Orbital
The electronic journal of chemistry

the electronic journal of chemistry

Full paper | http://dx.doi.org/10.17807/orbital.v17i4.22986

Synthesis and Characterization of Bemotrizinol Impurities

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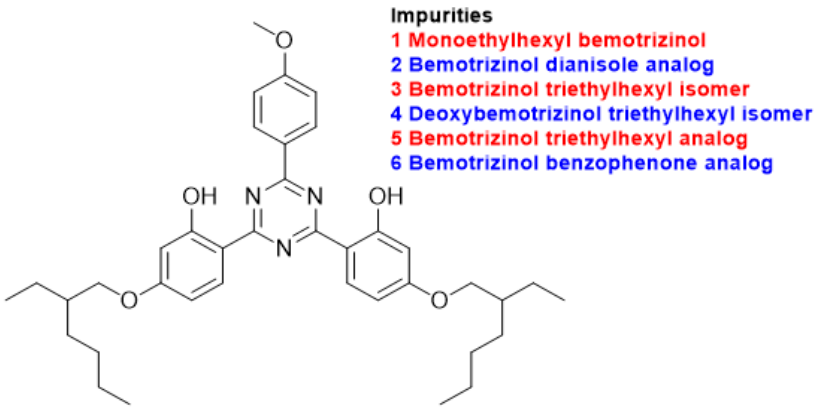
Bemotrizinol (Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine) is widely used ultraviolet filter in sunscreens and cosmetics, is critical for effective UV protection. However, the presence of impurities in bemotrizinol can impact both its efficacy and safety. Regulatory guidelines such as ICH Q3A(R2) and Q3B(R2) emphasize the identification and control of impurities in active pharmaceutical ingredients (APIs) to ensure safety, efficacy, and product quality. This study investigates the elaborate procedures for the synthesis of six impurities related to bemotrizinol. The synthetic methodologies for these impurities were not documented previously in the literature. Our findings reveal significant insights into the quality control of bemotrizinol to ensure product safety and efficacy. The results of this study provide valuable insight into the impurity profile of Bemotrizinol. These findings also contribute to regulatory compliance by enabling proper identification of impurities.

Graphical abstract



Keywords

Bemotrizinol
Impurities
Synthesis
UV

Article history

Received 14 Mar 2025
Revised 20 May 2025
Accepted 29 May 2025
Available online 26 Aug 2025

Handling Editor: Luiz C. Silva Filho

1. Introduction

There are two fundamental pillars in drug discovery: efficacy and safety. Efficacy refers to the drug's ability to produce the desired therapeutic effect while safety, pertains to the drug's risk of causing harm or adverse effects. A drug must not only be effective but also should have an acceptable safety profile, meaning the potential benefits outweigh the risks. To determine the safety of any drug one should be well aware of the possible impurities associated with the synthesis of the target molecule. Impurities can affect the quality, efficacy, and safety of the drug. Impurities can also influence the stability of the drug, potentially affecting its shelf life and overall effectiveness. Concerning this, Bemotrizinol is a benzotriazole derivative primarily used in sunscreens and other skincare products [1]. It functions as a broad-spectrum

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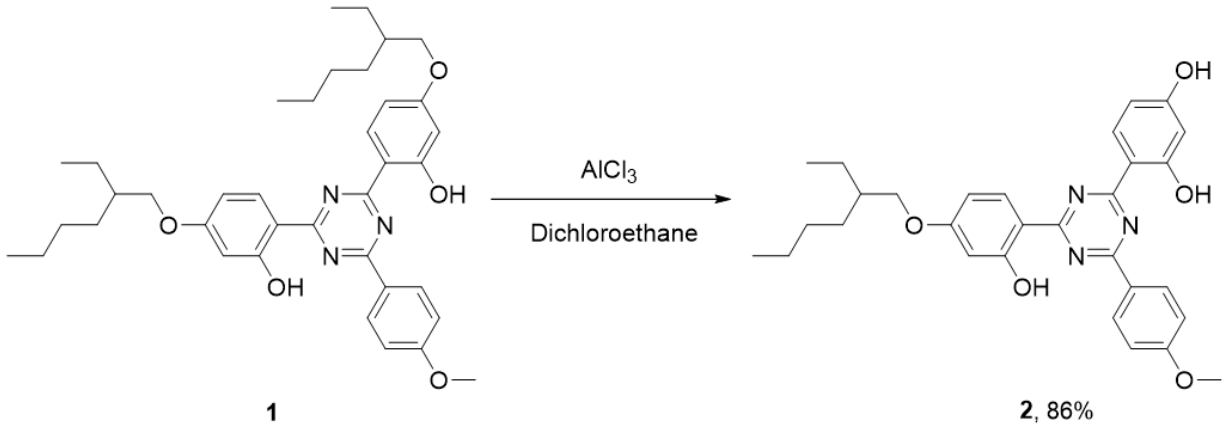
UV filter, providing protection against both UV_A and UV_Brays [2]. It is also commercialized under various brands such as Tinosorb S, Escalol S, Parsol Shield [3]. In addition to its protective properties, Bemotrizinol contributes to the overall stability and efficacy of sunscreen formulations, ensuring that they maintain their effectiveness over time. Bemotrizinol can be combined with other UV filters to enhance the overall sun protection factor (SPF) of a product, offering more comprehensive coverage against different wavelengths of UV radiation [4]. Bemotrizinol, like other chemical compounds used in pharmaceuticals and cosmetics, can have impurities that need to be carefully detect and monitored [5]. It is used in various cosmetic formulations, including sunscreens, lotions, and creams, to enhance UV protection. Due to its stability, it remains effective even in challenging environmental conditions. Herein we have synthesized six possible impurities of bemotrizinol and discovered first time.

