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Phomoxins B and C: Polyketides from an endophytic fungus of the genus *Eupenicillium*

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Abstract

Chemical investigations of the culture broth from an endophytic fungus *Eupenicillium* sp. have afforded two natural products phomoxins B (**1**) and C (**2**) as well as the previously reported fungal metabolite eupenoxide (**3**). Compounds **1** and **2** both contain a cyclic carbonate moiety that is rare among natural products. This paper reports the full spectroscopic characterisation of phomoxins B (**1**) and C (**2**) by NMR, UV, IR and MS data. All compounds were inactive against a panel of nosocomial microbes.

Keywords: Endophytic fungus; *Eupenicillium* sp.; *Glochidion ferdinandi*; Natural products; Polyketides; Phomoxin B; Phomoxin C; Eupenoxide; Cyclic carbonate

1. Introduction

Polyketides are a class of natural products that have been shown to display a wide range of medicinally important activities such as antibiotic, anticancer, antifungal, hypolipidemic and immunosuppressive properties (Staunton and Weissman, 2001). Fungi have been prolific producers of new polyketide natural products over the decades (Turner and Aldridge, 1983) and they continue to be the sources of new structural and/or bioactive polyketide chemistry. Recent examples include the antitumour berkeleydione from *Penicillium* sp., (Stierle et al., 2004) the antibacterial agents annularins A and B from *Annulatascus triseptatus* (Li et al., 2003), the HIV-1 integrase inhibitor integrasone from an unidentified sterile mycelium (Herath et al., 2004) and the antiviral compound hesseltin A from *P. hesseltinei* (Phipps et al., 2004). We are currently undertaking a research program that is focusing on the discovery of new structural and bioactive secondary metabolites from endophytic fungi that have been isolated from Australian endemic plants (Davis et al., 2005; Healy et al., 2004). Examination of a local rainforest tree, *Glochidion ferdinandi* (family Euphorbiaceae) afforded several microfungal strains, one of which was identified as *Eupenicillium* sp. Herein, we report the chemical investigations of this strain, which have resulted in the identification of two new polyketides, phomoxins B (**1**) and C (**2**).

2. Results and discussion

The fungal isolate *Eupenicillium* sp. (BRIP 39874) was grown in shaken malt extract broth. The culture broth was extracted with EtOAc and the organic extract was separated using Sephadex LH-20 (100% MeOH) to yield five fractions. Fractions 3 and 4 were subjected to phenyl preparative HPLC (MeOH/H_2O) to afford pure phomoxin B (**1**, 4.5 mg), phomoxin C (**2**, 4.5 mg) and eupenoxide (**3**, 35.9 mg).

Phomoxin B (**1**) was isolated as a white amorphous solid. A pseudomolecular ion in the (−)-HRESIMS at

