

Article

New Briarane Diterpenoids from the Gorgonian Coral *Junceella juncea*

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Abstract: Chemical investigation of *Junceella juncea* has resulted in the isolation of three new briaranes designated juncenolides M–O (**1–3**). The structures of these compounds were determined by spectroscopic analysis including 2D-NMR (COSY, HMBC and NOESY) and HRMS. Compound **1** is a new chlorinated briarane while compound **3** contains a rare methyl ester at C-16. The anti-inflammatory activities tested on superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB were evaluated.

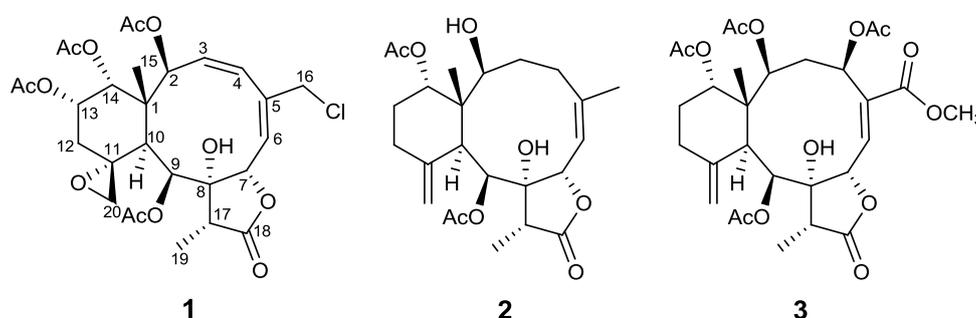
Keywords: *Junceella juncea*; briaranes; anti-inflammatory activity

1. Introduction

Gorgonian corals of the genus *Junceella* (Ellisellidae) are common in subtropical and tropical waters in a number of places around the world, such as the South China Sea and Indo-Pacific Ocean, and are well known as a source of highly oxidized diterpenes of the briarane class (3,8-cyclized cembranoids) [1]. Many *in vitro* and *in vivo* studies on diterpenes isolated from gorgonians showed a variety of biological activities including anti-tumor, anti-inflammatory, antiplasmodial, antibacterial, antiviral, antimalarial

and antioxidant, as well as ecologically relevant activities such as fish-feeding deterrence. Diterpenes isolated from gorgonian corals have a large structural diversity with 40 different diterpene classes being represented [2]. Recently, three new 8-hydroxybriarane diterpenoids (junceols A–C) and four new briarane diterpenoids (juncenolides H–K) were reported from a chemical investigation of *Junceella juncea* Pallas collected off the southern Taiwan coast, and some of these metabolites were found to exhibit inhibitory effects on superoxide anion generation and elastase release by human neutrophils [3,4]. Fourteen new briarane diterpenes, juncins O–ZII, were isolated from the EtOH/CH₂Cl₂ extract of a South China Sea sample of *J. juncea* and some of them have been shown to exhibit potent antifouling and antifeedant activities [5–7]. A bioassay-guided fractionation of the acetone extract of a Taiwanese collection of *J. juncea* led to the identification of seven new diterpenoids, juncenolides A–G [8–11]. Moreover, a chemical investigation of the Indian Ocean gorgonian *J. juncea* resulted in the isolation of eight new briarane-type diterpenoids, juncins G–N [12–14]. A new briarane diterpenoid with antifungal activity was also isolated [15]. In continuation of our research programs oriented towards discovering new metabolites from the gorgonians collected off Taiwanese waters, we reinvestigated *J. juncea*. Examination of different chromatographic fractions of an AcOEt-soluble extract of the Taiwanese *J. juncea* Pallas resulted in the isolation of three new briaranes, designated juncenolides M–O (**1–3**) (Figure 1). Their structures were elucidated through detailed spectroscopic analyses, mainly 2D NMR experiments (¹H, ¹H COSY, HQMC, HMBC). The relative stereochemistry of the chiral centers and the geometry of the double bonds were deduced from NOESY spectra.

Figure 1. Structures of compounds **1–3**.



