



Phenylpropanoids and neolignans from *Smilax trinervula*



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ARTICLE INFO

Article history:

Received 20 April 2015

Accepted in revised form 12 May 2015

Available online 16 May 2015

Keywords:

Smilax trinervula
Phenylpropanoids
Neolignans
Cytotoxic activity

ABSTRACT

A new phenylpropanoid glucoside and two new neolignans, namely (1S, 2R)-1-(3, 4, 5-trimethoxyphenyl)-3-(β-D-glucopyranosyloxy)-1, 2, 3-propanetriol (**1**), and (7R, 8R)-4, 7, 9, 9'-tetrahydroxy-3, 5, 3', 5'-tetramethoxy-8-4'-oxyneolignan 4-O-β-D-glucopyranoside (**2**) and 3', 9, 9'-trihydroxy-3, 5-dimethoxy-8-O-4'-neolignan-4-O-β-D-glucopyranoside (**3**), together with a new natural product (1S, 2R)-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3-propanetriol (**4**) and four known compounds (**5–8**) were isolated from the rhizomes of *Smilax trinervula*. Their structures were established mainly on the basis of 1D and 2D NMR spectral data, ESI-MS and literature comparisons. Compounds **1–8** were tested in vitro for their cytotoxic activities against 5 human tumor cell lines (SH-SY5Y, SGC-7901, HCT-116, Lovo and Vero). Compounds **7** and **8** exhibited cytotoxic activity against Lovo, with IC₅₀ values of 18.7 μM and 16.8 μM, respectively.

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1. Introduction

The genus *Smilax* (Smilacaceae) comprises about 370 species, which are mainly distributed in the tropical and temperate zones throughout the world, especially in East Asia and North America [1], and there are 2 genera and about 200 species of plants in China [2]. *Smilax trinervula* (*S. trinervula*), a perennial plant distributed widely in South China, such as Jiangxi, Guizhou and Anhui Provinces, and the rhizomes and roots are source of Chinese crude drug “Ba-Qia”, which has been used to eliminate dampness and treat pelvic inflammation and chronic pelvic inflammation [2]. It is commonly used as traditional Chinese medicine and it has been recorded in an endemic Pharmacopoeia in China. It's interesting that our previously investigation found that the extract of *S. trinervula* has good cytotoxic and antitumor bioactivities [3].

Previous phytochemical studies of this genus focused on *Smilax china*, *Smilax macrophylla*, *Smilax riparia*, *Smilax glabra*, and *Smilax bracteata*, and have led to the isolation of some characteristic steroidal saponins, flavonoids and lignans [4–8]. However, to our best knowledge, until now, no literature was reported on constituents isolated from *S. trinervula*. In our continuous search of potentially bioactive compounds from the genus *Smilax* medicinal plants, we examined the crude EtOH extract from the rhizomes of *S. trinervula*. The paper described the isolation, structure elucidation and cytotoxic activity components.

2. Experimental

2.1. General procedure and reagents

¹H (400 MHz), ¹³C (100 MHz), and 2D NMR spectra were obtained on Bruker AV-400 and with TMS as internal reference, used methanol-*d*₄ as solvents. Electrospray ionization (ESI) mass spectra were acquired in the positive ion mode on a LCQ DECAXP instrument (Thermo Finnigan, San Jose, CA, USA) equipped with an ion trap mass analyzer. HR-ESI-MS were obtained in the positive ion mode on a Waters UPLC Premier Q-TOF mass spectrometer. CD spectra were obtained on an Olis DSM 1000 spectrometer. Optical rotations were acquired on a Krüss-P800-T polarimeter. TLC plates were HSGF254 SiO₂ from Yantai Jjiangyou Silica Gel Development Co., Ltd., China. Column chromatography (CC) silica gel (SiO₂; 200–300 mesh; Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), Sephadex LH-20 (GE-Healthcare Bio-Sciences AB, Uppsala, Sweden), and ODS (Grace C₁₈, Grace Davison Discovery Sciences) were employed as packing materials, semi-preparative HPLC (Grace Prevail C₁₈ column, 5 μm, 10.0 mm I.D. × 250 mm, USA). All other chemicals were of analytical reagent grade.

2.2. Plant materials

The rhizomes of *S. trinervula* were collected from Yichun City, Jiangxi Province, China in May 2011. A voucher specimen (No. 20110502) was deposited at the Key Laboratory of Modern Preparation of TCM, Jiangxi University of Traditional Chinese Medicine, China.

