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New lactone and isocoumarin derivatives from the marine mangrove-derived endophytic fungus *Penicillium coffeae* MA-314

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ABSTRACT

A new *δ*-lactone (penicoffeazine A, **1**) and two pairs of new isocoumarin derivatives (penicoffrazins B and C, **2** and **3**), along with five known isocoumarin derivatives (**4**−**8**), were isolated from *Penicillium coffeae* MA-314, an endophytic fungus obtained from the fresh inner tissue of the leaf of marine mangrove plant *Laguncularia racemosa*. The structures of all these compounds were elucidated by spectroscopic analysis and the absolute configuration of compound **1** was determined by ECD experiments and compared with that of calculated ECD spectrum. The relative configurations of compounds **2** and **3**, which were two pairs of enantiomers, were confirmed by NOESY experiments. Compound **1** was tested for antibacterial activity and the other compounds were tested for antioxidant activity. This is the first report on the natural products of the fungus *Penicillium coffeae*.

1. Introduction

Mangrove ecosystems, located at the confluence of inland and marine systems, provide a unique and selective environment that shapes local morphological, physiological, and behavioral adaptations (Luther and Greenberg, 2009). As the important role in mangrove ecosystems, mangrove plants host a great variety of endophytic fungi which represent the second largest ecological group of marine-derived fungi (Ananda and Sridhar, 2002; Sengupta and Chaudhuri, 2002; Sridhar, 2004). For assisting mangrove adaptation to their extreme habitat, mangrove-derived endophytic fungi provide a large number of natural products with novel structures and potent biological activity (Debbab et al., 2013). The number of new metabolites reported from mangrove-associated fungi continues to grow in recent years and the majority was coming from endophytic species (Blunt et al., 2018). In our ongoing research for new natural products from mangrove-derived fungus (Luo et al., 2014; Xu et al., 2016; Li et al., 2018), *Penicillium coffeae* MA-314, obtained from fresh inner tissue of the leaf of marine mangrove plant *Laguncularia racemosa*, attracted our attention. Because the metabolites of *P. coffeae* have not been reported previously, the chemical investigation had been launched and resulted in the isolation of one new *δ*-lactone derivative (penicoffeazine A, **1**) and two new isocoumarin derivatives (penicoffrazins B and C, **2** and **3**) which were two pairs of enantiomers (Fig. 1), along with five known isocoumarin derivatives (Fig. S1): 3-methoxy-6,8-dihydroxy-3-methyl-3,4-dihydroisocoumarin (**4**) (Kameda et al., 1973), *cis*-4,6-dihydroxymellein (**5**) (Assante et al., 1977), saccharonol A (**6**) (Singh et al., 2013), 6,8-dihydroxy-3-hydroxymethyl-1*H*-2-benzopyran-1-one (**7**) (McGraw and Hemingway, 1977), and *O*-demethyldiaporthin (**8**) (Sviridov, 1991). Compound **1** was tested for the inhibitory activities against two plant-pathogenic fungi, while compounds **2–8** were tested for their ability to scavenging DPPH radicals. In this paper, details of the isolation, structure elucidation, and bioactivity evaluation of these compounds are presented.

2. Results and discussion

Compound **1**, obtained as yellow oil, was assigned the molecular formula $C_{11}H_{18}O_3$ on the basis of HRESIMS data. Detailed inspection of the ^{13}C NMR (Table 1) and DEPT data revealed the presence of four methyls, five methines (with one aromatic/olefinic and two oxygenated), and two non-protonated (with one ester carbonyl and one aromatic/olefinic) carbon atoms. The ^{1}H NMR (Table 1) and HSQC data showed the presence of four methyl groups (H-8 through H-11), one olefinic proton (H-7), two oxymethine protons (H-3 and H-5), and one exchangeable proton (OH-3). The 1D NMR and COSY data (Fig. 2)