2. Results and Discussion

Compound **1** was isolated as a colorless amorphous solid. The molecular formula was determined to be C₂₈H₃₅ClO₁₂ (11 degrees of unsaturation) from the HR-ESI-MS data (*m/z* 621.1711 ([M + Na]⁺)), which also showed a M + 2 peak at *m/z* 623.1685 (3:1), indicating the presence of one chlorine atom. Its IR bands revealed the presence of a hydroxyl group (3402 cm⁻¹), a five-membered lactone (1779 cm⁻¹) and ester groups (1741 cm⁻¹). ¹H- and ¹³C-NMR data (Tables 1 and 2) indicated the presence of four acetates (δ_{H} 2.18, s; 2.07, s; 1.97, s; 1.95, s) and δ_{C} 170.2 \times 2; 170.0 \times 2; 21.6; 21.3; 21.0; 20.8, one carbonyl carbon (δ_{C} 175.3), and two double bonds (δ_{C} 126.1; 128.1; 131.7; 140.0), suggesting four rings in the structure. The protons of CH₂-20 (δ_{H} 3.54, br. s; 2.74, br. s), its corresponding carbon (δ_{C} 50.2) and the quaternary carbon at δ_{C} 58.1, were assigned to an exocyclic epoxide [16]. The presence of a γ -lactone ring was ascertained by the carbonyl carbon at δ_{C} 175.3 (C-18), and the O-bearing carbons at δ_{C} 78.5 (C-7) and 81.2 (C-8), and confirmed the HMBC correlations (Figure 2) of Me-19/C-8, C-17,

C-18 and C-7/C-8, C-18 [16,17]. Four OAc groups were attached to C-2, C-9, C-13 and C-14 by the observation of HMBC correlations (Figure 2). A tertiary methyl signal (δ_{H} 1.09, Me-15) correlated with a quaternary carbon (C-1), two oxymethines at δ_{C} 74.2 and 73.8, and the CH at δ_{C} 41.4, (C-10), implying oxygenation at C-2 and C-14. HMBC correlations of Me-15/C-1, C-2, C-10, C-14, CH₂-16/C-4, C-5, C-6, CH-7/C-5, C-8, C-18, CH-9/C-8, C-11, and CH-10/C-1, C-8, C-11, C-20, as well as ¹H–¹H COSY connectivities between CH-2/CH-3/CH-4, CH-6/CH-7, CH-9/CH-10, CH₂-12/CH-13/CH-14 (Figure 1), suggested that compound **1** possesses 8-hydroxybriarane-type diterpenoid skeleton together with an exocyclic epoxy group which was corroborated by HMBC correlations of CH₂-12/C-11, C-20.

Table 1. ¹H NMR Data of Compounds **1–3**. δ in ppm, J in Hz.

Position	1 ^a	2 ^b	3 ^b
2	5.37 (d, $J = 9.6$)	4.94 (overlap)	4.86 (d, $J = 7.6$)
3	5.62 (t, $J = 9.6$)	1.74–1.78 (m) 2.46–2.50 (m)	2.13–2.16 (m) 2.72 (t, $J = 10.0$)
4	6.35 (d, $J = 9.6$)	2.19–2.15 (m) 2.64 (br. d, $J = 13.6$)	5.91–5.94 (m)
6	6.00 (d, $J = 9.0$)	5.67 (d, $J = 10.4$)	7.06 (d, $J = 10.0$)
7	4.95 (d, $J = 9.0$)	5.26 (d, $J = 10.4$)	5.62 (d, $J = 10.0$)
9	4.71 (d, $J = 4.8$)	5.31 (d, $J = 6.0$)	5.56 (d, $J = 2.8$)
10	3.04 (d, $J = 4.8$)	3.45 (d, $J = 6.0$)	3.25 (d, $J = 2.8$)
12	1.34–1.38 (m) 2.48 (d, $J = 14.0$)	2.16–2.19 (m) 2.34–2.36 (m)	2.18–2.23 (2H, m)
13	4.96 (overlap)	1.82–1.86 (m) 1.97–1.99 (m)	1.80–1.87 (2H, m)
14	5.20 (br. s)	4.59 (br. s)	4.69 (br. s)
15	1.09 (s)	1.12 (s)	1.03 (s)
16	4.58 (2H, s)	2.05 (s)	-
17	2.26 (q, $J = 6.9$)	2.46 (q, $J = 6.8$)	2.63 (q, $J = 6.8$)
19	1.13 (d, $J = 6.9$)	1.11 (d, $J = 6.8$)	1.19 (d, $J = 6.8$)
20	2.74 (br. s) 3.54 (br. s)	4.92 (s) 5.05 (s)	4.95 (s) 5.05 (s)
AcO-2	1.95 (s)	-	1.97 (s)
AcO-4	-	-	2.06 (s)
AcO-9	2.18 (s)	2.20 (s)	2.21 (s)
AcO-13	2.07 (s)	-	-
AcO-14	1.97 (s)	1.92 (s)	1.90 (s)
OMe-16	-	-	3.83 (s)

^a Recorded in CDCl₃ at 300 MHz; ^b Recorded in CDCl₃ at 400 MHz.

