

Article

New Sinularianin Sesquiterpenes from Soft Coral *Sinularia* sp.

Bin Yang, Shengrong Liao, Xiuping Lin, Junfeng Wang, Juan Liu, Xuefeng Zhou,
Xianwen Yang and Yonghong Liu *

CAS Key Laboratory of Tropical Marine Bio-resources and Ecology/Guangdong Key Laboratory of Marine Materia Medica/Research Center for Marine Microbes, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou 510301, China;

E-Mails: bingo525@163.com (B.Y.); ljrss@126.com (S.L.); xiupinglin@hotmail.com (X.L.); junfeng1982a@163.com (J.W.); ljuan2010@qq.com (J.L.); xfzhou@scsio.ac.cn (X.Z.); xwyang@scsio.ac.cn (X.Y.)

* Author to whom correspondence should be addressed; E-Mail: yonghongliu@scsio.ac.cn;
Tel./Fax: +86-020-8902-3244.

Received: 5 September 2013; in revised form: 4 November 2013 / Accepted: 4 November 2013 /
Published: 2 December 2013

Abstract: Four new sesquiterpenes, sinularianins C–F (**3–6**), together with known sinularianins A (**1**) and B (**2**) were identified from a South China Sea soft coral *Sinularia* sp. Compounds **1–6** were evaluated for inhibition of NF- κ B activation using the cell-based HEK293 NF- κ B luciferase reporter gene assay. Compounds **1** and **4** were exhibited a potent effect with inhibitory rates of 41.3% and 43.0% at the concentration of 10 μ g/mL, respectively.

Keywords: soft coral; *Sinularia* sp.; sesquiterpenes; sinularianins; NF- κ B

1. Introduction

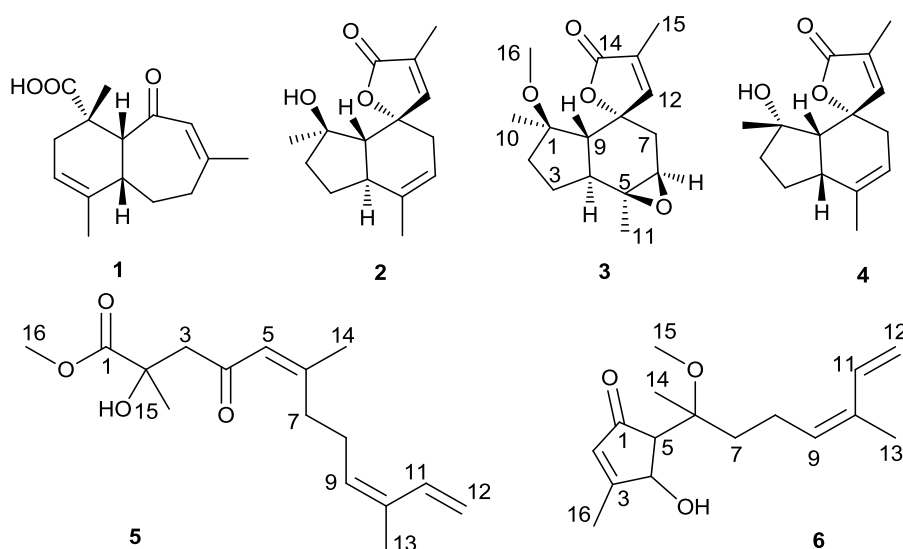
The genus *Sinularia* is the most widely distributed soft coral, consisting of almost 90 species, of which more than 50 have been chemically examined [1–5]. Up to now, *Sinularia* has yielded many metabolites, including sesquiterpenes, diterpenes, alkaloids, and polyhydroxylated steroids [6–12]. These metabolites display a wide range of biological activities, such as antimicrobial, anti-inflammatory, and cytotoxic activities [13–18]. In our endeavor to explore the bioactive secondary metabolites from marine invertebrates, sinularianins A (**1**) and B (**2**) were reisolated along with four new sesquiterpenes, sinularianins C–F (**3–6**) from soft coral *Sinularia* sp., collected at Dongluo Island, Hainan province,

China, at a depth of 10 m. Sinularianin A and B have been isolated from the Formosan coral *Sinularia* sp., but their anti-inflammatory activation were tested for the first time. Similar sesquiterpenes had been isolated mostly from the plant *Valeriana officinalis*, which was used as an anti-inflammatory remedy in Europe, and were active as inhibitors of NF- κ B [19]. In this paper, we describe the isolation, structure elucidation, and the NF- κ B inhibitory potential of these compounds.

