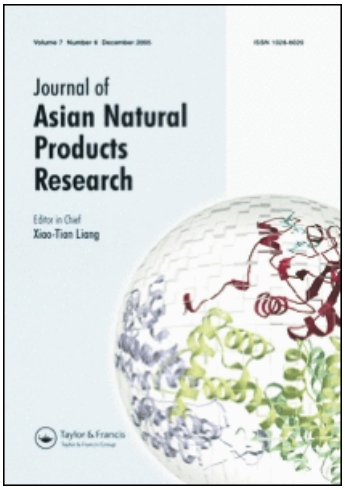

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Pyrrole and indole alkaloids from an endophytic *Fusarium incarnatum* (HKI00504) isolated from the mangrove plant *Aegiceras corniculatum*

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Two new pyrrole alkaloids, *N*-[4-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide (**1**) and *N*-[5-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-pentyl]-acetamide (**2**), and a new indole derivative (3a*R*,8a*R*)-3a-acetoxyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol (**3**) were isolated, together with (−)-3a-hydroxyfuroindoline, (3a*R*,8a*S*)-1-acetyl-1,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol-3a-ol, and *N*-acetyltryptamine A, from an endophytic ascomycetous fungus, *Fusarium incarnatum* (HKI00504), which was isolated from the mangrove plant *Aegiceras corniculatum*. The structures of compounds **1**–**3** were determined on the basis of extensive spectroscopic data analyses.

Keywords: *Fusarium incarnatum*; *Aegiceras corniculatum*; mangrove; pyrrole alkaloid

1. Introduction

Endophytic microorganisms from mangrove plants have become an important source of pharmacologically active metabolites [1–6]. Endophytes are microorganisms that invade the healthy tissues of living plants without causing diseases symptoms, but may increase plant growing, deter fungal pathogens, prevent herbivory, and induce drought tolerance. Previous chemical investigation of an endophytic *Fusarium incarnatum* (HKI00504) from the mangrove plant *Aegiceras corniculatum* resulted in the isolation and characterization of four new cyclopentenone derivatives [7]. In this paper, we describe the isolation and structural elucidation of two new pyrrole alkaloids, *N*-[4-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide (**1**) and *N*-[5-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-pentyl]-acetamide (**2**), and a new indole derivative (3a*R*,8a*R*)-3a-acetoxy-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indole (**3**), along with three known compounds (−)-3a-hydroxyfuroindoline, (3a*R*,8a*S*)-1-acetyl-1,3,3a,8,8a-hexahydropyrrolo-[2,3-b] indol-3a-ol, and *N*-acetyltryptamine A (Figure 1).

2. Results and discussion

A fungal isolate (HKI00504) was identified as *F. incarnatum* (Roberge) Saccardo 1848 by morphological and molecular taxonomical parameters (Khoa *et al.* 2004). According to the GenBank entries, *F. incarnatum* was earlier reported in wetland (Dongton) in China, as endophyte in wine (*Vitis vinifera*) or

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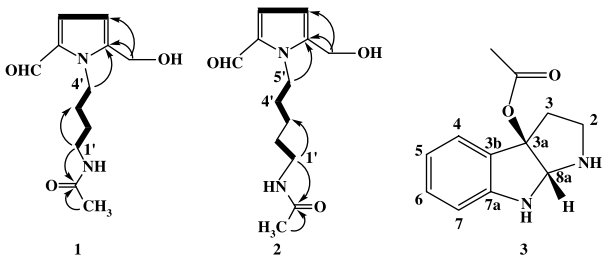

Figure 1. Structures of compounds **1**–**3**.

opportunistic pathogen in animals and human [8,9].

