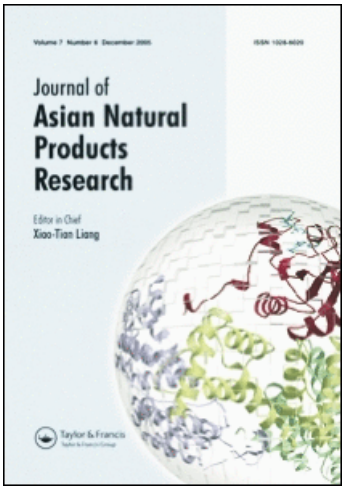

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Two new sesquiterpenoids from the soft coral *Sinularia polydactyla* (Ehreberg)

Cui-Xian Zhang[ab], Chen-Chen Zhu[a], Su-Jun Yan[b], Jun Li[b], Jing-Yu Su[b], Yong-Ju Liang[c], Xiao-Ping Yang[c], Kang-Cheng Zheng‡ and Long-Mei Zeng[b]*

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Two new sesquiterpenoids, polydactins A (**1**) and B (**2**) and a known sesquiterpene, 10α-hydroxycadin-4-en-15-al (**3**), were isolated from the soft coral *Sinularia polydactyla* (Ehreberg). Their structures were determined mainly by spectroscopic methods. Polydactin A (**1**) showed moderate cytotoxic activities against human oral epidermoid carcinoma cell lines (KB) and human breast carcinoma (MCF) tumour cell lines (*in vitro*).

Keywords: soft coral; *Sinularia polydactyla*; sesquiterpenoids; anti-tumour; polydactin A; polydactin B

1. Introduction

The corals and marine sponges are abundant natural resources in the South Sea of China. Many bioactive terpenoids have been found from these marine organisms.[1–7] As a part of our continuing search for bioactive substances from marine organisms, the soft coral *Sinularia polydactyla* (Ehreberg) was investigated. Bowden *et al.*[8] and Duh *et al.*[9] have isolated five diterpenes and two norditerpenes from this soft coral, respectively. In our study, two new sesquiterpenes, named polydactins A (**1**) and B (**2**), together with a known sesquiterpene, 10α-hydroxycadin-4-en-15-al (**3**)[10] were isolated but no diterpenes were found from the same soft coral. Bioassay exhibited that **1** has moderate cytotoxic activities against human oral epidermoid carcinoma cell lines (KB) and human breast carcinoma (MCF) tumour cell lines.

2. Results and discussion

Polydactin A (**1**) was isolated as colourless oil. HREI-MS established the molecular formula $C_{14}H_{22}O_2$ with four degrees of unsaturation. NMR spectral data suggested the presence of an α,β-conjugated keto group [δ_C 203.6 (s), 153.7 (d), 130.3 (d); δ_H 6.34 (1H, dd, $J = 16.0$, 10.5 Hz), 5.94 (1H, d, $J = 16.0$ Hz), a secondary hydroxyl carbon [δ_C 75.4 (d); δ_H 3.81 (1H, dd, $J = 4.5$, 10.0 Hz)], an isopropyl group [δ_C 31.5 (d), 20.6 (q), 20.8 (q); δ_H 1.62 (1H, m), 0.93 (3H, d, $J = 6.0$ Hz), 0.85 (3H, d, $J = 6.0$ Hz)] and a terminal double bond [δ_C 151.9 (s), 112.7 (t); δ_H 5.33 (1H, d, $J = 2.0$ Hz), 5.14 (1H, d, $J = 2.0$ Hz)]. According to the molecular formula and the functionalities mentioned above, compound **1** was suggested to be monocyclic nor-sesquiterpene.

The gross structure of **1** was determined by a detailed analysis of 1D and 2D NMR spectra. The HMQC experiment led to the assignment of all the protons (Table 1). $^1H-^1H$ COSY revealed the sequences of the correlations depicted by the bold lines in Figure 2. The three sequences along with the functions mentioned above were assembled by HMBC correlations from H-14 to C-3 and C-5; H-3 to C-4; H-5 to C-4; H-1 to C-10; H-9 to C-10; H-7 to C-8 and H-8 to C-11 permitted the connectivity of the isolated spin systems (Figure 2).

The relative stereochemistry of **1** was established through the coupling constant and NOESY spectrum. An *E*-configuration for the $\Delta^{8,9}$ double bond was determined by the large coupling constant between H-8 and H-9 ($J = 16.0$ Hz). A NOESY interaction between H-3 (δ_H 3.81)/Hb-5 (δ_H1.65), Hb-5/H-7 (δ_H 1.97) and Ha-5 (δ_H 2.64)/H-11 (δ_H1.62) (Figure 3) revealed that H-3 and H-7 were located on the same face of the molecule. Thus, the structure of polydactin A (**1**) was determined as shown in Figure 1.

