Purine Alkaloids from the South China Sea Gorgonian *Subergorgia suberosa*

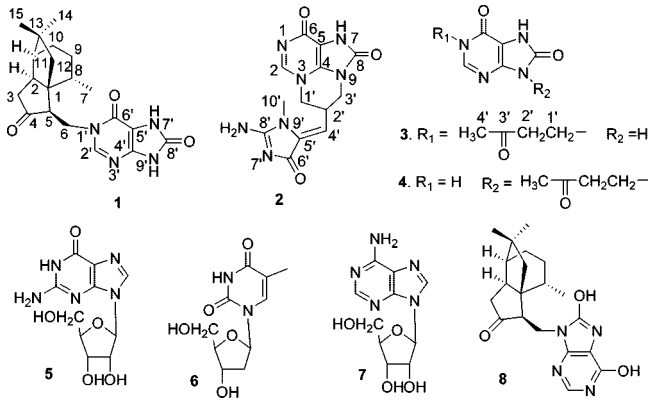
Shu-Hua Qi,* Si Zhang, and Hui Huang

Key Laboratory of Marine Bio-resourses Sustainable Utilization/Guangdong Key Laboratory of Marine Materia Medica, South China Sea Institute of Oceanology, The Chinese Academy of Sciences, 164 West Xingang Road, Guangzhou 510301 Guangdong, People's Republic of China

Received September 24, 2007

Four new purine alkaloids, namely, 6-(1′-purine-6′,8′-dionyl)suberosanone (**1**), 3,9-(2-imino-1-methyl-4-imidazolidinone-5-yl)isopropenylpurine-6,8-dione (**2**), 1-(3′-carbonylbutyl)purine-6,8-dione (**3**), and 9-(3′-carbonylbutyl)purine-6,8-dione (**4**), together with three known compounds, guanosine (**5**), thymidine (**6**), and adenosine (**7**), were isolated from the EtOH/CH_2Cl_2 extracts of the South China Sea gorgonian *Subergorgia suberosa*. The structures of **1**–**4** were determined on the basis of extensive spectroscopic analysis, including 1D and 2D NMR data. Compounds **1**−**4** all showed weak cytotoxicity toward human cancer cell lines MDA-MB-231 and A435.

Nitrogen-containing compounds including alkaloids, nucleosides, and peptides are known to have an important role in medicinal chemistry on account of their widespread biological activity. Marine invertebrates such as sponges, soft corals, gorgonians, mollusks, coelenterates, and ascidians produce secondary metabolites of unprecedented structures; sponges and ascidians, in particular, produce nitrogen-containing compounds. However, there are few reports about alkaloids from gorgonians. The gorgonian *Subergorgia suberosa* was known to produce novel sesquiterpenes[1–5] and 9,11-secosteroids.[6–8] In our previous investigation on *S. suberosa,* a new sesquiterpene-alkaloid, 6-(9′-purine-6′,8′-diolyl)suberosanone, was obtained.[9] Now, in our further chemical investigation on the EtOH/CH_2Cl_2 extract of *S. suberosa,* four new purine alkaloids, 6-(1′-purine-6′,8′-dionyl)suberosanone (**1**), 3,9-(2-imino-1-methyl-4-imidazolidinone-5-yl)isopropenylpurine-6,8-dione (**2**), 1-(3′-carbonylbutyl)purine-6,8-dione (**3**), and 9-(3′-carbonylbutyl)purine-6,8-dione (**4**), together with three known compounds, guanosine (**5**),[10] thymidine (**6**),[10] and adenosine (**7**),[10] were obtained. This paper deals with the isolation and structural elucidation of **1**–**4**.



The EtOH/CH_2Cl_2 extract of *S. suberosa* was suspended in H_2O and extracted with $CHCl_3$ and *n*-BuOH, respectively. The $CHCl_3$ and *n*-BuOH solubles were chromatographed over silica gel, and selected fractions were rechromatographed on Sephadex LH-20 and silica gel to yield compounds **1**−**7**. All of the compounds contained a purine skeleton.

