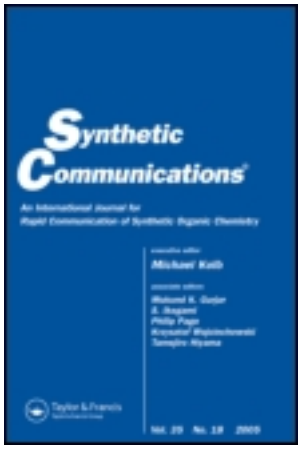

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 15 Dec 2010.

To cite this article: N. Senthilkumar , Y. S. Somannavar , Shankar B. Reddy , Brajesh Kumar Sinha , G. K. A. S. S. Narayan , Ramesh Dandala & Kaga Mukkanti (2010): Synthesis of Active Metabolites of Carvedilol, an Antihypertensive Drug, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:2, 268-276

To link to this article: http://dx.doi.org/10.1080/00397910903534072

*Synthetic Communications*®, 41: 268–276, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903534072

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# SYNTHESIS OF ACTIVE METABOLITES OF CARVEDILOL, AN ANTIHYPERTENSIVE DRUG

**N. Senthilkumar,[1] Y. S. Somannavar,[1] Shankar B. Reddy,[1] Brajesh Kumar Sinha,[1] G. K. A. S. S. Narayan,[1] Ramesh Dandala,[1] and Kaga Mukkanti[2]**

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***A simple synthetic route for active metabolites of carvedilol is reported. The metabolites 4′-hydroxycarvedilol and 5′-hydroxycarvedilol have exhibited high activity for β-blockade. We have disclosed syntheses of 4′-hydroxycarvedilol and 5′-hydroxycarvedilol from commercially available vanillin and isovanillin, respectively.***

***Keywords***: Angina; antihypertension; carvedilol; congestive heart failure; metabolite; 4-oxiranylmethoxy-9H-carbazole

## INTRODUCTION

Carvedilol **1** is a multiple-action drug useful in the treatment of hypertension and angina,[1,2] which is known to be both a competitive nonselective β-adrenoceptor antagonist and a vasodilator. The vasodilatory action of carvedilol **1** results primarily from $\alpha_1$-adrenoceptor blockade, whereas the β-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. Common structural features of β-adrenoreceptor blockers include either an arylethanolamine or an aryloxyisopropanolamine moiety.[3] The compounds differ in the nature of the aryl group as well as the group linked to the amine moiety.

Carvedilol **1** contains an oxyisopropanolamine moiety with aromatic substituents linked to both the oxy and amine ends of the molecule, which provide its combined activity, and carvedilol **1** also has much greater antioxidant activity than other commonly used β-blockers.[4,5]

Additionally, carvedilol **1** is useful in the treatment of congestive heart failure[6] and is marketed as racemic mixture as Coreg. Carvedilol **1** is used clinically

Received October 1, 2009.

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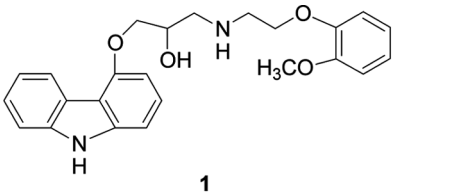
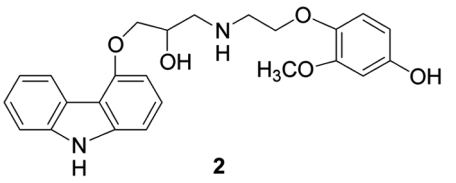
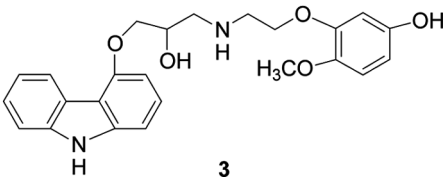
as a racemic mixture of R(+)- and S(−)-enantiomers. Carvedilol **1** is extensively metabolized primarily by aromatic oxidation and glucuronidation. Hydroxylation at the phenol ring produces two active metabolites with β-receptor blocking activity. Based on preclinical studies, the 4′-hydroxycarvedilol **2**, the active metabolite, is approximately 13 times more potent than carvedilol for β-blockade. CYP2D6 is thought to be the major enzyme in the 4′- and 5′-hydroxylation of carvedilol, with a potential contribution from CYP3A4.[7]




