



This open access document is published as a preprint in the Beilstein Archives with doi: 10.3762/bxiv.2020.64.v1 and is considered to be an early communication for feedback before peer review. Before citing this document, please check if a final, peer-reviewed version has been published in the Beilstein Journal of Organic Chemistry.

This document is not formatted, has not undergone copyediting or typesetting, and may contain errors, unsubstantiated scientific claims or preliminary data.

Preprint Title Dibenzocyclooctadiene Lignans from *Artemisia sieversiana* and Their Nitric Oxide Inhibitory Effects

Authors Xu-Dong Zhou, Chao-Xi Chen, Xi-Kang Zheng, Li-Min Gong, Ke-Wu Zeng, Wei Wang and Peng-Fei Tu

Publication Date 26 May 2020

Article Type Letter

Supporting Information File 1 Supporting Information.docx; 2.0 MB

ORCID® IDs Xu-Dong Zhou - <https://orcid.org/0000-0001-7445-5428>

Dibenzocyclooctadiene Lignans from *Artemisia sieversiana* and Their Nitric Oxide Inhibitory Effects

Xu-Dong Zhou ^{a, b}, Chao-Xi Chen ^c, Xi-Kang Zheng ^a, Li-Min Gong ^b, Ke-Wu Zeng ^a,
Wei Wang ^{b*}, Peng-Fei Tu ^{a*}

^a *State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, China*

^b *TCM and Ethnomedicine Innovation & Development International Laboratory, Innovative Materia Medica Research Institute, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, 410208, P.R. China*

^c *College of Life Science and Technology, Southwest Minzu University, Chengdu, Sichuan 610041, China*

*Corresponding author. Tel: +86 731 8845 8240; fax:+86 8845 8227.

E-mail address: wangwei402@hotmail.com (W. Wang).

*Corresponding author. Tel/Fax: +86 10 8280 2750

E-mail address: pengfeitu@vip.163.com (P.-F. Tu).

Abstract

Two previously undescribed dibenzocyclooctadiene lignans, named sieverlignans D–E (**1-2**), as well as eight known ones (**3-10**), were isolated from the aerial parts of *Artemisia sieversiana*. Their structures were elucidated from extensive spectroscopic analysis, including HRMS, NMR and circular dichroism experiments. This study is the first to report dibenzocyclooctadiene lignans in the genus *Artemisia* and this plant. All the compounds were evaluated for their anti-neuroinflammatory effects on the lipopolysaccharides (LPS)-induced nitric oxide production in BV-2 murine microglial cells. Compounds **1** and **6** exhibited the moderate activity with their IC₅₀ values of 47.7 and 21.9 μM, compared to a positive control quercetin with the IC₅₀ value of 16.0 μM.

Keywords

Artemisia sieversiana; Dibenzocyclooctadiene lignans; Sieverlignans D–E; Nitric oxide inhibitory

Introduction

Artemisia sieversiana Ehrhart ex Willd, also known as ‘Da-Zi-Hao’, ‘Bai-Hao’, ‘Bai-Ai-Hao’ and ‘You-Hu’ in Chinese, is an annual or biennial herb of the Compositae and widespread in China, Pakistan, Mongolia and Central Asia. In China, it has a long medicinal history in traditional Chinese medicine and Mongolian medicine, which has been used to treat diarrhea and jaundice [1]. Encouraged by the chemical diversity and notable biological activities of *A. sieversiana* [2-6], we have re-investigated the ingredients of the aerial parts of this plant, which led to the identification of three previously undescribed dibenzocyclooctadiene lignans and eight known compounds. Herein, we have described their isolation and structural elucidation of these compounds together with their anti-neuroinflammatory effects on the lipopolysaccharides (LPS)-induced nitric oxide production in BV-2 murine microglial cells.