Polydactin B (**2**) was a pale yellow transparent oil. HREI-MS established the molecular formula $C_{15}H_{26}O_2$ with three degrees of unsaturation. ^1H NMR and ^{13}C NMR spectral data suggested the presence of two secondary hydroxyl carbons [δ_C 78.9 (d), 67.0 (d); δ_H 3.41 (1H, dd, $J = 5.0$, 11.5 Hz), 3.71 (1H, t, $J = 10.0$ Hz)], an isopropyl group [δ_C 25.9 (d), 21.0 (q), 16.1 (q); δ_H 2.20 (1H, m), 0.93 (3H, d, $J = 7.0$ Hz); 0.86 (3H, d, $J = 7.0$ Hz)], and a terminal double bond

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Table 1. ^{1}H NMR and ^{13}C NMR spectral data of compounds **1** and **2** (recorded at 500/125 MHz in $CDCl_3$; δ in ppm, J in Hz).

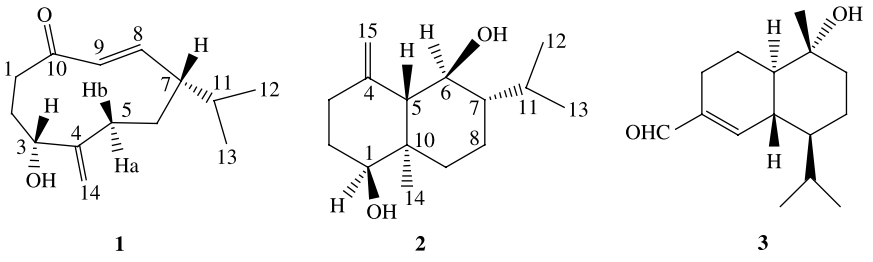
	1		**2**	
Position	^{13}C	^{1}H (J in Hz)	^{13}C	^{1}H (J in Hz)
1	36.2 (CH_2)	2.99 m 2.25 m	78.9 (CH)	3.41 dd (5.0, 11.5)
2	31.4 (CH_2)	2.05 m	31.8 (CH_2)	1.58 m 1.87 m
3	75.4 (CH)	3.81 dd (10.0, 4.5)	35.0 (CH_2)	2.14 m 2.06 m
4	151.9 (C)		146.1 (C)	
5	33.5 (CH_2)	2.64 m, Ha 1.65 m, Hb	55.7 (CH)	1.74 d (10.0)
6	34.9 (CH_2)	2.12 m 1.72 m	67.0 (CH)	3.71 t (10.0)
7	53.0 (CH)	1.97 m	49.2 (CH)	1.28 m
8	153.7 (CH)	6.34 dd (16.0, 10.5)	18.0 (CH_2)	1.50 m 1.26 m
9	130.3 (CH)	5.94 d (16.0)	36.2 (CH_2)	1.91 m 1.16 dd (3.0, 11.0)
10	203.6 (C)		41.6 (C)	
11	31.5 (CH)	1.62 m	25.9 (C)	2.20 m
12	20.6 (CH_3)	0.93 d (6.0), 3H	16.1(CH_3)	0.86 d (7.0), 3H
13	20.8 (CH_3)	0.85 d (6.0), 3H	21.0 (CH_3)	0.93 d (7.0), 3H
14	112.7 (CH_2)	5.33 d (2.0) 5.14 d (2.0)	11.5 (CH_3)	0.70 s, 3H
15			107.7 (CH_2)	5.01 s, Ha 4.73 s, Hb

[δ_C 146.1 (s), 107.7 (t); δ_H 5.01 (1H, s), 4.73 (1H, s)]. According to the molecular formula and the functionalities mentioned above, compound **2** was suggested to be a bicyclic sesquiterpene.

$^{1}H-^{1}H$ COSY revealed two sequences depicted by the bold lines in Figure 2. The two sequences along with the terminal double bond, methyl group and a quaternary carbon were assembled by HMBC experiment. HMBC correlations between C-4 (δ_C 146.1) and H-3, H-5 and H-6; C-10 (δ_C 41.6) and H-5, H-1, H-9 and H_3-14; C-14 and H-5, H-9 and H-1 permitted the connectivity of the isolated spin systems (Figure 2).

The stereochemistry of **2** was determined on the base of the NOESY spectrum and coupling constants. A NOESY interactions between H_3-14 (δ_H 0.70)/H-1 (δ_H 3.41) and H-6 (δ_H 3.71) and H-6/H-11 (δ_H 2.20) (Figure 3) revealed that H-1, H-6, 14-methyl group and 7-isopropyl group were located on the same face of the molecule. In addition, NOESY interaction between H-5 (δ_H 1.74) and H-7 (δ_H 1.28) together with the coupling constant $J_{H\text{-}5}/_{H\text{-}6} = 10.0$ Hz implied that H-5 and H-7 were located on the opposite side of H-6. Thus, the structure of polydactin B (**2**) was determined as shown in Figure 1.

