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Article

Neglschisandrins E–F: Two New Lignans and Related Cytotoxic Lignans from *Schisandra neglecta*

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Abstract: Phytochemical investigation of an ethanolic extract of stems of *Schisandra neglecta* led to the isolation and identification of two new dibenzocyclooctadiene lignans, designated neglschisandrins E (**1**) and F (**2**), and thirteen known lignans. All structures and stereochemistries were determined by spectroscopic methods, including 2D-NMR techniques. The isolates were evaluated for *in vitro* cytotoxic activity. Among them, compounds **2**–**6** exhibited moderate to weak cytotoxicity against the human colorectal carcinoma HCT-8 cell line with EC_{50} values of 7.33~19.8 μg/mL. In addition, compounds **2**–**4** also exhibited marginal cytotoxicity against the human lung carcinoma A549 cell line with EC_{50} values of 11.8~15.0 μg/mL.

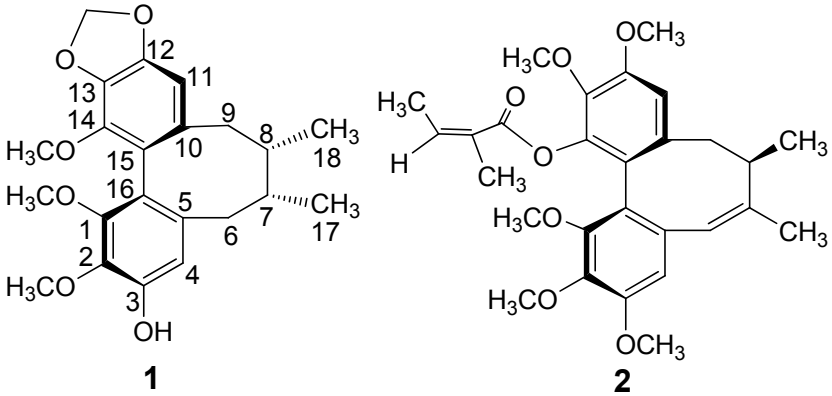
Keywords: *Schisandra neglecta*; Schisandraceae; dibenzocyclooctadiene lignan; neglschisandrins E–F; cytotoxicity

1. Introduction

Stems or fruits of plants in the Schisandraceae family are used widely in China as tonic and astringent agents for the treatment of rheumatic arthritis, traumatic injury, and related diseases [1]. Schisandraceae plants are rich in lignans, especially dibenzocyclooctadiene lignans, which show beneficial pharmacological effects, including anti-HIV, antitumor-promoting, calcium antagonistic, and anti-lipid peroxidative actions [2–13].

In our previous study, we reported four new dibenzocyclooctadiene lignans from the stems of *Schisandra neglecta*, which is indigenous to the Tibet Autonomous Region of China [14,15]. Our further investigation of the same plant has now led to the isolation and identification of two new dibenzocyclooctadiene lignans, named neglschisandrins E (**1**) and F (**2**) (Figure 1), together with thirteen known lignans, 6-*O*-benzoylgomisin O (**3**) [16], (+)-γ-rubschisandrin (**4**) [17], rubschisantherin (**5**) [17], benzoylisogomisin O (**6**) [18], schisandrin A (**7**) [19], schisanhenol (**8**) [20], angeloylgomisin H (**9**) [21], gomisin H (**10**) [21], tigloylgomisin H (**11**) [21], benzoylgomisin H (**12**) [21], schisandrin (**13**) [22], gomisin B (**14**) [23], and angeloyl-(+)-gomisin K_3 (**15**) [24]. This paper reports the isolation and structural elucidation of these compounds as well as their *in vitro* cytotoxicity against human lung carcinoma A549 and human colorectal carcinoma HCT-8 cell lines.

Figure 1. Structures of Compounds **1**–**2**.



2. Results and Discussion

A 95% alcoholic extract prepared from stems of *Schisandra neglecta* was partitioned between diethyl ether and water. The diethyl ether extract was subjected to silica gel column chromatography (CC), preparative TLC, and semi-preparative reversed phase HPLC to give the two new and thirteen known dibenzocyclooctadiene lignans named above.

