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A NEW BISEPOXYLIGNAN GLUCOSIDE FROM THE LEAVES OF *Forsythia suspensa*

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*A new bisepoxylignan glucoside, named phillygenin 4-*O*-(6″-*O*-acetyl)-β-D-glucopyranoside (**1**), along with two known compounds, 3β-acetoxyurs-11-en-28,13-olide (**2**) and epipinoresinol-4-*O*-β-D-glusoside (**3**), was isolated from the leaves of* Forsythia suspensa. *The structure was established on the basis of spectroscopic data and chemical evidence.*

Keywords: *Forsythia suspensa*, leaves, lignan, triterpenoid.

Forsythia suspensa Vahl (Oleaceae) is a medicinal and ornamental plant widely distributed in Asia and Europe. Its leaves have been used as a health-promoting functional tea by Chinese folks for centuries [1]. In recent years, a broad spectrum of pharmacological activities of *F. suspensa* leaf extract, such as antioxidant, antiproliferative, hepatoprotective, hypolipidemic, hypoglycemic, cardioprotective, antiaging, antiobesity, antiallergy, and antifatigue effects, have been reported [2–6]. To date, 36 chemical constituents including triterpenoids, phenylethanoid glycosides, flavonoids, lignans, steroids, phenylpropionic acid esters, and phenolic acids have been isolated and identified from the leaves of *F. suspensa* by [7–10]. Further investigation on this plant part resulted in the discovery of a new compound, phillygenin 4-*O*-(6″-*O*-acetyl)-*β*-D-glucopyranoside (**1**), along with two known compounds, 3*β*-acetoxyurs-11-en-28,13-olide (**2**) and epipinoresinol-4-*O*-*β*-D-glusoside (**3**). To the best of our knowledge, compound **1** is a new bisepoxylignan glucoside, **2** has not been isolated previously from the *Forsythia* genus, and **3** is reported in the leaves of this plant for the first time. Herein, details of the isolation and structure elucidation of the compounds are presented.

Compound **1** was assigned the molecular formula $C_{29}H_{36}O_{12}$ from its $[M - H]^-$ ion peak at *m*/*z* 575.2126 in the HR-FAB-MS. The ^1H NMR and ^{13}C NMR spectra (Table 1) demonstrated signals of two sets of trisubstituted aromatic rings at δ 7.16 (1H, d, J = 8.2 Hz, H-5), 6.97 (1H, d, J = 1.8 Hz, H-2), and 6.88 (1H, dd, J = 8.2, 1.8 Hz, H-6) and 6.93 (1H, br.s, H-2′) and 6.86 (2H, br.s, H-5′, H-6′), and 12 aromatic carbons ranging from δ 109.0 to 150.8. Three methoxyl group protons at δ 3.91 (3H, s) and 3.89 (6H, s), and a glucopyranosyl anomeric proton at δ 4.64 (1H, d, J = 7.2 Hz, H-1″) were also observed. The signals of four aliphatic methines at δ 87.3 (C-7), 54.6 (C-8), 82.0 (C-7′), and 50.2 (C-8′), and two aliphatic methylenes at δ 71.0 (C-9) and 69.8 (C-9′), as well as their corresponding proton signals at δ 4.48 (1H, d, J = 7.1 Hz, H-7), 2.90 (1H, q, J = 7.7 Hz, H-8), 4.15 (1H, d, J = 9.2 Hz, H-9a), 3.87 (1H, overlapped, H-9b) and 4.88 (1H, d, J = 5.4 Hz, H-7′), 3.35 (1H, m, H-8′), 3.85 (1H, overlapped, H-9′a), 3.34 (1H, overlapped, H-9′b) established the occurrence of a dioxabicyclo[3.3.0]octyl unit, which was also supported by analysis of the ^1H–^1H COSY, HMBC, and TOCSY spectra. The above NMR spectroscopic data of **1** suggested it to be a bisepoxylignan glucoside, and its structure was similar to forsythin isolated as one major active constituent from *F. suspensa* leaves [7], except for the presence of an additional acetyl group (δ_H 2.13; δ_C 171.8, 20.9). The HMBC (Fig. 1) correlations from H-6″ (δ 4.52, 4.33) and a carbonyl carbon (δ 171.8) suggested that the acetyl group was attached to the oxygen at the C-6″ hydroxyl group of the glucose unit. The presence of the strong NOESY correlation of H-7′/H-8 and the absence of a NOESY correlation of H-8′/H-7 indicated that compound **1** should have the same stereochemistry configuration as forsythin. According to the above evidence, the structure of **1** was proposed as phillygenin 4-*O*-(6″-*O*-acetyl)-*β*-D-glucopyranoside.

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TABLE 1. ^{1}H and ^{13}C NMR Data of **1** ($CDCl_3$, δ, ppm, J/Hz)

C atom	δ_C	δ_H	C atom	δ_C	δ_H
1	138.3	–	7′	82.0	4.88 (d, J = 5.4)
2	109.8	6.97 (d, J = 1.8)	8′	50.2	3.35 (m)
3	150.8	–	9′	69.8	3.85 (o); 3.34 (o)
4	145.5	–	1″	103.9	4.64 (d, J = 7.2)
5	121.0	7.16 (d, J = 8.2)	2″	73.4	3.63 (o)
6	118.6	6.88 (dd, J = 8.2, 1.8)	3″	75.9	3.63 (o)
7	87.3	4.48 (d, J = 7.1)	4″	69.5	3.49 (m)
8	54.6	2.90 (q, J = 7.7)	5″	74.3	3.52 (m)
9	71.0	4.15 (d, J = 9.2); 3.87 (o)*	6″	63.0	4.52 (dd, J = 12.2, 4.3);
1′	130.8	–			4.33 (dd, J = 12.2. 2.1)
2′	109.0	6.93 (br.s)	OAc	20.9, 171.8	2.13 (s)
3′	148.9	–	3-OMe	55.94	3.91 (s)
4′	148.1	–	3′-OMe	56.0	3.89 (s)
5′	111.1	6.86 (br.s)	4′-OMe	55.92	3.89 (s)
6′	117.7	6.86 (br.s)			

*(o) – overlapped.