2. Results and Discussion

The soft coral *Sinularia* sp. was dissolved in 85% EtOH, and the extract separated by silica gel column chromatography, Sephadex LH-20, and semi-preparative HPLC to obtain new sesquiterpenes, sinularianins C–F (**3–6**), and two known compounds (**1**, **2**) (Figure 1).

Figure 1. Structures of the compounds **1–6**.



Sinularianins A (**1**) and B (**2**) were previously isolated from the soft coral *Sinularia* sp., collected off the northeastern Taiwan coast, in May 2004, at a depth of 10 m. Sinularianin A (**1**) possesses an unprecedented bicyclic skeleton sinulariolane. Sinularianin B (**2**) was the only example of valerenane-related sesquiterpene with a spiro-butenolide moiety [10]. The valerenane-related sesquiterpenes had been firstly reported from the plant *Valeriana officinalis* [20,21], and several representatives have been reported from a marine alga [22] and a soft coral [23]. Sinularianin A (**1**) and B (**2**), were reisolated and identified by comparison of their ^1H and ^{13}C NMR data with those reported [10].

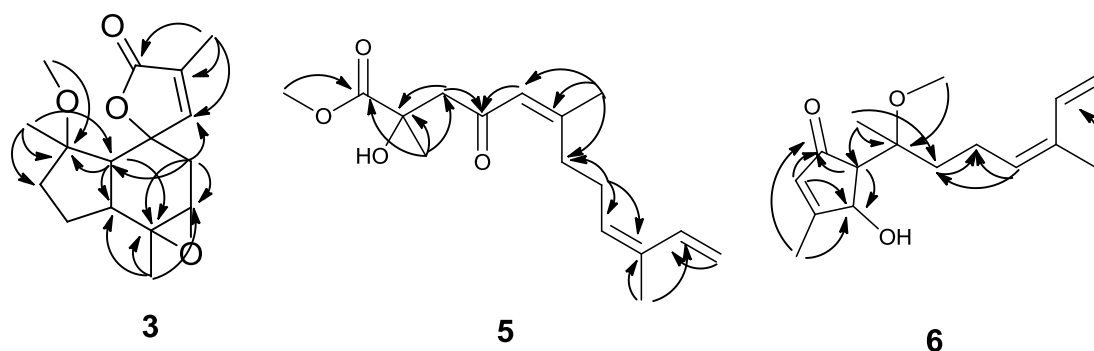
Sinularianin C (**3**) was isolated as a colorless oil. Its molecular formula was established as $\text{C}_{16}\text{H}_{22}\text{O}_4$ on the basis of the positive HRESIMS at m/z 301.1416 (Calcd for $\text{C}_{16}\text{H}_{22}\text{NaO}_4$, 301.1416), indicating six degrees of unsaturation (Supplementary Figure S1). The ^1H NMR spectrum (Table 1) revealed the presence of four singlet methyls (δ_{H} 1.00, 1.41, 1.86, 3.17), three methylene signals (δ_{H} 1.95, 1H, m; 1.53, 1H, m; 1.96, 1H, m; 1.56, 1H, m; 2.26, 1H, d, $J = 16.0$ Hz; 1.76, 1H, dd, $J = 16.0, 5.0$ Hz), three methine signals (2.00, 1H, d, $J = 13.0$ Hz; 2.43, 1H, m; 3.11, 1H, d, $J = 5.0$ Hz), and one olefinic proton (δ_{H} 7.17, 1H, d, $J = 1.5$ Hz) (Supplementary Figure S2). The ^{13}C NMR spectra, together with HSQC, showed 16 signals for four methyls (δ_{C} 10.3, 20.5, 21.3, 50.8), three sp^3 methylenes (δ_{C} 23.6, 35.7, 38.7), three sp^3 methines (δ_{C} 41.1, 50.4, 59.5), three sp^3 oxygenated quaternary carbons (δ_{C} 61.8,

84.2, 86.5), one sp^2 methine (δ_C 154.7), one sp^2 quaternary carbon (δ_C 129.5), and one carbonyl carbon (δ_C 175.6) (Supplementary Figures S3 and S4). Both the 1H and ^{13}C NMR spectra of **3** showed a close similarity to those of **2** [10]. However, the close comparison of the ^{13}C NMR spectroscopic data of **2** and **3** revealed some differences: one trisubstituted double bond in **2** was changed to the epoxy three-membered ring (δ_C 61.8, 59.5) in **3**, and an additional methoxyl (δ_C 50.8, δ_H 3.17, 3H, s, H-16) was observed in **3**. This assumption was supported by the correlation of H-11 to C-4, C-5, and C-6, H-6 to C-5, and C-7, H-7 to C-5 and C-6 in the HMBC spectrum (Figure 2). Furthermore, the methoxyl substituent was determined to be connected to position C-1 on the basis of the HMBC correlation from 16-OMe to C-1 (Supplementary Figure S5).