Compound **1**, obtained as amorphous powder, had the molecular formula $C_{22}H_{26}O_6$ based on HR-ESI-MS (*m/z* 387.1810 $[M+H]^+$). The UV and NMR spectra indicated that **1** was a dibenzocyclooctadiene lignan [25]. The ^{1}H-NMR spectrum of **1** (Table 1) showed signals due to two secondary methyl groups (δ_H 0.97, 0.73, each 3H, *d*, *J* = 7.1 Hz), assignable to the *cis*-oriented Me-7 and Me-8, respectively [26]. The presence of four benzylic methylene signals (δ_H 2.25, 1H, *dd*, *J* = 13.0, 9.6; 2.01 Hz, 1H, *d*, *J* = 13.0 Hz; 2.55, 1H, *dd*, *J* = 13.6, 7.4; 2.45 Hz, 1H, *dd*, *J* = 13.6, 1.5 Hz) indicated that C-6 and C-9 were unsubstituted. The ^{1}H-NMR spectrum also showed signals for two

aromatic protons (δ_H 6.63, 6.49 each 1H, s), assignable to CH-4 and CH-11, respectively. Three methoxy groups [δ_H 3.50, 3.79 and 3.93, each 3H, s) and a methylenedioxy (–OCH_2O–) moiety (δ_H 5.96, 5.95, each 1H, *d*, *J* = 1.3 Hz] were also observed as substituents on the aromatic rings. The proton signal at δ_H 5.68 (br s) showed no correlations in the HMQC spectrum, and was assigned as an hydroxyl on the aromatic ring. This assignment was supported by an IR band at 3447 cm^{-1} [27].

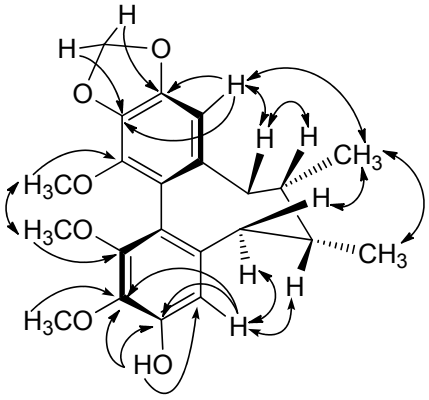
Table 1. ^1H- (400 MHz) and ^{13}C- (100 MHz) NMR data (measured in *CDCl₃*) for compounds **1** and **2** (δ in ppm, *J* in Hz).

	1		**2**	
Position	δ_C	δ_H	δ_C	δ_H
			S	
1	150.3 (*s*)	-	152.3 (*s*)	-
2	137.4 (*s*)	-	139.9 (*s*)	-
3	148.8 (*s*)	-	152.6 (*s*)	-
4	110.2 (*d*)	6.63 (*s*)	106.3 (*d*)	6.38 (*s*)
5	140.3 (*s*)	-	136.5 (*s*)	-
6	35.1 (*t*)	2.25 (*dd*, *J* = 9.6,13.0)	125.3 (*t*)	6.20 (*s*)
		2.01 (*d*, *J* = 13.0)		-
7	40.9 (*d*)	1.79 (*m*)	142.2 (*s*)	-
8	33.8 (*d*)	1.88 (*m*)	34.2 (*d*)	2.79 (*m*)
9	38.9 (*t*)	2.55 (*dd*, *J* = 13.6,7.4)	42.9 (*t*)	3.10 (*dd*, *J* = 9,15.1)
		2.45 (*dd*, *J* = 13.6,1.5)		2.38 (*dd*, *J* = 10.0,15.1)
10	132.7 (*s*)	-	135.3 (*s*)	-
11	106.2 (*d*)	6.49 (*s*)	111.5 (*d*)	6.57 (*s*)
12	147.7 (*s*)	-	151.6 (*s*)	-
13	135.1 (*s*)	-	139.3 (*s*)	-
14	141.3 (*s*)	-	142.5 (*s*)	-
15	122.5 (*s*)	-	124.1 (*s*)	-
16	121.3 (*s*)	-	122.1 (*s*)	-
17	21.8 (*q*)	0.97 (*d*, *J* = 7.1)	18.9 (*q*)	1.63 (*s*)
18	12.4 (*q*)	0.73 (*d*, *J* = 7.1)	19.4 (*q*)	1.03 (*d*, *J* = 6.9)
*Me*O-C (1)	60.1 (*q*)	3.50 (*s*)	60.7 (*q*)	3.61 (*s*)
*Me*O-C (2)	61.0 (*q*)	3.93 (*s*)	60.8 (*q*)	3.84 (*s*)
*Me*O-C (3)	-	-	55.9 (*q*)	3.83 (*s*)
*Me*O-C (12)	-	-	55.9 (*q*)	3.88 (*s*)
*Me*O-C (13)	-	-	60.7 (*q*)	3.80 (*s*)
*Me*O-C (14)	59.7 (*q*)	3.79 (*s*)	-	-
HO-C (3)		5.68 (*br s*)		-
OCH_2O	100.8 (*t*)	5.96, 5.95 (*d*, *J* = 1.3)	-	-
Ang:1'	-	-	165.2 (*s*)	-
2'	-	-	127.8 (*s*)	-
3'	-	-	136.8 (*d*)	5.86 (*m*)
4'	-	-	15.3 (*q*)	1.78 (*s*)
5'	-	-	20.3 (*q*)	1.72 (*d*, *J* = 7.1)

