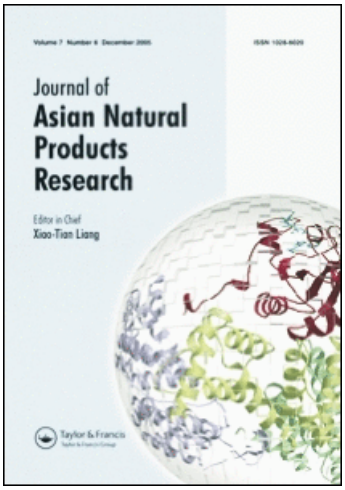

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Phenyl and phenylethyl glycosides from *Picrorhiza scrophulariiflora*

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Phenyl and phenylethyl glycosides from *Picrorhiza scrophulariiflora*

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A new phenyl glycoside, scrophenoside D (**1**) and a new phenylethyl glycoside, scroside F (**2**), together with three known phenylethyl glycosides, scroside A (**3**), plantainoside D (**4**), and plantamajoside (**5**), were isolated from the stems of *Picrorhiza scrophulariiflora*. Their structures were elucidated by spectroscopic and chemical methods.

Keywords: Scrophularlaceae; *Picrorhiza scrophulariiflora*; Scrophenoside D; Scroside F

1. Introduction

Picrorhiza scrophulariiflora Pennell (Scrophularlaceae) is a perennial herbage distributed in high altitude region (3600–5500 m) of southeast of Tibet and northwest of Yunnan, China [1]. This plant is widely used in traditional medicine of China, Nepal, and India as a bitter tonic, an antiperiodic and a cholagogue [2]. In previous phytochemical studies on this species, the chemical constituents reported were iridoid glycosides, cucurbitacin glycosides, and phenylethyl glycosides [1] [3–5].

In this paper, we report the structural elucidation of a new phenyl glycoside, scrophenoside D (**1**), and a new phenylethyl glycoside, scroside F (**2**), along with three known phenylethyl glycosides, scroside A (**3**) [3], plantainoside D (**4**) [6], and plantamajoside (**5**) [7], isolated from the *n*-BuOH extracts of the stems of *P. scrophulariiflora*. **1**, **2**, and **4** were obtained from this plant for the first time.

2. Results and discussion

The EtOH extract of *P. scrophulariiflora* was suspended in water, and partitioned successively with petroleum ether, EtOAc and *n*-BuOH. The *n*-BuOH fraction was subjected to column chromatography (silica gel and Sephadex LH-20) to give one phenyl glycoside (**1**) and four phenylethyl glycosides (**2**–**5**).

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Structural elucidation of the compounds was mainly achieved by their NMR, ESIMS spectra, and comparison with those of reported data. After acid hydrolysis, the sugars of **1** were identified as glucose and those of **2** were glucose and rhamnose by comparison with authentic samples on TLC.

Scrophenoside D (**1**) was obtained as white amorphous powder. Its molecular formula was determined as $C_{28}H_{34}O_{17}$ by HRESIMS (*m/z* 665.1703 $[M + Na]^+$). The IR spectrum of **1** indicated the presence of hydroxyl [3500–3300 cm^{-1} (br)], carbonyl, ester groups (1716, 1678 cm^{-1}), and aromatic ring (1592, 1515, 1457, 1421 cm^{-1}). The ^{1}H- and ^{13}C-NMR data of **1** showed the presence of two methoxyl groups (δ_H 3.79, 3.81; δ_C 56.1, 56.2), while six aromatic proton singles between δ_H 7.14–7.52 for two ABX systems (δ_H 7.47, 1H, d, $J = 1.7$ Hz; 7.41, 1H, dd, $J = 8.5$, 1.7 Hz; 7.19, 1H, d, $J = 8.5$ Hz and δ_H 7.46, 1H, d, $J = 1.6$ Hz; 7.52, 1H, dd, $J = 9.1$, 1.6 Hz; 7.17, 1H, d, $J = 9.1$ Hz) were ascribable to two 1,3,4-trisubstituted phenyl groups. Comparison of the ^{1}H- and ^{13}C-NMR data with those of vanillic acid (4-hydroxy-3-methoxybenzoic acid) suggested that both of the two trisubstituted phenyl groups were vanilloyl moieties. In addition, acid hydrolysis of **1** yielded glucose. Two doublets observed at δ_H 5.05 (1H, d, $J = 7.4$ Hz) and 5.14 (1H, d, $J = 7.2$ Hz) in ^{1}H-NMR and the ^{13}C-NMR signals at δ 100.0 and 99.7 were due to two β-glucoses in **1**. In the ESIMS spectrum, three significant ion peaks at *m/z* 479 $[M - 163]^-$, 313 $[M - 163–166]^-$, and 167 $[M - 163–166–146]^-$ were corresponding to the sequential loss of a glucose, a vanilloyl and a glucose. Unequivocal assignment of the connection of those subunits could be obtained by 2D-NMR. The HMBC cross peak between 1″-H (δ 5.05) and C-4 (δ 151.2), 6″-H (δ 4.62, 4.18) and C-7′ (δ 165.6), 1‴-H (δ 5.14) and C-4′ (δ 150.4) indicated that C-1″ of the first glucose was attached to C-4 of the vanilloyl, C-6″

