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Pericoannosin A, a Polyketide Synthase–Nonribosomal Peptide Synthetase Hybrid Metabolite with New Carbon Skeleton from the Endophytic Fungus *Periconia* sp.

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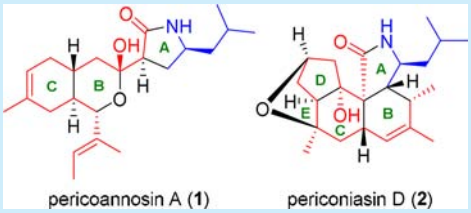
Supporting Information

ABSTRACT: Four new polyketide synthase–nonribosomal peptide synthetase (PKS–NRPS) hybrid metabolites, pericoannosin A (**1**), with an unusual hexahydro-1*H*-isochromen-5-isobutylpyrrolidin-2-one skeleton, and three cytochalasans, periconiasins D–F (**2**–**4**), were isolated from the endophytic fungus *Periconia* sp. F-31. Their structures and absolute configurations were elucidated through extensive spectroscopic analyses, calculated ECD, and single-crystal X-ray diffraction (Cu Kα). A possible biogenetic pathway is proposed. Compounds **1** and **4** showed anti-HIV activity with IC_{50}s of 69.6 and 29.2 μM, respectively.



Fungi inhabiting special and competitive environments have been demonstrated to be a rich source of bioactive secondary metabolites with diverse structural features.[1] One intriguing class of such metabolites is polyketide synthase–nonribosomal peptide synthetase (PKS–NRPS) hybrid metabolites, which display a wide range of impressive biological properties such as antibiotic, antitumor, and insecticidal activities.[2] Therefore, PKS–NRPS hybrid metabolites from fungi have caused wide public concern over recent years. The endophytic fungus *Periconia* sp. F-31, isolated from the medicinal plant *Annona muricata*, displays antiviral, antitumor, and anti-inflammatory activities in preliminary in vitro assays. Chemical studies on crude extracts of the fermentation broth of this endophytic fungus afforded structurally unusual natural products showing antitumor and anti-inflammatory activities.[3] In our continuing research on the discovery of structurally unique PKS–NRPS metabolites with interesting biological activities from this strain, extracts of the fermentation broth and mycelia were further investigated, leading to the isolation of four new PKS–NRPS hybrid metabolites: pericoannosin A (**1**), with a unique hexahydro-1*H*-isochromen-5-isobutylpyrrolidin-2-one skeleton, and three cytochalasans, periconiasins D–F (**2**–**4**) (Figure 1). Their structures were elucidated by extensive spectroscopic data analyses. The absolute configurations of compounds **1**–**4** were established by ECD calculations and single-crystal X-ray diffractions. Their biosynthetic pathways were proposed to be typical pathways of fungal PKS–NRPS hybrids assembled from one acetyl-CoA starter and six malonyl-CoA extenders combined with one leucine-CoA. Intriguingly, they shared the same precursors, including polyketide and amino acid building blocks and PKS–NRPS hybrid synthetases.

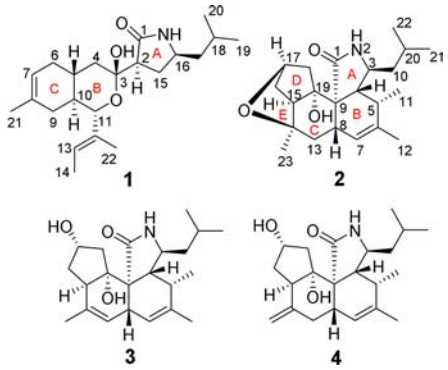


Figure 1. Chemical structures of compounds **1**–**4**.

However, the distinct cyclizations give rise to skeletal divergence by different tailoring enzymes. Herein, we report the isolation, structural elucidation, plausible biogenetic pathway, and biological activity of these PKS–NRPS hybrid metabolites.