Table 1. 1H and ^{13}C NMR spectroscopic data for compounds **3** (500/125 MHz, in MeOD, δ in ppm, J in Hz) and **4** (in $CDCl_3$).

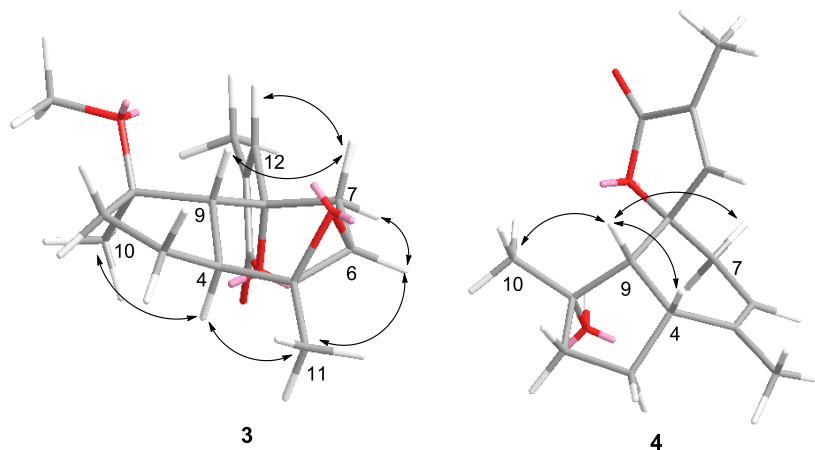
Position	3		4	
	1H	^{13}C	1H	^{13}C
1		84.2		78.4
2	1.95 m	35.7	1.92 m	43.1
	1.53 m		1.79 m	
3	1.96 m	23.6	2.01 m	25.9
	1.56 m			
4	2.43 m	41.1	2.90 m	41.8
5		61.8		137.5
6	3.11 d (5.0)	59.5	5.26 s	117.2
7	2.26 d (16.0)	38.7	2.53 m	39.4
	1.76 dd (16.0, 5.0)		1.91 m	
8		86.5		85.6
9	2.00 d (13.0)	50.4	1.55 d (12.5)	55.5
10	1.00 s	21.3	1.26 s	28.5
11	1.41 s	20.5	1.74 s	20.5
12	7.17 d (1.5)	154.7	7.03 d (1.5)	150.9
13		129.5		129.7
14		175.6		174
15	1.86 s	10.3	1.94 d (1.5)	10.6
16	3.17 s	50.8		

Figure 2. Selected HMBC correlations (H \rightarrow C) of compounds **3**, **5**, and **6**.



The relative stereochemistry of **3** was established by the detailed analysis of correlations observed in the NOESY spectrum (Figure 3). In the NOESY spectrum, H-9 showed correlation with H-7 β (δ_{H} 2.26, d, $J = 16.0$ Hz), which in turn correlated with H-12, suggesting the β orientations of H-9 and H-12. Furthermore, NOE interactions were observed between H₃-10/H-4, H₃-11/H-4, H₃-11/H-6, and H-6/H-7 α (δ_{H} 1.76, dd, $J = 16.0, 5.0$ Hz), while both H₃-10 and H-4 did not show correlations with H-9, suggesting the α orientation of H₃-10, H₃-11, H-4, and H-6 (Supplementary Figure S6).

Figure 3. Selected NOE correlations of compounds **3** and **4**.



Sinularianin D (**4**) was isolated as a colorless oil. The ESI-MS showed the $[M + \text{Na}]^+$ ion at m/z : 271 (Supplementary Figure S7). Its ^1H and ^{13}C NMR spectroscopic data were also very similar to those of **2** (Supplementary Figures S8 and S9). However, a close inspection of their ^1H NMR spectroscopic data revealed some difference: H-4 and H₃-10 were shifted downfield from 2.57 to 2.90, and from 1.12 to 1.26 respectively, and H-9 was shifted upfield from 1.99 to 1.55. This suggested that the configuration at H-1 and H-4 in **4** should be β orientation compared to α orientation in **2**, which was supported by the NOESY experiment (Figure 3). In the NOESY spectrum, H-9 showed correlation with H₃-10, H-4, and H-7 β , suggesting the β orientations of H-4, H-9, H-7 β , and H₃-10 (Supplementary Figure S10).