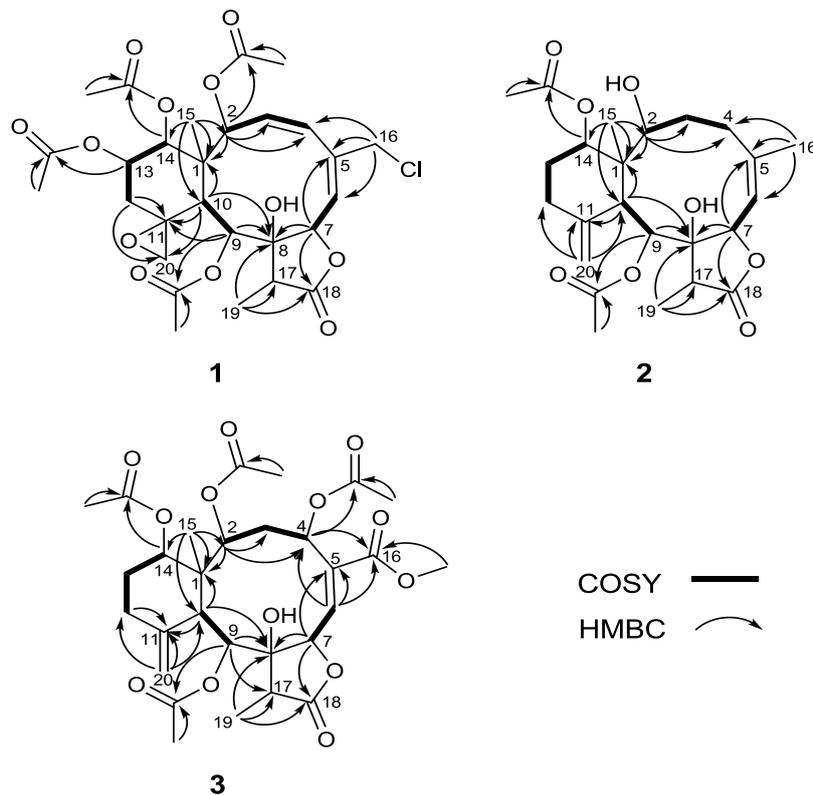
Table 2. ¹³C-NMR Data of Compounds **1–3**. δ in ppm.

Position	1 ^a	2 ^b	3 ^b
1	46.5 (s)	46.9 (s)	47.8 (s)
2	74.2 (d)	75.7 (d)	72.1 (d)
3	131.7 (d)	31.3 (t)	37.3 (t)
4	128.1 (d)	29.2 (t)	67.4 (d)
5	140.0 (s)	144.8 (s)	136.8 (s)
6	126.1 (d)	120.5 (d)	139.1 (d)
7	78.5 (d)	77.8 (d)	76.7 (d)

Table 2. Cont.

