Study on the Structure-Activity Relations of Brominated Hydroxy Diphenyl Ethers Derivatives with Anilines

BIN LUO¹, HUA-HONG ZHOU², KANG-KANG YU¹, KAI-QUN WU^{1,*}, TIAN CHEN^{2,**} and YU-LIANG WANG¹

¹Faculty of Chemistry, Sichuan University, Chengdu 610065, P.R. China

²Department of Pathogenic Biology, School of Biomedical Science, Chengdu Medical College, Chengdu 610083, P.R. China

*Corresponding author: Tel: +86 13708058490, E-mail: wukaiqun@tom.com; luobinhxscu@126.com

**Corresponding author (For biological activities assay): Tel: +86 13540047681, E-mail: tianchen66@gmail.com

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In order to study the influence of anilines on antibacterial activity, eight novel brominated hydroxy diphenyl ethers derivatives were designed and synthesized. The antibacterial activities of the new compounds were tested *via* agar-well diffusion method *in vitro* under different concentrations. The results showed the derivatives had antibacterial activities at the concentration 50 µg/mL against *Staphylococcus aureus* SC and *Staphylococcus aureus* ATCC26112.

Key Words: Brominated hydroxy diphenyl ethers, Structure-activity, Anilines, Antibacterial activity.

INTRODUCTION

Brominated 2-hydroxy diphenyl ethers was first isolated from the marine sponge *Dysidea herbacea* by Sharma *et al.*¹ (Fig. 1, 1) and it was reported that brominated 2-hydroxy diphenyl ethers could inhibit gram positive bacteria and gram negative bacteria^{1,2}. Afterwards, many literatures have focused on the isolation and synthesise new brominated hydroxy diphenyl ethers and their antibacterial activities³⁻⁵. These studies showed that the hydroxy was necessary for keeping antibacterial activity^{6,7} and fluorine as well as nitro substituent were favourable for enhancing antibacterial activity^{8,9}. They also employed that some synthetic derivatives had a special antibacterial activities such as a series of brominated dihydroxy diphenyl ethers derivatives have been designed and synthesized with good antibacterial activities^{10,11} (Fig. 1, 2). However, dioxins were found during the separation of natural brominated 2-hydroxy diphenyl ethers^{12,13} (Fig. 1, 3). In order to avoid the generation of dioxins a series of brominated 3-hydroxy (Fig. 1, 4) and 4-hydroxy (Fig. 1, 5) diphenyl ethers derivatives were designed and synthesized. The results showed that brominated 3-hydroxy and 4-hydroxy diphenyl ethers derivatives had also a good antibacterial activities and will never form dioxins^{14,15}.

In order to avoid the generation of dioxins and to study the influence of anilines on antibacterial activity systematically, a series of novel brominated 4-hydroxy diphenyl ethers derivatives containing aniline have been designed and synthesized. The antibacterial activities of the target compounds have been

tested *via* the agar-well diffusion method *in vitro*. The results showed that target compounds had some antibacterial activities against *Staphylococcus aureus* SC, *Staphylococcus aureus* ATCC26112. The synthetic route is shown in **Scheme-I**.

Fig. 1. Brominated hydroxy diphenyl ethers and related derivatives

Scheme-I: Synthetic route of compounds 7a-7h

EXPERIMENTAL

Melting points were recorded on an XRC-1 melting point apparatus (Sichuan University Instrument Inc., Chengdu, China) without being corrected. 1H NMR spectra were run on a Varian INOVA-400 spectrometer (Varian Inc., Palo Alto, CA, USA) with $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were recorded with an Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionization (ESI) method. IR spectra were recorded with a Perkin-Elmer 16PC-FT instrument (Perkin-Elmer Inc., Norwalk Conn, CA, USA). Compounds 1 and 2 were commercially available, compounds 3 and 4 were synthesized according to the literature¹⁶.

