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Secondary Metabolites from Marine-Derived Fungus *Aspergillus carneus* GXIMD00519

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Abstract: Two new compounds, carneusins A-B (**1-2**), as well as fifteen known compounds (**3-17**), were isolated from the marine-derived fungus *Aspergillus carneus* GXIMD00519. Their structures were elucidated by the analysis of detailed spectroscopic data and quantum chemistry calculations. All the compounds were evaluated for their antibacterial, antibiofilm and cytotoxic effects. Compound **1** showed a moderate inhibitory effect against MRSA with the MIC value of 32 μg/mL. Compound **2** exhibited an anti-microfouling effect against biofouling bacterial *Vibrio rotiferianus* and *Alteromonas macleodii* with MIC value of 64 μg/mL. Compound **5** displayed antibiofilm activity against *A. macleodii* with the EC_{50} value of 10.42 ± 0.58 μg/mL. Compounds **1**, **3**, **4**, **8** and **15** showed cytotoxicity against human pancreatic cancer cell lines SW1990, colorectal adenocarcinoma cell line DLD1, human pancreatic cancer cell line PANC1, and human hepatocellular carcinoma cell line Bel7402 with IC_{50} values ranging of 2.75-17.77 μM.

Keywords: *Aspergillus carneus* GXIMD00519, antibacterial, antibiofilm, cytotoxicity.

1. Introduction

Marine-derived fungi, which are isolated from marine environment including seawater, marine sediments and marine organisms, are important sources for the discovery of novel bioactive secondary metabolites [1]. Over one third bioactive marine compounds were obtained from marine-derived fungi in 2020 [2]. Compounds isolated from marine fungi also attracted considerable attention for their diverse chemical structures and a broad range of potent biological activities [3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. epidermidis* are pathogenic bacteria caused skin infections, sepsis, pneumonia and bloodstream infections. MRSA is resistant to several commonly used antibiotics [4]. Marine biofouling is undesirable accumulation of fouling organisms resulted in substantial environmental and economic consequence [5]. Bacterial biofilms are structured groups of different bacterial species that are responsible for most chronic and recurrent infections. Marine bacterial biofilms are also key mediators of marine biofouling [5]. Cancer is a leading cause of death worldwide [6]. As our ongoing search for bioactive compounds from marine fungi, *Aspergillus carneus* GXIMD00519, which is associated with gorgonian sample obtained from Weizhou Island, Guangxi Province, was selected for further studies. Chemical investigation of the extract led to the isolation of two new compounds (**1** and **2**), together with fifteen known compounds (**3-17**) (Figure 1). The anti-bacteria, anti-biofilm activities and cytotoxicity of the compounds were assayed. Herein, we reported the details of the isolation, structure elucidation and biological determination of these compounds.

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2. Materials and Methods

2.1. Microorganism Material

The strain GXIMD 00519 was isolated from coral *Anthogorgia* sp. tissue sample that was collected from the Weizhou Islands coral reef in Guangxi Zhuang autonomous region, China. It was identified as *Aspergillus carneus* based on sequence (GenBank accession No. MT672623) analysis of the internal spacer regions of the rDNA.

2.2. Fermentation and Isolation

The fungal strain was static cultivated in the one hundred 1000 mL Erlenmeyer flasks each contained modified solid rice medium (80 g of rice, 0.4 g of yeast extract, 0.4 g of glucose, 3.6 g of artificial sea salt and 120 mL of H_2O) for 30 days at room temperature. The fermented cultures were extracted with EtOAc three times and were concentrated *in vacuo* to provide extract (350g).

