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Schisanwilsonins A–G and related anti-HBV lignans from the fruits of *Schisandra wilsoniana*

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ABSTRACT

Seven new dibenzocyclooctane lignans, schisanwilsonins A–G (1–7), were isolated from the fruits of *Schisandra wilsoniana*, together with five known lignans (8–12). The structures of these new compounds were elucidated by spectroscopic methods including 2D-NMR techniques. The 12 lignans were tested for anti-hepatitis B virus (HBV) activity in vitro. Schisanwilsonin D (4), schisantherin C (9), deoxyschizandrin (10) and (+)-gomisin K_3 (11) showed anti-HBV activity. 9 exhibited the most potent anti-HBV activity with potency against HBsAg and HBeAg secretion by 59.7% and 34.7%, respectively, at 50 μg/mL.

Dibenzocyclooctane lignans, mostly isolated from the Schisandraceae plants,[1] are important natural products with many beneficial pharmacological effects, such as calcium antagonism, anti-lipid peroxidation, and antitumor effect.[2–4] Several dibenzocyclooctane lignans isolated from *Kadsura interior* and *Schisandra rubriflora* were found to show strong antiviral effect against human immunodeficiency virus (HIV).[5–7] It's interesting that some dibenzocyclooctane lignans obtained from *Kadsura induta*, *Kadsura japonica*, and *Schisandra. arisanensis* were also reported to be active against hepatitis B virus (HBV).[8–10] The fruits of *Schisandra wilsoniana* A. C. Smith (Schisandraceae) are used in Chinese folk medicine as a substitute for 'wu-wei-zi' to treat hepatitis, and the Et_2O extract was found to show anti-HBV activity. In our continuing effort to search for anti-HBV agents from Chinese herbs, a phytochemical investigation on the fruits of this plant[11] led to the isolation and characterization of seven new dibenzocyclooctane lignans,[12] schisanwilsonins A–G (**1**–**7**), along with five known lignans (**8**–**12**), which were identified as schisantherin A (**8**),[13] schisantherin C (**9**),[13] deoxyschizandrin (**10**),[14] (+)-gomisin K_3 (**11**),[15] and gomisin H (**12**),[16] respectively, by comparison of their physical and spectroscopic data with those reported. This paper reports the isolation and structure elucidation of the new compounds, as well as the in vitro anti-HBV activity of these isolated lignans.

Schisanwilsonin A (**1**), white powder, had molecular formula $C_{28}H_{34}O_9$ on the basis of HREIMS data (*m*/*z* 514.2209). The UV and NMR spectra indicated that **1** was a dibenzocyclooctane-type lignan.[14] The ^1H NMR spectrum of **1** (Table 1) showed the presence of four MeO groups at δ_H 3.52, 3.69, 3.89 and 3.91 (3H each, s), and a methylenedioxy (OCH_2O) moiety at δ_H 5.87 (1H, d, $J = 1.4$ Hz) and 5.90 (1H, d, $J = 1.4$ Hz) on aromatic ring. The O-atoms of the methylenedioxy moiety were attached to C-12 (δ_C 148.7) and C-13 (δ_C 134.5), on the basis of HMBC correlations of the proton signal at δ_H 6.46 (H-11) and OCH_2O resonances with C-12 and C-13 (Fig. 2). Four MeO groups were thus connected to C-1, C-2, C-3 and C-14, respectively, and which were confirmed by HMBC.

The EIMS fragments at *m*/*z* 414 ($[M-C_4H_7COOH]^+$), 83 ($C_5H_7O^+$) and 55 ($C_4H_7^+$) suggested the presence of an angeloyl (=(*Z*)-2-methylbut-2-enoyl; Ang) group, as confirmed by the ^1H NMR signals at δ_H 6.00 (1H, m, H-3′), 1.86 (3H, d, $J = 7.0$ Hz, Me-4′) and 1.38 (3H, s, Me-5′), along with the corresponding ^{13}C NMR signals (Table 2) at δ_C 166.1 (C-1′), 127.1 (C-2′), 140.4 (C-3′), 15.8 (C-4′) and 19.6 (C-5′).[16] The HMBC correlations of H-6 at δ_H 5.63 with C-1′ at δ_C 166.1, as well as the ROESY cross-peak between H-4 and H-6 indicated that a β-AngO group was located at C-6.