Pericoannosin A (**1**) was isolated as colorless crystals (MeOH–H_2O) and gave an HRESIMS ion peak at m/z 384.2505 $[M + Na]^+$, corresponding to a molecular formula of $C_{22}H_{35}NO_3$ with six degrees of unsaturation. The IR absorption bands at 3249, 3109, and 1673 cm^{-1} indicated the presence of hydroxyl, amidogen, and carbonyl groups. The ^{13}C NMR and DEPT spectra (Table 1) exhibited 22 carbon resonances, including four quaternary carbons (one carbonyl, two olefinic, one oxygenated), eight methines (including two olefinic, one

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Table 1. NMR Data of Pericoannosin A (1) in Acetone-d_6[a]

no.	δ_C	δ_H
1	178.8	
2	49.7	2.56 (1H, t, 10.2)
3	97.5	
4	40.9	1.66 (1H, dd, 12.6, 3.6, Hβ)
		1.20 (1H, dd, 12.6, 11.2, Hα)
5	30.9	1.82 (1H, m)
6	33.4	1.99 (1H, m, Hβ)
		1.61 (1H, overlapped, Hα)
7	120.9	5.35 (1H, br s)
8	133.7	
9	33.0	1.60 (1H, overlapped)
		1.50 (1H, m)
10	38.8	1.37 (1H, m)
11	82.1	3.99 (1H, d, 10.2)
12	135.4	
13	122.9	5.41 (1H, m)
14	13.0	1.58 (3H, overlapped)
15	30.8	2.36 (1H, m, Hα)
		1.80 (1H, m, Hβ)
16	50.8	3.67 (1H, m)
17	47.3	1.51 (1H, m), 1.31 (1H, m)
18	25.6	1.77 (1H, m)
19	22.9	0.93 (3H, d, 7.2)
20	23.1	0.92 (3H, d, 7.2)
21	23.9	1.59 (3H, s)
22	11.2	1.60 (3H, s)
3-OH		6.67 (1H, d, 2.4)

[a] ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz).

oxygenated), five methylenes, and five methyls. Among the 22 carbons, one carbonyl carbon and two double bonds accounted for three degrees of unsaturation, indicating that **1** possesses a tricyclic ring system.

The proton and proton-connected carbon resonances in the NMR spectra of **1** were assigned unambiguously by interpreting ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H−^{1}H COSY, and HSQC spectroscopic data. According to ^{1}H−^{1}H COSY and HSQC spectra, three spin systems [**I** (**I**-1: H_2-4/H-5/H_2-6/H-7; **I**-2: H_2-9/H-10/H-11; **I**-3: H-5/H-9); **II**: H-13/H_3-14; **III** (**III**-1: H-2/H_2-15/H-16/H_2-17/H-18/H_3-19; **III**-2: H-18/H_3-20)] were established, as shown in Figure 2. The HMBC correlations

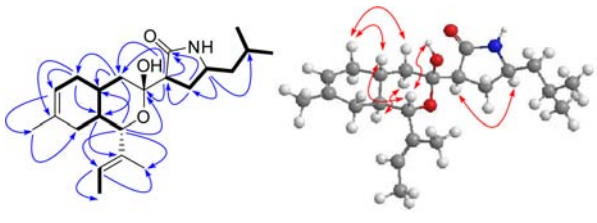

Figure 2. ^{1}H−^{1}H COSY (—), key HMBC (→), and NOESY (↔) correlations of **1**.