Results and Discussion

The chloroform-soluble residue from the aerial parts of *A. sieversiana* was applied to varied chromatography techniques and recrystallization, including CC on silica gel, ODS, Sephadex LH-20 and semi-preparative HPLC, to afford sieverlignan D (**1**, 6 mg), sieverlignan E (**2**, 4 mg), rubrisandrin B (**3**, 5 mg) [7], (+)schizandra (**4**, 9 mg) [8], ((*R*-biar)-12-angeloyloxy-6,7,8,9-tetrahydro-1,2,3,13,14-penta-methoxy-7,8-dimethyl-7-dibenzo[a,c]cyclooctenol) (**5**, 8 mg) [9], (*R*-biar)-12-benzoyloxy-6,7,8,9-tetrahydro-1,2,3,13,14-pentamethoxy-7,8-dimethyl-7-dibenzo [a,c] cyclooctenol (**6**, 8 mg) [9], micrantherin A (**7**, 10 mg) [10], (–)-gomisin G (**8**, 12 mg) [11], schisantherin A (**9**, 12

mg) **12**, gomisin D (**10**, 7 mg) [13] (Figure 1).

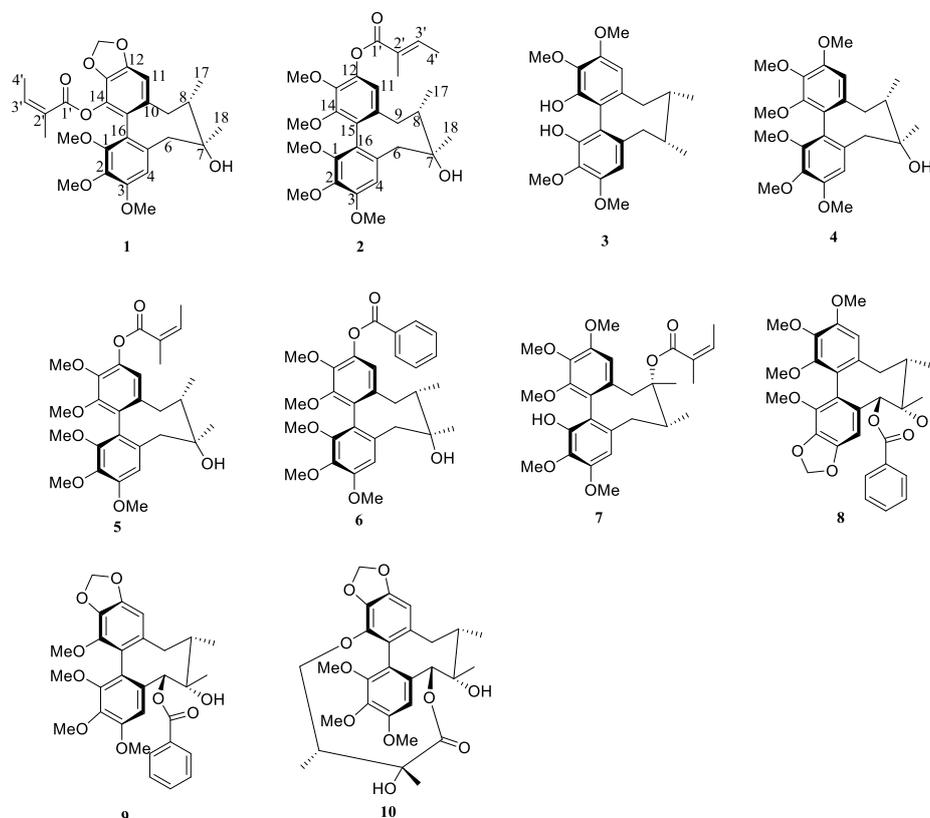


Figure 1. Chemical structures of **1–10** isolated from *A. sieversiana*.

