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Antimicrobial activities of the bromophenols from the red alga *Odonthalia corymbifera* and some synthetic derivatives

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Abstract—A series of bromophenols was obtained by isolation from red alga *Odonthalia corymbifera* and by reactions of bis(hydroxyphenyl)methanes with bromine. New bromophenols including 3,3′,5,5′-tetrabromo-2,2′,4,4′-tetrahydroxydiphenylmethane (**10**), a regioisomer of the potent antimicrobial natural product, together with known derivatives were synthesized in high yield. All of the isolated and synthesized compounds were tested for antimicrobial activity against Gram-negative, Gram-positive bacteria and fungi. The preliminary structure–activity relationship, to elucidate the essential structure requirements for antimicrobial activity, has been described. Among the isolated natural products 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**4**) was found to be the most active derivative against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. The synthetic bromophenols 3,3′-dibromo-6,6′-dihydroxydiphenylmethane (**13**) and 3,3′,5,5′-tetrabromo-6,6′-dihydroxydiphenylmethane (**14**) showed potent antibacterial effect against *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Proteus vulgaris*, and *Salmonella typhimurium*.

Bromophenol compounds have been frequently encountered in various marine organisms including red algae, brown algae, ascidians, and sponges. Especially, the red algae of the family Rhodomelaceae are known as a rich source of bromophenols.[1–17] Some of these compounds previously isolated from the family exhibited a wide spectrum of pharmacological activities such as enzyme inhibition,[3,9] cytotoxic,[4] antioxidant,[8] feeding-deterrent,[10] anti-inflammatory,[11] and antimicrobial[13] activities.

In the course of our search for biologically active constituents from marine algae, we collected *Odonthalia corymbifera*, (family, Rhodomelaceae), whose crude extract exhibited moderate antimicrobial activity against various microorganisms. Bioassay-guided separation of the crude extract using a variety of chromatographic techniques afforded several bromophenol compounds.[18] Based upon the results of combined spectral analyses, the metabolites were identified to be 4-(2-aminoethyl)-2,6-dibromophenol (**1**),[19,20] 2,3-dibromo-4,5-dihydroxybenzyl alcohol (**2**),[10] 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**3**),[17] 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**4**),[15] 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-hydroxymethyl diphenylmethane (**5**),[6] and 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol (**6**) (Fig. 1).[15]

The in vitro antimicrobial activities of the bromophenols **1**–**6** were assessed against three representative Gram-positive bacteria viz. *Staphylococcus aureus* (ATCC6538p), *Bacillus subtilis* (ATCC 6633), and *Micrococcus luteus* (IFC 12708), three Gram-positive bacteria viz. *Proteus vulgaris* (ATCC3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922), and four fungal organisms viz. *Candida albicans* (ATCC10231), *Aspergillus fumigatus* (HIC6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO

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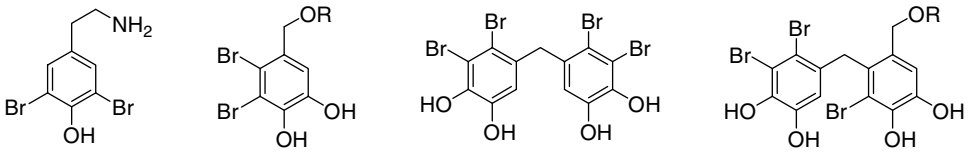

1 **2** R = H, **3** R = CH_3 **4** **5** R = H, **6** R = CH_3

Figure 1. Bromophenols from *Odonthalia corymbifera*.

40996).[21,22] Data for the metabolites are presented in Tables 1 and 2 as the minimal inhibitory concentration (MIC). Among the isolated natural products compound **4** was found to be the most active derivative against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes*. Specially, the di-phenolic metabolites **4**–**6** display good inhibition activity against Gram-positive and Gram-negative organisms except *E. coli*, whereas the mono-phenolic metabolites **1**–**3** showed no antibacterial activities (Table 1). However, this trend does not translate exactly

Table 1. Antibacterial activity

Compound	Antibacterial activity (MIC, μg/ml)					
	S. aureus	*B. subtilis*	*M. luteus*	*P. vulgaris*	*S. typhimurium*	*E. coli*
1	100	>100	>100	>100	>100	>100
2	>100	>100	>100	>100	>100	>100
3	>100	>100	>100	>100	>100	>100
4	25	25	25	50	50	>100
5	50	100	50	100	100	>100
6	25	25	25	25	25	>100
7	>100	>100	>100	>100	>100	>100
8	>100	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100	>100
12	25	25	25	25	25	>100
13	3.12	3.12	1.56	3.12	3.12	>100
14	1.56	1.56	1.56	1.56	3.12	>100
16	25	12.5	12.5	25	25	>100
17	12.5	6.25	6.25	6.25	6.25	>100
18	>100	>100	>100	>100	>100	>100
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.5

Microorganisms: *Staphylococcus aureus* ATCC6538p; *Bacillus subtilis* ATCC 6633; *Micrococcus luteus* IFC 12708; *Proteus vulgaris* ATCC3851; *Salmonella typhimurium* ATCC 14028; *Escherichia coli* ATCC 25922.

Table 2. Antifungal Activity

Compound	Antifungal activity (MIC, μg/ml)			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagrophytes*
1	100	>100	>100	>100
2	>100	>100	50	50
3	100	>100	12.5	12.5
4	1.56	0.78	1.56	1.56
5	100	>100	50	50
6	25	25	25	25
7	>100	>100	>100	>100
8	>100	>100	>100	>100
10	>100	>100	>100	>100
12	>100	>100	>100	>100
13	>100	>100	>100	>100
14	>100	>100	>100	>100
16	>100	>100	>100	>100
17	>100	>100	>100	>100
18	>100	>100	>100	>100
Amphotericin B	6.25	3.12	3.12	3.12

Microorganisms: *Candida albicans* ATCC10231; *Aspergillus fumigatus* HIC6094; *Trichophyton rubrum* IFO 9185; *Trichophyton mentagrophytes* IFO 40996.