Supporting Information

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Ultrasound-assisted efficient synthesis of 3-[4-(2-methoxyethyl) phenoxy] propane -1,2 -diol (Metoprolol EP impurity D)

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2. Experimental Procedures

2.1 Materials and Methods

Column chromatography was performed using Merck Silica Gel 60-120 mesh and petroleum ether and ethylacetate as eluents. Thin layer chromatography was perfomed on Silica gel GF 254. Deionised water was prepared using a Milli-Q plus water purification system from Millipore (Bedford, MA, USA). HPLC grade Ammonium acetate, Triethyl amine, Phosphoric acid, Glacial acetic acid and Acetonitrile and All other basic chemicals were purchased from Merck Limited (India).

2.2. Analytical Techniques

Chromatogrpahy was performed as per European Pharmacopoeial (Ph. Eur.) Method using Waters e2695 HPLC system equipped with UV-Vis 2489 detector and an Auto sampler. Samples in the auto sampler and column oven were set at 25°C. EmpowerTM software (Version 3) from Waters was used for peak analysis, integration and calculation of linear regression of the calibration curve.

^{1}D NMR (^{1}H and ^{13}C) were performed on Bruker 400 MHz NMR spectrometer (Bruker, Fallanden, Switzerland) using deuterated Dimethyl sulfoxide (DMSO-d_6) as a solvent and tetramethylsilane (TMS) as an internal standard. The ^{1}H chemical shift values were reported on δ scale in parts per million (ppm), relative to TMS (δ=0.00 ppm) and the ^{13}C chemical shift values were reported relative to DMSO- d_6 (δ=39.5 ppm).

Infrared spectra were recorded on FTIR Perkin Elmer spectrophotometer using potassium bromide optics.

Mass spectra were obtained using Thermo Scientific Corporation, DSQ II Mass Spectrometer. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400).

*2.3. Synthesis of 3-[4-(2-Methoxyethyl)phenoxy]-1,2-epoxy propane (**4**)*:

4-(2-Methoxyethyl)phenol (**2**, 5g), potassium hydroxide (1.4g) in water (15mL) and Epichlorohydrin (**3**, 2.6 mL) were sequentially transferred to round bottom flask at room temperature and irradiated with ultrasound (80 W, 50 Hz) for 90 mins in pulses. The progress of reaction was monitored by TLC. On completion of reaction, 10 mL water was added to reaction mixture and the same was extracted with dichloromethane. The organic layer was distilled off under vacuum to give crude intermediate **4** which was purified by preparative TLC.

*2.4. Synthesis of 3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol (Ph.Eur. Impurity D, **1**)*:

3-[4-(2-Methoxyethyl)phenoxy]-1,2-epoxy propane (4, 3g) and sulphuric acid (0.7 mL) were sequentially transferred to round bottom flask at room temperature and irradiated with ultrasound (80 W, 50 Hz) for 30 mins in pulses. The progress of reaction was monitored by TLC. On completion of reaction, 10 mL water was added to reaction mixture and the same was extracted with dichloromethane. The organic layer was distilled off under vacuum to give crude EP impurity D **1** which was purified by column chromatography.