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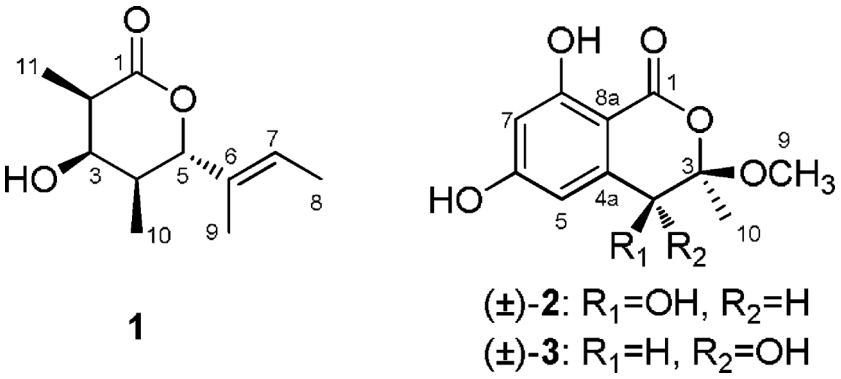

Fig. 1. Structures of the new compounds **1**–**3**.

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of compound **1**, measured in DMSO-d_6.

Compound 1		
No.	δ_H (mult, *J* in Hz)	δ_C, type
1		173.6, C
2	2.65, qd (2.8, 7.0)	42.1, CH
3	3.66, br s	70.7, CH
4	2.00, dqd (11.0, 6.8, 0.9)	35.2, CH
5	4.49, d (11.0)	87.4, CH
6		132.3, C
7	5.51, q (6.6)	124.8, CH
8	1.61, d (6.6)	12,9, CH_3
9	1.54, s	10.2, CH_3
10	0.79, d (6.8)	13.7, CH_3
11	1.11, d (7.0)	12.9, CH_3
3-OH	5.33, s	

indicated the presence of a lactone moiety, a trisubstituted double bond, one hydroxy group, and two vinylic methyl groups. These functional groups were assembled by the analysis of HMBC correlations (Fig. 2) and the planar structure of **1** was determined. The geometry for the double-bond and relative configuration of **1** were assigned by NOESY experiment and by analysis of the coupling constants. The NOESY correlation from H-5 to H-7 suggested the *E*-configuration of the double bond at C-6 (Fig. 3). The coupling constants $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ were measured as 2.8, 0.9, and 11.0 Hz, respectively, suggesting that H-2/H-3 and H-3/H-4 are *cis*-relationship and that H-4/H-5 is *trans*-diaxial. The relative configurations proposed for **1** were also authenticated by the NOESY correlations from H-2 to H-3, from H-3 to H-4, and from H-5 to H-10 (Fig. 3).

Based on reported *δ*-lactones (Korver, 1970; Poch and Gloer, 1989), the ECD curve for **1** which displayed a negative Cotton effect at 221.5 nm (Fig. 4), suggested that the *δ*-lactone moiety in **1** has a half-chair conformation and the dihedral angle C-3–C-2–C-1–O was positive, which means the C-3−C-2 bond has to be rotated clockwise to bring it into alignment with the C-1−O bond in the Newman projection along the bond from C-2 to C-1 (Korver, 1970). Because the molecule of **1** exists predominantly in the more stable half-chair form which places the 5-(1-methyl-1-propenyl) substituent in *pseudo*-equatorial position, the *S*-configuration at C-5 was determined. The absolute configuration of **1** was thus assigned as 2*R*, 3*R*, 4*S* and 5*S*, which was also proved by ECD quantum chemical calculations in Gaussian 09 (Frisch et al., 2013). The experimental ECD spectrum for **1** showed excellent agreement with the calculated (2*R*, 3*R*, 4*S*, 5*S*)-absolute configuration of **1** (Fig. 4) which was computed with the time-dependent density function theory (TD-DFT) method at PBE0/TZVP using the SCRF/PCM method. Therefore, the structure of compound **1**, which was named penicoffeazine A, was determined.

