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Antifouling activity of terpenoids from the corals *Sinularia flexibilis* and *Muricella* sp. against the bryozoan *Bugula neritina*

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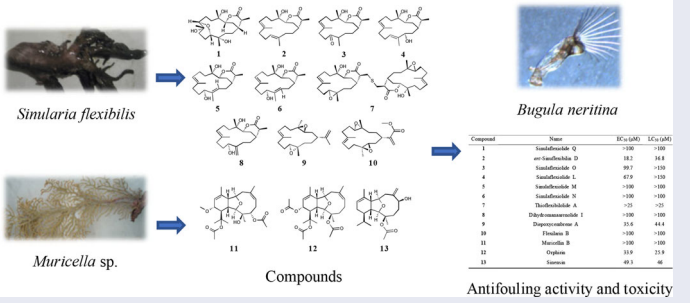
ABSTRACT

Marine natural products are promising sources of green antifoulants. Here, a new compound (**1**) was isolated from the soft coral *Sinularia flexibilis*. This compound, another nine cembranoids (**2**–**10**) from *S. flexibilis*, and three eunicellin-type diterpenoids (**11**–**13**) from the gorgonian *Muricella* sp. were tested for antifouling activity against larval settlement of the bryozoan *Bugula neritina*. Compounds **2**, **3**, **4**, **9**, **12**, and **13** exhibited significant antifouling activity, with EC_{50} values of 18.2, 99.7, 67.9, 35.6, 33.9, and 49.3 μM, respectively. Analysis of the structure-activity relationships suggested that the hydroxy group at C-13 in compound **4** reduced its antifouling activity.



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Antifouling terpenoids; *Sinularia flexibilis*; *Muricella* sp.; *Bugula neritina*; structure-activity relationship (SAR)

1. Introduction

Marine biofouling on ships and other submerged structures is a persistent problem that causes serious economic losses globally [1]. Metal-based antifoulants such as copper and tributyltin have been widely used to prevent biofouling [1]. Owing to the negative environmental effects of toxic metal-based antifoulants [1], environmentally

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friendly antifoulants are urgently needed. Marine natural products have been suggested as promising sources of environmentally friendly antifoulants [2].

Corals are well known for producing various bioactive natural products. A large number of bioactive compounds have been discovered in soft corals and gorgonians from the subclass Octocorallia [3]. Despite the lack of physical defenses, soft corals and gorgonians can survive in hostile and competitive environments, and it has been suggested that they rely on their chemical defensive strategies [3]. The secondary metabolites of corals have been found to exhibit antimicrobial, antipredatory, and antifouling activities [3]. Therefore, soft corals and gorgonians are attractive for screening natural products that may serve as valuable leading compounds for environmentally friendly antifoulants.

The soft coral *Sinularia flexibilis* is widely distributed in the Indo-Pacific Ocean [4] and has yielded a variety of secondary metabolites, including terpenoids [5], steroids [6], and lipid acids [7]. These natural products of *S. flexibilis* have been reported to exhibit various bioactivities, such as cytotoxicity [4], antimicrobial activity [8], anti-inflammatory activity [4, 9], and antifouling activity [10]. The gorgonians of the genus *Muricella* have been reported to produce diterpenoids [11, 12] and steroids [13, 14] with bioactivities of anti-rheumatoid arthritis activity [11], antifouling activity [12], antiviral activity [13], and cytotoxicity [14].

Here, ten cembranoids (**1**–**10**, including a new compound) from the soft coral *S. flexibilis* and three eunicellin-type diterpenoids (**11**–**13**) from the gorgonian *Muricella* sp. were tested for antifouling activity against larval settlement of the bryozoan *Bugula neritina*. The structure-activity relationship (SAR) of the antifouling activity of cembranoids is discussed.