**1**




**2**



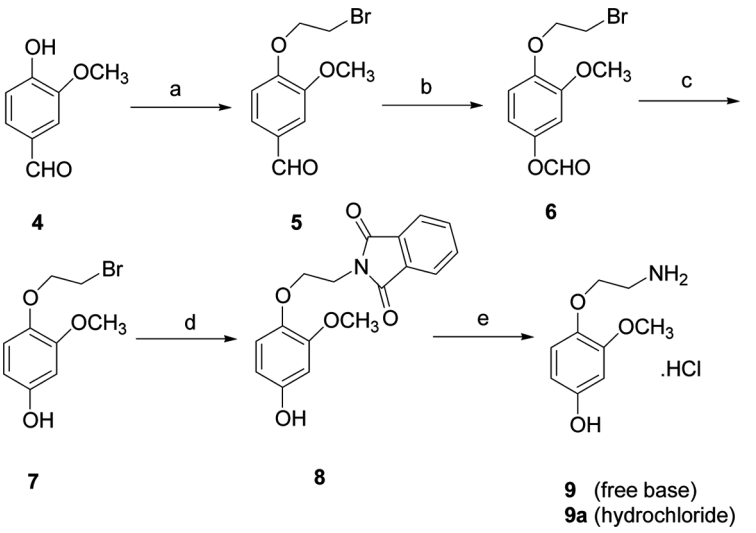

**3**

5′-Hydroxycarvedilol **3**[3] and 4′-hydroxycarvedilol **2** are most valuable metabolites, which are required to determine absorbility and bioavailability of carvedilol. Synthesis of these metabolites has not been reported in literature. We disclose convergent syntheses of metabolites **2** and **3**, starting with commercially available vanillin **4** and isovanillin **11** respectively.

## RESULTS AND DISCUSSION

The synthesis of metabolite **2** (Scheme 1) involves O-alkylation of the phenolic group of vanillin **4** with 1,2-dibromoethane in the presence of a base at 95 °C gave **5**[8] in 93% yield. Dakin oxidation of the formyl group of **5** using m-chloroperbenzoic acid (m-CPBA) at room temperature gave **6** in 81% yield.

Further, hydrolysis[9] of **6** with sodium hydroxide in methanol at 0 °C afforded **7** in 75% yield. Compound **7** was condensed with potassium phthalimide in the presence of NaI (catalyst) in dimethylformamide (DMF) at 60 °C, and compound **8** was isolated. Dephthalimidation of **8** with methanolic monomethylamine at 30 °C resulted in corresponding amine **9**,[10] which was isolated as hydrochloride salt

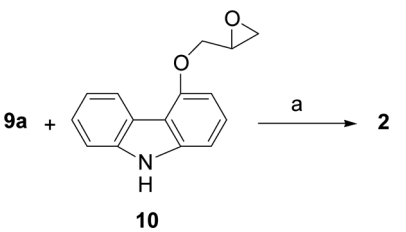



**Scheme 1.** Reagents and conditions: (a) 1,2-dibromoethane, NaOH (1.6 N), 95 °C; (b) m-CPBA, $CH_2Cl_2$, 30 °C; (c) NaOH (6 N), MeOH, 0 °C; (d) potassium phthalimide, NaI, DMF, 60 °C; (e) MeOH-$CH_3NH_2$, i-PrOH-HCl, MeCN, 30 °C.