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Table 1
¹H NMR of compounds **1**, **4** and **5** at 400 MHz in MeOH-*d*₄ (δ in ppm, *J* in Hz).

Position	1	4	5
1	4.66 (<i>d</i> , <i>J</i> = 6.0)	4.55 (<i>d</i> , <i>J</i> = 6.2)	4.59 (<i>d</i> , <i>J</i> = 5.4)
2	3.81 (<i>m</i>)	3.72 (<i>m</i>)	3.68 (<i>m</i>)
3	3.90 (<i>dd</i> , <i>J</i> = 5.4, 10.3)	3.66 (<i>dd</i> , <i>J</i> = 5.3, 11.2)	3.54 (<i>dd</i> , <i>J</i> = 4.2, 11.0)
	3.38 (<i>dd</i> , <i>J</i> = 6.5, 10.3)	3.59 (<i>dd</i> , <i>J</i> = 6.5, 11.2)	3.40 (<i>dd</i> , <i>J</i> = 6.2, 11.0)
1'	–	–	–
2'	6.75 (<i>s</i>)	6.72 (<i>s</i>)	6.72 (<i>s</i>)
3'	–	–	–
4'	–	–	–
5'	–	–	–
6'	6.75 (<i>s</i>)	6.72 (<i>s</i>)	6.72 (<i>s</i>)
3',5'-OCH ₃	3.84 (<i>s</i>)	3.84 (<i>s</i>)	3.84 (<i>s</i>)
4'-OCH ₃	3.74 (<i>s</i>)	3.74 (<i>s</i>)	3.74 (<i>s</i>)
glc-1	4.22 (<i>d</i> , <i>J</i> = 7.7)	–	–
glc-2	3.20–3.32 (<i>m</i>)	–	–
glc-3	3.20–3.32 (<i>m</i>)	–	–
glc-4	3.20–3.32 (<i>m</i>)	–	–
glc-5	3.20–3.32 (<i>m</i>)	–	–
glc-6	3.64 (<i>dd</i> , <i>J</i> = 5.4, 11.9)	–	–
	3.82 (<i>m</i>) ^a	–	–

2.3. Extraction and isolation

The rhizomes of *S. trinervula* (30 kg) were extracted with 70% (v/v) aqueous ethanol. The 70% EtOH extract was concentrated under reduced pressure to give a residue (2705 g), which was extracted with EtOAc and *n*-BuOH, respectively. The EtOAc extract was concentrated to yield the EtOAc fraction 249.2 g, and the *n*-BuOH extract was concentrated to get the *n*-BuOH fraction 470.3 g. Part of the dried *n*-BuOH extract (about 350 g) was subjected to macroporous resin column chromatography with gradient mixtures of H₂O/MeOH (100% H₂O, 30% MeOH, 50% MeOH, 70% MeOH and 95% MeOH), which yielded six major fractions (*Fr*s. 1–6). *Fr*. 1 (64.4 g) was further subjected to repeated CC (silica gel, CHCl₃/MeOH and Sephadex LH-20, MeOH), then followed by semipreparative HPLC (18% MeOH/H₂O, 3.0 ml/min) to yield **1** (30 mg, *t_R* 18.2 min), **2** (6 mg, *t_R* 20.5 min), **3** (5 mg, *t_R* 28.1 min), **4** (14 mg, *t_R* 14.5 min), **5** (8 mg, *t_R* 17.5 min), **6** (8.2 mg, *t_R* 17.1 min), **7** (7.5 mg, *t_R* 32.5 min), and **8** (22 mg, *t_R* 37.0 min).

2.3.1. (1*S*, 2*R*)-1-(3, 4, 5-trimethoxyphenyl)-3-(β-*D*-glucopyranosyloxy)-1, 2, 3-propanetriol (**1**)

Whiter powder (MeOH); [α]_D²⁵ – 26° (c 0.0012, MeOH); UV (MeOH) λ_{max} (log ε) 230 (0.28) nm; HR-ESI-MS *m/z* 421.1706 [M + H]⁺ (calcd for C₁₈H₂₉O₁₁); ¹H NMR and ¹³C NMR see Tables 1 and 2.

Table 2
¹³C NMR of compounds **1**, **4** and **5** at 100 MHz in MeOH-*d*₄ (δ in ppm).

