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# An Efficient, Novel Synthetic Route to (*R*)-Salmeterol Xinafoate and Facile Synthetic Protocols for Preparation of its Process Related Potential Impurities

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In present work, an effective, innovative enantioselective synthetic strategy for the synthesis of salmeterol xinafoate and its probable process-related impurities was reported. Seven pharmacopeia specified impurities were synthesized and confirmed by FT-IR, mass, $^{1}$H & $^{13}$C NMR spectroscopy. With respect to the corresponding retention factors, these contaminants were validated using the available RP-HPLC method. These compounds can be used as a reference standard for the active pharmaceutical ingredient manufactures and research organizations.

**Keywords: Salmeterol xinafoate, Potential impurities, Long-acting β2-adrenergic agonist (LABA), Impurities.**

## INTRODUCTION

Salmeterol xinafoate, chemically known as (*RS*)-2-(hydroxymethyl)-4-(1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}-ethyl)phenol 1-hydroxynaphthalene-2-carboxylic acid (1:1)) is a selective β2-adrenergic receptor agonist. Due to their long-acting β2-adrenergic agonist capabilities, its salts which are approved for use in pharmaceutical formulations are commonly used to treat asthma (LABA). It is clinically used as a long-acting inhaled bronchodilator for treatment of asthma, chronic obstructive pulmonary disease (COPD) and to control nocturnal asthma. Unlike other bronchodilator drugs, salmeterol xinafoate (**1**) is much more lipophilic and displays many unusual pharmacological properties of like anti-inflammatory activity [1-4].

Salmeterol xinafoate effectiveness has demonstrated at least of 12 h in both adult [5] and pediatric [6] asthma patients. Salmeterol has proven for its activity in the adult [7,8] and pediatric [9] asthma patients, which shows remarkable improvement in lung functioning and control of symptoms with no harmful effects. Although most of the drug is initially breathed, ingested and then absorbed into the systematic circulation from the gastrointestinal tract by inhalation [10], it is supplied through such a route. Thus, the oral route was one of the main routes used for the safety evaluation of salmeterol xinafoate (**1**).

Only severe persistent asthma is typically treated with salmeterol xinafoate (brand name: Serevent), which is then prescribed after SABA such as salbutamol and concurrently with an inhaled corticosteroid (ICS) such as fluticasone [11, 12]. The combination of the LABA and ICS has been shown superior efficacy than separately [13] higher dose of ICS alone [14,15] or combination of ICS and leukotriene antagonist [16] or theophylline [17].

The quality and safety of the pharmaceutical products can be significantly impacted by the process-related contaminants in an active pharmaceutical ingredient (API). Limiting associated impurities is a key part of the "regulatory" portion of drug approval. Therefore, it is essential to research and manage the impurity profile of any API when manufacturing a medicinal drug. Any contaminants which are developing at a level of ≥ 0.10% with respect to the API should be recognized, synthesize and extensively described in accordance with ICH requirements. However, the impurity profiling study of APIs requires highly pure impurities to perform analytical investigation to determine parameters such as specificity, linearity, range, accuracy, precision, limit of detection (LOD), robustness limit of quantification (LQD), reproducibility, system suitability testing and relative retention factor [18,19]. The different pharmacopoeias, such as the British Pharmacopoeia (BP),

European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP) [20] are emphasizing on the acceptable limits of impurities in the APIs of formulations.

The literature is severely lack in its descriptions of the synthesis and characterization of salmeterol xinafoate's essential impurities [21,22]. The impurities arise during its laboratory optimization and commercial scale process were identified as well. The identified impurities were confirmed by its synthesis, spectral analysis and chromatographic analytical data. Salmeterol xinafoate has seven impurities that were synthesized, but they have not yet been reported. These are **A**, **B**, **C**, **D**, **E**, **F** and **G** according to the British and European Pharmacopoeia.

The reported second [23,24] and third generation [25] synthetic procedures have drawbacks of low yield, fiddly work up and usage of pyrrophoric reagent like $LiAlH_4$. However, third generation process [26] has successfully demonstrated the synthesis of salmeterol and its intermediates using modified *N*-benzyl-6-(4-phenylbutoxy)hexan-1-amine hydrochloride and methyl 2-(benzyloxy)-5-(2-bromoacetyl)benzoate intermediates. The method has reduced the formation of impurities **D** and **G** significantly to improve the quality of the salmeterol base as oily residue. *N*-Benzyl-6-(4-phenylbutoxy)hexan-1-amine (free base) is also used as key intermediate in the synthesis of salmeterol [27,28].

Based on literature, in this work, a simple, an efficient, scalable novel synthetic protocol for synthesis of (*R*)-salmeterol is designed . The present paper describes the origin, synthesis, characterization of identified process related specified potential impurities **A**, **B**, **C**, **D**, **E**, **F** and **G** during its laboratory process development and the pilot scale preparation of salmeterol and control of these related substances.

## EXPERIMENTAL

KBr disc and solid state infrared spectra were obtained using a Perkin-Elmer model 1600 FTIR spectrophotometer (Perkin-Elmer, USA). On the triple quadruple API 4000 apparatus (MDSSCIEX, Canada), electrospray ionization mass spectra were recorded. Agilent 1100 series LC-MSD-TRAP-SL system mass spectrometer was used to record the LC-mass spectra. The Hosli CH-Analyzer was used for the elemental analysis and the results were within 0.35% range of the calculated values. Using Bruker proton NMR spectrometer (Fallanden, Switzerland), $^1$H NMR spectra were recorded at 400 MHz. Deutrated solvents (TMS) were obtained commercially and of highest grade. The Poloman MP-96 melting point instrument was used to calculate the uncorrected melting points. The column chromatography (flash chromatography) was carried out using 100-200 mesh silica gel under nitrogen pressure. The details of specified impurities **2** to **8** (**A**-**G**) are depicted in Table-1. The HPLC analysis of salmeterol displayed eight impurity peaks in the range of 0.05-0.15 % levels along with the salmeterol peak.

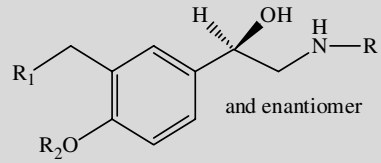
### General synthesis procedure

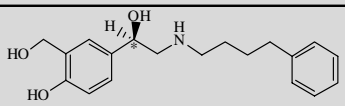
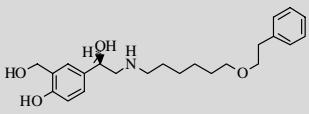
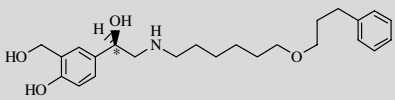
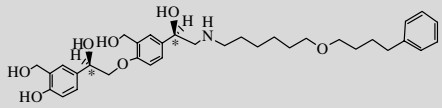
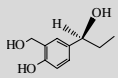
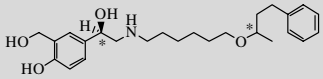
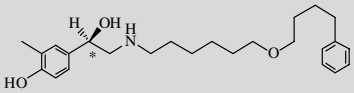
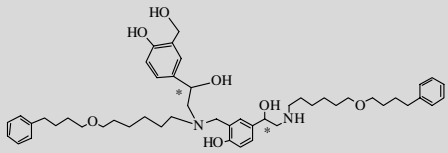
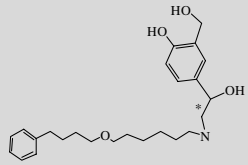
**Synthesis of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*]-[1,3]dioxin-6-yl)ethanol (14):** A solution of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**) (7.1 g, 24.98 mmol) in 55 mL methanol was cooled (below -15 ºC) over a period of 10 min. Then sodium borohydride (1.13 g, 29.98 mmol) was added in-portion under nitrogen atmosphere over a period of 10 min and maintained at 20-25 ºC for 3 h. The reaction mixture was stirred for an additional hour at the same temperature and TLC was used to monitor the progress of the reaction. The reaction mixture was quenched on 120 mL of 10% aqueous $NH_4Cl$ solution when the reaction was completed. The reaction mass was diluted with 100 mL of water and then the product was extracted with 2 × 100 mL of ethyl acetate. The combined organic layer was washed with brine solution (2 × 50 mL) and water (2 × 50 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to obtain a syrupy mass 2-bromo-1-(2,2-dimethyl-4H-benzo[*d*][1,3]dioxin-6-yl)-ethanol. The product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (2: 8) to obtain 6.5 g of product **14** as gummy mass. Yield: 90%. $^1$H NMR (400 MHz, $CDCl_3$): δ 1.52-1.5 (s, 6H), 2.21, (broad 1H, Ar-CH-OH), 3.54-3.56 (dd, 2H, Br-$CH_2$-C), 4.85-4.87 (m, 1H, AR-CH-OH), 4.92 (s, 2H, AR-$OCH_2$), 6.80-6.78 (d, $J$ = 8.0 MHz, 1H), 6.98-6.99 (d, 1H), 7.10-7.22 (m, 1H); MS (ESI, *m/z*): 281.15 $[M-17]^+$; Anal. calcd. found (%) for $C_{12}H_{15}O_3Br$ (*m.w.* 286.02): C, 50.19 (50.22); H, 5.27 (5.29); O, 16.72 (16.74).

**Synthesis of 4-((6-azidohexyl)oxy)butyl)benzene (10):** To a stirred solution of 4-((6-bromohexyl)oxy)butyl)benzene (**9**) (7.4 g, 23 mmol), DMF (40 mL) were charged at room temperature and cooled to 0-5 ºC. Then sodium azide (1.842 g, 28.34 mmol) was added portion wise for 10 min and maintained at room temperature for 4 h. The reaction progress was monitored by TLC (*n*-hexane:ethyl acetate, 4:1); after completion of reaction, it was quenched in 100 mL of demineralized water and extracted with (3 × 50 mL) of ethyl acetate. The combined organic layer was washed with brine solution (2 × 50 mL), water (2 × 50 mL), dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure at below 55 ºC to obtain **10** as syrupy mass, dried on high-vacuum below 55 ºC. Yield: 6.2 g, 95%. This crude compound was used for next stage. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.3-2.0 (m, 12H), 2.6 (t, 2H, -$CH_2$-$C_6H_5$), 3.3 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2N_3$), 7.1-7.4 (m, 5H, -$C_6H_5$); MS (ESI, *m/z*): 276.39 $[M+H]^+$, 298.2 $[M+Na]^+$. Anal. calcd. (found) (%) for $C_{16}H_{25}N_3O$ (*m.w.* 275.0): C, 69.75 (69.78); H, 9.14 (9.15); N, 15.22 (15.23); O, 5.80 (5.81).

**Synthesis of 6-(4-phenylbutoxy)hexan-1-amine hydrochloride (12):** To a stirred solution of 4-((6-azidohexyl)oxy)-butyl)benzene (**10**, 6.2 g, 22.51 mmol), methanol (80 mL) and 10% Pd/C (1.24 g, 0.2 equiv. w/w) were charged at room temperature. Then hydrogen gas was continuously purged under 3 kg pressure at ambient temperature for 15 min and maintained at 25-30 ºC for 4 h. The reaction progress was monitored by TLC (methylene dichloride:methanol, 4:1). The reaction mixture was cooled to below room temperature after completion of reaction and recovered the Pd/C through filtration assembly, washed with (2 × 20 mL) of methanol to get reddish colour mass **11**. Then the filtrate was taken into three necked round

TABLE-1
CHEMICAL STRUCTURE OF SALMETEROL PROCESS-RELATED SPECIFIED IMPURITIES **2-8** [**A, B, C, D, E, F** AND **G**]




| Impurity number | Impurity structure | R | $R_1$ | $R_2$ |
|---|---|---|---|---|
| **2** or **A** |  | $[CH_2]_4$-$C_6H_5$ | OH | H |
| **3** or **B** |  | $[CH_2]_6$-O-$[CH_2]_2$-$C_6H_5$ | OH | H |
| **4** or **C** |  | $[CH_2]_6$-O-$[CH_2]_3$-$C_6H_5$ | OH | H |
| **5** or **D** |  | $CH_2]_6$-O-$[CH_2]_4$-$C_6H_5$ | OH |  |
| **6** or **E** |  | $CH_2]_6$-O-$[CH_2]_4$-$C_6H_5$ | OH | H |
| **7** or **F** |  | $[CH_2]_6$-O-$[CH_2]_4$-$C_6H_5$ | H | H |
| **8** or **G** |  | $[CH_2]_6$-O-$[CH_2]_4$-$C_6H_5$ |  | OH |

**2** or **A** = (1RS)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[(4-phenylbutyl)amino]ethanol; **3** or **B** = (1RS)-1-[4-Hydroxy-3-(hydroxymethyl)-phenyl]-2-[[6-(2-phenylethox)hexyl]amino]ethanol; **4** or **C** = (1RS)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(3-phenylpropoxy)hexyl]-amino]ethanol; **5** or **D** = 1-[4-[2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-ethoxy]-3(hydroxymethy)phenyl]-2-[[6-(3-phenylbutoxy)-hexyl]amino]ethanol; **6** or **E** = 1-[4-Hydroxy-3(hydroxymethyl) phenyl]-2-[[6-(1-methyl-3-phenylpropoxy)hexyl]amino]ethanol; **7** or **F** = (1RS)-1-(4-Hydroxy-3-methylphenyl)-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol; **8** or **G** = 1-[4-Hydroxy-3-[[[2-hydroxy-2-[4-hydroxy-3-(hydroxy-methyl)-phenyl] ethyl][6-(4- phenylbutoxy)-hexyl]amino] methyl]phenyl]-2-[[6-(4-phenylbutox)exyl]amino]ethanol.

bottom flask and cooled to 5-10 ºC for 20 min. To this, dry HCl gas was purged for 2-3 h under inert atmosphere till dark brown gummy mass formed. Then the solvent was removed under reduced pressure below 60 ºC and recrystallized from *n*-hexane (30 mL) as a brown crystalline solid **12**. Yield: 6.1 g, 95.01%). $^1$H NMR (400 MHz, $CDCl_3$): 1.3-2.0 (m, 12H), 2.6 (t, 2H, -$CH_2$-$C_6H_5$), 3.5 (m, 8H, -$CH_2$-O-$CH_2$- + -$CH_2NH_2$), 7.1-7.4 (m, 5H, -$C_6H_5$). MS (ESI, *m/z*): 250.39 $[M+H]^+$, 272.39 $[M+Na]^+$. Anal. calcd. (found) (%) for $C_{16}H_{28}NOCl$ (*m.w.* 249.21): C, 67.20 (67.23); H, 9.84 (9.87); N, 4.89 (4.90); O, 5.59 (5.60).

**Synthesis of 1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((6- (4-phenylbutoxy)hexyl) amino)ethanol (15):** To a stirred solution of 6-(4-phenylbutoxy)hexan-1-amine hydrochloride (**12**), 1.2 g, 4.2 mmol), DMF (10 mL), water (5 mL) and CsOH (0.7 g, 4.2 mmol) were charged at room temperature. To this 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanol (**14**) (1.07 g, 3.77 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 20 min and maintained at 25-30 ºC for 10 h. Thin layer chromatograpy (TLC) (chloroform:methanol, 4:1) was used to monitor the progress of reaction. Once it was completed, the solvent was extracted under reduced pressure below 65 ºC and the crude product was quenched in 50 mL of demineralized water. Ethyl acetate (2 × 50 mL) was used to extract the target substance. An ochre-colored oil of compound **15** was obtained by centrifuging the collected organic layer under decreased pressure after it had been cleaned with brine solution (50 mL), dried over anhydrous $Na_2SO_4$ and dried again. The product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (7:1) to obtain 1.51 g of desired product as colourless solid. Yield: 79 % and 99 % purity by HPLC, m.p.: 65-66 ºC; $[\alpha]_D^{25}$ = -22.6º (*c* = 1.0, methanol) (lit. yellow slurry); $[\alpha]_D^{25}$ = -16.5º (*c* = 1.2, $CHCl_3$); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3357.5, 3192.9, 2925.5, 2853.1, 1635, 1498, 1261, 1118; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.36-1.37 (4H, m, $N(CH_2)_2$-$(CH_2)_2(CH_2)_2O$), 1.54 (10H, m, $2CH_3$, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.63-1.68

(6H, m, $J$ = 7 Hz, $PhCH_2CH_2CH_2CH_2O$), 2.58-2.65 (3H, m, $PhCH_2$, CHN), 2.68-2.70 (2H, m, $CH_2N$), 2.82-2.86 (1H, dd, $J$ = 8.1 Hz, CHN), 3.36-3.40 (4H,m, $CH_2OCH_2$), 4.56-4.59 (1H, dd, $J$ = 8.0 Hz, HOCHAr), 4.87 (2H, s, $OCH_2$), 6.75-6.82 (1H, d, $J$ = 7.9 Hz, ArH), 7.02 (1H, s, ArH), 7.14-7.16 (1H, dd, $J$ = 8 Hz, ArH), 7.18-7.20 (3H, m, PhH), 7.23-7.24 (2H, m, PhH). $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 24.6, 24.9, 26.1, 27.1, 28.1, 29.4, 29.7, 30.2, 35.8, 49.4, 57.1, 61.0, 70.7, 70.9, 71.3, 99.5, 116.9, 119.3, 122.1, 125.7, 125.8, 128.3, 128.4, 134.5, 142.5, 150.6; MS (ESI, *m/z*): 456.3 ($[M + H]^+$). Anal. calcd. (found) (%) for $C_{28}H_{41}NO_4$ (455.3): C, 73.80 (73.81); H, 9.05 (9.07); N, 3.03 (3.07); O, 14.02 (14.05).