2. Results and Discussion

The effective synthesis and thorough characterisation of probable impurities of Bemotrizinol mark a crucial advancement in ensuring the safety and quality of this often used UV filter in cosmetic and medicinal products. A thorough literature survey shows that there is no report is available for the individual synthesis of Bemotrizinol Impurities. As per the data available in USP for impurity profiling of Bemotrizinol, mixture of impurities were available (catalog no. 1048583). The primary objective of the research was to discover, synthesise, and structurally analyse individual impurities that may occur during the production or storage of Bemotrizinol, in accordance with regulatory standards for impurity profiling. The invention discloses a preparation method of a Bemotrizinol process impurity. 2, 4-bis [[4-(2-ethyl-hexyloxy) -2-hydroxy)]-phenyl radical]-6- (4-methoxyphenyl)-1,3,5-triazine, available under the name of Bemotrizinol In the synthesis methods of bis-ethylhexyloxyphenol methoxyphenyl triazine reported at home and abroad at present, 2-(4-methoxyphenyl) -4, 6-dichloro-1, 3, 5-triazine and resorcinol are subjected to Friedel-crafts acylation reaction under the catalysis of Lewis acid to obtain an intermediate 2, 4-bis (2, 4-dihydroxyphenyl) -6- (4-methoxyphenyl) -1,3, 5-triazine, and then are subjected to alkylation reaction with halogenated alkane under the catalysis of alkali to obtain the bis-ethylhexyloxyphenol methoxyphenyl triazine [6].

Six impurities synthesized in this paper includes IMP-I: (4-(4-(4-(2-ethylhexyloxy)-2-hydroxyphenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)benzene-1,3-diol), IMP-II: (5-(2-ethylhexyloxy)-2-(4,6-bis(4-methoxyphenyl)-1,3,5-triazin-2-yl)phenol), IMP-III: 6,6',6''-(1,3,5-triazine-2,4,6-triyl)tris(3-((2-ethylhexyl) oxy)phenol), IMP-IV: 6,6'-(6-(4-((2-ethylhexyl)oxy)phenyl)-1,3,5-triazine-2,4-diyl)bis(3-((2-ethylhexyl)oxy)phenol), IMP-V: 2-(4-(2,4-bis((2-ethylhexyl)oxy)phenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)-5-((2-ethylhexyl)oxy)phenol, IMP-VI: (4-((2-ethylhexyl)oxy)-2-hydroxyphenyl)(phenyl)methanone, are synthesized individually in pure form and well characterized based on their spectral data (IR, 1H NMR and Mass). Each impurity was acquired in enough purity and yield to provide appropriate analytical characterisation. Optimising the reaction was essential to reduce side products and to ensure synthetic relevance to probable manufacturing contaminants.These impurities can be synthesized in an oriented manner, can be used for detecting the quality of Bemotrizinol drugs or preparation samples of the Bemotrizinol drugs and has great significance for industrial production monitoring and quality research of Bemotrizinol. The method has the advantages that the product purity is high, process raw materials are easy to obtain, the reaction conditions are mild, the operation is simple and convenient and the like, belongs to an environment-friendly production process and can provide guarantee for industrial production monitoring and quality research of Bemotrizinol.

