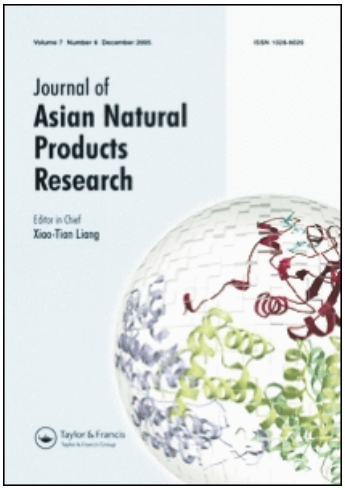

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Two new indole alkaloids from *Nauclea officinalis*

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Two new indole alkaloids, naucleactonin A and B, along with two known compounds, naucleficine and nauclefidine, were isolated from the bark and wood of *Nauclea officinalis*, which has been used as an anti-inflammatory and anti-bacterial agent in folk medicine. Their chemical structures were elucidated by the spectral data, especially 1D and 2D NMR experiments.

Keywords: *Nauclea officinalis*; Rubiaceae; Indole alkaloids; Naucleactonin A; Naucleactonin B

1. Introduction

Nauclea officinalis Pierre ex Pitard (Rubiaceae) has been used as an anti-inflammatory and anti-bacterial agent in traditional Chinese medicine. A number of indole alkaloids have been isolated from *Nauclea* species, which have interesting biological activities [1–3]. In our search for new bioactive constituents, two new indole alkaloids, naucleactonin A **(1)** and B **(2)**, along with two known indole alkaloids, naucleficine **(3)** [1] and nauclefidine **(4)** [1,4], were isolated from the bark and wood of *Nauclea officinalis*. The chemical structures of these compounds were identified based on spectral analysis (^{1}H NMR, ^{13}C NMR, 2D NMR, MS, UV and IR) and by comparison of their spectral data with those reported previously in the literature.

2. Results and discussion

Naucleactonin A (**1**) was isolated as a yellowish amorphous solid with yellow fluorescence. HRESI-MS showed a quasimolecular molecular ion peak at *m/z* 319.1084 $[M + H]^+$, supporting a molecular formula of $C_{19}H_{14}N_2O_3$.The UV absorptions at 255, 313 and 416 nm

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indicated the presence of a highly conjugated system; its IR spectrum implied the presence of an α,β-unsaturated carbonyl (1667 cm^{-1}) group and a lactam carbonyl (1601 cm^{-1}) group.

The ^1H NMR, ^{13}C NMR data (table 1), and DEPT and HMQC spectra of **1** indicated that the molecule contained two carbonyls, 14 aromatic carbons, two methylenes and one methyl. The C-18 (δ_C 26.62, δ_H 2.54) methyl group correlating with the C-19 (δ_C 186.03) carbonyl in HMBC spectrum indicated the presence of an acetyl group. In addition, a singlet at δ_H11.86 indicated the presence of an NH unit. The downfield region (δ_H 7.00–9.00) of the ^1H NMR spectrum of **1** showed six aromatic proton signals, of which two triplets at δ_H 7.07 and 7.23 were attributed to H-10 and H-11, two doublets at δ_H 7.42 and 7.59 were assigned to H-12 and H-9, and two singlets at δ_H 7.25 and 8.82 were assigned to H-14 and H-17, respectively. The triplets at δ_H 3.06 and 4.30 correlating with the carbon signals at δ_C 19.35 and 39.70 in the HMQC were assigned to H_2-5 and H_2-6. The ^1H-^1H COSY and NOESY correlations among H_2-5 and H_2-6 revealed the presence of a $-CH_2CH_2-$ group. These data suggested that **1** had the indole [2,3-a] quinolizine skeleton, the same as that of naucleafoline [1] except for the presence of an additional acetyl unit. The connectivity of the acetyl to C-20 (δ_C 144.38) was confirmed by HMBC correlations from H-18 to C-20, H-17 to C-15 (δ_C 127.06), C-16, and C-20 and the long-range $^1H-^1H$ COSY correlation between H-14 and H17. Therefore, the structure of compound **1** was determined as 3-acetyl-indole[2,3-a]quinolizin[2,3-c]furo-4-one, named naucleactonin A (figure 1).