2. Results and discussion

In this study, a new compound (**1**) was isolated from the soft coral *S. flexibilis*. Compound **1** was purified as a colorless oil. The molecular formula of compound **1** was confirmed as $C_{20}H_{34}O_6$ by HR-ESI-MS data (*m/z* 393.2267 $[M+Na]^+$). In the ^{1}H NMR spectrum of compound **1**, three oxygenated methine signals [δ_H 4.13 (1H, dd, $J=7.5$, 9.0 Hz), 3.53 (1H, dd, $J=4.8$, 11.6 Hz), and 3.39 (1H, br d, $J=9.7$ Hz)], three methyl singlets [δ_H 1.60, 1.46, and 1.25, (each 3H, s)], and one methyl doublet [δ_H 1.28 (3H, d, $J=7.5$ Hz)] (Table 1) were observed. In the ^{13}C NMR spectrum, 20 carbons were observed. Combined with the DEPT-135 and HSQC spectra, four methyl groups, seven methylene groups, five methines (three oxygenated), four quaternary carbons (three oxygenated), and one carbonyl carbon at δ_C 174.7 (Table 1) were detected. The ^{13}C NMR signals at δ_C 42.1 (C-1), 20.7 (C-2), 83.0 (C-3), 35.8 (C-15), 174.7 (C-16), and 14.5 (C-17) showed an α-methyl-δ-lactone ring functionality by comparison with the data of sinulaflexiolide L (**4**) [5]. The cembranoid skeleton of compound **1** was assigned by two-dimensional NMR spectra (Figure 2). By analyzing the correlations of the ^{1}H-^{1}H COSY spectrum, four separate spin systems of H_2-13/H_2-14/H-1/H_2-2/H-3, H-1/H-15/H_3-17, H_2-5/H_2-6/H-7, and H_2-9/H_2-10/H-11 were established. These data together with the HMBC correlations between H_3-18/C-3, C-4, and C-5; H_3-17/C-1, C-15, and C-16; H_3-19/C-7, C-8, and C-9; H_3-20/C-11, C-12,

Table 1. ^{1}H and ^{13}C NMR spectral data of compound **1** (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, in $CDCl_3$, δ in ppm, J in Hz).

No.	δ_H	δ_C
1	2.55 (d, 7.7)	42.1 d
2	2.10–2.17 (m)	20.7 t
	1.85–1.93 (m)	
3	4.13 (dd, 7.5, 9.0)	83.0 d
4		74.1 s
5	1.59–1.68 (m)	30.4 t
	1.39–1.47 (m)	
6	1.86–1.93 (m)	24.2 t
	2.01–2.08 (m)	
7	3.53 (dd, 4.8, 11.6)	69.5 d
8		77.1 s
9	2.12–2.21 (m)	36.6 t
	1.44–1.53 (m)	
10	1.30–1.44 (m)	24.4 t
11	3.39 (br d, 9.7)	79.4 d
12		78.5 s
13	2.11–2.21 (m)	41.3 t
	1.92–2.03 (m)	
14	1.18–1.34 (m)	29.4 t
15	1.66–1.74 (m)	35.8 d
16		174.7 s
17	1.28 (d, 7.5)	14.5 q
18	1.46 (s)	24.5 q
19	1.25 (s)	22.1 q
20	1.60 (s)	27.4 q

and C-13; H-7/C-11; and H_2-13/C-12, C-14, and C-20, permitted the determination of the conformation of the planar structure of compound **1**. The relative configuration of compound **1** was identified by comparison with the data of similar compounds [9, 15, 16] and the ROESY spectrum. The ROESY correlations between H_3-18/H-3, H-3/H-1, and H-1/H_3-17 indicated the H-1, H-3, H_3-17, and H_3-18 are β-oriented. H-3 had a cross peak with H_3-20, and H_3-18 had a cross peak with H_3-19, indicating β-orientations for H_3-19 and H_3-20 (Figure 3). The β-configurations of the H-7 and H-11 were determined based on the ^{1}H NMR chemical shifts and peak shapes of H-7 at δ_H 3.53 (1H, dd, $J = 4.8$, 11.6 Hz) and H-11 at δ_H 3.39 (1H, br d, $J = 9.7$ Hz) and the ROESY spectrum. In the ROESY spectrum, H-7 was correlated with H_3-19, and H-11 was correlated with H_3-20. Based on the above analysis, the structure of compound **1** was determined as shown in Figure 1, and named as sinulaflexiolide Q.

The other nine known cembranoids (**2**–**10**) obtained from the soft coral *S. flexibilis* were *ent*-sinuflexibilin D (**2**) [5], sinulaflexiolide O (**3**) [5], sinulaflexiolide L (**4**) [5], sinulaflexiolide M (**5**) [5], sinulaflexiolide N (**6**) [5], thioflexibilolide A (**7**) [17], dihydromanaarenolide I (**8**) [9], diepoxycembrene A (**9**) [18], and flexilarin B (**10**) [15]. There were three known eunicellin-type diterpenoids (**11**–**13**) obtained from the gorgonian *Muricella* sp., which were muricellin B (**11**) [11], orphirin (**12**) [19], and sinensin (**13**) [20]. Their chemical structures are shown in Figure 1.

