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Synthesis and characterization of potential impurities in key intermediates of Carvedilol: a β-adrenergic receptor

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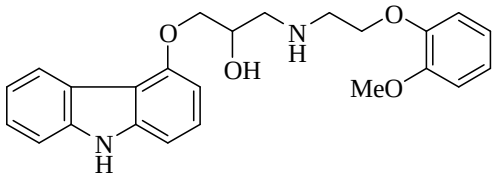
ABSTRACT

Carvedilol is prepared by different synthetic approaches. One of the approach is the condensation of 4-(2, 3-epoxyprpoxy) carbazole with 2-(2-methoxyphenoxy) ethyl amine in monoglyme solvent. In this publication, impurities and their origin of formation during the synthesis of 4-(2, 3-epoxypropoxy) carbazole and 2-(2-methoxyphenoxy) ethyl amine is discussed. These impurities are synthesized and well characterized by spectral analysis.

Keywords: Carvedilol, 4-(2, 3-Epoxyprpoxy) carbazole, 2-(2-Methoxyphenoxy) ethyl amine, Potential impurities, Spectral analysis.

INTRODUCTION

Carvedilol (1) an adrenergic antagonist with nonselective β and α1 receptor blocking agent and a vasodilatation drug with antioxidant activity [1-3]. Carvedilol has demonstrated significant clinical benefits in the management of patients with heart failure and in the post-myocardial infarction setting. It also possesses unique ancillary properties that may account for positive results in a number of clinical trials. It appears to offer particular advantages in the treatment of co-morbid conditions, including coronary artery disease, stroke hypertension, renal failure, diabetes and arterial fibrillation [4-6] that can independently contribute to the progression of heart failure.



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Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. Impurities of key intermediates affect the impurity profile of APIs.

These unwanted chemicals (impurities) of key intermediates may or may not convert into other impurities in the APIs. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (i.e. the identity as well as the quantity of impurity in the pharmaceuticals), is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) are slowly in-corporating limits to allowable levels of impurities present in the APIs or formulations.

The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances [7], products [8] and residual solvents [9]. There is a good significant demand for the impurity-reference standards along with the API reference standards for both regulatory authorities and pharmaceutical companies. A number of recent articles [10-12] have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using mass spectrometry, Nuclear Magnetic Resonance (NMR). High-performance liquid chromatography (HPLC), Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS), and tandem mass spectrometry for pharmaceutical substances.

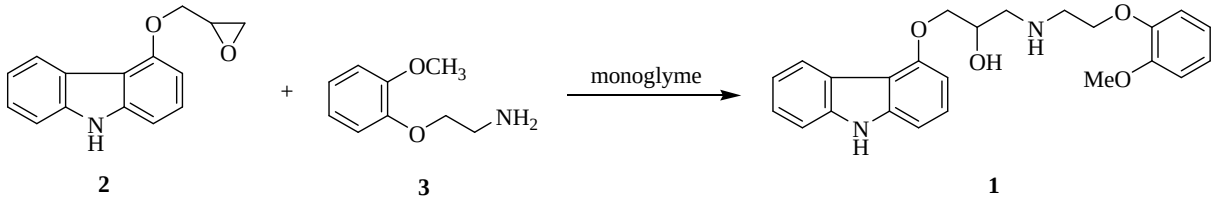
The procedure of impurity profiling, begins with the detection of the impurities using the thin-layer chromatography, high-performance liquid chromatography or gas chromatography. Procurement of standard impurity samples from the synthetic organic chemists which include, last intermediate of the synthesis, products of predictable side reaction, degradation products if any, etc.

The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI/ESI facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

The important step in the impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is useful for analytical method development and validation.

Carvedilol [13] is well reported in the literature. The innovator [14], Boehringer Mannheim, synthetic approach for the preparation of Carvedilol describes the opening of oxirane ring of 4-

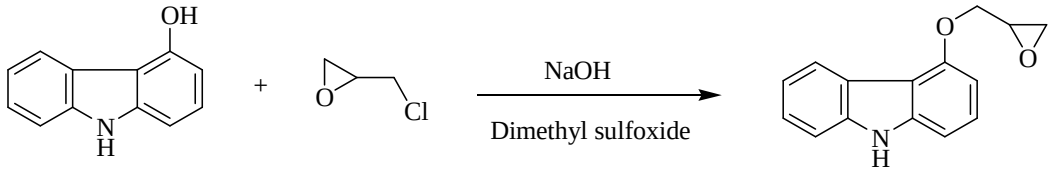
(2, 3-epoxyprpoxy) carbazole (2) with 2-(2-methoxyphenoxy) ethanamine (3) in monoglyme solvent (scheme 1).