from H_2-6 to C-7, C-8, and C-10; from H-7 to C-6, C-9, and C-21; and from H-10 to C-5, C-6, and C-9 indicated the presence of a cyclohexene ring (ring C) consisting of C-5, C-6, C-7, C-8, C-9, and C-10 with a tertiary methyl (CH_3-21) at C-8. The HMBC cross-peaks from H_2-4 to C-3, C-5, C-6, and C-10; from H-11 to C-3, C-5, C-9, and C-10; and from 3-O*H* to C-3 and C-4 along with the corresponding shifts (H-11 at δ_H 3.99; C-3 at δ_C 97.5, C-11 at δ_C 82.1) and ^{1}H−^{1}H COSY correlations (spin system I) demonstrated the presence of an oxygen-bearing six-membered ring (ring B) with a hydroxyl at C-3 fused to positions C-5 and C-10 on the cyclohexene ring (ring C), which combined into a hexahydroisochromen moiety. The HMBC correlations from H-11 to C-12, C-13 and C-22, and from H-13 to C-11, C-14, and C-22 established one but-2-ene group (including C-12, C-13, C-14, and C-22) attached to C-11 by the position of C-12. Furthermore, the HMBC correlations from H-2 to C-1 and C-15 and from H-15 to C-1, C-2, and C-16 along with the spin system from H-15 to H-20 (spin system III) on the basis of the ^{1}H−^{1}H COSY correlations, the degrees of unsaturation, and the chemical shifts indicated the presence of a five-membered lactam ring (ring A) with an isobutyl group at C-16. The critical HMBC correlations from H-2 to C-3 and C-4 and from 3-O*H* to C-2 suggested the direct connection between C-2 and C-3. Therefore, the planar structure of **1** was determined to be a new hexahydro-1*H*-isochromen-5-isobutylpyrrolidin-2-one skeleton (Figure 1).

The relative configuration of **1** was deduced by NOEs. The irradiation of H-11 enhanced H-5 and 3-O*H*, the irradiation of H-6β enhanced H-5 and H-4β, and the irradiation of H-4α enhanced H-10. These results along with the large coupling constants of $^3J_{\text{H-4}\alpha,\text{H-5}}$ (11.2 Hz) and $^3J_{\text{H-10,H-11}}$ (10.2 Hz), and the small coupling constant of $^3J_{\text{H-4}\beta,\text{H-5}}$ (3.6 Hz) indicated that H-4β, H-5, H-6β, H-11, and 3-O*H* were *syn*-oriented, while H-4α, H-6α, and H-10 were on the opposite side. The enhancement of H-2 with the irradiation of H-16 suggested the *syn*-orientation of the two protons. Because of the short distance between H-2 and 3-O*H*, the relative stereochemistry of C-2 and C-3 could not be determined by the NOE correlation between H-2 and 3-O*H*.

The ECD spectra were theoretically calculated using time-dependent density functional theory (TD-DFT) at the B3LYP/6-31G(d) level. According to the NOE experiments, four possible stereoisomers (**1A**−**D**, Figure S1) of **1** exist. A comparison of the theoretically calculated and experimental ECD curves (Figure 3) showed that the calculated ECD curves of

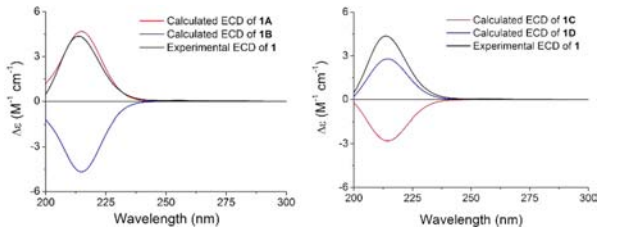

Figure 3. Calculated ECD spectra of **1A**−**D** and the experimental CD spectrum of **1**.

1A and **1D** were both similar to the experimental ones. Thus, more evidence is necessary to determine the absolute configuration of **1**. Careful analysis of the structure indicated the presence of one hydroxyl attached to the chiral carbon (C-3) in **1**; thus, the absolute configuration of C-3 can be assigned using the CD data of the in situ formed [$Rh_2(OCOCF_3)_4$] complex.[4] After the addition of [$Rh_2(OCOCF_3)_4$] to a solution of **1** in $CHCl_3$, a metal complex was produced as an auxiliary chromophore. The Rh complex of **1** showed a negative E band (approximately 350 nm), suggesting the *R* configuration of C-3 by applying the bulkiness rule (Figure S23). Therefore, the absolute configuration of **1** was determined as

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2*S*,3*R*,5*R*,10*S*,11*S*,16*S*. Moreover, the complete structure and stereochemistry of **1** were further confirmed by single-crystal X-ray diffraction experiments using Cu Kα radiation with a Flack parameter of 0.14(8) (Figure 4),[5] and the absolute configuration of **1** was unambiguously determined as 2*S*,3*R*,5*R*,10*S*,11*S*,16*S*.