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m/z 333.11148 $[M + {}^{35}Cl]^-$ in conjunction with the ^1H and ^{13}C NMR data (Table 1) allowed a molecular formula of $C_{15}H_{22}O_6$ to be assigned to **1**. Broad IR absorptions at 3500–3100 and 1785 cm^{-1} indicated the presence of hydroxyl and carbonyl groups, respectively (Pretsch et al., 2000). The ^1H NMR spectrum of **1** contained three hydroxyl protons, four hydroxymethines, two signals corresponding to a hydroxymethylene system, two protons which constituted a *trans*-double bond and four aliphatic signals. The ^{13}C NMR spectrum of **1** displayed 15 signals which consisted of four olefinic, five oxygen bearing, one downfield quaternary and five aliphatic carbons. All non-exchangeable protons were attached to carbons following gHSQC analysis. Interpretation of the gCOSY data established four contiguous methylene units that were positioned between a terminal methyl group and the *trans*-double bond. The gCOSY data also allowed the assignment of all hydroxyl groups to their corresponding oxymethine or oxymethylene systems. Furthermore, the gCOSY experiment allowed four contiguous oxymethine groups to be linked together. HMBC correlations for both oxymethine protons at δ 4.22 (H-3) and 5.48 (H-6) to 137.1 (C-2), 127.1 (C-1), 68.9 (C-4) and 75.8 ppm (C-5) allowed construction of a cyclohexene moiety. HMBC correlations from δ 3.82 (H-4) to C-2, C-3, C-5 and C-6 and δ 4.74 (H-5) to C-1, C-3 and C-4 further supported this assignment. This monocyclic system was linked to the pentyl terminated *trans*-double bond at C-2 via HMBC correlations from δ 5.98 (H-2′) to C-2 and δ 6.35 (H-1′) to C-2 and C-1. In a similar manner the hydroxy methylene system was linked to C-1 of the cyclohexene ring on the basis of HMBC correlations from both δ 4.32 (H-7b) and δ 3.97 (H-7a) to C-1, C-2 and C-6. The downfield quaternary carbon at 154.1 ppm was assigned to a carbonate carbonyl functionality (C-8′) involving two oxygen bearing carbons at C-5 and C-6 on the basis of the HMBC correlations from both δ 4.74 (H-5) and δ 5.48 (H-6) to 154.1 ppm. This carbonate functional group assignment was supported by the IR absorption at 1785 cm^{-1} (Pretsch et al., 2000). Thus, the gross structure of phomoxin B was assigned. The relative stereochemistry of **1** was determined by ROESY data analysis. Strong ROESY correlations from δ 4.74 (H-5) to 3.82 (H-4) and 5.48 (H-6) indicated that these three protons were all orientated on the same side of the cyclohexene system. ROESY correlations between δ 3.82 (H-4) and 4.22 (H-3) and 5.20 (3-OH) along with cross peaks between δ 5.39 (4-OH) and 4.22 (H-3) suggested that the hydroxyl groups at C-3 and C-4 were orientated *trans* relative to each other. The small vicinal ^1H–^1H coupling constant of 4.2 Hz between H-3 and H-4 indicated that these two protons both had equatorial orientations. With the relative stereochemistry determined structure **1** was assigned to phomoxin B (Fig. 1). Phomoxin B (**1**) is an isomer of the previously isolated fungal metabolite phomoxin (**4**) (Liu et al., 2003).

Phomoxin C (**2**) was isolated as an optically active white powder. Interpretation of the (−)-HRESIMS and the ^1H and ^{13}C NMR data (Table 2) allowed the molecular formula $C_{15}H_{22}O_6$ to be assigned to compound **2**. These data confirmed that **2** was an isomer of phomoxin B (**1**). The ^1H NMR spectrum of **2** showed many similarities with that of phomoxin B. Spectral differences between **1** and **2** were observed between δ 3.50 and 5.70 suggesting structural changes about the cyclohexene ring system. Analysis of the gHSQC and gCOSY spectra showed that the oxygenation pattern about the six-membered ring was identical to phomoxin B (**1**). HMBC correlations from δ 5.51 (H-3) and 4.68 (H-4) to the carbonate carbon at 154.9 ppm allowed the carbonate functionality to be attached to C-3 and C-4, with the remaining hydroxyl groups positioned at C-5 and C-6. Hence, the gross structure of phomoxin C (**2**) was assigned. In a similar manner to **1**, the relative stereochemistry about the cyclohexene system for **2** was

Table 1
NMR data for phomoxin B (**1**)[a]

Position	^{13}C	^1H (mult., *J*, int.)	gCOSY	gHMBC	ROESY
1	127.1				
2	137.1				
3	66.8	4.22 (*dd*, 4.8, 4.2, 1H)	3-OH, 4	1, 2, 4, 5, 1′	3-OH, 4, 4-OH, 2′
3-OH		5.20 (*d*, 4.8, 1H)	3	2, 3, 4	3, 4
4	68.9	3.82 (*ddd*, 4.2, 4.2, 3.6, 1H)	3, 4-OH, 5	2, 3, 5, 6	3, 3-OH, 4-OH, 5
4-OH		5.39 (*d*, 4.2, 1H)	4	3, 4, 5	3, 4
5	75.8	4.74 (*dd*, 8.4, 3.6, 1H)	4, 6	1, 3, 4, 8′	4, 6
6	72.7	5.48 (*d*, 8.4, 1H)	5	1, 2, 4, 5, 7, 8′	5, 7a
7a	57.7	3.97 (*dd*, 13.2, 6.0, 1H)	7b, 7-OH	1, 2, 6	6, 7b, 7-OH
7b		4.32 (*dd*, 13.2, 4.8, 1H)	7a, 7-OH	1, 2, 6	7a, 1′, 7-OH
7-OH		4.93 (*dd*, 6.0, 4.8, 1H)	7a, 7b	1, 7	7a, 7b
1′	125.8	6.35 (*d*, 15.6, 1H)	2′, 3′	1, 2, 3, 3′	7b, 3′
2′	134.8	5.98 (*dt*, 15.6, 7.2, 1H)	1′, 3′	2, 1′, 3′, 4′	3, 3′
3′	32.7	2.13 (*td*, 7.2, 7.2, 2H)	1′, 2′, 4′	1′, 2′, 4′, 5′	1′, 2′, 4′, 5′
4′	28.3	1.38 (*tt*, 7.2, 7.2, 2H)	3′, 5′	2′, 3′, 5′, 6′	3′, 5′
5′	30.8	1.28 (*m*, 2H)	4′	6′, 7′	3′, 4′
6′	21.9	1.28 (*m*, 2H)	7′	5′, 7′	7′
7′	13.9	0.86 (*t*, 7.2, 3H)	6′	5′, 6′	5′, 6′
8′	154.1				