HMBC correlations of CH-11 (δ_H 6.49) and methylenedioxy (δ_H 5.96, 5.95) protons with aromatic carbons at δ_C 147.7, 135.1 indicated that the methylenedioxy group was located at C-12 and C-13. Correlations of the CH-4 proton (δ_H 6.63) with carbons at δ_C 148.8 (C-3) and 137.4 (C-2) and of the hydroxyl proton at δ_H 5.68 with carbons at δ_C 110.2 (C-4), 148.8 (C-3) and 137.4 (C-2), indicated that the hydroxyl was located at C-3. Thus, the three methoxy groups were located at C-1, C-2, and C-14, based on HMBC correlations of the protons at δ_H 3.79, 3.93 and 3.50 with aromatic carbons at δ_C 141.3 (C-14), 137.4 (C-2) and 150.3 (C-1), respectively.

The circular dichroism (CD) spectrum of **1** showed a negative Cotton effect at 216 nm and a positive *Cotton* effect at 254 nm, which indicated an *R*-biphenyl configuration in **1** [28]. NOESY correlations between CH-11/Me-18, CH-4/CH-6α and CH-11/CH-9β indicated a twist-boat-chair (TBC) conformation for the cyclooctadiene ring [29] (Figure 2). The substituent positions and stereochemical assignments in the cyclooctadiene ring of **1** were further supported by NOESY correlations of MeO-1/MeO-14, Me-17/Me-18, CH-6β/Me-18 and CH-4/CH-7. Thus, the structure of **1** was determined as that shown in Figure 1. Compound **1** and (−)-gomisin L_2 have the same planar structure, but different stereochemistry [30].

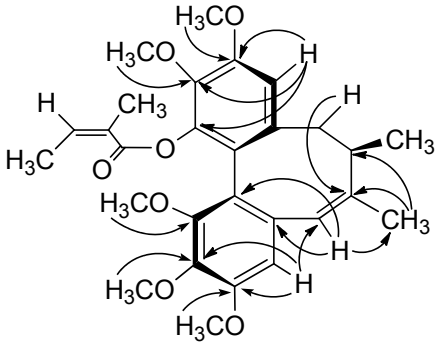
Figure 2. Key HMBC (→) and NOESY (↔) Correlations of **1**.



Compound **2**, obtained as colorless powder, has the molecular formula $C_{28}H_{34}O_7$ according to HR-ESI-MS (*m/z* 505.2187 $[M+Na]^+$). Its IR, UV, CD and NMR data indicated that **2** is a also a dibenzocyclooctadiene lignan. The ^{1}H-NMR spectrum of **2** (Table 1) showed the presence of five methoxy groups at δ_H 3.61, 3.80, 3.83, 3.84 and 3.88 (each 3H, s), and an angeloyl group at δ_H 5.86 (1H, m), 1.78 (3H, s), 1.72 (3H, *d*, *J* = 7.1 Hz) on aromatic rings [24].

The following proton-carbon HMBC correlations were observed: CH-4 (δ_H 6.38) with C-3 (δ_C 152.6) and C-2 (δ_C 139.9), CH-11 (δ_H 6.57) with C-12 (δ_C 151.6), C-13 (δ_C 139.3) and C-14 (δ_C 142.5), and the five methoxy signals at δ_H 3.61, 3.84, 3.83, 3.88 and 3.80 with aromatic carbon signals at δ_C 152.3 (C-1), 139.9 (C-2), 152.6 (C-3), 151.6 (C-12) and 139.3 (C-13), respectively. These correlations indicated that the five methoxy groups were attached to C-1, C-2, C-3, C-12, and C-13, and the angeloyl group was located at C-14 (Figure 3).