Compound **1** was isolated as a pale yellow oil, and its molecular formula $C_{12}H_{18}N_2O_3$ was established by the HR-FAB-MS (*m/z* 261.1209 $[M + Na]^+$) and NMR data, indicating five degrees of unsaturation. The UV absorption maximum at 292 nm is the characteristic of pyrrole-2-aldehyde [10,11], while the IR absorptions at 3290, 1641, and 1552 cm^{-1} suggested the presence of hydroxy or amino functionalities and amide groups. The ^{13}C NMR and DEPT spectra indicated the presence of 12 carbons, which included four contiguous methylenes (δ_C 45.9, 39.4, 29.8, and 27.6), one CHO (δ_C 180.4), one CH_2OH (δ_C 55.9), and four carbon resonances (δ_C 132.8, 122.0, 111.0, 144.0) of a pyrrolylic ring. Those NMR data were consistent with a 2-formyl-5-hydroxymethylenepyrrolybutylamine segment of magnolamide [12]. The assignment was confirmed by HMBC correlations from aldehyde proton at δ_H 9.44 (1H, s, H-1) to δ_C 132.8 (s, C-2) and 122.0 (d, C-3), and from hydroxymethylene protons at δ_H 4.48 (2H, s, H-6) to δ_C 144.0 (s, C-5) and 111.0 (d, C-4), and also between the methylene protons at δ_H 4.23 (2H, t, $J = 7.5$ Hz, H_2-4′) and C-2 and C-5. Compound **1** differed from magnolamide in the presence of an acetyl instead of a feruloyl moiety to form an amide at the terminal amine, as evidenced by the acetyl resonances (δ_C 23.8, 169.0; δ_H 1.76) and the HMBC relationship between both δ_H 1.76 (3H, s) and 2.95 (2H, t, $J = 6.5$ Hz, H_2-1′), and the carbonyl carbon at δ_C 169.0 (s). Therefore, the structure of **1** was determined to be *N*-[4-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide.

Compound **2** was obtained as a pale yellow oil. Its molecular formula was assigned to be $C_{13}H_{20}N_2O_3$ based on the HR-FAB-MS (*m/z* 253.1549 $[M + H]^+$) and NMR data. The ^1H and ^{13}C NMR data of **2** were very similar to those of **1**, except for the presence of an additional methylene group (δ_C 1.25, m; δ_H 24.7, t). ^1H–^1H COSY correlations indicated a pentylamine unit of **2** instead of the butylamine unit of **1**. The acetyl group of **1** was also present in **2** as deduced by the NMR resonances at δ_H 1.78 (3H, s), δ_C 23.6 (q) and 170.3 (s), and the HMBC correlations of carbonyl carbon with δ_H 2.99 (2H, t, $J = 6.5$ Hz, H_2-1′) and 1.78 (s). Thus, the structure of **2** was assigned to be *N*-[5-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-pentyl]-acetamide.

Compound **3** was obtained as an optically active colorless gum, and its molecular formula was determined to be $C_{12}H_{14}N_2O_2$ by the HR-ESI-MS (*m/z* 218.1053 $[M]^+$) and NMR data, indicating seven degrees of unsaturation. Its ^1H and ^{13}C NMR data revealed four continuously coupled aromatic protons at δ_H 7.26 (1H, d, $J = 7.5$ Hz, H-4), 7.14 (1H, t, $J = 7.5$ Hz, H-6), 6.80 (1H, t, $J = 7.5$ Hz, H-5), and 6.68 (1H, d, $J = 7.5$ Hz, H-7); a methine at δ_H 5.31(1H, s, H-8); four coupled aliphatic protons at δ_H 3.95, 3.05 (2H, m, H-2), and 2.32 (2H, m, H-3); and an acetyl methyl singlet at δ_H 2.18 (3H, s, CH_3), and 12 carbons (Experimental section) including six of an aromatic ring, and δ_C 21.9 (q, CH_3) and 172.7 (s, C═O) of an acetyl group. The NMR data of **3** were very

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data and HMBC correlations of **1** and **2**.