General preparation procedure of 5a-b: A mixture of 4 (1 mmol) and NaOH (5 mmol) in solvent (20 mL, dry ethanol:water = 3:1) was stirred at 0–5 °C, then dimethyl sulfate (6 mmol) was added dropwise. Reaction solution was stirred at 0–15 °C for 24 h. Then the pH was adjusted to 7 with diluted hydrochloric acid, 20 mL water was added and the mixture was extracted with ethyl acetate. The organic layer was filtered, dried and evaporated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel using petroleum ether/ethyl acetate (16:1) as eluent to afford a pure product (yield 50–55 %).

General preparation procedure of 5c-g: A mixture of 4 (1 mmol), dry Na_2CO_3 (3 mmol) and RBr (3–6 mmol) in dry DMF (20 mL) was stirred at 60–110 °C for 3–24 h, cooled. 20 mL water was added and the mixture was extracted with ethyl acetate. The organic layer was filtered, dried and evaporated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel using petroleum ether/ethyl acetate (16:1) as eluent to afford a pure product (yield 60–92 %).

General preparation procedure of 6a-g: A mixture of 5a-g (1 mmol) and 40 % HBr (6 mmol) in acetic acid (20 mL) was refluxed at 125 °C for 9–11 h, cooled, the pH was adjusted to 7 with saturated $NaHCO_3$ solution and the mixture was extracted with ethyl acetate. The organic layer was filtered, dried and evaporated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel using petroleum ether/ethyl acetate (4:1) as eluent to afford a pure product (yield 45–85 %).

General preparation procedure of 7a-h: 6a-g (1 mmol) was dissolved in ethyl acetate/dichloromethane (1:1, 20 mL) and the mixture was heated to reflux. Liquid bromide (6 mmol) was dissolved in ethyl acetate/dichloromethane (1:1, 4 mL) and the solution was added dropwise. The reaction mixture was refluxed for 7 h, cooled, the reaction mixture was washed by 5 % $Na_2S_2O_3$, saturated $NaHCO_3$ solution, water. The organic layer was filtered, dried and evaporated *in vacuo* to give the crude product. The crude product was chromatographed on silica gel using petroleum ether/ethyl acetate (20:1) as eluent to afford a pure product (yield 45–55 %).

5a, 5c are known compounds reported in literature¹⁷ and were identified by melting point test, 1H NMR and IR, all data was the same with the literature.

3-Chloro-4-(4-methoxyphenoxy)-N,N-dimethylbenzenamine (5b): Yellow solid; yield: 52.3 %, m.p.: 52–54 °C; 1H NMR spectrum (400 MHz; d_1 - $CDCl_3$; TMS): δ (ppm) = 2.93 (6H, s), 3.77 (3H, s), 6.58 (1H, dd, $J_1=8.8$ Hz, $J_2=2.8$ Hz), 6.77 (1H, d, $J=2.8$ Hz), 6.81–7.03 (5H, m); IR (KBr, ν_{max} , cm^{-1}) 3040, 2936, 2834, 1607, 1562, 1499, 1443, 1234, 1202, 1039, 961, 879, 828, 772.

3-Chloro-4-(4-methoxyphenoxy)-N,N-diethylbenzenamine (5d): Yellow oily liquid; yield: 80.2 %; 1H NMR spectrum (400 MHz; d_1 - $CDCl_3$; TMS): δ (ppm) = 0.93 (6H, t, $J=7.6$ Hz), 3.19 (4H, q, $J=7.6$ Hz), 3.77 (3H, s), 6.53 (1H, dd, $J_1=8.8$ Hz, $J_2=2.8$ Hz), 6.66 (1H, d, $J=2.8$ Hz), 6.81–7.00 (5H, m); IR (KBr, ν_{max} , cm^{-1}) 3046, 2970, 2835, 1607, 1556, 1498, 1376, 1356, 1232, 1200, 1039, 874, 826, 794, 756.