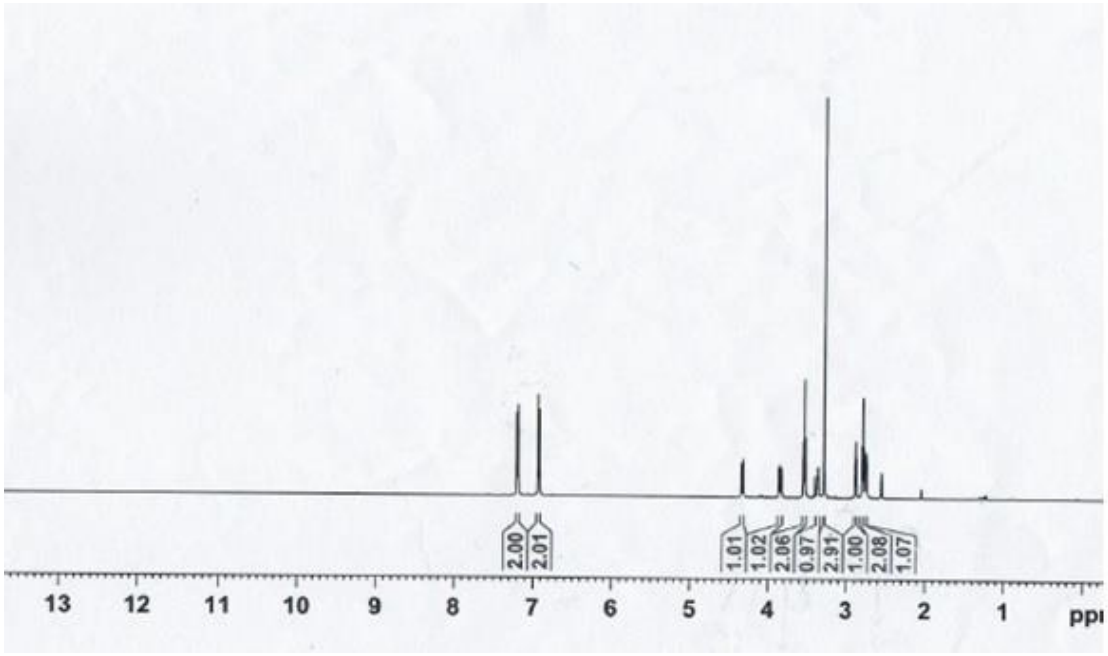

Figure S1: [1]H NMR spectra of 3-[4-(2-Methoxyethyl)phenoxy]-1,2-epoxy propane

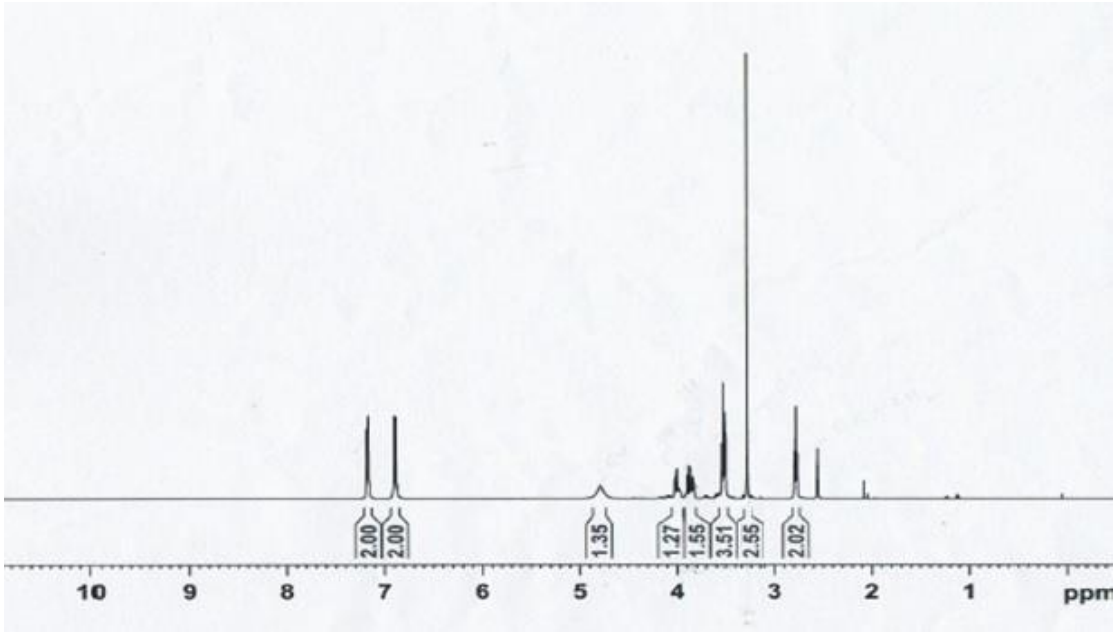

Figure S2:[1]H NMR spectra of 3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol (EP Impurity D)