The effects of compounds **1**–**13** on the settlement and mortality of larvae of the bryozoan *B. neritina* are shown in Figure 4. Their EC_{50} and LC_{50} values are shown in Table 2. To our knowledge, this is the first study to report antifouling activity of these 13 terpenoids (**1**–**13**) against *B. neritina* larval settlement. The results showed

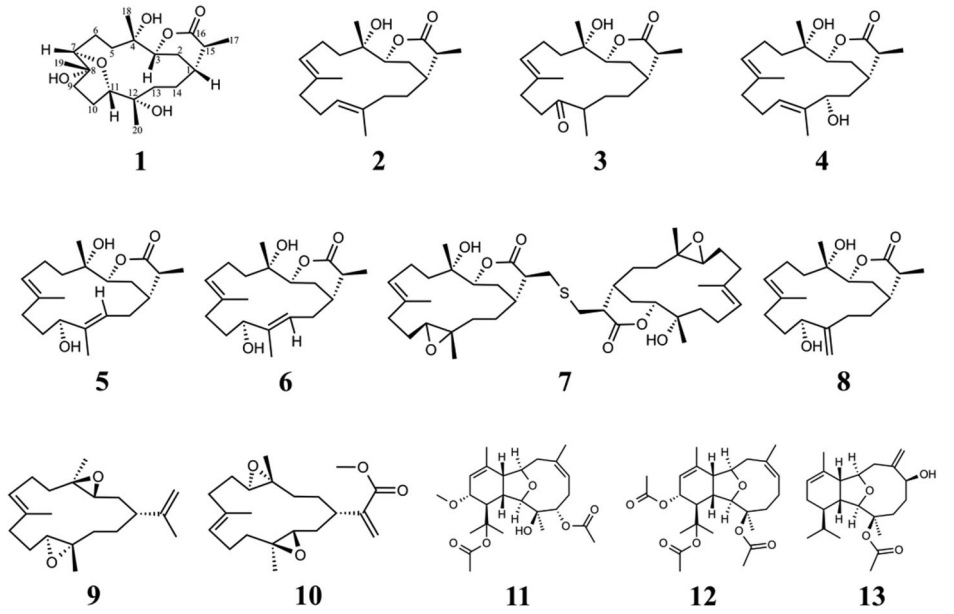

Figure 1. Chemical structures of compounds **1**–**13**.

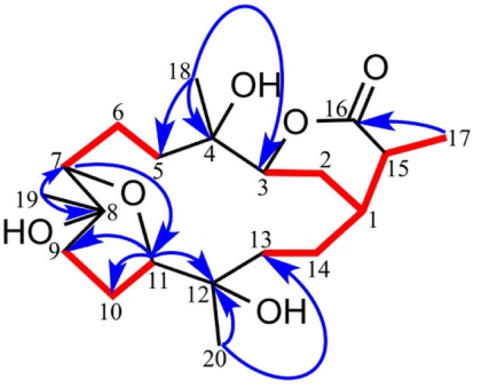

Figure 2. Key HMBC (H→C) and ^{1}H-^{1}H COSY (H↔H) correlations for compound **1**.

that settlement of *B. neritina* larvae was significantly inhibited by compounds **2**, **3**, **4**, **9**, **12**, and **13** in a dose-dependent manner ($P < 0.05$), with compound **2** being most potent (EC_{50} value of 18.2 μM). The other seven compounds (**1**, **5**, **6**, **7**, **8**, **10**, and **11**) showed no significant effect on *B. neritina* larval settlement at the concentrations tested here ($P > 0.05$). Furthermore, compounds **3** and **4** completely inhibited larval settlement at 150 μM with no mortality (Figure 4), suggesting that these two compounds inhibited larval settlement via a non-toxic mechanism, demonstrating their potential as environmentally friendly antifoulants. The other antifouling active compounds **2**, **9**, **12**, and **13** were toxic to *B. neritina* larvae (Table 2 and Figure 4). Qian

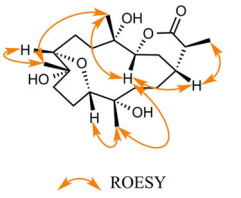

Figure 3. Key ROESY correlations for compound **1**.

et al. [21] suggested that a relatively toxic compound with a low LC_{50}/EC_{50} ratio may still be considered for further development as an antifouling product if it can be easily degraded in the marine environment. It would be of interest to investigate the degradation behavior of these four compounds in seawater.