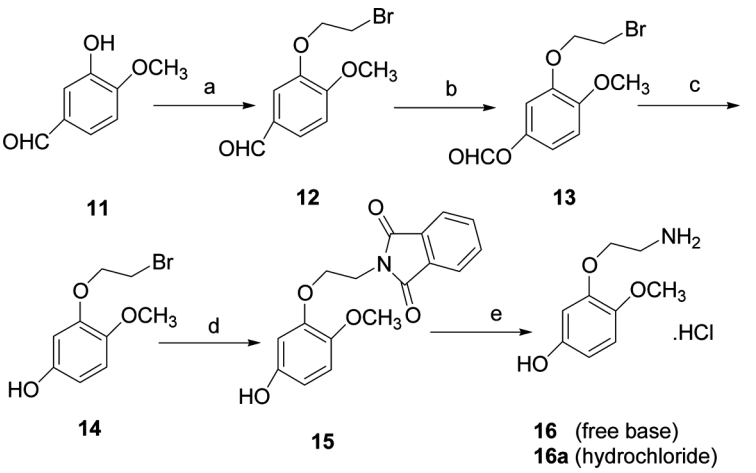
**9a** from acetonitrile. Finally, amine hydrochloride **9a** was coupled with oxirane **10**[11–13] (Scheme 2) to produce 4′-hydroxycarvedilol metabolite **2**.

The synthesis of metabolite **3** (Scheme 3) involves O-alkylation of the phenolic group of isovanillin **11** with 1,2-dibromoethane in the presence of a base at 95 °C and gave **12**[8] in 93% yield. Dakin oxidation of the formyl group of **12** using m-CPBA at room temperature gave **13** in 81% yield.

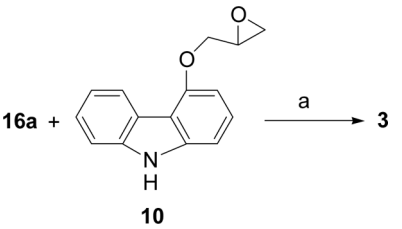
Further, hydrolysis[9] of **13** with sodium hydroxide in methanol at 0 °C afforded **14** in 75% yield. Compound **14** was condensed with potassium phthalimide in the presence of NaI (catalyst) in DMF at 60 °C, and compound **15** was isolated. Dephthalimidation of **15** with methanolic monomethylamine at 30 °C resulted in the corresponding amine **16**,[10] which was isolated as hydrochloride salt **16a** from acetonitrile. Finally, amine hydrochloride **16a** was coupled with oxirane **10**[11–13] (Scheme 4) to produce 5′-hydroxycarvedilol metabolite **3**.




**Scheme 2.** Reagents and conditions: (a) i-PrOH, TEA, 45 °C.




**Scheme 3.** Reagents and conditions: (a) 1,2-dibromoethane, NaOH (1.6 N), 95 °C; (b) m-CPBA, $CH_2Cl_2$, 30 °C; (c) NaOH (6 N), MeOH, 0 °C; (d) potassium phthalimide, NaI, DMF, 60 °C; (e) MeOH-$CH_3NH_2$, i-PrOH-HCl, MeCN, 30 °C.




**Scheme 4.** Reagents and conditions: (a) i-PrOH, TEA, 45 °C.

## CONCLUSION

To summarize, we have developed simple syntheses of 4′-hydroxycarvedilol **2** and 5′-hydroxycarvedilol **3** from easily available starting materials.

## EXPERIMENTAL

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker 300 spectrometer at 300 MHz, and the chemical shifts were reported as δ values in parts per million relative to tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded in the solid state as KBr dispersions using a Perkin-Elmer spectrophotometer. Mass spectra were recorded on an API 2000 Perkin-Elmer PE-SCIEX mass spectrometer. The melting points were recorded on open capillaries and are uncorrected.

### 4-(2-Bromoethoxy)-3-methoxybenzaldehyde (5)

Vanillin (**4**, 50 g, 0.329 mol) was added to mixture of 1,2-dibromoethane (246 g, 1.31 mol) and aq. 1.6 N NaOH (416 mL) at 30 °C. The reaction mixture was heated

to 95 °C and maintained until completion of reaction. The reaction mixture was cooled to 30 °C and extracted with $CH_2Cl_2$ (700 mL), followed by washing with $H_2O$ (400 mL). The organic layer was concentrated at 50 °C under reduced pressure to yield **5** (58 g, 96.6%). Mp 68–69 °C; IR (KBr): $\nu = 3343$, 3080, 3040, 3002, 1698, 1683, 1673, 1594, 1585, 1509, 1463, 1444, 1427, 1397, 1380, 1348, 1280, 1268, 1215, 1196, 1177, 1156, 1079, 1016, 1003, 960, 865, 812 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.68$–3.75 (t, 2H), 3.94 (s, 3H), 4.40–4.44 (t, $J = 6$ Hz, 2H), 6.98–7.01 (d, $J = 9$ Hz, 1H), 7.44–7.46 (m, 2H), 9.9 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 28$, 56, 69, 110, 112, 126, 131, 150, 153, 191; MS: $m/z = 261.0$ $[M^+]$.