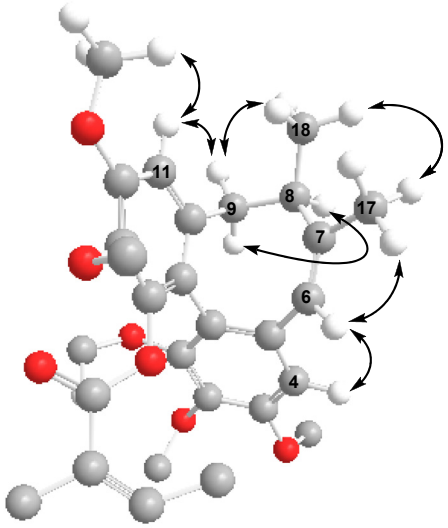
Figure 3. Key HMBC correlations of **2**.



Furthermore, the ^{1}H-NMR spectrum of **2** showed a proton signal at δ_H 6.20 (1H, *s*) and the ^{13}C-NMR spectrum showed a quaternary olefinic carbon at δ_C 142.2 and a methine olefinic carbon at δ_C 125.3, suggesting the formation of a double bond. A singlet methyl signal at δ_H 1.63 (3H, *s*, Me-17) in the ^{1}H-NMR spectrum indicated that the double bond was located between C-6 and C-7 and was substituted with a methyl group. HMBC correlations of δ_H 6.38 (CH-4) with δ_C 125.3 (C-6), δ_H 6.20 (CH-6) with δ_C 136.5 (C-5), 122.1 (C-16) and 18.9 (C-17), δ_H1.63 (Me-17) with δ_C 142.2 (C-7) and 34.2 (C-8), δ_H 2.38 and 3.10 (CH_2-9) with δ_C 142.2 (C-7) confirmed the substructure.

The CD spectrum of **2** had a negative *Cotton* effect at 219 nm and a positive *Cotton* effect at 251 nm, indicating that **2** has an *R*-biphenyl configuration. The NOESY correlations between CH-4/CH-6, CH-6/Me-17, and CH-11/CH-9β, CH-9α/CH-8, CH-11/MeO-12, CH-9β/Me-18, and Me-17/Me-18 fully supported the assigned structure and stereochemistry (Figure 4). Compound **2** has an endocylic double bond rather than the exocyclic double bond found in the previously reported neglschisandrin B [14].

Figure 4. Key NOESY correlations of **2**.



The lignans were evaluated *in vitro* for cytotoxicity against human lung carcinoma A549 and human colorectal carcinoma HCT-8 cell lines employing a MTT-assay with paclitaxel as the positive control (Table 2). Five lignans exhibited moderate cytotoxicity, while the remaining lignans showed no activity. Against HCT-8, compounds **3** and **6** showed moderate cytotoxicity (EC_{50} 9.58 and 7.33 μg/mL, respectively); compounds **2** and **4** exhibited marginal cytotoxicity (EC_{50} 13.8 and 12.6 μg/mL,

respectively), and compound **5** showed weak cytotoxicity (EC_{50} 19.6 μg/mL). Against A549, compounds **2**–**4** exhibited marginal cytotoxicity with EC_{50} values ranging from 11.8 to 15.0 μg/mL.

Table 2. Cytotoxicity data of lignans from *Schisandra neglecta.*

Compound	Cytotoxicity (EC_{50}, μg/mL)	
	HCT-8	A549
2	13.8	11.8
3	9.58	13.8
4	12.6	15.09
5	19.8	NA [a]
6	7.33	NA [a]
Paclitaxel	0.21	<0.005

[a] NA (not active)--test compound (20 μg/mL) did not reach 50% inhibition.

3. Experimental

3.1. General

Optical rotations: *P-1020* digital spectropolarimeter (JASCO) with MeOH as solvent. UV spectra: *Hitachi U-3010* spectrophotometer in MeOH; λ_{max} (log ε) in nm. ^{1}H-, ^{13}C-, 2D-NMR spectra: *Bruker DRX400* (400 MHz for ^{1}H, 100 MHz for ^{13}C) spectrometer in *$CDCl_3$*; δ in ppm rel. to Me_4Si as internal references. *J* in Hz. ESI mass: *Bio TOF Q* spectrometer; in *m/z* (rel. %). HR-ESI-MS: *Bruker Daltonics BioToF-IIIQ* mass spectrometer in positive-ion mode (Bremen, Germany). IR spectra: *Avatar Thermo Nicolet 360-ESP* spectrophotometer. TLC was performed on silica gel plates GF_{254} (Yantai Institute of Chemical Technology, Yantai, China). The TLC spots were visualized by UV light (254 nm) and sprayed with 10% H_2SO_4, followed by heating. Column chromatography (CC) was carried out on silica gel (200–300 mesh or 300–400 mesh Qingdao Marine Chemical Factory, Qingdao, China). Semi-prep HPLC was carried out on an octadecylsilane column (*RP-18*, 250 × 10 mm, 10 μm, YMC, detector: *Amersham UV-900*) with a flow rate of 3.0 mL/min.

