Schisphenlignans A–E: Five New Dibenzocyclooctadiene Lignans from *Schisandra sphenanthera*

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Five new dibenzocyclooctadiene lignans, schisphenlignans A–E (1–5), together with eight known ones, were isolated from the stems of *Schisandra sphenanthera*. The structures of 1–5 were elucidated based on the analysis of their NMR, MS and circular dichroism (CD) spectra. Some isolates were tested for their acute activities on insulin sensitivity in 3T3-L1 differentiated adipocytes, but none of them showed significant bioactivity with 10 μM administration of the tested compounds.

Key words *Schisandra sphenanthera*; Schisandraceae; schisphenlignan; insulin sensitivity

The genera *Schisandra* belonging to the plant family Schisandraceae have been commonly used in traditional Chinese medicine for the treatment of hepatitis, diabetes, diarrhea, cough and so on.[1,2] It has been reported that many kinds of lignans were isolated from this genus, such as dibenzocyclooctadiene, dibenzylbutane and tetrahedrofurane types, and some of them exhibited antimicrobic, antiviral, herbicidal, antifeedant and improving insulin sensitivity activities.[3–7]

Schisandra sphenanthera Rehd. *et* Wils is a kind of liana of *Schisandra* genus which can be found in the southern and middle parts of China.[8] Our group has conducted the phytochemical study of this plant collected in the Er lang mountain area of Sichuan province of China, which led to the finding of a series of nortriterpenoids.[9,10] In order to search for new natural compounds with interesting biological activity, we continued to investigate the chemical components on the stems of this plant collected from the Qinling region of Shanxi of China. As a result, five new lignans, along with eight known ones, were isolated and characterized. This article reports the isolation, structural elucidation and insulin sensitivity bioactivities of the isolates.

Results and Discussion

A 70% aqueous acetone extract of the stems of *S. sphenanthera* was partitioned between EtOAc and H_2O. The EtOAc part were dried and subjected to silica gel, MCI CHP-20 gel, Lichroprep RP-18 gel column chromatography and semipreparative HPLC to afford five new compounds, schisphenlignans A–E (**1**–**5**), together with eight known lignans, including gomisin O (**6**),[11] epigomisin O (**7**),[11] schisantherin A (**8**),[12] gomisin B (**9**),[13,14] shisantherin D (**10**),[15] (−)-gomisin G (**11**),[14] marlignan E (**12**),[16] and angeloylgomisin Q (**13**).[17,18] The structures of the known compounds were determined by comparing spectroscopic data with literature values.

Schisphenlignan A (**1**), isolated as amorphous powder, has the molecular formula $C_{29}H_{30}O_9$ as revealed by its high resolution-electrospray ionization (HR-ESI)-MS (*m*/*z* 545.1792, $[M+Na]^+$), requiring 15 degrees of unsaturation. The ^{1}H-NMR spectrum (Table 1) of **1** showed signals of two aromatic protons of a biphenyl moiety at δ_H 6.79 (H-4) and 6.48 (H-11), three signals for methoxy groups at δ_H 3.94, 3.85, and 3.23, and two characteristic signals of a methylenedioxy group as substituent on the biphenyl rings at δ_H 6.02 and 5.98. Heteronuclear multiple bond connectivity (HMBC) correlations of H-4 with C-2, C-3, C-5, C-6, C-15, and C-16, of H-11 with C-9, C-10, C-12, C-13, C-15, and C-16, and ^{1}H–^{1}H correlation spectroscopy (COSY) correlations of H-8/H-9/H_3-18 (Fig. 2), together with UV absorption band at 240 nm, and its IR absorption bands at 3476 (OH), 1720 (C=O), 1614, 1480 and 1463 (aromatic moiety) cm^{-1} indicated that **1** was a dibenzocyclooctadiene lignan with hydroxyl and ester groups.[19] Moreover, HMBC correlations of the methylenedioxy protons (δ_H 6.02, 5.98) and H-4 (δ_H 6.79, s) with C-2 and C-3, of the proton signals of three methoxy group with C-1, C-12, and C-13, and of the OH-14 (δ_H 5.33, s) with C-13, C-14, and C-15, showed that the methylenedioxy group connected to C-2 and C-3, the three methoxy groups located at C-1, C-12, and C-13, and the OH-14 located at C-14, respectively (Fig. 2). The ^{1}H- and ^{13}C-NMR spectral data of **1** (Table 1) suggested the presence of a benzoyl moiety, and HMBC correlations of H-6 (δ_H 5.70, s) with the carbonyl (C-1′, δ_C 164.6) of the benzoyl moiety revealed that the benzoyl group located at C-6.