The IR absorption at 3442 cm^{-1} and the Me signals at δ_H1.13 (d, $J = 7.0$ Hz) and 1.08 (s) in the ^1H NMR spectrum suggested the presence of an OH group at C-6 or C-7.[17] The HMBC correlations of H-6 with C-7 at δ_C 75.4 and Me-18 at δ_C 19.2, as well as the ROESY cross-peaks observed between H-4 and Me-18, H-6 and Me-18 revealed that the β-OH group was located at C-7.

The circular dichroism (CD) spectrum of **1** showed a negative *Cotton* effect at 255 nm, and a positive one at 230 nm, in accord with a *S* biphenyl configuration.[18] The ROESY cross-peaks between H-4 and H-6, H-4 and Me-18, as well as H-6 and Me-18 (Fig. 3) indicated a 'twist-boat-chair' (TBC) conformation for the cyclooc-

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Table 1
^{1}H NMR (400 MHz) data of compounds **1**–**7** ($CDCl_3$, δ_H in ppm, J in Hz)

	1	**2**	**3**	**4**	**5**	**6**	**7**
4	6.71 (s)	6.70 (s)	6.77 (s)	6.71 (s)	6.67 (s)	6.66 (s)	6.79 (s)
6	5.63 (s)	5.68 (s)	5.84 (s)	5.76 (s)	5.63 (s)	5.58 (s)	5.93 (s)
8	1.98 (m)	2.01 (m)	2.17 (m)	2.078 (m)	1.95 (m)	1.94 (m)	2.22 (m)
9	2.22 (m)	2.24 (m)	2.31 (m)	2.26 (m)	2.23 (m)	2.21 (m)	2.34 (m)
11	6.46 (s)	6.50 (s)	6.57 (s)	6.68 (s)	6.48 (s)	6.47 (s)	6.78 (s)
17	1.13 (d, 7.0)	1.13 (d, 7.0)	1.18 (d, 7.0)	1.14 (d, 7.0)	1.11 (d, 7.0)	1.09 (d, 7.0)	1.18 (d, 7.0)
18	1.08 (s)	1.08 (s)	1.14 (s)	1.07 (s)	1.06 (s)	1.04 (s)	1.12 (s)
MeO-1	3.52 (s)	3.53 (s)	3.55 (s)	3.57 (s)	3.52 (s)	3.52 (s)	3.54 (s)
MeO-2	3.89 (s)	3.88 (s)	3.88 (s)	3.88 (s)	3.89 (s)	3.88 (s)	3.89 (s)
MeO-3	3.91 (s)	3.90 (s)	3.93 (s)	3.92 (s)	3.89 (s)	3.87 (s)	3.95 (s)
MeO-13				3.86 (s)			3.39 (s)
MeO-14	3.69 (s)	3.66 (s)	3.26 (s)	3.31 (s)	3.83 (s)	3.82 (s)	3.11 (s)
OCH_2O	5.87 (d, 1.4)	5.87 (d, 1.2)	5.72 (d, 1.5)		5.90 (d, 1.4)	5.90 (s)	
	5.90 (d, 1.4)	5.93 (d, 1.2)	5.80 (d, 1.5)		5.92 (d, 1.4)	5.91 (s)	
HO-12				5.71 (br s)			5.71 (br s)
2′					2.10 (m)	1.64 (s)	
3′	6.00 (m)	6.00 (m)	7.48 (d, 7.0)	5.97 (m)	0.90 (d, 7.0)		7.42 (d, 7.0)
4′	1.86 (d, 7.0)	1.67 (d, 7.0)	7.31 (t, 7.4)	1.61 (d, 7.0)	0.91 (d, 7.0)		7.29 (t, 7.4)
5′	1.38 (s)	1.58 (s)	7.50 (t, 7.4)	1.52 (s)			7.45 (t, 7.4)
6′			7.31 (t, 7.4)				7.29 (t, 7.4)
7′			7.48 (d, 7.0)				7.42 (d, 7.0)

tane ring.[19] From the above data, the structure of **1**[20] was elucidated as shown in Figure 1.

The IR, UV, CD and NMR data of compounds **2**–**7** were similar to those of **1**, indicating that **2**–**7** were all dibenzocyclooctane-type lignans.

