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A New Lignan from the Fruit of *Schisandra propinqua* var. *propinqua* and its Anti-HIV Activity

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Phytochemical investigation of the fruit of *Schisandra propinqua* var. *propinqua* led to the isolation and identification of a new lignan named **Schproplignan C**. It structure was elucidated by spectroscopic methods including extensive 1 D- and 2 D-NMR techniques and its HIV-1 activity was evaluated. It shows an anti-HIV activity with EC_{50} (median effect concentration) value of 8.26 mg/mL and a therapeutic index (TI) above 22.8.

Key Words: *Schisandra propinqua* var. *propinqua*, Schproplignan C, Anti-HIV-1 activity.

INTRODUCTION

Schisandra propinqua var. *propinqua* is a member of *Schisandraceae* family growing in the forests in China[1]. The fruits of *Schisandra propinqua* var. *propinqua* are commonly used in Chinese traditional medicine as tonic, sedative and astringent agents[1]. Pioneering phytochemical work on them were achieved by Ikeya *et al*. resulting in a series of dibenzocyclooctadiene lignans ("gomisins" in Japanese),[2-6] which are then found to possess various biological activities including antihepatitis, antitumor and antilipid peroxidation effects[7-10]. In order to investigate the components of the aerial parts and search for potential leads for drug development, phytochemical investigation on the aerial parts of *Schisandra propinqua* var. *propinqua*, a Chinese traditional medicine indigenous to Yunnan province, was carried out in our group. This study led to the isolation of a new lignan from the fruit of *Schisandra propinqua* var. The structure was established by means of HRESIMS and extensive NMR spectra and it activity against HIV-1 was also evaluated.

EXPERIMENTAL

Optical rotation was measured in Horiba SEPA-300 high sensitive polarimeter. IR spectra was obtained in KBr disc on a bio-rad Wininfmred spectrophotometer. ESI-MS were measured on a VG auto Spec-3000 MS spectrometer. ^{1}H, ^{13}C and 2D NMR spectra were recorded on Bruker DRX-500 instruments with TMS as internal standard. On second separate used Agilent 1100 HPLC equipped with ZORBAX-C_{18} (9.4 nm × 250 nm, 5.0 μm) column and DAD detector. Column chromatography was performed on silica gel (200-300 mesh) or on silica gel H (10-40 μm, Qingdao Marine Chemical Inc., China).

The fruit of *Schisandra propinqua* var. *propinqua* were collected in Tengchong County, Yunnan Province, P.R. China, in June 2007, and identified by Prof. S. G. Wu. A voucher specimen (No. YNU 01-8-07) was deposited in our laboratory.

Extraction and isolation: The air-dried and powdered fruit of *Schisandra propinqua* var. *propinqua* (0.2 kg) were extracted with 70 % aqueous Me_2CO (2.0 L × 3, 24 h each) at room temperature and the extract was partitioned successively with petroleum ether (1.0 L × 2) and EtOAc (1.0 L × 2), respectively. The EtOAc extract (18.5 g) was subjected to CC over silica gel eluting with a $CHCl_3$-Me_2CO (1:0-0:1, 10 L) gradient system to give fractions 1-5. Fr.3 (8:2) was further purified by HPLC with mobile phase (MeOH-H_2O 60:40) to yield Schproplignan C (36.5 mg).

Anti-HIV-1 assay: The cytotoxicity assay against C8166 cells (CC_{50}) was assessed using the MTT method and anti-HIV-1 activity was evaluated by the inhibition assay for the cytopathic effects of HIV-1 (EC_{50})[11].

RESULTS AND DISCUSSION

Schproplignan C (Fig. 1) was obtained as white amorphous solid. The molecular formula of Schproplignan C was determined as $C_{26}H_{30}O_{10}$ from its HRESIMS at m/z 525.1734 $[M + Na]^+$ (calcd 525.1737). The ^1H and ^{13}C NMR data indicated the presence of aromatic rings. Strong absorption bands accounting for aromatic groups (1612, 1587, 1562, 1538, 1450 cm^{-1}) could also be observed in its IR spectrum. The UV spectrum of Schproplignan C showed maximum absorption at 282, 208 nm, which confirmed the existence of the aromatic functions. ^1H, ^{13}C and DEPT-NMR spectra (Table-1) exhibited 13 carbon atoms (possessed one aromatic ring, two methoxyls groups on the aromatic rings, two secondary methyl groups (include one oxygenated secondary methyl group), one oxygenated methylene group and one acetyl group). By comparison, the skeleton of Schproplignan C was the same as that of known compound (Yangambin)[12]. The major difference is that the Schproplignan C possesses an acetyl group signal and lacks a methoxyls group on the aromatic rings. According to the HMBC correlations from H-7 to C-1, C-2, C-6, H-8 to C-1 (Fig. 2), the aromatic groups were attached to C-7. The ^1H-^1H COSY correlations of H-7/H-8, H-8/H-9, as well as the HMBC correlations from H-9 to C-7, C-8, H-7 to C-9 indicated Schproplignan C is a ditetrahydrofurofuran lignan (Fig. 2). The methoxyls groups located at C-3, C-4 and the acetyl group located at C-5 can also be deduced from its HMBC spectrum (Fig. 2). The proposed relative stereochemistry was further supported by the NOESY experiment (Fig. 3). Thus, the structure of Schproplignan C was established as shown.

