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Article

New Cembrane Diterpenoids from a Hainan Soft Coral *Sinularia* sp.

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Abstract: Five new cembrane diterpenoids, named sinuflexibilins A–E (**1**–**5**), along with nine other known diterpenoids (**6**–**14**), have been isolated from the organic extract of a Hainan soft coral *Sinularia* sp. Their structures were determined on the basis of extensive spectroscopic analyses and by comparison of their spectral data with those of related metabolites. Compound **13**, flexibilide, exhibited significant inhibitory activity of NF-κB activation using the cell-based HEK293 NF-κB luciferase reporter gene assay.

Keywords: *Sinularia* sp.; cembrane diterpenoids; NF-κB inhibitor

1. Introduction

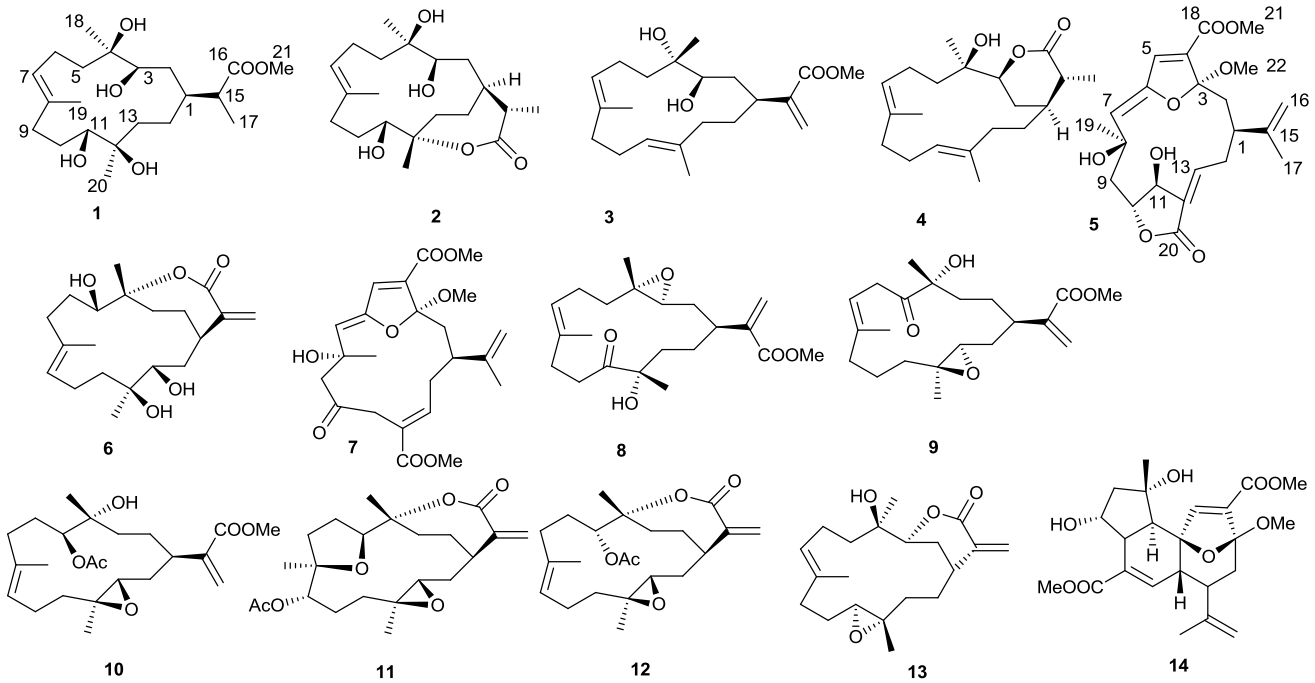
Cembrane diterpenoids and their cyclized derivatives are the most abundant secondary metabolites of soft corals and gorgonians [1–3]. There is a wide range of structural complexity within this series. These cembranes represent the main chemical defense tools of animals against their natural predators such as other corals, and fishes, as well as the settlement of microorganisms [4,5]. In addition,

cembranes also exhibit a wide range of biological activities including anti-inflammatory [6–8], and antitumor properties [9,10].