The extract was subjected to *silica gel* column chromatography (CH_2Cl_2/MeOH, gradient 100 : 0 – 80 : 20, v/v) to generate twelve fractions (*Fr. 1–Fr. 12*). *Fr.4* was recrystallized by CH_2Cl_2/MeOH to obtain **15** (289 mg). The remainder of *Fr.4* was isolated by *ODS silica gel* chromatography and further purified by semipreparative HPLC to afford **1** (26 mg). *Fr.6* was separated into 24 subfractions (*sFr.6-1–6-24*) via *ODS silica gel* chromatography. *sFr.6-7* was subjected to *Sephadex LH-20* column and then further purified by semipreparative HPLC (65% MeOH/H_2O) to afford **7** (12 mg) and **10** (28 mg). *sFr.6-10* was purified by semipreparative HPLC to afford **9** (20 mg), **16** (19 mg), and **17** (15 mg). *Fr.8* was separated into 21 subfractions (*sFr.8-1–8-21*) via *ODS silica gel* chromatography eluted with MeCN/H_2O. *sFr.8-15* was purified by semi-preparative HPLC (65% MeOH/H_2O) to afford **8** (15 mg). *sFr.8-20* and *sFr.8-21* were purified by silica gel to afford **3** (94 mg) and **4** (11 mg). *Fr.9* was separated into 21 subfractions (*sFr.9-1–9-21*) via *ODS silica gel* chromatography eluted with ACN/H_2O. *sFr.9-10* was purified by semipreparative HPLC (56% MeOH/H_2O) to afford **11** (12 mg). *Fr.9-11* was purified by semipreparative HPLC (45 % ACN/H_2O) to afford **2** (30 mg). *Fr.10* was separated into 20 subfractions (*sFr.10-1–10-20*) via silica gel column (CH_2Cl_2/EtOAc, gradient 80 : 20 – 0 : 100, v/v). *Fr.10-16* was purified by semipreparative HPLC (37% ACN/H_2O) to afford **14** (15 mg). *sFr.10-19* was isolated by *ODS silica gel* chromatography and further purified by semipreparative HPLC (45% ACN/H_2O) to afford **6** (8 mg). *Fr.11* was separated into 10 subfractions (*sFr.11-1∼11-10*) via silica gel column (CH_2Cl_2/EtOAc, gradient 80 : 20 – 0 : 100, v/v,). *sFr.11-7* was isolated by *ODS silica gel* chromatography and purified by semipreparative HPLC (41% ACN/H_2O) to afford **5** (16.7 mg), **12** (13.5 mg), and **13** (10 mg).

2.3. Spectroscopic Data

*Carneusin A (**1**)*: Orange amorphous powder; $[\alpha]_D^{25}$ = + 17.8 (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ε) 224 (3.11), 239 (2.66), 294 (3.03), 322 (2.57), 352 (2.13), 441 (2.61) nm. CD (MeOH) λ_{max} (Δε) 209 (+1.11), 230 (−1.74), 247 (+0.62), 263 (+0.45), 288 (−0.96), 307 (+0.21), 374 (−0.63); ^{1}H and ^{13}C NMR data, Tables 1; HR-ESI-MS *m/z* 383.0760 $[M - H]^-$ (calcd. for $C_{20}H_{16}O_7^-$, 383.0767).

*Carneusin B (**2**)*: Colorless oil; $[\alpha]_D^{25}$ = – 146.4 (*c* 0.43, MeOH); UV (MeOH) λ_{max} (log ε) no obvious absorption peak in the 200-400 nm range. CD (MeOH) λ_{max} (Δε) 200 (+2.44), 223 (−0.21), 233 (−0.09), 243 (−0.24); ^{1}H and ^{13}C NMR data, Tables 2. HR-ESI-MS *m/z* 238.0696 $[M + Na]^+$ (calcd. for $C_9H_{13}NNaO_5^+$, *m/z* 238.0691).

2.4 Computational Methods

Merck Molecular Force Field (MMFF94s) and DFT/TDDFT calculations were performed with CONFLEX 8.5 (Conflex Corp., Tokyo, Japan) and Gaussian16 program package (Wavefunction Inc., Irvine, CA, USA) [7], respectively. The CD spectra were generated by the program SpecDis [8] using

a Gaussian band shape from dipole-length dipolar and rotational strengths. Gauge-Independent Atomic Orbital (GIAO) calculations of the ^{13}C NMR chemical shifts were accomplished by DFT at the B97-2/def2TZVP level in DMSO with PCM. The calculated ^{13}C NMR spectroscopic data were averaged according to the Boltzmann distribution by the program Multiwfn 3.7 [9].