[a] Spectra were recorded in DMSO-d_6 at 30 °C.

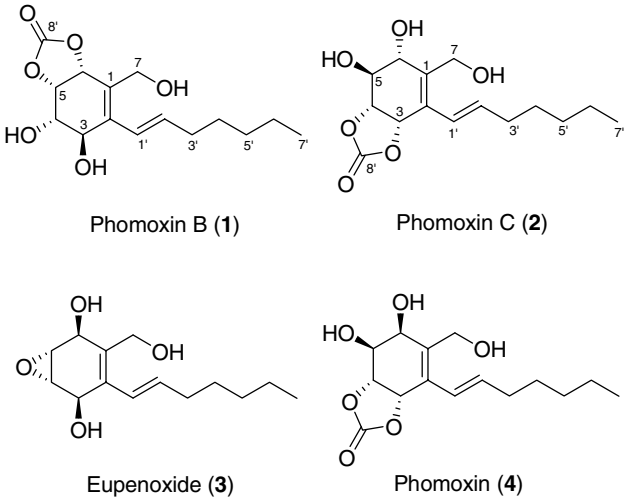

Fig. 1. Structures for compounds **1**–**4**.

established by ROESY data analysis and ^{1}H–^{1}H coupling constants. Strong ROESY correlations from δ 4.68 (H-4) to 5.51 (H-3) and 4.06 (H-6) indicated that all three protons were orientated on the same side of the cyclohexene system. The axial–axial orientations of H-4 with H-5 and H-5 with H-6 were confirmed by their large coupling constants of 7.8 and 7.2 Hz, respectively (Pretsch et al., 2000). With the relative stereochemistry determined structure **2** was assigned to phomoxin C. Phomoxin C (**2**) is the C-6 epimer of phomoxin (**4**) (Liu et al., 2003).

The major metabolite eupenoxide (**3**) was isolated as an optically active pale yellow oil. Eupenoxide has previously been isolated from a terrestrial *Eupenicillium* sp. (Duke and Rickards, 1984) and more recently from a marine-derived *Phoma* sp. (Liu et al., 2003). Comparison of our spectroscopic data with the literature values (Liu et al., 2003) confirmed that compound **3** was eupenoxide.

Although eupenoxide was initially reported to have antifungal activity (Duke and Rickards, 1984) in the more recent paper by Liu et al. (2003) neither eupenoxide (**3**) or phomoxin (**4**) showed any significant antibacterial, antifungal or anticancer activity. We tested compounds **1**–**3** against a panel of microbial strains known to be associated with nosocomial infection, which included multi-drug resistant *Staphylococcus aureus* (wild type MRSA), *S. aureus* (NCCLS 29523), *Escherichia coli* (ATCC 25922), *Enterococcus faecalis* (NCCLS 29212), *Pseudomonas aeruginosa* (ATCC 27853), *Streptococcus pyogenes* (ATCC 19615), *Acinetobacter anitratus* (wild type) and *Candida albicans* (ATCC 60193). Antimicrobial activities were evaluated using a broth microdilution assay (Jorgensen et al., 2000; Lister, 2002) with each compound screened at concentrations of 100, 50, 25, 12.5, 6.3, 3.2, 1.6, 0.8, 0.4 and 0.2 μg/mL. No microbial growth inhibition was observed for **1**–**3** at any of these concentrations after 20 h of dosing.

In conclusion, we have isolated and determined the relative stereochemical structures of two new polyketides, phomoxins B (**1**) and C (**2**). Both these secondary metabolites contain a cyclic carbonate moiety which is rare among natural products (Chapman and Hall Electronic Publishing, 2005). The previously identified fungal natural product eupenoxide (**3**) was also isolated and compounds **1**–**3** were all tested in a number of antimicrobial assays. No microbial growth inhibition was observed for any of the fungal natural products.