Genus *Sinularia* is one of the most widely distributed soft corals. It constitutes a dominant portion of the biomass in the tropical reef environment. *Sinularia* elaborates a rich harvest of secondary metabolites, including sesquiterpenes, diterpenoids, polyhydroxylated steroids, and polyamine compounds [11–14]. These metabolites were recently shown to possess a range of biological activities [15]. Cembranes are the most frequent secondary metabolites isolated from various *Sinularia* species [16–18].

Nuclear factor-kappa B (NF-κB) is a protein complex that controls the transcription of DNA. NF-κB plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development [19]. Our recent investigation of bioactive natural products from a Hainan soft coral, *Sinularia* sp., has led to the isolation of five new cembranes (**1**–**5**), along with nine other known diterpenoids (**6**–**14**) (Figure 1). In this paper, we report the isolation and structural elucidation of these diterpenoids and their activities as inhibitors of NF-κB.

Figure 1. Structures of compounds **1**–**14** from *Sinularia* sp.



2. Results and Discussion

Compound **1** was isolated as a colorless oil. The HRESIMS of **1** established its molecular formula as $C_{21}H_{38}O_6$, indicating three unsaturations. Resonances due to olefinic carbons (δ_C 133.9, 128.7), and one carboxyl (δ_C 178.9) in the ^{13}C NMR spectrum accounted for two double-bond equivalents, indicating that **1** was a monocyclic compound (Table 1). Signals for a vinyl methyl at δ 1.68 (3H, s), one methoxy group at δ 3.68 (3H, s), a methyl doublet at δ 1.17 (3H, d, J = 7.0 Hz), and two tertiary oxygenated methyl groups at δ 1.15 (3H, s), and 1.08 (3H, s) were observed in the ^1H NMR spectrum (Table 2). Carbon signals at δ 70.6, 71.0, 75.3, and 75.7, and two proton signals at δ 3.52, and 3.65 indicated the presence of two secondary and two tertiary hydroxyl groups. A signal at δ 5.43 attributed

to an olefinic proton, together with a methyl carbon signal at δ 17.0, indicated the *E* configuration for this double bond. These data suggested that **1** was a rearranged cembrane. Key HMBC correlations from H_3-20 to C-13, C-12, and C-11; H-11 to C-12, C-10, and C-20; H_3-19 to C-7, C-8, and C-9; H-7 to C-9, C-6, and C-19; H_3-18 to C-5, C-4, and C-3; and H-13 to C-14, and C-1 established the 14-membered ring structure of **1** (Figure 2). The isopropyl acid group was found based on the HMBC correlations observed from H_3-21 to C-1, C-15, and C-16; H-15 to C-1, C-2, C-21, and C-16. Furthermore, the methoxyl substituent was shown to be connected to position C-16 on the basis of the HMBC correlation between the oxymethyl protons (δ_H 3.68) and the carbonyl carbon (δ_C 178.9). The NMR spectra of compound **1** were almost identical with those of sinuflexibilin [20] with the exception that the *exo*-methylene proton resonances of the latter were replaced by a methyl doublet. The stereochemistry of **1** was determined on the basis of the chemical shift and NOESY spectrum (Figure 3). NOE correlations from H-3 to H-1, H-11, H_3-18 and from H-11 to H-20 indicated that all four hydroxy groups in **1** were β-oriented and H-1, H-3, H-11, H_3-18, and CH_3-20 were α-oriented with respect to this ring.

Table 1. ^{13}C NMR (125 MHz) data for compounds **1**–**5** in $CDCl_3$.