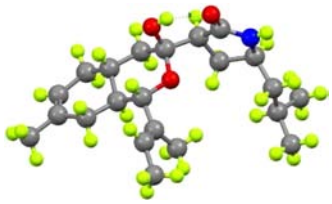


Figure 4. Single-crystal X-ray diffraction of **1**.

Notably, the calculated ECD curves of **1A** and **1B** were the same as those of **1D** and **1C** (Figure 3 and Figure S1), respectively. Detailed analysis of stereochemistry of **1A**−**D** found that the configuration of lactam ring of **1A** was identical with those of **1D**, and the configuration of lactam ring of **1B** was also same as that of **1C**. This result suggested that the stereochemistry of the lactam ring played a decisive role in the determination of the absolute configuration of these types of derivatives.

Periconiasin D (**2**) was isolated as colorless lamellar crystals (acetone−EtOAc−H_2O). Its molecular formula was established as $C_{22}H_{33}NO_3$ by HRESIMS with a *m*/*z* of 360.2530 $[M + H]^+$ (calcd 360.2533) corresponding to seven degrees of unsaturation. The IR spectrum indicated the presence of hydroxyl (3343 cm^{-1}), amidogen (3228 cm^{-1}), and carbonyl (1682 cm^{-1}) moieties. The ^1H NMR spectrum (Table S1) showed the presence of five methyls at δ_H 1.68 (3H, s), 1.08 (3H, d, *J* = 7.2 Hz), 1.03 (3H, s), 0.82 (3H, d, *J* = 6.0 Hz), and 0.81 (3H, d, *J* = 6.0 Hz) as well as an olefinic proton at δ_H 5.35 (1H, s). The ^{13}C NMR and DEPT spectra (Table S1) showed 22 carbon resonances, including five quaternary carbons (δ_C 177.4, 138.2, 78.9, 78.2, and 55.9, including one carbonyl, one olefinic and two oxygenated), eight methines (δ_C 126.5, 75.5, 50.9, 50.8, 50.1, 35.9, 34.2, and 24.0, including one olefinic and one oxygenated), four methylenes (δ_C 47.5, 45.2, 34.6, and 34.2), and five methyls (δ_C 28.0, 24.0, 21.2, 20.0, and 13.6). The HMBC correlations (Figure 5) of H-2/C-1, C-4, and C-9; H-4/C-1, C-3, C-5, C-6, C-8, C-9, C-10, C-11, and C-19; H_3-12/C-5, C-6, and C-7; and H_2-10/C-3, C-4, C-20, C-21, and C-22 together with two spin systems of H_3-11/H-5/H-4/H-3/H_2-10/H-20/H_3-21, and H-7/H-8/H_2-13 in the $^1H-^1H$ COSY spectrum (Figure 5) confirmed the presence of a substituted isoindolone moiety (a five-membered lactam ring fused with cyclohexene) and one isobutyl. The HMBC cross-peaks of H_2-13/C-7, C-8, C-9, C-14, C-15 and C-23; H-15/C-17, C-18, C-19 and C-23; H_2-18/C-9, C-16, C-17 and C-19; and 19-O*H*/C-9, C-15, C-18 and C-19 together with the $^1H-^1H$ COSY correlations of H-15/H_2-16/H-17/H_2-18 suggested the existence of a fused 6/5 carbocycle moiety. Furthermore, a $C_{14}-O-C_{17}$ oxygen bridge was determined on the basis of the HMBC correlation of H-17/C-14 and the degrees of unsaturation. Thus, compound **2** was identified as a new cytochalasan with 5/6/6/5/5 pentacyclic ring system. The relative configuration of **2** was determined by using its NOESY spectrum (Figure 5). The NOESY correlations of H-8/H-13β and H-18β; 19-O*H*/H-18α and H-15; H-17/H-18α; and H-15/H_3-23 indicated that H-15, H-17, H_3-23, and 19-O*H* were α-oriented.