**Synthesis of 4-(1-hydroxy-2-((6-(4-phenylbutoxy)-hexyl)amino)ethyl)-2-(hydroxymethyl)phenol (Salmeterol base) (1):** 1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((6-(4-phenylbutoxy)hexyl)amino)ethanol (**15**) (1.51 g, 3.31 mmol), were added to glacial acetic acid (0.89 g, 14.91 mmol) and 8.0 mL of water at 25-30 ºC. Raised the reaction temperature gradually to 55-60 ºC and maintained it for 5 h. The reaction was monitored by TLC (chloroform:methanol, 4:1). After the reaction was finished, the solvent was withdrawn under decreased pressure at > 65 ºC and cooled at -2 to 10 ºC. After neutralizing with 20 mL of 5% $Na_2CO_3$ solution, the product was extracted with ethyl acetate (2 × 25 mL). An ochre-coloured oil of compound **1** was obtained by the condensation under reduced pressure after the combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated. The product was purified by column chromatography using eluent system being ethyl acetate and *n*-hexane (7:1) to obtain 1.24 g of product **1** as white solid. Yield: 85% and 99.45% purity by HPLC. Then it was prepared as xinafoate salt with 1:1 mol ratio of 2-hydroxy naphthoic acid in methanol as solvent. m.p.: 78-79 ºC (free base). LCMS RT: 6 min, 100%; $[\alpha]_D^{25}$ = -23.32º ($c$ = 1.0, methanol) (lit. colourless gum); $[\alpha]_D^{25}$ = -18.5º ($c$ = 0.81, methanol)); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3356, 3024, 2928, 2853, 1607, 1454, 1260, 1109; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.32-1.33 (4H, m, N-$(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2$O), 1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.60-1.70 (4H, m, $PhCH_2CH_2CH_2CH_2O$), 2.54-2.70 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.36-3.43 (4H, dt, $J$ = 6.6 Hz, $CH_2OCH_2$), 4.51-4.55 (1H, m, CHOH), 4.76 (2H, s, Ar-$CH_2OH$), 6.79-6.80 (1H, d, $J$ = 8.2 Hz, Ar-H), 6.94 (1H, s, Ar-H), 7.09-7.11 (1H, d, $J$ = 8.2 Hz, Ar-H), 7.17-7.19 (3H, d, $J$ = 7.0 Hz, PhH), 7.25-7.29 (2H, m, PhH); $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 26.23, 26.9, 28.3, 29.33, 29.65, 29.80, 35.65, 49.25, 56.82, 64.29, 70.72, 70.89, 71.29, 116.38, 125.05, 125.29, 125.69, 126.79, 128.23, 128.41, 133.86, 142.55, 155.82; MS (ESI) *m/z*: 415.65 $[M + H]^+$. Anal. calcd. (found) % for $C_{25}H_{37}NO_4$ (*m.w.* 415.57): C, 72.26 (72.19); H, 8.97 (9.05); N, 3.37 (N, 3.38).

**Synthesis of 2-azido-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)ethanone (16):** To a stirred solution of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanol (**13**) (1.0 g, 3.5 mmol), DMF (10 mL) were charged at room temperature and reaction mixture was cooled to 0-5 ºC. Then sodium azide (0.29 g, 4.56 mmol) was added portionwise at same temperature for 5 min. Then reaction mixture was allowed to room temperature and maintained at for 3 h. The reaction progress was monitored by TLC (*n*-hexane:ethyl acetate, 4:1) after completion of reaction, it was quenched in 50 mL of demineralized water and extracted with (2 × 25 mL) of ethylacete. The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 25 mL), dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure at below 55 ºC to obtain title compound **16** as syrupy mass, which dried on high-vacuum (0.8 g, 93%). $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.52-1.5 (s, 6H), 4.53 (s, 2H, $N_2$-$CH_2$-C), 4.92 (s, 2H, Ar-$OCH_2$), 6.80-6.78 (d, $J$ = 8.0 MHz, 1H), 7.75-7.73 (d, 1H), 7.80-7.79 (m, 1H); MS (ESI, *m/z*): 248.25 $[M+H]^+$; Anal. calcd. (found) (%) for $C_{12}H_{13}N_3O_3$ (*m.w.* 247.25): C, 58.27 (58.29); H, 5.27 (5.29); N, 16.98 (16.99); O, 19.42 (19.41).

**Synthesis of (*R*)-2-amino-1-(2,2-dimethyl-4*H*-benzo[*d*]-[1,3]dioxin-6-yl)ethanol (17):** A solution of 2-azido-1-(2,2-diethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**16**) (0.8 g, 3.23 mmol) in 20 mL methanol was cooled (below -15 ºC) over a period of 5 min. Then $NaBH_4$ (0.17 g, 4.52 mmol) was added portionwise under $N_2$ atmosphere and maintained the reaction temperature at 20-25 ºC for 4 h. The reaction mixture was further stirred for 1 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched onto 30 mL of 10% aqueous $NH_4Cl$ solution. The reaction mass was diluted with 40 mL of water and extracted the product with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to obtain as syrupy mass (1.1 g). Then, methanol (30 mL) and 10% Pd/C (0.22 g, 0.2 equiv. w/w) were charged at room temperature and hydrogen gas was purged under 3 kg pressure at ambient temperature for 15 min and maintained at 25-30 ºC for 4 h. The reaction progress was monitored by TLC (methylene dichloride:methanol, 4:1) after completion of reaction, it was cooled to below room temperature and Pd/C was recovered through filtration assembly, washed with 20 mL × 2 of methanol to get reddish colour product. Then, the solvent was removed under reduced pressure below 60 ºC to afford 1.1 g to crude compound. The product was purified by column chromatography using eluent system of ethyl acetate and *n*-hexane (2:8) to obtain 0.62 g of product **17** as white solid. Yield: 86%, HPLC: 98%; m.p.: 119-120 ºC; $[\alpha]_D^{25}$ = -28.1º ($c$ = 0.3, $CH_3OH$); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3354, 3058, 2998, 2918, 2853, 1592, 1498, 1460, 1375, 1265, 1210, 1145, 1075, 1060; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.55 (6H, s, 2×$CH_3$), 2.77-2.90 (1H, dd, $J$ = 12.7 and 7.9 Hz, CHN), 2.94-2.96 (1H, dd, $J$ = 12.70 and 4.10 Hz, CHN), 4.55-4.58 (1H, m, CHOH), 4.85 (2H, s, $OCH_2$), 6.79-6.82 (1H, d, $J$ = 8.5 Hz, Ar-H), 6.95-6.99 (1H, s, Ar-H), 7.10-7.14 (1H, d, $J$ = 8.45 Hz, Ar-H); $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 24.65, 24.89, 49.21, 61.35, 73.89, 99.62, 117.11, 119.28, 122.19, 125.79, 134.29, 150.66; MS (ESI) *m/z*: 206.17 $[M + H–H_2O]^+$; Anal. calcd. (found) (%) for $C_{12}H_{17}NO_3$ (*m.w.* 223.27): C, 64.45 (64.55); H, 7.65 (7.67); N, 6.28 (6.27); O, 21.60 (21.50).

**Synthesis of 4-phenylbutyl methanesulfonate (19):** A solution of 4-phenyl-butan-1-ol (**18**) (0.8 g, 5.32 mmol) in 20

mL dichloromethane and triethylamine 1.13 g, 11.18 mmol) were cooled (below -2 to 10 ºC) over a period of 10 min. Then a solution of methanesulfonyl chloride (0.68 g, 5.85 mmol) in dichloromethane (10 mL) was added slowly over a period of 10 min and maintained the reaction temperature at 10-15 ºC under nitrogen atmosphere. The reaction mixture was further stirred for 3 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched into 50 mL cold water. The reaction mass was acidified with conc. HCl till solution pH becomes 4 and extracted the product with dichloromethane (2 × 25 mL). The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 40 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to obtain 4-phenylbutyl methanesulfonate (**19**) as an oily (1.1 g) product.

**Synthesis of (*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-((4-phenylbutyl) amino)ethanol (20):** To a stirred solution of (*R*)-2-amino-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)ethanol (**17**) (0.5 g, 2.24 mmol), DMF (10 mL) and $K_2CO_3$ (0.68 g, 4.93 mmol) were charged at room temperature. 4-Phenylbutyl methanesulfonate (**19**) (0.56 g, 2.46 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 10 min and maintained at 25-30 ºC for 3 h. The reaction progress was monitored by TLC (methylene dichloride:methanol, 4:1). After completion of reaction, it was cooled to room temperature and filtered. Filtrate was taken and the solvent was removed under reduced pressure below 60 ºC and recrystallized from *n*-hexane (15 mL) as a low melting white crystalline semi-solid **20**. Yield: 0.65 g, 81% (Purity by HPLC: 97.5%). FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3358, 3193, 2923, 2852, 1632, 1499, 1262, 1115; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34-1.35 (4H, m, $N(CH_2)_2$-$(CH_2)_2C_6H_5$), 1.54 (8H, m, $2CH_3$, $NCH_2CH_2$-$(CH_2)_2$-$CH_2$), 2.58-2.64 (3H, m, $PhCH_2$, CHN), 2.64-2.72(2H, m, $CH_2N$), 2.74-2.82 (1H, dd, *J* = 8 Hz, CHN), 4.57-4.60 (1H, dd, *J* = 8 Hz, HOCHAr), 4.85 (2H, s, $OCH_2$), 6.78-6.80 (1H, d, *J* = 8 Hz, Ar-H), 7.01 (1H, s, Ar-H), 7.11-7.13 (1H, dd, *J* = 8 Hz, Ar-H), 7.17-7.19 (3H, m, PhH), 7.25-7.29 (2H, m, PhH); MS (ESI, *m/z*): 356.47 $[M+H]^+$. Anal. calcd. (found) (%) for $C_{22}H_{29}NO_3$ (*m.w.* 355.47): C, 74.34 (74.33); H, 8.25 (8.22); N, 3.93 (3.94); O, 13.52 (13.50).

**Synthesis of (*R*)-4-(1-hydroxy-2-((4-phenylbutyl)-amino)ethyl)-2-(hydroxymethyl)phenol 2(*R*)-Salmeterol-EP-impurity-A:** (*R*)-1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((4-phenylbutyl)amino)ethanol (**20**) (0.65 g, 1.82 mmol), was added to glacial acetic acid (0.54 g, 9.14 mmol) and 8.0 mL of water at 25-30 ºC. The reaction temperature was raised to 55-60 ºC and maintained at same temperature for 5 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the mass with 15 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as an ochre coloured oil of compound **2**. The product was purified by column chromatography, ethyl acetate and *n*-hexane (7:1) as eluent to obtain 0.39 g of product **2** as white solid. Yield: 66%, purity by HPLC: 95.97%. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3378, 3191, 2923, 2850, 1632, 1497, 1260, 1112; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34-1.35 (4H, m, $N(CH_2)_2$-$(CH_2)_2C_6H_5$), 1.54 (2H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2$), 2.58-2.64 (3H, m, $PhCH_2$, CHN), 2.64-2.72(2H, m, $CH_2N$), 2.74-2.82 (1H, dd, *J* = 8 Hz, CHN), 3.6 (1 H, broad. ArOH), 4.68 (1H, dd, *J* = 8 Hz, HOCHAr), 6.78-6.80 (1H, d, *J* = 8 Hz, Ar-H), 7.01 (1H, s, Ar-H), 7.11-7.13 (1H, dd, *J* = 8 Hz, Ar-H), 7.17-7.19 (3H, m, PhH), 7.25-7.29 (2H, m, PhH); $^{13}$C NMR (400 MHz, $CDCl_3$): δ 25.62, 26.54, 48.2, 70.77, 99.6, 114.0, 119.3, 124.2, 125.8, 134.3, 141.75, 153.12; MS (ESI, *m/z*): 316.41 $[M+H]^+$. Anal. calcd. (found) (%) for $C_{19}H_{25}NO_3$ (355.47): C, 72.34 (72.33); H, 8.12 (7.99); N, 4.43 (4.44); O, 15.20 (15.20).

**Synthesis of (2-((6-bromohexyl)oxy)ethyl)benzene (23):** To a suspension of KOH (5.0 g, 0.9 mmol) in 80 mL toluene, 2-phenylethanol (**21**) (1.22 g, 1.0 mmol) was added at 25-30 ºC followed by 1,6-dibromohexane (**22**) (2.92 g, 1.2 mmol), KI and tetrabutylammonium bromide in catalytic amounts were added. The reaction mixture was stirred at 45-50 ºC under inert conditions for 15-20 h. The reaction mixture was quenched with 80 mL of water. The toluene layer was washed by water and the solvent was distilled of under reduced pressure to obtain a light yellow coloured liquid (2.6 g, 90% yield), the product was used without purification for the next step. $^1$H NMR (400 MHz, $CDCl_3$): 1.3-2.0 (m, 10H), 2.6 (t, 2H, $-CH_2$-$C_6H_5$), 3.52 (m, 4H, $-CH_2$-O-$CH_2$-), 7.1-7.4 (m, 5H,-$C_6H_5$). MS (ESI, *m/z*): 286.33 $[M + H]^+$, 308.33 $[M + Na]^+$. Anal. calcd. (found) (%) for $C_{14}H_{21}OBr$ (285.22): C, 58.99 (58.95); H, 7.54 (7.52); Br, 28.20 (28.01); O, 5.59 (5.61).

**Synthesis of (*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2- ((6-phenethoxyhexyl)amino)ethanol (24):** To a stirred solution of (*R*)-2-amino-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)ethanol (**17**) (0.6 g, 2.6 mmol), DMF (7 mL), water (3 mL) and CsOH (0.54 g, 3.2 mmol) were charged at room temperature. (2-((6-Bromohexyl)oxy)ethyl)benzene (**23**) (0.76 g, 2.6 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 10 min and maintained at 25-30 ºC for 13 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and the crude product was quenched in 40 mL of demineralized water, extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine solution (40 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as an ochre coloured oil of compound **24**. The product was purified by column chromatography with eluent system of ethyl acetate and *n*-hexane (7:1) to obtain 0.7 g of product as brown gummy mass. Yield: 61.40%, purity by HPLC: 97%. $[\alpha]_D^{25}$ = -24.6º (*c* = 1.0, methanol) (lit. brown slurry); $[\alpha]_D^{25}$ = -19.5º (*c* = 1.2, $CHCl_3$); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3351, 3183, 2920, 2852, 1630, 1499, 1261, 1110; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34-1.35 (4H, m, $N(CH_2)_2$-$(CH_2)_2(CH_2)_2O$), 1.54(10H, m, $2CH_3$, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.63-1.68 (2H, m, *J* = 7 Hz, $PhCH_2CH_2O$), 2.58-2.65 (3H, m, $PhCH_2$, CHN), 2.68-2.70 (2H, m, $CH_2N$), 2.82-2.86 (1H, dd, *J* = 8 Hz, CHN), 3.37-3.43 (4H, m, $CH_2OCH_2$), 4.57-4.60 (1H, dd, *J* =

8 Hz, HOCHAr), 4.85 (2H, s, $OCH_2$), 6.78-6.80 (1H, d, *J* = 8 Hz, Ar-H), 7.01 (1H, s, Ar-H), 7.11-7.13 (1H, dd, *J* = 8 Hz, Ar-H), 7.17-7.19 (3H, m, PhH), 7.25-7.29 (2H, m, PhH). $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 24.9, 26.1, 28.1, 29.4, 29.7, 30.2, 35.8, 49.4, 57.1, 61.0, 70.7, 70.9, 71.3, 99.5, 116.9, 119.3,122.1, 125.7, 125.8, 128.3, 128.4, 134.5, 142.5, 150.6; MS (ESI, *m/z*): 428.58 $[M + H]^+$. Anal. calcd. (found) (%) for $C_{26}H_{37}NO_4$ (*m.w.* 427.58): C, 73.10 (73.03); H, 8.85 (8.72); N, 3.23 (3.28); O, 14.92 (14.97).