The circular dichroism (CD) spectrum of **1** had a negative Cotton effect around 241 nm and a positive Cotton effect around 211 nm, suggesting that **1** possessed an *S*-biphenyl configuration.[20] The rotating frame Overhauser enhancement spectroscopy (ROESY) correlations (Fig. 3) of H-4 with H-6 and H_3-17, and of H-6/H_3-17 in the molecule of **1** suggested a twisted boat/chair conformation for the cyclooctadiene ring.[21] The substituent positions and stereochemical assignments in the cyclooctadiene ring of **1** were also deduced by the ROESY correlations. The ROESY correlations of H-6 with H-4 and H_3-17, of H-9β with H-11 and H_3-18, and of H-8 with H_3-17 indicated that H-6 and H_3-17 were α-oriented, and that H_3-18 was β-oriented. Thus, the structure of **1** was determined as shown in the Fig. 1 and given the name as schisphenlignan A.

The molecular formulas of compounds **2** and **3** were determined by HR-ESI-MS to be $C_{29}H_{30}O_9$ (*m*/*z* 545.1796 $[M+Na]^+$)

The authors declare no conflict of interest.

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Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **1**–**3**[a)]

Position	**1**		**2**		**3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		141.4		141.5		141.6
2		137.0		137.2		137.6
3		148.3		148.0		148.2
4	6.79 s	106.2	6.78[b)]	106.3	6.81 s	106.9
5		129.3		128.8		129.1
6	5.70 s	85.0	5.86 s	84.4	6.02 d (1.6)	83.7
7		72.4		72.4		72.6
8	2.13 m	42.4	2.13 m	42.3	2.09 m	42.3
9α	2.47 dd (14.0, 10.1)	36.5	2.42 dd (14.0, 10.1)	36.3	2.45 dd (14.2, 10.0)	36.1
9β	2.26 d (14.0)		2.26 d (14.0)		2.26 d (14.2)	
10		137.0		137.3		133.5
11	6.48 s	103.8	6.78[b)]	109.9	6.80 s	111.1
12		151.9		149.1		134.3
13		133.3		137.3		144.3
14		146.4		149.3		143.9
15		115.7		121.2		120.3
16		120.4		121.7		121.8
17	1.36 s	28.4	1.33 s	28.2	1.31 s	28.1
18	1.21 d (7.2)	18.9	1.18 d (7.0)	18.8	1.16 d (7.1)	18.7
1′		164.6		164.8		165.0
2′		129.3		129.2		133.2
3′, 7′	7.26[b)]	128.0	7.41[b)]	128.1	7.31[b)]	128.1
4′, 6′	7.43[b)]	129.3	7.29[b)]	129.6	7.31[b)]	129.2
5′	7.43[b)]	132.7	7.47 m	133.1	7.48 m	133.2
CH_3O-1	3.85 s	59.7	3.78 s	59.7	3.73 s	59.8
CH_3O-12	3.94 s	55.8				
CH_3O-13	3.23 s	60.0	3.40 s	59.9		
CH_3O-14			3.13 s	59.3	2.84 s	59.2
OCH_2O-2, 3	6.02 d (1.5)	101.4	6.02 d (1.5)	101.4	6.01[b)]	101.5
	5.98 d (1.5)		6.00 d (1.5)			
OH-7	1.51 s					
OH-12			5.70 s			
OH-14	5.33 s					

a) Data were recorded in $CDCl_3$ at 125 MHz (^{13}C-NMR) and 500 MHz (^{1}H-NMR); chemical shifts (δ) are expressed in ppm; *J* in Hz. *b*) Overlapping signals.

and $C_{28}H_{28}O_9$ (*m/z* 531.1639 $[M+Na]^+$), respectively. The UV, IR, CD, and NMR spectral signals of both **2** and **3** were similar to those of **1**. The difference between **2** and **1** in the structure was that the hydroxyl group located at C-14 in **1** was changed to locate at C-12 in **2**, which was confirmed by HMBC correlations of the proton signal of the hydroxyl group at δ_H 5.70 to C-11, C-12 and C-13. Analyses of the 2D-NMR data of compounds **2** and **3** revealed that the main difference between the two compounds was a methoxy group located at C-13 in **2** other than a hydroxyl group in **3**. The HMBC correlations of the protons of two methoxy groups (δ_H 3.73, 2.84) to C-1 and C-14, and of H-11 (δ_H 6.80) with C-12 (δ_C 134.3) and C-13 (δ_C 144.3) supported the above deduction. In addition, the similarity of CD spectra of both **2** and **3** with that of **1** suggest that both **2** and **3** possessed the *S*-biphenyl configuration.[20)] Thus, the structure of **2** and **3** were determined as shown in Fig. 1 and given the name as schisphenlignans B (**2**) and C (**3**), respectively.