Sieverlignan D (**1**) was obtained as an amorphous gum and assigned the molecular formula $C_{27}H_{32}O_8$ from the $[M + Na]^+$ peak at m/z 507.2003 (calcd for 507.1995) and $[M + NH_4]^+$ peak at m/z 502.2446 (calcd for 502.2441) in the HR-ESI-MS and supported by the ^{13}C -NMR data (Table1). The IR spectrum of **1** exhibited absorptions at 3516 cm^{-1} (OH), 1737 cm^{-1} (C=O), and 1481 cm^{-1} (Ar-). The 1H -NMR spectrum of **1** showed the presence of four methyl groups resonating at δ_H 0.87 (d, $J = 7.0$ Hz), 1.23 (s), 1.72 (s), and 1.77 (m); three methoxy group at δ_H 3.41 (s), 3.78 (s), 3.88 (s); one methylenedioxy moiety at δ_H 6.01 (d, $J = 1.0$ Hz) and 6.03 (d, $J = 1.0$ Hz); one olefinic proton at δ_H 6.04 (m); and two aromatic protons at δ_H 6.75 (s) and δ_H 6.72 (s); The ^{13}C -NMR and HSQC spectrum of **1** showed 4 CH_3 , 3 CH_2 , 4 CH , 13 C and 3 OCH_3 . There were 16 carbon

signals were observed in the low field of the ^{13}C -NMR spectrum, including fourteen olefinic carbon signals (δ_{C} 109.9, 112.7, 123.4, 125.2, 128.4, 132.6, 134.4, 136.0, 139.0, 140.2, 141.3, 149.2, 152.5, 153.6), one carbonyl group (δ_{C} 165.9), one methlenedioxy group (δ_{C} 103.2) (Table 1). The above data and the 12 degrees of unsaturation deduced from the molecular formula $\text{C}_{27}\text{H}_{32}\text{O}_8$, revealed the presence of two aromatic rings, one carbonyl group, one double bond and two another rings. The 1D and 2D NMR spectrum implied **1** was a dibenzocyclooctadiene lignan, together with their comparison with those of the reported analogues. The HMBC correlations of the methlenedioxy proton signals (δ_{H} 6.03 and 6.01) with C-12 (δ_{C} 139.0) and C-13 (δ_{C} 149.2) suggested the oxygen atoms of the methlenedioxy were at C-12 and C-13, which formed a ring with the benzene moiety. Attachment of three methoxy groups (δ_{H} 3.41, 3.78 and 3.88) at C-1(δ_{C} 152.5), C-2(δ_{C} 141.3) and C-3(δ_{C} 153.6) respectively was confirmed by HMBC correlations of them. In the cyclooctadiene moiety, the oxygenated quaternary carbon was assigned to C-7 on the basis of the downfield chemical shift (δ_{C} 73.4) and the HMBC correlation of H-18 (δ_{H} 1.23) with C-7. In addition, detailed analysis revealed that **1** contained an angeloyl moiety except the skeleton of lignan, the methlenedioxy group and three methoxy groups. The position of angeloyl group was attached at the oxygen atom of C-14 by the NOESY correlation of 2'-Me and 1-OMe (Figure 2). Thus, the planar structure of **1** was established.

Table 1. The ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) data of **1** (in CD_3OD) and **2** (in CDCl_3) (δ in ppm, J in Hz)

No.	1		2	
	δ_{C}	δ_{H}	δ_{C}	δ_{H}
1	152.5	--	151.8	
2	141.3	--	140.8	
3	153.6	--	152.4	--
4	112.7	6.72, s	110.2	6.56, s
5	136.0	--	133.0	
6 α	42.5	2.35, d, (13.8)	40.6	2.35, d, (13.5)
6 β		2.62, d, (13.8)		2.74, d, (13.5)
7	73.4	--	71.9	--
8	42.3	1.82, m	42.0	1.90, m
9 α	35.7	2.41, dd, (14.3, 8.1)	34.2	2.41, dd, (14.5, 7.4)
9 β		2.87, dd, (14.3, 2.1)		2.72, d, (14.5)
10	134.4	--	133.7	--
11	109.9	6.75, s	112.7	6.70, s
12	139.9	--	142.7	--
13	149.2	--	139.8	--
14	132.6	--	151.7	--
15	125.2	--	123.2	--
16	123.4	--	122.9	--
17	15.8	0.87, d, (7.0)	15.9	0.86, d, (7.0)
18	30.0	1.23, s	29.9	1.26, s
1'	165.9	--	165.7	--
2'	128.4	--	127.9	--
3'	140.2	6.04, m	138.2	6.84, q, (5.6)
4'	12.1	1.77, m	12.1	1.72, d, (5.6)
2'-Me	14.7	1.72, s	14.7	1.71, s
1-OMe	60.9	3.41, s	60.8	3.52, s
2-OMe	61.2	3.78, s	61.0	3.85, s
3-OMe	56.4	3.88, s	56.1	3.89, s
13-OMe			60.6	3.84, s
14-OMe			56.0	3.92, s
-OCH ₂ O-	103.2	6.01, d, (1.0)		
		6.03, d, (1.0)		

