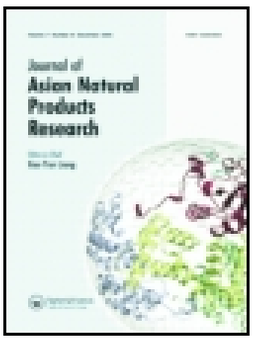

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A new coumarin and a new norlignan from *Ficus tsiangii*

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ABSTRACT

Chemical investigation of the stem bark of *Ficus tsiangii* led to the isolation of a new coumarin ficuscoumarin (**1**) and a new norlignan ficuslignan (**2**) by chromatographic methods. Their structures were elucidated on the basis of spectroscopic analyses.

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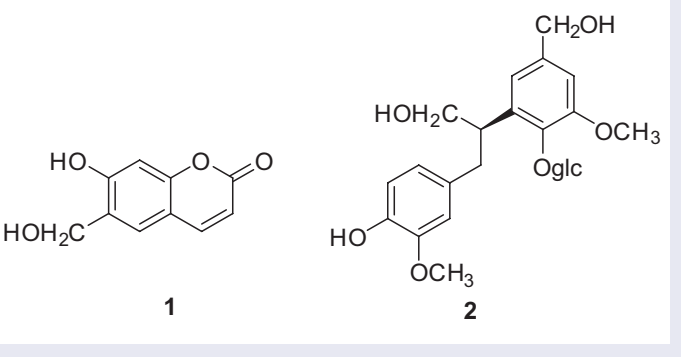

1. Introduction

The genus *Ficus* of the plant family Moraceae is represented by about 1000 species mainly distributed in tropics and subtropics in the world, and 98 species are found from the southwest to the east and the south of China [1]. *Ficus tsiangii* Merr. ex Corner is shrubs or trees growing in valleys up to altitudes between 200 and 2400 m, largely distributed in Guangxi, Guizhou, Hubei, Hunan, Sichuan, and Yunnan provinces in China [2]. *F. tsiangii* is used to treat cardiovascular diseases, especially as antithrombotic agent in some civil areas of Sichuan province. Previous phytochemical and biological investigations on *F. tsiangii* indicated the presence of triterpenes, flavonoids, coumarins, lignans, and fatty acids [3–8]. This work deals with the isolation and structural elucidation of a new coumarin ficuscoumarin (**1**) and a new norlignan ficuslignan (**2**) (Figure 1) from the stem bark of *F. tsiangii*.

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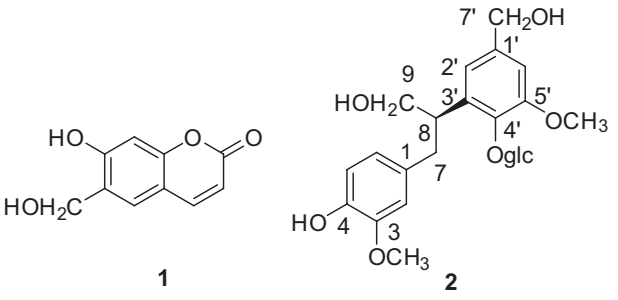

Figure 1. Structures of compounds **1** and **2.**

2. Results and discussion

The EtOAc soluble part of the ethanol extract of *F. tsiangii* was subjected to silica gel and Sephadex LH-20 column chromatography to afford compound **1**, and the BuOH soluble part was subjected to HP-20 column chromatography and C18 column chromatography to afford compound **2**.

Compound **1** was obtained as amorphous powder, with a molecular formula $C_{10}H_8O_4$ established by negative HRESI-MS at *m/z* 191.0344 $[M - H]^-$. The ^{1}H NMR spectrum gave two ortho-coupled proton signals at δ 6.18 (1H, d, J = 9.3 Hz) and 7.99 (1H, d, J = 9.3 Hz), two aromatic proton signals at δ 7.59 (1H, s) and 6.71 (1H, s), and aliphatic proton signal at δ 4.48 (2H, s), displaying the presence of hydroxymethyl group. The ^{13}C NMR spectrum showed eight aromatic or olefinic carbon signals (δ 101.3–158.1), one carbonyl carbon signal (δ 160.6), and one aliphatic carbon signal (δ 57.5). The ^{1}H NMR and ^{13}C NMR data (Table 1) of **1** suggested that **1** was a coumarin [9]. In the NOESY experiment (Figure 2), the aliphatic proton signal at δ 4.48 (2H, s) correlated with the downfield aromatic proton signal at δ 7.59, indicating that the hydroxymethyl group was attached to C-6. The structure of **1** was elucidated as 7-hydroxy-6-hydroxymethylcoumarin, named ficuscoumarin.