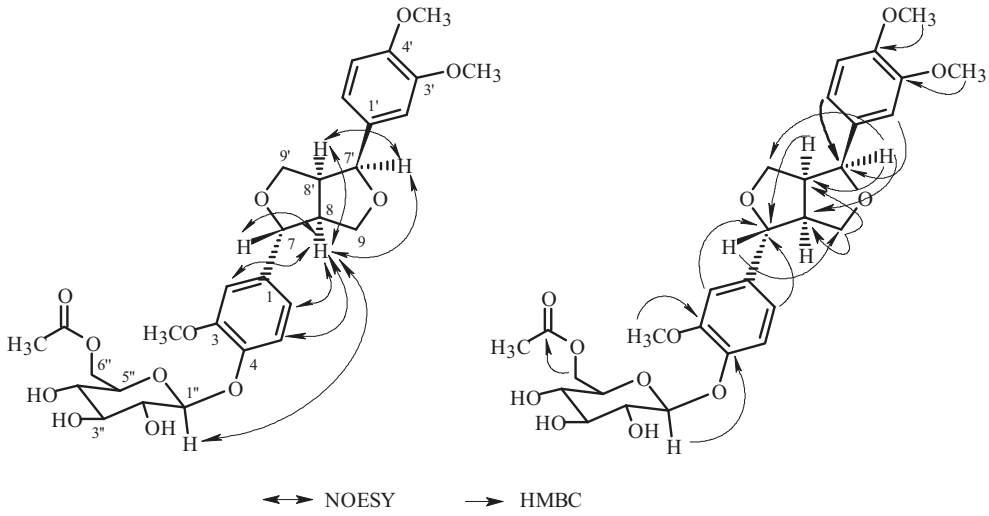

Fig. 1. Key NOESY and HMBC correlations of compound **1**.

Compound **2**, obtained as white crystals (petroleum ether–EtOAc), was determined to be 3*β*-acetoxyurs-11-en-28,13-olide [11].

Compound **3**, obtained as an amorphous powder (MeOH), was determined to be epipinoresinol-4-*O*-*β*-D-glucoside [12].

EXPERIMENTAL

General Procedures. NMR: Bruker Avance DRX 500 NMR spectrometer using TMS as internal standard. HR-FAB-MS: Bruker Apex II FI-ICR mass spectrometer. Optical rotations: Autopol IV polarimeter. Chromatography: silica gel 200–300 mesh (Qingdao Marine Chemical Factory, China), ODS-AA12S50 (YMC Co., Ltd, Japan).

Plant Material. The leaves of *F. suspensa* were collected from Taihang Mountain on May 19, 2009, Hebei Province, and identified by Prof. Jianhua Wang, Pharmacognosy Laboratory, School of Pharmaceutical Sciences, Hebei Medical University. A voucher specimen (NMC-2009-FSL-2) has been deposited in our Herbarium.

Extraction and Isolation. Dried *F. suspensa* leaves (4.4 kg) were extracted with 95% ethanol at room temperature. After evaporation of the solvent under reduced pressure, the residue was suspended in water and extracted with petroleum ether, CH_2Cl_2, EtOAc, and *n*-BuOH, successively. The EtOAc extract (115.4 g) was chromatographed on a silica gel column and eluted with CH_2Cl_2–MeOH (98:2→1:1) to furnish fractions E1–E6. Fraction E3 afforded compound **1** (5.1 mg) on an ODS column (MeOH–H_2O, 25:75→100:0). Compound **3** (3.5 mg) was obtained by recrystallization from fraction E4. The petroleum ether extraction (194.1 g) was chromatographed on a silica gel column and eluted with CH_2Cl_2–EtOAc (17:1→1:1) to furnish fractions P1–P8. Fraction P2 was separated by preparative TLC (petroleum ether–EtOAc, 4:1) to yield compound **2** (4.2 mg).

Acid Hydrolysis. A 2 N HCl solution containing compound **1** (3.0 mg) was heated at 90°C for 2 h. After cooling, the reaction mixture was diluted with H_2O and extracted with $CDCl_3$. The $CHCl_3$ layer was evaporated to dryness, and the residue was chromatographed on a silica gel column (petroleum ether–acetone, 4:1) to give its aglycone part, phillygenin, which was identified by comparison with ^1H NMR, MS, and $[\alpha]_D$ in the literature [13, 14].

Phillygenin 4-*O*-(6″-*O*-Acetyl)-*β*-*D*-glucopyranoside (1). White crystals ($CHCl_3$). $[\alpha]_D^{25}$ +12.9° (*c* 0.12, $CHCl_3$). HR-FAB-MS *m*/*z* 575.2126 $[M - H]^-$ (calcd for $C_{29}H_{35}O_{12}$, 575.2129).

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