The relative stereochemistry was determined by the NOESY spectra (Figure 2).

The NOE cross-peaks of H-4/H-6 α , H-6 α /H-18, H-17/H-18 and H-11/H-9 α , indicated

a twist-boat-chair conformation for the cyclooctane ring [14]. The configuration of biphenyl group was determined by the reported publications and the circular dichroism (CD) spectra. Many previous literatures have found that the chemical shift of 17-Me in the ^{13}C -NMR of *R*-aryl derivatives was about δ_{C} 12-16, while in *S*-aryl derivatives it always showed to be δ_{C} 19 [15]. The CD spectrum of **1** gave a positive Cotton effect at 250 nm and a negative Cotton effect 220 nm, confirming that **1** had a *R*-biphenyl configuration [16].

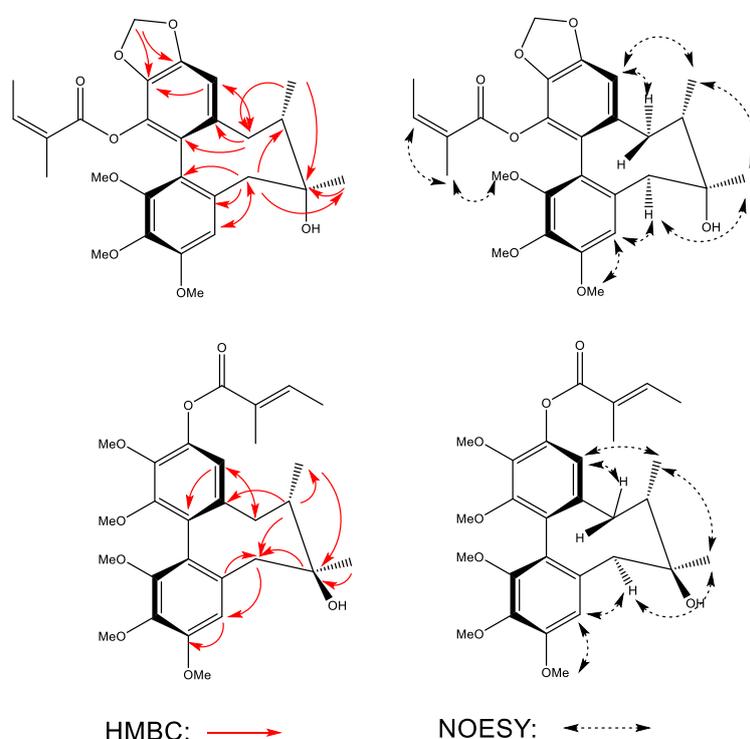


Figure 2. Key HMBC and NOESY correlations of compounds **1–2**.