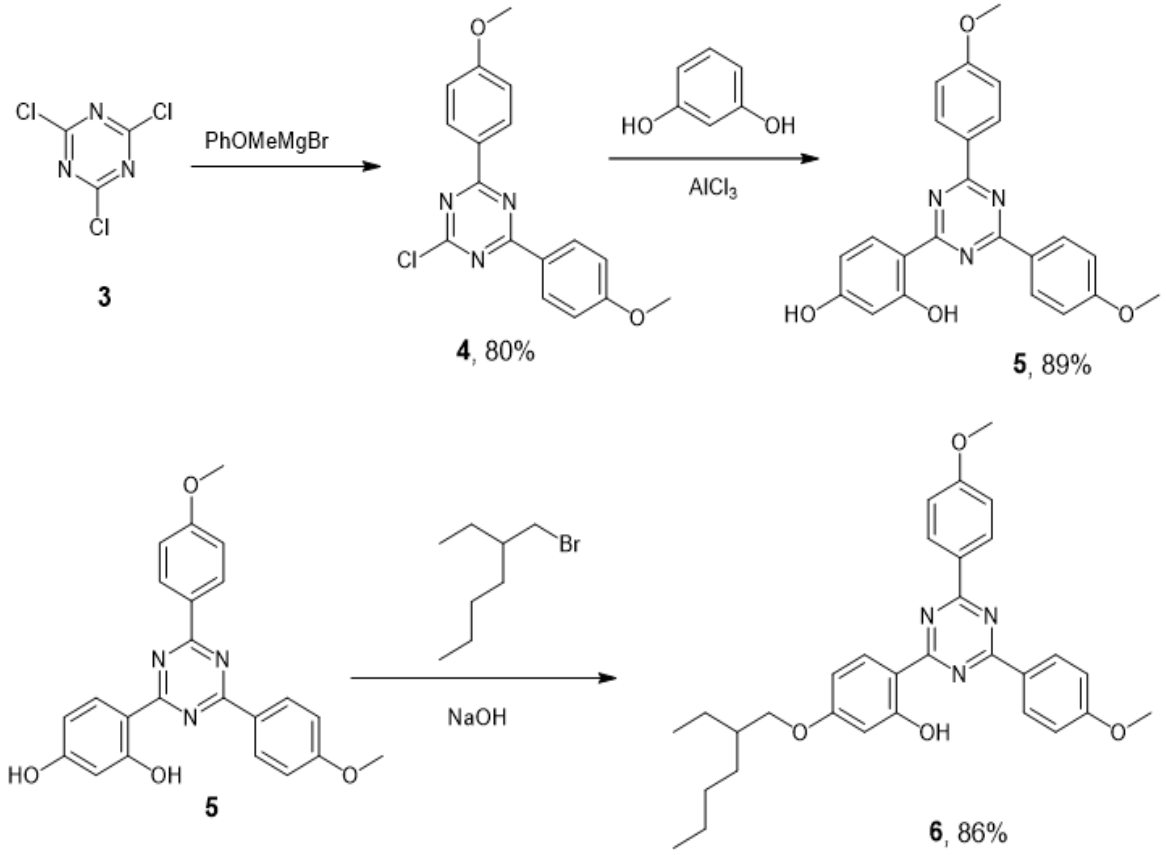
The first impurity of bemotrizinol was synthesized by the selective cleavage of one of the long chain ether in the bemotrizinol **1** molecule. It was synthesized with treatment of the bemotrizinol **1** molecule with $AlCl_3$ in Dichloro ethane (DCE) solvent under reflux conditions, resulted the selective cleavage of single long chain ether delivered the mono hydrolysed product (4-(4-(4-(2-ethylhexyloxy)-2-hydroxyphenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)benzene-1,3-diol) **2** (86% Yield) **(Scheme 1).**



Scheme 1. Synthesis of IMP-I: (4-(4-(4-(2-ethylhexyloxy)-2-hydroxyphenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)benzene-1,3-diol) (**2**).

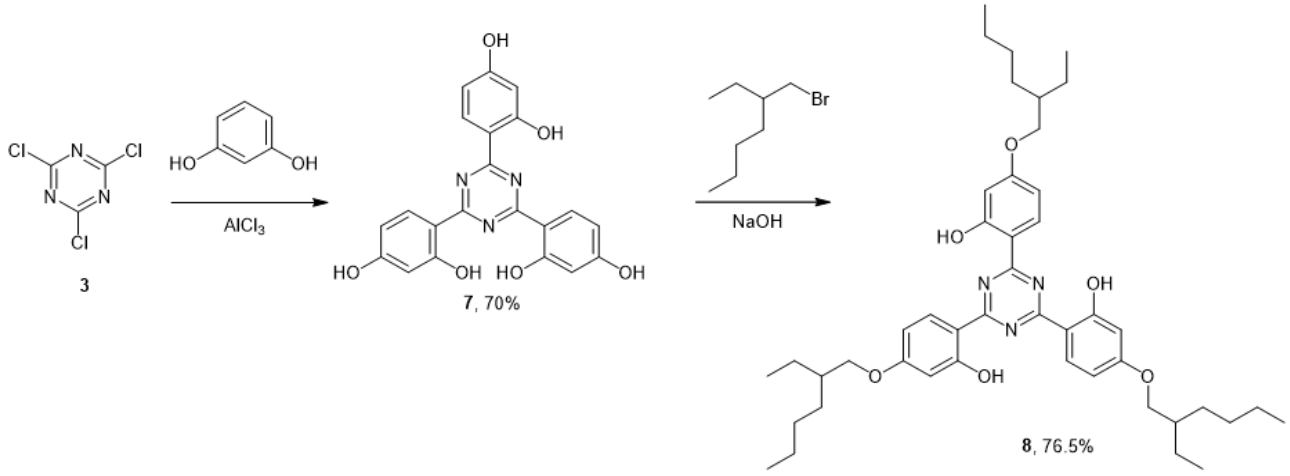
The second impurity of bemotrizinol (5-(2-ethylhexyloxy)-2-(4,6-bis(4-methoxyphenyl)-1,3,5-triazin-2-yl)phenol) **6** was synthesized through a sequence of reaction steps. The first step involved a classic Grignard reagent reaction between 2,4,6-trichloro-1,3,5-triazine **3** and (2-methoxyphenyl)magnesium bromide, subsequently, Freidel Crafts arylation with resorcinol under lewis acid mediated conditions produced 4-(4,6-bis(4-methoxyphenyl)-1,3,5-triazin-2-yl)benzene-1,3-diol **5**. Further, it underwent alkylation

reaction with 3-(bromomethyl) heptane to delivered the respective impurity-II **6** (86% yield) **(Scheme 2).**