Compound **2** was obtained as a white amorphous powder and its molecular formula was assigned as $C_{11}H_{12}O_6$ on the basis of HEREIMS data. The ^{13}C NMR and DEPT data (Table 2) indicated the presence of one methyl, one methoxyl, three methines (with one oxygenated and two aromatic/olefinic), and six non-protonated (with one ester carbonyl, one oxygenated aliphatic, and four aromatic/olefinic) carbons. Detailed inspection of its ^{1}H and ^{13}C NMR data (Table 2) revealed the presence of a tetra-substituted benzene ring, an ester carbonyl, an oxygenated methine, a methoxyl, and a methyl groups in the molecule of **2**. The HMBC correlations from H-4 to C-4a and C-5, from H-5 to C-4, C-7, and C-8a, and from H-7 to C-5 and C-8a suggested that compound **2** was an isocoumarin derivative and similar to 4,6,8-trihydroxy-3-methoxy-3,7-dimethylisochroman-1-one (Liu et al., 2015). The only difference between them is that the methyl group at C-7 in the 4,6,8-trihydroxy-3-methoxy-3,7-dimethylisochroman-1-one is not presented in compound **2**. Therefore, the planar structure of **2** was determined. The NOE correlation from H-4 to H_3-10 placed these two groups on the same face of the molecule (Fig. 3). The absence of any Cotton effect in the ECD spectrum (Fig. S17) indicating the racemic nature of **2**, and the optical rotation was zero, which also supported this deduction. The possible enantiomers were well-separated by chiral HPLC which showed two peaks in the profile (Fig. S16).

Compound **3,** obtained as a white amorphous powder, was also assigned the molecular formula $C_{11}H_{12}O_6$ on the basis of HRESIMS data, which is same as that of compound **2**. Comparison of the ^{1}H and ^{13}C NMR data of **3** (Table 2) with that of **2** revealed the same structural core of these two compounds. Further analysis of the HMBC data of **3** (Fig. 2) revealed the same planar structure of **3** as that of **2**. However, chemical shifts at δ_C 68.2/δ_H 4.24 (CH-4), at δ_C 110.0/δ_H 6.23 (CH-5), and at δ_C 18.0/δ_H 1.49 (CH_3-10) in the NMR data of **3** were obviously different from that of **2**, and these differences are affected by the configuration at C-3 and/or C-4. NOE correlation from H-4 to H_3-9 indicated cofacial relation of them (Fig. 3). Compound **3** was also a racemic mixture, as suggested by optical rotation ($[\alpha]_D^{25}$ 0 (*c* 0.23, MeOH)) and by the absence of any Cotton effect in the ECD spectrum. The possible enantiomers were also well-separated by chiral HPLC (Fig. S24).

Compounds **1** was tested for antimicrobial activities against two plant-pathogenic fungi (*Fusarium oxysporum* f. sp. *momordicae* nov. f. and *Colletotrichum gloeosporioides*), and exhibited potent activity against both strains with MIC values of 5 μM, which was close to that of the positive control, amphotericin B (MIC = 0.5 μM). Because compounds **2**–**8** were isocoumarin derivatives which contained Ar-OH, they were screened for the DPPH radical scavenging activity. Only compound **4** exhibited moderate activity with IC_{50} value of 656 μM, which is weaker than that of the positive control butylated hydroxytoluene (BHT, IC_{50} = 159 μM). Other compounds showed no apparent activities (IC_{50} > 900 μM).

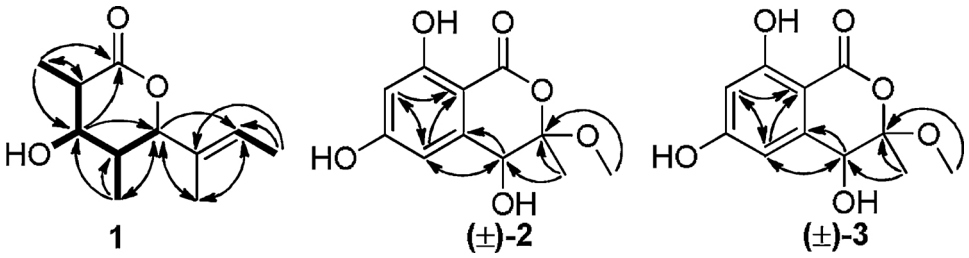

Fig. 2. Key HMBC (arrows) and COSY (bold lines) correlations for compounds **1–3**.