Sinularianin E (**5**) was isolated as a colorless oil, and assigned the molecular formula of $\text{C}_{16}\text{H}_{24}\text{O}_4$ by the positive HRESIMS at m/z 303.1563 (Calcd for $\text{C}_{16}\text{H}_{24}\text{NaO}_4$, 303.1572) (Supplementary Figure S11). The ^1H and ^{13}C NMR spectroscopic data of **5** indicated sixteen carbon signals: four singlet methyls, four methylenes, three olefinic methines, and five quaternary carbons (Supplementary Figures S12–S14). The ^1H NMR spectrum showed signals of four olefinic protons (δ_{H} 5.42, 1H, t, $J = 7.0$ Hz; 6.36, 1H, dd, $J = 17.5, 10.5$ Hz; 5.13, 1H, d, $J = 17.5$ Hz; 4.96, 1H, d, $J = 10.5$ Hz), one methoxy group (δ_{H} 3.72), two vinyl methyls (δ_{H} 2.14, s; 1.74, s), and one other methyl (δ_{H} 1.40, s) (Table 2). The gross structure of **5** was established by the assistance of extensive 2D NMR analysis (Figure 2). The methoxycarbonyl was confirmed by HMBC correlations from 16-OMe to C-1. The methyl protons resonating at δ_{H} 1.40 and the quaternary carbon resonating at δ_{C} 72.9 indicated that this methyl and a hydroxyl group should be positioned at C-2 by the HMBC correlations from H-15 to C-1, C-2, and C-3 (Supplementary Figure S15). The olefinic methyls (δ_{H} 2.14, s; 1.74, s) attached at C-6 and C-10 were confirmed by the HMBC correlations from H-14 to C-5, C-6, and C-7 and H-13 to C-9,

C-10, and C-11. Furthermore, the HMBC correlations from H-9 to C-8, and C-10, H-12 to C-10, and C-11 established the terminal diene unit. Other key informative HMBC correlations from H-3 to C-2, and C-4, H-5 to C-4, H-8 to C-7, C-9, and C-10, established the planar structure of **5**. The double bond at C-5 was assigned the *Z*-geometry on the basis of the downfield chemical shifts of C-14 (δ_{H} 19.7) [24]. The geometry of the disubstituted double bond (C-9) was determined to be *E* by comparison of the spectral data with those reported in literature [24], whereas the configurations at C-2 remained to be determined. On the basis of above evidences, compound **5** was then identified, and named sinularianin E.

Table 2. ^1H and ^{13}C NMR spectroscopic data for compounds **5** and **6** (500/125 MHz, in CDCl_3 , δ in ppm, J in Hz).

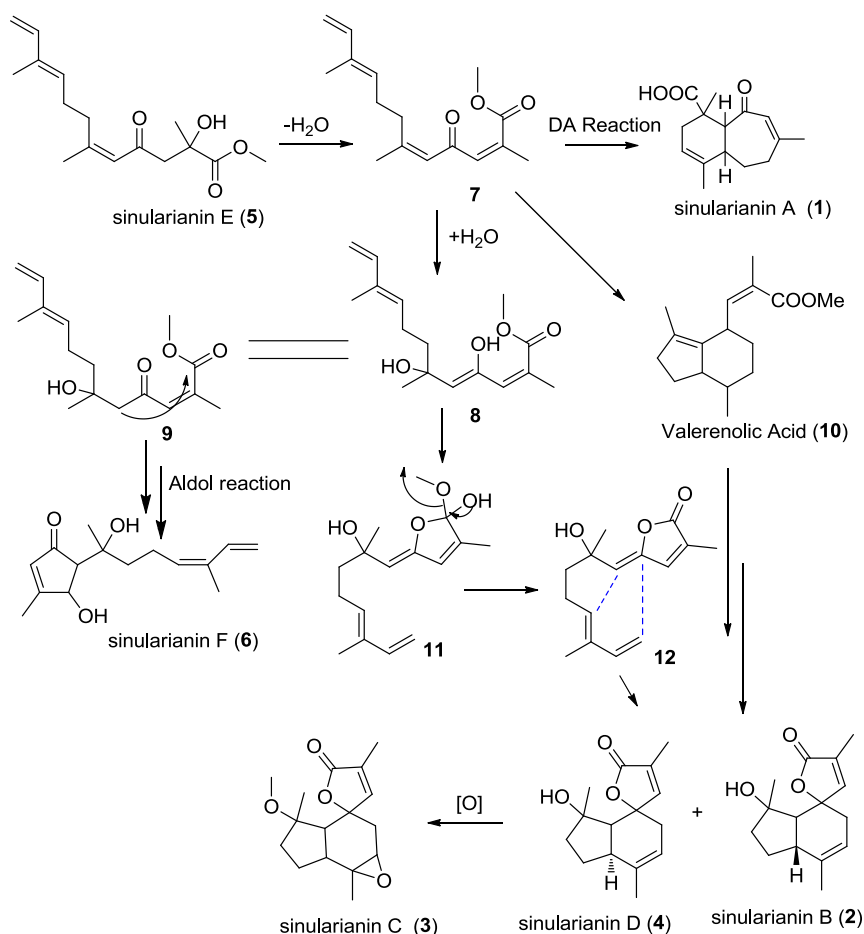
Position	5		6	
	^1H	^{13}C	^1H	^{13}C
1		176.5		203.2
2		72.9	5.86 s	131.2
3	3.15 d (17.5) 2.80 d (17.5)	52.9		174.9
4		199.3	4.79 s	75.3
5	6.01 s	122.9	2.65 s	61.5
6		160.3		78
7	2.22 m	40.9	1.82 m 2.12 m	34.1
8	2.34 m 2.20 m	25.8	2.19 m	22.1
9	5.42 t (7.0)	130.8	5.52 m	132.3
10		135		134.1
11	6.36 dd (17.5, 10.5)	141	6.36 dd (17.0, 10.5)	141.5
12	5.13 d (17.5) 4.96 d (10.5)	111.3	5.10 d (17.0) 4.94 d (10.5)	110.7
13	1.74 s	11.7	1.76 s	11.6
14	2.14 s	19.7	1.03 s	22.7
15	1.40 s	26.2	3.21 s	48.5
16	3.72 s	52.7	2.16 s	15.6