### 3-(2-Bromoethoxy)-4-methoxybenzaldehyde (12)

Mp 80–81 °C; IR (KBr): $\nu = 3426$, 3075, 3040, 2977, 2925, 1679, 1596, 1583, 1510, 1436, 1392, 1263, 1241, 1132, 798, 737 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.67$–3.71 (t, 2H), 3.96 (s, 3H), 4.37–4.41 (t, $J = 6.3$ Hz, 2H), 6.9–7.0 (d, 1H), 7.4 (s, 1H), 7.49–7.52 (d, $J = 8.4$ Hz, 1H), 9.85 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 29$, 56, 69, 111, 112, 127, 130, 148, 155, 191; MS: $m/z = 261.0$ $[M^+]$.

### Formic Acid 4-(2-Bromoethoxy)-3-methoxyphenylester (6)

Compound **5** (50 g, 0.193 mol) was added to the solution of m-CPBA (66.7 g, 0.387 mol) in $CH_2Cl_2$ (500 mL) at 30 °C. The reaction mixture was maintained at 30 °C until completion of the reaction. The reaction mixture was quenched into 10% w/w aq. $Na_2CO_3$ (2 L). The organic layer was separated and concentrated completely to yield **6** (43 g, 81.1%) as a solid. Mp 67–68 °C; IR (KBr): $\nu = 3435$, 3124, 3087, 3067, 1723, 1606, 1514, 1474, 1448, 1275, 1268, 1225, 1159, 1109, 1031, 871 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.62$–3.64 (t, 2H), 3.8 (s, 3H), 4.29–4.34 (t, $J = 13.2$ Hz, 2H), 6.65–6.69 (m, 2H), 6.91–6.93 (d, $J = 8.1$ Hz, 1H), 8.28 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 29$, 56, 70, 106, 113, 115, 145, 146, 151, 160; MS: $m/z = 294.1$ $[M + NH_4]^+$.

### Formic Acid 3-(2-Bromoethoxy)-4-methoxyphenylester (13)

Mp 73–74 °C; IR (KBr): $\nu = 3442$, 2969, 1729, 1605, 1512, 1454, 1426, 1281, 1267, 1226, 1162, 1126, 1097, 873, 783 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.64$–3.69 (t, 2H), 3.8 (s, 3H), 4.29–4.34 (t, $J = 6$ Hz, 2H), 6.72–6.77 (m, 2H), 6.88–6.91 (d, $J = 9$ Hz, 1H), 8.2 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 29$, 56, 69, 109, 113, 114, 144, 148, 160; MS: $m/z = 293.9$ $[M + NH_4]^+$.

### 4-(2-Bromoethoxy)-3-methoxyphenol (7)

Compound **6** (38 g, 0.138 mol) was added to methanol (266 mL) and treated with aq. 6 N NaOH (38 mL) at 0 °C. The reaction mixture was maintained for 2 h at 0 °C. Methanol was distilled out completely from the reaction mixture at 45 °C under reduced pressure. The solid obtained was added to mixture of $CH_2Cl_2$ (200 mL) and $H_2O$ (100 mL), filtered, and separated. The organic layer was washed with $H_2O$ (2 × 100 mL), dried with $Na_2SO_4$, filtered, and concentrated completely at

35 °C under reduced pressure to yield **7** (27 g, 79.6%) as a solid. Mp 95–96 °C; IR (KBr): $\nu = 3371$, 3126, 3010, 2972, 1604, 1522, 1471, 1463, 1455, 1282, 1220, 1197, 1125, 1036, 1014, 829 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.61$–3.65 (t, $J = 6.3$ Hz, Hz, 2H), 3.8 (s, 3H), 4.24–4.29 (t, 2H), 6.39–6.41 (m, 1H), 6.47–6.48 (s, 1H), 6.75–6.78 (d, $J = 8.7$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 29$, 56, 71, 101, 106, 118, 141, 151, 152; MS: $m/z = 247$ [$M^+$].