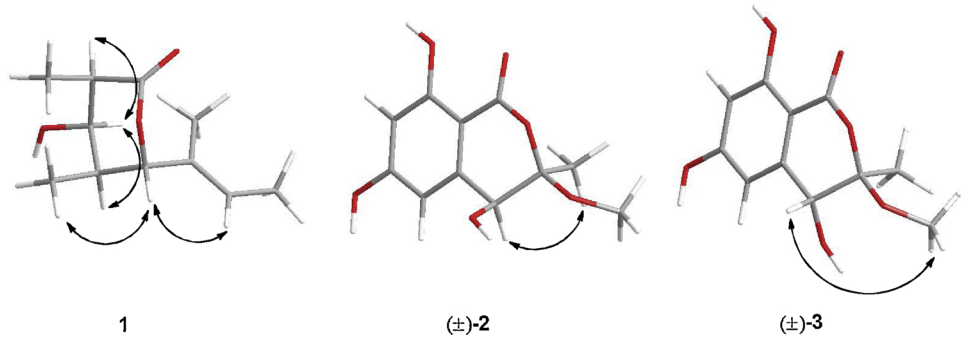

Fig. 3. Key NOESY correlations for compounds **1–3**.

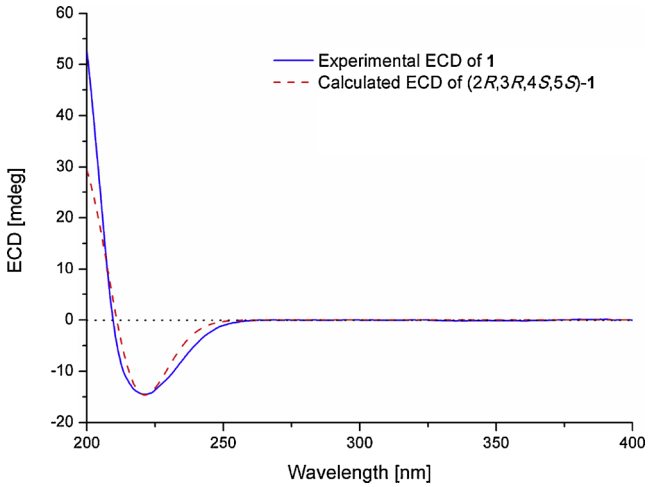

Fig. 4. Experimental and calculated ECD spectra of compound **1**.

Table 2
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of compounds **2** and **3**, measured in DMSO-d_6.

Compound 2			Compound **3**		
No.	δ_H (mult, *J* in Hz)	δ_C, type	No.	δ_H (mult, *J* in Hz)	δ_C, type
1		167.3, C	1		167.5, C
3		106.2, C	3		106.6, C
4	4.70, s	70.3, CH	4	4.24, s	68.2, CH
4a		144.3, C	4a		143.0, C
5	6.39, s	106.6, CH	5	6.23, s	110.0, CH
6		169.4, C	6		170.3, C
7	6.04, s	100.9, CH	7	6.02, s	101.9, CH
8		163.2, C	8		163.3, C
8a		95.9, C	8a		95.1, C
9	3.24, s	49.7, CH_3	9	3.27, s	49.5, CH_3
10	1.59, s	19.6, CH_3	10	1.49, s	18.0, CH_3

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on an Optical Activity AA-55 polarimeter. UV spectra were measured by a Lengguang Gold S54 photometer. ECD spectra were acquired on a Chirascan spectropolarimeter. 1D and 2D NMR spectra were recorded at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, on a Bruker Avance 500 spectrometer with TMS as internal standard. Mass spectra were determined on a VG Autospec 3000 or an API QSTAR Pulsar 1 mass spectrometer. HPLC analysis was performed using a Dionex HPLC system (P680 pump, ASI-100 automated sample injector, and UVD 340U UV–vis detector) and a C18 column (5 μm, 8.0 mm × 250 mm, 1 mL/min). Commercially available Si gel (200–300 mesh, Qingdao Haiyang Chemical Co.), Lobar LiChroprep RP–18 (40–63 μm, Merck), and Sephadex LH–20 (Pharmacia) were used for open column chromatography. All solvents used were distilled prior to use.