2 **3** **1**

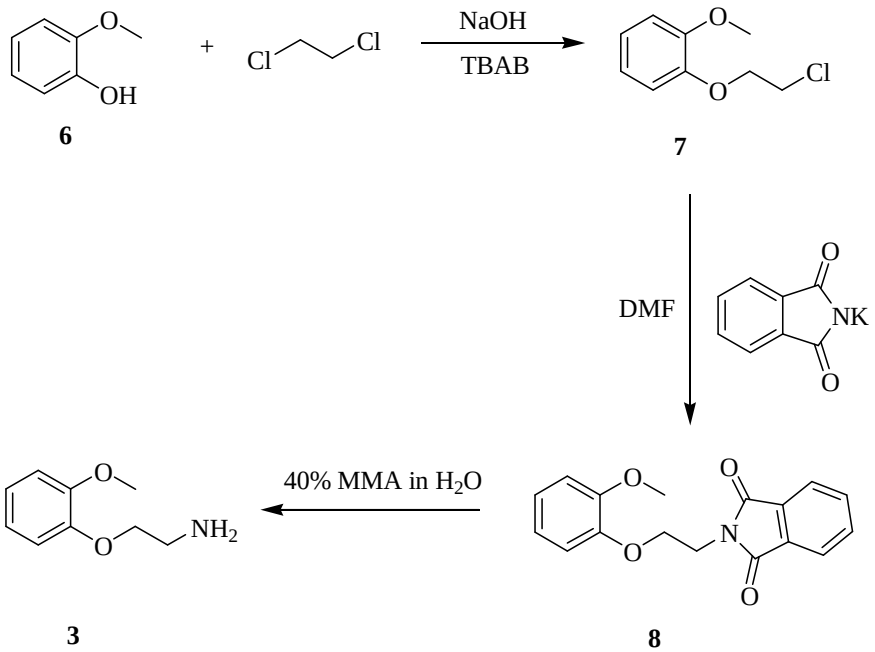
Scheme 1: General synthetic approach of Carvedilol

There are many synthetic methods known in the literature for the synthesis of 4-(2, 3-epoxyprpoxy) carbazole (2) [15]. One general method is condensation of 4-hydroxy carbazole (4) with epichlorohydrin (5) as per the scheme 2.



4 **5** **2**

Scheme 2: General synthetic approach of 4-(2, 3-epoxyprpoxy) carbazole (2)



6 **7** **3** **8**

Scheme 3: General synthesis of 2-(2-methoxyphenoxy) ethanamine (3)

During the synthesis of 4-(2, 3-epoxyprpoxy) carbazole (2), four impurities were observed in the isolated material by reverse phase HPLC method. These impurities were synthesized and identified by spectral analysis as 1-(9H - Carbazol-5-yloxy)-3-chloropropan-2-ol (impurity 1), 4-((Oxiran-2-yl)methoxy)-9-((oxiran-2-yl)methyl)-9H- carbazole (impurity 2), 1-(9H-Carbazol-4-

yloxy)-3-(9H-carbazol-5-yloxy) propan-2-ol (impurity 3), 3-(9H-Carbazol-5-yloxy) propane-1,2-diol (impurity 4).

There are many synthetic approaches are available in the literature for the synthesis of 2-(2-methoxyphenoxy) ethanamine (3) [16]. The best available process for large scale synthesis is from Guiacol as per scheme 3.

Compound 3 was synthesized according to the scheme 3. During synthesis, six impurities were observed in 2-(2-methoxyphenoxy) ethanamine (3) crude material. These impurities were synthesized and characterized by spectral analysis and also confirmed by the spiked analysis by GC. Identified impurities were 1-(2-chloroethoxy)-2-methoxybenzene (impurity 5), 1,2-bis(2-Methoxyphenoxy)ethane (impurity 6), 2-(2-(2-Methoxyphenoxy)ethyl)isoindoline-1,3-dione (impurity 7), 2-(2-Chloroethyl)isoindoline-1,3-dione (impurity 8), N,N' -Ethane-1,2-diyl-bis-phthalimide (impurity 9), bis(2-(2-Methoxyphenoxy)ethyl)amine (impurity 10).

EXPERIMENTAL SECTION

General procedure. FT-IR spectra are recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H NMR spectra are recorded on Varian 300 MHz spectrometer using DMSO-d6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra are recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts are dried over sodium sulfate after work up. Unless otherwise mentioned all the solvents and reagents used are of commercial grade.

In this paper, the synthesis and characterization of impurities 1 to 10 have been presented. Physicochemical, spectroscopic and other related data for the synthesized compounds are also discussed.

Synthesis of 4-(2, 3-epoxyprpoxy) carbazole (2): To a stirred solution of 300 mL water and sodium hydroxide (23.0 g, 0.575 mol), 4-hydroxy carbazole (3) (100 g, 0.545 mol) is added over a period of 10-15 min. The reaction mass is cooled to 10-15°C and added 150 mL DMSO drop wise for 45 min. After stirring for 15 min, epichlorohydrin (75.6 g, 0.817 mol) is added over 1 hr duration by maintain the temp at 10-15°C. The reaction mass temperature is slowly raised to 45°C and the suspension is maintained for 6 hrs under stirring. After completion of the reaction, checked by TLC, the product is diluted with 400 mL water, filtered and washed with water. The obtained crude product is recrystallized in methanol to afford pure glycidyl aryl ether 2 as an off white crystalline powder.

Description: Off white crystalline powder; M. F. $C_{15}H_{13}NO_2$; M. Wt. 239.27; IR (KBr, cm^{-1}): 2945 (C-H in -CH_2-), 3083 (C-H aromatic), 1612, 1508 and 1456 (C-C aromatic), 1255 (C-O in epoxy), 1009 (C-O in ether), 1327 (C-N); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.2 (s, 1H, -NH), 8.17(d, 1H ArH), 7.2 (m, 1H ArH), 7.2 (m, 1H ArH), 7.56 (d, 1H ArH), 7.19 (t, 1H ArH), 7.2 (d, 1H ArH), 6.85 (d, 1H ArH), 4.2 (m, 2H, -CH_2-), 3.2 (m, -CH_2- epoxy), 3.1 (m, -CH-).; MS *m/z* (%) = 240 (M+1); Anal. Calcd for $C_{15}H_{13}NO_2$: C – 75.30, H – 5.48, N – 5.85%; Found: C – 75.32, H – 5.50, O – 5.87%.