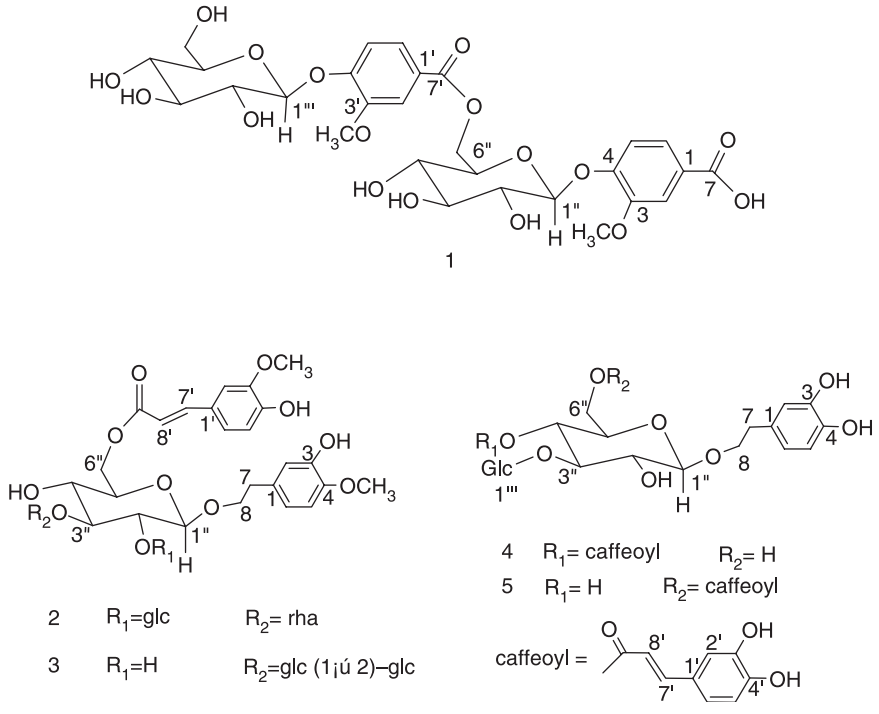

Figure 1. Structure of compounds **1**–**5**.

of this glucose to the carboxyl of another vanilloyl, and C-1‴ of the second glucose was attached to C-4′ of the second vanilloyl, respectively (figure 2). Therefore, the structure of **1** was identified to 1-carboxyl-3-methoxyphenyl 6-*O*-[4-(*β*-D-glucopyrano- syloxy) vanilloyl]-*β*-D-glucopyranside which was the dimer of picein from *Davallia mariesii* [8], named scrophenoside D (figure 1).