4-(4-Methoxyphenoxy)-N,N-dipropylbenzenamine (5e): Yellow oily liquid; yield: 65.3 %; 1H NMR spectrum (400 MHz; d_1 - $CDCl_3$; TMS): δ (ppm) = 0.92 (6H, t, $J=7.6$ Hz), 1.59 (4H, m), 3.19 (4H, t, $J=7.6$ Hz), 3.83 (3H, s), 6.60 (2H, d, $J=8.8$ Hz), 6.81–6.92 (6H, m); IR (KBr, ν_{max} , cm^{-1}): 3045, 2960, 2873, 2835, 1612, 1500, 1462, 1370, 1225, 1100, 1037, 873, 824, 746.

4-(4-Methoxyphenoxy)-N,N-dibutylbenzenamine (5f): Yellow oily liquid; yield: 60.3 %; 1H NMR spectrum (400 MHz; d_1 - $CDCl_3$; TMS): δ (ppm) = 0.95 (6H, t, $J=7.2$ Hz), 1.34 (4H, m), 1.50 (4H, m), 3.22 (4H, t, $J=7.6$ Hz), 3.80 (3H, s), 6.60 (2H, d, $J=8.8$ Hz), 6.81–6.90 (6H, m); IR (KBr, ν_{max} , cm^{-1}): 3044, 2957, 2868, 1611, 1500, 1462, 1369, 1277, 1227, 1105, 1037, 824.

3-Chloro-4-(4-methoxyphenoxy)-N,N-dibenzylbenzenamine (5g): Colourless oily liquid; yield: 91.3 %; 1H NMR spectrum (400 MHz; d_1 - $CDCl_3$; TMS): δ (ppm) = 3.77 (3H, s), 4.67 (4H, s), 6.56 (1H, dd, $J_1=8.8$ Hz, $J_2=3.2$ Hz), 6.79–6.91 (6H, m), 7.07–7.39 (10H, m); IR (KBr, ν_{max} , cm^{-1}): 3029, 2946, 2833, 1604, 1497, 1452, 1393, 1361, 1230, 1200, 1030, 957, 883, 821, 733, 696.

4-[4-(Dimethylamino)phenoxy]phenol (6a): White solid; yield: 84.7 %, m.p.: 133-135 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 2.93 (6H, s), 4.61 (1H, s), 6.76 (2H, d, $J = 8.4$ Hz), 6.85 (4H, d, $J = 8.8$ Hz), 6.92 (2H, d, $J = 8.8$ Hz); IR (KBr, ν_{max} , cm^{-1}): 3430, 3043, 2895, 2813, 1603, 1502, 1451, 1366, 1303, 1227, 1145, 1096, 1051, 932, 871, 826.

4-[2-Chloro-4-(dimethylamino)phenoxy]phenol (6b): White solid; yield: 83.6 %, m.p.: 127-129 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 2.94 (6H, s), 4.53 (1H, s), 6.61-6.83 (5H, m), 6.91 (2H, d, $J = 8.8$ Hz); IR (KBr, ν_{max} , cm^{-1}): 3097, 2921, 2821, 1600, 1495, 1443, 1355, 1237, 1142, 1052, 948, 879, 822, 782, 509.

4-[4-(Diethylamino)phenoxy]phenol (6c): White solid; yield: 82.0 %, m.p.: 113-115 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 1.16 (6H, t, $J = 3.6$ Hz), 3.31 (4H, q, $J = 6.8$ Hz), 4.87 (1H, s), 6.76 (2H, d, $J = 8.8$ Hz), 6.86 (4H, d, $J = 8.8$ Hz), 6.89 (2H, d, $J = 9.2$ Hz); IR (KBr, ν_{max} , cm^{-1}): 3385, 3041, 2972, 2931, 1607, 1500, 1448, 1354, 1224, 1094, 1010, 872, 820.