**Synthesis of (*R*)-4-(1-hydroxy-2-((6-phenethoxyhexyl)-amino)ethyl)-2- (hydroxymethyl)phenol 3(R)-Salmeterol-EP-Impurity-B:** (*R*)-1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((6-phenethoxyhexyl)amino)ethanol (**24**) (0.65 g, 1.52 mmol),was added to glacial acetic acid (0.56 g, 7.6 mmol) and 7.0 mL of water at 25-30 ºC. The reaction mass temperature increased to 55-60 ºC and maintained at the same temperature for 5 h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the mass with 12 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as an ochre coloured oil of compound **3**. The product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (7:1) to obtain 0.4 g of product **3** as white solid. Yield: 68%, purity by HPLC: 96%). $[\alpha]_D^{25}$ = -21.2º (*c* = 1.0, methanol) (lit. colourless gum); $[\alpha]_D^{25}$ = -17.5º (*c* = 0.81, methanol); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3350, 3022, 2929, 2854, 1601, 1443, 1282, 1102; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30-1.31 (4H, m, $N(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2O$),1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.60-1.70 (2H, m, $PhCH_2CH_2O$), 2.54-2.70 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.36-3.43 (4H,dt, *J* = 6.6 Hz, $CH_2OCH_2$), 4.51-4.55 (1H, m, CHOH), 4.76 (2H, s, Ar-$CH_2OH$), 6.79-6.80 (1H, d, *J* = 8.2 Hz, Ar-H), 6.94 (1H, s, Ar-H), 7.09-7.11 (1H, d, *J* = 8.2 Hz, Ar-H), 7.17-7.19 (3H, d, *J* = 7.0 Hz, PhH), 7.25-7.29 (2H, m, PhH). $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 27.0, 28.1, 29.7, 29.8, 35.7, 49.3, 56.8, 64.3, 70.7, 70.9, 71.3, 116.4, 125.1, 125.3, 125.7, 126.8, 128.3, 128.4, 133.8, 142.5, 155.8; MS (ESI) *m/z*: 387.51 $[M + H]^+$. Anal. calcd. (found) % for $C_{23}H_{33}NO_4$ (*m.w.* 387.51): C, 71.26 (71.29); H, 8.57 (8.58); N, 3.62 (3.61); O, 16.55 (16.51).

**Synthesis of (3-((6-bromohexyl)oxy)propyl)benzene (26):** To a suspension of potassium hydroxide (5.0 g, 0.9 mmol) in 80 mL toluene, 3-phenyl-propan-1-ol (**25**) (1.36 g, 1.0 mmol) was added at 25-30 ºC followed by addition of 1,6-dibromo-hexane (**22**) (2.92 g, 1.2 mmol), KI and tetrabutylammonium bromide in catalytic amounts. The reaction mixture was stirred at 45-50 ºC under a nitrogen gas atmosphere for 15-20 h. The reaction mixture was quenched with 80 mL of water. The toluene layer was washed by water and the solvent was distilled of under reduced pressure to obtain a light yellow coloured liquid (2.65 g, 88% yield). $^1$H NMR (400 MHz, $CDCl_3$): 1.3-2.0 (m, 10H), 2.6 (t, 4H, -$CH_2$-$C_6H_5$), 3.52 (m, 4H, -$CH_2$-O-$CH_2$- + -$CH_2$Br), 7.1-7.4 (m, 5H, -$C_6H_5$). MS (ESI, *m/z*): 300.25 $[M + H]^+$, 323.25 $[M + Na]^+$. Anal. calcd. (found) (%) for $C_{15}H_{23}OBr$ (*m.w.* 299.25): C, 60.22 (60.20); H, 7.74 (7.75); Br, 26.50 (26.70); O, 5.39 (5.35).

**Synthesis of (*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-((6-(3- phenylpropoxy)hexyl) amino)ethanol (27):** To a stirred solution of (*R*)-2-amino-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanol (**17**) (0.6 g, 2.6 mmol), DMF (7 mL), water (3 mL) and CsOH (0.54 g, 3.2 mmol) were charged at room temperature, (3-((6-bromohexyl)oxy)propyl)-benzene (**26**) (0.78 g, 2.6 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 10 min and maintained at 25-30 ºC for 12 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and the crude product was quenched in 40 mL of demineralized water, extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine solution (40 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as an ochre coloured oil of compound **27**. The product was purified by column chromatography using ethyl acetate and *n*-hexane (7:1) to obtain 0.75 g of product **27** as brown gummy mass. Yield: 65%, purity by HPLC: 98.9%. $[\alpha]_D^{25}$ = -22.6º (*c* = 1.0, methanol) (lit. brown slurry); $[\alpha]_D^{25}$ = -15.5º (*c* = 1.2, $CHCl_3$); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3348, 3189, 2921, 2848, 1630, 1495, 1260, 1105; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34-1.35 (4H, m, $N(CH_2)_2$-$(CH_2)_2(CH_2)_2O$), 1.54(10H, m, 2×$CH_3$, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.63-1.68 (4H, m, *J* = 7 Hz, $PhCH_2CH_2CH_2O$), 2.58-2.65 (3H, m, $PhCH_2$, CHN), 2.68-2.70 (2H, m, $CH_2N$), 2.82-2.86 (1H, dd, *J* = 8 Hz, CHN), 3.37-3.43 (4H, m, $CH_2OCH_2$), 4.57-4.60 (1H, dd, *J* = 8 Hz, HOCHAr), 4.85 (2H, s,$OCH_2$), 6.78-6.80 (1H, d, *J* = 8 Hz, Ar-H), 7.01 (1H, s, Ar-H), 7.11-7.13 (1H, dd, *J* = 8 Hz, Ar-H), 7.17-7.19 (3H, m, PhH), 7.25-7.29 (2H, m, PhH); MS (ESI, *m/z*): 442.60 ($[M+H]^+$). Anal. calcd. (found) (%) for $C_{27}H_{39}NO_4$ (*m.w.* 441.60): C, 73.40 (73.43); H, 8.85 (8.90); N, 3.19 (3.17); O, 14.46 (14.49).

**Synthesis of (*R*)-4-(1-hydroxy-2-((6-(3-phenylpropoxy)-hexyl)amino)ethyl)-2-(hydroxymethyl)phenol 4(*R*)-Salmeterol-EP-Impurity-C:** (*R*)-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)-2-((6-(3-phenylpropoxy)hexyl)-amino)ethanol (**27**) (0.7 g, 1.58 mmol) was added to glacial acetic acid (0.57 g, 9.48 mmol) and 7.0 mL of water at 25-30 ºC. Slowly raised the reaction temperature to 55-60 ºC and maintained at same temperature for 5 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC. The reaction mixture was cooled to below -2 to 10 ºC, neutralized the mass with 12 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as an ochre coloured oil of compound **4**. The product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (7:1) to obtain 0.44 g of product **4** as white solid (yield: 69%, Purity by HPLC: 96%). $[\alpha]_D^{25}$ = -24.2º (*c* = 1.0, methanol) (lit. colourless gum); $[\alpha]_D^{25}$ = -19.5º (*c* = 0.81, methanol)); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3357, 3025, 2929, 2854, 1608, 1453, 1262, 1112; $^1$H NMR (400 MHz,

$CDCl_3$) δ ppm: 1.30-1.31 (4H, m, N $(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2O$), 1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.60-1.70 (4H, m, $PhCH_2CH_2CH_2O$), 2.53-2.80 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.36-3.43 (4H,dt, $J$ = 6.6 Hz, $CH_2OCH_2$), 4.51-4.54 (1H, m, CHOH), 4.76 (2H, s, Ar-$CH_2OH$), 6.69-6.79 (1H, d, $J$ = 8.2 Hz, Ar-H), 6.96 (1H, s, Ar-H), 7.09-7.11 (1H, d, $J$ = 8.2 Hz, Ar-H), 7.17-7.19 (3H, d, $J$ = 7.0 Hz, PhH), 7.25-7.29 (2H, m, PhH); $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 25.62, 28.89, 29.7, 29.19, 30.97, 31.72, 48.64, 57.18, 58.29, 69.07, 70.77, 114.4, 124.1, 125.3, 125.7, 126.8, 128.3, 128.4, 133.8, 142.5, 155.8; MS (ESI) *m/z*: 402.54 $[M + H]^+$. Anal. calcd. (found) % for $C_{24}H_{35}NO_4$ (*m.w.* 401.54): C, 71.78 (71.79); H, 8.77 (8.79); N, 3.50 (3.49); O, 15.95 (15.94).

**Synthesis of 5-(2-bromoacetyl)-2-hydroxybenzaldehyde (29):** To a suspension of $AlCl_3$ (53.53 g, 40 mmol) in dichloromethane (10 volumes), bromoacetyl bromide (24.22 g, 12 mmol) was added gradually at 10 ºC and then temperature raised to 30 ºC. The reaction mass was stirred at this temperature for 1 h and solution of 2-hydroxybenzaldehyde (**28**) (12.21 g, 10 mmol) in dichloromethane was added at 30 ºC. The reaction mixture was stirred at 35-40 °C for 12-15 h and then quenched in water at 0-5 ºC. The dichloromethane layer was separated and distilled off. To the slurry obtained, *n*-heptane was added and stirred for 15 min. This slurry was then filtered and the lump was washed with *n*-heptane (2 volumes) and finally dried at 50 ºC to obtain yellow solid intermediate **29** (14 g). Yield: 57% w/w. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 4.40 (s, 2H, Br-$CH_2$-CO), 7.10-7.24 (m, 1H, Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 10.10 (s, 1H, Ar-CHO); 11.49 (s, 1H, Ar-OH). MS (ESI, *m/z*): 241.05 $[M-H]^+$, Anal. calcd. (found) (%) for $C_9H_7O_3Br$ (*m.w.* 243.05): C, 44.48 (44.47); H, 2.89 (2.90); Br, 32.88 (32.87) ; O, 19.76 (19.75).

**Synthesis of 2-bromo-1-(4-hydroxy-3-(hydroxymethyl) phenyl)ethanone (30):** $NaBH_4$ (2.84 g, 7.48 mmol) was added portionwise over a suspension of 14 g (5.76 mmol) of 5-(2-bromoacetyl)-2-hydroxybenzaldehyde (**29**) in 56 mL acetic acid at 0-5 ºC followed by the addition of $NH_4Cl$ (3.22 g, 5.76 mmol) and then the reaction mixture was stirred for 1 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the product was quenched in 100 mL of ice-cold water and extracted with ethyl acetate (2 × 100 mL). The combined organic layer was neutralized with 5% $Na_2CO_3$ solution (2 × 50 mL). Finally, the combined organic layer was washed with brine solution (2 × 100 mL) and dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (20%EtOAc in *n*-hexane) to obtain compound **30** as light yellow solid. Yield: 74%, 10.5 g. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 4.42 (s, 2H, Br-$CH_2$-CO), 4.76 (2H, s, Ar-$CH_2OH$), 7.1-7.24 (m, 1H, Ar-H); 8.21-8.23(d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 11.49 (s, 1H, Ar-OH). MS (ESI, *m/z*): 244.07 $[M-H]^+$, Anal. calcd. (found) (%) for $C_9H_9O_3Br$ (*m.w.* 245.07): C, 44.10 (44.11); H, 3.69 (3.70); Br, 32.59 (32.60); O, 19.57 (19.59).

**Synthesis of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*]-[1,3]dioxin-6-yl)ethanone (13):** To a suspension of 2-bromo-1-(4-hydroxy-3-(hydroxymethyl) phenyl)ethanone (**30**) (5.0 g, 20.40 mmol) in 50 mL MDC, 2,2-dimethoxy propane (2.33 g, 22.4 mmol), *p*-TSA in catalytic amounts was added. The reaction mixture was stirred at 25-30 ºC under a nitrogen gas atmosphere for 4 h. The reaction mixture was quenched with 50 mL of water. The MDC layer was washed by water and the solvent was distilled under reduced pressure to obtain a light yellow coloured liquid **13** (5.0 g, 91% yield). Product **13** was used without purification for the next step. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.52-1.5 (s, 6H), 4.53 (s, 2H, Br-$CH_2$-C), 4.92 (s, 2H, AR-$OCH_2$), 6.80-6.78 (d, $J$ = 8.0 MHz, 1H), 7.75-7.73 (d, 1H), 7.80-7.79 (m, 1H); MS (ESI, *m/z*): 286.13 $[M+H]^+$; Anal. calcd. (found) (%) for $C_{12}H_{13}O_3Br$ (*m.w.* 285.13): C, 55.57 (50.55); H, 4.59 (4.60); Br, 28.03 (28.02); O, 16.82 (16.83).

**Synthesis of 2-azido-1-(4-hydroxy-3-(hydroxymethyl) phenyl)ethanone (31):** 2-Azido-1-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)ethanone (**16**) (2.47 g, 1.0 mmol) was added to glacial acetic acid (3.6 g, 6.0 mmol) and 20 mL of water at 25-30 ºC. The reaction temperature was raised to 50-55 ºC and maintained at same temperature for 4 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1), after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the mass with 25 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give as light yellow coloured oil of compound **31**. The product was purified by column chromatography, using ethyl acetate and *n*-hexane (2:8) to obtain 1.8 g of product **31** as light yellow solid. Yield: 86%, purity by HPLC: 98%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 4.52 (s, 2H, $N_3$-$CH_2$-CO), 4.92 (2H, s, Ar-$CH_2OH$), 7.1-7.24 (m, 1H, -Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 11.52 (s, 1H, Ar-OH). MS (ESI, *m/z*): 206.19 $[M-H]^+$, Anal. calcd. (found) (%) for $C_9H_9N_3O_3$ (*m.w.* 207.19): C, 52.18 (52.17); H, 4.39 (4.38); N, 20.29 (20.28); O, 23.19 (23.17).

**Synthesis of 2-azido-1-(4-(2-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)-2-oxoethoxy)-3-(hydroxymethyl)-phenyl)ethanone (32):** 2-Azido-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone (**31**) (1.5 g, 7.23 mmol) was added to acetone (25 mL) followed by successive addition of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**) (1.95 g, 7.23 mmol), $K_2CO_3$ (2.09 g, 15.20 mmol) at 10-15 ºC. The reaction was maintained at 25-30 ºC for 3 h under nitrogen atmosphere. The reaction progress was monitored by TLC (chloroform:methanol, 4:1), after completion of reaction, it was cooled to room temperature and quenched with water (50 mL). The desired product was extracted twice using ethyl acetate (50 mL); the combined ethyl acetate layer was washed with water (80 mL). The ethyacetate layer was then concentrated by rotary evaporator at below 65 ºC under reduced pressure to obtain a residue and purified by column chromatography using ethyl acetate and *n*-hexane (3:7) to obtain 1.9 g of product **32** as light yellow crystalline solid. Yield: 64%, purity by HPLC: 98%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.62-1.57 (s, 6H), 4.51 (s, 2H, $N_3$-$CH_2$-CO), 4.80 (s, 2H, AR-$OCH_2$), 4.89 (2H, s, Ar-$CH_2OH$), 5.42 (s, 2H, ArO-$CH_2$-CO), 6.86-6.92 (m, 2H, Ar-H);

7.67-7.68 (d, 2H, Ar-H); 7.78-7.90 (dd, 2H, Ar-H); MS (ESI, *m/z*): 410.41 $[M-H]^+$, Anal. calcd. (found) (%) for $C_{21}H_{21}N_3O_6$ (*m.w.* 411.41): C, 61.30 (61.31); H, 5.13 (5.14); N, 10.20 (10.21); O, 23.31 (23.33).

**Synthesis of 2-amino-1-(4-(2-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)-2-hydroxyethoxy)-3-(hydroxymethyl)-phenyl)ethanol (33):** A solution of 2-azido-1-(4-(2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-oxoethoxy)-3-(hydroxymethyl) phenyl)ethanone (**32)** (0.8 g, 1.94 mmol) in 20 mL methanol was cooled (below -15 ºC) over a period of 5 min. Then $NaBH_4$ (0.19 g, 5.0 mmol) was added in portion under nitrogen environment over a period of 5 min and maintained the reaction temperature at 20-25 ºC for 3 h. The reaction mixture was further stirred for another 1 h at same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched onto 30 mL of 10% aqueous $NH_4Cl$ solution. The reaction mass was diluted with 40 mL of demineralized water and extracted the product with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to obtain syrupy product (1.1 g). Excess ethanol (30 mL) and 10% Pd/C (0.22 g, 0.2 equiv. w/w) were charged at room temperature, hydrogen gas was purged under 3 kg pressure at ambient temperature for 15 min and maintained at 25-30 ºC for 4 h. The reaction progress was monitored by TLC (methylene dichloride:methanol, 4:1), after completion of reaction, it was cooled to below room temperature and recovered Pd/C through ceilite filtration assembly, washed with 2 × 20 mL of methanol to get reddish colour mass. Then solvent was removed under reduced pressure below 60 ºC to afford 1.1 g of crude compound. This product was purified by column chromatography by eluting with ethyl acetate and *n*-hexane (8:2) to obtain 0.6 g of product **33** as gummy mass. Yield: 80%, $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.62-1.57 (s, 6H), 2.76-2.89 (1H, dd, *J* = 12.7 and 7.9 Hz, CHN), 2.95-2.99 (1H, dd, *J* = 12.7 and 4 Hz, CHN), 4.53-4.56 (1H, m, CHOH), 4.61-4.59 (1H, m, CHOH), 4.83 (2H, s, $OCH_2$), 4.80 (s, 2H, AR-$OCH_2$), 4.89 (2H, s, Ar-$CH_2$OH), 5.1 (broad, 2H, $NH_2$-CH), 5.42 (s, 3H,ArO-CH-OH), 6.86-6.92 (m, 2H, Ar-H); 7.67-7.68 (d, 2H, Ar-H); 7.78-7.90 (dd, 2H, Ar-H). MS (ESI, *m/z*): 388.44 $[M-H]^+$, Anal. calcd. (found) (%) for $C_{21}H_{27}NO_6$ (*m.w.* 389.44): C, 64.75 (64.77); H, 6.98 (6.99); N, 3.59 (3.60); O, 24.63 (24.65).