The compounds isolated from the soft coral *S. flexibilis* (**1**–**10**) were all cembranoids containing a representative 14-membered carbocyclic structure, and most of the compounds possessed a 6-membered or 7-membered lactone functionality fused to a 14-membered cembrane ring. Cembranoids are commonly found in soft corals of the genus *Sinularia* and are regarded as the chemotaxonomic markers of *Sinularia* species [22]. The soft coral *S. flexibilis* was reported to yield numerous terpenoids, and a majority of the isolated diterpenoids were cembranoids. The reported bioactivities of cembranoids isolated from *S. flexibilis* mostly included cytotoxicity against different cancer cell lines. The antifouling activity of cembranoids isolated from this species has rarely been reported. In our previous study [10], we isolated seven cembranoids from *S. flexibilis*, and six of them showed significant antifouling activity against the bryozoan *B. neritina* or the barnacle *Balanus albicostatus*. Cembranoids isolated from *S. flexibilis* are diverse in structure and have remarkable bioactivity. Therefore, we continued to explore more cembranoids from *S. flexibilis* in this study. Here, the antifouling activity tests of these cembranoids from *S. flexibilis* have deepened our understanding of their bioactivity. Furthermore, the finding of a new compound (**1**) helps us to better understand the chemical constituents of soft corals. It should be noted that the only difference between the structures of compounds **2** and **4** is the presence of the hydroxy group at C-13 in compound **4** (Figure 1). However, there was a clear difference in antifouling activity between these two compounds (EC_{50} values of 18.2 μM for compound **2** and 67.9 μM for compound **4**). Analysis of the structure-activity relationships of compounds **1**–**6** and **8** suggested that for those cembranoids with an α-methyl-δ-lactone ring, the presence of the 7,8-double bond and the 11,12-double bond might be important for antifouling activity against *B. neritina*, because the comparison of the EC_{50} values of these compounds indicated that the activity was reduced when one or two of these double bounds were saturated. However, this possibility needs to be further confirmed by including more compounds with similar structures in future work. For the compounds with the 7,8-double bond and the 11,12-double bond (compounds **2** and **4**), analysis of the structure-activity relationships suggested that the hydroxy group at C-13 in compound **4** reduced its antifouling activity against *B. neritina*.

The compounds isolated from the gorgonian *Muricella* sp. (**11**–**13**) were all eunicellin-type diterpenoids characterized by a cladiellane skeleton with an O-bridge