Compound **2** was obtained as amorphous powder and its molecular formula was determined to be $C_{24}H_{32}O_{11}$ from the ^{13}C NMR data and the negative HRESI-MS at *m/z* 495.1870 $[M - H]^-$ and 541.1924 $[M + HCOO]^-$. The ^{1}H NMR spectrum of **2** (Table 2) revealed an ABX system aromatic ring [δ 6.64 (1H, d, J = 1.6 Hz, H-2), 6.55 (1H, d, J = 8.0 Hz, H-5), 6.46 (1H, dd, J = 8.0, 1.6 Hz, H-6)] and a 1,3,4,5-tetrasubstituted aromatic ring [δ 6.83 (1H, brs, H-2′) and 6.82 (1H, brs, H-6′)] in the downfield region. The ^{1}H NMR spectrum revealed two methoxy groups at δ 3.74 (3H, s, 5′-OCH_3) and 3.65 (3H, s, 3-OCH_3), and a sugar

Table 1. ^{1}H- and ^{13}C-NMR spectral data of **1** (DMSO-d_6).

No.	δ_H (m, J Hz)	δ_C
2		160.6
3	6.18(d,9.3)	110.8
4	7.99(d,9.3)	144.8
4a		111.2
5	7.59(s)	126.9
6		126.6
7		158.1
8	6.71(s)	101.3
8a		154.1
CH_2OH	4.48(s)	57.5

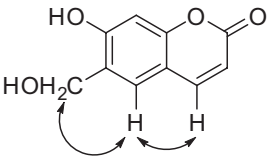

Figure 2. Key NOESY correlations of **1**.

Table 2. ^{1}H- and ^{13}C-NMR spectral data of **2** (DMSO-d_6).

No.	δ_H (m, *J* Hz)	δ_C	HMBC
1		131.5	
2	6.64(d,1.6)	112.6	C-1/C-3/ C-4/C-6/C-7
3		147.0	
4		144.2	
5	6.55(d,8.0)	114.9	C-1/C-3/C-4
6	6.46(dd,8.0,1.6)	120.8	C-2/C-4/ C-7
7	2.90(dd,6.0,14.0)	37.5	
	2.62(dd,8.8, 14.0)		C-1/C-2/C-6/C-8/C-9/C-3′
8	3.78–3.83(m)	40.6	C-7/C-2′/C-3′
9	3.43–3.47(m), 3.62(dd,3.2,9.6)	64.8	
1′		138.5	
2′	6.83(br s)	117.1	C-8/C-4′/ C-6′/ C-7′
3′		137.7	
4′		151.4	
5′		142.1	
6′	6.82(br s)	108.9	C-2′/C-4′/ C-5′/C-7′
7′	4.42(s)	63.0	C-1′/C-2′/C-6′
1″	4.62(d,7.2)	103.7	C-4′
2″	3.23–3.28(m)	74.4	C-1″/C-3″
3″	3.19–3.23(m)	76.4	C-4″
4″	3.13–3.18(m)	69.6	C-5″
5″	2.97–3.01(m)	76.7	C-3″
6″	3.57–3.60(m), 3.44–3.47(m)	60.9	
$OCH_{3-5'}$	3.74(s)	55.8	C-5′
OCH_{3-3}	3.65(s)	55.3	C-3