Compound **1** had the molecular formula $C_{20}H_{26}N_4O_3$ as deduced from NMR spectra and HRESIMS. Its ^{13}C NMR spectrum showed the presence of three methyls (δ_C 16.3, 26.6, 33.9), five methylenes (δ_C 26.4, 27.3, 40.2, 40.3, 47.1), four methines (δ_C 35.6, 43.1, 48.9, 53.2), two quaternary carbons (δ_C 55.9, 39.1), and a ketone carbon (δ_C 216.4), along with five low-field carbons [δ_C 116.6 (C), 137.9 (CH), 151.1 (C), 153.3 (C), 156.6 (C)]. The ^1H NMR spectrum displayed three methyl groups at δ_H 0.73 (3H, d, J = 7.0 Hz), 1.07 (3H, s), and 1.11 (3H, s) and a proton at δ_H 7.63 (1H, s). According to HSQC, HMBC, and $^1H-^1H$ COSY experiments, all of the ^1H and ^{13}C NMR signals of **1** were assigned (Table 1). These ^1H and ^{13}C NMR data were very similar to those of 6-(9′-purine-6′,8′-diolyl)suberosanone (**8**) (Table 1), which was previously isolated from the same species,[9] and indicated that **1** should also be a suberosanone-type sesquiterpene linked to a purine-6,8-dione group. Actually, purine-8-one derivatives have previously been isolated from many marine organisms, such as gorgonians,[11] ascidians,[12] and sponges.[13]

The only obvious difference between them was the chemical shift values of five low-field carbons [δ_C 137.9 (CH, C-2′), 156.6 (C, C-4′), 116.6 (C, C-5′), 151.1 (C, C-6′), 153.3 (C, C-8′) in **1**, and δ_C 140.6 (CH, C-2′), 150.2 (C, C-4′), 108.1 (C, C-5′), 155.8 (C, C-6′), 151.9 (C, C-8′) in **8**], which might be caused by the location of the connection between the 6′,8′-purinedione moiety and the suberosanone moiety. This was supported by the HMBC data. In the HMBC spectrum of **1**, correlations of δ_H 4.17 (1H, dd, J = 4.9, 14.4 Hz, H-6a) and 3.87 (1H, dd, J = 8.8, 14.4 Hz, H-6b) with C-6′/C-2′ suggested the connection of the 6′,8′-purinedione moiety with the suberosanone moiety by a C(6)−N(1′) bond instead of a C(6)−N(9′) bond.

The relative configuration of **1** was deduced from a 2D NOE experiment. The NOESY spectrum of **1** showed correlations of H-9a (δ_H 1.85, 1H, m) with Me-14 (δ_H 1.11, 3H, s); Me-15 (δ_H 1.07, 3H, s) with H-9b (δ_H 1.20, 1H, m), H-3b (δ_H 2.22, 1H, dd, J = 6.9, 19.8 Hz), and H-11 (δ_H 1.70, 1H, m); and H-3a (δ_H 2.62, 1H, dd, J = 12.0, 19.8 Hz) with H-2 (δ_H 2.40, 1H, dd, J = 6.9, 12.0 Hz). In addition, to form a five-membered ring across the six-membered ring, the C1−C12 and C11−C13 bonds had to both be axial, leaving H-11 equatorial. These suggested the β-orientation of Me-15 and α-orientation of H-2, H-11, and Me-14. Meanwhile, NOE correlations of Me-7 (δ_H 0.73, 3H, d, J = 7.0 Hz) with H-2 and H-5 (δ_H 3.12, 1H, dd, J = 4.9, 8.8 Hz) indicated that Me-7 and H-5 were α-orientated. On the basis of the above data, the structure of **1**was elucidated as 6-(1′-purine-6′,8′-dionyl)suberosanone. Therefore, in compound **8** H-2 should also be in the α-orientation.