Position	1	2	3	4	5
1	38.4 CH	34.8 CH	39.4 CH	36.4 CH	40.9 CH
2	33.3 CH_2	37.2 CH_2	35.1 CH_2	36.6 CH_2	38.3 CH_2
3	71.0 CH	74.2 CH	71.7 CH	84.3 CH	116.6 C
4	75.7 C	76.3 C	75.2 C	74.3 C	131.1 C
5	39.4 CH_2	39.9 CH_2	35.2 CH_2	37.8 CH_2	139.5 CH
6	24.1 CH_2	23.7 CH_2	25.3 CH_2	23.9 CH_2	150.0 C
7	128.7 CH	128.9 CH	124.1 CH	124.6 CH	117.2 CH
8	133.9 C	135.4 C	135.9 C	134.5 C	71.5 C
9	35.6 CH_2	37.5 CH_2	39.5 CH_2	39.4 CH_2	40.9 CH_2
10	27.9 CH_2	28.8 CH_2	26.4 CH_2	22.4 CH_2	81.9 CH
11	70.6 CH	68.6 CH	126.1 CH	126.5 CH	75.4 CH
12	75.3 C	88.7 C	134.1 C	132.3 C	131.5 C
13	34.9 CH_2	33.2 CH_2	34.7 CH_2	26.8 CH_2	145.4 CH
14	22.2 CH_2	26.5 CH_2	28.2 CH_2	30.4 CH_2	32.5 CH_2
15	44.5 CH	42.2 CH_2	144.3 C	42.0 CH	147.3 C
16	178.9 C	181.5 C	168.8 C	175.1 C	112.9 CH_2
17	15.2 CH_3	11.0 CH_3	124.3 CH_2	16.3 CH_3	18.4 CH_3
18	23.6 CH_3	24.0 CH_3	23.4 CH_3	24.8 CH_3	162.2 C
19	17.0 CH_3	15.8 CH_3	16.4 CH_3	14.1 CH_3	30.3 CH_3
20	24.1 CH_3	23.1 CH_3	15.6 CH_3	15.2 CH_3	168.1 C
21	51.9 CH_3		52.0 CH_3		51.9 CH_3
22					50.2 CH_3

Table 2. ^{1}H NMR (500 MHz) data for compounds **1**–**5** in $CDCl_3$, δ in ppm and J in Hz.

Position	1	2	3	4	5
1	1.98 m	1.96 m	2.90 m	1.30 m	2.27 m
2	1.64 m	1.87 m	2.05 m	2.12 m	2.48 dd (8.0, 6.0)
	1.19 m	1.23 m	1.42 m		1.87 d (14.0)
3	3.65 d (10.5)	3.36 m	3.67 m	4.03 d (10.5)	
5	2.02 m	1.82 m	2.26 m	1.75 m	7.02 s
	1.57 m	1.42 m	1.48 m	1.65 m	
6	2.32 m	2.10 m	2.32 m	2.26 m	
	2.40 m	1.84 m	2.12 m	2.14 m	
7	5.43 t (6.5)	5.12 d (8.0)	5.11 m	5.06 t (8.0)	5.03 s
9	2.18 m	2.20 m	2.18 m	2.19 m	3.02 m
			2.09 m	1.98 m	1.94 dd (5.5, 9.0)
10	1.81 m	1.98 m	1.68 m	1.89 m	4.75 dd (5.5, 6.0)
	1.45 m	1.42 m	1.30 m		
11	3.52 d (10.0)	4.17 d (7.5)	5.11 m	5.12 t (7.0)	4.38 s
13	1.15 m	2.14 m	1.95 m	2.09 m	6.72 t (7.5)
	1.65 m	1.69 m		1.28 m	
14	1.47 m	1.90 m	1.25 m	1.77 m	2.77 m
		1.35 m		1.14 m	2.16 m
15	2.43 m	2.92 m		2.09 m	
16			6.25 s		4.70 s
			5.56 s		4.67 s
17	1.17 d (7.0)	1.28 d (7.5)		1.32 d (7.0)	1.64 s
18	1.08 s	1.25 s	1.04 s	1.39 s	
19	1.68 s	1.51 s	1.58 s	1.56 s	1.39 s
20	1.15 s	1.23 s	1.60 s	1.56 s	
21	3.68 s		3.76 s		3.69 s
22					3.06 s

Figure 2. Key HMBC correlations **1** and **5**.

