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Periconiasin G, a new cytochalasan with unprecedented 7/6/5 tricyclic ring system from the endophytic fungus *Periconia* sp.

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ABSTRACT

Two new cytochalasans, periconiasin G (**1**) and periconiasin H (**2**) were isolated from endophytic fungus *Periconia* sp. F-31. Compound **1** is the first cytochalasan with a 7/6/5 tricyclic ring system, and compound **2** possesses a rare sulfoxide group. Their structures including absolute configurations were elucidated by extensive spectroscopic analyses and ECD calculations. A possible biogenetic pathway for these two compounds was proposed. Compound **1** showed weak anti-HIV activity with IC_{50} value of 67.0 μM.

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Cytochalasans are a large group of polyketide synthase–nonribosomal peptide synthetase (PKS–NRPS) hybrid metabolites which display a wide range of diverse biological activities, such as antitumor,[1–3] antibacterial,[4] immunomodulatory,[5] nematicidal,[6] and phytotoxic activities.[3,7] Generally, cytochalasans feature tricyclic core in which a macrocyclic ring is fused to an isoindolone moiety, and their macrocyclic rings commonly possess 11- and 13-membered carbocyclic rings or fused ring system,[8] and some unique cytochalasans with 9- and 12-membered carbocyclic rings or derivative fused rings were reported in recent years.[9–11] The endophytic fungus *Periconia* sp. F-31, isolated from the medicinal plant *Annona muricata*, displayed antiviral, cytotoxic, and anti-inflammatory activities. Our previous chemical investigation of this fungi afforded structurally rare tricyclic cytochalasans with nine-membered carbocycle fused to isoindolone moiety, which showed significant cytotoxic activity.[9] As part of ongoing search for diverse bioactive metabolites from this fungus, two new cytochalasans, periconiasins G (**1**) and H (**2**) were isolated (Fig. 1). Interestingly, compound **1** features unique 7/6/5 tricyclic ring system, in which the seven-membered ring is the smallest carbocyclic ring (part of macrocyclic ring) in typical tricyclic cytochalasans so far. Compound **2** possesses a rare sulfoxide group in all types of cytochalasans. Herein, we report their isolation, structure elucidation, plausible biogenetic pathway, and bioactivities.

The fungi *Periconia* sp. F-31 was incubated in PDA medium. The cultures were filtered under reduced pressure to yield the filtrate and mycelia. The mycelia was extracted with CH_3OH to yield a crude extract (240 g), which was suspended in H_2O and partitioned using EtOAc to afford EtOAc extract (66 g). The EtOAc extract was further separated by silica gel column chromatography (CC), Sephadex LH-20 CC, and semipreparative HPLC to give **1** (6.0 mg). The filtrate (140 l) was applied through an Amberlite XAD-16 macroporous adsorbent resin column eluting with H_2O and 95% EtOH, successively. The EtOH residue was extracted with EtOAc, and then EtOAc extract (25 g) was fractionated by silica gel CC, Sephadex LH-20 CC, and semipreparative HPLC to afford **2** (4.8 mg).

Periconiasin G (**1**)[12] was isolated as white powder and gave a HRESIMS ion peak at *m/z* 318.2427 $[M+H]^+$, corresponding to a molecular formula of $C_{20}H_{31}NO_2$ with six degrees of unsaturation. The IR absorption bands at 3207, 1694, and 1678 cm^{-1} indicated the presence of NH and carbonyl groups. The ^{13}C NMR and DEPT spectra displayed 20 carbon resonances including two carbonyl carbons (δ_C 213.8, 174.6), two olefinic carbons (δ_C 138.8, 129.0), one quaternary carbon (δ_C 66.3), six methines (δ_C 54.3, 51.2, 38.4, 36.2, 34.6, 24.1), four methylenes (δ_C 48.1, 42.4, 37.5, 31.8), as well as five methyls (δ_C 23.9, 23.3, 21.3, 19.8, 13.5). The protons and proton-connected carbons in the NMR spectra of **1** were assigned

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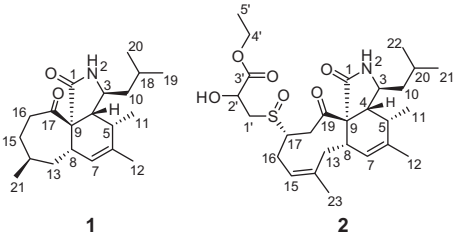

Figure 1. Chemical structures of **1** and **2**.