Synthesis of 1-(9H - Carbazol-5-yloxy)-3-chloropropan-2-ol (impurity 1): Charged methanol (100 mL) into a fresh RBF and started stirring at 25-30^{o}C. Compound 2 (10 g) was added and mass was cooled to 0-5^{o}C. Concentrated HCl (15 mL) was added slowly drop wise over a period of 30-45 minutes at the same temperature. Reaction mass allowed to ambient temperature and progress of the reaction was monitored by TLC (mobile phase: Toluene: methanol – 8:2). Reaction completed after 6 hours of maintenance and distilled off methanol completely under vacuum to get the material as a residue. Residue was purified by column chromatography by eluting with 5-15% ethyl acetate in hexane to get pure impurity 1.

Description: Off white crystalline powder; M. F. $C_{15}H_{14}ClNO_2$; M. Wt. 275.73; IR (KBr, cm^{-1}): 2870 (C-H in –O-CH_2-), 3050 (C-H aromatic), 1604, 1505 and 1453 (C-C aromatic), 3394 (O-H), 1585 (N-H), 1259 (C-O), 725 (C-Cl); ^{1}H-NMR (300 MHz, DMSO-d6): δ 3.4 (m, 2H, -CH_2-), 4.2 (m, 3H, -CH_2- and –CH-), 6.7 (d, 1H, ArH), 7.1 (m, 2H, ArH), 7.3 (m, 2H, ArH), 7.5 (d, 1H, ArH), 8.2 (d, 1H, ArH), 11.2 (s, 1H, -NH); MS *m/z* (%) = 275 (M); Anal. Calcd for $C_{15}H_{14}ClNO_2$: C – 65.34, H – 5.12, N – 5.08%; Found: C – 65.36, H – 5.11, O – 5.07%.

Synthesis of 4-((Oxiran-2-yl)methoxy)-9-((oxiran-2-yl)methyl)-9H- carbazole (impurity 2): Epichlorohydrin (5) (66 mL, 11 volumes) was charged into a fresh RBF and started stirring at ambient temperature. Charged compound 2 (6 g) and potassium carbonate (10.4 g) in the mass under stirring. Reaction mass was heated to reflux and progress was monitored by in-process TLC (mobile phase: Toluene: ethyl acetate – 1:1). Reaction completed after 10 hours of maintenance and then cooled to 25^{o}C. Distilled off the mass under reduced pressure to remove unreacted epichlohydrin completely. Charged water and ethyl acetate to the residue and agitated for 30 minutes. Separated the organic layer and distilled off completely under reduced pressure to get residue. Residue was purified by column chromatography by eluting with 15% ethyl acetate in n-hexane to get impurity 2 as an off white crystalline powder.

Description: Off white crystalline powder; M. F. $C_{18}H_{17}NO_3$; M. Wt. 295.33; IR (KBr, cm^{-1}): 2871 (C-H), 3051 (C-H aromatic), 1585, 1504 and 1463 (C-C aromatic), 1273 (C-N); ^{1}H-NMR (300 MHz, DMSO-d6): δ 2.45-2.55 4(m, 2H, -CH_2- in epoxy), 2.75-2.85 (m, 2H, -CH_2- in epoxy), 2.9 (m, 1H, -CH- in epoxy), 4.1 (m, 1H, -CH- in epoxy), 4.5-4.8 (m, 4H, -CH_2-), 6.9 (d, 1H, ArH), 7.2 (m, 2H, ArH), 7.4 (d, 2H, ArH), 7.6 (d, 1H, ArH), 8.2 (d, 1H, ArH); MS *m/z* (%) = 295 (M); Anal. Calcd for $C_{18}H_{17}NO_3$: C – 73.20, H – 5.80, N – 4.74%; Found: C – 73.21, H – 5.82, N – 4.73%.

Synthesis of 1-(9H-Carbazol-4-yloxy)-3-(9H-carbazol-5-yloxy) propan-2-ol (impurity 3) and 3-(9H-Carbazol-5-yloxy) propane-1,2-diol (impurity 4): Charged water (75 mL) and sodium hydroxide (10.8 g) into a RBF and started stirring at 25-30^{o}C. After reaction mass became clear, added 4-hydroxy carbazole (4) (25.0 g) and dimethyl sulfoxide (35.5 mL) under agitation. Reaction mass was heated to 90^{o}C and added epichlorohydrin (16 g) slowly over a period 20-30 minutes at the same temperature. Reaction completed after 3 hours of maintenance and reaction progress was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane – 3:2). Mass cooled to ambient temperature and dissolved in methanol (100 mL). Mass added slowly to ice cold water under agitation. Centrifuged the separated solid and purified by column chromatography by eluting with 20% ethyl acetate in n-hexane. The obtained first fraction was confirmed as impurity 3 and second fraction as impurity 4 by spectral data.