Sieverlignan E (**2**) was obtained as amorphous solid and assigned the molecular formula $\text{C}_{28}\text{H}_{36}\text{O}_8$ from the $[\text{M} + \text{H}]^+$ peak at m/z 501.2507 (calcd for 501.2488) in the HR-ESI-MS, corresponding to 11 degrees of unsaturation. The 1D NMR spectrum presented five methoxy groups and four methyl groups. Detailed comparison of data of **2** with those of these published derivatives suggested the structure of **2** was similar to

that of known compound (*R*-biar)-12-angeloyloxy-6,7,8,9-tetrahydro-1,2,3,13,14-pentamethoxy-7,8-dimethyl-7-dibenzo[*a,c*]cyclooctenol [9], except that the angeloyl group was replaced by the tigloyl group in **2** (Table1). The presence of the tigloyl group was determined on the basis of the chemical shifts of this group and C-12. The chemical shift of the tigloyl group (δ_{H} 6.84) in NMR spectra was lower than that of the angeloyl group (5.89) in $^1\text{H-NMR}$. Because of the different configurations of the two double bond, these chemical shifts of the methyl groups are distinct: δ_{C} 15.3 (C-4') and 20.3 (2'-Me) in the angeloyl moiety while δ_{C} 12.1 (C-4') and 14.7 (2'-Me) in the tigloyl moiety. In addition, the chemical shift of C-12 would be δ_{C} 142.7 (-Tig) rather than δ_{C} 142.2 (-Ang). And if C-12 was substituted by -OMe, its chemical shift came to be δ_{C} 153.5. The above deduction was confirmed by the NOESY correlation between H-11 and 2'-Me. Thus, the structure of **2** was established as shown.

The relative stereochemistry of **2** was determined by the ROESY spectra (Figure 2), combined with the comparison of relevant reported literature. The relative conformation of H-17 and H-18 were confirmed by the NOESY cross-peaks between H-17 and H-18. The CD spectrum of **2** gave a positive Cotton effect at 252 nm and a negative Cotton effect 220 nm, indicating that **2** had a *R*-biphenyl configuration [16].

All the isolated compounds were for their anti-neuroinflammatory effects on the lipopolysaccharides (LPS)-induced nitric oxide production in BV-2 murine microglial cells by using the method previously reported (Table 2) [17]. The known compound quercetin ($\text{IC}_{50} = 16.0 \mu\text{M}$) were used as positive control in the bioassay. Compounds **1** and **6** exhibited the moderate activity with their IC_{50} values of 47.7 and 21.9 μM .

Table 2. Inhibitory effects of compounds **1–10** on NO production induced by LPS in BV-2 cells

Compounds	IC ₅₀ (μM)	Compounds	IC ₅₀ (μM)
1	47.7	6	21.9
2	>100	7	95.3
3	>100	8	49.9
4	>100	9	89.5
5	81.1	10	>100
Quercetin ^a	16.0		

^a Quercetin was used as a positive control.

Conclusion

In conclusion, this study investigated chemically the aerial parts of *Artemisia sieversiana*, which resulted in ten dibenzocyclooctadiene lignans (**1-10**), including two unknown ones (**1-2**). Their structures were elucidated from extensive spectroscopic analysis, including MS, NMR and circular dichroism experiments. To our knowledge, this study is the first to report dibenzocyclooctadiene lignans in the genus *Artemisia* and this plant. Lignans can be considered as one of its main and characteristic components in *Artemisia* genus, but tetrahydrofuran lignans are the most common and related references on dibenzocyclooctadiene lignans in this genus are scarcely. Therefore these ingredients can be interesting for chemotaxonomic significance of *Artemisia sieversiana*. Since ‘Da-Zi-Hao’ has been used as traditional Chinese medicine for antiphlogosis and heat-clearing, all the isolates were evaluated for their anti-neuroinflammatory effects on the lipopolysaccharides (LPS)-induced nitric oxide production in BV-2 murine microglial cells. Compounds **1** and **6** exhibited the moderate activity with their IC₅₀ values of 47.7 and 21.9 μM, compared to a positive control

quercetin with the IC_{50} value of $16.0 \mu M$. In those *S*-isomers, compound **8** exhibited more active when compared to **9**, which concluded that the location of the methylenedioxy group could affect their inhibition activities. Comparing compounds **1**, **4**, **5**, **6** and **7**, compound **6** showed stronger inhibitory activity than the other compounds in *R*-isomers, which indicated the occurrence and the location of the angeloyl group were key features for the lignans.