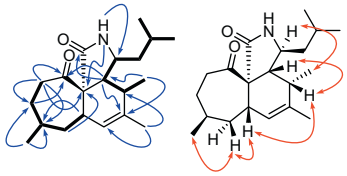

Figure 2. ^{1}H–^{1}H COSY (▬), HMBC (→), and NOESY (↔) correlations of **1**.

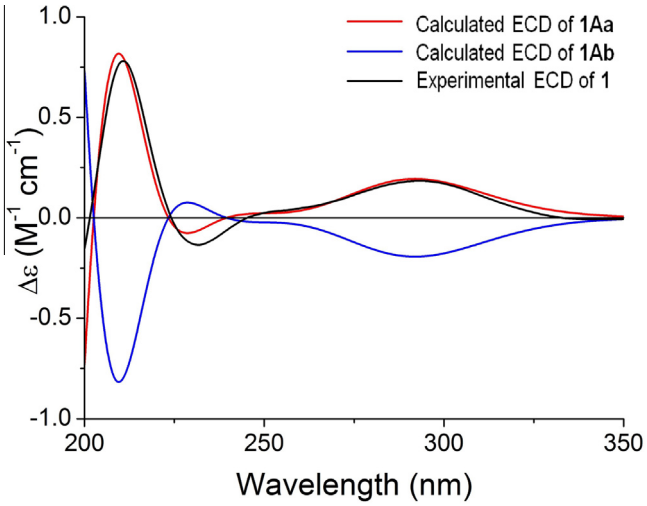

Figure 3. The calculated ECD spectra of **1A** and the experimental CD spectrum of **1**.

unambiguously by DEPT and HSQC spectroscopic data. The HMBC correlations (Fig. 2) of H-2/C-3, C-4, and C-9, H-4/C-1, C-3, C-5, C-6, C-10, and C-17, H_3-12/C-5, C-6, and C-7, along with the correlations from H-8 to H-7 and H_2-13, and the spin system of H-3/H_2-10/H-18/H_3-19/H_3-20 in the ^{1}H–^{1}H COSY spectrum indicated the presence of an isoindolone with isobutyl moiety at C-3. Furthermore, the HMBC correlations for H_2-13/C-8 and C-9, H_3-21/C-13, C-14, and C-15, H_2-16/C-9, C-14, C-15, and C-17, H-4/C-17, together with the ^{1}H–^{1}H COSY correlations of H_2-13/H-14/H_2-15/H_2-16 established another seven-membered ring. Therefore, the planar structure of **1** was determined to be a new type of cytochalasans with a unusual 7/6/5 tricyclic ring system. Intriguingly, compound **1** possesses smallest tricyclic ring system in typical cytochalasans.

The relative configuration of **1** was established by NOESY spectrum. The NOEs between H-3 and H_3-11 indicated that H-3 and H_3-11 were α-oriented, the no NOEs between H-4 and H-3 established the β-orientation of H-4, the NOEs from H-5 to H-4 and H-8 suggested that they were β-oriented. The NOEs of H-8/H-7 and H-13β, H-13β/H_3-21, along with no NOEs of H-13α/H-7 and H_3-21 assigned the β-oriented of methyl group (CH_3-21). Computational methods were used to determine the absolute configuration of **1**