Schisphenlignan D (**4**) was determined to have the molecular formula $C_{30}H_{30}O_9$ by HR-ESI-MS (*m/z* 557.1779 $[M+Na]^+$). The ^{1}H- and ^{13}C-NMR spectra of **4** exhibited 18 carbon atoms for the dibenzocyclooctadiene skeleton (including twelve aromatic ones, two methines, two methylenes, one quaternary carbon and one secondary methyl), in addition to one benzoyl group (δ_C 164.6, 129.4, 129.6, 127.8, 132.8, 127.8, 129.6), a methylenedioxy group, and four methoxy groups (Table 2). The HMBC correlations of H-6 (δ_H 5.40, s) with the ester carbonyl (C-1′, δ_C 164.6) suggested that the benzoyl group was located at C-6 in the structure of **4**. The HMBC correlations of the methylenedioxy protons and H-11 with C-12 and C-13, and of the proton signals for the four methoxy groups with C-1, C-2, C-3 and C-14, indicated that the methylenedioxy group was connected to C-12 and C-13 and the four methoxy groups were located at C-1, C-2, C-3, and C-14, respectively. Comparison of the spectroscopic data of **4** with those of **8** revealed that they were quite similar except that the molecular weight of **4** was two mass units lower than that of **8**. The characteristic chemical shift of C-7 (δ_C 62.3) and C-17 (δ_C 47.1) hint that there was an epoxy ring between C-7 and C-17 in **4**, which was further comfirmed by HMBC correlations of H-6 (δ_H 5.40) to C-7, C-8, and C-17, and of H-17β (δ_H 2.85, d, J=3.6 Hz) to C-6, C-7, and C-8.

The CD spectrum of **4** had a negative Cotton effect around 242 nm and a positive Cotton effect around 226 nm, suggesting that **4** possessed an *S*-biphenyl configuration.[20)] The observed ROESY correlations of H-6 (δ_H 5.40) with H-4 (δ_H 6.62)