Impurity 3: Description: Off white crystalline powder; M. F. $C_{27}H_{22}N_2O_3$; M. Wt. 422.48; IR (KBr, cm^{-1}): 2932 (C-H), 3065 (C-H aromatic), 1604, 1587, 1505 and 1453 (C-C aromatic), 3580 (O-H), 3393(N-H), 1258 (C-O); ^{1}H-NMR (300 MHz, DMSO-d6): δ 4.4-4.6 (m, 5H, -CH_2- and –CH-), 6.7 (d, 2H, -ArH), 7.05 (m, 4H, ArH), 7.3 (q, 4H, ArH), 7.45 (d, 2H, ArH), 8.25 (d, 2H, ArH), 11.2 (s, 2H, NH); MS *m/z* (%) = 422 (M); Anal. Calcd for $C_{27}H_{22}N_2O_3$: C – 76.76, H – 5.25, N – 6.63%; Found: C – 76.77, H – 5.26, N – 6.66%.

Impurity 4: Description: Off white crystalline powder; M. F. $C_{15}H_{15}NO_3$; M. Wt. 257.28; IR (KBr, cm^{-1}): 3389 (O-H), 2940 (C-H), 3051 (C-H aromatic), 1605 and 1585 (C-C aromatic), 1264 (C-O); ^{1}H-NMR (300 MHz, DMSO-d6): δ3.6 (m, 2H, -OH), 4.0-4.2 (m, 3H, -CH_2- and –CH-), 4.7 and 5.0 (m, 2H, -CH_2-), 6.7 (d, 1H, ArH), 7.0 (d, 1H, ArH), 7.15 (m, 1H, ArH), 7.3 (m, 2H, ArH), 7.45 (d, 1H, ArH), 8.2 (d, 1H, ArH), 11.2 (s, 1H, NH); MS *m/z* (%) = 257 (M); Anal. Calcd for $C_{15}H_{15}NO_3$: C – 70.02, H – 5.88, N – 5.44%; Found: C – 70.05, H – 5.87, N – 5.45%.

Synthesis of 1-(2-chloroethoxy)-2-methoxybenzene (impurity 5): Charged water (500 mL) and sodium hydroxide (97 g, 1.9 moles) into a RBF and started stirring to get clear solution. Charged TBAB (7 g, 0.016 moles), guiacol (100 mL, 0.61 moles) and 1,2-dichloroethane (500 mL, 4.8 moles) under stirring. Maintained the reaction mass under reflux and reaction progress was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane – 2:3). Reaction completed after 2 hours maintenance and cooled the mass to 25-30^{o}C. Separated the organic layer and discarded the aqueous layer. Distilled off solvent completely under reduced pressure at below 80^{o}C to get the impurity 5 as an off white residue.

Description: Off white residue; M. F. $C_9H_{11}ClO_2$; M. Wt. 186.64; IR (KBr, cm^{-1}): 2938 (C-H), 2839 (C-H methoxy), 3068 (C-H aromatic), 1593, 1507 and 1461 (C-C aromatic), 1253 (C-O), 739 (C-Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.8-3.9 (m, 5H, -CH_3 and –CH_2-), 4.3 (t, 2H, -OCH_2-), 6.9 (m, 2H, ArH), 7.0 (m, 2H, ArH); MS *m/z* (%) = 186 (M); Anal. Calcd for $C_9H_{11}ClO_2$: C – 57.92, H – 5.94%; Found: C – 57.93, H – 5.95%.

Synthesis of 1,2-bis(2-Methoxyphenoxy)ethane (impurity 6): Charged water (100 mL) and sodium hydroxide (35 g) into a RBF and stirred for clear solution at 25-30^{o}C. Charged TBAB (1.36 g) slowly under agitation. Guaicol (20 g) was added slowly over a period of 10 minutes followed by 1,2-dichloromethane (32 g). Reaction maintained at 70^{o}C and monitored by in-process TLC (mobile phase: toluene: methanol – 9:1). Cooled the mass to ambient temperature and filtered the mass to get the impurity 6 as a brown color material. Dissolved the material in dichloromethane and washed with water. Dichloromethane was distilled of under reduced pressure and purified the obtained residue by column chromatography by eluting with 10% ethyl acetate in hexane to get impurity 6 as off white crystalline powder.

Description: Off white crystalline powder; M. F. $C_{16}H_{18}O_4$; M. Wt. 274.31; IR (KBr, cm^{-1}): 2835 (C-H in –OCH_3), 2947 (C-H), 3072 (C-H aromatic), 1592, 1511 and 1480 (C-C aromatic); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.8 (s, 6H, -OCH_3), 4.4 (s, 4H, -CH_2-), 6.9 (m, 4H, ArH), 7.0 (m, 4H, ArH); MS *m/z* (%) = 274 (M); Anal. Calcd for $C_{16}H_{18}O$: C – 70.06, H – 6.61%; Found: C – 70.08, H – 6.60%.

Synthesis of 2-(2-(2-Methoxyphenoxy)ethyl)isoindoline-1,3-dione (impurity 7): Charged dimethyl formamide (25 mL) and impurity 5 (25 g, 0.14 moles) and stated agitation at 25-30^{o}C. Charged potassium phthalimide (29.7 g) at 25-30^{o}C slowly within 15-30 minutes duration. Reaction mass was heated to 120^{o}C and monitored by in-process TLC (mobile phase: chloroform: methanol – 2:3). Reaction completed after 2-3 hours maintenance and cooled to 25-30^{o}C. Water (75 mL) added slowly for 30-60 minutes at the same temperature and maintained for 1-2 hours. Filtered the separated solid and washed with water followed by methanol. Wet material was recrystallized from methanol to get pure impurity 7 as off white powder.