### 3-(2-Bromoethoxy)-4-methoxyphenol (14)

Mp 84–85 °C; IR (KBr): $\nu = 3365$, 3126, 3010, 2972, 1602, 1525, 1513, 1441, 1271, 1227, 1172, 1124, 1020, 828, 733 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 3.58$–3.62 (t, 2H), 3.8 (s, 3H), 4.22–4.27 (t, 2H), 6.32–6.34 (m, 1H), 6.43–6.47 (s, 1H), 6.80–6.83 (d, $J = 8.4$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 29$, 57, 69, 103, 108, 114, 143, 149, 151; MS: $m/z = 247$ [$M^+$].

### 3-Methoxy-4-(2-phthalimidoethoxy)phenol (8)

Compound **7** (10 g, 0.0407 mol) was added to the mixture of potassium phthalimide (11.3 g, 0.0609 mol) and DMF (40 mL) at 30 °C. NaI (1 g, 10 wt%) was added and heated to 60 °C until the completion of reaction. The reaction mixture was cooled to 30 °C. The mixture of $CH_2Cl_2$ (50 mL) and $H_2O$ (160 mL) was added to rection mixture and stirred for 10 min. The organic layer was separated, washed with $H_2O$ ($2 \times 25$ mL) and dried with $Na_2SO_4$. The resulting organic layer was concentrated completely at 35 °C under reduced pressure. The solid obtained was slurried with $CH_2Cl_2$ (20 mL), filtered, and dried to yield **8** (10.96 g, 84.96%). Mp 164–165 °C; IR (KBr): $\nu = 3323$, 2941, 1764, 1693, 1615, 1596, 1509, 1479, 1466, 1431, 1400, 1309, 1203, 1170, 1014, 831, 723 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-d6): $\delta = 3.48$(s, 3H), 3.86–3.90 (m, 2H), 4.02–4.06 (m, 2H), 6.17–6.21 (m, 1H), 6.33–6.34 (s, 1H), 6.74–6.77 (d, $J = 8.7$ Hz, 1H), 7.82–7.91 (m, 4H), 9.0 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 38$, 56, 68, 101, 106, 118, 124, 132, 135, 141, 151, 154, 168; MS: $m/z = 314.1$ [$M^+$].

### 4-Methoxy-3-(2-phthalimidoethoxy)phenol (15)

Mp 136–137 °C; IR (KBr): $\nu = 3454$, 2940, 1768, 1653, 1621, 1515, 1465, 1448, 1435, 1422, 1400, 1397, 1211, 1191, 1173, 1020, 983, 828 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 3.4$ (s, 3H), 3.92–3.96 (m, 2H), 4.11–4.15 (m, $J = 5.7$ Hz, 2H), 6.25–6.28 (m, 1H), 6.40–6.41 (s, 1H), 6.68–6.71 (d, $J = 8.7$ Hz, 1H), 7.81–7.87 (m, 4H), 9.0 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 38$, 57, 66, 104, 108, 115, 123, 132, 135, 143, 149, 152, 168; MS: $m/z = 314.1$ [$M^+$].

### 4-(2-Aminoethoxy)-3-methoxyphenol Hydrochloride (9a)

Compound **8** (3 g, 0.0096 mol) was reacted with 20% w/w monomethyl amine (12 mL in $CH_3OH$) at 30 °C. The reaction mixture was stirred at 30 °C for 1 h, and the by-product was filtered. The filtrate was concentrated completely at 45 °C under reduced pressure. The resulting residue was dissolved in methanol and treated

with isopropyl alcohol (IPA)-HCl. The methanol was distilled out completely at 45 °C under reduced pressure. The solid obtained was purified with acetonitrile to yield **9a** (1.52 g, 72.3%). Mp 137–138 °C; IR (KBr): $\nu = 3435$, 3304, 3117, 2979, 2905, 1611, 1520, 1479, 1465, 1454, 1289, 1214, 1189, 1138, 1123, 1010, 952, 832 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 3.06$–3.10 (m, 2H), 3.72 (s, 3H), 4.01–4.05 (m, 2H), 6.29 (m, 1H), 6.46–6.47 (s, 1H), 6.85–6.87 (d, $J = 8.4$ Hz, 1H), 8.16 (br, 3H), 9.25 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 39$, 56, 68, 101, 106, 118, 140, 151, 154; MS: $m/z = 184.2$ [$M^+$].