**Synthesis of 1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-(4-(1-hydroxy-2-((6-(4-phenylbutoxy)hexyl)amino)-ethyl)-2-(hydroxymethyl)phenoxy)ethanol (34):** To a stirred solution of 2-amino-1-(4-(2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-hydroxyethoxy)-3-(hydroxymethyl)phenyl)-ethanol (**33**) (0.5 g, 1.28 mmol), DMF (6 mL), water (3 mL) and CsOH (0.23 g, 1.41 mmol) were charged at room temperature. (4-((6-Bromohexyl)oxy)butyl)benzene (**9**) (0.4 g, 1.28 mmol) in DMF (4 mL) was added dropwise at ambient temperature for 20 min and maintained at 25-30 ºC for 12 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and the crude product was quenched in 40 mL of demineralized water, extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give an ochre coloured oil of compound **34**. The product was purified by column chromatography using ethyl acetate and *n*-hexane (7:3) to obtain 0.75 g of product as brown gummy mass. It was recrystallized from *n*-heptane (20 mL) to yield a white solid **34** (0.52 g, 65%). Purity by HPLC: 94%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.3-2.0 (m, 12H), 1.62-1.57 (s, 6H), 2.6 (t, 2H, -$CH_2$-$C_6H_5$), 2.76-2.89 (1H, dd, *J* = 12.7 and 7.9 Hz, CHN), 2.95-2.99 (1H, dd, *J* = 12.7 and 4 Hz, CHN), 3.3 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2$NH), 4.53-4.56 (1H, m, CHOH), 4.61-4.59 (1H, m, CHOH), 4.83 (2H, s, $OCH_2$), 4.80 (s, 2H, AR-$OCH_2$), 4.89 (2H, s, Ar-$CH_2$OH), 5.1 (m, 1H, NH-C), 5.42 (s, 3H, Ar-O-CH-OH), 6.86-6.92 (m, 2H,Ar-H); 7.4 (m, 5H, -$C_6H_5$); 7.67-7.68 (d, 2H, Ar-H); 7.78-7.90 (dd, 2H, Ar-H). MS (ESI, *m/z*): 620.80 $[M-H]^+$, Anal. calcd. (found) (%) for $C_{37}H_{51}NO_7$ (*m.w.* 621.80): C, 71.45 (71.47); H, 8.26 (8.27); N, 2.24 (2.25); O, 18.0 (18.01).

**Synthesis of 4-(1-hydroxy-2-(4-(1-hydroxy-2-((6-(4-phenylbutoxy)hexyl)amino)ethyl)-2-(hydroxymethyl)-phenoxy)ethyl)-2-(hydroxymethyl)phenol 5(*R*)-Salmeterol-EP-Impurity-D:** 1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-(4-(1-hydroxy-2-((6-(4-phenyl butoxy)hexyl)amino)-ethyl)-2-(hydroxymethyl)phenoxy)ethanol (**34**) (0.45 g, 0.72 mmol) was added to glacial acetic acid (0.26 g, 4.32 mmol) and 7.0 mL of water at 25-30 ºC. The reaction temperature was gradually raised to 55-60 ºC and maintained at same temperature for 5 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1) after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the reaction mass with 10 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give brown coloured oil of compound **5**. The technical product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (7:3) to obtain 0.35 g of product **5** as off-white solid. Yield: 85%; Purity by HPLC: 96%. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3352, 3021, 2922, 2850, 1601, 1445, 1256, 1102; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30-1.31 (4H, m, N $(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2$O), 1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2$O), 1.60-1.70 (4H, m, $PhCH_2CH_2CH_2CH_2$O), 2.54-2.70 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.3 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2$NH), 4.53-4.56 (1H, m, CHOH), 4.61-4.59 (1H, m, CHOH), 4.83 (2H, s, $OCH_2$), 4.80 (s, 2H, AR-$OCH_2$), 4.89 (2H, s, Ar-$CH_2$OH), 5.1 (m, 1H, NH-C), 5.42 (s, 3H, Ar-O-CH-OH), 6.86-6.92 (m, 2H, Ar-H); 7.4 (m, 5H, -$C_6H_5$), 7.67-7.68 (d, 2H, Ar-H); 7.78-7.90 (dd, 2H, Ar-H). $^{13}$C NMR (400 MHz, $CDCl_3$): δ 26.1, 27.0, 28.1, 29.4, 29.7, 29.8, 35.7, 49.3, 56.8, 64.3, 69.7, 70.7, 70.9, 72.2, 75.3, 11.3, 116.4, 125.1, 125.3, 125.7, 126.8,127.5, 128.3, 128.4, 129.5, 133.8, 142.5, 155.1, 155.8. MS (ESI) *m/z*: 580.74 ($[M-H]^+$). Anal. calcd. (found) % for $C_{34}H_{47}NO_7$ (*m.w.* 581.74): C, 70.19 (70.20); H, 8.13 (8.14); N, 2.40 (2.41); O, 19.24 (19.25).

**Synthesis of (3-((6-bromohexyl)oxy)butyl)benzene (36):** To a suspension of KOH (5.0 g, 0.9 mmol) in 80 mL

toluene, 4-phenyl-butan-2-ol (**35**) (1.5 g, 1.0 mmol) was added at 25-30 ºC followed by 1,6-dibromohexane (**22**) (2.92 g, 1.2 mmol), KI and tetrabutylammonium bromide in catalytic amount were added. The reaction mixture was stirred at 45-50 ºC under a nitrogen gas atmosphere for 15-20 h. The reaction mixture was quenched with 80 mL of water. The organic fractions were washed with water and then solvent was distilled under reduced pressure to obtain **36** as light yellow coloured liquid. Yield: 2.8 g; 89%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.29-2.0 (m, 13H, $CH_2$), 2.61 (t, 2H, -$CH_2$-$C_6H_5$), 3.01 (1H, m, $CH_3CH$-$OCH_2$), 337-3.52 (m, 4H, -$CH_2$-O-$CH_2$- + -$CH_2$Br), 7.1-7.4 (m, 5H, -$C_6H_5$). MS (ESI, *m/z*): 314.27 $[M + H]^+$, 336.27 $[M + Na]^+$. Anal. calcd. found (%) for $C_{16}H_{25}OBr$ (*m.w.* 313.27): C, 61.32 (61.34); H, 8.02 (8.04); Br, 25.50 (25.51); O, 5.10 (5.11).

**Synthesis of (1*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-((6-((4-phenylbutan-2-yl)oxy)hexyl)amino)-ethanol (37):** To a stirred solution of (*R*)-2-amino-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanol (**17**) (0.6 g, 2.6 mmol), DMF (7 mL), water (3 mL) and CsOH (0.54 g, 3.2 mmol) were charged at room temperature. (3-((6-Bromohexyl)oxy)-butyl)benzene (**36**) (0.81 g, 2.6 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 10 min and maintained at 25-30 ºC for 10 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1), after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and the crude product was quenched in 40 mL of water, extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine solution (40 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give an ochre coloured oil (**37**). The product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (7:1) to obtain 0.80 g of product **37** as brown gummy mass. Yield: 65%, purity by HPLC: 99%. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3348, 3183, 2913, 2852, 1622, 1489, 1252, 1105; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.24-1.35 (7H, m, d, $CH_3$, $N(CH_2)_2$-$(CH_2)_2(CH_2)_2O$), 1.54(10H, m, $2CH_3$, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CHO$), 1.63-1.68 (4H, m, *J* = 7 Hz, $PhCH_2CH_2CH_2O$), 2.58-2.65 (3H, m, $PhCH_2$, CHN), 2.68-2.70 (2H, m, $CH_2N$), 2.82-2.86 (1H, dd, *J* = 8 Hz, CHN), 3.03 (1H, m, $CH_3CH$-O), 3.37-3.43 (2H, m, $CH_2OCH$), 4.57-4.60 (1H, dd, *J* = 8 Hz, HOCHAr), 4.85 (2H, s, $OCH_2$), 6.78-6.80 (1H, d, *J* = 8 Hz, Ar-H), 7.01 (1H, s, Ar-H), 7.11-7.13 (1H, dd, *J* = 8 Hz, Ar-H), 7.17-7.19 (3H, m, PhH), 7.25-7.29 (2H, m, PhH). MS (ESI, *m/z*): 456.63 $[M + H]^+$. Anal. calcd. (found) (%) for $C_{28}H_{41}NO_4$ (*m.w.* 455.63): C, 73.80 (73.81); H, 9.05 (9.07); N, 3.08 (3.07); O, 14.06 (14.05).

**Synthesis of 4-((1R)-1-hydroxy-2-((6-((4-phenylbutan-2-yl)oxy)hexyl)amino)ethyl)-2-(hydroxymethyl)phenol 6(R)-Salmeterol-EP-impurity-E:** (1*R*)-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-((6-((4-phenylbutan-2-yl)oxy)-hexyl)amino)ethanol (**37**) (0.7 g, 1.53 mmol) was added to glacial acetic acid (0.55 g, 9.22 mmol) and 7.0 mL of water at 25-30 ºC. The reaction temparature was increased gradually to 55-60 ºC and maintained at same temperature for 5 h. The reaction progress was monitored by TLC (chloroform:methanol, 4:1); after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the mass with 12 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give brown coloured oil of compound **6**. The product was purified by column chromatography using ethyl acetate and *n*-hexane (7:1) to obtain 0.44 g of product **6** as off-white solid. Yield: 69%; purity by HPLC: 96%. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3352, 3021, 2923, 2848, 1602, 1443, 1252, 1099. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.20-1.31 (7H, m, $CH_3$, $(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2O$), 1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CHO$), 1.60-1.70 (4H, m, $PhCH_2CH_2CHO$), 2.53-2.80 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.05 (1H, m, CH-O $CH_2$) 3.36-3.43 (4H, dt, *J* = 6.6 Hz, $CH_2OCH$), 4.51-4.54 (1H, m, CHOH), 4.76 (2H, s, Ar-$CH_2OH$), 6.69-6.79 (1H, d, *J* = 8.2 Hz, ArH), 6.96 (1H, s, ArH), 7.09-7.11 (1H, d, *J* = 8.2 Hz, ArH), 7.17-7.19 (3H, d, *J* = 7.0 Hz, PhH), 7.25-7.29 (2H, m, PhH).$^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 25.62, 28.89, 29.7, 29.19, 30.97, 31.72, 48.64, 57.18, 58.29, 69.07, 70.77, 114.4, 124.1, 125.3, 125.7, 126.8, 128.3, 128.4, 133.8, 142.5, 155.8. MS (ESI) *m/z*: 416.57 ($[M + H]^+$). Anal. calcd. (found) % for $C_{25}H_{37}NO_4$ (*m.w.* 415.57): C, 72.27 (72.26); H, 8.97 (8.97); N, 3.36 (3.37); O, 15.41 (15.40).

**Synthesis of 2-bromo-1-(4-hydroxy-3-methylphenyl)-ethanone (39):** To a suspension of $AlCl_3$ (26.23 g, 199.77 mmol) in dichloromethane 262 mL (10 volumes), bromoacetyl bromide (12 g, 59.9 mmol) was added carefully at 10 ºC and then the reaction mixture was maintained at 30 ºC. The reaction contents were stirred for 1 h and 2-methylphenol (**38**) (6.2 g, 49.83 mmol) in 30 mL of dichloromethane was added. The reaction mixture was stirred at 35-40 ºC for 8-10 h and then quenched in 250 mL of water at 0-5 ºC. The dichloromethane layer was separated and distilled off. To a slurry obtained, *n*-heptane was added and stirred for 15 min. This slurry was then filtered and the lump was washed with *n*-heptane (2 vol.) and dried at 50 ºC to get intermediate **39**. Yield: 6.25 g, 55%), purity by HPLC: 97%. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm: 2.09 (s, 3H, $CH_3$), 4.42 (s, 2H, Br-$CH_2$-CO), 7.1-7.24 (m, 1H, -Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 10.49 (s, 1H, Ar-OH). MS (ESI, *m/z*): 230.07 $[M-H]^+$, Anal. calcd. (found) (%) for $C_9H_9O_2Br$ (*m.w.* 229.07): C, 47.19 (47.19); H, 3.95 (3.96); Br, 34.89 (34.88); O, 13.96 (13.97).

**Synthesis of 2-azido-1-(4-hydroxy-3-methylphenyl)-ethanone (40):** To a stirred solution of 2-bromo-1-(4-hydroxy-3-methylphenyl)ethanone (**39**) (4.4 g, 19.2 mmol), DMF (25 mL) was added at room temperature. The reaction mixture was cooled to 0-5 ºC. Then sodium azide (1.62 g, 24.97 mmol) was added portionwise at same temperature for 5 min and maintained at room temparature for 4 h. The reaction progress was monitored by TLC (*n*-hexane:ethylacetate, 4:1), after completion of reaction, reaction mass was quenched in 80 mL of demineralized water and extracted with 3 × 50 mL of ethyl acetate. The combined organic layer was washed with brine solution (2 × 50 mL), water (2 × 50 mL), dried over anhydrous $Na_2SO_4$ and filtered. Filtrate was taken and the solvent was removed under reduced pressure at below 55 ºC to obtain **40** as syrupy

mass, dried on high-vacuum. Yield: 2.5 g, 68%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 2.09 (s, 3H, $CH_3$), 4.52 (s, 2H, $N_3$-$CH_2$-CO), 4.95 (1H, s, Ar-OH), 7.1-7.24 (m, 1H, Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H). MS (ESI, *m/z*): 192.19 $[M-H]^+$, Anal. calcd. (found) (%) for $C_9H_9N_3O_3$ (*m.w.* 191.19): C, 56.53 (56.54); H, 4.75 (4.74); N, 21.99 (21.98); O, 16.73 (16.74).

**Synthesis of 4-(2-amino-1-hydroxyethyl)-2-methylphenol (41):** A solution of 2-azido-1-(4-hydroxy-3-methylphenyl)ethanone (**40**) (1.91 g, 1.0 mmol) in 20 mL methanol was cooled (below -15 ºC) over a period of 5 min. Then sodium borohydride (0.53 g, 1.4 mmol) was added portionwise under nitrogen atmosphere for a period of 5 min and maintained the reaction at 20-25 ºC for 3 h. The reaction mixture was further stirred for 1 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched onto 30 mL of 10% aqueous $NH_4Cl$ solution. The reaction mass was diluted with 40 mL of demineralized water and extracted the product with ethyl acetate (2 × 25 mL). The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 25 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to obtain 1.1 g of syrupy mass. Then methanol (30 mL) and 10% Pd/C (0.38 g, 0.2 equiv. w/w) were charged at room temperature, hydrogen gas was purged under 3 kg pressure at ambient temperature for 15 min and maintained at 25-30 ºC for 4 h. The reaction progress was monitored by TLC using methylene dichloride:methanol, 4:1), after completion of reaction, it was cooled to below room temperature and recovered Pd/C through filtration assembly, washed with 2 × 20 mL of methanol to get reddish colour mass. Then the solvent was removed under reduced pressure below 60 ºC to afford 1.5 g of crude compound. This crude product was purified by column chromatography, eluent system being ethyl acetate and *n*-hexane (2:8) to obtain 0.72 g of product **41** as gummy mass. Yield: 41.91%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 2.09 (s, 3H, $CH_3$), 2.38-2.54 (1H, dd, *J* = 12.7 and 7.9 Hz, CHN), 2.95-2.99 (1H, dd, *J* = 12.7 and 4 Hz, CHN), 4.28-4.31 (1H, m, CHOH), 4.61-4.59 (1H, m, CHOH), 4.95 (1H, s, Ar-OH), 6.68-6.70 (m, 1H, Ar-H); 6.89-6.91(d, 1H, Ar-H); 6.97-6.98 (dd, 1H, Ar-H). MS (ESI, *m/z*): 150.21 $[M-OH]^+$, Anal. calcd. (found) (%) for $C_9H_{13}NO_2$ (*m.w.* 167.21): C, 64.65 (64.65); H, 7.83 (7.84); N, 8.39 (8.38); O, 19.13 (19.14).