The molecular formula $C_{13}H_{13}N_7O_3$ of **2** was deduced from its NMR spectra and ESIMS. The compound was conferred by the HRFABMS (positive ions) with a peak at m/z 316.1076 $[M + H]^+$ (calculated value: m/z 316.1080). Its ^{13}C NMR spectrum showed

* Corresponding author. Tel: +86-20-89023105. Fax: +86-20-84458964. E-mail: shuhuaqi2001@yahoo.com.

10.1021/np0705110 CCC: $40.75
Published on Web 02/22/2008

Table 1. NMR Data for Compound **1**[a]

no.	**1** in DMSO-d_6 ^{1}H NMR	^{13}C NMR	HMBC	NOESY	**8** in $CDCl_3$ ^{13}C NMR
1		55.9	H-2, 3, 5, 6, 7, 8, 12		56.7
2	2.40 (dd, 6.9, 12.0),	43.1	H-3, 5, 8, 11	H-3a, 7	44.0
3a	2.62 (dd, 12.0, 19.8)	40.2	H-2, 5, 11	H-2	40.8
3b	2.22 (dd, 6.9, 19.8)			H-15	
4		216.4	H-2, 3, 5, 6		216.5
5	3.12 (dd, 4.9, 8.8)	53.2	H-2, 3, 6	H-2, 7	52.4
6	4.17 (dd, 4.9, 14.4), 3.87(dd, 8.8, 14.4)	40.3	H-5, 2′		41.3
7	0.73 (d, 7.0)	16.3	H-8, 9	H-2, 5	16.7
8	1.58 (m)	35.6	H-2, 7, 9, 10	H-9b	36.6
9a	1.85 (m)	26.4	H-7, 8, 10, 11	H-14	27.0
9b	1.20 (m)			H-15	
10	1.52 (m)	27.3	H-8, 9, 11		27.9
11	1.70 (m)	48.9	H-2, 3, 10, 14, 15		49.7
12	1.60 (d, 14.4), 1.44(d, 14.4)	47.1	H-2, 11, 14, 15		48.5
13		39.1	H-11, 12, 14, 15		39.7
14	1.11 (s)	26.6	H-15	H-9a	27.0
15	1.07 (s)	33.9	H-14	H-9b	34.4
2′	7.63 (s)	137.9	H-6		140.6
4′		156.6	H-2′		150.2
5′		116.6	H-2′		108.1
6′		151.1	H-2′, 6		155.8
8′		153.3			151.9

[a] Chemical shift values δ are in ppm, and coupling constant values J in Hz.

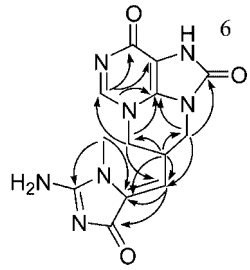


Figure 1. Key HMBC correlations of **2**.

nine low-field carbons [δ_C 107.8 (C), 117.4 (CH), 131.8 (C), 136.9 (C), 139.0 (C), 150.3 (C), 154.3 (C), 155.4 (C), 162.4 (C)], together with one methyl (δ_C 28.5), two methylenes (δ_C 42.4, 46.2), and one methine (δ_C 28.2). The ^{1}H NMR spectrum displayed one methyl at δ_H 3.24 (3H, s), two methylenes at δ_H 3.82 (1H, dd, J = 9.0, 12.9 Hz), 4.25 (1H, dd, J = 4.2, 12.9 Hz), 4.29 (1H, dd, J = 8.8, 12.9 Hz), and 4.62 (1H, dd, J = 4.4, 12.9 Hz), one methine at δ_H 4.48 (1H, m), and two protons at δ_H 5.95 (1H, d, J = 9.5 Hz) and 8.83 (1H, s). These ^{13}C and ^{1}H NMR data were correspondingly assigned by 2D NMR spectra, including HSQC, HMBC, and ^{1}H−^{1}H COSY. Comparison of the NMR spectral data of **2** with those of **1** suggested that **2** also should be a purine-6,8-dione derivative.

