(2,6-dimethylphenyl)acetamide). Were successfully synthesized and characterized employing a quick and easy technique. This synthesis facilitates the creation of an impurity profile in addition to the manufacturing of superior therapeutic compounds.

Overall, we present a technique for producing Ranolazine impurities with a high yield and purity. These compounds' spectral data (HPLC, IR, 1H-NMR, and MS) were also described.

Abbreviations

DCM	Dichloromethane
NMR	Nuclear Megnatic Resonance
IR	Infrared Spectroscopy
TLC	Thin Layer Chromatography
RED	Ranolazine Ether Dimer

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

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