Scroside F (**2**) was isolated as white amorphous powder. The HRESIMS established the molecular formula $C_{37}H_{50}O_{20}$ (*m/z* 837.2762 $[M + Na]^+$). Acid hydrolysis of **2** yielded glucose and rhamnose which were identified by comparison with authentic samples on TLC. Its ESIMS spectrum displayed two major fragments at *m/z* 667 $[M - 147]^-$ and 651 $[M - 163]^-$ which were in accordance with the loss of rhamnose and glucose units. The IR spectrum of **2** suggested the presence of hydroxyl (3380 cm^{-1}), conjugated ester groups (1770, 1685 cm^{-1}), and aromatic ring (1595, 1518, 1455, 1434 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra (table 1) indicated one (*E*)-double bond (δ_H 6.52, 1H, d, $J = 15.8$ Hz and 7.54, 1H, d, $J = 15.8$ Hz; δ_C 114.8 and 145.7), two 1,3,4-trisubstituted phenyl groups (δ 6.64, 1H, d, $J = 1.8$ Hz; 6.59, 1H, dd, $J = 8.2$, 1.8 Hz; 6.70, 1H, d, $J = 8.2$ Hz and δ 7.33, 1H, d, $J = 1.4$ Hz; 7.07, 1H, dd, $J = 8.3$, 1.4 Hz; 6.77, 1H, d, $J = 8.3$ Hz), two methoxyl groups (δ_H 3.67, 3.80, each 3H, s; δ_C 56.1 56.2), and two phenylhydroxyl groups (δ 9.61, 8.76). As shown in figure 3, the HMBC correlations of OMe/C-4, H-5/C-4, H-6/C-4 indicated that one 1,3,4-trisubstituted phenyl moiety was 3-hydroxy-4-methoxyphenylethanol; while the correlations of OMe/C-3′, H-7′/C-2′, H-8′/C-1′, and H-7′/C = O indicated that the other 1,3,4-trisubstituted phenyl moiety was feruloyl. The ^{1}H-NMR spectrum of **2** displays three anomeric proton signals at δ 4.44 (d, $J = 6.9$ Hz), 4.41 (d, $J = 7.3$ Hz), and 5.02 (br.s), correlating with the anomeric carbon signals of those sugar moieties at δ 101.9, 103.3, 101.2, respectively. A doublet at δ 1.81 (3H, d, $J = 6.1$ Hz) was assigned to the 6-H of rhamnose. Therefore compound **2** has two *β*-D-glucoses and one -L-rhamnose units. In addition, the HMBC experiments were employed in order to determine the connections between those moieties. The correlations of 6″-H/C = O enabled the assignment of the feruloyl group at C-6″ of the inner glucose, and the correlations of 1‴-H/C-2″ and 1‴-H/C-3″ indicated that the outer glucose and rhamnose should be attached to C-2″ and C-3″, respectively of the inner glucose. The structure of **2**, thus, was established as (3-hydroxy-4-methoxyphenyl) ethyl-*O*-[*β*-D- glucopyranosyl-(1 → 2)]-*O*-[(-L-rhamnopyranosyl-(1 → 3)]-6-*O*-[(*E*)-feruloyl]-*β*-D-glucopyranoside, named scroside F.

Comparison of the ^{1}H- and ^{13}C-NMR spectral data with the reported data lead to the identification of compounds **3**–**5** as scroside A (**3**) [3], plantainoside D (**4**) [6], and plantamajoside (**5**) [7].

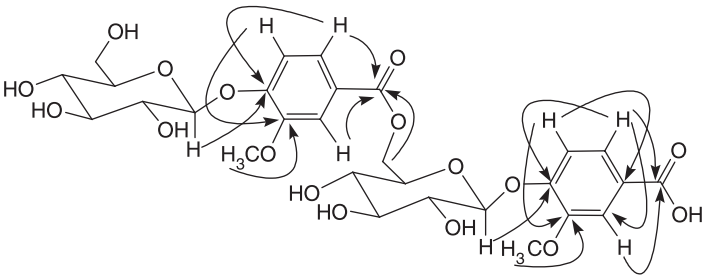

Figure 2. Key HMBC correlations for **1**.