Schisanwilsonin B (**2**),[21] had molecular formula $C_{28}H_{34}O_9$ according to the HRESIMS data (m/z 537.2103, $[M+Na]^+$). The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of **2** were quite similar to those of **1** except for the characteristic signals due to a tigloyl (Tig) group instead of the angeloyl group in **1**. The ^{1}H NMR signals at δ_H 6.00 (1H, m, H-3′), 1.67 (3H, d, J = 7.0 Hz, Me-4′) and 1.58 (3H, s, Me-5′), along with the corresponding ^{13}C NMR signals at δ_C 166.7 (C-1′), 127.6 (C-2′), 137.7 (C-3′), 14.2 (C-4′) and 11.5 (C-5′) indicated the presence of a Tig group.[22]

Schisanwilsonin C (**3**),[23] was assigned the molecular formula $C_{30}H_{32}O_9$ based on HREIMS (m/z 536.2045). Comparison of the NMR data of **3** with those of **1** indicated that the angeloyl group in **1** was replaced by a benzoyl (Bz) group in **3**. The EIMS fragments at m/z 414 ($[M-C_6H_5COOH]^+$), 105 ($C_6H_5CO^+$), and 77 ($C_6H_5^+$) suggested the presence of a benzoyl group, which was confirmed by the ^{1}H NMR signals at δ_H 7.31 (t, J = 7.0 Hz, H-4′,6′), 7.48 (d, J = 7.0 Hz, H-3′,7′), 7.50 (t, J = 7.0 Hz, H-5′), and ^{13}C NMR signals

Table 2
^{13}C NMR (100 MHz) data of compounds **1**–**7** ($CDCl_3$, δ in ppm)

	1	**2**	**3**	**4**	**5**	**6**	**7**
1	152.0 s	152.0 s	152.1 s	152.1 s	152.0 s	152.0 s	152.1 s
2	141.6 s	141.6 s	141.7 s	141.8 s	141.6 s	141.6 s	141.9 s
3	151.7 s	151.7 s	151.8 s	151.8 s	151.7 s	151.9 s	151.8 s
4	110.0 d	110.0 d	109.9 d	110.3 d	110.1 d	110.0 d	110.3 d
5	131.5 s	131.7 s	131.3 s	131.4 s	131.5 s	131.5 s	131.1 s
6	86.3 d	86.1 d	86.8 d	85.9 d	86.1 d	86.3 d	85.5 d
7	75.4 s	75.4 s	75.5 s	75.8 s	75.6 s	72.0 s	75.9 s
8	43.0 d	43.0 d	43.4 d	42.7 d	42.6 d	42.7 d	42.9 d
9	37.2 t	37.2 t	37.2 t	37.1 t	37.2 t	37.0 t	37.2 t
10	135.0 s	135.1 s	135.0 s	137.1 s	135.1 s	135.2 s	137.0 s
11	102.6 d	102.5 d	102.3 d	109.8 d	102.5 d	102.6 d	109.7 d
12	148.7 s	148.5 s	148.8 s	148.8 s	148.6 s	148.6 s	149.0 s
13	134.5 s	134.5 s	134.4 s	137.7 s	134.3 s	134.2 s	137.7 s
14	140.7 s	140.7 s	140.4 s	149.4 s	140.5 s	140.3 s	149.4 s
15	121.0 s	121.2 s	120.9 s	121.7 s	120.9 s	121.1 s	121.4 s
16	121.7 s	121.6 s	121.7 s	121.6 s	121.9 s	121.3 s	121.7 s
17	18.8 q	18.8 q	18.8 q	18.7 q	18.7 q	18.6 q	18.8 q
18	19.2 q	19.2 q	19.2 q	19.2 q	19.5 q	19.2 q	19.2 q
MeO-1	60.6 q	60.7 q	60.7 q	60.8 q	60.6 q	60.6 q	60.7 q
MeO-2	60.9 q	60.9 q	60.9 q	60.9 q	60.9 q	60.9 q	60.9 q
MeO-3	55.8 q	55.9 q	55.9 q	55.8 q	55.9 q	55.9 q	56.0 q
MeO-13				60.6 q			60.0 q
MeO-14	59.1 q	59.0 q	58.6 q	59.2 q	59.2 q	59.2 q	59.2 q
OCH_2O	100.6 t	100.5 t	100.5 t		100.6 t	100.6 t	
1′	166.1 s	166.7 s	165.2 s	166.7 s	176.3 s	170.0 s	165.2 s
2′	127.1 s	127.6 s	129.4 s	127.4 s	33.9 s	20.2 q	129.4 s
3′	140.4 d	137.7 d	129.6 d	138.5 d	18.9 d		129.6 d
4′	15.8 q	14.2 q	127.8 d	14.3 q	17.9 q		128.1 d
5′	19.6 q	11.5 q	133.0 d	11.5 q			133.1 d
6′			127.8 d				128.1 d
7′			129.6 d				129.6 d