Description: Off white crystalline powder; M. F. $C_{17}H_{15}NO_4$; M. Wt. 297.31; IR (KBr, cm^{-1}): 2938 (C-H), 2842 (C-H methoxy), 3067 (C-H aromatic), 1589, 1505 and 1472 (C-C aromatic), 1714 (C=O), 1394 (C-N); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, -OCH_3), 4.1 (t, 2H, -OCH_2-), 4.3 (t, 2H, -CH_2-), 6.85 (m, 2H, ArH), 6.95 (m, 2H, ArH), 7.7 (m, 2H, ArH), 7.85 (m, 2H, ArH); MS *m/z* (%) = 297 (M); Anal. Calcd for $C_{17}H_{15}NO_4$: C – 68.68, H – 5.09, N – 4.71%; Found: C – 68.69, H – 5.10, N – 4.4.69%.

Synthesis of 2-(2-Chloroethyl)isoindoline-1,3-dione (impurity 8): Potassium phthalamide (20 g, 0.136 mol) and 1,2-dichloroethane (20.2 g, 0.20 mol) were charged into a fresh RBF and started stirring at 25-30^{o}C. Reaction mass heated to 68-72^{o}C and monitored the progress by in-process TLC (mobile phase: ethyl acetate: n-hexane – 6:4). Reaction completed within 3 hours and cooled the mass to ambient temperature. Reaction mass filtered under vacuum and filtrate was extracted with dichloromethane. Dichloromethane layer was kept overnight without agitation for crystal formation. Filtered the separated crystals and distilled off the filtrate under reduced pressure to get residue, which was purified by column chromatography by eluting with 5% ethyl acetate in n-hexane to get impurity 8 as an off white color powder.

Description: Off white crystalline powder; M. F. $C_{10}H_8ClNO_2$; M. Wt. 209.63; IR (KBr, cm^{-1}): 2925 (C-H), 3063 (C-H aromatic), 1614 and 1467 (C-C aromatic), 1717 (C=O), 1396 (C-N), 717 (C-Cl); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.8 (t, 2H, -CH_2-), 4.05 (t, 2H, -CH_2-), 7.7 (m, 2H, ArH), 7.9 (m, 2H, ArH); MS *m/z* (%) = 209 (M); Anal. Calcd for $C_{10}H_8ClNO_2$: C – 57.30, H – 3.85, N – 6.68%; Found: C – 57.62, H – 3.84, N – 6.66%.

Synthesis of N,N' -Ethane-1,2-diyl-bis-phthalimide (impurity 9): Potassium phthalamide (5 g, 0.034 mol) and 1,2-dichloroethane (1.7 g, 0.017 mol) were charged into a RBF and started stirring at 25-30^{o}C. Reaction mass heated to 68-72^{o}C and maintained for 6 hours. Reaction progress was monitored by in-process TLC (mobile phase: ethyl acetate: n-hexane – 6:4). Cooled the reaction mass to 25-30^{o}C and added water and ethyl acetate under stirring. Separated the organic layer and washed with water. Organic layer dried over with sodium sulfate and distilled off completely under reduced pressure. Obtained residue was purified by column chromatography by eluting with 5% ethyl acetate in n-hexane to get pure impurity 9 as an off white powder.

Description: Off white powder; M. F. $C_{18}H_{12}N_2O_4$; M. Wt. 320.3; IR (KBr, cm^{-1}): 2950 (C-H), 3065 (C-H aromatic), 1610 and 1564 (C-C aromatic), 1714 (C=O), 1392 (C-N); ^{1}H-NMR (300 MHz, DMSO-d6): δ 3.3 (s, 2H, -CH_2-), 3.8 (s, 2H, -CH_2-), 7.8 (m, 8H, ArH); MS *m/z* (%) = 320

(M); Anal. Calcd for $C_{18}H_{12}N_2O_4$: C – 67.50, H – 3.78, N – 8.75%; Found: C – 67.52, H – 3.77, N – 8.77%.

Synthesis of bis(2-(2-Methoxyphenoxy)ethyl)amine (impurity 10): Charged 1-(2-chloroethoxy)-2-methoxybenzene (15.6 g) into a RBF and started stirring at 25-30^{o}C. Heated the reaction mass to 120^{o}C and added 2-(2-methoxyphenoxy)ethanamine (20 g) slowly at 120^{o}C. Maintained the reaction mass at 120-125^{o}C and monitored the progress by in-process TLC (mobile phase: ethyl acetate: n-hexane – 3:2). Cooled the mass to ambient temperature and added methanol slowly under stirring. Filtered the separated solid and washed with methanol lot-2. Obtained material was dried at 50^{o}C to get impurity 10 a slight brown crystalline powder.