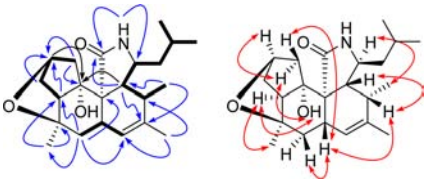


Figure 5. $^1H-^1H$ COSY (—), key HMBC (→), and NOESY (↔) correlations of **2**.

Compound **2** displayed a 22-carbon resonance but possessed a pentacyclic ring system and nine chiral centers. Fortunately, a single crystal of **2** suitable for single-crystal X-ray diffraction was obtained from a solution in a mixture of acetone−EtOAc−H_2O (2:2:1) after numerous experiments. The structure of **2** was confirmed by single-crystal X-ray diffraction using the anomalous scattering of Cu Kα radiation with a Flack parameter of −0.06(17) (Figure 6).[6] Its absolute configuration was unambiguously assigned as 3*S*,4*R*,5*S*,8*S*,9*S*,14*R*,15*S*,17*R*,19*S*. Furthermore, ECD calculations (see pages S9,10) confirmed the absolute configuration of **2**.

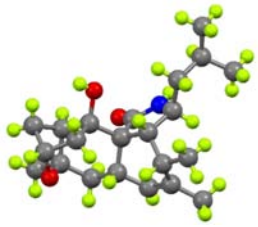
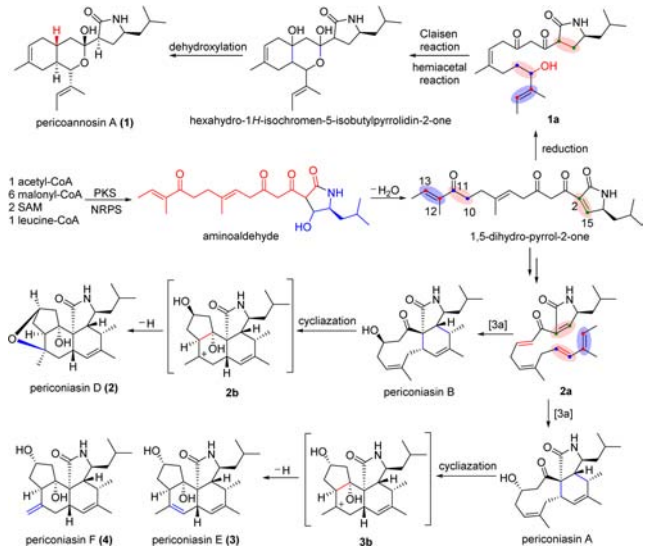


Figure 6. Single-crystal X-ray diffraction of **2**.

The structures of compounds **3** and **4** were determined as shown in Figure 1 by extensive spectroscopic data analyses (Table S1; Figures S3, S4, S6−9, and S35−57) and elucidated in detail in the Supporting Information (see pages S10,11).

The biosynthesis of **1**−**4** is proposed to be a hybrid PKS−NRPS biosynthetic pathway (Scheme 1). Compounds **1**−**4** share the same aminoaldehyde intermediate originating from a

Scheme 1. Proposed biosynthetic pathway of pericoannosin A (1) and periconiasins D−F (2−4)



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polyketide backbone (one acetyl-CoA starter and six malonyl-CoA extenders) and amino acid (leucine) followed by dehydration to produce the same precursor, 1,5-dihydro-pyrrol-2-one. The specific reduction led to intermediate **1a**, which underwent the Claisen reaction and hemiacetal reaction to yield the hexahydro-1*H*-isochromen-5-isobutylpyrrolidin-2-one skeleton, and the subsequent dehydroxylation produces **1** (route I). In another pathway, the precursor (1,5-dihydropyrrol-2-one) undergoes an intramolecular Diels−Alder reaction, reduction, and oxidation to give 9/6/5 tricyclic cytochalasans (periconiasins A/B).[3a] Periconiasins A/B can undergo protonation and intramolecular nucleophilic addition to yield the 5/6/6/5 tetracyclic intermediate **2b**/**3b** with a carbocation center. The subsequent intramolecular cyclization of **2b** affords a furan ring and leads to the formation of **2**, which possesses 5/6/6/5/5 pentacyclic ring system. The subsequent dehydrogenation of **3b** produces **3** and **4** with 5/6/6/5 tetracy clic skeletons (route II). The common intermediate (1,5-dihydro-pyrrol-2-one) goes through divergent enzymatic catalysis to afford completely different skeletons. The critical checkpoint might be the occurred reactions of double bond C-2/C-15 and the carbonyl at C-11. For route I, the reductions of double bond C-2/C-15 and the carbonyl at C-11 miscarry intramolecular [4 + 2] Diels−Alder reaction, leading to the formation of intermediate **1a** and a hemiacetal intermediate of **1**. In contrast, for route II, the existence of three double bonds (C-2/C-15, C-10/C-11, C-12/C-13) leads to the occurrence of Diels−Alder [4 + 2] cycloaddition and subsequent generation of **2**−**4** by enzymatic post-PKS−NRPS modification steps.