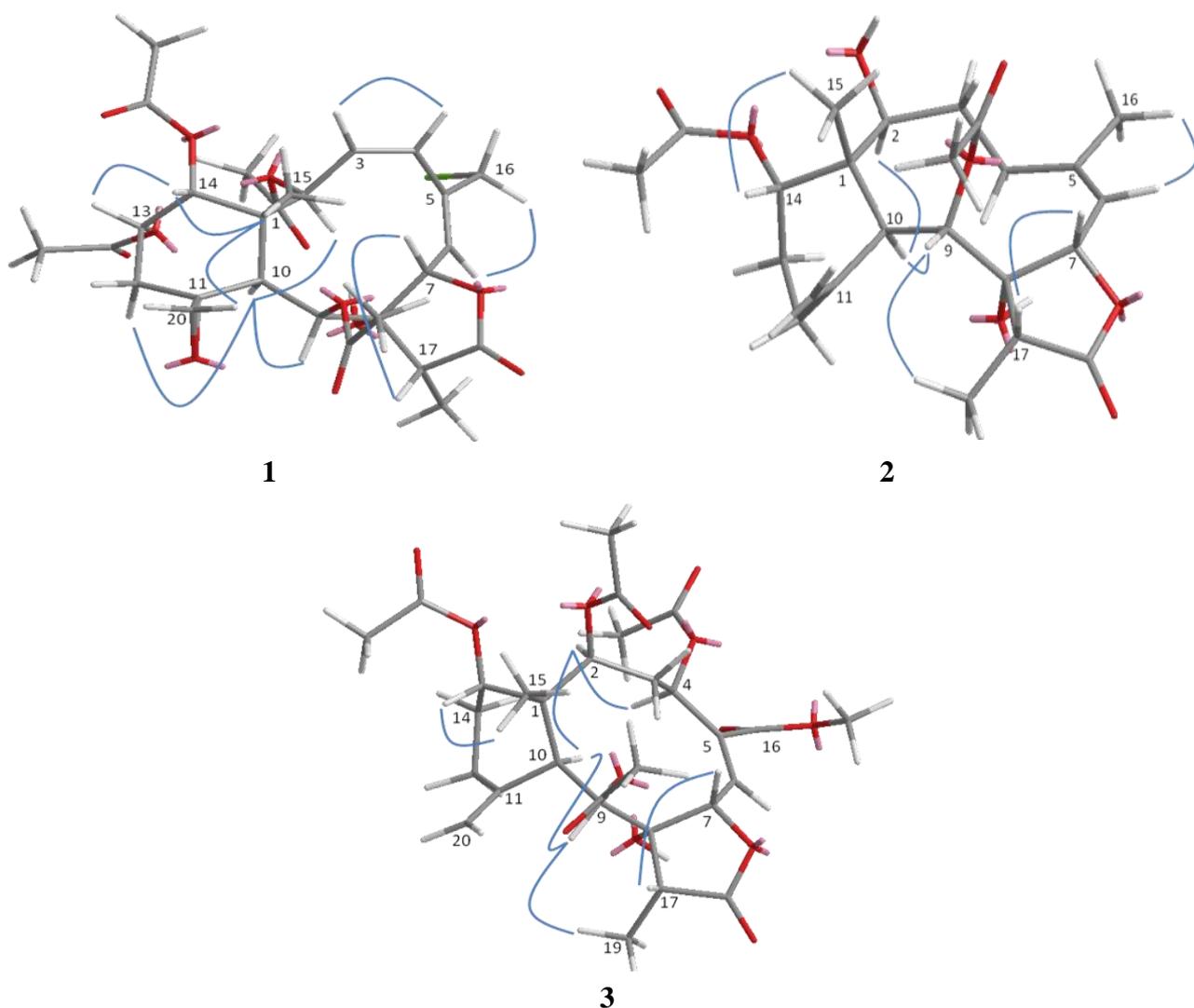
8	80.8 (s)	83.0 (s)	82.9 (s)
9	64.3 (d)	71.3 (d)	72.7 (d)
10	35.7 (d)	41.8 (d)	42.6 (d)
11	58.1 (s)	150.8 (s)	150.5 (s)
12	34.3 (t)	26.3 (t)	29.2 (t)
13	67.7 (d)	26.9 (t)	27.5 (t)
14	73.8 (d)	74.5 (d)	74.0 (d)
15	14.4 (q)	15.4 (q)	14.4 (q)
16	44.7 (t)	27.2 (q)	166.6 (s)
17	43.9 (d)	42.5 (d)	43.3 (d)
18	175.3 (s)	175.9 (s)	175.3 (s)
19	6.3 (q)	6.5 (q)	6.4 (q)
20	50.2 (t)	113.3 (t)	113.3 (t)
AcO-2	170.2 (s)	-	169.9 (s)
	20.8 (q)		20.8 (q)
AcO-4	-	-	169.6 (s)
			21.2 (q)
AcO-9	170.0 (s)	169.3 (s)	169.2 (s)
	21.6 (q)	21.7 (q)	21.7 (q)
AcO-13	170.0 (s)	-	-
	21.3 (q)		
AcO-14	170.2 (s)	170.4 (s)	170.5 (s)
	21.0 (q)	21.2 (q)	21.1 (q)
OMe-16	-	-	52.8 (q)

^a Recorded in CDCl₃ at 75 MHz; ^b Recorded in CDCl₃ at 100 MHz.