3.2. Fungal material

The fungal strains *P. coffeae* MA-314 was isolated from the leaf of marine mangrove plant *Laguncularia racemosa* collected at Hainan island, China, in March 2015, using a protocol as described in our previous report (Wang et al., 2006). The plant (voucher number: HNDZ1503) was identified by Dr. Zhang C Y in Hainan Mangrove Protection Zone, while the fungus was identified based on its ITS region of the rDNA as described previously (Wang et al., 2006). The sequence data derived from the fungal strain have been deposited at GenBank (accession no. MK087643). A BLAST search result showed that the sequence was most similar (99%) to the sequence of *P. coffeae* (accession no. LC057404.1). The strain was preserved at Key Laboratory of Experimental Marine Biology, Institute of Oceanology of the Chinese Academy of Sciences (IOCAS).

3.3. Fermentation, extraction, and isolation

For chemical investigations, the fungal strain, grown on PDA medium at 28 C for one week, was statically fermented in 80 × 1 L

conical flasks for 30 days at room temperature on PDB medium (potato dextrose broth: 2% mannitol, 0.3% yeast extract, 0.5% sodium glutamate, 0.5% peptone, 1% glucose and 200 mL naturally sourced and filtered seawater, which was obtained from the Huiquan Gulf of the Yellow Sea near the campus of IOCAS, pH 6.5–7.0). The whole fermented cultures were filtered to separate the broth from the mycelia. The fermentation broth was extracted three times with EtOAc, while the mycelia were extracted three times with a mixture of 80% acetone and 20% H_2O. The acetone solution was evaporated under reduced pressure to afford an aqueous solution which was extracted three times with EtOAc. The two EtOAc extracts were combined on account of identical HPLC and TLC profiles, and the combined crude extract (72.6 g) was fractionated by Si gel vacuum liquid chromatography (VLC) using different solvents of increasing polarity from petroleum ether (PE) to MeOH to yield nine fractions (Frs. 1–9) based on TLC and HPLC analysis. Fr. 4 (3.8 g) was further resolved into nine subfractions (Frs. 4.1–4.9) by column chromatography (CC) over Lobar LiChroprep RP-18 with a MeOH-H_2O gradient (from 10: 90 to 90: 10). Fr. 4.3 was purified by CC on Si gel eluting with a CH_2Cl_2–MeOH gradient (from 100: 1 to 20: 1) to obtain compounds **5** (6.0 mg) and **6** (19.3 mg) and the remainder was purified by CC on Si gel eluting with a PE–EtOAc gradient (from 10: 1 to 2: 1) to obtain compound **1** (4.0 mg). Fr. 5 (8.9 g) was also purified by CC over Lobar LiChroprep RP-18 with a MeOH-H_2O gradient (from 10: 90 to 90: 10) to afford nine subfractions (Frs. 5.1–5.9). Fr. 5.1 was further purified by CC on Si gel eluting with a PE–EtOAc gradient (from 10: 1 to 2: 1) and then by Sephadex LH-20 (MeOH) to obtain compound **7** (14.9 mg). Fr. 5.2 was purified by preparative TLC (plate: 20 × 20 cm, developing solvents: PE/EtOAc, 1: 1) to yield compound **4** (10.0 mg). Fr. 5.3 was further purified by CC on Si gel eluting with a CH_2Cl_2–MeOH gradient (from 100: 1 to 20: 1) and then by Sephadex LH-20 (MeOH) to obtain compound **8** (17.4 mg). Further purification of Fr. 7 (16.9 g) by CC over Lobar LiChroprep RP-18 with a MeOH-H_2O gradient (from 10: 90 to 90: 10) afforded two subfractions (Fr. 7.1 and Fr. 7.2). Fr. 7.1 was further purified by CC on Sephadex LH-20 (MeOH) and then by preparative TLC (plate: 20 × 20 cm, developing solvents: PE/EtOAc, 1: 1) to obtain compounds **2** (21.0 mg) and **3** (10.1 mg).