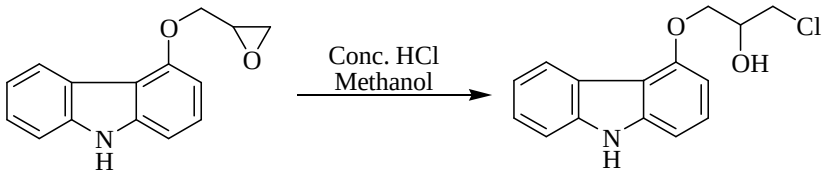
Description: Slight brown crystalline powder; M. F. $C_{18}H_{23}NO_4$; M. Wt. 317.38; IR (KBr, cm^{-1}): 2835 (C-H in $–OCH_3$), 2959 (C-H), 3566 (N-H), 3065 (C-H aromatic), 1593 and 1508 (C-C aromatic); ^{1}H-NMR (300 MHz, DMSO-d6): δ 3.2 (t, 2H, $-CH_2-$), 3.45 (t, 2H, $-CH_2-$), 3.75 (s, 6H, $-OCH_3$), 4.15 (t, 2H, $-CH_2-$), 4.3 (t, 2H, $-CH_2-$), 6.9-7.0 (m, 8H, ArH); MS *m/z* (%) = 317 (M); Anal. Calcd for $C_{18}H_{23}NO_4$: C – 68.12, H – 7.30, N – 4.41%; Found: C – 68.14, H – 7.31, N – 4.40%

RESULTS AND DISCUSSION

This paper reports a simple and effective method for the synthesis of impurities of Carvedilol (1) key intermediates.

According to the scheme 1, general process for the synthesis of Carvedilol (1) is by the condensation of its key intermediates 2 and 3 in the presence of monoglyme solvent. General synthesis of these key intermediates is described in scheme 2 and 3.

Scheme 2 describes the synthesis of 4-(2, 3-epoxyprpoxy) carbazole (2) by the condensation of 4-hydroxy carbazole (4) with epichlorohydrin (5) in the presence of sodium hydroxide and dimethyl sulfoxide. Epoxy ring of the epichlorohydrin is easily cleavable in the presence of base or acid.
Synthetic process of compound 2 was described in experimental section. According to our observation, reaction was very sensitive to the reaction conditions. 4-Hydroxy carbazole (4) and diemthyl sulfoxide addition are very critical and fast addition leads to degradation of the reaction mass. Epichlorhydrin (5) should be added at the specified temperature and duration. Otherwise, it leads to cleavage of epoxy ring and leads to the formation of impurities 1 to 4.



2 **Imprity 1**

Impurity 1
This is a process impurity and formed during the synthesis of compound 2. Hydrochloric acid is a byproduct during the reaction, which reacts with compound 2 and generates impurity 1 by the

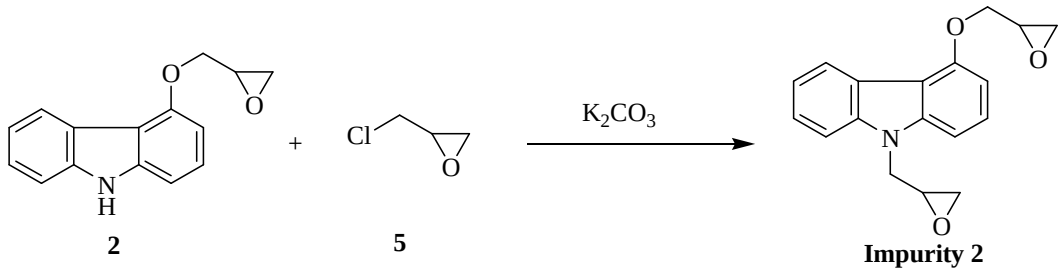
cleavage of epoxy ring. The formation of free hydrochloric acid can be avoided by maintaining the reaction mass pH basic. Synthetic process of impurity 1 was described in scheme 4.

Scheme 4: Synthetic process of impurity 1

1-(9H - Carbazol-5-yloxy)-3-chloropropan-2-ol (impurity 1) of $C_{15}H_{14}ClNO_2$ with molecular ion peak at (M) showed that m/z is equivalent to molecular weight (275.73) of proposed compound. Hence m/z value confirms the molecular weight of the compound. The IR peak at 3394 cm^{-1} suggesting the presence of O-H group. The IR peaks at 1604 cm^{-1} and 1453 cm^{-1} indicates aromatic C-C stretching. Deformation IR peak at 1585 cm^{-1} indicates presence of N-H group. The HNMR peak at δ 11.2 (s, 1H) indicates the presence of one N-H group.

Impurity 2

This is a process impurity and generates during the synthesis of compound 2. Impurity 2 synthesis process was described in scheme 5. During the synthesis of compound 2, base removes the proton from the nitrogen of the carbazole ring, which condenses with epichlorohydrin gives impurity 2.



2 **5** **Impurity 2**

Scheme 5: Synthetic process of impurity 2

4-((Oxiran-2-yl)methoxy)-9-((oxiran-2-yl)methyl)-9H- carbazole (impurity 2) has molecular formula $C_{18}H_{17}NO_3$ and the molecular weight of the compound is equivalent to the molecular ion peak at (M) of the compound. Hence m/z value confirms the molecular weight (295.33) of compound. The IR peak at 2871 cm^{-1} suggesting the presence of C-H stretching of a stringed ring. The IR peak at 1585 cm^{-1} and 1463 cm^{-1} indicates aromatic C-C stretching. The IR peak at 1273 cm^{-1} indicates presence of C-N stretching. The HNMR peak at δ 2.4 – 2.8 indicates the presence of –CH2- group and δ 2.9 and 4.1 indicates –CH- group of a stringed epoxy ring.