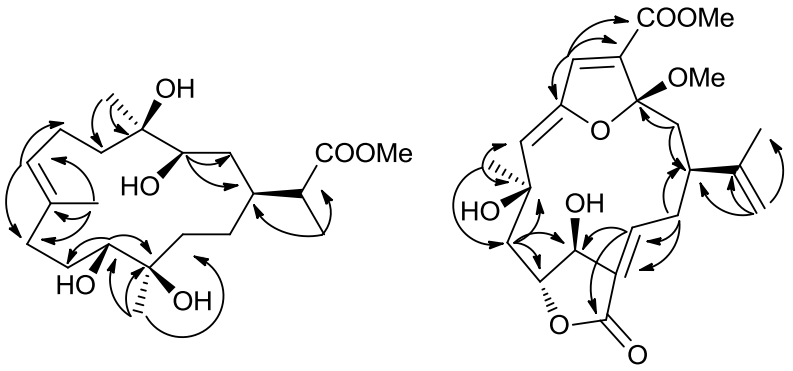
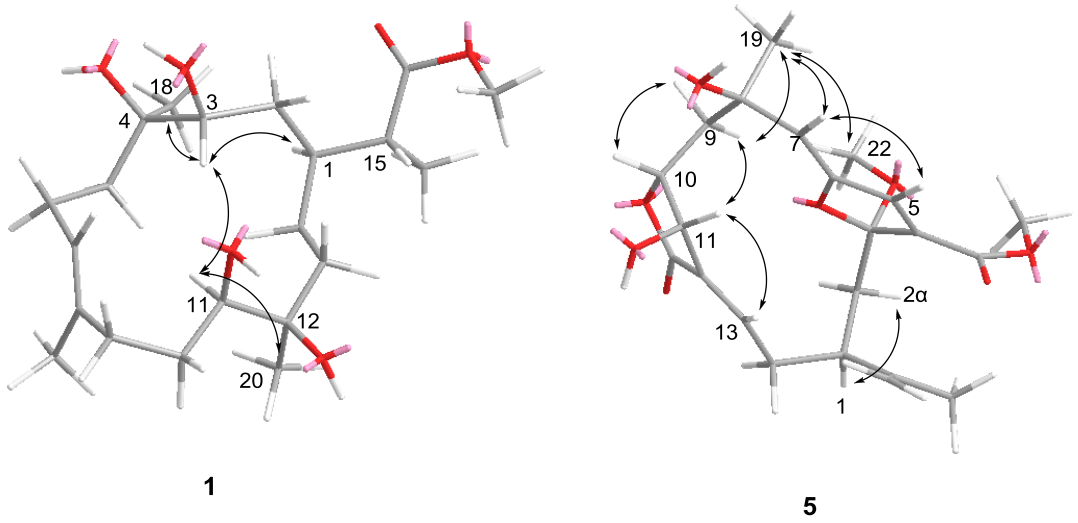


Figure 3. Key NOE correlations **1** and **5**.



1 **5**

Compound **2** was isolated as a colorless oil. The HRESIMS of **2** established its molecular formula as $C_{20}H_{34}O_5$, indicating four unsaturations. The ^{1}H and ^{13}C NMR spectra of **2** were similar to those of capillolide [21], with the exception that the *exo*-methylene proton resonances of the latter were replaced by a methyl doublet at δ 1.28 (3H, d, J = 7.5 Hz) coupled to a signal at δ 2.92. The relative stereochemistry of **2** was deduced mainly by NOESY and by comparison with that found for capillolide. Both H-3 and H-11 showed NOEs with H-1, which further correlated with H-15. Moreover, H_3-18 shared mutual NOE enhancement with H-3 and H-15. These observations indicated that all H-1, H-3, H-11, H_3-18, and H-15 were α-oriented with respect to this ring. Furthermore, it was found that the H_3-20 did not exhibit NOE response with H-11, indicating the β-configuration.

Compound **3** was isolated as a colorless oil. The HRESIMS of **3** established its molecular formula as $C_{21}H_{34}O_4$, indicating five unsaturations. The ^{1}H and ^{13}C NMR spectra of **3** were similar to those of pseudoplexauric acid methyl ester except for the downfield shifts of C-3 (62.8→71.7), C-4 (60.7→75.2), and C-18 (16.9→23.4) (Table 1) [22], which indicated that two hydroxylated carbons replaced the 3,4-epoxy carbons of the known analogue. This was also supported by the molecular weight of **3**, which was 18 amu higher than that of pseudoplexauric acid methyl ester, as indicated by the HRESIMS data. In the NOESY spectrum of **3**, H-3 showed NOE with H-1, but not with H-18, justifying the assigned relative stereochemistry at C-1, C-3, and C-4.