3. Experimental

3.1. General

NMR spectra were recorded at 30 °C on either a Varian 500 or 600 MHz Unity INOVA spectrometer. The latter spectrometer was equipped with a triple resonance

Table 2
NMR data for phomoxin C (**2**)[a]

Position	^{13}C	^{1}H (mult., *J*, int.)	gCOSY	gHMBC	ROESY
1	141.7				
2	124.8				
3	73.6	5.51 (*d*, 7.2, 1H)	4, 6, 7	1, 2, 4, 5, 1′, 8′	4, 2′
4	77.5	4.68 (*dd*, 7.2, 7.8, 1H)	3, 5	2, 5, 6, 8′	3, 6
5	70.7	3.52 (*dd*, 7.2, 7.8, 1H)	4, 5-OH, 6	1, 3, 4, 6	5-OH
5-OH		5.57 (*br s*, 1H)	5		5
6	68.7	4.06 (*d*, 7.2, 1H)	5, 6-OH	1, 2, 4, 5	4, 7
6-OH		5.27 (*br s*, 1H)	6		
7	56.5	4.21 (*m*, 2H)	7-OH	1, 2, 6	6, 7-OH, 1′
7-OH		4.59 (*br s*, 1H)	7		7
1′	125.3	6.47 (*d*, 15.6, 1H)	2′, 3′	1, 2, 3, 2′, 3′	7, 3′
2′	133.6	5.88 (*dt*, 15.6, 7.2, 1H)	1′, 3′	1′, 3′, 4′	3, 3′
3′	32.7	2.13 (*td*, 7.2, 7.2, 2H)	1′, 2′, 4′	1′, 2′, 4′, 5′	1′, 2′, 4′
4′	28.4	1.38 (*tt*, 7.2, 7.2, 2H)	3′, 5′	3′, 5′, 6′	3′, 5′
5′	30.7	1.28 (*m*, 2H)	4′	6′, 7′	4′
6′	21.9	1.28 (*m*, 2H)	7′	5′, 7′	7′
7′	13.8	0.86 (*t*, 6.6, 3H)	6′	5′, 6	6′
8′	154.0				

[a] Spectra were recorded in DMSO-d_6 at 30 °C.

cold probe. The ^{1}H and ^{13}C chemical shifts were referenced to the solvent peak for DMSO-d_6 at δ 2.49 and 39.51 ppm, respectively. LRESIMS were recorded on a Fisons mass spectrometer. HRESIMS were recorded on a Bruker Daltronics Apex III 4.7e Fourier-transform mass spectrometer. Optical rotations were recorded on a Jasco P-1020 polarimeter. FTIR and UV spectra were recorded on a Perkin–Elmer 1725X spectrophotometer and a GBC UV/vis 916 spectrophotometer, respectively. A Waters 600 pump equipped with a Waters 996 PDA detector and a Rheodyne injector were used for HPLC. Sephadex LH-20 packed into an open glass column (45 mm × 500 mm) was used for gel permeation chromatography. A Thermo Hypersil Phenyl BDS 5 μm 143 Å preparative column (21.2 mm × 150 mm) was used for HPLC separations. All solvents used for chromatography, UV and MS were Lab-Scan HPLC grade, and the H_2O was Millipore Milli-Q PF filtered. All fungal culture media were purchased from Difco and the materials used for the antimicrobial assays were all obtained from Oxoid.

3.2. Collection and identification

Eupenicillium sp. was isolated from a surface sterilised (EtOH/flame) piece of outer bark from the rainforest tree *Glochidion ferdinandi* (Williams et al., 1984) collected from Toohey Forest, Qld, Australia during February of 2003. The identification of the fungus was based on the presence of immature cleistothecia (sclerotia) in 10 week old colonies grown on potato dextrose agar (Pitt, 1979). A voucher specimen and culture (BRIP 39874) have been deposited at the Department of Primary Industries and Fisheries, Indooroopilly, Qld 4068, Australia.