The potencies of Schproplignan C in preventing the cytopathic efects of HIV-1 in MT_4 cells, as well as compound-induced cytotoxicity in MT_4 cells in parallel with the antiviral activity were evaluated. The results from the cell-based assays demonstrated potent anti-HIV-1 activity with EC_{50} (median effect concentration) value of 8.26 mg/mL and a therapeutic index (TI) of greater than 22.8. Schproplignan C shows anti-HIV activity.

TABLE-1
^{1}H AND ^{13}C NMR DATA OF Schproplignan C IN C_5D_5N

No.	δ_C (mult.)	δ_H (mult, J, Hz)	No.	δ_C (mult.)	δ_H (mult, J, Hz)
1	133.2 s		1'	133.2 s	
2	110.9 d	6.51, s	2'	110.9 d	6.51, s
3	148.9 s		3'	148.9 s	
4	146.8 s		4'	146.8 s	
5	139.8 s		5'	139.8 s	
6	116.5 d	7.09 s	6'	116.5 d	7.09 s
7	86.4 d	4.95 (d 4.2)	7'	86.4 d	4.95 (d 4.2)
8	54.8 d	3.24, m	8'	54.8 d	3.24, m
9α	71.9 t	4.32 (dd, 6.8, 8.5)	9'α	71.9 t	4.32 (dd, 6.8, 8.5)
9β		4.08 (dd, 4.0, 9.5)	9'β		4.08 (dd, 4.0, 9.5)
3-OMe	55.9 q	3.77, s	3'-OMe	55.9 q	3.77, s
4-OMe	60.3 q	3.71, s	4'-OMe	60.3 q	3.71, s
5-OAc	169.9 s		5'-OAc	169.9 s	
	21.0 q	1.95 s		21.0 q	1.95 s

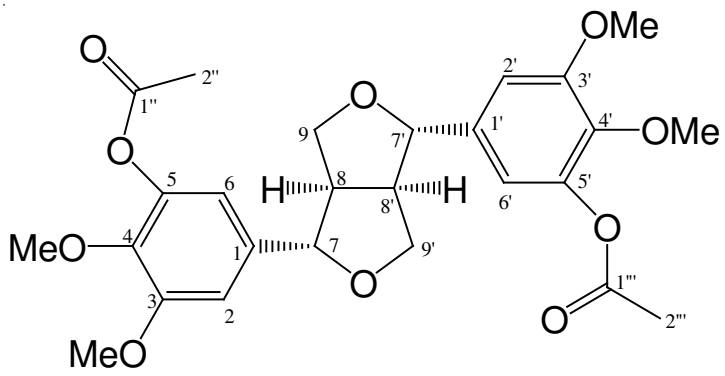

Fig. 1. Structure of Schproplignan C

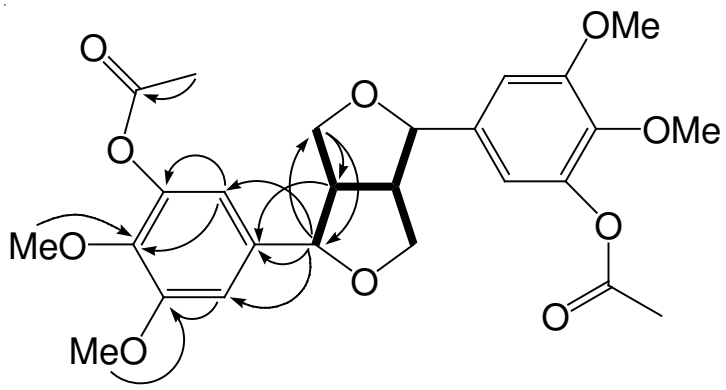

Fig. 2. Selected HMBC (—) and ^{1}H-^{1}H COSY (▬) correlations of Schproplignan C

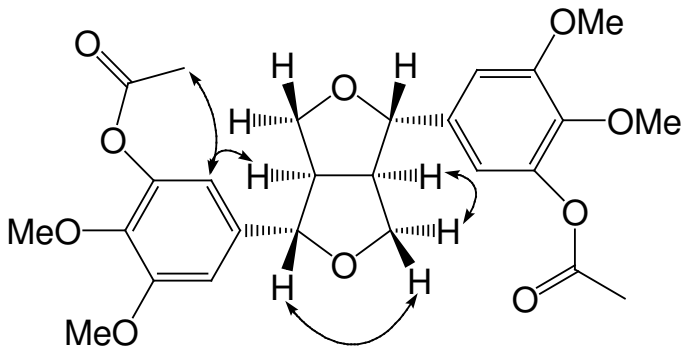

Fig. 3. Selected NOESY correlations for Schproplignan C

Schproplignan C: $C_{26}H_{30}O_{10}$, white amorphous solid; $[\alpha]2_D^{24.2}$ + 6.02 (c 0.12, MeOH); UV (MeOH), λ_{max} (log ε) 282 (4.88), 208 (5.96) nm; IR (KBr, ν_{max}, cm^{-1}) 2946, 2912, 2841, 2806, 1754, 1612, 1587, 1562, 1538, 1450, 1407, 1355, 1286, 1208, 1172, 1136, 1022, 976, 874, 832; ^1H and ^{13}C NMR data (C_5D_5N, 500 MHz), Table-1; HRESIMS (positive ion mode) m/z 525.1734 $[M + Na]^+$ (calcd. 525.1737 for $C_{26}H_{30}O_{10}Na$).

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