2.5 Antimicrobial and Antibiofilm Activity Assay

Antibacterial effect was determined by using standard broth micro-dilution assay according to the Clinical and Laboratory Standards Institute (CLSI) guideline. The bacterial strains under study were human pathogens methicillin-resistant *Staphylococcus aureus* ATCC43300, *Staphylococcus epidermidis* ATCC12228, and marine biofouling bacteria *Microbulbifer variabilis*, *Marinobacterium jannaschii*, *Vibrio pelagius*, *Vibrio rotiferianus*, *Alteromonas macleodii*. All experiments were performed in triplicates and repeated three times. Penicillin and chloramphenicol were used as the positive control. Antibiofilm activities of compounds **1-17** against MRSA and *A. macleodii* were determined by crystal violet staining assay [10-13].

2.6 Cytotoxicity Assay

Cytotoxicities of **1-17** were evaluated against human pancreatic cancer cell line SW1990, colorectal adenocarcinoma cell line DLD1, human pancreatic cancer cell line PANC1, and human hepatocellular carcinoma cell line Bel7402 using MTT method [14].

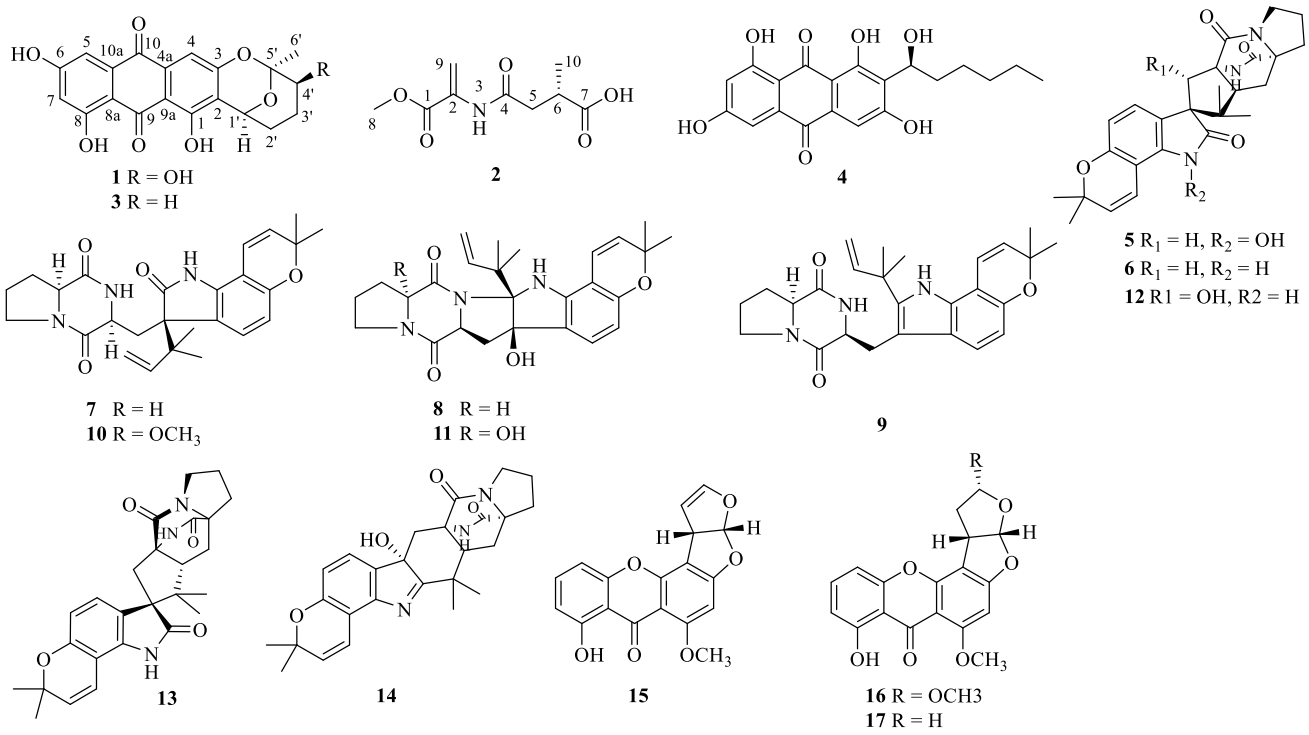

Figure 1. The chemical structures of compounds **1-17**

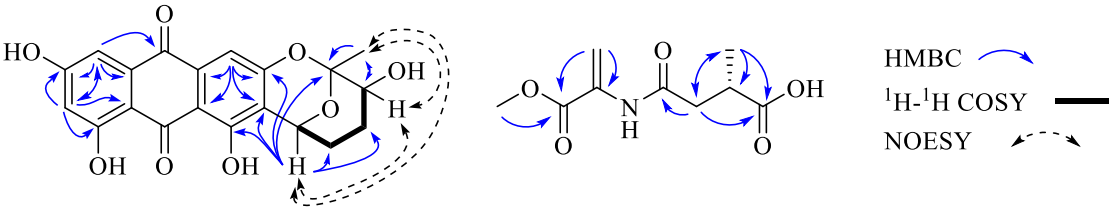

Figure 2. The key ^{1}H-^{1}H COSY correlations, HMBC correlations and NOESY correlations of compounds **1** and **2**

3. Results and Discussion

3.1. Structure Elucidation

Compound **1** was orange amorphous powder with molecular formula $C_{20}H_{16}O_8$ by the HR-ESI-MS spectrum (*m/z* 383.0760 $[M - H]^-$, calcd. 