Polydactins A (**1**) and B (**2**) were evaluated for cytotoxic activities against human tumour cell lines KB and MCF. **1** exhibited moderate cytotoxic activity against KB and MCF cell lines with IC_{50} values 13.0 and 14.0 μg /ml,



1 **2** **3**

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

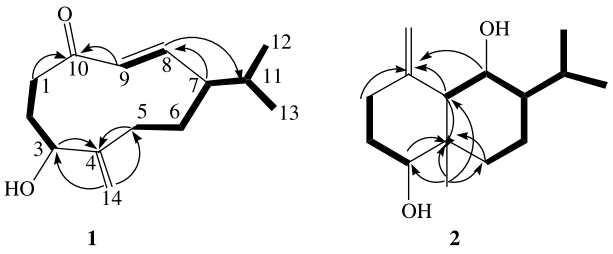


Figure 2. $^{1}H-^{1}H$ COSY correlations (bold lines) and key HMBC correlations (H → C) of **1** and **2**.

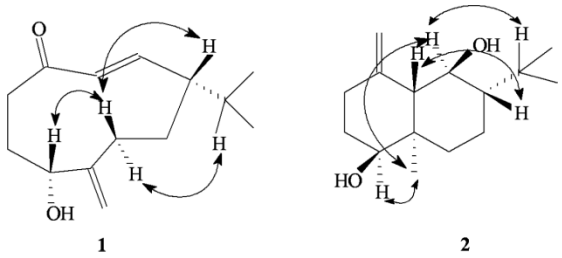


Figure 3. Key NOE correlations of **1** and **2**.

respectively, while **2** exhibited weak cytotoxic activity on KB and MCF cell lines with IC_{50} values 49.4 and 37.8 μg /ml, respectively.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a Schmidt & Haensch polaptronic hnqw5 polarimeter. IR spectra were recorded with an EQUINOX55 (Bruker) spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Unity INOVA spectrometer at 500 MHz respectively, with TMS as internal standard. FAB-MS spectra were obtained with MAT95XP and HR-EI-MS was obtained with MAT95XP (Thermo) Mass Spectrometer. HPLC was conducted on a Perkin–Elmer series 200 using a Diode Array detector 235C and a reversed-phase Symmetry Prep C18 column (7 μm, 7.8 × 300 mm). Preparative TLC was performed with Silica gel H F_{254}. Silica gel H (200–300 mesh) was used for flash chromatography.

3.2 Biological material

The specimens of *Sinularia polydactyla* (Ehreberg) were collected from the Bay of Sanya, Hainan Island, China, in 1998. Zhi-Can Tang of the Qingdao Institute of Oceanology, Academia Sinica, identified the soft coral species. A voucher specimen (No. 98-SY-17) is preserved in the Research Centre of Organic Natural Products, Sun Yat-Sen University.

3.3 Extraction and isolation

The soft coral *S. polydactyla* (dry weight 3.05 kg) was extracted with EtOH. The EtOH extract was concentrated and the residue (130 g) was partitioned between EtOAc and H_2O. The EtOAc fraction (63 g) was subjected to column chromatography on silica gel, using petroleum-ether (PE) and EtOAc mixtures of increasing polarity as eluant to yield 11 fractions (1–11). Fraction 1 (500 mg) eluted with PE/EtOAc (9:1) was further subjected to flash chromatography over silica gel H using PE/EtOAc (6:1) to give compound **1** (15 mg). Fraction 2 (1.5 g) eluted with PE/EtOAc (4:1) was further subjected to flash chromatography over silica gel H using PE/EtOAc (4:1) to give two fractions 2A (261 mg) and 2B (537 mg). Fraction 2B was separated by RP-HPLC on C18 silica gel using MeOH/H_2O (17:3) as eluant to yield five fractions ($2B_1-2B_5$). After evaporation of fraction $2B_3$, pure compound **2** (30 mg) was obtained. Fraction $2B_5$ (50 mg) was further separated by RP-HPLC on C18 silica gel using MeOH/H_2O (17:3) as eluant to afford compound **3** (20 mg).

3.3.1 Polydactin A (1)

Colourless oil, $[\alpha]_D^{20} = -28.95$ (*c* 0.076, $CHCl_3$); IR ν_{max} KBr cm^{-1}: 3431 (OH), 3077 (=C–H), 1717(C=O), 1673, 1461, 1386, 1256, 1037; ^{1}H NMR and ^{13}C NMR spectral data: see table 1. HREI-MS *m/z* 222.1609 $[M]^+$ (calcd for $C_{14}H_{22}O_2$, 222.1614); FAB-MS *m/z* 223 $[M + H]^+$.

3.3.2 Polydactin B (2)

Pale yellow oil, $[\alpha]_D^{20} = +23.61$ (*c* 0.072, $CHCl_3$); IR ν_{max} KBr cm^{-1}: 3418 (OH), 3078 (=C–H), 1706, 1648, 1460, 1383, 1060, 1005; ^{1}H NMR and ^{13}C NMR spectral data: see table 1. HREI-MS *m/z* 238.1894 $[M]^+$ (calcd for $C_{15}H_{26}O_2$, 238.1927); FAB-MS *m/z* 239 $[M + H]^+$.

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