**Synthesis of 4-(1-hydroxy-2-((6-(4-phenylbutoxy)-hexyl)amino)ethyl)-2-methylphenol 7(*R*)-Salmeterol-EP-impurity-F:** To a stirred solution of 4-(2-amino-1-hydroxyethyl)-2-methylphenol (**41**) (0.5 g, 2.99 mmol), DMF (8 mL), water (4 mL) and CsOH (0.55 g, 3.28 mmol) were charged at room temperature. (4-((6-Bromohexyl)oxy)butyl)benzene (**9**) (0.84 g, 2.69 mmol) in DMF (5 mL) was added dropwise at ambient temperature for 20 min and maintained at 25-30 ºC for 12 h. TLC ($CHCl_3$:$CH_3OH$, 4:1) was used to monitor the progress of reaction. Once the reaction was completed, the solvent was removed under reduced pressure >65 ºC and the crude product was cooled in 40 mL of water before being extracted twice with ethyl acetate. An ochre-coloured oil of compound **7** was Obtained after the combined organic layer was washed with brine solution (50 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure.The product was purified by column chromatography using ethyl acetate and *n*-hexane (7:1) to obtain 0.71 g of product as brown gummy mass and then recrystallized from *n*-heptane (20 mL) to yield a white coloured solid **7**. Yield: 0.65 g, 54%, purity by HPLC: 96%. $[\alpha]_D^{25}$ = -20.2º (*c* = 1.0, methanol) (lit. colourless gum); $[\alpha]_D^{25}$ = -16.5º (*c* = 0.81, methanol); FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3451, 3023, 2920, 2853, 1602, 1453, 1260, 1102; $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.30-1.31 (4H, m, N $(CH_2)_2$-$(CH_2)_2$-$(CH_2)_2O$), 1.44-1.56 (4H, m, $NCH_2CH_2$-$(CH_2)_2$-$CH_2CH_2O$), 1.60-1.70 (4H, m, $PhCH_2$-$CH_2CH_2CH_2O$), 2.09 (s, 3H, $CH_3$), 2.54-2.70 (6H, m, $PhCH_2$, $CH_2NCH_2$), 3.36-3.43 (4H, dt, *J* = 6.6 Hz, $CH_2OCH_2$), 4.51-4.55 (1H, m, CHOH), 4.95 (1H, s, Ar-OH), 6.79-6.80 (1H, d, *J* = 8.2 Hz, Ar-H), 6.94 (1H, s, Ar-H), 7.09-7.11 (1H, d, *J* = 8.2 Hz, Ar-H), 7.17-7.19 (3H, d, *J* = 7.0 Hz, PhH), 7.23-7.27 (2H, m, PhH). $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 15.9, 26.1, 27.0, 28.1, 29.4, 29.7, 29.8, 35.7, 49.3, 56.8, 64.3, 70.7, 70.9, 71.3, 116.4, 125.1, 125.3, 125.7, 126.8, 128.3, 128.4, 133.8, 142.5, 155.8. MS (ESI) *m/z*: 398.57 ($[M-H]^+$). Anal. calcd. (found) % for $C_{25}H_{37}NO_3$ (*m.w.* 399.57): C, 72.14 (75.15); H, 9.32 (9.32); N, 3.50 (3.51); O, 12.00 (12.01).

**Synthesis of 5-(2-azidoacetyl)-2-hydroxybenzaldehyde (42):** To a stirred solution of 5-(2-bromoacetyl)-2-hydroxy benzaldehyde (**29**) (1.0 g, 4.11 mmol), DMF (10 mL) were charged at room temperature. The reaction mixture was cooled to 0-5 ºC. Then sodium azide (0.32 g, 4.93 mmol) was added portion wise at same temperature for 5 min and maintained at room temparature for 3 h. The reaction progress was monitored by TLC (*n*-hexane:ethylacetate, 4:1), after completion of reaction, and quenched in 50 mL of water and extracted with 3 × 30 mL of ethyl acetate. The combined organic layer was washed with brine solution (2 × 30 mL), water (2 × 30 mL), dried over anhydrous $Na_2SO_4$ and filtered. Filtrate was taken and the solvent was removed under reduced pressure at below 55 ºC to obtain **42** as syrupy mass, dried and then recrystallized from *n*-heptane (10 mL) to yield yellow coloured solid **42** . Yield: 0.65 g,77%, purity by HPLC: 98%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 3.6 (s, 2H, $N_3$-$CH_2$-CO), 7.1-7.24 (m, 1H, -Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 10.1(s, 1H, Ar-CHO); 11.49 (s, 1H, Ar-OH). MS (ESI, *m/z*): 206.17 $[M+H]^+$; Anal. calcd. (found) (%) for $C_9H_7N_3O_3$ (*m.w.* 205.17): C, 52.68 (52.69); H, 3.43 (3.44); N, 20.88 (20.48); O, 23.38 (23.39).

**Synthesis of 2-azido-1-(4-hydroxy-3-(((6-(4-phenylbutoxy)hexyl)amino)methyl)phenyl)ethanone (43):** To a stirred solution of 6-(4-phenylbutoxy)hexan-1-amine hydrochloride (**12**) (0.6 g, 2.43 mmol), EDC (20 mL), 5-(2-azidoacetyl)-2-hydroxy benzaldehyde (**42**) (0.5 g, 2.43 mmol) were charged at room temperature under nitrogen atmosphere. The reaction mixture was stirred thouroughly at 25-30 ºC for 8 h. Then sodium triacetoxyborohydride (0.55 g, 2.92 mmol) was added portionwise for 5 min and maintained at room temparature for 2 h. The reaction progress was monitored by TLC (*n*-hexane:ethylacetate, 1:4), after the completion of reaction, quenched in 50 mL of water and extracted with 30 mL of EDC. The combined organic layer was washed with brine solution

(2 × 30 mL), water (2 × 30 mL), dried over anhydrous $Na_2SO_4$ and filtered. Filtrate was taken and the solvent was removed under reduced pressure at below 45 ºC to obtain syrupy mass, dried on high-vacuum and then recrystallized from *n*-heptane (10 mL) to yield brown gummy mass **43.** Yield: 0.7 g, 70 %. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.29-2.3 (m, 14H, $CH_2$ & NH), 2.61 (t, 2H, -$CH_2$-$C_6H_5$), 3.01 (2H, m, $CH_2CH_2$-$OCH_2$), 3.37-3.52 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2$NH-AR), 3.6 (s, 2H, $N_3$-$CH_2$-CO), 7.1-7.4 (m, 5H, -$C_6H_5$) 7.1-7.24 (m, 1H, Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 5.36 (s, 1H, Ar-OH). MS (ESI, *m/z*): 439.56 $[M+H]^+$, 461.56 $[M+Na]^+$. Anal. calcd. (found) (%) for $C_{25}H_{34}N_4O_3$ (*m.w.* 438.56): C, 68.46 (68.47); H, 7.82 (7.81); N, 12.79 (12.78); O, 10.93 (10.94).

**Synthesis of 2-azido-1-(3-(((2-(2,2-dimethyl-4*H*-benzo-[*d*][1,3]dioxin-6-yl)-2-oxoethyl)(6-(4-phenylbutoxy)-hexyl)amino)methyl)-4-hydroxyphenyl)ethanone (44):** 2-Azido-1-(4-hydroxy-3-(((6-(4-phenyl butoxy)hexyl)amino)-methyl)phenyl)ethanone (**43**) (0.5 g, 1.14 mmol) in 20 mL dichloromethane and triethylamine (0.25 g, 2.39 mmol) were cooled (below -2 to 5 ºC) over a period of 10 min. Then added solution of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**) (0.33 g, 1.25 mmol) in dichloromethane (10 mL) slowly over a period of 5 min and maintained at 20-25 ºC under nitrogen atmosphere. At the same temperature, the reaction mixture was stirred for an additional 3 h. TLC was used to monitor the progress of the reaction and 40 mL of cold water was used to quench the reaction mixture once it had completed. The product was extracted with dichloromethane (2 × 25 mL) after the reaction mass was acidified with conc. HCl until the solution pH reached 4. An oily crude product was obtained after the combined organic layer was washed with brine solution (2 × 25 mL) and water (2 × 40 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure (1.1 g). The product was purified by column chromatography using ethyl acetate and *n*-hexane (7:3) to obtain 0.81 g of product as brown gummy mass and then recrystallized from *n*-heptane (10 mL) to yield a white coloured solid **44**. Yield: 0.61 g, 83%, purity by HPLC: 98.82%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.29-2.3 (m, 12H, $CH_2$), 1.62-1.57 (s, 6H), 2.61 (t, 2H, -$CH_2$-$C_6H_5$), 3.01 (2H, m, $CH_2CH_2$-$OCH_2$), 3.37-3.52 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2$NH-Ar), 3.66 (s, 4H, N-$CH_2$-CO & $N_3$-$CH_2$-CO), 4.80 (s, 2H, Ar-$OCH_2$), 4.89 (2H, s, Ar-$CH_2$OH), 6.86-6.92 (m, 1H, -Ar-H); 7.1-7.4 (m, 5H, -$C_6H_5$) 7.1-7.24 (m, 1H, Ar-H) 7.67-7.68 (d, 1H, Ar-H); 7.78-7.90 (dd, 1H, Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 5.36 (s, 1H, Ar-OH). MS (ESI, *m/z*): 645.80 $[M+H]^+$, 667.80 $[M+Na]^+$. Anal. calcd. (found) (%) for $C_{37}H_{48}N_4O_6$ (*m.w.* 644.80): C, 68.91 (68.92); H, 7.51 (7.50); N, 8.68 (8.69); O, 14.88 (14.89).

**Synthesis of 4-(2-amino-1-hydroxyethyl)-2-(((2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-hydroxyethyl)(6-(4-phenylbutoxy)hexyl)amino)methyl)phenol (45):** A solution of 2-azido-1-(3-(((2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-oxoethyl)(6-(4-phenylbutoxy)hexyl)amino)-methyl)-4-hydroxyphenyl)ethanone (**44**) (0.6 g, 0.93 mmol) in 10 mL methanol was cooled (below -15 ºC) over a period of 5 min. Then sodium borohydride (0.1 g, 2.79 mmol) was added portionwise under nitrogen atmosphere slowly over a period of 5 min and maintained the reaction temperature at 20-25 ºC for 3 h. The reaction mixture was further stirred for 1 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched onto 15 mL of 10% aqueous $NH_4Cl$ solution. The reaction mass was diluted with 20 mL of water and extracted the product with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (2 × 25 mL), water (2 × 20 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to obtain as syrupy product. Then methanol (20 mL) and 10% Pd/C (0.13 g, 0.2 equiv. w/w) were charged at room temperature, hydrogen gas was purged under 3 kg pressure at ambient temperature for 15 min and maintained at 25-30 ºC for 4 h. The reaction progress was monitored by TLC (methylene dichloride: methanol, 4:1) after completion of reaction, it was cooled to below room temperature and recovered Pd/C through ceilite filtration assembly, washed with 2 × 10 mL of methanol to get reddish coloured mass. Then the solvent was removed under reduced pressure below 60 ºC to afford 0.9 g to crude compound. The product was purified by column chromatography with eluent mixture of ethyl acetate and *n*-hexane (8:2) to obtain 0.38 g of product **45** as gummy mass. Yield: 66%. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 1.29-2.3 (m, 12H, $CH_2$), 1.62-1.57 (s, 6H), 2.61 (t, 2H, -$CH_2$-$C_6H_5$), 2.76-2.89 (1H, dd, $J$ = 12.7 and 7.9 Hz, CHN), 2.95-2.99 (1H, dd, $J$ = 12.7 and 4 Hz, CHN), 3.01 (2H, m, $CH_2CH_2$-$OCH_2$), 3.37-3.52 (m, 6H, -$CH_2$-O-$CH_2$- + -$CH_2$NH-Ar), 3.66 (s, 4H, N-$CH_2$-CO & $NH_2$-$CH_2$-CO), 4.53-4.56 (1H, m, CHOH), 4.61-4.59 (1H, m, CHOH), 4.80 (s, 2H, Ar-$OCH_2$), 4.89 (2H, s, Ar-$CH_2$OH), 6.86-6.92(m, 1H, Ar-H); 7.1-7.4 (m, 5H,-$C_6H_5$) 7.1-7.24 (m, 1H, Ar-H) 7.67-7.68 (d, 1H, Ar-H); 7.78-7.90 (dd, 1H, Ar-H); 8.21-8.23 (d, 1H, Ar-H); 8.31-8.33 (dd, 1H, Ar-H); 5.36 (s, 1H, Ar-OH). MS (ESI, *m/z*): 621.82 $[M + H]^+$, 667.80 $[M + Na]^+$. Anal. calcd. (found) (%) for $C_{37}H_{52}N_2O_6$ (*m.w.* 620.82): C, 71.57 (71.58); H, 8.45 (8.44); N, 4.50 (4.51); O, 15.45 (15.46).

**Synthesis of 2-(((2-(2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxin-6-yl)-2-hydroxyethyl)(6-(4-phenylbutoxy)hexyl)-amino)methyl)-4-(1-hydroxy-2-((6-(4-phenylbutoxy)-hexyl)amino)ethyl)phenol (46):** To a stirred solution of 4-(2-amino-1-hydroxyethyl)-2-(((2-(2,2-dimethyl-4*H*-benzo[*d*]-[1,3]dioxin-6-yl)-2-hydroxyethyl)(6-(4-phenylbutoxy)-hexyl)amino)methyl)phenol (**45**) (0.36 g, 0.57 mmol), DMF (6 mL), water (4 mL) and CsOH (0.11 g, 0.69 mmol) were charged at room temperature. (4-((6-Bromohexyl)oxy)butyl)-benzene (**9**) (0.18 g, 0.58 mmol) in DMF (4 mL) was added dropwise at ambient temperature for 10 min and maintained at 25-30 ºC for 12 h. TLC (chloroform:methanol, 4:1) was used to monitor the progress of reaction mxiture. The solvent was removed under reduced pressure below 60 ºC after the completion of the reaction and the crude product was cooled in 30 mL of water before being quenched in 2 × 30 mL of ethyl acetate for extraction. An ochre-coloured oil of compound **46** was obtained by washing the combined organic layer with brine solution (30 mL), drying it over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The product was purified

by column chromatography with ethyl acetate and *n*-hexane (8:2) mixture to obtain 0.5 g of product as brown gummy mass. It was recrystallized from *n*-heptane (5 mL) to afford a white solid **46**. Yield: 0.35 g, 70%, purity by HPLC: 98%. $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm: 1.21-1.27 (m, 8H), 1.45-1.48 (m, 8H), 1.55-1.58 (m, 8H), 1.62-1.57 (s, 6H), 2.48-2.57 (m, 4H), 2.63-2.88 (m, 6H), 3.34-3.95 (m, 8H), 4.43-4.47 (m, 4H), 4.71-4.75 (m, 2H), 4.93-5.0 (m, 2H), 5.94 (m, 1H), 6.69-6.75 (m, 3H), 6.96-7.04 (m, 3H), 7.11-7.16 (m, 5H), 7.22-7.30 (m, 5H), 8.55 (m, 3H); MS (ESI, *m/z*): 854.18 $[M+H]^+$, 876.18 [M + Na]$^+$. Anal. calcd. (found) (%) for $C_{53}H_{76}N_2O_7$ (*m.w.* 853.18): C, 74.60 (74.61); H, 8.97 (8.98); N, 3.28 (3.28); O, 13.14 (13.13).

**Synthesis of 4-(1-hydroxy-2-((2-hydroxy-5-(1-hydroxy-2-((6-(4-phenylbutoxy)hexyl)amino)ethyl)benzyl)(6-(4-phenylbutoxy)hexyl)amino)ethyl)-2-(hydroxymethyl)-phenol 8(*R*)-Salmeterol-EP-Impurity-G:** 2-(((2-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-hydroxyethyl)(6-(4-phenyl butoxy)hexyl)amino)methyl)-4-(1-hydroxy-2-((6-(4-phenyl-butoxy)hexyl)amino)ethyl)phenol (**46**) (0.35 g, 0.41 mmol) was added to glacial acetic acid (0.15 g, 2.46 mmol) and 5.0 mL of water at 25-30 ºC. The reaction temperature was gradually increased to 55-60 ºC and maintained for 5 h. The reaction progress was monitored by TLC (chloroform: methanol, 4:1), after completion of reaction, the solvent was removed under reduced pressure below 65 ºC and cooled to below -2 to 10 ºC, neutralized the mass with 8 mL of 5% $Na_2CO_3$ solution and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was concentrated under reduced pressure to obtain a brown oil of compound **8** after being washed with brine solution (25 mL), dried over anhydrous $Na_2SO_4$ and concentrated. To obtain 0.2 g of product **8** as an offwhite solid, the product was purified using column chromatography with an eluent system of ethyl acetate and *n*-hexane (8:2). Yield: 60%, purity by HPLC: 96%). FT-IR (KBr, $\nu_{max}$, cm$^{-1}$): 3356, 3024, 2929, 2853, 1602, 1451, 1262, 1110; $^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm: 1.21-1.27 (m, 8H), 1.45-1.48 (m, 8H), 1.55-1.58 (m, 8H), 2.48-2.57 (m, 4H), 2.63-2.88 (m, 6H), 3.34-3.95 (m, 8H), 4.43-4.47 (m, 4H), 4.71-4.75 (m, 2H), 4.93-5.0 (m, 2H), 5.94 (m, 1H), 6.69-6.75 (m, 3H), 6.96-7.04 (m, 3H), 7.11-7.16 (m, 5H), 7.22-7.30 (m, 5H), 8.55 (m, 3H), 9.30 (s, 1H), 9.38 (s, 1H). $^{13}$C NMR (400 MHz, $CDCl_3$) δ ppm: 26.15, 27.09, 28.11, 29.5, 29.8, 29.9, 35.6, 49.4, 56.7, 57.8, 59.2, 64.4, 70.5, 70.9, 71.3, 116.4, 125.1, 125.3, 125.7, 126.8, 128.3, 128.4, 133.8, 142.5, 155.8; 157.12. MS (ESI, *m/z*): 814.12 $[M+H]^+$, Anal. calcd. (found) (%) for $C_{50}H_{72}N_2O_7$ (*m.w.* 813.12): C, 73.86 (73.86); H, 8.92 (8.93); N, 3.44 (3.45); O, 13.76 (13.77).