4-[2-Chloro-4-(diethylamino)phenoxy]phenol (6d): Yellow oilyliquid; yield: 79.5 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 1.16 (6H, t, $J = 7.2$ Hz), 3.32 (4H, q, $J = 7.2$ Hz), 4.58 (1H, s), 6.53 (1H, dd, $J_1 = 8.8$ Hz, $J_2 = 2.8$ Hz), 6.70 (1H, d, $J = 2.8$ Hz), 6.75 (1H, d, $J = 9.2$ Hz), 6.80 (2H, d, $J = 8.8$ Hz), 6.89 (2H, d, $J = 8.8$ Hz); IR (KBr, ν_{max} , cm^{-1}): 3390, 3033, 2972, 2931, 1605, 1557, 1505, 1356, 1233, 1096, 1045, 1013, 924, 874, 828, 768, 693, 607, 512.

4-[4-(Dipropylamino)phenoxy]phenol (6e): Yellow oilyliquid; yield: 73.8 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 0.92 (6H, t, $J = 7.6$ Hz), 1.59 (4H, m), 3.19 (4H, t, $J = 7.6$ Hz), 4.60 (1H, s), 6.60 (2H, d, $J = 8.8$ Hz), 6.75 (2H, d, $J = 8.8$ Hz), 6.84-6.87 (4H, m); IR (KBr, ν_{max} , cm^{-1}): 3404, 3046, 2962, 2931, 2873, 1608, 1500, 1460, 1364, 1222, 1098, 1046, 873, 818, 757.

4-[4-(Dibutylamino)phenoxy]phenol (6f): Yellow oilyliquid; yield: 70.1 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 0.95 (6H, t, $J = 7.2$ Hz), 1.34 (4H, m), 1.50 (4H, m), 3.22 (4H, t, $J = 7.6$ Hz), 6.61 (2H, d, $J = 8.4$ Hz), 6.75 (2H, d, $J = 8.8$ Hz), 6.85-6.89 (4H, m); IR (KBr, ν_{max} , cm^{-1}): 3044, 2957, 2868, 1611, 1500, 1462, 1369, 1277, 1227, 1105, 1037, 824.

4-[2-Chloro-4-(dibenzylamino)phenoxy]phenol (6g): Colourless oilyliquid; yield: 45.3 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 4.30 (4H, s), 4.60 (1H, s), 6.63 (1H, d, $J = 8.8$ Hz), 6.76 (1H, d, $J = 3.2$ Hz), 6.88-7.01 (5H, m), 7.28-7.39 (10H, m); IR (KBr, ν_{max} , cm^{-1}): 3335, 3030, 2874, 1604, 1504, 1449, 1357, 1250, 1095, 1053, 1006, 959, 884, 836, 801, 737, 698, 405.

2,6-Dibromo-4-[4-(dimethylamino)phenoxy]phenol (7a): Yellow solid; yield: 15.3%; m.p.: 126-128 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 2.78 (6H, s), 5.36 (1H, s), 6.88 (2H, d, $J = 2.8$ Hz), 7.01 (2H, d, $J = 5.6$ Hz), 7.16 (2H, s); IR (KBr, ν_{max} , cm^{-1}): 3503, 3069, 2929, 2866, 2784, 1592, 1498, 1415, 1324, 1267, 1212, 1185, 1034, 916, 883, 817, 781, 569; HR-MS (ESI): Calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}_2\text{Br}_2$ $[\text{M}+\text{H}]^+$: 385.9392, 387.9372, 389.9351; Found: 385.9381, 387.9363, 389.9345.