3.3.1. Penicoffeazine A (1)

Yellow oil; $[\alpha]_D^{25}$ +7.7 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 201 (3.32), 221 (2.94), 272 (2.22) nm; ECD (5.05 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 221 (-0.87) nm; ^{1}H and ^{13}C NMR data, see Table 1; ESIMS *m/z* 199.12 $[M+H]^+$, 221.10 $[M+Na]^+$; HRESIMS *m/z* 221.1145 $[M+Na]^+$ (calcd for $C_{11}H_{18}O_3Na$, 221.1148).

3.3.2. Penicoffeazine B (2)

Colorless amorphous powder; $[\alpha]_D^{25}$ 0 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 211 (4.06), 271 (3.87), 302 (3.64) nm; ^{1}H and ^{13}C NMR data, see Table 2; ESIMS *m/z* 239.04 $[M-H]^-$; HRESIMS *m/z* 239.0564 $[M-H]^-$ (calcd for $C_{11}H_{11}O_6$, 239.0561).

3.3.3. Penicoffeazine C (3)

Colorless amorphous powder; $[\alpha]_D^{25}$ 0 (*c* 0.23, MeOH); UV (MeOH) λ_{max} (log ε) 211 (3.66), 268 (3.38), 306 (3.27) nm; ^{1}H and ^{13}C NMR data, see Table 2; ESIMS *m/z* 239.04 $[M-H]^-$; HRESIMS *m/z* 239.0565 $[M-H]^-$ (calcd for $C_{11}H_{11}O_6$, 239.0561).

3.4. ECD calculations

Conformational searches for compound **1** was performed via molecular mechanics using the MM + method in HyperChem 8.0 software, and the geometries were further optimized at the B3LYP/6-31 G level via Gaussian 09 software to give the energy-minimized conformers. The optimized conformers were then subjected to the calculations of ECD spectra using the TD-DFT at PBE0/TZVP level; solvent effects of the MeOH solution were evaluated at the same DFT level using the SCRF/PCM method (Frisch et al., 2013).

3.5. Antimicrobial activity assay

Antimicrobial evaluation against plant-pathogenic fungi *Fusarium. oxysporum* f. sp. *momordicae* nov. f. and *Colletotrichum gloeosporioides*, which were obtained from the Institute of Oceanology, Chinese Academy of Sciences, was carried out by the microplate assay (Pierce et al., 2008). Briefly, compounds with different concentrations were added to the suspension of the fungi in 96-well microplate. After cultivation, if the mixture in the well was turbid and the transmittance decreased obviously, indicating that the concentration of compounds in the hole could not inhibit the growth of the fungus. On the contrary, clarified mixture in the well and the indistinctive decrease of transmittance indicated fungi could not grow in the concentration of compounds. The MIC of the compound was the lowest sample concentration for complete inhibition of fungal growth in the well. Amphotericin B was used as positive control.

3.6. DPPH radical scavenging activity testing

The DPPH radical was used to determine the antioxidant activity of compounds **2–8** with the method reported early (Duan et al., 2006). This test was performed in 96-well microplate. Briefly, 100 μL DPPH solution in MeOH (0.16 mmol/L) was added to a range of solutions of different concentrations (200, 100, 50, 25, 10, 5 μg/mL) of compounds to be tested in 100 μL MeOH. The mixture was vortexed for 1 min and then left to stand at room temperature for 30 min in the dark. Absorbance at 517 nm was determined and the percentage of activity was calculated. Butylated hydroxytoluene (BHT) was used as a positive control.

Acknowledgments

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2019.04.018.

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