Compound **4** was isolated as a colorless oil. The HRESIMS of **4** established its molecular formula as $C_{20}H_{32}O_3$, indicating five unsaturations. The ^{1}H and ^{13}C NMR spectra of **4** were similar to those of 14-deoxycrassin [22,23], with the exception that the *exo*-methylene proton resonances of the latter were replaced by a methyl doublet at δ 1.32 (3H, d, J = 7.0 Hz) coupled to a signal at δ 2.09, which was confirmed by the HMBC experiment. Analyses of NOESY and NMR data revealed that the relative stereochemistry of **4** was the same as 14-deoxycrassin. The relative configuration of the secondary methyl group at C-15 was assigned to be on the same side as the H-1 proton of the δ-lactone ring by comparison of ^{1}H NMR spectral data with those of dihydrosinularin [δ 1.35 (3H, d, J = 7 Hz, H_3-17), 2.2 (1H, m, H-15)] and its 15-epimer [δ 1.21 (3H, H_3-17), 2.80 (1H, m, H-15)] [20,24].

Compound **5** was isolated as a colorless oil. The HRESIMS of **5** established its molecular formula as $C_{22}H_{28}O_8$, indicating nine unsaturations. The ^{1}H and ^{13}C NMR spectra of **5** showed great similarity

to those of 3α-ethoxyfuranocembrane [25] except that the ethoxyl was replaced by a methoxyl at C-3, and the acetoxy group was replaced by a hydroxy at C-11. The determination of the structure of **5** was further supported by detailed analysis of its 2D NMR data (Figure 2). The relative configuration of **5** was deduced by a NOESY experiment (Figure 3) and by comparison with those of 3α-ethoxyfuranocembranoid [25]. One proton attaching at C-2 and resonating at δ_H 2.48 was found to show NOE interactions with H-1 and was assigned arbitrarily as H-2α. The isopropenyl group located at C-1 should be β-oriented. NOE correlations between H-5 and H-7, H-7 and H-19 revealed the α-orientation of Me-19, and the *Z* configuration of the double bond $\Delta^{6(7)}$. The NOE interaction between H_3-19 and H_3-22 indicated the α-orientation of C-3. The trans-arrangement of H-10, and H-11 was implied by the coupling constant *J* (10, 11) ≈ 0 Hz. The NOE interaction between H-11 and H-13 indicated the *Z* configuration of the double bond at $\Delta^{12(13)}$ [25]. The 3α-ethoxyfuranocembranoid is an artifact created during isolation by reaction of the solvent ethanol with the natural product danielid [25]. However the danielid and its analogues have not been isolated in our investigation from *Sinularia* sp. In this context, whether compound **5** is created from danielid or its analogues remains to be established.

The identities of compounds **6**–**14** were established by comparison of their spectral data with those of the known compounds reported. They are capilloloid (**6**) [21], sethukarailin (**7**) [26], sinuladiterpenes I (**8**) [27], sinulaflexiolides H (**9**) [28], flexibilisin A (**10**) [29], (1*R*,13*S*,12*S*,9*S*, 8*R*,5*S*,4*R*)-9-acetoxy-5,8:12,13-diepoxycembr-15(17)-en-16,4-olide (**11**) [21], 11-*epi*-sinulariolide acetate (**12**) [30], flexibilide (**13**) [21], mandapamate (**14**) [31].

Compounds **1**–**14** were evaluated for inhibition of NF-κB activation using the cell-based HEK293 NF-κB luciferase reporter gene assay. The results showed that only **13** exhibited a potent effect with IC_{50} value of 5.30 μg/mL, while other compounds showed only marginal effects.

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. HR-ESI-MS data were measured on an AQUITY UPLC/Q-TOF micro spectrometer. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer. Optical rotations were measured on a PerKin Elmer 341 polarimeter using a 1 dm path length cell. ESI-MS data were measured on Bruker's amaZon SL ion trap LC/MS. Materials for column chromatography were silica gel (Qingdao Marine Chemical Factory, Qingdao, China), Sephadex LH20 (Amersham Pharmacia Biotech AB, Uppsala, Sweden), and YMC Gel ODS-A (YMC, MA, USA). The silica gel GF254 used for TLC was supplied by the Qingdao Marine Chemical Factory, Qingdao, China. HPLC was carried out on SHIMEDZU LC-10ATvp with YMC ODS SERIES.

3.2. Animal Material

The soft coral *Sinularia* sp. was collected from Dongluo Island, Hainan province of China in March 2010 (7–10 m depth) and identified by Professor Hui Huang, South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen (No. M100301) was deposited in the Key

Laboratory of Marine Bio-resources Sustainable Utilization, South China Sea Institute of Oceanology, Chinese Academy of Sciences, Guangzhou, China.