The HMBC spectrum of **2** showed correlations of δ_H 8.83 (1H, s, H-2) with δ_C 107.8 (C), 139.0 (C), and 155.4 (C) that supported the presence of the purine-6,8-dione substructure (Figure 1). The HMBC spectrum showed correlations of δ_H 4.29 (1H, dd, J = 8.8, 12.9 Hz, H-1′a), 4.62 (1H, dd, J = 4.4, 12.9 Hz, H-1′b), 3.82 (1H, dd, J = 9.0, 12.9 Hz, H-3′a), and 4.25 (1H, dd, J = 4.2, 12.9 Hz, H-3′b) with δ_C 28.2 (CH, C-2′) and 117.4 (CH, C-4′), δ_H 4.48 (1H, m, H-2′) with δ_C 46.2 (CH_2, C-1′), 42.4 (CH_2, C-3′), 117.4 (CH, C-4′), and 131.8 (C, C-5′), and δ_H 5.95 (1H, d, J = 9.5 Hz, H-4′) with C-1′/C-3′/C-5′. The ^{1}H−^{1}H COSY spectrum showed correlations of H-2′ with H-1′a/H-1′b/H-3′a/H-3′b/H-4′, suggesting the presence of a 1-isopentene group. HMBC correlations of H-1′a/H-1′b/H-3′a/H-3′b with C-4 (δ_C 139.0, C), H-1′a/H-1′b with C-2 (δ_C 136.9, C), and H-3′a/H-3′b with C-8 (δ_C 150.3, C) indicated that the 1-isopentene group was attached to the purine-6,8-dione substructure by two C−N bonds, C-1′ with N(3) and C-3′ with N(9). HMBC correlation of H-4′ with C-6′ (δ_C 162.4, C) and δ_H 3.24 (3H, s, Me-10′) with C-5′ and C-8′ (δ_C 154.3, C), and comparison of the NMR data [δ_C 131.8 (C), 154.3 (C), 162.4 (C), 28.5 (CH_3)] of the heteroatom in **2** with those of other alkaloids that contained an imidazole ring,[14–16] together with the amounts of nitrogen and oxygen atoms in the molecular formula of **2**, indicated the presence of a 2-imino-5-isopropenyl-1-methyl-4-imidazolidinone unit. On the basis of the above data, the structure of **2** was determined as shown.

The molecular formula of **3** was determined as $C_9H_{10}N_4O_3$ by analysis of its NMR spectra and ESIMS. Its ^{13}C NMR spectrum also showed five low-field carbons [δ_C 143.1 (CH), 151.1 (C), 107.4 (C), 157.0 (C), 153.1 (C)], together with one methyl (δ_C 29.7), two methylenes (δ_C 41.8, 43.7), and one carbonyl group (δ_C 205.9, s). The ^{1}H NMR spectrum displayed one methyl at δ_H 2.04 (3H, s), two methylenes at δ_H 4.58 (2H, t, J = 6.45 Hz) and 3.22 (2H, t, J = 6.45 Hz), and one proton at δ_H 8.09 (1H, s). Comparison of the NMR spectral data of **3** with those of **1** and HMBC correlations of δ_H 8.09 (1H, s) with δ_C 151.1 (C), 107.4 (C), and 157.0 (C) in the HMBC spectrum of **3** proved the presence of a 6,8-purinedione substructure in **3**. HMBC correlations of δ_H 4.58 (2H, t, J = 6.45 Hz), 3.22 (2H, t, J = 6.45 Hz), and 2.04 (3H, s) with δ_C 205.9 (C), in addition to ^{1}H−^{1}H COSY correlations of δ_H 4.58 with δ_H 3.22, suggested the presence of a CH_3−CO−CH_2CH_2− unit. Meanwhile, HMBC correlations of δ_H 4.58 with δ_C 157.0 (C, C-6) and 143.1 (CH, C-2) suggested that the CH_3−CO−CH_2CH_2− unit was attached to the 6,8-purinedione substructure by a C−N(1) bond. So, the structure of **3** was determined to be 1-(3′-carbonylbutyl)purine-6,8-dione.