2,6-Dibromo-4-[3-bromo-5-chloro-4-(dimethylamino)phenoxy]phenol (7b): White solid; yield: 47.7 %, m.p.: 109-111 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 2.80 (6H, s), 5.68 (1H, s), 7.08 (1H, s), 7.15 (1H, s), 7.20 (1H, s), 7.30 (1H, s); IR (KBr, ν_{max} , cm^{-1}): 3284, 3081, 2960, 2873, 2841, 2797, 1593, 1564, 1464, 1400, 1355, 1317, 1216, 1184, 1134, 1072, 1045, 970, 932, 887, 852, 801, 768, 733, 681, 580, 517, 466, 422; HR-MS (ESI): Calcd. for $\text{C}_{14}\text{H}_{12}\text{NO}_2\text{Br}_3\text{Cl}$ $[\text{M}+\text{H}]^+$: 497.8107, 499.8087, 501.8067; Found: 497.8091, 499.8069, 501.8048.

2,6-Dibromo-4-[4-(diethylamino)phenoxy]phenol (7c): White solid; yield: 48.9 %, m.p.: 103-105 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 1.17 (6H, t, $J = 6.8$ Hz), 3.34 (4H, q, $J = 6.8$ Hz), 5.58 (1H, s), 6.66 (2H, d, $J = 8.8$ Hz), 6.88 (2H, d, $J = 9.2$ Hz), 7.08 (2H, s); IR (KBr, ν_{max} , cm^{-1}): 3501, 3076, 2970, 2928, 1606, 1510, 1465, 1402, 1320, 1263, 1218, 1150, 1011, 934, 820, 792, 742, 576; HR-MS (ESI): Calcd. for $\text{C}_{16}\text{H}_{18}\text{NO}_2\text{Br}_2$ $[\text{M}+\text{H}]^+$: 413.9705, 415.9685, 417.9664; Found: 413.9698, 415.9706, 417.9661.

2,6-Dibromo-4-[2-chloro-4-(diethylamino)phenoxy]phenol (7d): Yellow solid; yield: 54.3 %; m.p.: 106-108 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 1.18 (6H, t, $J = 7.2$ Hz), 3.33 (4H, q, $J = 7.2$ Hz), 5.57 (1H, s), 6.53 (1H, d, $J = 8.8$ Hz), 6.68 (1H, d, $J = 2.4$ Hz), 6.91 (1H, d, $J = 8.8$ Hz), 7.02 (2H, s); IR (KBr, ν_{max} , cm^{-1}): 3517, 3073, 2969, 2927, 1607, 1562, 1503, 1466, 1403, 1356, 1318, 1276, 1233, 1196, 1150, 1071, 1042, 1016, 930, 800, 752, 695, 580, 436; HR-MS (ESI): Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{Br}_2\text{Cl}$ $[\text{M}+\text{H}]^+$: 447.9315, 449.9295, 451.9274; Found: 447.9305, 449.9284, 451.9267.

2,6-Dibromo-4-[4-(dipropylamino)phenoxy]phenol (7e): Yellow oilyliquid; yield: 48.7 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 0.93 (6H, t, $J = 7.2$ Hz), 1.63 (4H, m, $J = 7.6$ Hz), 3.22 (4H, t, $J = 7.6$ Hz), 5.55 (1H, s), 6.60 (2H, d, $J = 9.2$ Hz), 6.86 (2H, d, $J = 9.2$ Hz), 7.07 (2H, s); IR (KBr, ν_{max} , cm^{-1}): 3505, 3077, 2960, 2872, 1607, 1565, 1510, 1465, 1402, 1321, 1218, 1150, 1101, 1047, 932, 819, 744, 549; HR-MS (ESI): Calcd. for $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{Br}_2$ $[\text{M}+\text{H}]^+$: 442.0018, 443.9998, 445.9977; Found: 442.0013, 443.9999, 445.9976.