383.0767). The UV spectral absorption at λ_{max} (log ε) 224 (3.11), 239 (2.66), 294 (3.03), 322 (2.57), 352 (2.13), 441 (2.61) nm suggested the **1** was anthraquinone derivative [15]. It was confirmed by the NMR spectral data (Table 1). The ^{1}H NMR spectrum of **1** exhibited signals of three aromatic protons δ_H 6.85 (1H, s, H-4), 6.94 (1H, d, *J* = 2.4 Hz, H-5) and 6.43 (1H, d, *J* = 2.4 Hz, H-7), two oxy-methines δ_H 5.09 (1H, d, *J* = 3.0 Hz, H-1´) and 3.55 (1H, t, *J* = 2.8 Hz, H-4'), a methyl δ_H 1.49 (3H, s, H-5'). The ^{13}C NMR and HSQC spectra of **1** indicated the presence of one methyl group, two methylene groups, five methines including three aromatic methines and two oxy-methines, twelve quaternary carbons including two carbonyl carbons δ_C 188.3 (C-9) and 180.6 (C-10), nine aromatic carbons δ_C 166.2, 164.4, 158.7, 158.1, 134.6, 133.0, 116.1, 108.4, 108.0. The HMBC correlations from H-4 to C-2, C-3, C-4a, C-9, C-9a, C-10, from H-5 to C-6, C-7, C-9, C-10, C-10a, from H-7 to C-5, C-6, C-8, C-8a, C-9 declared that compound **1** was 1,2,3,6,8-pentasubstituented anthraquinone derivative (Figure 2). The HMBC spectrum also exhibited correlations from H-1' to C-1, C-2, C-3, C-2', C-3', C-5', from C*H*$_2$-2' to C-2, C-1', C-3', C-4', from C*H*$_2$-3' to C-1', 4', 5', from H-4' to C-2', 3', 5', from C*H*$_3$-6' to C-4', C-5'. All the data exhibited close similarity with those of averufin (**3**) [16] except an additional hydroxyl substitution at C-4', which was downfield shifted ($\Delta\delta_C$ 31.2 ppm). The NOESY correlations among H-1', H-4' and C*H*$_3$-6' indicated they were on the same side of the tetrahydropyran ring (Figure 2). The absolute configuration of **1** was further confirmed based on the comparison of calculated ECD curves of (1'*S*,4'*S*,5'*S*)-**1** with the experimental CD spectrum (Figure 3).

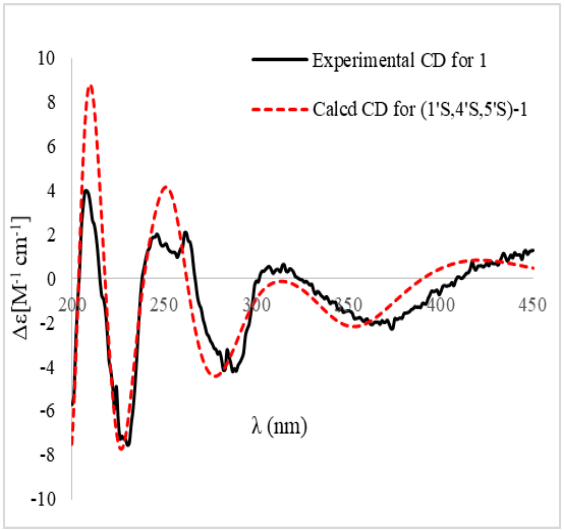

Figure 3. Comparison of calculated CD spectra of (1'*S*,4'*S*,5'*S*)-**1** (red) and experimental CD (black) in MeOH. σ = 0.30 eV, UV shift = 25 nm.