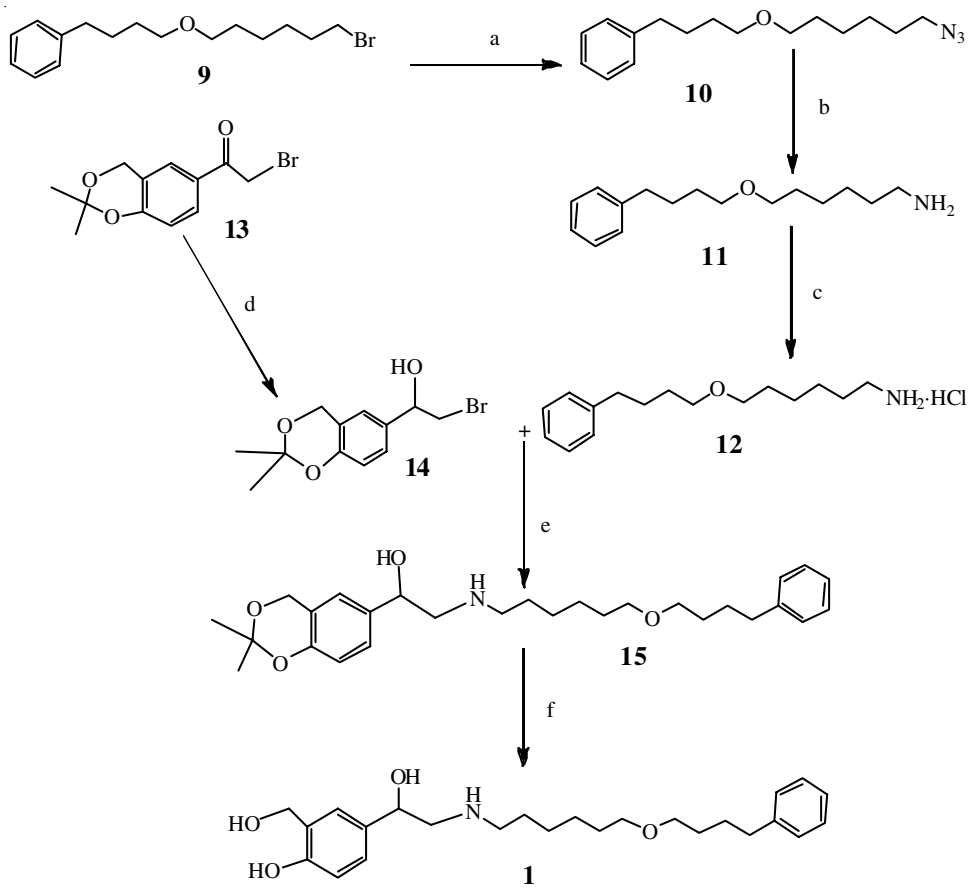
## RESULTS AND DISCUSSION

Synthesis of (*R*)-salmeterol active pharmaceutical ingredients [25-28] and its feasible synthetic routes and synthetic procedure of (*R*)-salmeterol (**1**) are well-known in the literature [26-32]. However, the synthetic protocol of process impurities associated with (*R*)-salmeterol are not yet reported. Impurities in the drug products may reduce the drug activity and its potential quality. Control of impurities of a drug during its manufacturing process where they either enter or form is plays a vital role in the process development of a drug. Thus, the development of task feasible effective process of a drug is essential. Therefore, we have aimed to develop a commercial, effective and novel process for preparation of salmeterol.

Based on the literature, we have designed the synthesis of (*R*)-salmeterol (**1**) as depicted in **Scheme-I**. Each step of the synthetic protocol is optimized for developing a commercial process of salmeterol **1**. In the first stage, synthesis of enantioselective synthesis of (*R*)-salmeterol (**1**) starts from *via* asymmetric reduction of the desired prochiral α-bromoketone intermediate **13** by sodium borohydride in methanol under ambient conditions to give desired product α-bromoalcohol (**14**) with good yields and enantioselectivity (98%ee). In the next step, compound (**12**) was synthesized from 4-((6-bromohexyl)oxy)-butyl)benzene (**9**), which was treated with sodium azide in DMF under optimized conditions to give 4-((6-azidohexyl)-oxy)butyl)benzene (**10**) with good yields and purity. This azido ether **10** was then hydrogenated over Pd/C in methanol under ambient conditions to provide amino ether compound **11** in good yields and then it was converted into hydrochloride salt of amino ether **12** with dry HCl gas in methanol under optimized conditions in good yields and purity. In the final step, the condensation of the α-bromo alcohol **14** and hydrochloride salt of amino ether **12** was achieved with CsOH as base and DMF as solvent under ambient condition to provide secondary amine compound **15**. Deprotection to ketol group of compound **15** with aqueous acetic acid afforded (*R*)-salmeterol acetate salt in quantitative yields as 98%ee and neutralized compound **15** by using 5% $Na_2CO_3$ under cold conditions to provide pure (*R*)-salmeterol (**1**) base as syrupy mass and recrystallized with 10 mL of *n*-hexane in 85% yield and 99.45% HPLC purity. The structure of compound **1** was characterized through the spectral analysis. The protonated molecular ion peak of (*R*)-salmeterol (**1**) appears at *m/z* 416.27 $[M+H]^+$ amu in the mass spectra. The main advantage of this synthetic protocol in comparison with the reported methods, reducing the amount of contaminants **D** and **G** in drug and also yield has greatly improved quality of the final products.

**Impurity A:** In British Pharmacopoeia, (1RS)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[(4-phenylbutyl)amino]ethanol chemical name represents the **2** as a process related impurity and same thing as per European Pharmacopoeia known as **impurity A**. This specified **impurity A** formation was observed as metabolite of salmeterol (**1**). Presence of 4-phenyl-1-butanol (**18**) in (4-((6-bromohexyl)oxy)butyl)benzene (**9**) as contaminant may hinder the formation of **impurity A**. The possible formation of enantioselectivity synthesis of **2** is demonstrated by a synthetic protocol, which starts from the displacement reaction of prochiral α-bromoketone intermediate **13** converted to α-azidoketone **16** in the presence of sodium azide in DMF at ambient temperature conditions in good yields 93% and HPLC purity.

The asymmetric reduction of azidoketone **16** by sodium borohydride in methanol at ambient conditions to provide azido alcohol intermediate and then followed by azido alcohol was hydrogenated over Pd/C in methanol to gives amino alcohol **17** in 86% yields. O-mesylated intermediate **19** was prepared

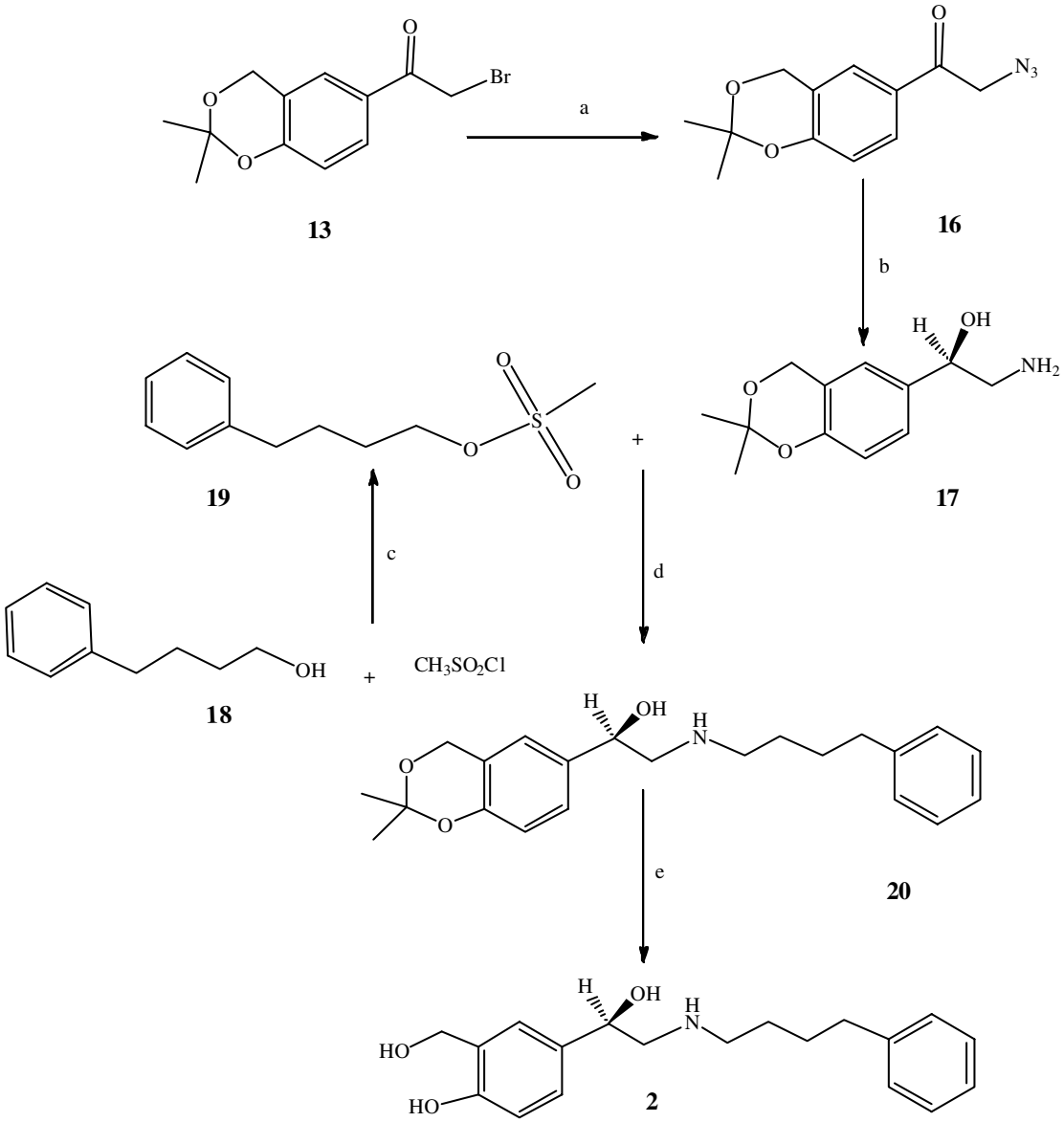



**Scheme-I:** Synthesis of (*R*)-salmeterol (**1**); Reagents and conditions: a) $NaN_3$, DMF, 3 h, 0-5 ºC, 95%, b) $H_2$, 10% Pd/C, MeOH, 4 h, 20-25 ºC, c) dry HCl gas, MeOH, 3 h, 5-10 ºC, 90%, d) $NaBH_4$, MeOH, 4 h, 20-25 ºC, e) CsOH. $H_2O$, DMF, water, 10 h, 20-25 ºC, 80%, f) acetic acid, water, 5 h, 55-60 ºC and 5% $Na_2CO_3$, -2 to 10 ºC, 85%

by the condensation of 4-phenyl-1-butanol (**18**) with methane sulfonyl chloride in presence of triethylamine as base and MDC as solvent under milled conditions. In the next step, the condensation reaction of **17** with the O-mesylated intermediate **19** gives the secondary amine compound **20** with $K_2CO_3$ as base and DMF as solvent under ambient conditions. Compound **20** was purified by column chromatography with petroleum ether/ethyl acetate as eluent. In the final step, deprotection to ketol group of compound **20** with aqueous acetic acid gives (*R*)-salmeterol-EP-impurity-A acetate salt in quantitative yields as 98%ee and neutralized (*R*)-salmeterol-EP-impurity-A acetate salt by using 5% $Na_2CO_3$ under cold conditions to provide pure of (*R*)-salmeterol-EP-impurity-A (**2**) as an offwhite colour solid in 66% yield and 96% HPLC purity. The synthetic protocol is depicted in **Scheme-II**. The structure of compound **2** is characterized by spectral analysis. The protonated molecular ion peak of compound **2** appeared at *m/z* 316.18 $[M+H]^+$ amu and its potassium adduct at *m/z* 356.3 amu $[(M+H+K)^+]$.

**Impurity B:** The chemical name (1RS)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(2-phenylethoxy)hexyl]-amino]ethanol is a process related impurity which referred as **3** and **Impurity B** as per British Pharmacopoeia and European pharmacopoeia, respectively. Specified impurity B formation is observed as metabolite of salmeterol (**1**) and also identified as potential impurity in the synthesis of salmeterol. The presence of 4-phenyl-1-butanol (**18**) in 2-phenyl ethanol (**21**) as contaminant may be the origin for the formation of **impurity B** while synthesis of (4-((6-bromohexyl)oxy)butyl)benzene (**9**). The enantioselective synthesis of **impurity-B** starts from the condensation reaction of **17** with bromide intermediate **23** (**Scheme-III**). The key intermediate **23** was synthesized by alkylation of 2-phenyl-1-ethanol (**21**) with 1,6-dibromohaxane (**22**) in the presence of KOH as base and toluene as solvent under phase transfer conditions. Condensation reaction of **17** with bromide intermediate **23** using CsOH as base and DMF as solvent under ambient condition to produce secondary amine compound **24**, which was purified by column chromatography with petroleum ether/ethyl acetate as eluent and subjected for deprotection of ketol group with aqueous acetic acid to give (*R*)-salmeterol-EP-impurity-B acetate salt in quantitative yields as 98.3%ee. Neutralization of (*R*)-salmeterol-EP-impurity-B acetate salt is done using 5% $Na_2CO_3$under cold conditions to provide pure of (*R*)-salmeterol-EP-impurity-B as an off white colour solid in 68% yield and 96% HPLC purity. The structure of impurity-B was characterized by spectral analysis. The protonated molecular ion peak of **3** appeared at *m/z* 388.51 $[M+H]^+$ amu and its sodium adduct at *m/z* 427.51 amu $[(M+H+K)^+]$.

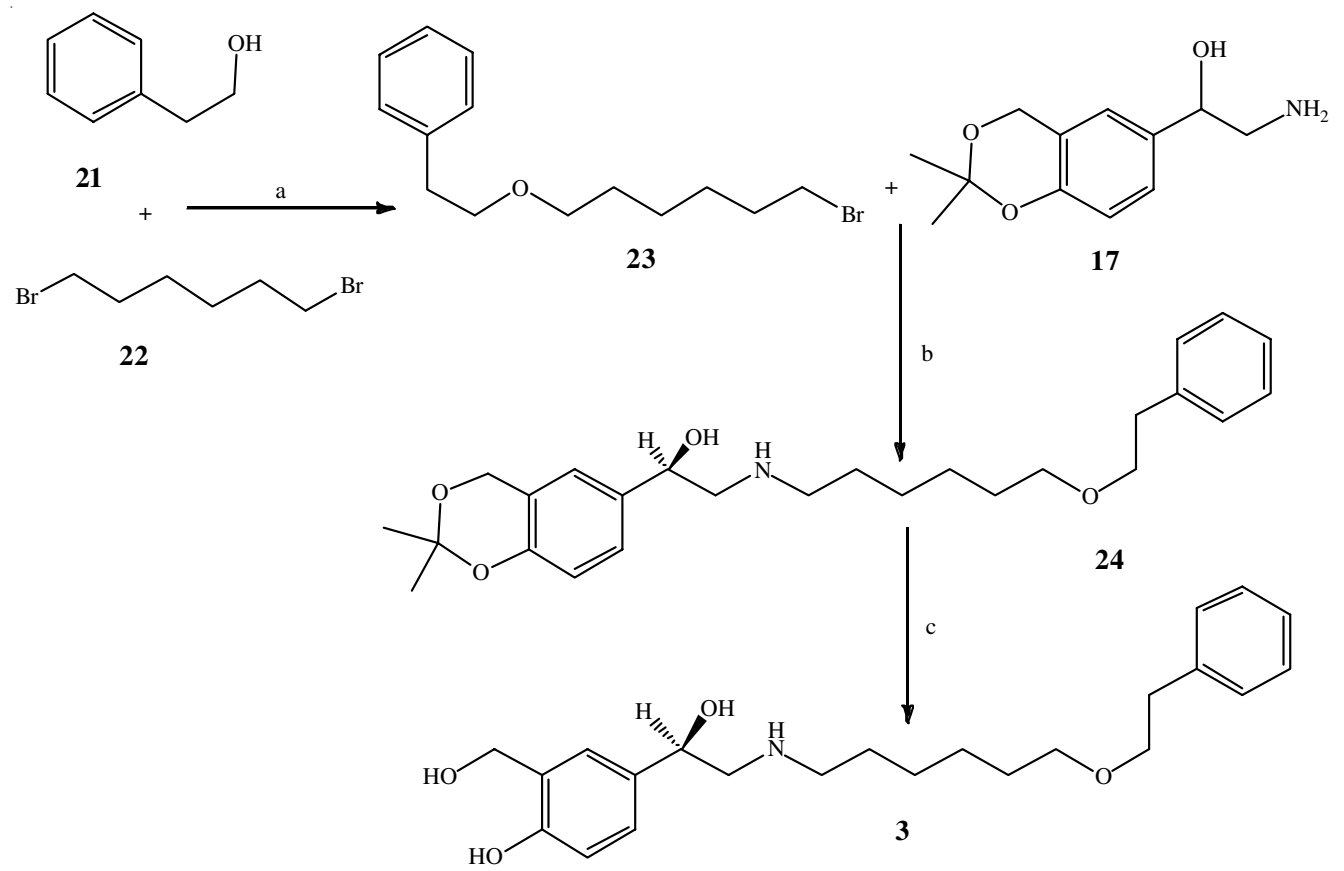
**Impurity C:** (1RS)-1-[4-Hydroxy-3-(hydroxymethyl)-phenyl]-2-[[6-(3-phenylpropoxy)hexyl]amino]ethanol is a process related impurity of salmeterol and referred as **4** and