Figure 2. Key ¹H–¹H COSY and HMBC correlations of 1–3.

The relative configuration of **1** was determined on the basis of NOESY experiment, MM2 minimized energy calculated molecular modeling (Figure 3), and comparison with other naturally occurring briarane diterpenoids. Briarane-type diterpenoids were previously reported to contain the Me-15 in the β -orientation and H-10 in the α -orientation. As expected, there is no NOE correlation between CH-10 and Me-15. The orientations of CH-10 and the methyl group Me-15 should be opposite. According to MM2 study, we thus concluded that compound **1** had the Me-15 in the β -orientation and CH-10 in the α -orientation as reported [18]. NOESY correlations of CH-10/H-2, CH-9, CH $_{\alpha}$ -12, Me-15/CH $_2$ -20, CH-14, CH $_2$ -20/CH-13, CH $_{\beta}$ -12 and CH-14/CH-13 suggested the β -orientation of CH-13 and CH-14 and α -orientation of CH-2 and CH-9, a β -oriented exocyclic epoxy group attached to cyclohexane moiety as previously assigned from the ^1H - and ^{13}C NMR data of C-11 and C-20 [19] and the α -orientation of CH-2. The *cis* configuration of the C-3/C-4 double bond was suggested by the NOESY correlations (Figure 3) between CH-3/CH-4 and the *J* value (9.6 Hz). Compound **1** appears to be the chlorinated derivative of juncenolide B isolated from the same species previously [9]. They have the same configuration of chiral centers. Based on the above interpretation, compound **1** is a new chlorinated briarane-type diterpene designated juncenolide M.

Figure 3. Key NOESY correlations of compounds **1–3** in molecular modeling.



Compound **2**, isolated as a colorless solid, and had a molecular formula of $C_{24}H_{34}O_8$, deduced from HR-ESI-MS at m/z 473.2155 ($[M + Na]^+$), showing eight degrees of unsaturation. The presence of hydroxyl, a γ -lactone ring, and ester groups were consistent with IR absorptions at 3481, 1772 and 1732 cm^{-1} . The 1H and ^{13}C NMR (Tables 1 and 2), revealed the presence of an exomethylene (δ_C 150.8, 113.3), one trisubstituted double bond (δ_C 144.8, 120.5), two OAc carbonyl (C=O) (δ_C 170.4, 169.3) and one γ -lactone carbonyl (C=O) (δ_C 175.9), which accounted for five degrees of unsaturation and were suggestive of a tricyclic briarane bearing a γ -lactone ring. The carbonyl signal at δ_C 175.9 (C-18) was ascribed to a γ -lactone ring with the oxymethine at δ_C 78.3 (C-7) and the *O*-bearing quaternary carbon at δ_C 82.2 (C-7). The proton singlets at δ_H 5.05 and 4.92 (δ_C 113.3) were assigned to the exocyclic methylene group and correlated to C-10, C-12, and C-11 in the HMBC spectrum (Figure 2), suggesting the presence of a C-11/C-20 double bond. HMBC correlations of Me-15/C-1, C-2, C-14, C-10, Me-16/C-4, C-5, C-6, CH-7/C-5, C-8, C-18, CH-9/C-8, CH-10/C-11, C-1, C-8 and the 1H , 1H COSY correlations of CH-2/CH₂-3/CH₂-4, CH-6/CH-7, CH-9/CH-10, CH₂-12/CH₂-13/CH-14 revealed the tricyclic skeleton of **2**. Furthermore, two OAc groups positioned at C-9 and C-14 were established by the key correlations observed in the HMBC spectrum of **2**. NOESY experiment revealed that the absence of correlation between and suggested orientation of and disposition of compound **2**. The NOESY correlations (Figure 3) between Me-15/CH-14; CH-10/CH-2, CH-9, CH-9/Me-19, and CH-7/CH-17 were in agreement with the β -orientation of CH-7, CH-14 and CH-17, and α -orientation of CH-2, CH-9 and Me-19. Therefore, compound **2** is a new tricyclic briarane bearing a γ -lactone ring, and was given the name of juncenolide N.

