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Five new phenolic glycosides from *Hedyotis scandens*

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ABSTRACT

Five new phenolic glycosides, hedyotosides A–E (**1**–**5**), including a new cyanogenic glycoside (**1**), along with 10 known compounds (**6**–**15**) were isolated from the whole plants of *Hedyotis scandens*. The structures of compounds **1**–**5** were established by extensive spectroscopic analyses and acid hydrolysis. All the isolated compounds were evaluated for their in vitro antiviral activity against respiratory syncytial virus (RSV) with cytopathic effect (CPE) reduction assay. Compounds **6** and **15** showed anti-RSV effects with IC_{50} values of 20 and 25 μg/mL, respectively.

The genus *Hedyotis* belongs to the family Rubiaceae and comprises 699 species, with 69 species found in China.[1] Previous chemical investigations on this genus have led to the isolation of a series of triterpenoids, iridoids, flavonoids, and anthraquinones. The plant *Hedyotis scandens* Roxb. is widely distributed in tropic and subtropic areas. The whole plants of *H. scandens*, called as 'Li Fei San' in minority groups, have been widely used in Chinese folk medicines for the treatment of respiratory diseases. Several triterpenoids and flavonoids had been reported from *H. scandens* in the previous phytochemical studies.[2,3] In the course of our ongoing search for biologically active compounds from traditional Chinese medicines, 15 more secondary metabolites including five new phenolic glycosides (**1**–**5**) were isolated from the whole plants of *H. scandens* (Fig. 1). Details of the isolation, structure elucidation of these compounds, and their in vitro antiviral activities against respiratory syncytial virus (RSV) are reported herein.

The dried plant material of *H. scandens* (9.0 kg) was powdered and extracted with 95% EtOH by percolation at room temperature for three times. After removal of the solvent in vacuo, the viscous concentrate (380 g) obtained was suspended in H_2O and then partitioned with petroleum ether, EtOAc, and *n*-BuOH consecutively. The EtOAc part (120 g) was separated on silica gel column chromatography (12 × 150 cm, 1500 g) and eluted with a gradient mixture of $CHCl_3$/MeOH (100:0→0:100) to generate fractions 1–10. Fraction 6 (7.5 g) was chromatographed on silica gel (3 × 80 cm, 120 g) using gradient elution of $CHCl_3$/MeOH (98:2→80:20) to afford **9** (50 mg) and **14** (25 mg). Fraction 7 (6.8 g) was purified by Sephadex LH-20 column (3 × 80 cm, $CHCl_3$/MeOH, 1:1) and preparative RP-HPLC (Cosmosil 5C18-MS-|| waters column, 20 × 250 mm, MeOH/H_2O, 55:45) to yield **1** (12 mg), **3** (17 mg), **5** (14 mg) and **10** (15 mg), respectively. Fraction 8 (8.5 g) was purified by Sephadex LH-20 column (3 × 80 cm, $CHCl_3$/MeOH, 1:1) and preparative RP-HPLC (Cosmosil 5C18-MS-|| waters column, 20 × 250 mm, MeOH/H_2O) to give **8** (12 mg), **11** (40 mg), **12** (20 mg) and **13** (11 mg). The *n*-BuOH part (48 g) was fractionated using a D101 resin column with a gradient system of ethanol/H_2O (0:100; 30:70; 50:50; 70:30) to afford fractions A–D. Fraction B and C were further separated by CC using ODS, Sephadex LH-20 and preparative RP-HPLC to obtain **2** (15 mg), **4** (8 mg), **6** (12 mg), **7** (20 mg), and **15** (5 mg).

Compound **1**[4] was obtained as a black solid. The molecular formula of **1** was established as $C_{28}H_{31}NO_{12}$ by a quasi-molecular ion at *m/z* 572.1769 $[M-H]^-$ (calcd for $C_{28}H_{30}NO_{12}$: 572.1774) in HRESIMS. The IR spectrum revealed the presence of hydroxyl (3442 cm^{-1}), carbonyl (1635 cm^{-1}), and cyano (2362 cm^{-1}) groups. The ^1H NMR spectrum (Table 1) displayed five olefinic protons at δ_H 7.58 (2H, dd, *J* = 8.0, 2.0 Hz) and 7.43 (3H, m), suggesting the presence of a single-substituted benzene ring. Four olefinic protons at δ_H 7.44 (2H, m) and 6.80 (2H, m) indicated the existence of a *p*-disubstituted benzene ring. Two olefinic protons at δ_H 7.66 (1H, d, *J* = 16.0 Hz) and 6.37 (1H, d, *J* = 16.0 Hz) assignable to a *trans* double bond were also observed. The ^{13}C NMR spectrum (Table 1) showed 28 carbon signals, including three methylenes, 19 methines, and six quaternary carbons (including one ester carbonyl at δ_C 169.2 and one cyano group at δ_C 119.5). The NMR data