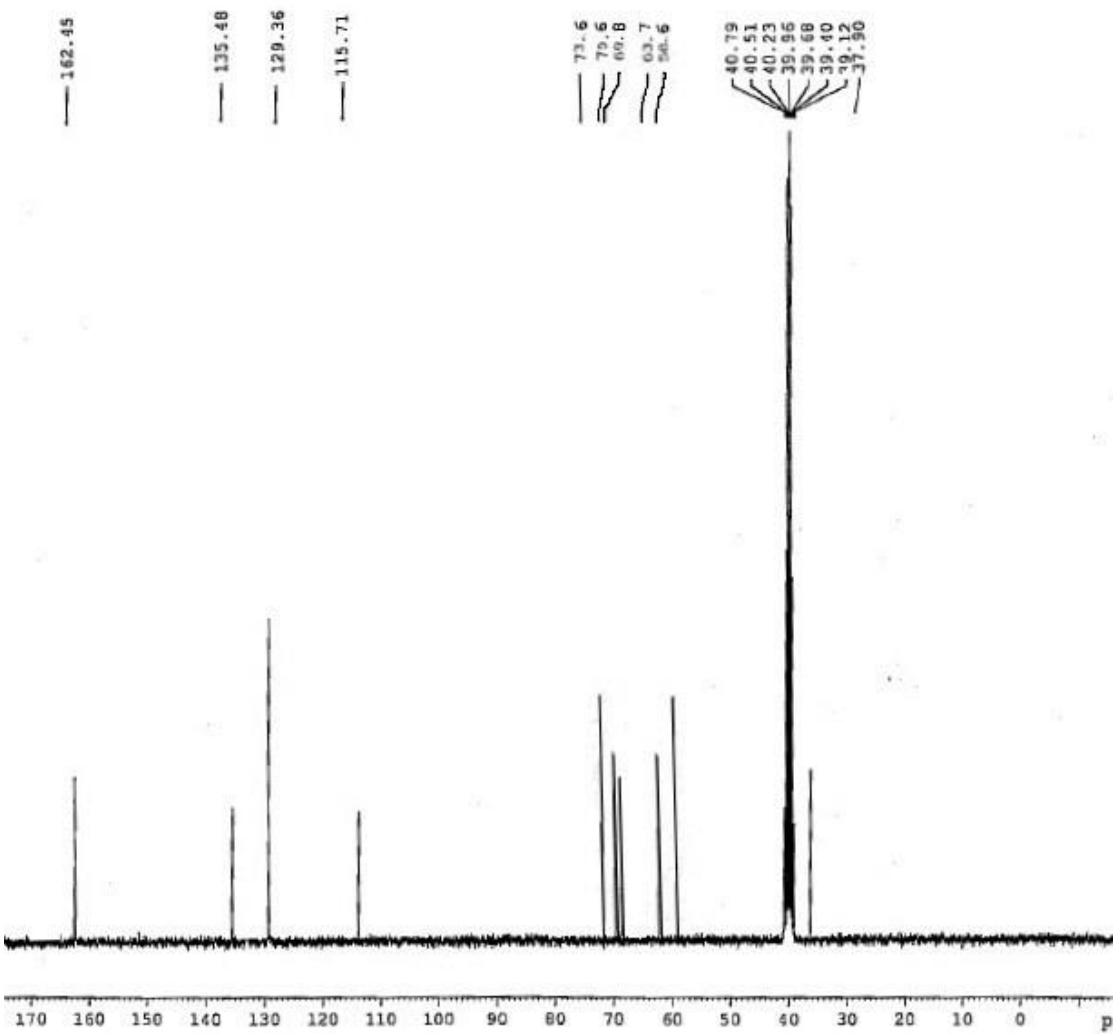

Figure S3:[13] CNMR spectra of 3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol (EP Impurity D)