anomeric proton at δ 4.62 (1H, d, J = 7.2 Hz, H-1″). Additionally, the ^{1}H NMR spectrum revealed two oxygenated methylenes at δ 4.42 (2H, s, H-7′), 3.62 (1H, dd, J = 3.2, 9.6 Hz, H-9), and 3.43–3.47 (1H, m, H-9), one methine proton at δ 3.78–3.83 (1H, m, H-8), and one methylene proton at δ 2.90 (1H, dd, J = 6.0, 14.0 Hz, H-7) and 2.62 (1H, dd, J = 8.8, 14.0 Hz, H-7). The ^{13}C NMR spectrum of **2** (Table 2) revealed the presence of 24 carbon atoms, of which six carbons could be assigned to a sugar moiety (δ 103.7, 76.7, 76.4, 74.4, 69.6, 60.9), two methoxy groups (δ 55.8, 55.3), and the remaining 16 carbons could be assigned to a norlignan skeleton (including 12 aromatic carbons, two oxygenated methylenes at δ 64.8 and 63.0, one methylene at δ 37.5, and one methine at δ 40.6). Acid hydrolysis of **2** gave an aglycone **2a** and a sugar moiety, which was identified as D-glucose by HPLC analysis of its arylthiocarbamate derivative with an authentic sample [10]. The structure of **2** was determined on the basis of HMBC experiment (Figure 3). In the HMBC spectrum, H-6 at δ_H 6.46 correlated with C-2 at δ_C 112.6, C-4 at δ_C 144.2, and C-7 at δ_H 37.5, H-5 at δ_H 6.55 correlated with C-3 at δ_C 147.0, C-4 at δ_C 144.2, and C-1 at δ_C 131.5, CH_3O-3 at δ_H 3.65 correlated with C-3 at δ_C 147.0, indicating that the methoxy and the hydroxy group were attached to C-3 and C-4, respectively. HMBC spectrum also displayed correlations between H-6′ at δ_H 6.82 and C-2′ at δ_C 117.1, C-4′ at δ_C 151.4, C-5′ at δ_C 142.1, and C-7′ at

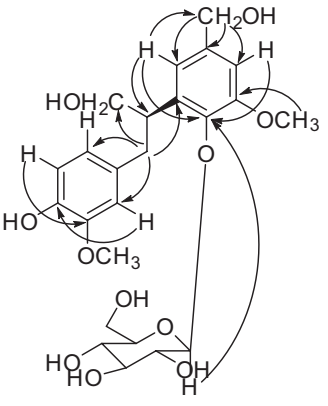

Figure 3. Key HMBC correlations of **2.**

δ_C 63.0, H-2′ at δ_H 6.83 and C-4′ at δ_C 151.4, C-6′ at δ_C 108.9, C-7′ at δ_C 63.0, and C-8 at δ_C 40.6, H-7′ at δ_H 4.42 and C-1′ at δ_C 138.5, C-2′ at δ_C 117.1, and C-6′ at δ_C 108.9, CH_3O-5′ at δ_H 3.74 and C-5′ at δ_C 142.1, H-1″ at δ_H 4.62 and C-4′ at δ_C 151.4, indicating that the methoxy and the glucosyl group were attached to C-5′ and C-4′, respectively. The HMBC spectrum showed the correlations between H-7 at δ_H 2.90, 2.62 and C-3′ at δ_C 137.7, H-2′ at δ_H 6.83 and C-8 at δ_C 40.6, indicating that C-8 was linked to C-3′. In addition, the absolute configuration of C-8 in **2a** was deduced to be *R* by comparison of its optical rotation data $[\alpha]_d^{25}$ -236 (*c* 0.2, MeOH) with those reported in the literature [11]. Thus, the structure of **2** was elucidated to be as shown in Figure 1 and was named ficuslignan.

3. Experimental

3.1. General experimental procedures

Optical rotations were obtained on a Rudolph Autopol IV automatic polarimeter (Rudolph Research Analytical, New Jersey, USA). UV spectra were recorded on a Shimadzu UV–2450 UV–vis spectrophotometer (Shimadzu, Kyoto, Japan). IR spectra were taken on a Thermo Nicolet Nexus 470 FT-IR spectrometer (Thermo Nicolet, Austin, TX, USA). NMR spectra were measured on Bruker VXR-300 and AVANCE III-400 spectrometer (Bruker, Fällanden, Switzerland) with tetramethylsilane as an internal standard. High-resolution electro-spray ionization mass spectrometry (HRESI-MS) was obtained on a Waters Xevo G2 Q-TOF/YCA mass spectrometer (Waters Corporation, Manchester, UK).

Column chromatography (CC) was performed on Diaion HP-20 (200–300 mesh, Mitsubishi Chemical Co., Kyoto, Japan), silica gel (200–300 mesh; Qingdao Marine Chemical Co. Ltd., Qingdao, China), Sephadex LH-20 (GE Healthcare, Uppsala, Sweden), ODS-A (50 μm, YMC Co. Ltd., Kyoto, Japan). Analytical TLC was carried out on silica gel GF_{254} (10–40 μm; Qingdao Marine Chemical Co. Ltd., Qingdao, China). HPLC grade solvents used for HPLC analysis were purchased from Fisher Scientific International (Fair Lawn, New Jersey, USA), and deionized water was purified by Milli-Q Synthesis A10 (Bedford, MA, USA). Other solvents used for extraction and isolation were of analytical grade and purchased from Beijing Tongguang Chemicals (Beijing, China). All other chemicals were purchased from J & K Co. Ltd. (Beijing, China).