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

	1		***2***	
	δ_C	δ_H	δ_C	δ_H
Aglycone				
C (1)	130.5 s		131.6 s	
C (2)	113.1 d	7.47 (d, $J = 1.7$)	116.8 d	6.64 (d, $J = 1.8$)
C (3)	148.9 s		146.7 s	
C (4)	151.2 s		146.5 s	
C (5)	114.7 d	7.19 (d, $J = 8.5$)	112.7 d	6.70 (d, $J = 8.2$)
C (6)	123.0 d	7.41 (dd, $J = 8.5$, 1.7)	119.9 d	6.59 (dd, $J = 8.2$,1.8)
C (7)	167.4 s		35.5 t	2.68 (m)
C (8)			70.4 t	3.60,3.78*
OCH_3	56.2[a] q	3.79[a] (s)	56.1[b] q	3.67 (s)
Ester				
C (1′)	123.4 s		126.1 s	
C (2′)	113.2 d	7.46 (d, $J = 1.6$)	111.5 d	7.33 (d, $J = 1.4$)
C (3′)	149.0 s		148.4 s	
C (4′)	150.3 s		149.8 s	
C (5′)	114.8 d	7.17 (d, $J = 9.1$)	115.9 d	6.77 (d, $J = 8.3$)
C (6′)	123.4 d	7.52 (dd, $J = 9.1$, 1.6)	123.9 d	7.07 (dd, $J = 8.3$,1.4)
C (7′)	165.6 s		145.7 d	7.54(d, $J = 15.8$)
C (8′)			114.8 d	6.52 (d, $J = 15.8$)
OCH_3	56.1 [a] q	3.81 [a] (s)	56.2 [b] q	3.80 (s)
C═O			167.1 s	
Inner Glc.				
C (1″)	100.0 d	5.05 (d, $J = 7.4$)	101.9 d	4.44 (d, $J = 6.9$)
C (2″)	73.5 d	3.35*	80.8 d	3.46*
C (3″)	77.1 d	3.36*	81.2 d	3.55*
C (4″)	70.4 d	3.28*	68.4 d	3.65*
C (5″)	74.4 d	3.83 (m)	75.7 d	3.28 (m)
C (6″)	64.5 t	4.62 (d, $J = 11.4$)	63.8 t	4.36 (d, $J = 11.9$)
				4.22(dd, $J = 11.9$, 4.8)
Outer Glc.				
C (1‴)	99.7 d	5.14 (d, $J = 7.2$)	103.3 d	4.41 (d, $J = 7.3$)
C (2‴)	73.6 d	3.30*	71.1 d	3.48*
C (3‴)	77.5 d	3.37*	74.3 d	3.52* (t, $J = 9.1$)
C (4‴)	69.9 d	3.22	71.9 d	3.30*
C (5‴)	77.2 d	3.31*	73.7 d	3.26*
C (6‴)	61.0 t	3.65 (d, $J = 10.8$)	60.7 t	3.58, 3.49
rha				
C (1⁗)			101.2 d	5.02 (br.s)
C (2⁗)			70.8 d	3.82*
C (3⁗)			69.0 d	3.32*
C (4⁗)			72.6 d	3.18 (m)
C (5⁗)			68.9 d	3.87 (m)
C (6⁗)			18.3 q	1.10 (d, $J = 6.1$)

[a] [b] Signals in each vertical column can be interchangeable. *Signal pattern unclear due to overlapping.

3. Experimental

3.1 General experimental procedures

UV spectra were obtained on a Perkin-Elmer Lambda 35 Spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. NMR spectra were recorded on a Bruker Advanced-600 spectrometer using TMS as internal standard. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. BRUKER BioTOF Q spectrometer was used

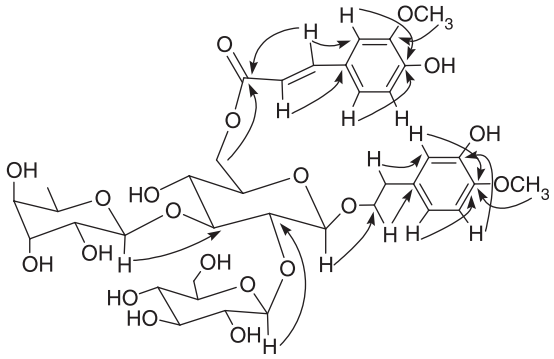

Figure 3. Key HMBC correlations for **2**.

to record HRESIMS and a Finnigan LCQ^{DECA} to record ESI-MS. Column chromatography was performed on Sephadex LH-20 (Pharmacia) and Silica gel (200–300 mesh, Qingdao Marine Chemical Group, Co.), Lobar LiChroprep RP-18 (40–63 μm, Merck), Lobar LiChroprep Si-60 (Merck), and MCI-gel (Mitsubishi Chemical Corporation), and ODS (Cosmosil 75 C_{18}-OPN) (Nacalai Tesque).