Experimental

General experimental procedures

Optical rotations were measured on an Autopol-IV polarimeter (RudoPH Research analytical). IR spectra were recorded on a NEXUS-470 FTIR (Nicolet) spectrometer. NMR spectra were acquired on Varian INOVA-500 FT NMR spectrometer using deuterated solvents as references. HRESIMS were measured on a Waters Xevo G2 Q-TOF mass spectrometer. Semi-preparative HPLC was performed on a DIONEX Ultimate 3000 system with UV-VIS detector employing an Agilent Edipse XDB C18 column (250×9.4 mm i.d., $5 \mu m$). Thin-layer and column chromatography were performed using silica gel (Qingdao Haiyang Chemical Co. Ltd., GF₂₅₄ or 200–300 mesh) and Sephadex LH-20 (Pharmacia Biotech Ltd.) and ODS (Merck & Co., Inc. USA). All the solvents were of analytical grade and were purchased from Beijing Chemical Company Ltd.. TLC spots were observed under UV light or by spraying with 5% sulfuric acid vanillin solution.

Plant material

The aerial parts of *A. sieversiana* were originally collected from Qinghai Province in March 2013, and identified by Prof. Peng-Fei Tu, one of the authors. A voucher specimen (No. DZH201304) was deposited at the Herbarium of the Peking University Modern Research Center for Traditional Chinese Medicine, Peking University.

Extraction and isolation

The dried aerial parts of *A. sieversiana* (60 kg) were grinded and extracted with 95% EtOH three times, each for two hours. After removal of the ethanol in vacuo, the slabby concentrated residue (10.2 kg) was suspended in H₂O (20 L) and partitioned with petroleum ether (20 L × 3) and CHCl₃ (20 L × 3) successively. The CHCl₃-soluble fraction (1.6 kg) was subjected to a silica gel column chromatography (CC) (200-300 mesh; PE/EtOAc, 1:0→0:1) to yield ten fractions (Fr.1-10). Silica gel CC (200-300 mesh; dichloromethane/ EtOAc, 1:0→0:1) of Fr.6 led to eighteen fractions (Fr.A-R) and Fr.K was separated over a ODS C₁₈ column (MeOH/H₂O, 20:80→80:20) to yield ten major sub-fractions (Fr.K1~Fr.K10). Compound **7** (10 mg) was obtained by recrystallization of Fr.K7. The remaining fractions was separated by semi-preparative HPLC (MeOH/H₂O 52:48, 2.0 mL/min) yield compounds **1** (6 mg), **4** (9 mg) and **8** (12 mg). Fr.K9 was chromatographed on Sephadex LH-20 in MeOH afforded three fractions (Fr.K9.1~Fr.K9.5) and Fr. K9.3 was separated by semi-preparative HPLC (MeOH/H₂O, 36:64, 2.0 mL/min) yield compound **3** (5 mg). Fr.M was separated on Sephadex LH-20 to afford thirty fractions (Fr.M1~Fr.M30). Fr.M22 was subjected to RP-C₁₈ CC eluted with MeOH-H₂O (20:80→80:20) to get fifteen sub-fractions (Fr.M22.1~ Fr.M22.15) and Fr.M22.6 further purified by semi-preparative HPLC

(MeOH/H₂O 50:50, 2.0 mL/min) yield compounds **6** (8 mg) and **9** (12 mg). Fr.M28 was chromatographed on silica gel with a gradient of Petroleum ether-CH₂Cl₂ (10:1–1:1) elution to yield fifteen fractions (Fr.M28.15~ Fr.M28.15). Fr.M28.8 was obtained by semi-preparative HPLC (MeCN/H₂O, 70:30, 2.0 mL/min) yield compound **10** (7 mg). Sephadex LH-20 CC (MeOH) of Fr.8 resulted in nine fractions (Fr.8.1~Fr.8.9). and Fr.8.1~Fr.8.4 were combined and was purified by semi-preparative HPLC (MeCN/H₂O 50:50, 2.0 mL/min) yield compounds **2** (4 mg) and **5** (8 mg).

