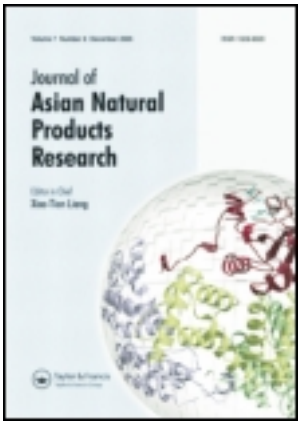

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Dibenzocyclooctadiene lignans from the fruits of Schisandra wilsoniana and their anti-HIV-1 activities

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ORIGINAL ARTICLE

Dibenzocyclooctadiene lignans from the fruits of *Schisandra wilsoniana* and their anti-HIV-1 activities

Guang-Yu Yang[ab], Yin-Ke Li[bc], Rui-Rui Wang[d], Wei-Lie Xiao[a]*, Liu-Meng Yang[d], Jian-Xin Pu[a], Yong-Tang Zheng[d] and Han-Dong Sun[a]*

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Three new dibenzocyclooctadiene lignans, wilsonilignans A–C (**1**–**3**), together with nine known ones, were isolated from the fruits of *Schisandra wilsoniana*. The structures of **1**–**3** were elucidated by spectroscopic methods including extensive 1D and 2D NMR techniques. Compounds **1**–**3** were also evaluated for their anti-HIV-1 activities and showed bioactivity with EC_{50} values of 3.26, 6.18, and 2.87 μg/ml, respectively.

Keywords: *Schisandra wilsoniana*; fruits; dibenzocyclooctadiene lignans; anti-HIV-1 activity

1. Introduction

Plants of the economically and medicinally important genus *Schisandra* (Schisandraceae) are known to be a rich source of dibenzocyclooctadiene lignans, lanostane, and cycloartane triterpenes, which have been found to possess various beneficial pharmacological effects [1–7]. Since 2003, the systematic chemical investigation of the genus *Schisandra* conducted by our group has led to the discovery of a series of novel nortriterpenoids with a diversity of highly oxygenated structures biogenetically related to cycloartane, some of which showed promising anti-HIV-1 activities with low toxicities [2,8–11].

Schisandra wilsoniana A.C. Smith belongs to the genus *Schisandra* of the family Schisandraceae. It is a climbing plant mainly distributed in Heqing, Dali, and Yulong prefectures of Yunnan Province of Mainland China [12,13]. In previous work, some bioactive compounds, including new highly oxygenated nortriterpenoids, carotane sesquiterpenoids, and lignans, were isolated from this plant [13–15]. To search for more new bioactive compounds from the plants of this genus, we examined the fruits of *S. wilsoniana*, which led to the isolation of three new dibenzocyclooctadiene lignans, wilsonilignans A–C (**1**–**3**), along with nine known ones. In addition, the anti-HIV-1 activities of compounds **1**–**3** were evaluated. This work deals with the

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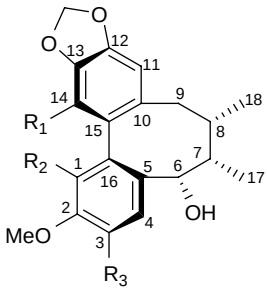
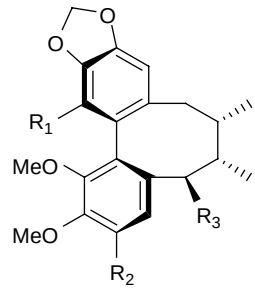
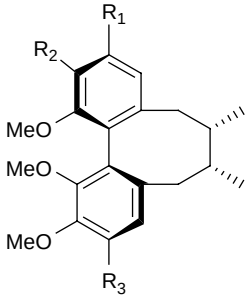


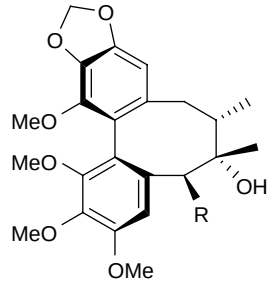
1 R_1 = OH; R_2 = R_3 = OMe
2 R_2 = OH; R_1 = R_3 = OMe
4 R_1 = R_2 = R_3 = OMe
5 R_1 = R_2 = OMe; R_3 = OH



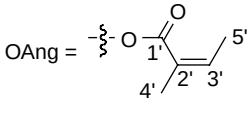
3 R_1 = OH; R_2 = R_3 = OMe
6 R_1 = R_2 = OMe; R_3 = OAc
7 R_1 = R_2 = OMe; R_3 = OH



8 R_1 = R_2 = OCH_2O; R_3 = OMe
9 R_1 = R_2 = OMe; R_3 = OH
10 R_1 = R_2 = R_3 = OMe



11 R = OAng
12 R = OBz



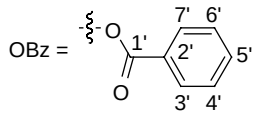


Figure 1. The structures of compounds **1**–**12**.

isolation, structural elucidation, and biological activities of these new compounds.