3.2 Plant material

The dried stems of *Picrorhiza scrophulariaeflora* were collected from Tibet, and identified by Professor Zuo-Cheng Zhao. A voucher specimen is deposited in the Herbarium of Chengdu Institute of Biology, Chinese Academy of Sciences.

3.3 Extraction and isolation

The stems of *P. scrophulariiflora* (6 kg) were powdered and extracted with EtOH under reflux. After filtration, the solvent was evaporated to give 2 kg of extracts. The extracts were suspended in H_2O and extracted successively with petroleum ether, EtOAc, and *n*-BuOH to yield *n*-BuOH extracts (500 g). The *n*-BuOH extracts (30 g) were subjected to silica gel column chromatography eluting with increasing amount of MeOH in $CHCl_3$ to give fractions 1–3.Fr.1 (5 g) was chromatographed on silica gel eluting with $CHCl_3$-MeOH-H_2O and then purified on reversed-phase gel (ODS) column to obtain compound **1** (17 mg) eluting with 25% MeOH and compound **5** (54 mg) with 35% MeOH. Fr.2 (3 g) was subjected to repeated silica gel column chromatography to afford **4** (36 mg) eluting with gradient $CHCl_3$-MeOH (from 6:1 to 3:1). Fr.3 (6 g) was repeatedly chromatographed on normal silica gel eluting with gradient $CHCl_3$-MeOH-H_2O (80:10:1 → 10:10:1), and then purified with Sephadex LH-20 and ODS to afford **2** (21 mg) and **3** (15 mg).

3.4 Scrophenoside D (1)

White amorphous powder (17 mg), $[\alpha]_D^{25}$ −69 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (nm) (log ε) 291 (3.69), 254 (4.06), 217 (4.29), 203 (4.22); IR (KBr) ν_{max} (cm^{-1}) 3500–3300 (br), 2919, 1716, 1678, 1592, 1515, 1457, 1421, 1278, 1217, 1080, 1029, 761; ^{1}H- and ^{13}C-NMR, see table 1; ESI-MS *m/z* 641 $[M - H]^-$, 479 $[M - 163]^-$, 313 $[M - 163–166]^-$,

and 167 [M − 163−166−146]$^-$; HRESIMS *m/z* 665.1703 [M + Na]$^+$ (calcd for $C_{28}H_{34}O_{17}Na$, 665.1688).

3.5 Scroside F (2)

White amorphous powder (21 mg), $[\alpha]_D^{25}$ −29 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (nm) (log ε) 326 (4.09), 288 (3.91), 230 (3.99), 220 (4.02), 202 (4.44); IR (KBr) ν_{max} (cm^{-1}) 3418 (br), 2926, 1770, 1685, 1668, 1634, 1595, 1518, 1455, 1434, 1271, 1132, 1085, 1036, 805; ^{1}H- and ^{13}C-NMR, see table 1; ESIMS *m/z* 813 [M − H]$^-$, 667 [M − 147]$^-$, 651 [M − 163]$^-$, 637 [M − 177]$^-$, 505 [M − H − 162−146]$^-$; HRESIMS *m/z* 837.2762 [M + Na]$^+$ (calcd for $C_{37}H_{50}O_{20}Na$, 837.2788).

3.6 TLC analysis of sugars of compounds 1 and 2

Compounds **1** and **2** were each applied to a TLC plate and then hydrolyzed under HCl vapor at 60°C for 40 min. After removal of the excess HCl, the standard glucose and rhamnose were applied to the same plate. TLC plate was developed with $CHCl_3$-MeOH-H_2O-AcOH (12:8:1:1), and visualized by spraying aniline/phthalic acid followed by heated at 110°C. The R_f values of glucose and rhamnose were 0.3 and 0.5, respectively.

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