Compound **4** showed the same molecular formula of $C_9H_{10}N_4O_3$ as **3**, which was deduced from the NMR and ESIMS data of **4**. Comparison of overall ^{1}H and ^{13}C NMR spectral data revealed similarity between **4** and **3**. The only obvious difference between them was the chemical shifts of low-field carbons. HMBC correlations of δ_H 4.66 (2H, t, J = 7.5 Hz), 3.15 (2H, t, J = 7.5 Hz), and 2.09 (3H, s) with δ_C 206.5 (C) and ^{1}H−^{1}H COSY correlations of δ_H 4.66 with δ_H 3.15 also suggested the presence of a CH_3−CO−CH_2CH_2− unit. However, HMBC correlations of δ_H 4.66 with δ_C 152.2 (C, C-8) and 150.1 (C, C-4) suggested that the CH_3−CO−CH_2CH_2− unit should be attached to the 6,8-purinedione substructure by a C−N(9) bond instead of a C−N(1) bond. So, the structure of **4** was determined to be 9-(3′-carbonylbutyl)purine-6,8-dione.

In total, four new purine alkaloids, **1**–**4**, were isolated from the South China Sea gorgonian *S. suberosa*. It was rare to find alkaloids

from gorgonians. These compounds represented mix biogenesis and definitely indicated elements of novelty in gorgonian natural products.

In cytotoxicity bioassays, compounds **1**–**4** all showed weak cytotoxicity toward human cancer cell lines MDA-MB-231 and A435. However, in our previous report, **8** had moderate cytotoxicity against the MDA-MB-231 cell line with an IC_{50} of 8.87 μg/mL.[9] The location of the connection between the 6′,8′-purinedione moiety and the suberosanone moiety in the isomers **1** and **8** could significantly affect their cytotoxic activity.

Experimental Section

General Experimental Procedures. The procedures were the same as previously reported.[9]

Animal Material. The material was the same as previously reported.[9]

Extraction and Isolation. The frozen specimen was extracted with EtOH/CH_2Cl_2 (2:1) three times at room temperature, and the solution was evaporated *in vacuo*. The residue was suspended in H_2O and extracted with $CHCl_3$ and *n*-BuOH three times, respectively. The $CHCl_3$ and *n*-BuOH layers were concentrated *in vacuo* to afford 50 and 8 g of residues, respectively. The $CHCl_3$ extract was subjected to column chromatography (CC) on silica, using $CHCl_3$/Me_2CO (from 10:0 to 0:10) as eluent. By combining the fractions with TLC (GF_{254}) monitoring, eight fractions were obtained. Fraction 7 was chromatographed over Sephadex LH-20 eluting with $CHCl_3$/MeOH (1:1), then repeatedly subjected to CC on Si gel, eluted with $CHCl_3$/MeOH (from 8:2 to 7:3) to yield **1** (8 mg), **3** (3 mg), and **4** (4 mg). The *n*-BuOH extract was subjected to CC on Si gel, using $CHCl_3$/MeOH (from 9:1 to 0:10) as eluent, to give five fractions. Fraction 2 was subjected to CC on Si gel, eluted with $CHCl_3$/MeOH (from 8:2 to 7:3), to yield **5** (8 mg), **6** (9 mg), and **7** (9 mg). Fraction 3 was subjected to CC on Si gel, eluted with $CHCl_3$/MeOH (1:1), to yield **2** (7 mg).

