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

BIN LUO[1], HUA-HONG ZHOU[2], KANG-KANG YU[1], KAI-QUN WU[1,*], TIAN CHEN[2,**] and YU-LIANG WANG[1]

[1]Faculty of Chemistry, Sichuan University, Chengdu 610065, P.R. China
[2]Department 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 focued on the isolation and synthesise new brominated hydroxy diphenyl ethers and their antibacterial activities[3-5]. 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 emplyed 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**.

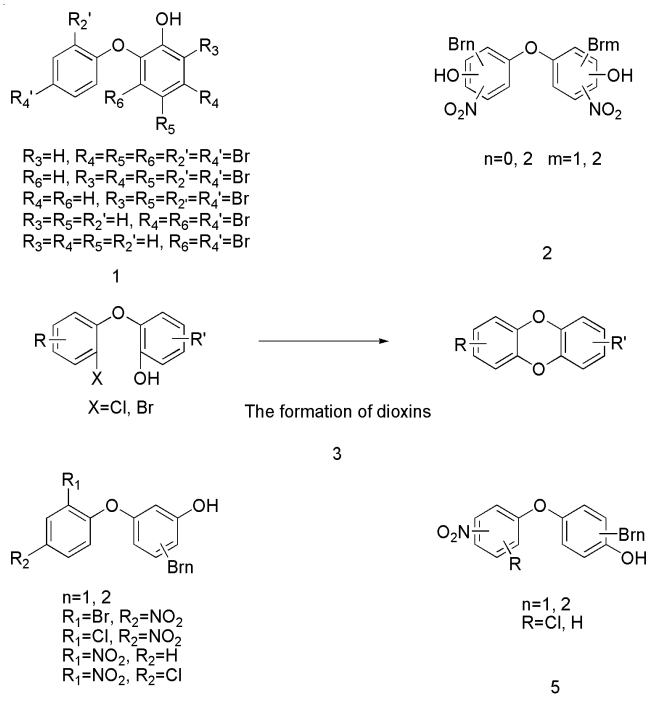
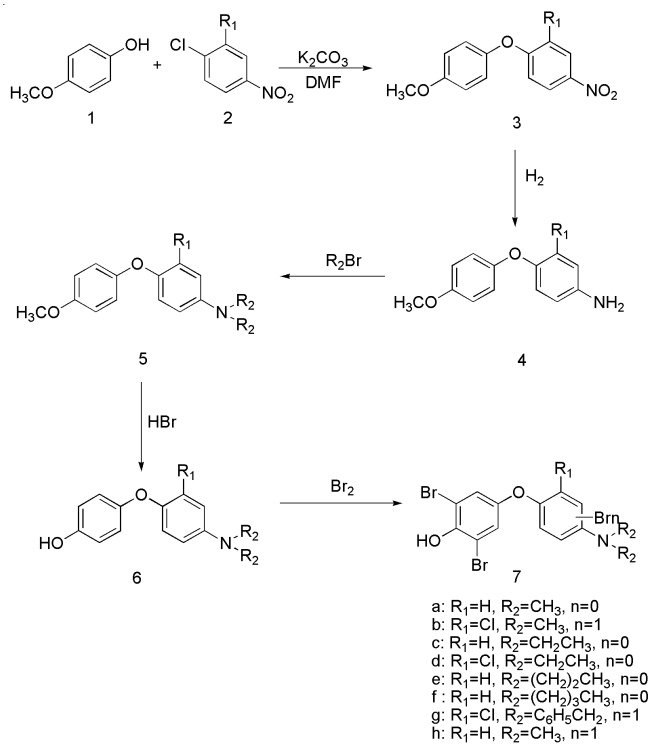


Fig. 1. Brominated hydroxy diphenyl ethers and related derivatives



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. ^{1}H 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 literature[16].

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 ºC, then dimethyl sulfate (6 mmol) was added dropwise. Reaction solution was stirred at 0-15 ºC 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 ºC 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 ºC 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 literature[17] and were identified by melting point test, ^{1}H NMR and IR, all data was the same with the literature.

3-Chloro-4-(4-methoxyphenoxy)-*N,N*-dimethyl-benzen-amine (5b): Yellow solid; yield:52.3 %, m.p.: 52-54 ºC; ^{1}H 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*-diethyl-benzenamine (5d): Yellow oilyliquid; yield: 80.2 %; ^{1}H 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 oilyliquid; yield: 65.3 %; ^{1}H 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*-dibutyl-benzenamine (5f): Yellow oily liquid; yield: 60.3 %; ^{1}H 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*-dibenzyl-benzenamine (5g): Colourless oilyliquid; yield: 91.3 %; ^{1}H 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm) = 1.16 (6H, t, *J* = 3.6 Hz), 3.31 (4H, q, *J* = 6.8Hz), 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 %; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm) = 1.16 (6H, t, *J* = 7.2 Hz), 3.32 (4H, q, *J* = 7.2Hz), 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 %; ^{1}H 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), 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 %; ^{1}H 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), 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 %; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{14}H_{14}NO_2Br_2$ $[M+H]^+$: 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{14}H_{12}NO_2Br_3Cl$ $[M+H]^+$: 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{16}H_{18}NO_2Br_2$ $[M+H]^+$: 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{16}H_{17}NO_2Br_2Cl$ $[M+H]^+$: 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 %; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{18}H_{22}NO_2Br_2$ $[M+H]^+$: 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 %; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{20}H_{26}NO_2Br_2$ $[M+H]^+$: 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{26}H_{20}NO_2Br_2Cl$

$[M+H]^+$: 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 ºC; ^{1}H NMR spectrum (400 MHz; d_1-$CDCl_3$; 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 $C_{14}H_{13}NO_2Br_3$ $[M+H]^+$: 463.8497, 465.8477, 466.8456; Found: 463.8488, 465.8466, 466.8443.

Biological assay: Wild *Staphylcoccus aures* SC and standard *Staphylcoccus aures* 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 ºC 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 *S. aureus* ATCC26112 and *S. aureus* SC

Compound	Diameter of inhibition zone (mm)	
	S. aureus ATCC26112	*S. aureus 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 derivatives[15] 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 activitiy. We will continue to study structure-activity relations of brominated hydroxy diphenyl ethers derivatives.

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