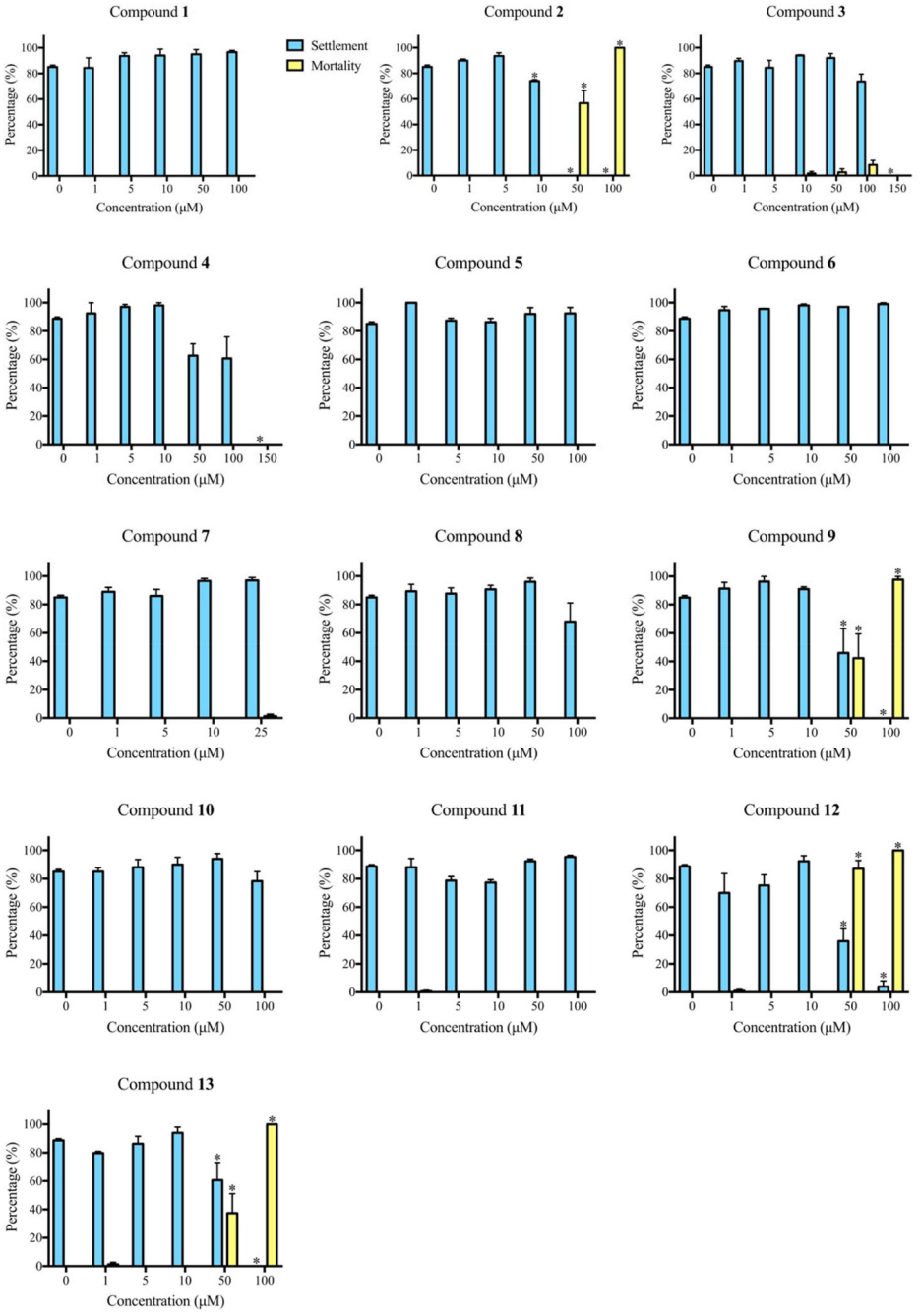

Figure 4. Effects of compounds **1–13** on the settlement and mortality of larvae of the bryozoan *B. neritina*. Data shown are the means + SEM of three replicates. Data that are significantly different from the control according to Tukey's HSD post-hoc test (one-way ANOVA, $P < 0.05$) are indicated by an asterisk above each bar.

across C-2 and C-9. These three compounds have been previously isolated from gorgonians of the genus *Muricella* [11, 20]. Compound **12** was also isolated from the gorgonian *Astrogorgia* sp., but was found to have no antifouling activity against larval

Table 2. Antifouling activity and toxicity of compounds **1**–**13** against the bryozoan *B. neritina*.

Compound	Name	EC_{50} (μM)	LC_{50} (μM)
1	Sinulaflexiolide Q	>100	>100
2	*ent*-Sinuflexibilin D	18.2	36.8
3	Sinulaflexiolide O	99.7	>150
4	Sinulaflexiolide L	67.9	>150
5	Sinulaflexiolide M	>100	>100
6	Sinulaflexiolide N	>100	>100
7	Thioflexibilolide A	>25	>25
8	Dihydromanaarenolide I	>100	>100
9	Diepoxycembrene A	35.6	44.4
10	Flexilarin B	>100	>100
11	Muricellin B	>100	>100
12	Orphirin	33.9	25.9
13	Sinensin	49.3	46

settlement of the barnacle *Balanus amphitrite* [23]. In contrast, Zhang et al. [12] found that compound **12** from the gorgonian *M. sibogae* exhibited significant antifouling activity against the green mussel *Perna viridis*. In this study, compound **12** inhibited larval settlement of the bryozoan *B. neritina*, indicating its antifouling activity against another important biofouling species besides mussels. Furthermore, the antifouling activities of compounds **11** and **13** were first reported here, thus enriching our knowledge of the natural antifouling products in gorgonians.

In conclusion, the present study tested the antifouling activity of 13 terpenoids from the soft coral *S. flexibilis* and the gorgonian *Muricella* sp. against *B. neritina* larval settlement. Compounds **2**, **3**, **4**, **9**, **12**, and **13** exhibited antifouling activity against *B. neritina*, with EC_{50} values of 18.2, 99.7, 67.9, 35.6, 33.9, and 49.3 μM, respectively. These six antifouling active compounds may play a role in chemical defense against fouling in corals. They also demonstrated their potential as candidates for new antifoulants.