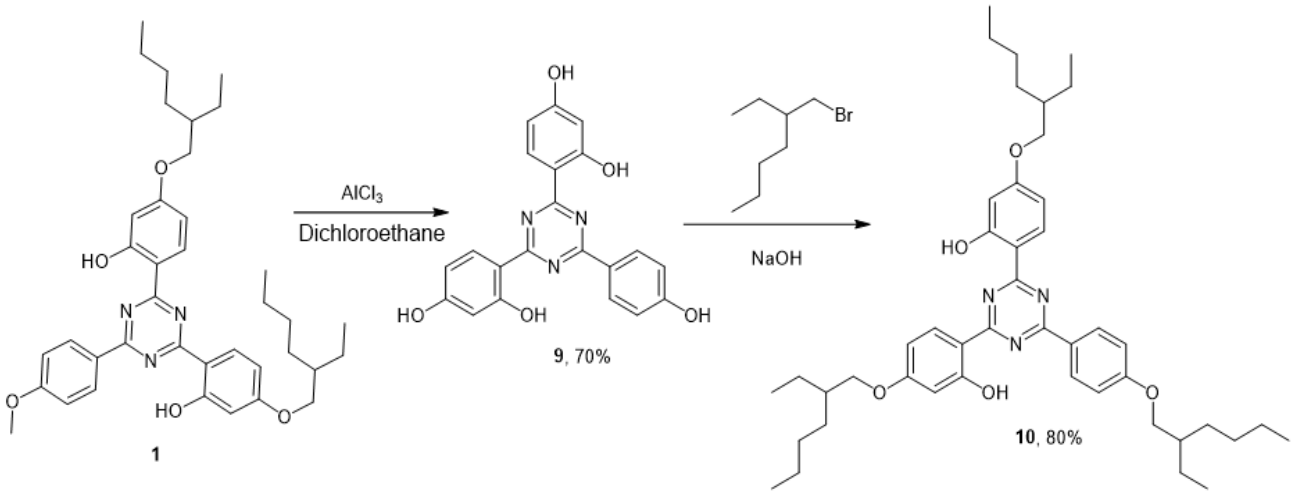
Scheme 2. Synthesis of IMP-II: (5-(2-ethylhexyloxy)-2-(4,6-bis(4-methoxyphenyl)-1,3,5-triazin-2-yl)phenol) (**6**).

The third impurity of bemotrizinol was synthesized from tri-arylation of 2,4,6-trichloro-1,3,5-triazine **3** with resorcinol resulting in the formation of 4,4',4''-(1,3,5-triazine-2,4,6-triyl)tris(benzene-1,3-diol) **7**. Further, it underwent tri-alkylation to give rise to 6,6',6''-(1,3,5-triazine-2,4,6-triyl)tris(3-((2-ethylhexyl)oxy)phenol) **8** (76.5% yield). Further, the impurity-III was confirmed with spectroscopic techniques **(Scheme 3).**



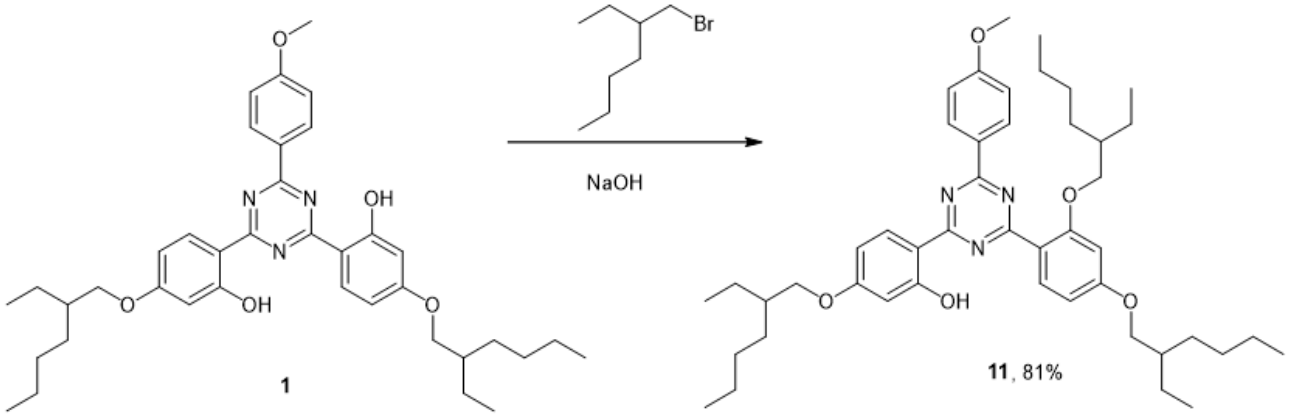
Scheme 3. Synthesis of IMP-III: 6,6',6''-(1,3,5-triazine-2,4,6-triyl)tris(3-((2-ethylhexyl) oxy)phenol) (**8**).