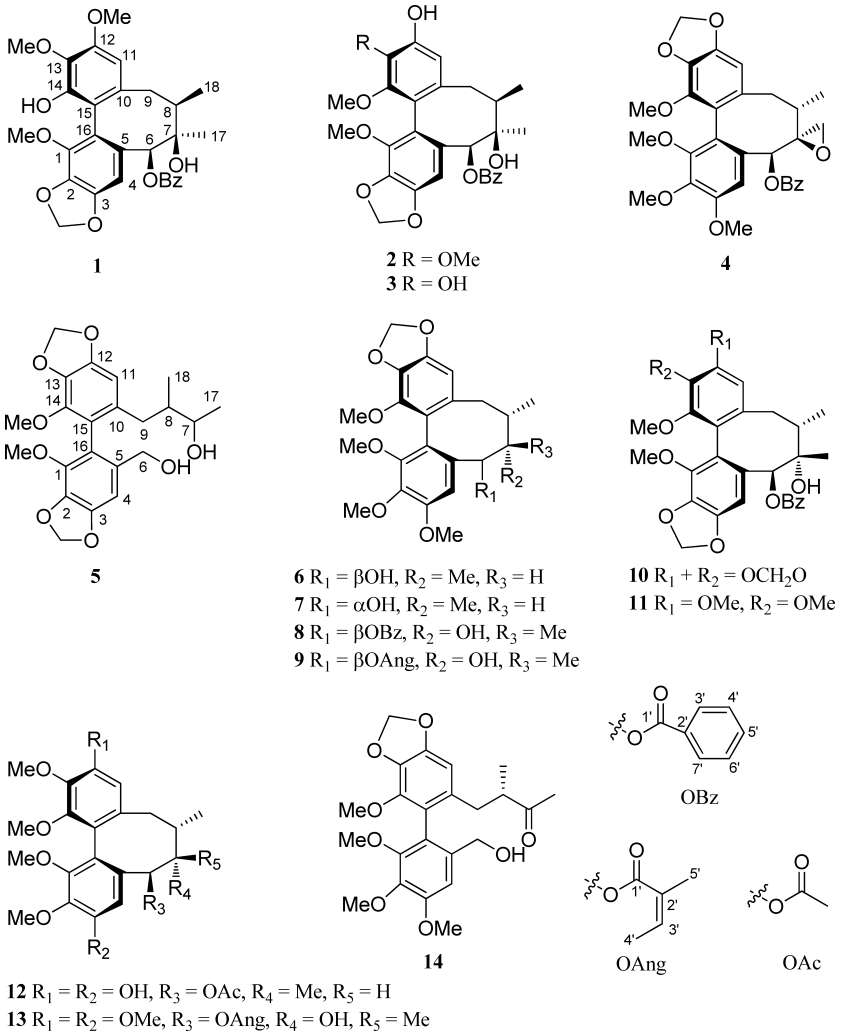

Fig. 1. Structures of Compounds **1**–**14**

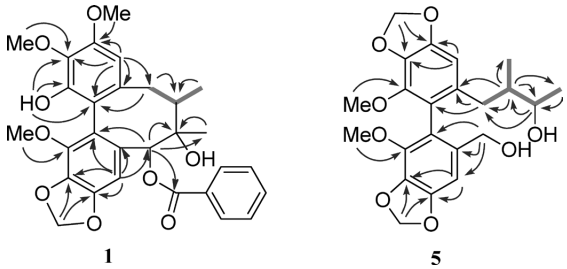

Fig. 2. Selected HMBC (↷) and ^{1}H–^{1}HCOSY (—) Correlations of **1** and **5**

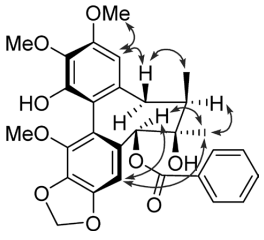

Fig. 3. Selected ROESY Correlations of **1**

and H-17α (δ_H 2.96, d, J=3.6 Hz), and of H-17β (δ_H 2.85, d, J=3.6 Hz) with H-18 (δ_H 0.94, d, J=7.1 Hz) indicated that H-6, H_2-17 and H_3-18 were α-oriented, and that H-8 was β-oriented. Accordingly, the structure of **4** was determined as shown in Fig. 1 and termed as schisphenlignan D.

Schisphenlignan E (**5**) was isolated as amorphous powder with a molecular formula of $C_{22}H_{26}O_8$, as deduced from the HR-ESI-MS (*m/z* 441.1527 $[M+Na]^+$). Comparison of the spectroscopic data of **5** with those of schisphenone (**14**)[22] revealed the two compounds are structurally similar (Table 2). One of the differences between them was the carbonyl group at C-7 in the structure of schisphenone was changed into an oxymethine group, which was confirmed by HMBC correlations of H-7 (δ_H 3.51) with C-9 and C-18, of H-8 (δ_H 1.51) with C-7, C-9, C-10, C-17 and C-18, and ^{1}H-^{1}H COSY correlations of H-9/H-8/H-7/H_3-17 and H-8/H_3-18. Another difference is the methoxy groups located at C-2 and C-3 in schisphenone changed into a methylenedioxy group in **5**, which was confirmed by the HMBC correlations of the proton signals for the methylenedioxy group (δ_H 5.98) and H-4 (δ_H 6.79) with C-2 and C-3. Thus, the structure of **5** was established and given the trivial name as schisphenlignan E as shown in Fig. 1.

Table 2. ^{1}H- and ^{13}C-NMR Data of Compounds **4** and **5**[a)]

Position	**4**		**5**	
	δ_H	δ_C	δ_H	δ_C
1		152.4		140.9
2		141.8		136.0
3		152.5		148.9
4	6.62 s	108.1	6.79 s	103.3
5		132.1		120.9
6	5.40 s	84.2	4.17 s	63.2
7		62.3	3.51 m	69.1
8	2.58 m	34.9	1.51 m	40.0
9α	2.51[b)]	38.7	2.38 dd (14.1, 7.5)	36.2
9β	2.51[b)]		2.10 dd (14.1, 7.5)	
10		134.2		134.4
11	6.60 s	102.6	6.53 s	104.1
12		148.8		134.9
13		134.6		148.7
14		140.5		141.0
15		120.9		121.2
16		121.5		120.9
17α	2.96 d (3.6)	47.1	0.99 d (6.3)	20.2
17β	2.85 d (3.6)			
18	0.94 d (7.1)	17.2	0.78 d (6.7)	13.4
1′		164.6		
2′		129.4		
3′, 7′	7.31[b)]	127.8		
4′, 6′	7.52[b)]	129.6		
5′	7.50[b)]	132.8		
CH_3O-1	3.58 s	60.7	3.58 s	59.5
CH_3O-2	3.87 s	60.8		
CH_3O-3	3.91 s	55.9		
CH_3O-14	3.31 s	55.9	3.79 s	59.7
OCH_2O-2, 3	5.80 d (1.6)	100.5	5.98 s	101.0
	5.66 d (1.6)			
OCH_2O-12, 13			5.84 s	100.9