Naucleactonin B **(2)** was also obtained as a yellowish amorphous powder. The molecular formula of $C_{20}H_{18}N_2O_4$ was deduced from the HRESI-MS ion at *m/z* 373.1170 $[M + Na]^+$. The UV and IR absorptions suggested that the structure of **2** was similar to that of **1**. The ^1H NMR, ^{13}C NMR data (table 1) and HMBC correlations revealed the presence of the same indole [2,3-a] quinolizine ring in the structure of **2** as that of **1,** with additional groups of a

Table 1. ^1H NMR and ^{13}C NMR data for compounds **1** (DMSO-d_6, 500/125 MHz δ ppm) and **2** ($CDCl_3$, 500/125 MHz δ ppm).

Position	***1***		***2***	
	δ_C	δ_H	δ_C	δ_H
1		11.86 (1H,s)		8.68 (1H,s)
2	127.99 (s)		127.50 (s)	
3	136.38 (s)		139.11 (s)	
4				
5	39.70 (t)	4.30 (2H, t, 7.0)	41.36 (t)	4.46 (2H,m)
6	19.35 (t)	3.06 (2H, t, 7.0)	19.82 (t)	3.12 (2H, t, 7.0)
7	114.00 (s)		115.89 (s)	
8	125.31 (s)		126.04 (s)	
9	119.30 (d)	7.59 (1H, d, 7.0)	120.13 (d)	7.59 (1H, d, 8.0)
10	119.55 (d)	7.07 (1H, t, 7.0)	121.29 (d)	7.17 (1H, t, 7.0)
11	123.99 (d)	7.23 (1H, t, 7.0)	125.69 (d)	7.32 (1H, t, 7.0)
12	111.69 (d)	7.42 (1H, d, 7.0)	112.19 (d)	7.42 (1H, d, 8.0)
13	138.33 (s)		138.76 (s)	
14	91.41 (d)	7.25 (1H, s)	93.40 (d)	6.78 (1H, s)
15	127.06 (s)		135.37 (s)	
16	118.87 (s)		128.60 (s)	
17	147.66 (d)	8.82 (1H, s)	94.75 (d)	5.74 (1H, s)
18	26.62 (q)	2.54 (3H, s)	15.89 (q)	1.50 (3H, d, 7.0)
19	186.03 (s)		69.82 (d)	4.77 (1H, q, 7.0)
20	144.38 (s)		197.10 (s)	
22	157.80 (s)		161.05 (s)	
OCH_3			57.25 (q)	3.66 (3H, s)

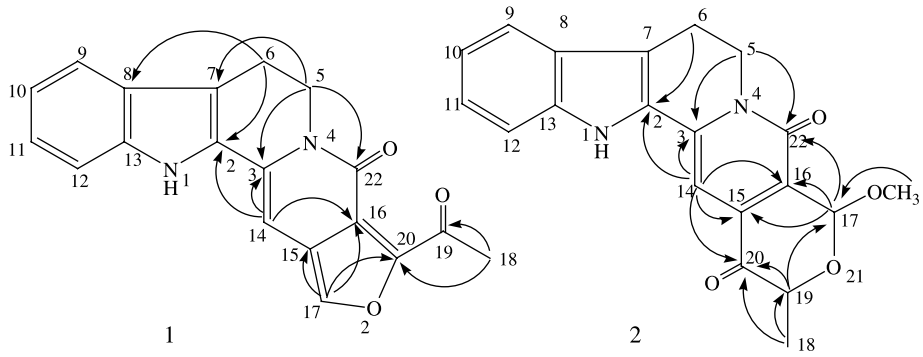

Figure 1. Structures and key HMBC correlations of compounds **1** and **2**.

carbonyl, a methyl, a methoxyl, and two oxymethines. The connectivity of methyl (C-18 δ_C 15.89) to C-19 (δ_C 69.82) was explained by the cross-signals between H-19 (δ_H 4.77) and H-18 (δ_H 1.50) in the ^{1}H-^{1}H COSY and NOESY spectra. The NOESY cross-signal of δ_H 3.66 (3H, s, OCH_3) with H-17 (δ_H 5.74) and HMBC correlation from the methoxyl proton to C-17 (δ_C 94.75) indicated that the methoxyl was located at C-17. HMBC correlations (figure 1) from H-14 to C-2 (δ_C 127.50), C-3 (δ_C 139.11), C-16 (δ_C 128.60) and C-20 (δ_C 197.10), and H-19 to C-20, C-17 revealed the connectivities of C-14–C-15–C-20–C19, and the HMBC correlations from H-17 to C-22 (δ_C 161.05), C-15 (δ_C 135.37), C-16 and C-19 verified the connectivities of C-17–C-16–C-22. Thus, the structure of compound **2** was assigned as 2-methyl-4-methoxy-indole[2,3-a]pyrano[3,4-g]quinolizin-1,5-dione, named naucleactonin B (figure 1).