	1[1]			**2**[1]		
No.	δ_C	δ_H	HMBC (H → C)	δ_C	δ_H	HMBC (H → C)
1	180.4	9.44 1H, s	C-2, C-3	180.2	9.43 1H, s	C-2, C-3
2	132.8			132.6		
3	122.0	6.96 1H, d, 4.0	C-1, C-5	122.9	6.96 1H, d, 4.0	C-1, C-5
4	111.0	6.19 1H, d, 4.0	C-2, C-5, C-6	111.6	6.19 1H, d, 4.0	C-2, C-5, C-6
5	144.0			144.4		
6	55.9	4.48 2H, s	C-4, C-5	55.8	4.49 2H, s	C-4, C-5
1′	39.4	2.95 2H, t, 6.5	C-2′, C-3′, C═O	39.4	2.99 2H, t, 6.5	C-3′, C-4′, C═O
2′	27.6	1.35 1H, m[2] 1.22 1H, m[2]	C-1′, C-2′, C-4′	29.8	1.38 1H, m[2] 1.25 1H, m[2]	C-2′, C-3′, C-5′
3′	29.8	1.60 2H, m[2]	C-1′, C-3′, C-4′	24.7	1.25 2H, m[2]	C-1′, C-2′, C-4′, C-5′
4′	45.9	4.23 2H, t, 7.5	C-2, C-5, C-2′, C-3′	31.8	1.60 2H, m[2]	C-1′, C-3′, C-4′
5′				46.0	4.23 2H, 7.5	C-2, C-5, C-2′, C-3′
CH_3	23.8	1.76 3H, s	C═O	23.6	1.78 3H, s	C═O
CO	169.0			170.3		

[1] Measured in DMSO-d_6.
[2] Overlapping signals.

Table 2. Cytotoxicity of alkaloids **1**–**3**.

	IC_{50} (μg/ml)		
Compound	HeLa	K-562	L-929
1	11.6	15.7	20.2
2	8.9	13.5	17.6
3	6.3	14.4	13.5
Taxol	0.01	0.05	

similar to those of (3a*R*,8a*S*)-1-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol-3a-ol [13,14] a known co-metabolite from the same fraction, only differing in a downfield shift of the ^{13}C NMR signal of C-3a in **3** (δ_C 90.3 (s) instead of δ_H 87.8 (s)) and upfield shifts of the ^1H NMR signals of H_2-2 and H-8a of **3** (Experimental section). These findings suggested that the acetyl group was located at C-3a of **3** to form an acetoxy group. NOE correlations (NOESY) between the acetyl protons and H_2-3, and H-8a and H-3, in conjunction with a weak NOE interaction between H-8a and the acetyl protons confirmed the acetoxy position and a *cis* ring junction between the tetrahydropyrrole rings. On the basis of biosynthetic relationship and similar optical rotation, compound **3** was suggested to possess the absolute stereochemistry of (3a*R*,8a*R*)-1-acetyl-1,3,3a,8,8a-hexahydropyrrolo-[2, 3-b]indol-3a-ol.

The known metabolites (−)-3a-hydroxyfuroindoline, (3a*R*,8a*S*)-1-acetyl-1,3,3a,8,8a-hexahydropyrrolo-[2,3-b]indol-3a-ol, and *N*-acetyltryptamine A were identified on the basis of their NMR and MS data, as well as their optical rotation. Compound **3** was suggested to be biogenetically derived from the fungal metabolite (3a*R*,8a*S*)-1-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol-3a-ol through acetyl immigration, while the latter was previously depicted to be generated from the precursor *N*-acetyltryptamine A [13]. It is noted that the alkaloid metabolites found from this fungus did not occur in the host mangrove plant *Aegiceras corniculatum* [15]. In addition, (−)-3a-hydroxyfuroindoline was originated from an intermediate to synthesize the interleukin-6 inhibitors madindolines A and B [14], but was isolated as a fungal metabolite for the first time. (3a*R*,8a*S*)-1-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol-3a-ol and *N*-acetyltryptamine A were previously reported to be isolated from the fungus *Streptomyces staurosporeus* [13].

The bioassay result indicated that the present alkaloids showed weak activity against tumor cell lines HeLa, K-562, and L-929 (Table 2), but inactive for the antibiotics *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* ($IC_{50} > 10$ μg/ml). The endophytic alkaloids co-existing with the host plant may play an ecological role for plant protection.