The fourth impurity of bemotrizinol was synthesized from the hydrolysis of bemotrizinol **1** via Lewis acid-assisted pathway. It resulted in the formation of 4,4'-(6-(4-hydroxyphenyl)-1,3,5-triazine-2,4-diyl)bis(benzene-1,3-diol) **9**. Further, it underwent alkylation with 3-(bromomethyl)heptane to afford the 6,6'-(6-(4-((2-ethylhexyl)oxy)phenyl)-1,3,5-triazine-2,4-diyl)bis(3-((2-ethylhexyl)oxy)phenol) **10** (80% yield) **(Scheme 4).**



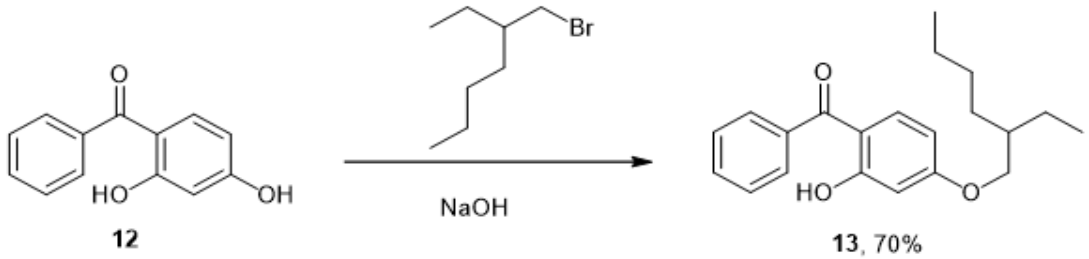
Scheme 4. Synthesis of IMP-IV: 6,6'-(6-(4-((2-ethylhexyl)oxy)phenyl)-1,3,5-triazine-2,4-diyl)bis(3-((2-ethylhexyl)oxy)phenol) (**10**).

The fifth impurity **11** with 81% yield of bemotrizinol was synthesized via monoalkylation of bemotrizinol **1** selectively with 3-(bromomethyl) heptane is depicted in Scheme 5.



Scheme 5. Synthesis of IMP-V: 2-(4-(2,4-bis((2-ethylhexyl)oxy)phenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)-5-((2-ethylhexyl)oxy)phenol **(11).**

The sixth impurity **13** of bemotrizinol was synthesized through the monoalkylation of 4-benzylbenzene-1,3-diol **12** along with 3-(bromomethyl)heptane affording (4-((2-ethylhexyl)oxy)-2-hydroxyphenyl)(phenyl)methanone **13** (70% yield) **(Scheme 6).**



Scheme 6. Synthesis of IMP-VI: (4-((2-ethylhexyl)oxy)-2-hydroxyphenyl)(phenyl)methanone **(13).**

3. Material and Methods

3.1 General informations

Unless otherwise stated, all starting materials, solvents and reagents were obtained commercially and were used as received without further purification. Infrared (IR) spectra were recorded on a FT/IR-4XtypeAinstrument. ^{1}H-NMR &^{13}C-NMR spectra were recorded on Bruker (400MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. Chemical shifts were reported w.r.t. tetramethylsilane in ppm on δ scale. $CDCl_3$ was used as the internal standard with chemical shifts value δ = 7.26 for ^{1}H-NMR, and 77.0 for ^{13}C-NMR)

Electrospray ionization (ESI) mass spectra were performed on the Thermo Finnigan LCQ Classic Mass Spectrometer. The progress of the reaction was monitored through TLC, Purification of Compounds was done by column

chromatography using a mixture of hexane/EtOAc. Chemical yields refer to pure isolated substances.

3.2 General experimental procedure for the preparation of compounds and characterization data

3.2.1 Synthesis of IMP-I: 4-(4-(4-(2-ethylhexyloxy)-2-hydroxyphenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)benzene-1,3-diol (2).

$AlCl_3$ (0.25g, 1.87 mmol) was added to the solution of bemotrizinol**1** (1g, 1.6 mmol) in 10 ml dichloroethane and allowed to be stirred for 15 min. The reaction mixture was refluxed for 8-10 hrs. The reaction mixture was cooled at 0-5°C and charged in ice-cold water. The crude was extracted with 100 ml of dichloroethane and concentrated under reduced pressure. Column chromatography purification was carried out through silica gel using a mixture of hexane/EtOAc as eluting solvent giving corresponding product **2** (yield: 86%, 0.71 gm); ^{1}HNMR (400 MHz, $CDCl_3$) δ13.28 (1H, s), 13.10(1H, s) 10.52 (1H, s) 8.34 – 8.28 (4H, m) 7.23 (2H, dt, *J* = 9.6, 2.3) 6.67 (1H, dd, *J* = 9.1, 2.5), 6.57 (1H, d, *J* = 2.5), 6.54(1H, dd, *J* = 8.8, 2.5), 6.40(1H, d, *J* = 2.2), 3.97(2H, d, *J* = 5.8), 3.91(3H, s) 1.71 (1H, q, *J* = 6.0), 1.42 – 1.39 (4H, m) 1.28 – 1.25 (4H, m) 0.90-0.85 (6H, m); (m/e-516.2 dalton); IR 3366.14, 2926.45, 2863.77, 2570.65, 2353.21, 2299.7, 2043.21, 1607.38, 1538.92, 1507.1, 1460.81, 1305.57, 1363.43, 1260.25, 1102.12; ^{13}C NMR (100 MHz, $CDCl_3$) δ172.37, 165.74, 164.72, 164.63, 164.55, 164.01, 161.96, 130.72, 114.46, 108.63, 108.33, 103.78, 101.83, 70.83, 55.59, 39.24, 30.47, 29.027, 23.82, 23.03, 14.09, 11.10.