Table 1
^{1}H and ^{13}C NMR data of **1** and **2**

No.	**1**[a]		**2**[b]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	174.6		176.6	
2		7.95 (s)		
3	51.2	2.93 (m)	51.1	3.20 (m)
4	54.3	2.23 (dd, 4.5, 4.0)	56.5	2.31 (dd, 5.4, 2.4)
5	34.6	2.41 (m)	36.2	2.52 (overlapped)
6	138.8		140.3	
7	129.0	5.34 (s)	130.0	5.45 (s)
8	38.4	2.56 (m)	44.6	2.50 (overlapped)
9	66.3		66.5	
10	48.1	1.36 (m), 1.09 (m)	49.9	1.27 (m), 1.14 (m)
11	13.5	1.06 (d, 7.5)	13.6	1.22 (d, 7.2)
12	19.8	1.69 (s)	19.8	1.76 (br s)
13	37.5	2.59 (m, Hα)	31.9	4.19 (overlapped, Hα)
		1.55 (br d, 12.5, Hβ)		1.67 (br d, 13.8, Hβ)
14	36.2	1.69 (overlapped)	138.8	
15	31.8	1.73 (m), 1.39 (m)	123.5	5.11 (dd, 10.2, 7.2)
16	42.4	2.90 (m), 2.35 (m)	26.9	2.76 (m, Hα)
				2.23 (dd, 13.8, 6.6, Hβ)
17	213.8		59.9	3.07 (td, 10.8, 3.6)
18	24.1	1.65 (m)	37.4	3.55 (dd, 12.6, 10.8)
				2.49 (overlapped)
19	21.3	0.82 (d, 6.0)	212.5	
20	23.9	0.84 (d, 7.0)	25.3	1.69 (m)
21	23.3	0.91 (d, 6.0)	21.8	0.89 (d, 6.6)
22			23.9	0.87 (d, 6.6)
23			23.9	1.62 (s)
1′			54.5	3.01 (dd, 13.2, 10.8)
				2.94 (dd, 13.2, 2.4)
2′			66.5	4.58 (dd, 10.8, 2.4)
3′			173.3	
4′			61.9	4.19 (q, 6.6)
5′			14.4	1.25 (t, 6.6)

[a] ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), DMSO-d_6.
[b] ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz), acetone-d_6.

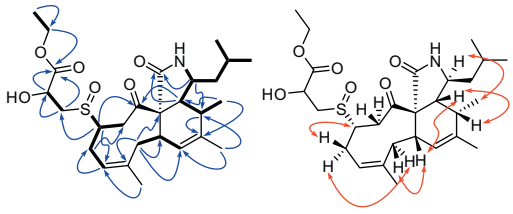

Figure 4. ^{1}H–^{1}H COSY (▬), HMBC (→), and NOESY (↔) correlations of **2**.

by comparing the experimental and simulated electronic circular dichroism (ECD) spectra using the TD-DFT method at the B3LYP/6-31G(d) level. Because the conformationally flexible side chain had no effect on the CD spectrum of **1**, a simplified structure of **1A** (Figs. S1 and S2), in which a methyl replaced isobutyl in **1**, was used for the ECD calculations. Two stereoisomers, (3*S*,4*R*,5*S*,8*S*,9*S*,14*S*)-**1Aa** and (3*R*,4*S*,5*R*,8*R*,9*R*,14*R*)-**1Ab** existed on the basis of the relative configuration. The calculated ECD spectrum of **1Aa** was consistent with the experimental CD curve (Fig. 3), indicating the absolute configuration of **1** as 3*S*,4*R*,5*S*,8*S*,9*S*,14*S*. Thus, the structure of **1** was established as periconiasin G (Table 1).

Periconiasin H (**2**)[13] was obtained as colorless gum. Its molecular formula of $C_{27}H_{41}NO_6S$ with nine degrees of unsaturation was established by a HRESIMS ion peak at *m*/*z* 508.2703 [M+H]$^{+}$. The IR spectrum with strong absorption at 1028 cm^{-1} display the existence of sulfoxide group.[14,15] Comparison of ^{1}H and ^{13}C NMR data of **2** with those of periconiasin A[9] indicated that they shared similar cytochalasan skeleton. However, compound **2** showed the additional presence of one methylene [δ_H 3.01 (1H, dd, *J* = 13.2, 10.8 Hz), 2.94 (1H, dd, *J* = 13.2, 2.4 Hz); δ_C 54.5], one oxygenated

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