Impurity 3

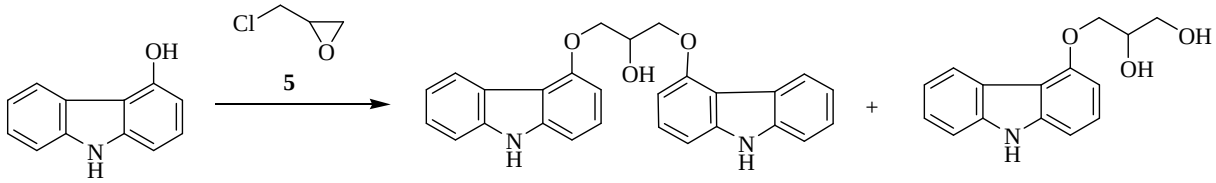
This is a process impurity and form at high temperature maintenance of the reaction mass during the reaction. Other possibility of formation is due to the fast addition of the raw materials. Synthesis of impurity 3 was described in scheme 6.

The molecular formula of 1-(9H-Carbazol-4-yloxy)-3-(9H-carbazol-5-yloxy) propan-2-ol (impurity 3) is $C_{27}H_{22}N_2O_3$ and the molecular weight of the compound is equivalent to the molecular ion peak at (M) of the compound. Hence m/z value confirms the molecular weight (422.48) of compound. The IR peak at 3580 cm^{-1} suggesting the presence of O-H group and 3393 cm^{-1} indicates the presence of N-H group. The IR peak at 1604 cm^{-1} and 1505 cm^{-1} indicates that the presence of aromatic C-C stretching. The HNMR peak at δ 11.2 indicates the presence of N-H group.

Impurity 4

This is a process impurity and sodium hydroxide is the culprit for the formation of this impurity. After formation of compound 2, traces of sodium hydroxide opens the epoxy ring and results the formation of impurity 4. Synthesis of impurity 4 was described in scheme 6.

The obtained molecular ion peak of 3-(9H-Carbazol-5-yloxy) propane-1,2-diol (impurity 4) (molecular formula, ($C_{15}H_{15}NO_3$) at 257 (M) that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight of compound. The IR peak at 3389 cm^{-1} suggesting the presence of O-H group and 3051 cm^{-1} indicates the presence of C-H of a aromatic ring. The IR peak at 1605 cm^{-1} indicates aromatic C-C stretching. The HNMR peak at δ 3.9 indicating the presence of –OH group and δ 11.2 suggests N-H group.

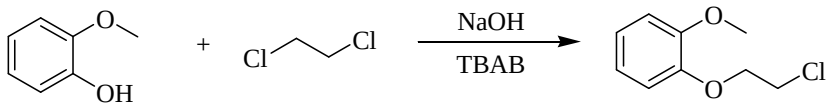


4 **Impurity 3** **Impurity 4**

Scheme 6: Synthetic process of impurity 3 and impurity 4

Impurity 5

This is a stage-1 intermediate during the synthesis of compound 3, 2-Methoxyphenol (6) condenses with 1,2-dichloroethane and results impurity 5. This impurity may carried over to final stage. Preparation of impurity 5 was described in Scheme 7.



6 **Impurity 5**

Scheme 7: Synthetic process of impurity 5

1-(2-chloroethoxy)-2-methoxybenzene (impurity 5) of $C_9H_{11}ClO_2$ with molecular ion peak at (186, M) showed that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight (186.64) of the compound. The IR peak at 2839 cm^{-1} suggesting the presence of methoxy group and 3068 cm^{-1} indicates aromatic C-H stretching. The IR peak at 739 cm^{-1} indicates that the presence of C-Cl group. The HNMR peak at δ 3.8 indicates the presence of $–OCH_3$ group.

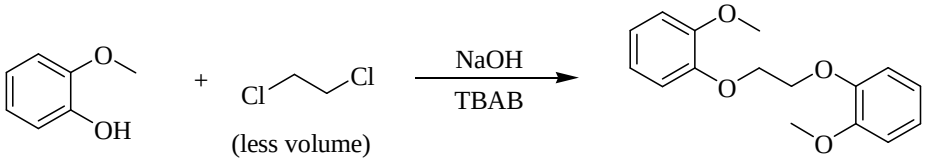
Impurity 6

This is a process impurity and the possibility of formation is during the preparation of compound 7. 1-(2-Chloroethoxy)-2-methoxybenzene (compound 7) condense with Guiacol (6) again and results impurity 6. Less volumes of 1,2-dichloroethane was used for the synthesis of impurity 6.

Scheme 8: Synthetic process of impurity 6

1,2-bis(2-Methoxyphenoxy)ethane (impurity 6) of $C_{16}H_{18}O_4$ with molecular ion peak at (274, M) showed that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight (274.31) of the compound. The IR peak at 2835 cm^{-1} (C-H

stretching) suggesting the presence of –OCH3 group and 3072 cm^{-1} (C-H stretching) indicates aromatic ring. The IR peak at 1592 and 1511 cm^{-1} indicates C-C stretching of a aromatic ring. The HNMR peak at δ 3.8 indicates the presence of –OCH3 group.