Position	1	4	5
1	75.8	76.2	75.3
2	76.0	76.7	77.4
3	72.2	64.4	64.2
1'	139.4	139.5	139.7
2'	105.1	105.4	105.0
3'	154.3	154.2	154.3
4'	138.2	138.2	138.2
5'	154.3	154.2	154.3
6'	105.1	105.4	105.0
3',5'-OCH ₃	56.6	56.5	56.5
4'-OCH ₃	61.1	61.1	61.1
glc-1	104.9	–	–
glc-2	75.2	–	–
glc-3	77.9	–	–
glc-4	71.6	–	–
glc-5	77.9	–	–
glc-6	62.6	–	–

Table 3
¹H NMR of compounds **2** and **3** at 400 MHz in MeOH-*d*₄ (δ in ppm, *J* in Hz).

Position	2	3
1	–	–
2	6.80 (<i>s</i>)	6.60 (<i>s</i>)
3	–	–
4	–	–
5	–	–
6	6.80 (<i>s</i>)	6.60 (<i>s</i>)
7	5.01 (<i>d</i> , <i>J</i> = 5.8)	2.94 (<i>dd</i> , <i>J</i> = 6.8, 12.5)
8	4.08 (<i>ddd</i> , <i>J</i> = 4.0, 5.8, 6.0)	4.40 (<i>m</i>)
9	3.40–3.42 (<i>m</i>)	3.63–3.66 (<i>m</i>)
	3.81 (<i>m</i>)	–
OCH ₃	3.82 (<i>s</i>)	3.79 (<i>s</i>)
1'	–	–
2'	6.52 (<i>s</i>)	6.80 (<i>d</i> , <i>J</i> = 2.0)
3'	–	–
4'	–	–
5'	–	6.81 (<i>d</i> , <i>J</i> = 8.2)
6'	6.52 (<i>s</i>)	6.67 (<i>dd</i> , <i>J</i> = 2.0, 8.2)
7'	2.63 (<i>t</i> , <i>J</i> = 7.5)	2.59 (<i>t</i> , <i>J</i> = 7.4)
8'	1.82 (<i>m</i>)	1.79 (<i>m</i>)
9'	3.56 (<i>t</i> , <i>J</i> = 6.4)	3.54 (<i>t</i> , <i>J</i> = 6.5)
OCH ₃	3.83 (<i>s</i>)	–
a, a', c, c'	–	–
b, b'	–	–
glc-1	4.82 (<i>d</i> , <i>J</i> = 7.5)	4.78 (<i>d</i> , <i>J</i> = 7.3)
glc-2	3.44–3.49 (<i>m</i>)	3.43–3.45 (<i>m</i>)
glc-3	3.40–3.42 (<i>m</i>)	3.38–3.41 (<i>m</i>)
glc-4	3.40–3.42 (<i>m</i>)	3.38–3.41 (<i>m</i>)
glc-5	3.20 (<i>m</i>)	3.17–3.20 (<i>m</i>)
glc-6	3.76 (<i>m</i>)	3.63–3.66 (<i>m</i>)
	3.67 (<i>dd</i> , <i>J</i> = 9.0, 12.0)	3.74–3.77 (<i>m</i>)

2.3.2. (7*R*, 8*R*)-4, 7, 9, 9'-tetrahydroxy-3, 5, 3', 5'-tetramethoxy-8-4'-oxyneolignan 4-*O*-β-*D*-glucopyranoside (**2**)

Whiter powder (MeOH); [α]_D²⁵ – 31° (c 0.0021, MeOH); UV (MeOH) λ_{max} (log ε) 232 (0.25) nm; HR-ESI-MS *m/z* 601.2500 [M + H]⁺ (calcd for C₂₈H₄₁O₁₄); ¹H NMR and ¹³C NMR see Tables 3 and 4.

Table 4
¹³C NMR of compounds **2** and **3** at 100 MHz in MeOH-*d*₄ (δ in ppm).

Position	2	3
1	139.2	136.5
2	105.8	108.6
3	153.9	153.9
4	135.4	134.8
5	153.9	153.9
6	105.8	108.6
7	74.2	38.5
8	88.3	82.9
9	61.8	63.9
OCH ₃	57.0	57.0
1'	140.0	137.7
2'	106.7	114.0
3'	154.1	151.7
4'	135.3	146.9
5'	154.1	118.5
6'	106.7	121.8
7'	33.4	32.7
8'	35.4	35.6
9'	62.2	62.2
OCH ₃	56.6	–
a, a', c, c'	–	–
b, b'	–	–
glc-1	105.5	105.6
glc-2	75.7	75.7
glc-3	77.8	77.8
glc-4	71.3	71.3
glc-5	78.4	78.3
glc-6	62.6	62.6

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