3.3. Extraction and Isolation

The soft coral *Sinularia* sp. (7 kg) was extracted three times with 95% EtOH. The extract was concentrated under reduced pressure, and partitioned between H_2O (4 L) and $CHCl_3$ (4 L); the $CHCl_3$ layer (101 g) was further partitioned between 85% EtOH (4 L) and petroleum ether (PE; 4 L) to yield 85% EtOH (30 g) and PE (55.3 g) fractions.

The PE extract was subjected to silica gel column chromatography, using a gradient of EtOAc in PE, to give 13 fractions (X1–X13). X8 (2.7 g) was subjected to silica gel column chromatography, using a gradient of EtOAc in PE, to give 7 fractions (X8-1–X8-7). X8-2 was purified by RP HPLC (70% MeOH in H_2O) to afford **7** (7.2 mg), and **11** (5.2 mg). X8-3 was purified by RP HPLC (70% MeOH in H_2O) to afford **9** (15.5 mg), and **12** (17.7 mg). X8-4 (430 mg) was further purified on a Sephadex LH20 column to give three subfractions (X8-4-1–X8-4-6). X8-4-2 was purified by RP HPLC (66.5% MeOH in H_2O) to afford **3** (5.1 mg). X8-4-6 was purified by RP HPLC (70% MeOH in H_2O) to afford **4** (15.0 mg). X8-6 was purified by RP HPLC (70% MeOH in H_2O) to afford **6** (11.7 mg).

The 85% EtOH extract was subjected to silica gel column chromatography, using a gradient of MeOH in $CDCl_3$, to give 12 fractions (Y1–Y12). Y3 (1.1 g) was subjected to silica gel column chromatography, using a gradient of EtOAc in PE, to give nine fractions (Y3-1–Y3-9). Y3-3 was further purified on a Sephadex LH20 column to give three subfractions (Y3-3-1–Y3-3-4). Y3-3-4 was purified by RP HPLC (66.5% MeOH in H_2O) to afford **5** (5.1 mg), and **10** (11.1 mg). Y3-7 was purified by RP HPLC (66.5% MeOH in H_2O) to afford **13** (5.0 mg), and **14** (4.8 mg). Y4 (1.2 g) was subjected to silica gel column chromatography, using a gradient of EtOAc in PE, to give six fractions (Y4-1–Y4-6). Y4-1 was purified by RP HPLC (55% MeOH in H_2O) to afford **2** (17.2 mg). Y4-3 was purified by RP HPLC (55% MeOH in H_2O) to afford **1** (4.3 mg), and **8** (3.9 mg).

Sinuflexibilin A (**1**): colorless oil; $[\alpha]_D^{25}$ = +16.7 (*c* = 0.03, $CHCl_3$); IR (KBr) ν_{max} 3364, 2967, 1709, 1650, 1453 cm^{-1}; ^1H and ^{13}C NMR in Tables 1 and 2; ESIMS *m*/*z* 409 $[M + Na]^+$, 795 $[2M + Na]^+$, HRESIMS *m*/*z* 409.2574 (calcd for $C_{21}H_{38}O_6Na$, 409.2566).

Sinuflexibilin B (**2**): colorless oil; $[\alpha]_D^{25}$ = +23.0 (*c* = 0.10, $CHCl_3$); IR (KBr) ν_{max} 3440, 2937, 1687, 1465 cm^{-1}; ^1H and ^{13}C NMR in Tables 1 and 2; HRESIMS *m*/*z* 377.2015 (calcd for $C_{20}H_{34}O_5Na$, 377.2018).

Sinuflexibilin C (**3**): colorless oil; $[\alpha]_D^{25}$ = +5.0 (*c* = 0.01, $CHCl_3$); IR (KBr) ν_{max} 3428, 2928, 1720, 1439 cm^{-1}; ^1H and ^{13}C NMR in Tables 1 and 2; HRESIMS *m*/*z* 373.2231 (calcd for $C_{21}H_{34}O_4Na$, 373.2202).

Sinuflexibilin D (**4**): colorless oil; $[\alpha]_D^{25}$ = +6.0 (*c* = 0.01, $CHCl_3$); IR (KBr) ν_{max} 3462, 2933, 1725, 1437 cm^{-1}; ^1H and ^{13}C NMR in Tables 1 and 2; HRESIMS *m*/*z* 343.2244 (calcd for $C_{20}H_{32}O_3Na$, 343.2249).