The molecular formula of **3** was established as $C_{29}H_{38}O_{13}$ from the molecular peak at m/z 617.2212 $[M + Na]^+$ in the HR-ESI-MS. The NMR data (Tables 1 and 2) revealed the basic features of a 8-hydroxybriarane type diterpenoid with a γ -lactone, one exomethylene double bond, one trisubstituted double bond (Tables 1 and 2), and four acetate esters. The C-20/C-11 exomethylene double bond was assigned with the aid of HMBC correlations of CH₂-20/C-10, C-11, C-12. The signal of CH-6 showed correlations to C-4, C-5 and C-16 in HMBC, revealing the C-5/C-6 trisubstituted double bond, and a COOMe group attached to C-5 (Figure 2). The four acetates were deduced to be located at C-2, C-4, C-9, and C-14 by HMBC correlations of the oxymethines at δ_H 4.86 (CH-2), 5.93 (CH-4), 5.56 (CH-13), and 4.69 (CH-14) to their respective acetate carbonyls. The 1H , 1H COSY connectivities (Figure 2) of CH-2/CH₂-3/CH-4, CH-6/CH-7, CH-9/CH-10, CH₂-12/CH₂-13/CH-14, as well as HMBC correlations of Me-15/C-1, C-2, C-10, C-14, CH-4/C-16, CH-7/C-8, C-18, CH-9/C-8, C-17, CH-10/C-1, C-8, C-11, CH₂-12/C-11 and Me-19/C-8, C-17, C-18, confirmed the tricyclic skeleton of **3**. The NOESY experiments (Figure 3) showed the relative configuration of compound **3**. Due to the α -orientation of CH-10, the methyl group Me-15 at the ring junction should be β -oriented as no NOE correlation was observed between CH-10 and Me-15. NOESY spectrum clearly displayed the interactions between Me-15/CH-14, CH-10/CH-9, CH-2, CH-2/CH-4, and CH-9/CH-19, indicating that the OAc at C-2, C-4 and C-9 are β -oriented, whereas the OAc at C-14 is in the α -position. Thus, compound **3** is a new briarane ester with a γ -lactone skeleton, and designated juncenolide O.

The isolated briaranes **1–3** were tested on inhibitory effects of superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB at a concentration of $10\text{ }\mu\text{g/mL}$. As illustrated in Table 3, compounds **2** and **3** showed moderate inhibitory activities against elastase release

with $29.0 \pm 5.6\%$, and $35.9 \pm 7.4\%$, respectively. Furthermore, compound **3** also exhibited moderate inhibitory activity against superoxide anion with $27.6 \pm 7.0\%$.

Table 3. Effects of compounds **1–3** on superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB ^a.

Compounds	Superoxide anion	Elastase release
	Inhibition (%) ^b	Inhibition (%)
1	7.6 ± 2.8	15.9 ± 5.5
2	6.7 ± 2.9	29.0 ± 5.6
3	27.6 ± 7.0	35.9 ± 7.4
Genistein	65.0 ± 5.7	51.6 ± 5.9

^a Results are presented as mean \pm S.E.M. ($n = 3$); ^b Percent of inhibition at 10 $\mu\text{g/mL}$.

3. Experimental Section

3.1. General

Column chromatography (CC); silica gel 60 (Merck, Darmstadt, Germany) and Sephadex LH-20 (Amersham Pharmacia Biotech AB, Uppsala, Sweden). Prep. TLC: pre-coated silica gel plates (Merck; silica gel 60 F-254, 1 mm). LiChrospher Si 60 (5 μm , 250-10, Merck) and LiChrospher 100 RP-18e (5 μm , 250-10, Merck) were used for NP-HPLC and RP-HPLC (Merck, Darmstadt, Germany), respectively. Spray reagent: *p*-anisaldehyde reagent with 5% H_2SO_4 . Optical rotations: Jasco DIP-1000 polarimeter. UV Spectra: Hitachi U-3210 spectrometer; λ_{max} (log ϵ) in nm. IR Spectra: Hitachi T-2001 spectrometer; in cm^{-1} . ¹H-, ¹³C-NMR, COSY, HMQC, HMBC, and NOESY experiments: Bruker Avance 300 NMR spectrometer or Varian MR 400 NMR spectrometer, SiMe_4 as internal standard; δ in ppm, coupling constants *J* in Hz. LRESIMS and HRESIMS: JEOL JMS-HX 110 mass spectrometer; in *m/z*.