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a Perkin-Elmer 343 polarimeter; melting point was measured on an RY-2 melting-point apparatus and are uncorrected. IR spectra were obtained on a Bruker Vector 22 (KBr) instrument; NMR spectra were operated on a Bruker DRX-500 spectrometer at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR; The chemical shift values were reported with TMS as internal standard; EI-MS was recorded on a Varian MAT-212 mass spectrometer and HRESI on a Q-TOF micro mass spectrometer. Silica gel (Yantai, China, 200–300 mesh), silica gel H (10–40 μm, Yantai, China) and Sephadex LH-20 (Pharmacia) were used for column chromatography (CC) and pre-coated plates silica gel ($HSGF_{254}$, 10–40 μm, Yantai, China) for TLC.

3.2 Plant material

The bark and wood of *Nauclea officinalis* were collected from Xinglong District, Hainan Province, P.R. China in May 2002, and identified by Director Zhu Ping. A voucher specimen has been deposited in the Hainan Branch Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences.

3.3 Extraction and isolation

Dried and powdered bark and wood of *Nauclea officinalis* (3.6 kg) were extracted with 95% EtOH (51 × 3). After removal of the solvent under reduced pressure, the residue (260 g) was suspended in 1000 ml water and partitioned with $CHCl_3$ (1l × 3) and EtOAC (1l × 3) successively. The $CHCl_3$ (12.5 g) extract was chromatographed on a silica gel column (∅ 4.5 × 60 cm, silica gel, 200–300 mesh, 100 g), and eluted with a gradient of petroleum ether/EtOAC (50:1, 10:1, 1:1 v/v, each in 3 l) to give three fractions (1–3). Fraction 2 (3.3 g) was passed through a silica gel column (∅ 3.5 × 60 cm, 200–300 mesh, 50 g) using petroleum ether/EtOAC (20:1) as eluent to afford subfractions 1–50; **3** (350 mg) was obtained from subfractions 10–18, and **1** (48 mg) from subfractions 26–30 after purification on a Sephadex LH-20 column eluted with $CHCl_3$/MeOH (1:1, v/v); subfractions 34–50 were combined and rechromatographed on a silica gel column (∅ 3.5 × 30 cm, silica gel, 40 μ, 30 g) using a gradient of $CHCl_3$/MeOH (10:1 to 5:1 v/v), and the eluate was further purified on a Sephadex LH 20 column ($CHCl_3$/MeOH 1:1, v/v) to yield **2** (30 mg) and **4** (75 mg).

3.4 Structure and identification

3.4.1 Naucleactonin A (1). Yellowish powder. UV (MeOH) λ_{max} nm (log ϵ): 255 (4.35), 313 (4.34), 348 (4.26), 416 (4.26); IR (KBr) ν_{max} (cm^{-1}): 3272, 2921, 1667, 1601, 1435, 1327, 1231, 1196, 1088, 954, 805, 732; ESI-MS *m/z*: 317, 302, 289, 275 (100), 261, 246, 235, 219, 209; HRESI-MS *m/z*: 319.1084 $[M + H]^+$ (calcd for $C_{19}H_{14}N_2O_3$, 319.1083); EI-MS *m/z*: 318 $[M]^+$(100), 303 $[M - CH_3]^+$, 274 $[M - COCH_3]^+$, 247, 191; ^1H NMR and ^{13}C NMR data are listed in table 1.

3.4.2 Naucleactonin B (2). Yellowish powder; $[\alpha]_D^{20}$ −1.92 (*c* 0.52, MeOH); UV (MeOH) λ_{max} nm (log ϵ): 217 (4.03), 309 (4.10), 423 (4.00); IR (KBr) ν_{max} (cm^{-1}): 3420, 1709, 1651, 1569, 1451, 1329, 1080, 1044, 802, 744; ESI-MS *m/z*: 723 $[2M + Na]^+$, 373 $[M + Na]^+$, 319, 274; HRESI-MS *m/z*: 373.1170 $[M + Na]^+$ (calcd for $C_{20}H_{18}N_2O_4Na$, 373.1164); EI-MS *m/z*: 350 $[M]^+$, 319 $[M - OCH_3]^+$(100), 304, 289,249, 205, 147, 84; ^1H NMR and ^{13}C NMR data listed in table 1.

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