3.2.2 Synthesis of IMP-II: (5-(2-ethylhexyloxy)-2-(4,6-bis(4-methoxyphenyl)-1,3,5-triazin-2-yl)phenol) (6).

3.2.2.1 Grignard reaction

(1.4 g, 60 mmol) of magnesium shavings and a few grains of iodine in dry tetrahydrofuran (12 ml) were placed in a 50 ml flask equipped with a stirrer, dropping funnel, cooler and internal thermometer. 4-bromoanisole (11.2 g, 60 mmol) was dissolved in 40 ml dry THF, was slowly added dropwise at 60 °C under an inert atmosphere of nitrogen gas. Once the Mg chips had completely dissolved, the mixture was stirred at 60 °C for 90 minutes. The Grignard solution was then added dropwise at 5 °C under nitrogen gas to the solution of cyanuric chloride **3** (5.53 g, 30 mmol) in THF (15 ml) and stirred for 15 min. 5 ml of water was added, followed by filtration and solid was dried under vacuum at 40°C gave compound **4** with 80% (7.8 gm) yield.

3.2.2.2 Friedel-Crafts acylation

In a 50 ml flask equipped with a stirrer, dropping funnel, cooler and internal thermometer, 2,4-bis(4-methoxyphenyl)-6-chloro-1,3,5-triazine (4.5 g, 13 mmol) **4** and resorcinol (1.8 g, 16.34 mmol) in a mixture of 15 ml xylene (mixture of isomers) and 15 ml sulfolane. Aluminium chloride (2.19 g, 16.42 mmol) was slowly introduced at 60-65 °C and the mixture was stirred until the evolution of HCl had ended (about 4 hours). The warm reaction solution was run into 75 ml methanol / 35 ml dilute hydrochloric acid with stirring, suction filtered and washed with water. Product was dried at 100 °C in a vacuum gave2,4-bis (4-methoxyphenyl) -6-(2,4 dihydroxyphenyl) -1,3,5-triazine **5** as a yellow powder (yield: 4.9 g, 89%).

3.2.2.3 Alkylation

In a 50 ml flask, compound **5** (2.2 g, 5 mmol) was added to 20 ml DMF and sodium hydroxide (0.32 g, 8 mmol). The mixture was allowed to stir at 25 °C for 30 minutes and 3-bromomethyl-heptane (1.58 g, 8 mmol) was added at the same temperature. The reaction mixture was heated at 112-114 °C for 8 h. The progress of the reaction was monitored through TLC, after completion of the reaction the compound was cooled to 25-30 °C and charged with 60 ml water, extracted with 50 ml of ethyl acetate and concentrated under vacuum afforded compounds **6** with 86.0% (2.42 gm) yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ13.73 (1H, s), 8.59 (4H, d, *J* = 9.07, 7.06),7.06 (1H, dd) 7.28 (4H, dd) 6.59 (1H, dd, *J* = 8.79, 2.47) 6.53 (1H, d, *J* = 2.47),4.01(1H, m) 3.93 (6H, s), 3.03 (1H, t, *J* = 7.69), 2.96 (1H, s), 2.89 (1H, s), 1.77 – 1.71 (2H, m), 1.47 – 1.41 (4H, m), 1.32 – 1.29 (6H, m), 0.92 – 0.70(4H, m); (m/e : 514 dalton) IR 3436.53, 2927.41, 2863.77, 2618.86, 2036.46, 1633.41, 1623.7, 1606.41, 1587.13, 1505.17, 1459.8, 1421.28, 1354.75, 1306.54, 1254.47, 1172.51, 1147.44, 107.9, 1030.77; ^{13}CNMR(100MHz,$CDCl_3$)δ 170.89, 165.08, 164.22, 163.50, 131.11, 130.80, 114.07, 110.73, 108.10, 101.71, 70.71,55.80, 39.25, 30.49, 29.07, 23.83, 23.04, 14.09, 11.10.