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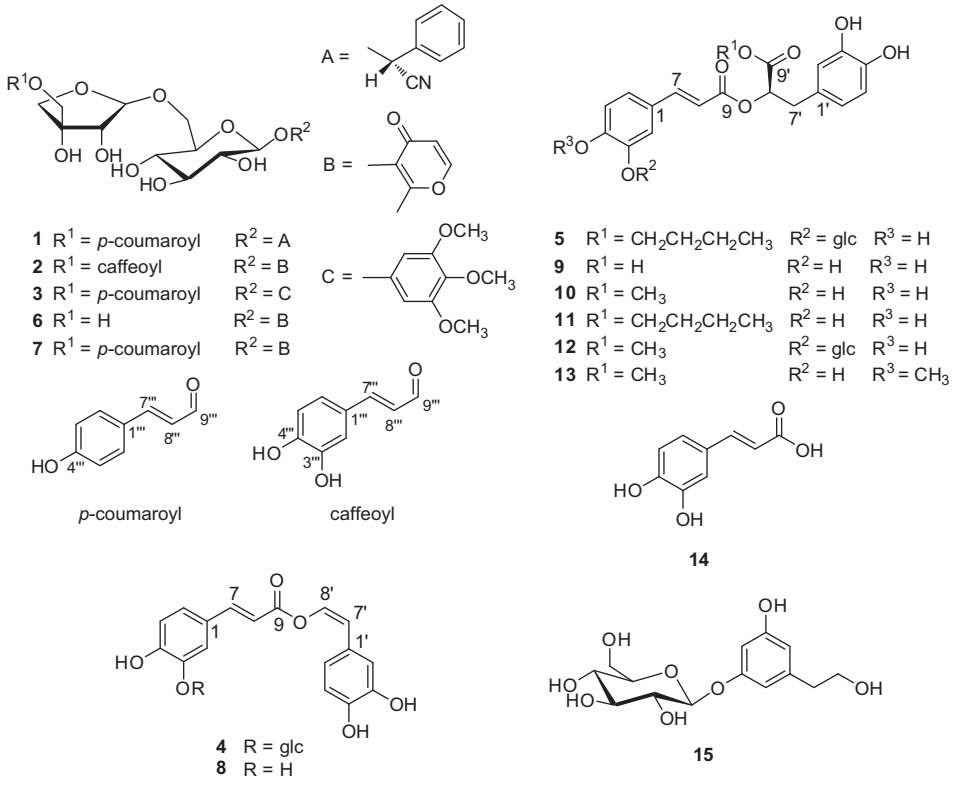

Figure 1. The structures of compounds **1**–**15**.

Table 1
NMR spectroscopic data for compounds **1**–**3**[a] in CD_3OD

Position	**1**		**2**		**3**	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	119.5				156.1	
2	69.1	5.79, s	164.8		96.7	6.45, s
3	135.1		143.6		154.9	
4	130.2	7.43, m	177.3		134.9	
5	129.1	7.58, dd (8.0, 2.0)	117.4	6.41, d (5.6)	154.9	
6	131.1	7.43, m	157.3	7.92, d (5.6)	96.7	6.45, s
7	129.1	7.58, dd (8.0, 2.0)	16.0	2.43, s		
8	130.2	7.43, m				
3,5-OMe					56.9	3.79, s
4-OMe					61.4	3.68, s
1‴	127.3		127.8		127.2	
2‴	131.4	7.44, m	115.4	7.04, d (1.6)	131.4	7.45, m
3‴	117.0	6.80, m	146.9		117.1	6.80, m
4‴	161.5		147.8		161.7	
5‴	117.0	6.80, m	116.7	6.78, d (8.0)	117.1	6.80, m
6‴	131.4	7.44, m	123.2	6.94, dd (8.0, 1.6)	131.4	7.45, m
7‴	147.1	7.66, d (16.0)	147.5	7.57, d (16.0)	147.1	7.65, d (16.0)
8‴	115.0	6.37, d (16.0)	114.8	6.28, d (16.0)	114.9	6.34, d (16.0)
9‴	169.2		169.0		169.1	
1′	102.7	4.29, d (7.2)	105.5	4.76, d (7.2)	103.3	4.79, d (7.6)
2′	74.8	3.29, m	75.4	3.31, m	75.0	3.33, m
3′	78.0	3.27, m	78.5	3.40, m	78.0	3.42, m
4′	71.6	3.32, m	71.5	3.41, m	71.7	3.45, m
5′	77.3	3.45, m	77.5	3.45, m	77.1	3.52, m
6′	68.6	4.06, dd (11.2, 1.6)	68.6	3.97, dd (11.2, 2.0)	67.6	4.20, dd (11.2, 2.1)
		3.66, dd (11.2, 6.0)		3.62, dd (11.2, 6.0)		3.84, dd (11.2, 6.0)
1″	110.7	5.09, d (2.4)	110.7	4.99, d (2.0)	110.6	5.00, d (2.4)
2″	78.6	4.01, d (2.4)	78.0	3.90, d (2.0)	78.7	3.90, d (2.4)
3″	79.2		80.6		79.1	
4″	75.2	4.11, d (9.6)	75.0	3.96, d (9.6)	75.1	4.06, d (9.6)
		3.88, d (9.6)		3.83, d (9.6)		4.02, d (9.6)
5″	67.7	4.32, m	65.7	4.25, d (11.2)	68.5	4.26, d (11.6)
				4.22, d (11.2)		4.23, d (11.6)

[a] Recorded at 400 MHz (^1H) and 100 MHz (^{13}C).