3. Experimental

3.1 General experimental procedures

Optional rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Bruker IFS 55 spectrometer. ^1H and ^{13}C NMR as well as 2D-NMR spectra were recorded on Varian-500, Bruker DPX-300 and Bruker DRX-500 spectrometers. HR-FAB-MS spectra were obtained on a VG Atospectrometer, while ESI-MS were recorded on a triple quadrupole mass spectrometer Quattro (VG Biotech, England). Column chromatography was carried out on silica gel (200–400 mesh, Merck, New Jersey, USA), and the HF-254 silica gel for TLC was provided by Sigma Co. Ltd. Sephadex LH-20 (110 μm) was obtained from Pharmacia Co. High-pressure liquid chromatography (HPLC) was performed on an Alltech-426 apparatus using Kromasil prepack column (ODS, 10 mm × 250 mm, for reverse phase) and monitored by the UV detector.

3.2 Strain isolation, taxonomy, and cultivation

F. incarnatum (HKI00504) was isolated from the leaves of mangrove plant *Aegiceras corniculatum* that was collected from Xiamen, Fujian province of China in August 2002 (Xu *et al.* 2007). The plant was

authenticated by Professor P. Lin from Xiamen University, China. A voucher sample of the plant (No. 200208082) is deposited in the School of Pharmaceutical Sciences, Peking University. The strain is deposited as HKI00504 in the strain collection of the Leibniz Institute for Natural Products Research and Infection Biology, Hans-Knöll-Institute (HKI, Jena, Germany) and as FSU6195 in the strain collection of the Fungal Reference Centre of the University Jena (FSU, Jena, Germany).

The fungus was taxonomically studied by morphological criteria and was assigned as *F. incarnatum* on the basis of macro- and micromorphological criteria. Slender, cylindrical, 1–5 septate blastic conidia with an acuate apical cell and a foot-shaped basal cell from monophialides are formed on sporodochial conidiophores bearing mono-polyblastic conidiogenous cells. Isolation of genomic DNA, amplification by polymerase chain reaction, cloning, and sequencing of the nuclear ribosomal DNA including internal transcribed spacer regions 1 and 2, 5.8S, and D1/D2 domain of the 28S ribosomal DNA was carried as previously described by Voigt *et al.* (2005). The nucleotide sequence spanning the ITS1–5.8S–ITS2–D1/D2 of the nuclear ribosomal DNA cluster was determined and deposited under the accession number EU111657 in the GenBank at www.ncbi.nlm.nih.gov. The 1094-long nucleotide sequence unequivocally matched AF130380, AY633745, EF158029, and EU030333 accession numbers of *F. incarnatum* in the GenBank BLAST searches.

The production culture was carried out in a 300 l fermentor filled with 200 l of culture medium (saccharose 20 g/l, soybean flour 10 g/l, corn steep 10 g/l, KCl 8 g/l (pH 6.5)). The cultivation was carried out for 10 days at 22°C (aeration 50 l/min (pH 6.5)) and stirred with 125 rpm. The inoculum (2 l) was obtained after several steps of resting cultures with increasing cultivation volume in a modified malt extract medium (malt extract 10.0 g/l, yeast extract 4.0 g/l, glucose 4.0 g/l, $(NH_4)_2HPO_4$ 0.5 g/l (pH 5.5)). The spores of *F. incarnatum* (HKI00504) were initially grown on agar slants (ISP2 culture medium).

3.3 Extraction and isolation

The fermentation broth (200 l) was obtained by filtration and then subjected to an Amberchrom 161c resin LC column (200 × 20 cm, 6 l). The elution was performed with a linear gradient of MeOH–H_2O (from 40 to 90% in 58 min) to afford seven fractions (FA–FG). These fractions were lyophilized and analyzed on TLC (chemical screening) to combine fractions FE–FG, which were desalted by extracting with methanol. The MeOH extract (19 g) was subjected to a silica gel column by eluting with $CHCl_3$–MeOH (10:1) to yield seven fractions. The forth fraction (30 mg) was chromatographed on silica gel column (chloroform–acetone, 8:1), followed by Sephadex LH-20 column eluted with 100% MeOH to give (−)-3a-hydroxyfuroindoline (4.0 mg), (3a*R*,8a*S*)-1-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indol-3a-ol (3.0 mg), compound **3** (6.5 mg), *N*-acetyltryptamine A (2.5 mg), and a mixture of **1** and **2** (10 mg), which showed one spot in TLC ($CHCl_3$: MeOH, 9:1, R_f 0.42), but exhibited a mixture of pyrrole derivatives in the ^{1}H NMR spectrum. This mixture was then submitted to semi-preparative reverse-phase HPLC (C-18) by eluting with MeOH–H_2O (80:20) (1.5 ml/min) to yield compounds **1** (2.5 mg) and **2** (3.5 mg).