2. Results and discussion

Air-dried and powdered fruits (1.2 kg) were extracted with 70% aqueous Me_2CO (3 × 2 liters) at room temperature and concentrated *in vacuo* to give a crude extract (130 g), which was partitioned between H_2O and EtOAc. The EtOAc portion (46 g) was subjected to column chromatography on Si gel, Sephadex LH-20, RP-18, and preparative HPLC to afford compounds **1**–**12**, including three new lignans named wilsonilignans A–C (**1**–**3**), together with nine known lignans, epigomisin O (**4**) [16], kadsuphilins B (**5**) [17], rubschizantherin (**6**) [18], isogomisin O (**7**) [16], gomisin N (**8**) [16], deoxygomisin S (**9**) [19], (−)-deoxyschizandrin (**10**) [20], benzoylgomisin Q (**11**) [21], and angeloygomisin Q (**12**) [22]. The structures of compounds **1**–**12** are shown in Figure 1, and ^{13}C NMR spectroscopic data of **1**–**3** are listed in Table 1.

Compound **1** was obtained as a yellow gum. Its molecular formula was determined as $C_{22}H_{26}O_7$ by its HR-ESI-MS

Table 1. ^{13}C NMR spectral data of compounds **1**–**3** (δ in ppm).

No.	**1**[a]	**2**[a]	**3**[b]	No.	**1**[a]	**2**[a]	**3**[b]
1	152.9 s	150.4 s	152.5 s	13	135.2 s	136.2 s	135.2 s
2	142.7 s	141.2 s	142.7 s	14	141.2 s	143.6 s	141.4 s
3	151.7 s	151.9 s	151.7 s	15	120.8 s	122.0 s	120.3 s
4	110.1 d	110.8 d	109.6 d	16	121.9 s	122.8 s	121.4 s
5	138.2 s	137.8 s	137.9 s	17	8.4 q	8.5 q	17.1 q
6	72.9 d	73.0 d	90.1 d	18	22.3 q	22.4 q	17.1 q
7	43.9 d	44.2 d	38.8 d	19	101.4 t	101.9 t	101.4 t
8	39.9 d	40.0 d	36.6 d	1-OMe	60.8 q		59.4 q
9	35.1 t	35.2 t	38.0 t	2-OMe	61.0 q	60.8 q	59.6 q
10	138.9 s	138.8 s	138.6 s	3-OMe	55.9 q	60.7 q	55.8 q
11	103.4 d	104.0 d	102.4 d	14-OMe		55.9 q	
12	149.4 s	149.6 s	148.9 s	6-OMe			55.7

Notes: [a]Data obtained in pyridine-d_5.
[b]Data obtained in $CDCl_3$.

at *m/z* 425.1579 $[M + Na]^+$. It showed absorption maxima in the UV spectrum at 215, 253, 314 nm, and a strong negative Cotton effect at 252 nm in the CD spectrum, indicating **1** is a C_{18} dibenzocyclooctadiene lignan with an *S*-biphenyl configuration [23]. The absorption band at 3450 cm^{-1} in the IR spectrum suggests the presence of hydroxyl groups in **1**. The ^{13}C NMR spectrum showed the signals of 12 carbons as belonging to a biphenyl at δ_C 103.4–152.9 (Table 1). In addition to the aromatic protons of biphenyl that appeared at δ_H 6.93 and 6.64 (1H each, s), the ^1H NMR spectrum of **1** also indicated the presence of one methylenedioxy unit at δ_H 5.90, 5.96 (1H each, s), three methoxy groups at δ_H 3.77, 3.84, 3.96 (3H each, s), one phenolic hydroxy group, and two secondary methyls at δ_H 0.92 (3H each, d, $J = 7.1$ Hz) and 0.98 (3H, d, $J = 7.2$ Hz). From the HMBC spectrum of **1**, it was found that the single sp^3 oxymethine carbon resonating at C-6 (δ_C 72.9, d) correlated with a proton at H-6 (δ_H 4.97, 1H, br s). The HMBC correlations observed from H-6 (δ_H 4.97, br s) to the aromatic C-4 (δ_C, 110.1 d) and C-16 (δ_C, 121.9 s) in the HMBC spectrum (Figure 2) were used to assign the oxymethine group at C-6. It was found that the ^{13}C NMR spectroscopic data (Table 1) of **1** were quite similar to those of epigomisin O [16]. The only difference was that a methoxy group in epigomisin O was substituted by a hydroxyl group in **1** on the aromatic rings, which was supported by the disappearance of the signal of a methoxy group in **1**. Further analysis of the HMBC spectrum showed that the methylenedioxy unit was attached to C-12 and C-13, three methoxy groups were located at C-1, C-2, and C-3, and the phenolic hydroxy group was located at C-14, respectively.