3.2. Plant Material

Stems of *Schisandra neglecta* were collected in Lin-zhi County, Tibet Autonomous Region, People's Republic of China in September of 2004, and identified by Professor Hong-ping Deng, School of Life Sciences, Southwest University. A voucher specimen (MC-LZ-040901) is deposited in the Herbarium of Medicinal Plant, School of Life Sciences, Southwest University, Chongqing, China.

3.3. Extraction and Isolation

Powdered air-dried stems (5.0 kg) of *Schisandra neglecta* were extracted exhaustively with 95% EtOH (5 × 10 L, each three days) at room temperature. The alcoholic extract was evaporated *in vacuo* to yield a semisolid (430 g), which was suspended in water (1,000 mL) and extracted five times with diethyl ether. The organic solution was concentrated to yield 112 g of residue, which was subjected to silica gel CC eluted with petroleum ether/acetone mixtures of increasing polarity (99:1 to 3:7) to obtain ten fractions. Fraction 3 (8.3 g), eluted with petroleum ether–acetone (95:5), gave **7** (1.2 g), and

then was further chromatographed with silica gel CC eluting with petroleum ether/$CHCl_3$ (9:2) to obtain six subfractions. Subfraction 3–3 (1.3 g) was subjected to preparative TLC with petroleum ether/$CHCl_3$ (1:1) to yield **4** (14 mg). Fraction 4 (7.4 g), eluted with petroleum ether/acetone (9:1), was subjected to CC with petroleum ether/EtOAc (15:1~4:1) to obtain eight subfractions. Subfraction 4–3 (0.5 g) was purified by preparative HPLC with MeOH/H_2O (70:30) to yield **5** (4 mg, RT 25.3 min) and **6** (10 mg, RT 31.1 min). Subfraction 4–4 (0.7 g) was subjected to preparative TLC with petroleum ether/$CHCl_3$ (1:1) to yield **3** (17 mg). Subfraction 4–5 (0.3 g) was purified by semi-preparative HPLC with MeOH-H_2O (70:30) to yield **1** (2 mg, RT 33.4 min). Subfraction 4–6 (3.2 g) was subjected to silica gel CC with petroleum ether-EtOAc (5:1) to yield **8** (2.3 g). Fraction 5 (6.7 g) eluted with petroleum ether-acetone (8:2) was subjected to silica gel CC with petroleum ether/EtOAc (10:2–5:2). Subfraction 5–2 (0.6 g) was purified by semi-preparative HPLC with MeOH/H_2O (75:25) to yield **9** (32 mg, RT 37.5) and **15** (46 mg, RT 40.2). Subfraction 5–3 (1.7 g) was subjected to silica gel CC with petroleum ether/EtOAc (9:2), then purified by semi-preparative HPLC with MeOH/H_2O (64:36–80:20) to yield **10** (4 mg, RT 25.6 min), **11** (10 mg, RT, 28.7 min), and **12** (43 mg, RT 37.9 min), Subfraction 5–5 (0.9 g) was subjected to silica gel CC with petroleum ether/$CHCl_3$ (5:6), and further purified by semi-preparative HPLC with MeOH/H_2O (7:3) to yield **13** (24 mg, RT 40.3 min) and **14** (19 mg, RT 44.5 min). Fraction 6 (5.2 g) eluted with petroleum ether-acetone (7:3) was subjected to silica gel CC with petroleum ether/EtOAc (10:3). Subfraction 6–3 (0.7 g) was purified by semi-preparative HPLC with MeOH-H_2O (75:25 to 85:15) to yield **2** (10 mg, RT 24. 7 min).