Sinularianin F (**6**) was isolated as a colorless oil. It was assigned a molecular formula of $\text{C}_{16}\text{H}_{24}\text{O}_3$ by positive HR-ESI-MS at m/z 287.1613 (Calcd for $\text{C}_{16}\text{H}_{24}\text{NaO}_3$, 287.1623) (Supplementary Figure S16). Analysis of ^1H and ^{13}C NMR data revealed the presence of four methyl groups, three methylene carbons, five methine carbons, and four quaternary carbons (Supplementary Figures S17–S19). The ^1H NMR spectrum showed signals of five olefinic protons (δ_{H} 5.86, s; 5.52, m; 6.36, dd, $J = 17.0$, 10.5 Hz; 5.10, d, $J = 17.0$ Hz; 4.94, d, $J = 10.5$ Hz), one oxygenated methane (δ_{H} 4.79, s), one methoxy group (δ_{H} 3.21, s), two vinyl methyls (δ_{H} 1.76, s; 2.16, s), and one other methyl (δ_{H} 1.03, s) (Table 2). The HMBC correlations from H-9 to C-8, and C-10, H-12 to C-10, and C-11, H-13 to C-10, and C-11 established the terminal diene unit (Supplementary Figure S20). The key HMBC correlations of H₃-16 to C-2, C-3, and C-4 and H-2 to C-1, C-3, C-4, and C-5 indicated the presence of a five-membered carbocycle containing a ketone carbonyl and a trisubstituted double bond (Figure 2), as well as by

comparison of the data with that of in agreement with the data of cycloabienesquene A [25]. The two fragments may be connected *via* the correlations of H-15 to C-5, C-6, and C-7, H-14 to C-6 and H-7 to C-6, C-7, and C-8 in the HMBC spectrum. Two double bonds in the molecule possessed 2*Z* and 9*E* configuration on the basis of the chemical shifts of C-16 and C-13 (δ 15.6 and 11.6, respectively) [24,25].

Although sinularianins E (5) and F (6) formally displayed a quite different skeleton from that of sinularianins A–D (1–4), however, they are actually related to each other. From a biosynthetic aspect, sinularianins A–D (1–4), and F (6) could be generated from sinularianin E (5), via different reaction cascades as illustrated in the hypothetical biosynthetic pathway (Scheme 1). As a precursor, sinularianin E (5) potentially could be transformed into the key intermediate A by dehydration reaction. Intermediate A could be through different intramolecular Diels Alder cyclization reaction to form sinularianin A (1) or valerenolic acid, respectively, and the latter was further modified to produce sinularianin B (2). Intermediate A could be also adapted by Michael addition under the H₂O attack and then immediately lactonized, followed by a DA cyclization to yield sinularianin B (2), which after epoxidation and dehydration potentially could be produce epoxide sinularianin C (3). Intermediate A might form sinularianin F (6) by an aldol condensation.

Scheme 1. Proposed biosynthetic pathway for 1–6.