2,6-Dibromo-4-[4-(dibutylamino)phenoxy]phenol (7f): Yellow oilyliquid; yield: 40.2 %; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 0.96 (6H, t, $J = 7.6$ Hz), 1.36 (4H, m), 1.57 (4H, m), 3.24 (4H, t, $J = 7.6$ Hz), 5.56 (1H, s), 6.60 (2H, d, $J = 8.8$ Hz), 6.86 (2H, d, $J = 8.8$ Hz), 7.08 (2H, s); IR (KBr, ν_{max} , cm^{-1}): 3511, 3078, 3044, 2956, 2866, 1608, 1565, 1510, 1465, 1402, 1369, 1321, 1215, 1149, 1109, 1051, 1008, 931, 818, 782, 744, 697, 578; HR-MS (ESI): Calcd. for $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{Br}_2$ $[\text{M}+\text{H}]^+$: 470.0331, 472.0311, 474.0290; Found: 470.0334, 472.0306, 474.0297.

2,6-Dibromo-4-[5-bromo-2-chloro-4-(dibenzylamino)phenoxy]phenol (7g): White solid; yield: 49.9 %, m.p.: 180-182 °C; ^1H NMR spectrum (400 MHz; $\text{d}_1\text{-CDCl}_3$; TMS): δ (ppm) = 4.67 (4H, s), 5.64 (1H, s), 7.02 (1H, s), 7.08 (3H, d, $J = 6.8$ Hz), 7.15-7.29 (10H, m); IR (KBr, ν_{max} , cm^{-1}): 3476, 3381, 3074, 2923, 2853, 1605, 1568, 1451, 1409, 1383, 1309, 1278, 1218, 1189, 1155, 1067, 973, 922, 848, 779, 737, 713, 582, 532, 493, 454; HR-MS (ESI): Calcd. for $\text{C}_{26}\text{H}_{20}\text{NO}_2\text{Br}_2\text{Cl}$

[M+H]⁺: 649.8733, 651.8713, 653.8693; Found: 649.8718, 651.8699, 653.8683.

2,6-Dibromo-4-[2-bromo-4-(dimethylamino)phenoxy]-phenol (7h): White solid; yield: 45.4 %, m.p.: 120-122 °C; ¹H NMR spectrum (400 MHz; d₁-CDCl₃; TMS): δ (ppm) = 2.78 (6H, s), 5.70 (1H, s), 6.90 (1H, dd, *J*₁ = 8.8 Hz, *J*₂ = 2.8 Hz), 7.08 (1H, d, *J* = 8.8 Hz), 7.14 (1H, s), 7.2 (2H, d, *J* = 2.8 Hz); IR (KBr, ν_{max}, cm⁻¹): 3418, 3078, 2954, 1586, 1559, 1464, 1403, 1338, 1263, 1213, 1153, 1034, 937, 864, 789, 752, 669, 584, 544; HR-MS (ESI): Calcd. for C₁₄H₁₃NO₂Br₃ [M+H]⁺: 463.8497, 465.8477, 466.8456; Found: 463.8488, 465.8466, 466.8443.

Biological assay: Wild *Staphylococcus aureus* SC and standard *Staphylococcus aureus* ATCC26112 were used in the studies. The antibacterial activities of the target compounds *in vitro* were tested *via* agar-well diffusion method. Every sample (1000 µg) was dissolved with ethanol (1 mL) and diluted to 50 µg/mL with ethanol. The resulting solution was added to the flat plate of an Oxford cup which was covered with culture and kept at 37 °C for 24 h. The results of average diameters of the bacteriostatic circle are listed in Table-1.

RESULTS AND DISCUSSION

The bioactivities of compounds **7a-h** against *S. aureus* ATCC26112 and *S. aureus* SC are shown in Table-1. The results showed that all target compounds exhibited antibacterial activity at the concentration of 50.0 µg/mL.