3.2. Plant material

The stem bark of *Ficus tsiangii* Merr. ex Corner was collected from Chongqing of China, in April 2006. A voucher specimen (No. 200604001) was identified by Prof. Sirong Yi (Chongqing Institute of Medicinal Plant Cultivation, Sanquan Zhen, Nanchuan District, Chongqing 408435, China) and deposited in the Herbarium of Department of Natural Medicines, School of Pharmaceutical Sciences, Peking University Health Science Center (PEM).

3.3. Extraction and isolation

Air-dried powder of the bark of *F. tsiangii* (10.0 kg) was percolated with 95% EtOH (100 L) and 50% EtOH (100 L), successively. The combined extract was suspended in H_2O and partitioned with EtOAc and *n*-BuOH, successively. The EtOAc soluble fraction (140.0 g) was subjected to silica gel column, eluted gradiently with petroleum ether-acetone (9:1 → 1:1) to give 18 fractions (E1–E18). Fr. E9 (1.47 g) was subjected to Sephadex LH-20 column, eluted with MeOH-H_2O (8:2) and then separated by preparative TLC, developed with $CHCl_3$-MeOH-HCOOH (15:1:0.1) to yield **1** (9.0 mg). The BuOH soluble fraction (75.0 g) was subjected to HP-20 column, eluted with H_2O, 30% EtOH, 50% EtOH, 70% EtOH, and 95% EtOH, successively. The 30% EtOH eluate (7.0 g) was subjected to C18 column, eluted with MeCN-H_2O (15:85) to yield **2** (3.0 mg).

3.4. Acid hydrolysis and determination of the absolute configuration of the sugar

Compound **2** (2.0 mg) was dissolved in 2 M HCl–H_2O (2.0 ml) and heated at 95 °C for 8 h. The mixture was extracted with EtOAc (2.0 ml) to give an aglycone **2a**, and the aqueous layer was evaporated under vacuum to furnish a neutral residue. L-Cysteine methyl ester hydrochloride (2.0 mg) and anhydrous pyridine (1.0 ml) were added to the mixture and stirred at 60 °C for 1 h. The product was mixed with *O*-tolylisothiocyanate (10 μl) and kept at 60 °C for 1 h. The reaction mixture was analyzed by HPLC under the following conditions: an Agilent 1260 chromatograph equipped with a phenomenex column (5 μm , 4.6 × 250 mm); column temperature: 35 °C; mobile phase: isocratic elution of 25% CH_3CN–H_2O containing 0.2% formic acid for 50 min and subsequent washing of the column with 90% CH_3CN–H_2O, flow rate: 0.8 ml/min; injection volume: 10 μl; UV detection wavelength: 250 nm. From the acid hydrolysate of **2**, D-glucose was confirmed by comparison of the retention time of its derivative with the standard sugar D-glucose derivatized in the same way, which showed retention time of 18.75 min.

3.4.1. *Ficuscoumarin* (1)

Amorphous powder. UV (MeOH) λ_{max} (lg ε) 204 (3.98), 220 (3.60), 328 (3.52) nm. IR (KBr) ν_{max} 3444, 3361, 2921, 1740, 1601, 1498, 1260, 1023, 904, 801, 691, 586 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) and ^{13}C NMR (75 MHz, DMSO-d_6) spectral data see Table 1. HRESI-MS (negative mode) *m/z* 191.0344 $[M - H]^-$ (calcd for $C_{10}H_8O_4$, 191.0344).

3.4.2. *Ficuslignan* (2)

Amorphous powder. $[\alpha]_D^{20}$ -134 (*c* 0.1, MeOH). UV (MeOH) λ_{max} (lg ε) 205 (4.62), 225 (4.14), 275 (3.69) nm. IR (KBr) ν_{max} 3431, 3357, 3034, 1706, 1621, 1601, 1498, 1363, 1262, 1226, 1025, 752, 692, 581, 504 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6) spectral data see Table 2. HRESI-MS (negative mode): *m/z* 495.1870 $[M - H]^-$ (calcd for $C_{24}H_{31}O_{11}$, 495.1866) and 541.1924 $[M + HCOO]^-$ (calcd for $C_{25}H_{33}O_{13}$, 541.1921). **2a** $[\alpha]_D^{25}$ -236 (*c* 0.2, MeOH).

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Disclosure statement

No potential conflict of interest was reported by the authors.

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