6-(1′-Purine-6′,8′-diolyl)suberosanone (1): white powder; $[\alpha]^{20}_D$ +27.3 (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} 212, 265 nm; IR (KBr) 3502, 3115, 1739, 1710, 1672, 1659 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) data, see Table 1; ^{13}C NMR (125 MHz, DMSO-d_6) data, see Table 1; HRESIMS *m/z* 369.1918 $[M - H]^-$ (calcd for $C_{20}H_{25}N_4O_3$ 369.1926).

3,9-(2-Imino-1-methyl-4-imidazolidinon-5-yl)isopropenylpurine-6,8-dione (2): white powder; UV (MeOH) λ_{max} 213, 264, 310 nm; IR (KBr) 3504, 3110, 1738, 1708, 1675, 1648 cm^{-1}; ^1H NMR (500 MHz, D_2O + 0.5 N HCl) δ_H 8.83 (1H, s, H-2), 5.95 (1H, d, J = 9.5 Hz, H-3′), 4.62 (1H, dd, J = 4.4, 12.9 Hz, H-1′b), 4.48 (1H, m, H-2′), 4.29 (1H, dd, J = 8.7, 12.9 Hz, H-1′a), 4.25 (1H, dd, J = 4.2, 12.9 Hz, H-5′b), 3.82 (1H, dd, J = 9.0, 12.9 Hz, H-5′a), 3.24 (3H, s, NMe); ^{13}C NMR (125 MHz, D_2O+0.5 N HCl) δ_C 162.4 (s, C-6′), 155.4 (s, C-6), 154.3 (s, C-8′), 150.3 (s, C-8), 139.0 (s, C-4), 136.7 (d. C-2), 131.8 (s, C-5′), 117.4 (d, C-4′), 46.2 (t, C-1′), 42.4 (t, C-3′), 28.5 (q, C-10′), 28.2 (d, C-2′); ESIMS(+) *m/z* 316 $[M + H]^+$; HRFABMS *m/z* 316.1076 $[M + H]^+$ (calcd for $C_{13}H_{14}N_7O_3$ 316.1080).

1-(3′-Carbonylbutyl)purine-6,8-dione (3): white powder; UV (MeOH) λ_{max} 212, 264 nm; IR (KBr) 3501, 3115, 1740, 1710, 1670, 1658 cm^{-1}; ^1H NMR (500 MHz, Pyr-d_5) δ_H 8.09 (1H, s, H-2), 4.58 (2H, t, J = 6.45 Hz, H-1′), 3.22 (2H, t, J = 6.45 Hz, H-2′), 2.04 (3H, s, H-4′); ^{13}C NMR (125 MHz, Pyr-d_5) δ_C 205.9 (s, C-3′), 157.0 (s, C-6), 153.1 (s, C-8), 151.1 (s, C-4), 143.1 (d, C-2), 107.4 (s, C-5), 43.7 (t, C-2′), 41.8 (t, C-1′), 29.7 (q, C-4′); ESIMS(−) *m/z* 221 $[M - H]^-$; HRFABMS *m/z* 221.0750 $[M - H]^-$ (calcd for $C_9H_9N_4O_3$ 221.0753).

9-(3′-Carbonylbutyl)purine-6,8-dione (4): white powder; UV (MeOH) λ_{max} 212, 264 nm; IR (KBr) 3501, 3115, 1740, 1710, 1670, 1658 cm^{-1}; ^1H NMR (500 MHz, Pyr-d_5) δ_H 8.27 (1H, s, H-2), 4.66 (2H, t, J = 7.5 Hz, H-1′), 3.15 (2H, t, J = 7.5 Hz, H-2′), 2.09 (3H, s, H-4′); ^{13}C NMR (125 MHz, Pyr-d_5) δ_C 206.5 (s, C-3′), 156.3 (s, C-6), 152.2 (s, C-8), 150.1 (s, C-4), 140.6 (d, C-2), 108.7 (s, C-5), 42.0 (t, C-2′), 38.3 (t, C-1′), 29.7 (q, C-4′); ESIMS(−) *m/z* 221 $[M - H]^-$; HRFABMS *m/z* 221.0749 $[M - H]^-$ (calcd for $C_9H_9N_4O_3$ 221.0753).