The α-orientation of the hydroxyl group at C-6 was confirmed by its chemical shift (δ_C 72.9, d; δ_H 4.97, br s), which was similar to that of the α-oriented derivatives of gomisins [16,17]. This was further confirmed by ROESY correlations of **1** (Figure 3). One of the C-9 protons

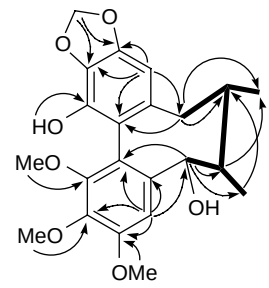


Figure 2. Selected HMBC (→) and ^1H–^1H COSY (–) correlations of **1**.

(δ_H 2.04) exhibited a ROESY correlation with the aromatic H-11 (δ_H 6.64) and was thus assigned as H-9β. The ROESY correlations found between H-9β (δ_H 2.04) and H-8 (δ_H 2.38) and between H-8 (δ_H 2.38) and H-6 (δ_H 4.97) confirmed the α-orientation of OH-6. The upfield-shifted C-17 (δ_C 8.4, CH_3) in **1**, relative to that of gomisin R [24] (δ_C 16.5, CH_3), could be explained by the strong γ-effect arising from the steric compression of a *gauche* interaction between the methyl group attached at C-7 and the α-hydroxy group attached at C-6 in **1**. The above observations were used to establish the structure of **1** as 6-*epi*-gomisin, and given the name wilsonilignan A.

Compound **2** was obtained as a yellow gum, showing a quasi-molecular weight of 425.1578 $[M + Na]^+$ in HR-ESI-MS, corresponding to the molecular formula $C_{22}H_{26}O_7$. The ^1H and ^{13}C NMR spectra of **2** were very similar to those of **1**. The obvious chemical shift differences resulted from the substituent groups in the aromatic rings. Analysis of HSQC and HMBC spectra of **2** showed that the methylenedioxy unit was attached to C-12 and C-13, three methoxy groups were located at C-2, C-3, and C-14, and the phenolic hydroxy group was located at C-1, respectively. Thus, the structure of **2** was established and given the name wilsonilignan B.

Compound **3** was also obtained as a yellow gum. It possesses a molecular formula of $C_{23}H_{28}O_7$, as derived from its HR-ESI-MS at *m/z* 439.1736 $[M + Na]^+$. Its ^1H and ^{13}C NMR spectra show the signals of 28 protons and 23 carbons, respectively, corresponding to two aromatic rings with two aromatic protons, one methylene carbon, two methine carbons, one oxidated methine carbon, two methyl groups, one methylenedioxy unit, four methoxy groups, and one phenolic hydroxy group. These evidences, together with the strong negative Cotton effect at 252 nm in its CD spectrum, indicated that **3** is a dibenzocyclooctadiene lignan with an *S*-biphenyl configuration. The methoxy proton signal at δ_H 3.06 and the chemical shift of C-6 (δ_C 90.1, d) indicated that a methoxy group was attached to C-6 [25], which was further confirmed by the HMBC correlation of this methoxy (δ_H 3.06) with C-6. The ^1H and ^{13}C NMR spectral data of **3** were found to be very close to those of methylisogomisin O [25]. The only difference was that a methoxy group in methylisogomisin O was substituted by a hydroxyl group in **3** on the aromatic rings, which was supported by the disappearance of the signal of a methoxy group in **3**. Further analysis of the HMBC spectrum showed that the methylenedioxy unit was attached to C-12 and C-13, three methoxy groups were located at C-1, C-2, and C-3, and the phenolic hydroxy group was located at C-14, respectively.

The configuration of 6-OMe was deduced as β-orientation by the chemical shift of C-6 (δ_C 90.1), which was similar to that of the 6-β-oriented derivatives of gomisins [23] and was distinct from that of 6-α-oriented components in dibenzocyclooctadiene lignan family [14,15]. The above deduction was further confirmed by the ROESY correlation between H-4 and H-6α. The cyclooctadiene ring of **3** was indicated to be a *twist-boat-chair* (TBC) conformation by the ROESY correlations of H-4/CH_3-17 and H-9β/H-11. Thus, the structure of **3** was established as shown, and given the name wilsonilignan C.