3.3. Fermentation, extraction and isolation

The fungal isolate was initially grown in three culture tubes each containing malt extract broth (10 mL) at 30 °C for 5 days. These cultures were transferred to three conical flasks (1000 mL) each containing liquid broth extract (5.0 g of malt extract plus 500 mL H_2O) and the fermentation was shaken at 150 rpm at 25 °C for 28 days. EtOAc extraction of the cultures followed by removal of the solvent in vacuo yielded a dark brown gum (200 mg). This extract was purified using a Sephadex LH-20 column with 100% MeOH as eluant at a flow rate of 7 mL/min and yielded 60 fractions. These fractions were analysed on silica TLC using 20% MeOH/80% DCM as the developing solvent. Combining of similar UV fractions resulted in five fractions. Fraction 3 (72 mg) and 4 (29 mg) were both subjected to phenyl preparative HPLC using a linear gradient from 60% H_2O/40% MeOH to 100% MeOH in 30 min at the flow rate of 6 mL/min. This yielded pure phomoxin B (**1**, 4.5 mg, $t_R = 13.0$ min), eupenoxide (**3**, 35.9 mg, $t_R = 15.0$ min) and phomoxin C (**2**, 4.5 mg, $t_R = 19.5$ min).

3.3.1. Phomoxin B (*1*)

Stable white amorphous solid: $[\alpha]_D^{23} - 5°$ (*c* 0.116, MeOH); UV (MeOH) λ_{max} (log ε) 206 (3.78), 244 nm (4.02); IR ν_{max} (NaCl) 3500–3000, 1785, 1598, 1377, 1182, 1065, 1039, 997, 778, 727 cm^{-1}; ^{1}H (600 MHz) and ^{13}C (125 MHz) NMR data see Table 1; (+)-LRESIMS *m/z* (rel. int.) 321 (100) $[M + Na]^+$; (−)-HRESIMS *m/z* 333.11148 ($C_{15}H_{22}{}^{35}ClO_6$ $[M + {}^{35}Cl]^-$ requires 333.11104).

3.3.2. Phomoxin C (*2*)

Stable white amorphous solid: $[\alpha]_D^{23} + 30°$ (*c* 0.116, MeOH); UV (MeOH) λ_{max} (log ε) 206 (3.56), 242 nm (3.71); IR ν_{max} (NaCl) 3500–3000, 1788, 1632, 1351, 1177, 1066, 1034, 1001, 772, 730 cm^{-1}; ^{1}H (600 MHz) and ^{13}C (125 MHz) NMR data see Table 2; (+)-LRESIMS *m/z* (rel. int.) 321 (100) $[M + Na]^+$; (−)-HRESIMS *m/z* 333.11210 ($C_{15}H_{22}{}^{35}ClO_6$ $[M + {}^{35}Cl]^-$ requires 333.11104).

3.4. Antimicrobial testing

Antimicrobial activity for each compound was tested against a variety of microorganisms commonly associated with nosocomial infections. Microbial isolates were a kind gift from the Toowoomba Base Hospital (Toowoomba, Queensland, Australia) and included multi-drug resistant *S. aureus* (wild type MRSA), *S. aureus* (NCCLS 29523), *E. coli* (ATCC 25922), *E. faecalis* (NCCLS 29212), *P. aeruginosa* (ATCC 27853), *S. pyogenes* (ATCC 19615), *A. anitratus* (wild type) and *C. albicans* (ATCC 60193). Antimicrobial activities were evaluated using a broth microdilution method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) with the exception that Todd-Hewitt (TH) broth (infusion fat-free minced meat 10.0 g/L, tryptone 20 g/L, glucose 2.0 g/L, sodium bicarbonate 2.0 g/L, di-sodium phosphate 0.4 g/L, pH 7.8) was used as the test medium because of the confluent growth rate exhibited by all microorganisms in this broth (Jorgensen et al., 2000; Lister, 2002). In brief, each microorganism was initially purified on horse blood agar, then grown in Brain Heart Infusion (BHI) broth (calf brain infusion solids 12.5 g/L, beef heart infusion solids 5.0 g/L, proteose peptone 10.0 g/L, glucose 2.0 g/L, sodium chloride 5.0 g/L, di-sodium phosphate 2.5 g/L, pH 7.4) overnight at 35 °C in air and subsequently diluted in TH broth for testing at about 10^5 CFU/mL. Test compounds were dissolved in 50% aqueous DMSO and serially double diluted from 100 to 0.2 μg/mL. The minimum inhibitory concentrations (MICs) for each organism were read as the concentrations in the first wells that showed no visible growth after incubation at 35 °C for 20 h. No microbial growth inhibition was observed at any of the concentrations after the 20 h dosing.

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