3.3.1 N-*[4-(2-Formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide (**1**)*

Pale yellow oil; UV (MeOH) λ_{max} (nm): 292; IR (KBr) ν_{max} (cm^{-1}): 3290, 2932, 2863, 1641, 1552, 1403, 1292, 1129, 1031; ESI-MS (positive) *m/z*: 238 $[M]^+$; HR-FAB-MS *m/z*: 261.1209 $[M + Na]^+$ (calcd for $C_{12}H_{18}N_2O_3Na$ 261.1209); ^{1}H and ^{13}C NMR data: see Table 1.

3.3.2 N-*[5-(2-Formyl-5-hydroxymethyl-pyrrol-1-yl)-pentyl]-acetamide (**2**)*

Pale yellow oil; UV (MeOH) λ_{max} (nm): 292; IR (KBr) ν_{max} (cm^{-1}): 3293, 2930, 2862, 1641, 1558, 1400, 1294, 1115, 1032; ESI-MS (positive) *m/z*: 253 $[M + 1]^+$; HR-FAB-MS *m/z*: 253.1549 $[M + H]^+$ (calcd for $C_{13}H_{21}N_2O_3$, 253.1546); ^1H and ^{13}C NMR data: see Table 1.

*3.3.3 (3a*R*,8a*R*)-3a-Acetoxyl-1,2,3, 3a,8,8a-hexahydropyrrolo-[2,3-b]indol (**3**)*

White gum; $[\alpha]_D^{25} + 84$ (*c* 0.24, CH_3OH); IR (KBr) ν_{max} cm^{-1}: 3380, 1620, 1610, 1558, 1464; ^1H NMR (500 MHz, CD_3OD): δ 7.26 (1H, d, $J = 7.5$ Hz, H-4), 7.14 (1H, t, $J = 7.5$ Hz, H-6), 6.80 (1H, t, $J = 7.5$ Hz, H-5), 6.68 (1H, d, $J = 7.5$ Hz, H-7), 5.31 (1H, s, H-8a), 3.95, 3.05 (2H, m, H-2), 2.32 (2H, m, H-3), 2.18 (3H, s, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 45.9 (t, C-2), 38.1 (t, C-3), 90.3 (s, C-3a), 131.9 (s, C-3b), 124.6 (d, C-4), 120.6 (d, C-5), 131.1 (d, C-6), 111.6 (d, C-7), 151.0 (s, C-7a), 84.8 (d, C-8a), 21.9 (q, CH_3), 172.7 (s, CO); ESI-MS *m/z*: 217 $[M]^-$. HR-ESI-MS *m/z*: 218.1053 $[M]^+$ (calcd for $C_{12}H_{14}N_2O_2$, 218.1055).

3.3.4 Cytotoxicity assays

The cytotoxic properties of the crude extraction were tested *in vitro* using human cancer cell lines including HL-60 (human leukemic cancer cell), BGC-823 (human gastric cancer cell), BeL-7402 (human hepatoma cancer cell), and KB (human nasopharyngeal cancer cell). The experimental result showed that the crude extraction had modulate inhibitory activity against BGC-823. The cytotoxic properties of the compounds were tested *in vitro* using human cancer cell lines including HeLa (human leukemic carcinoma cells), K-562 (human leukemic carcinoma cells), and L-929 (mouse fibroblast cell). The bioassay method using MTT as indicated in literature [16]. The antibiotic test was performed using drug-sensitive slips method and tube double dilution method.

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