### 3-(2-Aminoethoxy)-4-methoxyphenol Hydrochloride (16a)

Mp 125–126 °C; IR (KBr): $\nu = 3429$, 3252, 2985, 2902, 1674, 1616, 1518, 1484, 1464, 1291, 1226, 1163, 1125, 1016, 827 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 3.22$–3.29 (m, 2H), 3.72 (s, 3H), 4.08–4.13 (m, 2H), 6.33–6.37 (m, 1H), 6.47–6.48 (s, 1H), 6.78–6.81 (d, $J = 8.7$ Hz, 1H), 8.13 (br, 3H), 9.1 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 39$, 57, 66, 104, 108, 114, 143, 148, 152; MS: $m/z = 184.2$ [$M^+$].

### (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxy-4-hydroxyphenoxy)ethyl]amino]propan-2-ol (2)

Compound **9a** (1 g, 0.00456 mol) was neutralized in isopropyl alcohol (5 mL) at 30 °C by the addition of triethylamine (0.69 g, 0.00684 mol). The reaction mixture was heated to 45 °C. Compound **10** (0.54 g, 0.00226 mol) was added and stirred at 45 °C for 6 h (high-performance liquid chromatographic analysis showed 40% conversion). The reaction mixture was concentrated completely at 45 °C under vacuum. The resulting crude product was purified by column chromatography on silica gel (100–200 mesh, EtOAc–hexane, 3:2) to yield **2**. IR (KBr): $\nu = 3402$, 3056, 2933, 2874, 1626, 1606, 1509, 1455, 1402, 1347, 1161, 1100, 935, 785 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 2.83$–2.90 (m, 4H), 3.68 (s, 3H), 3.90–3.93 (m, 2H), 4.12–4.15 (m, 3H), 5.2 (m, 1H), 6.19–6.23 (m, 1H), 6.39–6.40 (m, 1H), 6.67–6.76 (m, 2H), 7.05–7.12 (m, 2H), 7.26–7.33 (m, 2H), 7.43–7.45 (d, 1H), 8.20–8.23 (d, $J = 9$ Hz, 1H), 9.0 (s, 1H), 11.25 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 49$, 53, 56, 68, 70, 71, 101, 104, 105, 111, 117, 119, 122, 123, 125, 127, 139, 141, 142, 151, 153, 155; MS: $m/z = 423.3$ [$M^+$].

### (2RS)-1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxy-5-hydroxyphenoxy)ethyl]amino]propan-2-ol (3)

IR (KBr): $\nu = 3399$, 3300, 2934, 2836, 1627, 1606, 1509, 1455, 1442, 1347, 1167, 1101, 991, 755, 724 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta = 2.96$–2.97 (m, 4H), 3.68 (s, 3H), 3.99–4.02 (m, 3H), 4.13–4.16 (m, 3H), 5.2 (m, 1H), 6.25–6.28 (m, 1H), 6.42–6.43 (m, 1H), 6.67–6.76 (m, 2H), 7.05–7.12 (m, 2H), 7.26–7.33 (m, 2H), 7.43–7.45 (d, 1H), 8.20–8.23 (d, $J = 9$ Hz, 1H), 8.96 (s, 1H), 11.24 (s, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$): $\delta = 49$, 53, 57, 69, 71, 101, 103, 104, 107, 111, 112, 114, 119, 122, 123, 125, 127, 139, 142, 143, 149, 152, 155; MS: $m/z = 423.3$ [$M^+$].

## ACKNOWLEDGMENTS

The authors thank Aurobindo Pharma Ltd. for supporting this work. The authors are also thankful to colleagues at the analytical research department and chemical research department of Aurobindo Research Center for the cooperation and fruitful discussions.

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