3. Experimental

3.1. General experimental procedures

NMR spectra were performed by a Bruker DRX-400 instrument (Bruker Biospin AG, Fällanden, Switzerland), and TMS was added as an internal standard. The mass spectra were obtained from a Thermo Q-Exactive™ (Thermo Fisher Scientific Inc., MA, USA). LC3000-type high performance liquid chromatograph (Beijing Chuangxintongheng Science and Technology Co., Ltd., Beijing, China) with a SilGreen HPLC column (Greenherbs Science and Technology Co., Ltd., Beijing, China) was used in a semi preparation separation process. The column chromatography packings matrix was silica gel (Qingdao Marin Chemical Ltd., Qingdao, China) and Toyopearl HW-40 (Tosoh Co., Ltd., Tokyo, Japan).

3.2. Animal materials

The soft coral *Sinularia flexibilis* (specimen serial number: HSA-11) was collected from Yalong Bay, Sanya, Hainan Province, China in September 2012. The gorgonian *Muricella* sp. (specimen serial number: DS20100601-2) was collected from Dongshan

Island, Fujian Province, China in June 2010. These specimens were deposited at the School of Pharmacy, Tianjin Medical University, China.

3.3. Extraction and isolation

The air-dried sample of *S. flexibilis* (198.0 g) was extracted with MeOH. The MeOH soluble extract (20.0 g) was partitioned between water and CH_2Cl_2 to yield a CH_2Cl_2-soluble fraction (10.6 g). The CH_2Cl_2-soluble fraction was separated by a silica gel column, eluted with CH_2Cl_2:MeOH (v/v, 99:1, 95:5, 9:1, 8:2, 3:1, 2:1, 1:99), and finally afforded seven fractions (A–G). Fraction E (3.1 g) was separated by column chromatography on a silica gel column, and eluted with petroleum ether:EtOAc (v/v, 25:1, 10:1, 4:1, 1:1, EtOAc) to afford five subfractions (Ea–Ee). Fraction Ec (0.66 g) was chromatographed over a HW-40 column, and eluted with CH_2Cl_2:MeOH (v/v, 2:1) to obtain seven portions (Eca–Ecg). Fraction Ecc (107.2 mg) was purified by semi-preparative HPLC (ODS, MeOH:H_2O, v/v, 75:25, 5 ml/min, 210 nm, 91.5 min), yielding compound **1** (9.6 mg). Furthermore, nine known cembranoids (**2**–**10**) and three known eunicellin-type diterpenoids (**11**–**13**) were obtained from the soft coral *S. flexibilis* and the gorgonian *Muricella* sp., respectively. The extraction and isolation processes of all known compounds are detailed in the published articles of our group [5, 11].

3.3.1. Sinulaflexiolide Q (1)

Colorless oil; $[\alpha]_D^{20}$ −9.6 (*c* 1.7, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 212 (3.0) nm; IR (KBr) ν_{max} 3423, 2935, 1730, 1635, 1022 cm^{-1}; ^1H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR spectral data: Table 1; HR-ESI-MS: *m/z* 393.2267 $[M + Na]^+$ (calcd for $C_{20}H_{34}O_6Na$, 393.2253).

3.4. Assay for antifouling activity against larvae of the bryozoan B. neritina

Colonies of adult *B. neritina* were collected from Wuyuan Bay located in Xiamen, China. The larvae of the bryozoan *B. neritina* were obtained from the adults according to the method of Feng et al. [24]. The larval settlement assays were conducted as described by Qi et al. [25]. Thirteen purified compounds isolated from corals in this study were dissolved in dimethylsulfoxide (DMSO), and 20 μl of each solution was added into each well of a 24-well plate containing 1.98 ml filtered (0.22 μm) seawater (FSW) and approximately 30 larvae. The control group was a solution of 20 μl DMSO and 1.98 ml FSW. There were three replicates for each treatment and control. The 24-well plates were incubated in the darkness at 25 °C for 24 h, after which the number of settled larvae, the number of dead larvae, and the total number of larvae in each well were counted under a stereomicroscope.

3.5. Statistical analysis

Differences in larval settlement or mortality of *B. neritina* between the treatments and control were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's HSD post-hoc test using SPSS 22.0 software. The significance level was

defined as $P < 0.05$. The EC_{50} value (the concentration that inhibited larval settlement by 50% relative to the control) and LC_{50} value (the concentration that resulted in 50% mortality relative to the control) were calculated by the Spearman-Karber method [10].

Disclosure statement

No potential conflict of interest was reported by the authors.

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