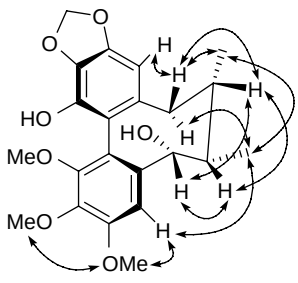


Figure 3. Key ROESY correlations (↔) of **1**.

Since some of the dibenzocyclooctadiene lignans from the species of the *Schisandra* genus exhibited modest or strong anti-HIV activities, new compounds **1**–**3** were tested for their potencies in preventing the cytopathic effects of HIV-1 in C8166 and cytotoxicity measured in parallel with the determination of antiviral activity, using AZT as a positive control (0.0043 μg/ml and $CC_{50} > 200$ μg/ml) [26]. The results are shown in Table 2. Compounds **1**–**3** showed anti-HIV-1 activity with EC_{50} values of 3.26, 6.18, and 2.87 μg/ml, respectively.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Horiba SEPA-300 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. CD spectra were measured on a JASCO J-810 spectropolarimeter. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy with KBr pellets. 1D and 2D NMR spectra were recorded on DRX-500 spectrometers with TMS as the internal standard. Unless otherwise indicated, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HR-ESI-MS were performed on a VG Autospec-3000 spectrometer. Preparative HPLC was performed on a Shimadzu LC-8A preparative liquid chromatography with a ZORBAX PrepHT GF (21.2 mm × 25 cm) column or a Venusil MP C_{18} (20 mm × 25 cm) column. Column chromatography was performed with Si gel (200–300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), Lichroprep RP-18 gel (40–63 μm; Merck, Darmstadt, Germany), and MCI gel (75–150 μm; Mitsubishi Chemical Corporation, Tokyo, Japan). The fractions were monitored by TLC, and spots were visualized by heating Si gel plates sprayed with 5% H_2SO_4 in EtOH.

Table 2. Anti-HIV activities of compounds **1**–**3**.

Compound	EC_{50} (μg/ml)	CC_{50} (μg/ml)	TI[a]
1	3.26	16.82	5.16
2	6.18	58.42	9.45
3	2.87	39.60	13.80

Note: [a]TI = EC_{50}/CC_{50}.

3.2 Plant material

The fruits of *S. wilsoniana* were collected in Heqing Prefecture of Yunnan Province, China, in July 2006. The identification of the plant material was verified by Prof. Xi-Wen Li. A voucher specimen (KIB 06-9-23) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, China.

3.3 Extraction and isolation

The air-dried and powdered fruits of *S. wilsoniana* (1.2 kg) were extracted with 70% aqueous Me_2CO (3 × 2 liters) at room temperature and filtered to yield a filtrate, which was successively evaporated under reduced pressure and partitioned with EtOAc (3 × 2 liters). The EtOAc partition (46 g) was applied to Si gel (200–300 mesh) column chromatography eluted with a $CHCl_3$–Me_2CO gradient system (9:1, 8:2, 7:3, 6:4, 5:5) to give five fractions A–E. The separation of fraction A (8.6 g) by Si gel column chromatography eluted with petroleum ether–acetone (20:1–1:2) yielded mixtures A1–A7. Fraction A1 (1.2 g) was subjected to Si gel column chromatography using petroleum ether–acetone and preparative HPLC (75% MeOH–H_2O, flow rate 12 ml/min) to give **4** (23 mg) and **6** (35 mg). Fraction A2 (0.8 g) was subjected to Si gel column chromatography using petroleum ether–acetone and preparative HPLC (60% MeOH–H_2O, flow rate 12 ml/min) to give **8** (15.6 mg), **10** (9.8 mg), **11** (18.9 mg), and **12**

(13.8 mg). Fraction A3 (1.5 g) was subjected to Si gel column chromatography using petroleum ether–acetone and preparative HPLC (60% MeOH–H_2O, flow rate 12 ml/min) to give **1** (8.1 mg), **2** (16.2 mg), **3** (4.8 mg), **5** (11.8 mg), **7** (18.5 mg), and **9** (6.4 mg).