TABLE-1 ANTIBACTERIAL ACTIVITY OF THE TARGET COMPOUNDS (7a-h) AT THE CONCENTRATION OF 50.0 µg/mL TOWARD <i>S. aureus</i> ATCC26112 and <i>S. aureus</i> SC		
Compound	Diameter of inhibition zone (mm)	
	<i>S. aureus</i> ATCC26112	<i>S. aureus</i> SC
7a	11	13
7b	9	10
7c	8	8
7d	11.5	11
7e	13	12
7f	7	9
7g	7	9
7h	8.5	10
Triclosan	22	20
Ethanol ^b	-	-

a: Concentration of triclosan: 20.0 µg/mL; as the positive control;
b: negative control: ethanol; diameter of the well in each plate: 6 mm

During the preparation of **5a-g**, by-products increased as the reduction of activities of RBr. So it's necessary to increase reaction temperature and time. Otherwise, RBr were vapourized along with long-playing heating, so more RBr needed during reaction process.

As shown in **Scheme-I**, the intermediates **6a-g** were synthesized by **5a-g** with HBr in HAc. On this condition the benzyl located in the nitrogen would fall off partially, so the yield of the intermediate **6g** was very low.

Conclusion

In conclusion, eight novel brominated hydroxy diphenyl ethers derivatives were designed and synthesized. Compared to 4-hydroxy (Fig. 1, **5**) diphenyl ethers derivatives¹⁵ with nitro group which exhibited good antibacterial activity at the concentration of 10 µg/mL, all target compounds have similar structures with them, but their antibacterial activities are much worse. This made a further proof that nitro group is important for enhancing antibacterial activity. We will continue to study structure-activity relations of brominated hydroxy diphenyl ethers derivatives.

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REFERENCES

- G.M. Sharma, B. Vig and P.R. Burkholder, Marine Technology Society, Washington D.C. (1969).
- G.M. Sharma and B. Vig, *Tetrahedron Lett.*, **13**, 1715 (1972).
- B. Carté and D.J. Faulkner, *Tetrahedron*, **37**, 2335 (1981).
- R.S. Norton, K.D. Croft and R.J. Wells, *Tetrahedron*, **37**, 2341 (1981).
- E.N. Segraves, R.R. Shah, N.L. Segraves, T.A. Johnson, S. Whitman, J.K. Sui, V.A. Kenyon, R.H. Cichewicz, P. Crews and T.R. Holman, *J. Med. Chem.*, **47**, 4060 (2004).
- J. Salvá and D.J. Faulkner, *J. Nat. Prod.*, **53**, 757 (1990).
- D. Handayani, R.A. Edrada, P. Proksch, V. Wray, L. Witte, R.W.M. Van Soest and A. Kunzmann, *J. Nat. Prod.*, **60**, 1313 (1997).
- Y.L. Wang, M.L. Ma and S.H. Chen, *Youji Huaxue*, **25**, 734 (2005).
- K.Q. Wu, Y.L. Wang and H. Zheng, CN 1597657 (2005).
- H. Jin, S. Chen and R.T. Hou, *Youji Huaxue*, **26**, 1424 (2006).
- S. Chen, Y. Xin and Y. Zhan, *Youji Huaxue*, **3**, 498 (2008).
- N.K. Utkina, V.A. Denisenko, O.V. Scholokova, M.V. Virovaya, A.V. Gerasimenko, D.Y. Popov, V.B. Krasokhin and A.M. Popov, *J. Nat. Prod.*, **64**, 151 (2001).
- N.K. Utkina, V.A. Denisenko, M.V. Virovaya, O.V. Scholokova and N.G. Prokofeva, *J. Nat. Prod.*, **65**, 1213 (2002).
- X. Tang, M. Xie, Y.X. Sun, J.H. Liu, Z.C. Zhong and Y.L. Wang, *Chin. Chem. Lett.*, **20**, 435 (2009).
- Y. Zou, J. Wu and R.T. Hou, *Youji Huaxue*, **1**, 111 (2008).
- Z.X. Yang, H. Chen and Y.L. Wang, *Youji Huaxue*, **3**, 432 (2008).
- T. Saitoh and J. Ichikawa, *J. Am. Chem. Soc.*, **127**, 9696 (2005).