Nuclear factor- κ B (NF- κ B) plays a key role in regulating the immune response to infection. Incorrect regulation of NF- κ B has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development [26]. Compounds 1–6 were evaluated

for inhibition of NF- κ B activation using the cell-based HEK293 NF- κ B luciferase reporter gene assay. At concentration of 10 μ g/mL, sinularianin A and D exhibits a potent effect with inhibitory rates of 41.3%, and 43.0%, respectively. At the same concentration, other compounds showed moderate effects at the same (Table 3). The past studies have provided biochemical evidence of valerenane-related sesquiterpenes as anti-inflammatory agents acting via the NF- κ B inhibitory potential. The valerenic acid (**3**) reduced NF- κ B activity to 25% at concentration of 100 μ g/mL [19].

Table 3. Inhibitory rates of NF- κ B activation of compounds 1–6.

Concentration	IR (%)					
	1	2	3	4	5	6
10 μ g/mL	41.3	29.6	24.3	43.0	30.0	36.1

3. Experimental Section

3.1. General Experimental Procedures

The NMR spectra were recorded on a Bruker AC 500 NMR spectrometer with TMS as an internal standard. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer. UV spectra were recorded on a Shimadzu UV-2600 UV-Vis spectrophotometer. Optical rotations were measured on a Perkin Elmer 341 polarimeter using a 1 dm path length cell. HR-ESI-MS data were measured on AQUITY UPLC/Q-TOF mass spectrometer. ESI-MS data were measured on Bruker's amaZon SL ion trap LC/MS. Materials for column chromatography were silica gel (100–200, 200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, China), Sephadex LH20 (40–70 μ m, Amersham Pharmacia Biotech AB, Uppsala, Sweden), and YMC Gel ODS-A (12 nm, S-50 μ m YMC, MA, USA). The silica gel GF₂₅₄ (0.4–0.5 mm) used for TLC were supplied by the Qingdao Marine Chemical Factory, Qingdao, China. HPLC was carried on shimadzu LC-10ATvp with YMC ODS SERIES (YMC-Pack ODS-A, 250 \times 10 mm I.D., S-5 μ m, 12 nm).

3.2. Animal Material

The soft coral *Sinularia* sp. was collected from Dongluo Island, Hainan province of China in July 2009 (7–10 m depth) and identified by Professor Hui Huang, South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen (No. 0907010) was deposited in the CAS Key Laboratory of Tropical Marine Bio-resources and Ecology, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, China.

3.3. Extraction and Isolation

The fresh soft coral (wet, 6 kg) was extracted three times with 95% EtOH (20 L). The extract was concentrated under reduced pressure, and partitioned between H₂O (4 L) and CHCl₃ (4 L); the CHCl₃ layer (120 g) was further partitioned between 85% EtOH (4 L) and petroleum ether (PE; 4 L) to yield 85% EtOH (34 g) and PE (75.6 g) fractions. The 85% EtOH fraction was separated by silica gel column using CHCl₃/MeOH to yield 11 portions (Frs. s1–s11). Fr. s3 was purified by silica gel column to yield 12 portions, and portion 10 was further purified with semi-preparative HPLC, eluting with

MeOH/H₂O = 65:35 at a flow rate of 2 mL/min, to afford **1** (6.0 mg) and **2** (7.2 mg). Fr. s5 was purified by Sephadex LH-20 using CHCl₃/MeOH = 1:1 to yield 3 portions, and portion 1 was further purified with semi-preparative HPLC, eluting with MeOH/H₂O = 57:43 at a flow rate of 2 mL/min, to afford **5** (2.2 mg) and **6** (2.6 mg). Fr. s6 was separated by silica gel column using PE/EtOAc to yield 7 portions, and portion 1 was further purified with semi-preparative HPLC, eluting with MeOH/H₂O = 70:30 at a flow rate of 2 mL/min, to afford **3** (2.2 mg) and **4** (3.7 mg).

Sinularianin C (**3**): Colorless oil; ¹H- and ¹³C-NMR (see Table 1); HR-ESI-MS *m/z* 301.1416 [M + Na]⁺, (Calcd for C₁₆H₂₂NaO₄, 301.1416).

Sinularianin D (**4**): Colorless oil; [α]_D²⁵ = -6.0 (*c* = 0.01, MeOH); UV (MeOH): λ_{max} (log ε) = 204.2 (1.70); IR (KBr) ν_{max} 3421, 2927, 2854, 1735, 1666 cm⁻¹ (Supplementary Figure S21); ¹H- and ¹³C-NMR (see Table 1); ESI-MS *m/z* 271 [M + Na]⁺, 519 [2M + Na]⁺.

Sinularianin E (**5**): Colorless oil; ¹H- and ¹³C-NMR (see Table 2); HR-ESI-MS *m/z* 303.1563 [M + Na]⁺, (Calcd for C₁₆H₂₄NaO₄, 303.1572).

Sinularianin F (**6**): Colorless oil; ¹H- and ¹³C-NMR (see Table 2); HR-ESI-MS *m/z* 287.1613 [M + Na]⁺, (Calcd for C₁₆H₂₄NaO₃, 287.1623).