6R,7S,R-biar-[5,6,7,8-Tetrahydro-1,2,13-trimethoxy-6,7-dimethyl-benzo-[3',4']cycloocta[1',2':4,5]-benzo[1,2-d][1,3]dioxol-3-ol (neglschisandrin E, **1**). White amorphous powder; $[\alpha]^{22}_D$ +26.9° (c = 0.26, MeOH). UV (MeOH): 216 (4.67), 250 (4.22), 280 (3.97). CD (c = 0.08, MeOH), $[\theta]^{15}$ (nm): −28275 (216), +28636 (254). IR (KBr): 3447, 2925, 1615, 1585, 1476, 737. ^{1}H-NMR and ^{13}C-NMR: see Table 1. HR-ESI-MS: found 387.1810 ($[M+H]^+$, $C_{22}H_{27}O_6^+$, calc. 387.1808).

5Z,7R,R-biar-7,8-Dihydro-1,2,3,10,11-pentamethoxy-13-(2Z)-methylbut-2-enoyl-6,7-dimethyl-dibenzo [a,c]cycloocten-5(6H)-one (neglschisandrin F, **2**). White amorphous powder; $[\alpha]^{22}_D$ +16.9° (c = 0.31, MeOH). UV (MeOH): 216 (4.78), 250 (4.37), 279 (3.97). CD (c = 0.052, MeOH), $[\theta]^{15}$ (nm): −295132 (219), +155445 (251). IR (KBr): 3404, 2936, 1737, 1636, 1591, 1488, 734. ^{1}H-NMR and ^{13}C-NMR: see Table 1. HR-ESI-MS: found 505.2187 ($[M+Na]^+$, $C_{28}H_{34}NaO_7^+$, calc. 505.2197).

3.4. Cytotoxicity Assay

Freshly trypsinized cell suspensions were seeded in 96-well microtiter plates at densities of 5,000–10,000 cells per well with compounds added from DMSO-diluted stock. After three days in culture, attached cells were incubated with cold 10% trichloroacetic acid (MTT, 0.5 mg/mL, 2 h) and subsequently solubilized in DMSO, and the isolates were tested against A549 and HCT-8 cancer cell lines using established colorimetric MTT assay protocols [31]. Paclitaxel was used as a positive control. All stock cultures were grown in T-25 flasks. The mean EC_{50} is the concentration of agent that reduces cell growth by 50% under the experimental conditions and is the average from at least three independent determinations that were reproducible and statistically significant. The absorbance was measured at 550 nm using a microplate reader.

4. Conclusions

Two new lignans, neglschisandrins E and F (**1** and **2**, respectively), and thirteen known lignans were isolated from stems of *Schisandra neglecta*. Their structures and stereochemistries were established by means of NMR and ESI-MS analyses, including 2D-NMR techniques. The isolates were evaluated for *in vitro* cytotoxic activity. Compounds **2**–**6** showed cytotoxicity against the human HCT-8 colorectal carcinoma cell line with EC_{50} values of 7.33~19.8 μg/mL, while compounds **2**–**4** also exhibited cytotoxicity against the human A549 lung carcinoma cell line with EC_{50} values of 11.8~15.0 μg/mL, respectively. Since other dibenzocyclooctadiene lignans in the genus *Schisandra* exhibit proven antitumor activities [32], further research to identify related potent cytotoxic compounds or explore detailed structure-activity relationships is merited.

Acknowledgments

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References

1. Chinese Pharmacopoeia Commission. *Pharmacopoeia of the People's Republic of China*; People's Medical Publishing House: Beijing, China, 2010; Volume 1, pp. 61, 227.
2. Peng, H.L.; Chen, D.F.; Lan, H.X.; Zhang, X.M.; Gu, Z.; Jiang, M.H. Anti-lipid Peroxidation of Gomisin J on Liver Mitochondria and Cultured Myocardial Cells. *Acta Pharmacol. Sin.* **1996**, *17*, 538–541.
3. Chen, D.F.; Zhang, S.X.; Xie, L.; Xie, J.X.; Chen, K.; Kashiwada, Y.; Zhou, B.N.; Wang, P.; Cosentino, L.M.; Lee, K.H. Anti-AIDS Agents—XXVI. Structure-Activity Correlations of Gomisin-G-related Anti-HIV Lignans from *Kadsura interior* and of Related Synthetic Analogues. *Bioorg. Med. Chem.* **1997**, *5*, 1715–1723.
4. Kuo, Y.H.; Huang, R.L.; Kuo, Y.L.K.; Chen, C. F Novel C19 Homolignans, Taiwanschirin A, B, and Cytotoxic Taiwanschirin C, and a New C18 Lignan, Schizanrin A, from *Schizandra arisanensis*. *J. Org. Chem.* **1999**, *64*, 7023–7027.
5. Zhang, X.M.; Chen, D.F.; He, X.J.; Yang, S.; Zheng, P.; Jiang, M.H. Blocking Effects of Heteroclitin D and Gomisin J on L-type Calcium Channels in Ventricular Cells of Guinea Pig. *Acta Pharmacol. Sin.* **2000**, *21*, 373–376.
6. Kuo, Y.H.; Li, S.Y.; Huang, R.L.; Wu, M.D.; Huang, H.C.; Lee, K.H. Schizarin B, C, D, and E, Four New Lignans from *Kadsura matsudai* and Their Antihepatitis Activities. *J. Nat. Prod.* **2001**, *64*, 487–490.
7. Lu, Y.; Chen, D.F. Analysis of *Schisandra chinensis* and *Schisandra sphenantera*. *J. Chromatogr. A* **2009**, *1216*, 1980–1990.