Table 1. NMR data for compound **1** (*J* in Hz, δ in ppm)

Position	δ_H [a]	δ_C (mult.) [b]	HMBC correlations	COSY correlations	NOESY correlations
1	-	158.1 (C)			
2	-	116.1 (C)			
3	-	158.7 (C)			
4	6.85, *s*	107.2 (CH)	C-2, 3, 4a, 9, 9a, 10		H-4', 6'
4a	-	133.0 (C)			
5	6.94, *d*, *J* = 2.4	109.4 (CH)	C-6, 7, 9, 10, 10a,	H-7	
6	-	166.2 (C)			
7	6.43, *d*, *J* = 2.4	107.9 (CH)	C-5, 6, 8, 8a, 9	H-5	
8	-	164.4 (C)			
8a	-	108.0 (C)			
9	-	188.3 (C)			
9a	-	108.4 (C)			
10	-	180.6 (C)			
10a	-	134.6 (C)			
1'	5.09, *d*, *J* = 3.0	65.7 (CH)	C-1, 2, 3, 2', 3', 5'	H-2'	H-4', 6'
2'	2.32, *ddt*, *J* = 17.3, 8.3, 3.8	21.9 (CH_2)	C-2, 1', 3'	H-1', 3'	
	1.45, *d*, *J* = 13.6		C-3', 4'	H-1', 3'	
3'	1.64, *d*, *J* = 13.0	23.5 (CH_2)	C-1', 5'	H-2', 4'	
	1.53, *td*, *J* = 13.0, 3.2		C-4', 5'	H-2', 4'	
4'	3.55, *t*, *J* = 2.8	66.7 (CH)	C-2', 3', 5'	H-3'	H-1', 6'
5'	-	102.6 (C)			
6'	1.49, *s*	24.0 (CH_3)	C-4', 5'		H-1', 4'

[a] 600 MHz in DMSO-d_6.
[b] 150 MHz in DMSO-d_6.

Table 2. NMR data for compound **2** (*J* in Hz, δ in ppm)

Position	δ_H [a]	δ_C (mult.) [b]	HMBC correlations
1	-	162.3 (C)	-
2	-	129.5 (C)	-
4	-	174.9 (C)	-
5	2.48, *d*, *J* = 13.5	36.2 (CH_2)	C-4, 6, 7, 10
	3.02, overlapped		C-4, 6, 7, 10
6	3.02, overlapped	34.6 (CH)	C-4, 6, 7, 10
7	-	179.0 (C)	-
8	3.73, *s*	52.7 (CH_3)	C-1
9	6.57, *d*, *J* = 0.7	128.8 (CH_2)	C-1, 2
	6.01, *d*, *J* = 0.7		C-1, 2
10	1.25, *d*, *J* = 7.0	15.9 (CH_3)	C-5, 6, 7

[a] 600 MHz in DMSO-d_6.
[b] 150 MHz in DMSO-d_6.

Compound **2** was colorless oil with molecular formula $C_9H_{13}NO_5$ inferred by HR-ESI-MS data *m/z* 238.0696 ($[M + Na]^+$, calcd. 238.0691), indicating 4 degrees of unsaturation. The 1D NMR and HSQC spectra signals (Table 2) of **2** exhibited the presence of two methyl groups, two methylene groups, one methines and four quaternary carbons including three carbonyl groups. HMBC correlations (Figure 2) from CH_2-9 to C-1 and C-2 indicated the existence of a 2-aminoprop-2-enoic

acid moiety [17]. The HMBC correlations from CH_2-5 to C-4, C-6, C-7, C-10, from CH_3-10 to C-5, C-6, C-7 indicated the presence of 4-amino-2-methyl-4-oxo-butanoic acid moiety. The oxy-methyl group was linked to the carbonyl carbon C-1 by the HMBC correlations from CH_3-8 to C-1. The absolute configuration of **2** was assigned as (6*S*) by the comparison of calculated CD curve (Figure 4) and calculated ^{13}C NMR data (Figure S22) with experimental data, it had been confirmed by the similar specific optical rotation value with compound (2*S*)-4-amino-2-methyl-4-oxo-butanoic acid [18].