3.4. The Cell-Based HEK293 NF-κB Luciferase Reporter Gene Assay

All compounds were evaluated for inhibition of NF-κB activation using the cell-based HEK 293 NF-κB luciferase reporter gene assay according to the previously reported procedures [19].

4. Conclusions

The investigation of bioactive natural products from a Hainan soft coral, *Sinularia* sp., has led to the isolation of four new sesquiterpenes, sinularianins C–F (**3–6**), along with two other analogues, sinularianins A (**1**) and B (**2**). Compounds **1** and **4** were exhibited a potent inhibitory effect with inhibitory rates of 41.3% and 43.0% at the concentration of 10 μg/mL, respectively. The discovery of new compounds **3–6** has added to an extremely diverse and complex array of soft coral sesquiterpenes.

Acknowledgments

This study was supported by grants from the National Key Basic Research Program of China (973)'s Project (2010CB833800 and 2011CB915503), the National High Technology Research and Development Program (863 Program, 2012AA092104), National Natural Science Foundation of China (21302198, 31270402, 21172230, 30973679, 41376162 and 41176148), Knowledge Innovation Program of Chinese Academy of Science (SQ201117 and SQ201019), Guangdong Province-CAS Joint Research Program (2011B090300023 and 2012B091100264), and Guangdong Marine Economic Development and Innovation of Regional Demonstration Project (GD2012-D01-001 and GD2012-D01-002).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Yang, B.; Zhou, X.F.; Huang, H.; Yang, X.W.; Liu, J.; Lin, X.P.; Li, X.B.; Peng, Y.; Liu, Y.H. New cembrane diterpenoids from a Hainan soft coral *Sinularia* sp. *Mar. Drugs* **2012**, *10*, 2023–2032.
2. Chao, C.H.; Chou, K.J.; Huang, C.Y.; Wen, Z.H.; Hsu, C.H.; Wu, Y.C.; Dai, C.F.; Sheu, J.H. Steroids from the soft coral *Sinularia crassa*. *Mar. Drugs* **2012**, *10*, 439–450.
3. Cheng, S.Y.; Huang, K.J.; Wang, S.K.; Duh, C.Y. Capilloquinol: A novel farnesyl quinol from the Dongsha atoll soft coral *Sinularia capillosa*. *Mar. Drugs* **2011**, *9*, 1469–1476.
4. Li, R.; Shao, C.L.; Qi, X.; Li, X.B.; Li, J.; Sun, L.L.; Wang, C.Y. Polyoxygenated sterols from the South China Sea soft coral *Sinularia* sp. *Mar. Drugs* **2012**, *10*, 1422–1432.
5. Kamel, H.N.; Slattery, M. Terpenoids of *Sinularia*: Chemistry and biomedical applications. *Pharm. Biol.* **2005**, *43*, 253–269.
6. Su, J.H.; Wen, Z.H. Bioactive cembrane-based diterpenoids from the soft coral *Sinularia triangular*. *Mar. Drugs* **2011**, *9*, 944–951.
7. Tsai, T.C.; Wu, Y.J.; Su, J.H.; Lin, W.T.; Lin, Y.S. A new spatane diterpenoid from the cultured soft coral *Sinularia leptoclados*. *Mar. Drugs* **2013**, *11*, 114–123.
8. Tseng, Y.J.; Shen, K.P.; Lin, H.L.; Huang, C.Y.; Dai, C.F.; Sheu, J.H. Lochmolins A–G, new sesquiterpenoids from the soft coral *Sinularia lochmodes*. *Mar. Drugs* **2012**, *10*, 1572–1581.
9. Lai, D.W.; Li, Y.X.; Xu, M.J.; Deng, Z.W.; van Ofwegen, L.; Qian, P.Y.; Proksch, P.; Lin, W.H. Sinulariols A–S, 19-oxygenated cembranoids from the Chinese soft coral *Sinularia rigida*. *Tetrahedron* **2011**, *67*, 6018–6029.
10. Chao, C.H.; Hsieh, C.H.; Chen, S.P.; Lu, C.K.; Dai, C.F.; Sheu, J.H. Sinularianins A and B, novel sesquiterpenoids from the Formosan soft coral *Sinularia* sp. *Tetrahedron Lett.* **2006**, *47*, 5889–5891.
11. Lu, M.C.; Lee, N.L.; Tseng, S.W.; Su, J.H. Sinutriangulin A, a novel diterpenoid from the soft coral *Sinularia triangular*. *Tetrahedron Lett.* **2011**, *52*, 5869–5871.
12. Putra, M.Y.; Ianaro, A.; Panza, E.; Bavestrello, G.; Cerrano, C.; Fattorusso, E.; Tagliatela-Scafati, O. Sinulasulfoxide and sinulasulfone, sulfur-containing alkaloids from the Indonesian soft coral *Sinularia* sp. *Tetrahedron Lett.* **2012**, *53*, 3937–3939.
13. Yamashita, T.; Nakao, Y.; Matsunaga, S.; Oikawa, T.; Imahara, Y.; Fusetani, N. A new antiangiogenic C-24 oxylipin from the soft coral *Sinularia numerosa*. *Bioorg. Med. Chem.* **2009**, *17*, 2181–2184.
14. Chai, M.C.; Wang, S.K.; Dai, C.F.; Duh, C.Y. A cytotoxic lobane diterpene from the Formosan soft coral *Sinularia inelegans*. *J. Nat. Prod.* **2000**, *63*, 843–844.
15. Sheu, J.H.; Chang, K.C.; Duh, C.Y. A cytotoxic 5 α ,8 α -epidioxysterol from a soft coral *Sinularia* species. *J. Nat. Prod.* **2000**, *63*, 149–151.
16. Chao, C.H.; Chou, K.J.; Huang, C.Y.; Wen, Z.H.; Hsu, C.H.; Wu, Y.C.; Dai, C.F.; Sheu, J.H. Bioactive cembranoids from the soft coral *Sinularia crassa*. *Mar. Drugs* **2011**, *9*, 1955–1968.
17. Shi, H.Y.; Yu, S.J.; Liu, D.; van Ofwegen, L.; Proksch, P.; Lin, W.H. Sinularones A–I, new cyclopentenone and butenolide derivatives from a marine soft coral *Sinularia* sp. and their antifouling activity. *Mar. Drugs* **2012**, *10*, 1331–1344.