8. Yang, G.Y.; Li, Y.K.; Wang, R.R.; Xiao, W.L.; Yang, L.M.; Pu, J.X.; Zheng, Y.T.; Sun, H.D. Dibenzocyclooctadiene Lignans from the Fruits of *Schisandra wilsoniana* and Their Anti-HIV-1 Activities. *J. Asian Nat. Prod.* **2010**, *12*, 470–476.
9. Liu, C.C.; Abd El-Razek, M.H.; Liaw, C.C.; Cheng, Y.B.; Chen, C.K.; Chien, C.T.; Kuo, Y.H.; Liou, S.S.; Shen, Y.C. Arisanschinins A-E, Lignans from *Schisandra arisanensis* hay. *Planta Med.* **2010**, *74*, 1605–1610.
10. Yang, J.M.; Ip, P.S.; Che, C.T.; Yeung, J.H. Relaxant Effects of *Schisandra chinensis* and Its Major Lignans on Agonists-induced Contraction in Guinea Pig Ileum. *Phytomedicine* **2011**, *18*, 1153–1160.
11. Mu, H.X.; Li, X.S.; Fan, P.; Yang, G.Y.; Pu, J.X.; Sun, H.D.; Hu, Q.F.; Xiao, W.L. Dibenzocyclooctadiene Lignans from the Fruits of *Schisandra rubriflora* and Their Anti-HIV-1 Activities. *J. Asian Nat. Prod.* **2011**, *13*, 393–399.
12. Xue, J.J.; Cao, J.L.; Yang, G.Y.; Pu, J.X.; Sun, H.D.; Hu, Q.F.; Xiao, W.L. Lignans from *Schisandra lancifolia*. *J. Asian Nat. Prod.* **2011**, *13*, 492–497.
13. Kang, K.; Lee, K.M.; Yoo, J.H.; Lee, H.J.; Kim, C.Y.; Nho, C.W. Dibenzocyclooctadiene Lignans, Gomisins J and N Inhibit the Wnt/β-catenin Signaling Pathway in HCT116 Cells. *Biochem. Biophys. Res. Commun.* **2012**, *428*, 285–291.
14. Chen, M.; Xu, X.M.; Liao, Z.H.; Dong, L.; Li, L.; Huang, C.Z. Neglschisandrins A-B: Two New Dibenzocyclooctene Lignans from *Schisandra neglecta*. *Molecules* **2008**, *13*, 548–555.
15. Chen, M.; Liao, Z.H.; Xu, X.M.; Wen, Y.; Sun, M.; Zhang, H.X.; Ma, W.H. Neglschisandrins C-D: Two New Dibenzocyclooctene Lignans from *Schisandra neglecta*. *Molecules* **2008**, *13*, 1148–1155.
16. Chen, C.C.; Shen, C.C.; Shih, Y.Z.; Pan, T.M. 6-*O*-Benzoylgomisin, a New Lignan from the Fruits of *Schizandra chinensis*. *J. Nat. Prod.* **1994**, *57*, 1164–1165.
17. Wang, H.J.; Chen, Y.Y. Studies of Lignans from *Schisandra rubriflora* Rhed et Wils. *Acta Pharm. Sin.* **1985**, *20*, 832–841.
18. Ikeya, Y.; Ookawa, N.; Taguchi, H.; Yosioka, I. The Constituents of *Schizandra chinensis* Baill. II. The Structures of 3 New Lignans, Angeloylgomisin-O, and Angeloylisogomisin-O and Benzoylisogomisin-O. *Chem. Pharm. Bull.* **1982**, *30*, 3202–3206.
19. Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. Constituents of *Schizandra chinensis* Baill. 5. Structures of 4 New Lignans, Gomisin-N, Gomisin-O, Epigomisin-O and Gomisin-E, and Transformation of Gomisin-N to Deangeloylgomisin-B. *Chem. Pharm. Bull.* **1979**, *27*, 2695–2709.
20. Chen, Y.Y.; Yang, Y.Q. Studies on the SGPT-lowering Active Component of the Fruits of *Schisandra rubriflora* Rhed et Wils. *Acta Pharm. Sin.* **1982**, *17*, 312–313.
21. Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. Constituents of *Schizandra-chinensis* Baill. 3. Structures of 4 New Lignans, Gomisin-H and Its Derivatives, Angeloyl-gomisin-H, Tigloyl-gomisin-H and Benzoyl-gomisin-H. *Chem. Pharm. Bull.* **1979**, *27*, 1576–1582.
22. Ikeya, Y.; Taguchi, H.; Yosioka, I. Constituents of *Schizandra-chinensis* Baill. 1. Isolation and Structure Determination of 5 New Lignans, Gomisin-A, Gomisin-B, Gomisin-C, Gomisin-F and Gomisin-G and the Absolute Structure of Schizandrin. *Chem. Pharm. Bull.* **1979**, *27*, 1383–1394.
23. Han, G.Q.; Dai, P.; Xue, R.; Arison, B.H.; Lanki, D.C.; Hwang, S.B. Dibenzocyclooctadiene Lignans with Platelet-activating Factor (PAF) Antagonist Activity from *Kadsura heteroclita*. *J. Chin. Pharm. Sci.* **1992**, *1*, 20–27.