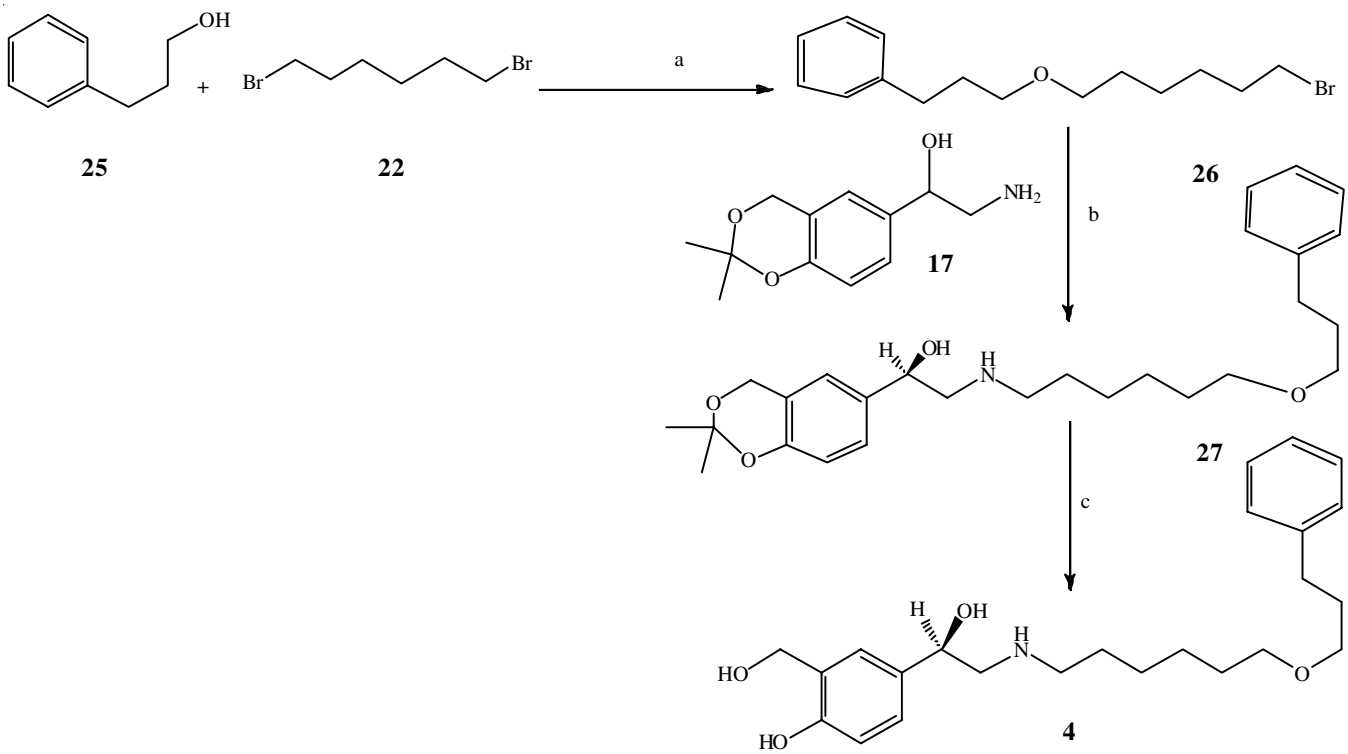

**Scheme-II:** Synthesis of (*R*)-salmeterol-EP-impurity-A (**2**); Reagents and conditions: a) $NaN_3$, DMF, 3 h, 0-5 ºC, 93 %, b) $NaBH_4$/MeOH and $H_2$, 10% Pd/C, MeOH, 4 h, 20-25 ºC, 86%, c) triethylamine, MDC, 3 h, -2 to 10 ºC, 90%, d) $K_2CO_3$, DMF, 4 h, 25-30 ºC, 82%, e) acetic acid, water, 5 h, 55-60 ºC, 5% $Na_2CO_3$, -2 to 10 ºC, 66%

**impurity C**. The specified impurity-C was observed as metabolite of salmeterol (**1**) and identified as potential impurity in the synthesis of salmeterol. This potential impurity may originate from 3-phenylpropan-1-ol (**25**) due the presence of 4-phenyl-1-butanol (**18**) as contaminant, which may hinder the formation of **impurity C** to the synthesis of (4-((6-bromo-hexyl)oxy)-butyl)benzene (**9**) of key intermediate. The enantio-selective synthesis of **impurity C** starts from the asymmetric reduction of azidoketone **16** to α-amino alcohol **17** (**Scheme-IV**). The condensation reaction of **17** with bromide intermediate **26** using CsOH as base and DMF as solvent under ambient condition to give the secondary amine compound **27**. Key intermediate **26** was synthesized by alkylation of 3-phenyl propan-1-ol (**25**) with 1,6-dibromohaxane (**22**) in the presence of KOH as base and toluene as solvent under phase transfer conditions. Compound **27** is purified by column chromatography with petroleum ether/ethyl acetate as eluent. Deprotection to ketol group of compound **27** with aqueous acetic acid produce (R)-Salmeterol-EP-impurity-C acetate salt in quantitative yield as 98.7%ee and neutralized (*R*)-salmeterol-EP-impurity-C acetate salt by using 5% $Na_2CO_3$ under cold conditions to provide pure (*R*)-salmeterol-EP-impurity-C as an offwhite colour solid in 69% yield and 94% HPLC purity%. The structure of **impurity C** is characterized by spectral analysis. The protonated molecular ion peak of **impurity C** appeared at *m/z* 402.54 $[M+H]^+$ amu and its sodium adduct at *m/z* 424.54 amu $[(M+H+Na)^+]$.

**Impurity D:** (*R*)-Salmeterol process related dimer impurity-D (**5**) is observed as an impurity in the synthesis of (*R*)-salmeterol (**1**). The chemical name, 1-[4-[2-hydroxy -2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethoxy]-3-(hydroxymethyl)phenyl]-2-[[6-(3-phenylbutoxy)hexyl]amino]ethanol




**Scheme-III:** Synthesis of (*R*)-salmeterol-EP-impurity-B (**3**); Reagents and conditions: a) KOH, KI, TBAB, toluene, 15 h, 45-50 ºC, 91%, b) $CsOH{\cdot}H_2O$, DMF, water, 10 h, 20-25 ºC, 65%, c) acetic acid, water, 5 h, 55-60 ºC, 5% $Na_2CO_3$, -2 to 10 ºC, 68%




**Scheme-IV:** Synthesis of (*R*)-salmeterol-EP-impurity-C (**4**); Reagents and conditions: a) KOH, KI, TBAB, toluene, 15 h, 45-50 ºC, 88%, b) $CsOH{\cdot}H_2O$, DMF, water, 9 h, 20-25 ºC, 89%, c) acetic acid, water, 5 h, 55-60 ºC, 5% $Na_2CO_3$, -2 to 10 ºC, 69%

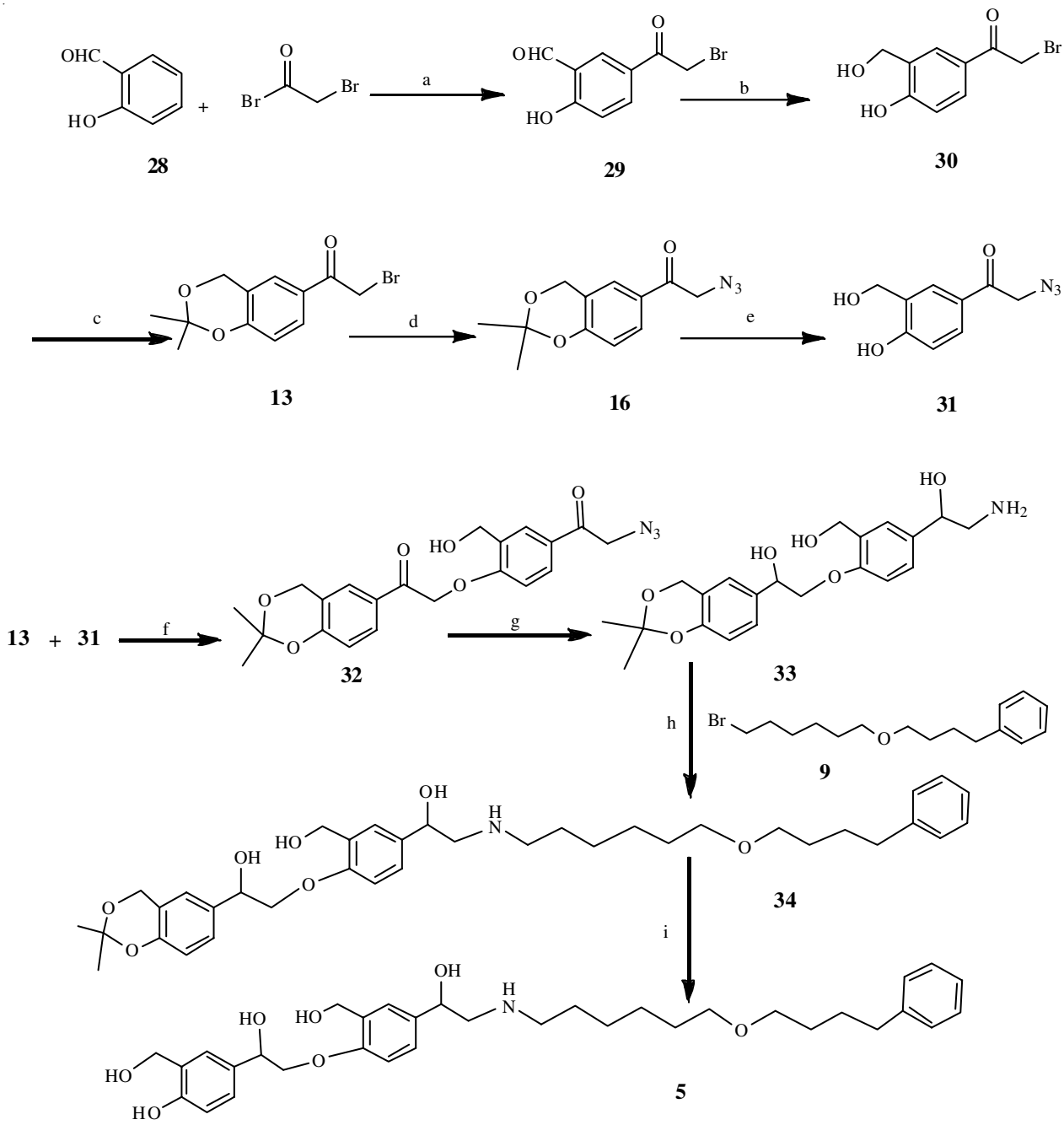
is represented as a process related potential dimer impurity. Process related dimer impurity **impurity D** results due to self-condensation of trace amount of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**) present in (*R*)-salmeterol (**1**). The possible formation of enantioselective synthesis of **impurity D** is demonstrated by synthesis of a key intermediate, 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**) reported methods available in the literature [31,32]. The Friedal-Craft acylation reaction of salicylaldehyde (**28**) with bromoacetyl bromide gives acetophenone derivative **29**. Then, the aldehydic group of compound **29** was reduced regioselectively by $NaBH_4$ in acetic acid to provide the intermediate **30** [30]. Compound **30** reacts with 2,2-dimethoxypropane, which catalyzed by *p*-toluenesulfonic acid to give the desired prochiral α-bromoketone **13**. In the next stage, the displacement reaction of prochiral α-bromo ketone intermediate **13** converted to α-azido ketone **16** in the presence of sodium azide in DMF at ambient temperature conditions in good yields 95% with 96% of HPLC purity then followed by acidolysis of ketol protective group with acetic acid affords 2-azido-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone intermediate (**31**) as light yellow solids with good yields and purity.

In the final stage, compound **32** was synthesized from the condensation reaction of 2-azido-1-(4-hydroxy-3-(hydroxymethyl)phenyl)ethanone intermediate **31** with prochiral α-bromo ketone intermediate **13** in presence of $K_2CO_3$ base acetone as solvent under ambient conditions. Compound **32** was purified by column chromatography with petroleum ether/ethyl acetate as eluent to obtain light yellow solid. The asymmetric reduction of azidoketone intermediate **32** [30-32] by $NaBH_4$ in methanol at ambient conditions to provide azido-alcohol intermediate and its hydrogenation with Pd/C in methanol gives amino alcohol **33** in 80% yield. Later, the condensation reaction of **33** and bromide intermediate **9** using cesium hydroxide monohydrate as base and DMF as solvent under ambient condition afford secondary amine compound **34**. This compound is purified by column chromatography with chloroform/methanol as eluent and deprotection of ketol group of compound **34** with aqueous acetic acid is performed to give (*R*)-salmeterol-BP-impurity-D acetate salt in quantitative yields as 98.6%ee which is produce (*R*)-salmeterol-BP-impurity-D acetate salt on neutralization with 5% $Na_2CO_3$ under cold conditions to provide pure (*R*)-salmeterol-BP-impurity-D (**5**) as pale yellow syrupy mass in 85% yield and 95% HPLC purity. The synthetic protocol is depicted in the **Scheme-V**. The structure of **impurity-D** was characterized by spectral analysis. The protonated molecular ion peak of (*R*)-salmeterol-BP-impurity-D appeared at *m/z* 580.34 $[M-H]^+$ amu and its sodium adduct at *m/z* 603.34 amu $[(M+H+Na)^+]$.

**Impurity-E:** The chemical name 1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(1-methyl-3-phenylpropoxy)hexyl]-amino]ethanol as a process related **impurity-E** (6). The specified impurity-E formation was observed as isomeric impurity of salmeterol (**1**). Salmeterol related **impurity-E** is also identified as potential impurity in the synthesis of salmeterol. This potential impurity is originating from 4-phenyl-1-butanol (**18**) in 4-phenyl butan-2-ol (**35**) as contaminant results the formation of **impurity E** (**Scheme-VI**), which starts from the asymmetric reduction of azidoketone **16** to α-amino alcohol **17** in 88% yield. The condensation reaction of **17** with bromide intermediate **36** using CsOH as base and DMF as solvent under ambient condition to gives the secondary amine compound **37**. The key intermediate **36** was synthesized by the direct alkylation of 4-phenylbutan-2-ol (**35**) with 1,6-dibromohaxane (**22**) in the presence of KOH as base and toluene as solvent under phase transfer conditions. Compound **37** was purified by column chromatography with petroleum ether/ethyl acetate as eluent. Deprotection to ketol group of compound **37** with aqueous acetic acid gives (*R*)-salmeterol-EP-impurity-E acetate salt in quantitative yields as 98.8%ee, which on neutralization using 5% $Na_2CO_3$ under cold conditions to provide pure (*R*)-salmeterol-EP-impurity-E (**6**) as an offwhite colour solid in 69% yield and 97% HPLC purity. The structure of **impurity-E** was successfully characterized by spectral analysis. The protonated molecular ion peak of **impurity E** appeared at *m/z* 416.27 $[M+H]^+$ amu and its sodium adduct at *m/z* 439.27 amu $[(M+H+Na)^+]$.