Sinuflexibilin E (**5**): colorless oil; $[\alpha]_D^{25}$ = +23.3 (*c* = 0.03, $CHCl_3$); IR (KBr) ν_{max} 3349, 2922, 1751, 1722, 1436 cm^{-1}; ^1H and ^{13}C NMR in Tables 1 and 2; HRESIMS *m*/*z* 443.1667 (calcd for $C_{22}H_{28}O_8Na$, 443.1682).

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 five new cembranes, sinuflexibilins A–E (**1**–**5**), along with nine other known diterpenoids (**6**–**14**). Compound **13** exhibited significant inhibition activity of NF-κB activation using the cell-based HEK293 NF-κB luciferase reporter gene assay with an IC_{50} of 5.30 μg/mL.

Acknowledgments

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References

1. Li, G.Q.; Zhang, Y.L.; Deng, Z.W.; van Ofwegen, L.; Proksch, P.; Lin, W.H. Cytotoxic cembranoid diterpenes from a soft coral *Sinularia gibberosa*. *J. Nat. Prod.* **2005**, *68*, 649–652.
2. Yang, B.; Zhou, X.F.; Lin, X.P.; Liu, J.; Peng, Y.; Yang, X.W.; Liu, Y.H. Cembrane diterpenes chemistry and biological properties. *Curr. Org. Chem.* **2012**, *16*, 1512–1539.
3. 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.
4. Li, Y.; Gao, A.H.; Huang, H.; Li, J.; Mollo, E.; Gavagnin, M.; Cimino, G.; Gu, Y.C.; Guo, Y.W. Diterpenoids from the Hainan soft coral *Sinularia parva*. *Helv. Chim. Acta* **2009**, *92*, 1341–1348.
5. Coll, J.C.; Price, I.R.; Konig, G.M.; Bowden, B.F. Algal overgrowth of alcyonacean soft corals. *Mar. Biol.* **1987**, *96*, 129–135.
6. Lu, Y.; Huang, C.Y.; Lin, Y.F.; Wen, Z.H.; Su, J.H.; Kuo, Y.H.; Chiang, M.Y.; Sheu, J.H. Anti-inflammatory cembranoids from the soft corals *Sinularia querciformis* and *Sinularia granosa*. *J. Nat. Prod.* **2008**, *71*, 1754–1759.