3.2.3 Synthesis of IMP-III: 6,6',6"-(1,3,5-triazine-2,4,6-triyl)tris(3-((2-ethylhexyl)oxy)phenol) (8).

3.2.3.1 Friedel-Crafts acylation

In a 50 ml flask equipped with a stirrer, dropping funnel, cooler and internal thermometer, was charged with a cyanuric chloride **3** (4.5 g, 24.40 mmol) and of resorcinol (8.32 g, 75.64 mmol) in 15 ml xylene (mixture of isomers) and 15 ml sulfolane. aluminum chloride (10.08 g) was slowly introduced at 60-65 °C and the mixture was stirred until the evolution of HCl has ended (about 4 hours). The warm reaction solution was run into 75 ml methanol /35 ml dilute hydrochloric acid with stirring, suction filtered and washed with waterafforded 7 as a yellow powder which was dried at 100 °C in a vacuum, given 85.7% (8.1 g) yield.

3.2.3.2 Alkylation

2,4,6-(dihydroxyphenyl)-1,3,5-triazine (5 g, 12.33 mmol) was placed in a 50 ml flask. 20 ml DMF and sodium hydroxide (2.5 g, 62.5 mmol) were added. The mixture was allowed to stir at 25 °C for 30 minutes after which 3-bromomethyl-heptane (7.62 g, 39.45 mmol) was added at the same temperature. The combined reaction mixture was further stirred at 85-90 °C for 8 h to ensure complete consumption of starting material, as confirmed by TLC. The reaction mixture was cooled to 25-30°C and charged 60 ml water. It was then extracted with 50 ml of ethyl acetate and concentrated under vacuum. Purified through column chromatography in ethyl acetate and n-hexane as the eluent afforded compounds **8** with 76.5% (7 gm) yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ13.48 (3H, s), 8.05 (3H, d, *J* = 8.79),6.60 (3H, dd, *J* = 9.07, 2.47), 6.54 (3H, d, *J* = 2.47), 3.94 (6H, d, *J* = 5.49), 1.77 – 1.74 (3H, m), 1.47 – 1.42 (12H, m), 1.34 – 1.30 (12H, m), 0.94 – 0.85(18H, m); (m/e-742 dalton); IR 3440.39, 2958.27 47, 2927.41, 2872.45, 2858.95, 2728.78, 2637.18, 2498.33, 2367.19, 2295.84, 2030.68, 1881.22, 1727.91, 1631.48, 1594.84, 1528.3, 1446.35, 1367.28, 1319.07, 1256.4, 1229.4; ^{13}C NMR (100 MHz, $CDCl_3$)δ 168.41, 166.10, 165.14, 130.24, 109.10, 108.80, 102.03, 71.00, 39.21, 30.45, 29.06, 23.88, 23.11, 14.09, 11.18.

3.2.4 Synthesis of IMP-IV: 6,6'-(6-(4-((2-ethylhexyl)oxy)phenyl)-1,3,5-triazine-2,4-diyl)bis(3-((2-ethylhexyl)oxy)phenol) (10).

3.2.4.1

$AlCl_3$ (9.87 g, 74.05 mmol) was added to the solution of bemotrizinol **1** (15g, 23.89 mmol) in dichloroethane (150 ml) and stirred for 15 min. The reaction mixture was heated to reflux for 8-10 hrs, after which it was cooled to 0-5°C. Finally, the combined reaction mixture was charged into ice-cold water. The crude was extracted in dichloroethane and purified through silica gel column chromatography using ethyl acetate and hexane as an eluting solvent obtained compound **9** with77.4% (7.2 g) yield.

3.2.4.2 Alkylation

Compound **9 (**5 g, 12.84 mmol) was placed in a 50 ml flask. DMF (20 ml) and sodium hydroxide (2.5 g, 62.5 mmol) were added to it. The reaction mixture was stirred at 25 °C for 30 minutes and 3-bromomethyl-heptane (7.68 g, 39.80 mmol) was added at the same temperature. The combined reaction mixture was further stirred at 85-90 °C for 8 h to ensure complete consumption of starting material, as confirmed by TLC. The reaction mixture was cooled down to 25-30°C and charged 60 ml water. Crude was extracted with 50 ml of ethyl acetate and concentrated under reduced pressure. Column chromatography purification was carried out through silica gel using a mixture of hexane/EtOAc as eluting solvent giving corresponding product **10** with 80% (7.5 gm) yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.58 (2H, s), 8.38 (1H, s), 7.21(1H, dd, *J* = 9.07, 2.47) 7.05 – 6.89 (2H, m), 6.59 (2H, dd, *J* = 9.07, 2.47), 6.53 (2H, d, *J* = 2.19, 3.96), 4.01 (2H,m) 3.99 (4H, m) 1.77 – 1.74 (3H, m) 1.48 – 1.43 (12H, m), 1.37 – 1.32 (12H, m), 0.99 (6H, m) 0.84 – 0.76 (12H, m) (m/e-727 dalton); IR 3441.35, 2960.2, 2931.27, 2866.67; ^{13}C NMR (100 MHz, $CDCl_3$)δ 165.54, 164.61, 163.84, 130.17, 114.92, 108.53, 101.82, 70.85, 70.81, 39.30, 39.24, 30.48, 29.07, 23.02, 23.04, 14.00, 11.18.

3.2.5 Synthesis of IMP-V: 2-(4-(2,4-bis((2-ethylhexyl)oxy)phenyl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)-5-((2-ethylhexyl)oxy)phenol (11).