Biological Assays. Human breast carcinoma MDA-MB-231 and liver carcinoma A435 cell lines were purchased from the American Type Culture Collection (ATCC, Rockville, MD). Cytotoxicity assays were measured by MTT methods as described previously.[13]

Acknowledgment. The authors are grateful to the Hi-tech Research and Development Program of China (grant SQ2007AA09Z435255), National Science Foundation of China (grant 20502027), Knowledge Innovation Program of the Chinese Academy of Science (grant KZCX2-YW-216-1), and Science and Technology Foundation of Guangdong Province (grant 2007B030300003) for financial support.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Groweiss, A.; Fenical, W.; He, C. H.; Clardy, J.; Wu, Z. D.; Yiao, Z. N.; Long, K. H. *Tetrahedron Lett.* **1985**, *26*, 2379–2382.
(2) Parameswaran, P. S.; Naik, C. G.; Kamat, S. Y.; Puar, M. S.; Das, P.; Hegde, V. R. *J. Nat. Prod.* **1998**, *61*, 832–834.
(3) Wang, G. H.; Ahmed, A. F.; Sheu, J. H.; Duh, C. Y.; Shen, Y. C.; Wang, L. T. *J. Nat. Prod.* **2002**, *65*, 887–891.
(4) Wang, G. H.; Ahmed, A. F.; Kuo, Y. H.; Sheu, J. H. *J. Nat. Prod.* **2002**, *65*, 1033–1036.
(5) Bokesch, H. R.; McKee, T. C.; Cardellina, J. H.; Boyd, M. R. *Tetrahedron Lett.* **1996**, *37*, 3259–3262.
(6) Anjaneyulu, A. S. R.; Rao, K.; Venkateswara, G. *Indian J. Chem.* **1997**, *36B*, 418–423.
(7) Aknin, M.; Costantino, V.; Mangoni, A. *Steroids* **1998**, *63*, 575–578.
(8) Subrahmanyam, C.; Kumar, S. R.; Reddy, G. D. *Indian J. Chem.* **2003**, *42B*, 219–220.
(9) Qi, S. H.; Zhang, S.; Li, X.; Xiao, Z. H.; Li, Q. X. *J. Nat. Prod.* **2005**, *68*, 1288–1289.
(10) Uemoto, H.; Tsuda, M.; Kobayashi, J. J. *Nat. Prod.* **1999**, *62*, 1581–1583.
(11) Su, J. Y.; Long, K. H.; Jian, Z. G. *Acta Sci. Nat. Univ. Sunyatseni* **1984**, *1*, 97–101.
(12) Lindsay, B. S.; Almeida, A. M. P.; Smith, C. J.; Berlinck, R. G. S.; da. Rocha, R. M.; Ireland, C. M. *J. Nat. Prod* **1999**, *62*, 1573–1575.
(13) Yosief, T.; Rudi, A.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 299–304.
(14) Aiello, A.; D'Esposito, M.; Fattorusso, E.; Menna, M.; Müller, W. E. G.; Perović-Ottstadt, S.; Schröderb, H. C. *Bioorg. Med. Chem.* **2006**, *14*, 17–24.
(15) Cafieri, F.; Fattorusso, E.; Mangoni, A.; Tagliatatela-Scafati, O.; Carnuccio, R. *Tetrahedron Lett.* **1996**, *37*, 3587–3590.
(16) Bednarski, P. J. *Biochem. Pharmacol.* **1992**, *43*, 2609–2620.

NP0705110