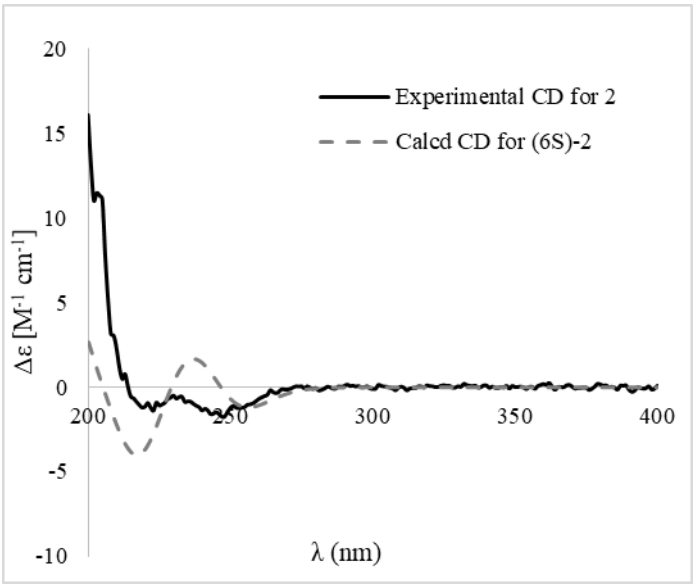

Figure 4. Comparison of calculated CD spectra of (6*S*)-**2** (gray) and experimental CD (black) in MeOH. σ = 0.30 eV, UV shift = 4 nm

The known compounds were determined by comparisons of their respective NMR data with those reported earlier, including averufin (**3**) [16], averantin (**4**) [16], notoamide A-E (**5-9**) [19, 20], notoamide Q (**10**) [21], speramide B (**11**) [22], sclerotiamide (**12**) [23], versicolamide B (**13**) [24], taichunamide A (**14**) [25], sterigmatocystin (**15**) [26], oxisterigmatocystin C (**16**) [27], and dihydrosterigmatocystin (**17**) [26].

3.2. Antimicrobial, Antibiofilm Activities and Cytotoxicity

The antimicrobial activities against MRSA, *S. epidermidis*, *V. rotiferianus*, *A. macleodii*, *M. jannaschii* and the cytotoxicity data against human SW1990, DLD1, PANC1, Bel7402 and LO2 cell lines of compounds **1-17** were shown in Table 3 and Table 4, respectively. Compound **5** displayed antibiofilm activity against *A. macleodii* with the EC_{50} value of 10.42 ± 0.58 μg/mL.

Table 3. Antibacterial activity of **1-17** (MIC, μg/mL)

	MRSA	***S. epidermidis***	***V. rotiferianus***	***A. macleodii***	***M. jannaschii***
1	32	>64	>64	>64	>64
2	>64	>64	64	64	>64
3	16	>64	>64	>64	32
4	8	8	>64	>64	16
8	>64	>64	32	>64	>64
penicillin [a]	<4	8	<4	>64	<4
chloramphenicol[a]	<4	<4	<4	>64	<4

[a] Penicillin and chloramphenicol as positive control.

Table 4. Cytotoxicity of compounds **1-17** against five human cell lines in vitro (IC_{50}, μM)

	SW1990	DLD1	PANC1	Bel7402	LO2
1	9.78 ± 1.12	>20	>20	>20	>20
3	4.33 ± 1.78	>20	>20	>20	>20
4	2.75 ± 0.28	7.02 ± 0.69	>20	>20	>20
8	>20	15 ± 4.15	>20	>20	>20
15	3.44 ± 0.23	<1.25	17.77 ± 3.51	6.15 ± 0.32	>20
cisplatin [a]	8.77 ± 0.73	>20	>20	>20	>20

[a] Cisplatin as positive control.

Acknowledgments

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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