18. Wright, A.D.; Nielson, J.L.; Tapiolas, D.M.; Liptrot, C.H.; Motti, C.A. A great barrier reef *Sinularia* sp. yields two new cytotoxic diterpenes. *Mar. Drugs* **2012**, *10*, 1619–1630.
19. Jacobo-Herrera, N.J.; Vartiainen, N.; Bremner, P.; Gibbons, S.; Koistinaho, J.; Heinrich, M. NF- κ B modulators from *Valeriana officinalis*. *Phytother. Res.* **2006**, *20*, 917–919.
20. Bos, R.; Hendriks, H.; Bruins, A.P.; Kloosterman, J.; Sipma, G. Isolation and identification of valerenane sesquiterpenoids from *Valeriana officinalis*. *Phytochemistry* **1986**, *25*, 133–135.
21. Birnbaum, G.I.; Findlay, J.A.; Krepinsky, J.J. Stereochemistry of valerenane sesquiterpenoids-crystal-structure of valerenolic acid. *J. Org. Chem.* **1978**, *43*, 272–276.
22. Mao, S.C.; Guo, Y.W.; Shen, X. Two novel aromatic valerenane-type sesquiterpenes from the Chinese green alga *Caulerpa taxifolia*. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2947–2950.
23. Kobayashi, M.; Yasuzawa, T.; Kyogoku, Y.; Kido, M.; Kitagawa, I. Three new ent-valerenane sesquiterpenes from an Okinawan soft coral. *Chem. Pharm. Bull.* **1982**, *30*, 3431–3434.
24. Bowden, B.F.; Coll, J.C.; Desilva, E.D.; Decosta, M.S.L.; Djura, P.J.; Mahendran, M.; Tapiolas, D.M. Studies of Australian soft corals. XXXI. Novel furanosesquiterpenes from several *Sinularian* soft corals (Coelenterata, Octocorallia, Alcyonacea). *Aust. J. Chem.* **1983**, *36*, 371–376.
25. Yang, X.W.; Ding, Y.Q.; Li, X.C.; Ferreira, D.; Shen, Y.H.; Li, S.M.; Wang, N.; Zhang, W.D. Cycloabienesquene A, a unique sesquiterpenoid from *Abies delavayi*. *Chem. Commun.* **2009**, *25*, 3771–3773.
26. Peddibhotla, S.; Shi, R.X.; Khan, P.; Smith, L.H.; Mangravita-Novo, A.; Vicchiarelli, M.; Su, Y.; Okolotowicz, K.J.; Cashman, J.R.; Reed, J.C.; *et al.* Inhibition of protein kinase C-driven nuclear factor-kappa B activation: Synthesis, structure-activity relationship, and pharmacological profiling of pathway specific benzimidazole probe molecules. *J. Med. Chem.* **2010**, *53*, 4793–4797.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).