6 **Impurity 6**

Impurity 7

This is a stage-2 intermediate during the synthesis of compound 3. 1-(2-chloroethoxy)-2-methoxybenzene (stage-1, impurity 5) condenses with potassium phthalimide and results the formation of 2-(2-(2-methoxyphenoxy)ethyl)isoindoline-1,3-dione (impurity 7). Synthesis of impurity 7 was described in scheme 7.

7 **Impurity 7**

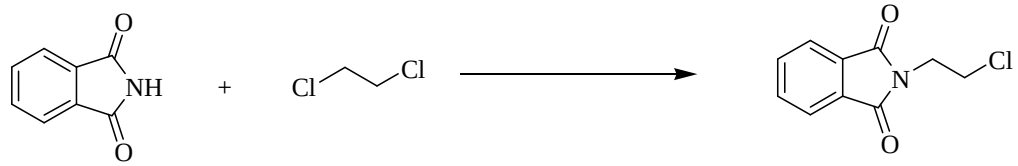
Scheme 9: Synthetic process of impurity 7

Synthesis of 2-(2-(2-Methoxyphenoxy)ethyl)isoindoline-1,3-dione (impurity 7) has molecular formula $C_{17}H_{15}NO_4$ and the molecular weight of the compound is equivalent to the molecular ion peak at (297, M) of the compound. Hence m/z value confirms the molecular weight (297.31) of compound. The IR peak at 2842 cm^{-1} suggests C-H stretching of a methoxy group and 3067 cm^{-1} indicates C-H stretching of aromatic ring. The IR peak at 1714 cm^{-1} indicates the presence of C=O group. The HNMR peak at δ 3.75 indicates the presence of $–OCH_3$ group.

Impurity 8 and Impurity 9

This is a process impurity and generates during the stage-2 reaction of compound 3. The main culprit for the formation of these impurities are the presence of 1,2-dichloroethane traces in compound 7. During the condensation of compound 7 with potassium phthalimide, traces of 1,2-dichloroethane react with potassium phthalimide and yields impurity 8 and impurity 9.

Impurity 8 was synthesized according to the process described in scheme 10. 1.5 molar equivalents of 1,2-dichloromethane was used to prepare impurity 8.

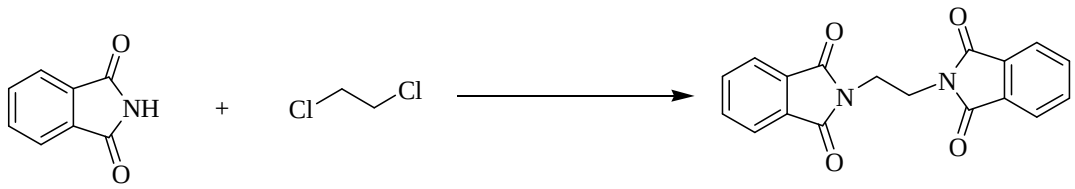


(1.5 molar equivalents) **Impurity 8**

Scheme 10: Synthetic process of impurity 8

The molecular formula of 2-(2-Chloroethyl)isoindoline-1,3-dione (impurity 8) is $C_{10}H_8ClNO_2$ molecular ion peak at (209, M) that m/z is equivalent to molecular weight of proposed compound Hence m/z value confirms the molecular weight (209.63) of compound. The IR peak at 1717 cm^{-1} suggesting the presence of C=O group and 3063 cm^{-1} indicates C-H stretching of a aromatic ring.

Impurity 9 was synthesized according to the process described in scheme 11. 0.5 molar equivalents of 1,2-dichloromethane was used to prepare impurity 9.



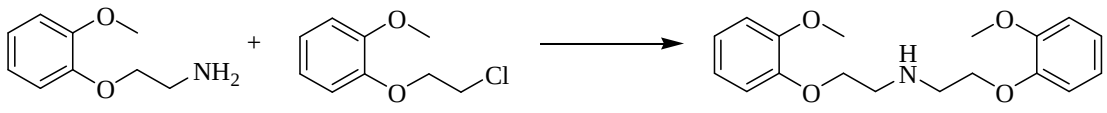
(0.5 molar equivalents) **Impurity 9**

Scheme 11: Synthetic process of impurity 9

The obtained molecular ion peak of N,N' -ethane-1,2-diyl-bis-phthalimide (impurity 9) (molecular formula, $C_{18}H_{12}N_2O_4$) at 320 (M) that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight (320.3) of compound. The IR peak at 1714 cm^{-1} suggesting the presence of C=O group. The IR peak at 3065 cm^{-1} indicates C-H stretching of a aromatic ring.

Impurity 10

This is a process impurity and possibility of formation is during the synthesis of compound 3 from compound 8. Compound 8 contains traces of unreacted compound 7, which undergoes reaction with compound 3 and lead to the formation of impurity 10. Synthesis of impurity 10 was described in scheme 11.



3 **7** **Impurity 10**

Scheme 12: Synthetic process of impurity 10

bis(2-(2-Methoxyphenoxy)ethyl)amine (impurity 10) of $C_{18}H_{23}NO_4$ with molecular ion peak at (317, M) showed that m/z is equivalent to molecular weight of proposed compound. Hence m/z value confirms the molecular weight (317.38) of the compound. The IR peak at 2835 cm^{-1} suggesting the presence of $-OCH_3$ group and 3366 cm^{-1} indicates the presence of N-H group. The HNMR peak at δ 3.75 (s, 3H) indicates the presence of $-OCH_3$ group.

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