Sieverlignan D (**1**): white, amorphous gum; $[\alpha]_D^{25} + 24.0$ (*c* 0.10, MeOH); IR (KBr) ν_{\max} 3528, 2930, 1737, 1115, 1069 cm⁻¹; ¹H and ¹³C NMR data (CD₃OD, 500/125 MHz), see **Table 1**; HRESIMS *m/z* 507.2003 [M + Na]⁺ (calcd for C₂₇H₃₂O₈Na, 507.1995) and *m/z* 502.2446 [M + NH₄]⁺ (calcd for C₂₇H₃₂O₈NH₄, 502.2441).

Sieverlignan E (**2**): white, amorphous solid; $[\alpha]_D^{25} + 24.7$ (*c* 0.15, MeOH); IR (KBr) ν_{\max} 3516, 2934, 1737, 1104, 1067 cm⁻¹; ¹H and ¹³C NMR data (CDCl₃, 500/125 MHz), see **Table 1**; HRESIMS *m/z* 501.2507 [M + H]⁺ (calcd for C₂₈H₃₇O₈, 501.2488).

NO production inhibitory assay

The production of NO in the medium was assessed by determining the nitrite concentration with Griess reagent (1% sulfanilamide and 0.1% naphthylenediamine in 5% phosphoric acid). BV-2 cells macrophages were seeded in 96-well plates (1×10⁵ cells/well). The cells were pre-treated with compounds **1-10** for 4 h, and then incubated

with LPS (1 $\mu\text{g}/\text{mL}$) for 24 h. The control group was treated with LPS only. The absorbance was recorded on a microplate reader at a wavelength of 540 nm. The IC_{50} value was generated by GraphPad Prism 5 software. Cell viability was measured by an MTT assay and the absorbance read at 570 nm with an ELISA analyzer. Quercetin was employed as a positive control.

Supporting Information

Spectral data of compound **1** and **2**.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/.....>]

Acknowledgments

The authors express thanks to the analytical center of Peking University Health Science Center for measurements of MS and NMR. This work is financially supported by grants from the National Natural Science Foundation of China (Nos. 81903514 and 81473106) and the key research and Development Projects of Hunan Science Technology Department (No.2016NK2133).

ORCID ID

Xu-Dong Zhou – <https://orcid.org/0000-0001-7445-5428>.

References

1. Jiangsu College of New Medicine. 1977. *A Comprehensive Dictionary of Traditional Chinese Medicine*; Shanghai science and technology: Shanghai, China. pp. 627–629.