Alkylation

Bemotrizinol **1** (5 g, 7.96 mmol), and sodium hydroxide (0.47 g, 11.75 mmol) were added to DMF (20 ml). The reaction mixture was stirred at 25 °C for 30 minutes and 3-bromomethyl-heptane (1.84g, 9.55 mmol) was added at the same temperature. The combined reaction mixture was further stirred at 85-90 °C for 8 h. TLC was used to monitor the reaction progress, after completion of the reaction the compound was cooled to 25-30 °C and charged with 60 ml water. Crude was extracted with 50 ml of ethyl acetate and concentrated under reduced pressure. The crude was purified through a silica gel column chromatography using a mixture of hexane/EtOAc as eluting solvent to produce corresponding product **11** with 81% (4.8 gm) yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ13.83 (1H, s), 8.61 (1H, s), 8.56 (1H, d, *J* = 9.07, 8.29), 7.04 (2H, d, *J* = 9.07), 6.62 – 6.58 (2H, m),6.55 (2H, dd, *J* = 9.07, 2.47), 6.50 (2H, s), 4.03 (2H, d, *J* = 6.04), 3.93(3H, m), 3.72 (3H, m), 3.65(1H, m), 2.11(1H, m) 2.01 (2H, s), 1.77 – 1.74 (10H, m), 1.42 (9H, m), 1.23 – 1.19 (5H, m), 0.94 – 0.90 (12H, m), 0.84 (3H, t, *J* = 7.42), 0.77 (3H, t, *J* = 7.14); (m/e-740 dalton); ^{13}C NMR (100 MHz, $CDCl_3$)δ 164.85, 164.41, 163.80, 163.24, 160.77, 133.82, 130.82, 113.86, 110.85, 107.69, 105.82, 102.45, 101.83, 100.44, 100.32, 99.01, 70.71, 70.63, 55.45, 39.34, 39.27, 30.49, 30.31, 29.07, 28.91, 23.83, 23.60, 23.04, 23.00, 14.09, 14.00, 11.18, 11.21, 10.87.

3.2.6 Synthesis of IMP-VI (4-((2-ethylhexyl)oxy)-2-hydroxyphenyl)(phenyl)methanone (13). Alkylation

(2, 4-dihydroxyphenyl)(phenyl)methanone **12 (**5 g, 23.35 mmol) was placed in a 50 ml flask. DMF (20 ml) and sodium hydroxide (2.5 g, 62.5 mmol) were added to it. The mixture was stirred at 25 °C for 30 minutes and 3-bromomethyl-heptane (7.68 g, 39.80 mmol) was added at the same temperature. The reaction mixture was heated at 112-114 °C for 8 h. The progress of the reaction was monitored through TLC. The reaction mixture was cooled to 25-30°C and charged 60 ml water. Crude was extracted with 50 ml of ethyl acetate and concentrated under a rota evaporator. Column chromatography purification was carried out through silica gel using a mixture of hexane/EtOAc as an eluting solvent affording product **13** with 70% (2.5 gm) yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ12.04 (1H, s), 7.64 (3H, m), 7.55 (2H, td,*J* = 6.53, 1.65), 7.44 (1H, d,*J*=8.79), 6.57 (1H, d,*J*=2.19), 6.53 (1H, dd,*J*=9.07, 2.47), 3.95 (2H, d,*J*=5.77), 1.70 – 1.63 (1H, m), 1.37 – 1.29 (9H, m), 0.89 – 0.72 (6H, m); (M/e-327 dalton).

4. Conclusions

Six potential impurities of bemotrizinol were synthesised separately from the drug. Hence, we have showcased the elaborate synthesis of six impurities of bemotrizinol which are being reported for the first time. We have characterized all the impurities with spectral and analytical data and also discussed the elaborate procedure for the synthesis of the impurities. The synthesised and well characterised impurities of Bemotrizinol create a robust impurity profile, essential for quality control and regulatory adherence. The work provides significant insights into possible degradation pathways, informing formulation and storage strategies. The research offers essential reference standards for method development, validation, and regulatory submission, enabling precise monitoring of impurity levels in products containing Bemotrizinol. These results are essential for adhering to ICH Q3A(R2) and Q3B(R2) recommendations and enhance the overall quality control framework for topical formulations. Future endeavours may include the toxicological assessment of significant impurities to facilitate certification and safety assessments.

Supporting Information

Spectral data and characterization spectra of synthesized compounds are given in supporting information.

Author Contributions

Dattatray Nandaram Thorat: Conceptualization, Methodology,Writing-Original draft. Anwesha Bhattacharya: Data Curation, Writing – Review and Editing. Sandip Dhaya Patil: Analysis, Visulatization. Anoop Singh: Resources, Investigation, Dnyaneshwar Nighot: providing laboratory facility, Pramod Awasthi: Supervision.

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How to cite this article

Thorat, D. N.; Bhattacharya, A.; Patil, S. D.; Singh, A.; Nighot, D.; Awasthi, P. *Orbital: Electronic J. Chem*. **2025**, *17*, 339. DOI: **http://dx.doi.org/10.17807/orbital.v17i4.22986**