3.2. Animal Material

The gorgonian *Junceella juncea* Pallas (Ellisellidae) was collected in Tai-Tong County, Taiwan, by scuba diving at a depth of 15 m, in November 2006. The fresh gorgonian was immediately frozen after collection and kept at $-20\text{ }^\circ\text{C}$ until processed. This species was identified by one of the authors (C.-C.L). A voucher specimen (WSG-5) was deposited in the School of Pharmacy, College of Medicine, National Taiwan University, Taiwan.

3.3. Extraction and Isolation

The outer grey layer of the gorgonian (1.4 kg, wet weight) was extracted with acetone ($3 \times 500\text{ mL}$) at r.t., and the acetone extract was concentrated under vacuum. The crude extract (8 g) was partitioned between AcOEt and H_2O (1:1). The AcOEt-soluble portion (4.9 g) was subjected to column chromatography (SiO_2 , *n*-Hexane/AcOEt 10:1–0:1; TLC (GF₂₅₄) monitoring) giving fractions 1-16. Fr. 12 (195 mg) was subjected to a NP-HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 150:1), affording Fr. 12a (12 mg) which was further purified by RP-HPLC ($\text{MeOH}/\text{H}_2\text{O}/\text{CH}_3\text{CN}$, 70:25:5) yielding compound **1** (6 mg). Fr. 16 (105 mg) was separated by NP-HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 80:1), giving Fr. 16a (38 mg) which was

subjected to RP-HPLC (MeOH/H₂O/CH₃CN, 55:40:5), yielding Fr. 16b (10 mg) that was further purified by RP-HPLC (MeOH/H₂O/CH₃CN, 55:40:5) furnishing compounds **2** (4 mg) and **3** (2 mg).

Juncenolide M (**1**): colorless amorphous solid; $[\alpha]_D^{25} = -42$ (*c* 0.05, CH₂Cl₂); UV (MeOH): 221 (3.20); IR (neat): 3402 (OH), 2930, 2853, 1779 (C=O γ -lactone), 1741 (C=O ester) cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) data, see Table 1; ¹³C-NMR (75 MHz, CDCl₃) data, see Table 2; HR-ESI-MS [M + Na]⁺ *m/z* 621.1711 (calcd. 621.1715, C₂₈H₃₅ClO₁₂Na).

Juncenolide N (**2**): colorless amorphous solid; $[\alpha]_D^{25} = -60$ (*c* 0.05, CH₂Cl₂); UV (MeOH): 204 (3.90); IR (neat): 3481 (OH), 1772 (C=O γ -lactone), 1732 (C=O ester) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) data, see Table 1; ¹³C-NMR (100 MHz, CDCl₃) data, see Table 2; HR-ESI-MS [M + Na]⁺ *m/z* 473.2155 (calcd. 473.2151, C₂₄H₃₄O₈Na).

Juncenolide O (**3**): colorless amorphous solid; $[\alpha]_D^{25} = +4$ (*c* 0.05, CH₂Cl₂); UV (MeOH): 220 (3.80), 205 (3.90); IR (neat): 3423 (OH), 3020, 2921, 2850, 1780 (C=O γ -lactone), 1738 (C=O ester) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) data, see Table 1; ¹³C-NMR (100 MHz, CDCl₃) data, see Table 2; HR-ESI-MS [M + Na]⁺ *m/z* 617.2212 (calcd. 617.2210, C₂₉H₃₈O₁₃Na).

3.4. Anti-Inflammatory Assays

Neutrophils were obtained by means of dextran sedimentation and Ficoll centrifugation. Superoxide generation and elastase release were carried out according to a procedure described previously [20]. Superoxide anion production was assayed by monitoring the superoxide dismutase-inhibitable reduction of ferricytochrome *c*. Elastase release experiments were performed using MeO-Suc-Ala-Ala-Pro-Valp-nitroanilide as the elastase substrate. Genistein was used as a positive control.

4. Conclusions

Three new diterpenoids, named juncenolides M–O (**1–3**), were isolated from the Taiwanese gorgonian *Junceella juncea* Pallas. Compound **1** is a new chlorinated briarane, compound **2** is a new briarane with a free hydroxy at C-2, while compound **3** contains a rare methyl ester at C-5. The anti-inflammatory activities tested on superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB were evaluated. As a result, compounds **2** and **3** showed moderate inhibitory activities against elastase release at 10 μ g/mL.

Acknowledgements

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