3.3.1 Wilsonilignan A (*1*)

Yellow gum, $[\alpha]_D^{23.5}$ −58.2 ($c = 0.28$, MeOH). CD ($c = 0.05$, MeOH): $\Delta\varepsilon_{252\,nm}$ −20.8, $\Delta\varepsilon_{240\,nm}$ −16.2, $\Delta\varepsilon_{220\,nm}$ +7.28, $\Delta\varepsilon_{212\,nm}$ −1.86. UV (MeOH) λ_{max} (log ε): 215 (4.64), 253 (3.84), 314 (0.62) nm. IR (KBr) ν_{max}: 3450, 3115, 2924, 2857, 1615, 1593, 1458, 1382, 1115, 1054, 1035, 964 cm^{-1}. ^1H NMR (pyridine-d_5, 500 MHz): δ 6.93 (1H, s, H-4), 4.97 (1H, br s, H-6), 2.02 (overlap H-7), 2.38 (1H, m, H-8), 2.33 (1H, d, $J = 9.5$ Hz, H-9α), 2.04 (1H, overlap, H-9β), 6.64 (1H, s, H-11), 0.92 (3H, d, $J = 7.1$ Hz, H-17), 0.98 (3H, d, $J = 7.2$ Hz, H-18), 5.90, 5.96 (2H, s, H-19), 3.77, 3.84, 3.96 (each 3H, s, 3 × OMe). ^{13}C NMR spectral data, see Table 1. HR-ESI-MS: *m/z* 425.1579 $[M + Na]^+$ (calcd for $C_{22}H_{26}O_7Na$, 425.1576).

3.3.2 Wilsonilignan B (*2*)

Yellow gum, $[\alpha]_D^{23.0}$ −59.3 ($c = 0.25$, MeOH). CD ($c = 0.05$, MeOH): $\Delta\varepsilon_{250\,nm}$ −26.2, $\Delta\varepsilon_{240\,nm}$ −18.2, $\Delta\varepsilon_{218\,nm}$ +8.52, $\Delta\varepsilon_{210\,nm}$ −2.11. UV (MeOH) λ_{max} (log ε): 210 (4.72), 252 (3.63), 314 (0.53) nm. IR (KBr) ν_{max}: 3448, 2927, 2849, 1616, 1590, 1462, 1374, 1327, 1062, 1047, 1025, 958 cm^{-1}. ^1H NMR (pyridine-d_5, 500 MHz): δ 6.99 (1H, s, H-4), 4.99 (1H, br s, H-6), 2.04 (m, H-7), 2.42 (1H, overlap, H-8), 2.40 (1H, overlap, H-9α), 2.12 (1H, d, $J = 16.3$ Hz, H-9β), 6.58 (1H, s, H-11), 0.94 (3H, d, $J = 7.1$ Hz, H-17), 1.01 (3H, d, $J = 7.2$ Hz, H-18), 5.91, 5.99 (2H, s, H-19), 3.75, 3.87, 3.91 (each 3H, s, 3 × OMe). ^{13}C NMR spectral data, see Table 1. HR-ESI-MS: *m/z* 425.1578 $[M + Na]^+$ (calcd for $C_{22}H_{26}O_7Na$, 425.1576).

3.3.3 Wilsonilignan C (*3*)

Yellow gum, $[\alpha]_D^{23.6}$ + 20.2 ($c = 0.20$, MeOH). CD ($c = 0.06$, MeOH): $\Delta\varepsilon_{252\,nm}$ −71.2, $\Delta\varepsilon_{240\,nm}$ −49.5, $\Delta\varepsilon_{222\,nm}$ +12.8, $\Delta\varepsilon_{218\,nm}$ −1.26. UV (MeOH) λ_{max} (log ε): 210 (5.32), 248 (3.35), 320 (1.26) nm. IR (KBr) ν_{max}: 3418, 3122, 2936, 2838, 1647, 1549, 1481, 1382, 1327, 1276, 1138, 1059, 1024, 978 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.82 (1H, s, H-4), 3.97 (1H, d, $J = 8.4$ Hz, H-6), 1.67 (1H, m, H-7), 1.86 (1H, m, H-8), 2.33 (1H, m, H-9α), 2.02 (1H, dd, $J = 10.6$, 12.8 Hz, H-9β), 6.62 (1H, s, H-11), 0.87 (3H, d, $J = 8.2$ Hz, H-17), 0.91 (3H, d, $J = 8.1$ Hz, H-18), 5.95, 5.98 (2H, s, H-19), 3.06 (3H, s, OMe-6), 3.78, 3.84, 3.90 (each 3H, s, 3 × OMe). ^{13}C NMR spectral data, see Table 1. HR-ESI-MS: *m/z* 439.1736 $[M + Na]^+$ (calcd for $C_{23}H_{28}O_7Na$, 439.1733).

3.4 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}) [26].

Acknowledgements

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