7. Cheng, S.Y.; Chuang, C.T.; Wen, Z.H.; Wang, S.K.; Chiou, S.F.; Hsu, C.H.; Dai, C.F.; Duh, C.Y. Bioactive norditerpenoids from the soft coral *Sinularia gyrosa*. *Bioorg. Med. Chem.* **2010**, *18*, 3379–3386.
8. Lu, Y.; Su, J.H.; Huang, C.Y.; Liu, Y.C.; Kuo, Y.H.; Wen, Z.H.; Hsu, C.H.; Sheu, J.H. Cembranoids from the soft corals *Sinularia granosa* and *Sinularia querciformis*. *Chem. Pharm. Bull.* **2010**, *58*, 464–466.
9. Liu, C.I.; Chen, C.C.; Chen, J.C.; Su, J.H.; Huang, H.H.; Chen, J.Y.F.; Wu, Y.J. Proteomic analysis of anti-tumor effects of 11-dehydrosinulariolide on CAL-27 cells. *Mar. Drugs* **2011**, *9*, 1254–1272.
10. Lin, Y.S.; Chen, C.H.; Liaw, C.C.; Chen, Y.C.; Kuo, Y.H.; Shen, Y.C. Cembrane diterpenoids from the Taiwanese soft coral *Sinularia flexibilis*. *Tetrahedron* **2009**, *65*, 9157–9164.
11. 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.
12. 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.
13. 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.
14. Iwagawa, T.; Shibata, Y.; Okamura, H.; Nakatani, M.; Shiro, M. Novel cembranoids with a 13-membered carbocyclic skeleton from a soft coral, *Sarcophyton* species. *Tetrahedron Lett.* **1994**, *35*, 8415–8416.
15. Lakshmi, V.; Kumar, R. Metabolites from *Sinularia* species. *Nat. Prod. Res.* **2009**, *23*, 801–850.
16. Ahmed, A.F.; Wen, Z.H.; Su, J.H.; Hsieh, Y.T.; Wu, Y.C.; Hu, W.P.; Sheu, J.H. Oxygenated cembranoids from a Formosan soft coral *Sinulatia gibberosa*. *J. Nat. Prod.* **2008**, *71*, 179–185.
17. Su, J.H.; Wen, Z.H. Bioactive cembrane-based diterpenoids from the soft coral *Sinularia triangular*. *Mar. Drugs* **2011**, *9*, 944–951.
18. Lin, Y.S.; Lee, N.L.; Lu, M.C.; Su, J.H. Two new cembrane-based diterpenoids from the marine soft coral *Sinularia crassa*. *Molecules* **2012**, *17*, 5422–5429.
19. 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.; Roth, G.P. 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.
20. Duh, C.Y.; Wang, S.K.; Tseng, H.K.; Sheu, J.H.; Chiang, M.Y. Novel cytotoxic cembranoids from the soft coral *Sinularia flexibilis*. *J. Nat. Prod.* **1998**, *61*, 844–847.
21. Su, J.Y.; Yang, R.L.; Kuang, Y.Y.; Zeng, L.M. A new cembranolide from the soft coral *Sinularia capillosa*. *J. Nat. Prod.* **2000**, *63*, 1543–1545.
22. Rodriguez, A.D.; Li, Y.X.; Dhasmana, H.; Barnes, C.L. New marine cembrane diterpenoids isolated from the Caribbean gorgonian *Eunicea mammosa*. *J. Nat. Prod.* **1993**, *56*, 1101–1113.
23. Rodriguez, A.D.; Martinez, N. Marine antitumor agents-14: Deoxycrassin and pseudoplexaurol, new cembranoid diterpenes from the Caribbean gorgonian *Pseudoplexaura porosa*. *Cell. Mol. Life Sci.* **1993**, *49*, 179–181.

24. Su, J.H.; Ahmed, A.F.; Sung, P.J.; Chao, C.H.; Kuo, Y.H.; Sheu, J.H. Manaarenolides A–I, diterpenoids from the soft coral *Sinularia manaarensis*. *J. Nat. Prod.* **2006**, *69*, 1134–1139.
25. Grote, D.; Dahse, H.M.; Seifert, K. Furanocembranoids from the soft corals *Sinularia asterolobata* and *Litophyton arboreum*. *Chem. Biodivers.* **2008**, *5*, 2449–2456.
26. Venkateswarlu, Y.; Sridevi, K.V.; Rao, M.R. New furanocembranoid diterpenes from the soft coral *Sinularia maxima*. *J. Nat. Prod.* **1999**, *62*, 756–758.
27. Lo, K.L.; Khalil, A.T.; Chen, M.H.; Shen, Y.C. New cembrane diterpenes from Taiwanese soft coral *Sinularia flexibilis*. *Helv. Chim. Acta* **2010**, *93*, 1329–1335.
28. Wen, T.; Ding, Y.; Deng, Z.W.; van Ofwegen, L.P.; Proksch, P.; Lin, W.H. Sinulaflexiolides A–K, cembrane-type diterpenoids from the Chinese soft coral *Sinularia flexibilis*. *J. Nat. Prod.* **2008**, *71*, 1133–1140.
29. Su, J.H.; Lin, Y.F.; Lu, Y.; Yeh, H.C.; Wang, W.H.; Fan, T.Y.; Sheu, J.H. Oxygenated cembranoids from the cultured and wild-type soft corals *Sinularia flexibilis*. *Chem. Pharm. Bull.* **2009**, *57*, 1189–1192.
30. Hsieh, P.W.; Chang, F.R.; McPhail, A.T.; Lee, K.; Wu, Y.C. New cembranolide analogues from the formosan soft coral *Sinularia flexibilis* and their cytotoxicity. *Nat. Prod. Res.* **2003**, *17*, 409–418.
31. Venkateswarlu, Y.; Biabani, M.A.F.; Reddy, M.V.R.; Rao, T.P.; Kunwar, A.C.; Faulkner, D.J. Mandapmate, a diterpenolid from the soft coral *sinularia dissecta*. *Tetrahedron Lett.* **1994**, *35*, 2249–2252.