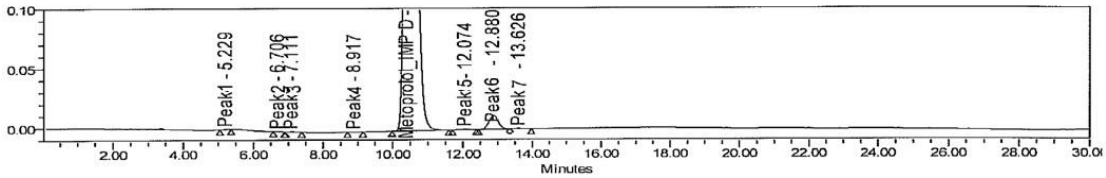

Figure S4:HPLC chromatogram of 3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol (EP Impurity D)

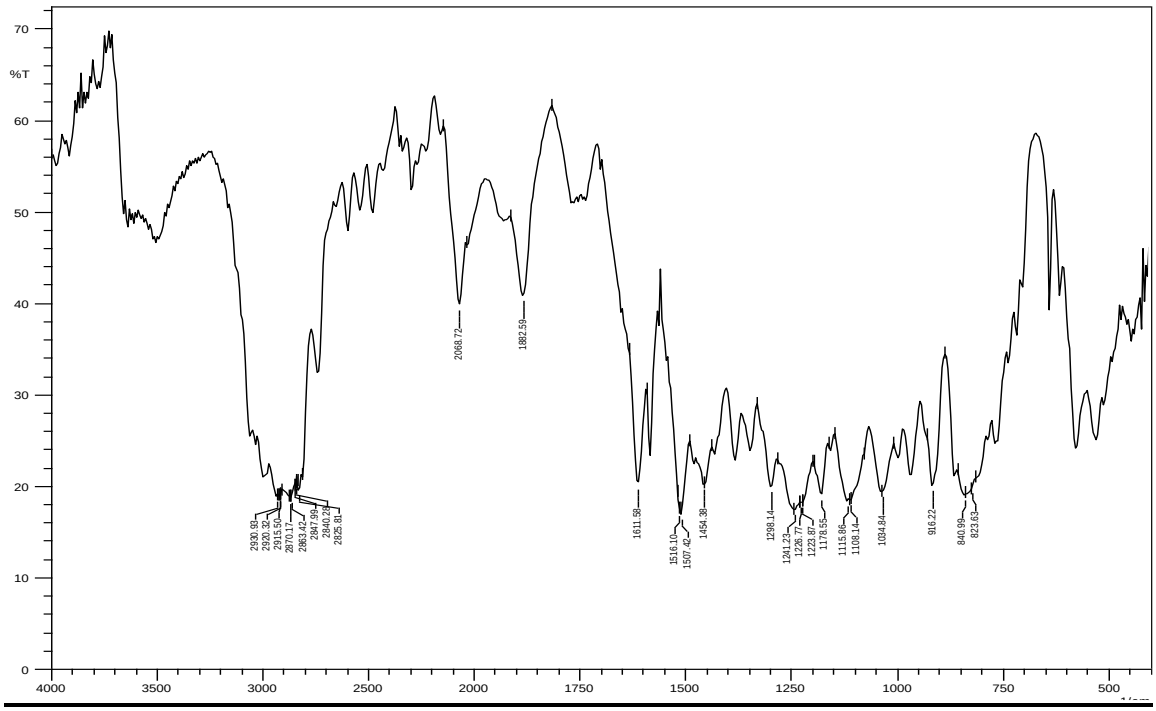

Figure S5:FTIR spectra of 3-[4-(2-methoxyethyl)phenoxy]propane-1,2-diol (EP Impurity D)