a) Data were recorded in $CDCl_3$ at 125 MHz (^{13}C-NMR) and 500 MHz (^{1}H-NMR); chemical shifts (δ) are expressed in ppm; *J* in Hz. *b*) Overlapping signals.

In our previous investigation, some compounds have been screened for their acute activities in cell-based insulin sensitivity assay.[23)] In the present study, compounds **1**–**4**, **6**, **7**, **9**, **10**, and **13** were tested for their acute activities on insulin sensitivity in 3T3-L1 differentiated adipocytes, but no significant activity was observed in these compounds when we applied a relatively high concentration (10 μM) for the compound treatments.

Experimental

General Procedure Optical rotations were measured on a JASCO P-1020 digital polarimeter. UV data were obtained using a Shimadzu UV-2401A spectrometer. CD spectra were tested using Applied Photophysics Chirascan Circular Dichroism spectrometer. IR spectra were obtained on a Tenor 27 spectrophotometer with KBr pellets. 1D- and 2D-NMR spectra were recorded on Bruker AM-400, DRX-500 and AVANCE III-600 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ESI-MS were performed on a Xevo TQ-S Mass spectrometer, HR-ESI-MS were performed on an API QSTAR time-of flight spectrometer. Semipreparative HPLC was performed on an Agilent 1100 or 1200 liquid chromatograph with a Zorbax SB-C_{18} (9.4 mm×25 cm) column. Column chromatography was performed with silica gel (100–200, 200–300 mesh, Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China), Lichroprep RP-18 gel (40–63 μM, Merck, Darmstadt, Germany), and MCI gel (75–150 μM, Mitsubishi Chemical Corporation, Tokyo, Japan). Petroleum ether (PE, 60–90°C), EtOAc, $CHCl_3$, acetone, CH_3OH, EtOH were analytical grade and produced by Sinopharm Chemical Reagent Co., Ltd., China. Fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 5% H_2SO_4 in EtOH.

Plant Material The stems of *S. sphenanthera* were collected in Qinling Country of Shanxi Province, People's Republic of China, in December 2008, and identified by Prof. Xi-Wen Li, Kunming Institute of Botany. A voucher specimen (KIB 2008121006) has been deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation The air-dried and powdered stems of *S. sphenanthera* (19.5 kg) were extracted with 70% aqueous Me_2CO three times (three days for each time) at room temperature and concentrated *in vacuo* to yield a residue, which was then partitioned between H_2O and EtOAc. The EtOAc extract (1.0 kg) was chromatographed on silica gel (100–200 mesh, 3.0 kg) column, eluting with a $CHCl_3$–Me_2CO gradient system (1 : 0, 9 : 1, 8 : 2, 2 : 1, 1 : 1, 0 : 1, each 20 L), to

give fractions 1–7. After decolorized on MCI gel, fraction 2 (153 g) was chromatographed on silica gel (200–300 mesh, petroleum ether–Me_2CO, 0 : 1–1 : 1, 8 L each of the solvent mixture) to give five subfractions (2.1–2.5). Fraction 2.2 (18.2 g) was subjected to RP-18 column chromatography (30–100% gradient CH_3OH–H_2O, 5 L each of the solvent mixture) to afford subfractions (2.2.1–2.2.5). Fraction 2.2.3 (8.5 g) was purified by semipreparative HPLC (45% CH_3CN–H_2O; 3 mL/min; UV detector, 210 nm) to give **6** (26.0 mg), **7** (9.0 mg), **9** (12.7 mg), and **13** (2.5 mg). Fraction 2.2.5 (1.5 g) was chromatographed on semipreparative HPLC (70% CH_3CN–H_2O; 3 mL/min; UV detector, 210 nm) to afford **4** (3.3 mg) and **10** (35.0 mg). Fraction 2.3 (13.8 g) was chromatographed on RP-18 (eluted with 50% to 100% CH_3OH–H_2O) to give **8** (1.2 g). Finally, fraction 2.4 (16.8 g) was chromatographed on RP-18 (eluted with 40% to 100% CH_3OH–H_2O, 4 L each of the solvent mixture) and then semipreparative HPLC repeatedly (eluted with 40% to 55% CH_3CN–H_2O; flow rate 3 mL/min; UV detector, 210 nm) to afford **1** (9.6 mg), **2** (9.5 mg), **3** (19.4 mg), **5** (6.0 mg), **11** (6.5 mg), and **12** (5.4 mg).