Compounds **1**−**4** were evaluated for in vitro cytotoxic (camptothecin as the positive control), anti-inflammatory (curcumin as the positive control), and anti-HIV (efavirenz as the positive control) activities. Compounds **1**−**4** displayed no cytotoxic and anti-inflammatory activities at 10^{-5} M (see pages S6,7). The inactivity of periconiasins D−F (**2**−**4**) and significant cytotoxicity of periconiasins A and B[3a] indicated that the 9-membered macrocycle might be critical to the cytotoxicity for C22-cytochalasans rather than 5/6 bicyclics. Compounds **1** and **4** displayed low anti-HIV activity with respective IC_{50} values of 69.6 and 29.2 μM, while efavirenz gave an IC_{50} of 1.4 nM (see page S7).

In summary, we isolated and fully characterized via extensive spectroscopic analyses the calculated ECD and a single-crystal X-ray diffraction (Cu Kα) four new PKS−NRPS hybrid metabolites (**1**−**4**) from the endophytic fungus *Periconia* sp., which represents two classes of PKS−NRPS hybrid metabolites. Interestingly, the distinct skeleton shared a common biosynthetic intermediate originating from the same polyketide backbone and amino acid block. Different types of biosynthetic tailoring reactions gave rise to entirely different structural frameworks. These findings indicate that diverging pathways result in the structural and bioactive diversity of metabolites in a microorganism and highlight the biosynthetic versatility in nature. Further biosynthetic investigation will address how the corresponding genes/enzymes switch such divergence.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02123.

Experimental procedures, HRESIMS, IR, UV, CD, 1D and 2D NMR spectra, and ECD calculations of **1**−**4**(PDF)

X-ray crystallographic data for **1** (CIF)

X-ray crystallographic data for **2** (CIF)

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Notes

The authors declare no competing financial interest.

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(5) Pericoannosin A (**1**): $C_{22}H_{35}NO_3$, M = 361.52, orthorhombic system, space group $P2_12_12_1$, crystal dimensions 0.22 × 0.31 × 0.64 mm, Cu Kα radiation, a = 6.212(2) Å, b = 12.231(3) Å, c = 28.133(7) Å, V = 2137.5(10)Å3, Z = 4, D_{calcd} = 1.123 g·cm^{-3}. The total number of independent reflections measured was 4031, of which 3805 were observed ($|F|^2 \geq 2\sigma|F|^2$). The final indices were R_1 = 0.0391, wR_2 = 0.1037 ($w = 1/\sigma|F|^2$), S = 1.044. CCDC deposition no. 1408677.

(6) Periconiasin D (**2**): $C_{22}H_{33}NO_3$, M = 359.51, orthorhombic system, space group $P2_12_12_1$, crystal dimensions 0.05 × 0.22 × 0.98 mm, Cu Kα radiation, a = 12.515(3) Å, b = 14.907(2) Å, c = 45.898(6) Å, V = 8562.8Å3, Z = 16, D_{calcd} = 1.140 g·cm^{-3}. The total number of independent reflections measured was 16462, of which 13175 were observed ($|F|^2 \geq 2\sigma|F|^2$). The final indices were R_1 = 0.0600, wR_2 = 0.1566 ($w = 1/\sigma|F|^2$), S = 1.083. CCDC deposition no. 963029.

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