24. Lei, C.; Huang, S.X.; Chen, J.J.; Pu, J.X.; Yang, L.B.; Zhao, Y.; Liu, J.P.; Gao, X.M.; Xiao, W.L.; Sun, H. Lignans from *Schisandra propinqua* var. propinqua. *Chem. Pharm. Bull.* **2007**, *55*, 1281–1283.
25. Chen, M.; Kilgore, N.; Lee, K.H.; Chen, D.F. Rubrisandrins A and B, Lignans and Related Anti-HIV Compounds from *Schisandra rubriflora*. *J. Nat. Prod.* **2006**, *69*, 1697–1901.
26. Ghera, E.; Ben-David, Y.; Becker, D. Deoxyschizandrin, Stereochemistry and Total Synthesis. *Tetrahedron Lett.* **1977**, *18*, 463–467.
27. Chen, M.; Liao, Z.X.; Chen, D.F. Four New Dibenzocyclooctene Lignans from *Kadsura renchangiana*. *Helv. Chim. Acta* **2004**, *87*, 1368–1376.
28. Li, H.R.; Feng, Y.L.; Yang, Z.G.; Wang, J.; Daikonya, A.; Kitanaka, S.; Xu, L.Z.; Yang, S.L. New Lignans from *Kadsura coccinea* and Their Nitric Oxide Inhibitory Activities. *Chem. Pharm. Bull.* **2006**, *54*, 1022–1025.
29. Liu, J.S.; Li, L. Schisantherins L-O and Acetylschisantherin L from *Kadsura coccinea. Phytochemistry* **1993**, *32*, 1293–1296.
30. Ikeya, Y.; Taguchi, H.; Yosioka, I. The Constituents of *Schizandra chinensis* Baill. 10. The Structures of γ-Schizandrin and 4 New Lignans, (−)-Gomisins L_1 and L_2, (±)-Gomisin M_1 and (+)-Gomisin M_2. *Chem. Pharm. Bull.* **1982**, *30*, 132–139.
31. Wu, J.H.; Zhao, M.; Qian, K.D.; Lee, K.H.; Morris-Natschke, S.; Peng, S.Q. Novel *N*-(3-Carboxyl-9-benzyl-beta-carboline-1-yl)ethylamino Acids: Synthesis, Anti-tumor Evaluation, Intercalating Determination, 3D QSAR Analysis and Docking Investigation. *Eur. J. Med. Chem.* **2009**, *44*, 4153–4161.
32. Xu, L.J.; Liu, H.T.; Peng, Y.; Xiao, P.G. A Preliminary Pharmacophylogenetic Investigation in Schisandraceae. *J. Syst. Evol.* **2008**, *46*, 692–723.

Sample Availability: Samples of the compounds **1** and **2** are available from the authors.