2. Tan, R.-X.; Tang, H.-Q.; Hu, J.; Shuai, B. Lignans and sesquiterpene lactones from *Artemisia sieversiana* and *Inula racemosa*. *Phytochemistry* **1998**, *49*, 157–161. doi: 10.1016/s0031-9422(97)00889-3
3. Tang, H.-Q.; Hu, J.; Yang, L.; Tan, R.-X. Terpenoids and flavonoids from *Artemisia* species. *Planta Med.* **2000**, *66*, 391–393. doi: 10.1055/s-2000-8538
4. Zhang, Q.; Guo, G.-N.; Miao, R.-D.; Chen, N.-Y.; Wang, Q. Studies on the chemical constituents of *Artemisia sieversiana* and their anticancer activities. *J. Lanzhou Univ. (Nat. Sci.)* **2004**, *40*, 68–71. doi: 10.13885/j.issn.0455-2059.2004.04.019
5. Zhou, X.-D.; Chai, X.-Y.; Zeng, K.-W.; Zhao, M.-B.; Jiang, Y.; Tu, P.-F. Artesin A, a new cage-shaped dimeric guaianolide from *Artemisia sieversiana*. *Tetrahedron Letters* **2015**, *56*, 1141–1143. doi: 10.1016/j.tetlet.2015.01.081
6. Zhou, X.-D.; Zhang, C.; He, S.; Zheng, B.; Zeng, K.-W.; Zhao, M.-B.; Jiang, Y.; Tu, P.-F. New terpenoids and thiophene derivatives from the aerial parts of *Artemisia sieversiana*. *Bioorganic & Medicinal Chemistry Letters* **2017**, *27*, 5441–5445. doi: 10.1016/j.bmcl.2017.10.077
7. 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*, 1697–1701. doi: 10.1021/np060239e
8. Piao, L.-Z.; Lee, Y.-J.; Phamp-hu, T.-T.; Shin, J.-K. Dibenzocyclooctene lignan compounds isolated from the fruits of *Schisandra chinensis* Bail. *Natural Product Sciences* **2005**, *11*, 248–252.
9. Zhao, X.-M.; Guo, F.-J.; Li, Y.-M.; Zhu, D.-Y. Two new lignans from *Celastrus*

flagellaris Rupr. *Journal of Asian Natural Products Research* **2012**, *14*, 159–164.

doi: 10.1080/10286020.2011.641535

10. Li, R.-T.; Han, Q.-B.; Zheng, Y.-T.; Wang, R.-R.; Yang, L.-M.; Peng, L.-Y.; Xiao, W.-L.; Sun, H.-D. Anti-HIV lignans from *Schisandra micrantha*. *Chinese Journal of Natural Medicines* **2005**, *3*, 208–212. doi:
11. Yang, L.-B.; Huang, S.-X.; Pu, J.-X.; Li, L.-M.; Zhao, Y. Lignans from *Schisandra elongate* (BI.) Baill. *Chinese Traditional Patent Medicine* **2012**, *34*, 2365–2368.
12. Jiang, S.-J.; Wang, Y.-H.; Chen, D.-F. Sphenanlignan, a new lignan from the seeds of *Schisandra sphenanthera*. *Chin. J. Nat. Med.* **2005**, *3*, 78–82. doi:
13. Chen, H.-Y.; Zhou, C.-X.; Yao, W.; Wang, L.-W.; Dou, H.; Dong, X.-W.; Zhao, Y. An NMR study of two lignans isolated from *Schisandra Chinensis*. *Chinese Journal of Magnetic Resonance* **2005**, *22*, 43–54.
14. Chen, M.; Xu, X.-M.; Xu, B.; Yang, P.-P.; Liao, Z.-H.; Morris-Natschke, S.L.; Lee, K.H.; Chen, D.-F. Neglschisandrins E-F: two new lignans and related cytotoxic lignans from *Schisandra neglecta*. *Molecules* **2013**, *18*, 2297–2306. doi: 10.3390/molecules18022297
15. Ikeya, Y.; Taguchi, H.; Sasaki, H.; Nakajima, K.; Yosioka, I. The constituents of *Schizandra chinensis* Baill VI ¹³C nuclear magnetic resonance spectroscopy of dibenzocyclooctadiene lignans. *Chem. Pharm. Bull.* **1980**, *28*, 2414–2421. doi: 10.1248/cpb.28.2414
16. Wu, H.-H.; Li, Z.-F.; Zhang, Q.-H.; Pei, Y.-H. Application of CD in study of the absolute configuration of lignans. *Journal of Shenyang Pharmaceutical University*

2010, 27, 587–594. doi: 10.14066/j.cnki.cn21-1349/r.2010.07.012

17.Zhang, C.; Wang, S.; Zeng, K.-W.; Cui, F.-X.; Jin, H.-W.; Guo, X.-Y.; Jiang, Y.; Tu,

P.-F. *Bioorganic & Medicinal Chemistry Letters* **2014**, 24, 4318–4322. doi:

10.1016/j.bmcl.2014.07.008