Schisphenlignan A (**1**): Amorphous powder. $[\alpha]_D^{27}$ −113.5° (c=0.17, $CHCl_3$). CD (CH_3OH) nm ($\Delta\varepsilon$) 211 (+4.0), 241 (−11.9). UV ($CHCl_3$) λ_{max} ($\log\varepsilon$): 240 (3.60) nm. IR (KBr) ν_{max} 3476, 2975, 2939, 1720, 1614, 1480, 1463, 1368, 1254, 1107, 921, 714 cm^{-1}. Positive ESI-MS m/z: 545 $[M+Na]^+$. Positive HR-ESI-MS $[M+Na]^+$ m/z: 545.1792 (Calcd for $C_{29}H_{30}O_9$ Na, 545.1787). NMR data: see Table 1.

Schisphenlignan B (**2**): Amorphous powder. $[\alpha]_D^{23}$ −245.7° (c=0.16, CH_3OH). CD (CH_3OH) nm ($\Delta\varepsilon$) 219 (+1.8), 232 (−8.5). UV (CH_3OH) λ_{max} ($\log\varepsilon$): 221 (4.31) nm. IR (KBr) ν_{max} 3456, 2976, 2940, 1720, 1619, 1588, 1480, 1464, 1368, 1273, 1072, 715 cm^{-1}. Positive ESI-MS m/z: 545 $[M+Na]^+$. Positive HR-ESI-MS $[M+Na]^+$ m/z: 545.1796 (Calcd for $C_{29}H_{30}O_9$ Na, 545.1787). NMR data: see Table 1.

Schisphenlignan C (**3**): Amorphous powder. $[\alpha]_D^{26}$ −120.5° (c=0.26, CH_3OH). CD (CH_3OH) nm ($\Delta\varepsilon$) 228 (+8.5), 246 (−19.7). UV (CH_3OH) λ_{max} ($\log\varepsilon$): 222 (4.13) nm. IR (KBr) ν_{max} 3438, 2976, 2939, 1717, 1618, 1480, 1465, 1270, 1113, 1066, 849, 730, 715 cm^{-1}. Positive ESI-MS m/z: 531 $[M+Na]^+$. Positive HR-ESI-MS $[M+Na]^+$ m/z: 531.1639 (Calcd for $C_{28}H_{28}O_9$Na, 531.1631). NMR data: see Table 1.

Schisphenlignan D (**4**): Amorphous powder. $[\alpha]_D^{14}$ −188.9° (c=0.15, $CHCl_3$). CD (CH_3OH) nm ($\Delta\varepsilon$) 226 (+2.5), 242 (−7.8). UV ($CHCl_3$) λ_{max} ($\log\varepsilon$): 240 (3.68) nm. IR (KBr) ν_{max} 3435, 2923, 1715, 1620, 1598, 1474, 1272, 1110, 713 cm^{-1}. Positive ESI-MS m/z: 557 $[M+Na]^+$. Positive HR-ESI-MS $[M+Na]^+$ m/z: 557.1779 (Calcd for $C_{30}H_{30}O_9$ Na, 557.1787). NMR data: see Table 2. 3

Schisphenlignan E (**5**): Amorphous powder. $[\alpha]_D^{26}$ +2.5° (c=0.22, $CHCl_3$). CD (CH_3OH) nm ($\Delta\varepsilon$) 225 (+6.7), 240 (−9.3). UV ($CHCl_3$) λ_{max} ($\log\varepsilon$): 240 (3.32) nm. IR (KBr) ν_{max} 3429, 2960, 2919, 2850, 1616, 1516, 1475, 1274, 1208, 1046, 949, 933 cm^{-1}. Positive ESI-MS m/z: 441 $[M+Na]^+$. Positive HR-ESI-MS $[M+Na]^+$ m/z: 441.1527 (Calcd for $C_{22}H_{26}O_8$Na, 441.1525). NMR data: see Table 2.

Insulin Sensitivity Assay Insulin Sensitivity Assays were performed using the method as reported previously.[23–25)]

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