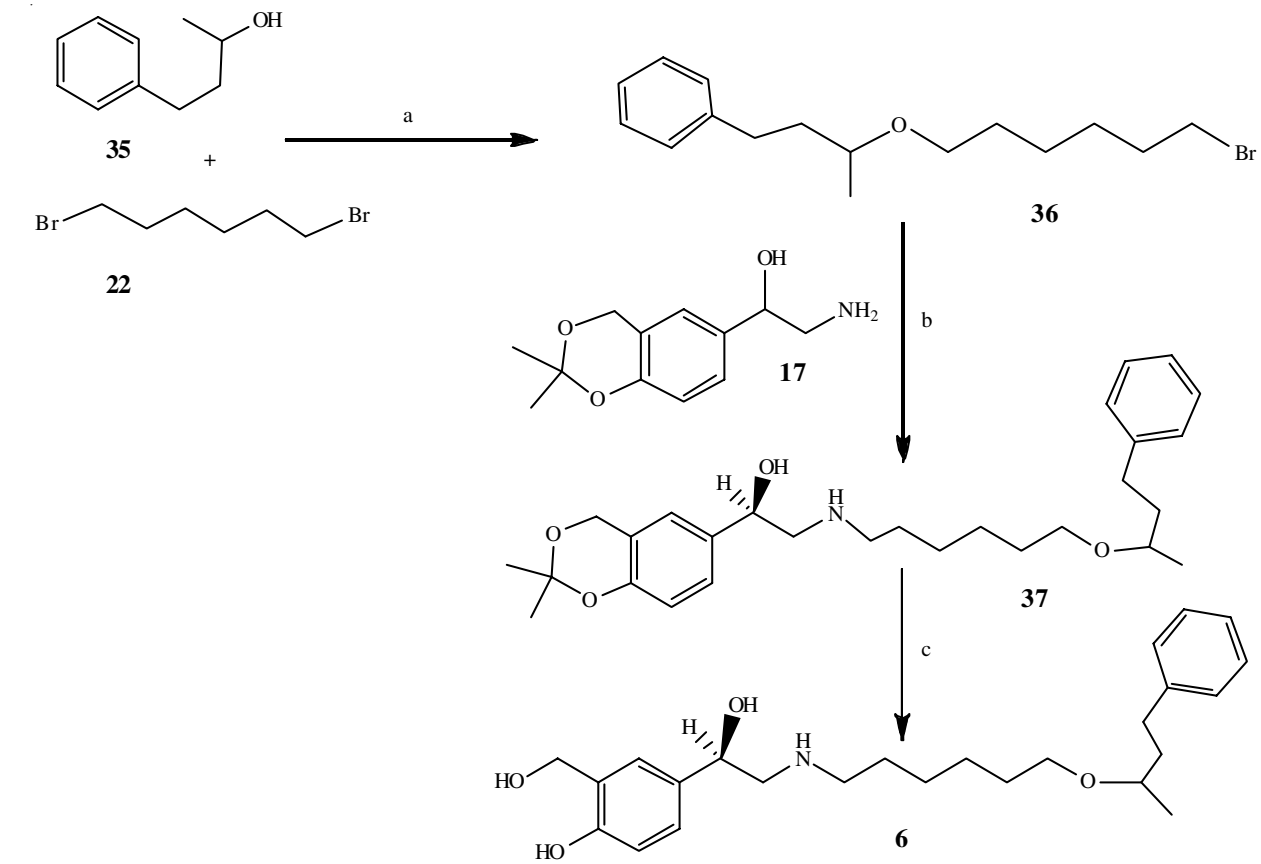
**Impurity-F:** (1RS)-1-(4-Hydroxy-3-methylphenyl)-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol (**7**) is referred as **impurity F** as per British pharmacopoeia and EP. The impurity (*R*)-salmeterol related compound **7** formation is observed as metabolite and also identified as an internal impurity in the synthesis of (R)-salmeterol (**1**). This is a potential impurity originated from manufacturing of 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)ethanone (**13**). The enantioselective synthesis of compound **7** was demonstrated by synthesis of key intermediate 2-bromo-1-(4-hydroxy-3-methylphenyl)-ethanone (**39**), which is reported in the literature methods [28-32]. The synthetic protocol of compound **39** starts from the reaction of 2-methyl phenol (**38**) with bromoacetyl bromide in the presence of $AlCl_3$ under Friedel-Craft acylation conditions to give α-bromoketone intermediate **39**. This prochiral α-bromoketone intermediate **39** converted to α-azidoketone **40** in the presence of sodium azide in DMF at ambient temperature conditions in good yields. Compound **40** was purified by column chromatography with petroleum ether/ethyl acetate as eluent. Then (*R*)-salmeterol-EP-Impurity-F is obtained by asymmetric reduction of azidoketone intermediate **40** using $NaBH_4$ in methanol at ambient conditions to provide azidoalcohol, which gives amine alcohol on hydrogenation over Pd/C in methanol **41** in 70% yield. Finally, the condensation reaction of compound **41** with bromide intermediate **9** affords secondary amine crude compound **7** in presence of CsOH as base and DMF as solvent under ambient conditions. Compound **7** was purified by column chromatography with petroleum ether/ethyl acetate as eluent afforded pure (*R*)-salmeterol-BP-impurity-F (**7**) as an offwhite colour solid in 68% yields and 94% HPLC purity. The synthetic procedure is depicted in **Scheme-VII**. The structure of **7** was successfully characterized by spectral analysis. The protonated molecular ion peak of (*R*)-salmeterol-EP-impurity-F (**7**) appeared at *m/z* 398.28 $[M-H]^+$ amu and its sodium adduct at *m/z* 421.28 amu $[(M+H+Na)^+]$.

**Impurity G:** 1-[4-Hydroxy-3-[[[2-hydroxy2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl][6(4-phenylbutoxy)hexyl]-

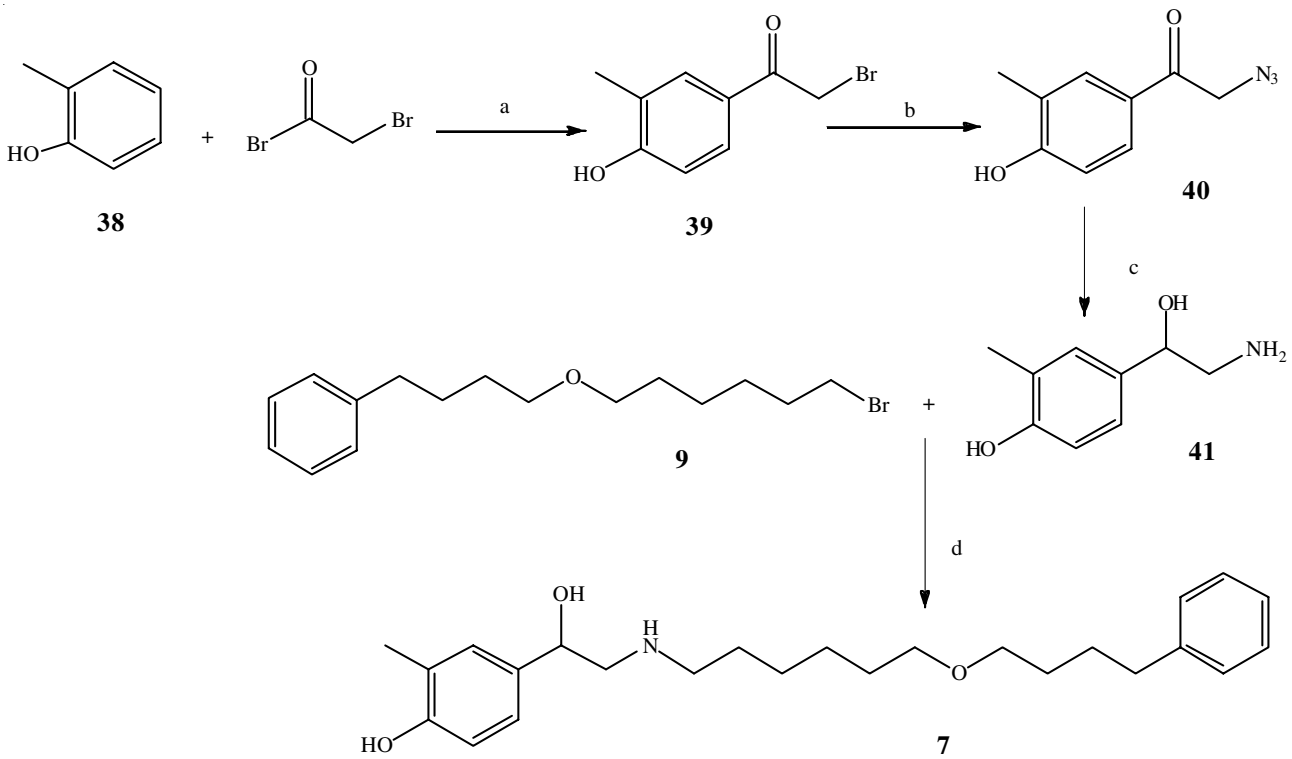



**Scheme-V:** Synthesis of (*R*)-salmeterol-BP-impurity-D (**5**); Reagents and conditions: a) bromoacetyl bromide, $AlCl_3$, MDC, 9 h, 30-35 ºC, 92%, b) $NaBH_4$, acetic acid, 0-5 °C, 2 h, 92%, c) 2,2-dimethoxy propane, *p*-TSA, MDC, 4 h, 20-25 ºC, 92%, d) $NaN_3$, DMF, 0-5 ºC, 72%, e) acetic acid, water, 3 h, 40 ºC, 65%, f) $K_2CO_3$, acetone, 4 h, 10-25 ºC, 82%, g) $NaBH_4$, MeOH, 4 h, 20-25 ºC, 92% $H_2$; 10% Pd/C, MeOH, 8 h, 20-25 ºC, 80%, h) $CsOH{\cdot}H_2O$, DMF, water, 9 h, 20-25 ºC, 85% i) acetic acid, water, 5 h, 55-60 ºC and 5% $Na_2CO_3$ solution, -2 to 10 ºC, 85%

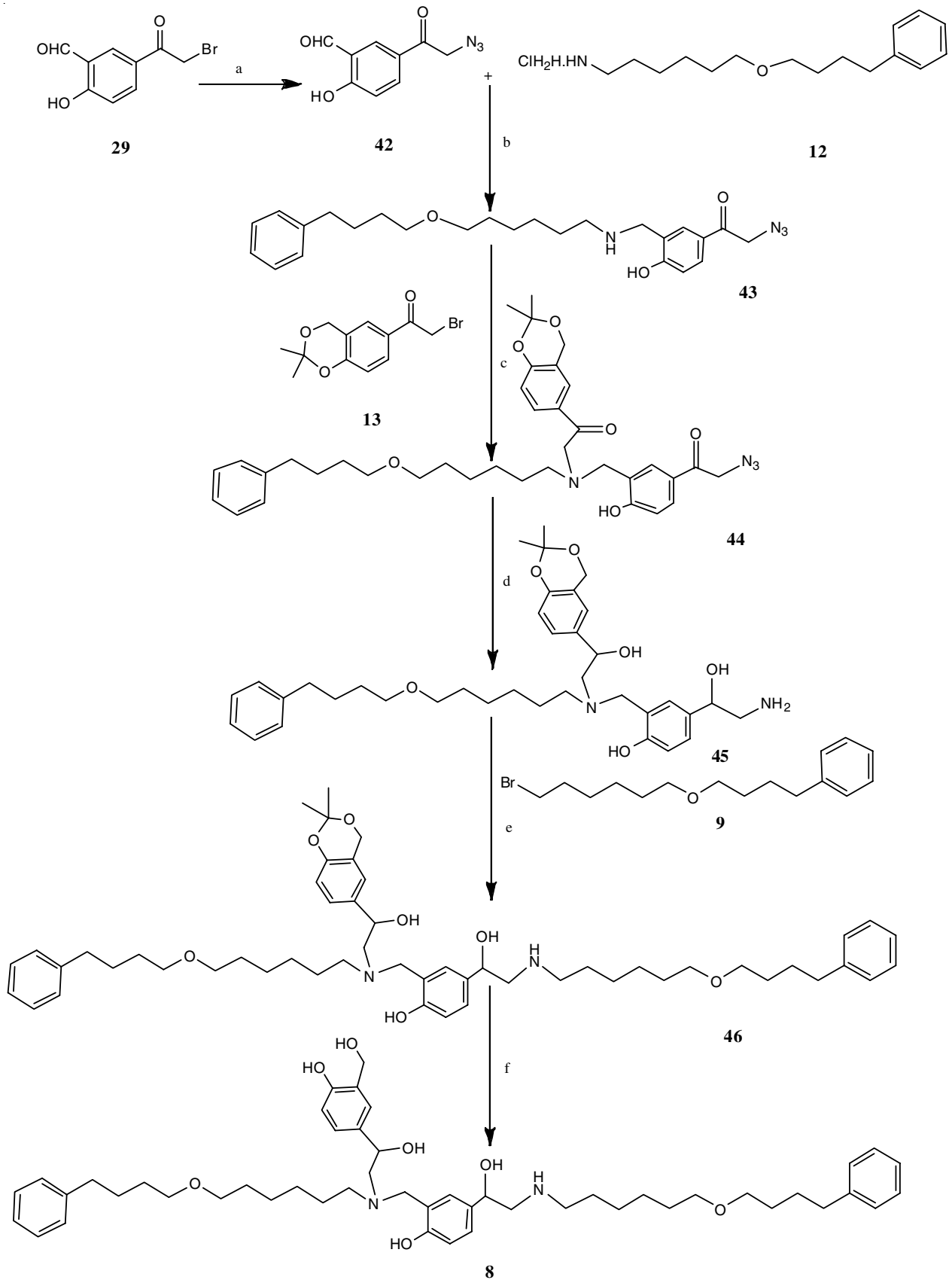
amino]methyl]phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]-ethanol (**8**) is considered as **impurity G** as per European Pharmacopoeia and (*R*)-salmeterol dimer impurity as per British Pharmacopoeia. (*R*)-Salmeterol process related compound **8** is also identified as dimerized potential impurity of (*R*)-salmeterol. The feasible enantioselective synthesis of **impurity G** is designed by retrosynthetic approach. The synthesis of potential impurity **impurity G** starts from conversion of 5-(2-bromoacetyl)-2-hydroxybenzaldehyde (**29**) to 5-(2-azidoacetyl)-2-hydroxybenzaldehyde (**42**) using sodium azide in DMF under mild conditions. Compound **42** was treated with 6-(4-phenylbutoxy)-hexan-1-amine base (**12**) in ethylene dichloride at ambient conditions to form imines derivative. Then, imines derivative is reduced to give secondary amine derivative **43** in good yields under reductive amination conditions with mild reducing agent sodium triacetoxy borohydride. Compound **43** was purified by column chromatography with chloroform/methanol as eluent to provide pure compound **43**. In the next stage, compound




**Scheme-VI:** Synthesis of (*R*)-salmeterol-EP-impurity-E **6**; Reagents and conditions: a) KOH, KI, TBAB, toluene, 15 h, 45-50 ºC, 88%, b) $CsOH \cdot H_2O$, DMF, water, 9 h, 20-25 ºC, 85%, c) acetic acid, water, 5 h, 55-60 ºC, 5% $Na_2CO_3$, -2 to 10 ºC, 69%




**Scheme-VII:** Synthesis of (*R*)-salmeterol-EP-impurity-F (**8**); Reagents and conditions: a) bromoacetyl bromide, $AlCl_3$, MDC, 8-10 h, 30-40 ºC, 55% w/w, b) $NaN_3$, DMF, 0-5 ºC, 70%, c) $NaBH_4$, MeOH and $H_2$, 10% Pd/C, MeOH, 9 h, 20-25 ºC, 70%, d) $CsOH \cdot H_2O$, DMF, water,10 h, 20-25 ºC, 68%




**Scheme-VIII:** Synthesis of (*R*)-salmeterol-EP-impurity-G (**8**); Reagents and conditions: a) $NaN_3$, DMF, 0-5 ºC, 72%, b) sodium triacetoxyborohydride, EDC, 20-25 ºC, 10 h, 65%, c) triethylamine, MDC, 4 h, 0-5 ºC, 80%, d) $NaBH_4$, MeOH, 4 h, 20-25 ºC, 92% and $H_2$, 10% Pd/C, MeOH, 9 h, 20-25 °C, 69%, e) $CsOH{\cdot}H_2O$, DMF, water,10 h, 20-25 ºC, 69% f) acetic acid, water, 5 h, 55-60 ºC and 5% $Na_2CO_3$ solution, -2 to 10 °C, 66%

**43** is condensed with 2-bromo-1-(2,2-dimethyl-4*H*-benzo[*d*]-[1,3]dioxin-6-yl)ethanone (**13**) in triethylamine as base in MDC solvent under cold conditions to give *tert*.-amine intermediate compound **44**, which was purified by column chromatography with chloroform/methanol as eluent. In the final stage, synthesis of enantioselective synthesis of (*R*)-salmeterol-EP-Impurity-G *via* asymmetric reduction of azidoketone intermediate **44** using $NaBH_4$ in methanol in ambient conditions to form azidoalcohol intermediate, which on hydrogenation over Pd/C in methanol affords amino alcohol intermediate **45** in 69% yields. Compound **45** on condensation with bromide intermediate **9** using CsOH as base and DMF as solvent under ambient condition produce secondary amine compound **46**, which is purified by column chromatography with ethyl acetate/methanol as eluent gives syrupy mass in 69% yield and 98% HPLC purity. Deprotection to ketol group of compound **46** with aqueous acetic acid gives (R)-salmeterol-EP-impurity-G acetate salt in quantitative yields as 98.7%ee and neutralized the acetate salt using 5% $Na_2CO_3$ under cold conditions to provide pure compound of (*R*)-salmeterol-EP-impurity-G (**8**) as pale yellow gummy mass in 66% yield and 96% HPLC purity. The synthetic procedure is presented in **Scheme-VIII**. The structure of impurity-G (**8**) was characterized by spectral analysis. The protonated molecular ion peak of (*R*)-salmeterol-EP-impurity-G appeared at *m/z* 813.53 $[M-H]^+$ amu and its sodium adduct at *m/z* 835.53amu $[(M+H+Na)^+]$.

## Conclusion

An improved efficient and novel synthetic protocol for the synthesis of the long-acting β-agonist drug (*R*)-salmeterol xinafoate with high yield and purity product in each stage is developed. The synthetic protocols proposed for the synthesis of each impurity of (*R*)-salmeterol is novel and unique. The identified seven specified impurities of (*R*)-salmeterol xinafoate; synthesis and their characterization is reported for the first time. The synthesized impurities were confirmed by structural elucidation and as well as their respective relative retention times in available RP-HPLC methods. Hence, the required relative substances of (*R*)-salmeterol were fulfilled as per Pharmacopeia requirements.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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