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SHORT REPORT

A new 8-O-4′-neolignan glycoside with anti-inflammatory activity from *Ailanthus altissima*

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Abstract: A new 8-O-4′-neolignan glycoside (**1**) and three known lignans were isolated from the roots of *Ailanthus altissima* (Mill.) Swingle. Its structure was elucidated by comprehensive analyses, including 1D and 2D NMR, HRESIMS, electronic circular dichroism (ECD) spectroscopy and hydrolysis derivatization analysis. Its *in vitro* anti-inflammatory activity was evaluated using a lipopolysaccharide (LPS)-induced inflammation model, with dexamethasone as the positive control. The results demonstrated that compound **1** significantly inhibited the secretion of nitric oxide (NO) secretion at all tested concentrations (3.75–15 μM), indicating that compound **1** possesses notable anti-inflammatory activity.

Keywords: *Ailanthus altissima*, 8-O-4′-neolignan glycoside, anti-inflammatory activity

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1 Plant Source

The root bark of *Ailanthus altissima* used in this study was provided by Sichuan Neautus Pharmaceutical Co., Ltd. This source was selected to ensure the precise identification of the plant material. To further verify the authenticity of the specimens, they were certified by Prof. Guang-Zhi Wang, a botanist with expertise at Chengdu University of Traditional Chinese Medicine. The voucher specimen has been assigned the accession number 20240909/CDCM/SCA and is deposited in the university's herbarium.

2 Previous Studies

Previous phytochemical investigations on *A. altissima* have led to the isolation and identification of a variety of constituents, including quassinoids (Peng et al., 2026), alkaloids (Cho et al., 2018), lignans (Huang et al., 2026), coumarins (Guo et al., 2026), flavonoids (Kim et al., 2015) and aromatic compounds (Zhang et al., 2025). The plant possesses a broad spectrum of pharmacological activities, such as anti-inflammatory, antitumor, antibacterial, and antioxidant effects, largely attributed to these structurally diverse compounds (Li et al., 2021).

3 Present Study

A total of 50 kg of dried bark from *A. altissima* was powdered and extracted three times using 95% MeOH. After recovering the solvent, 2.75 kg of extract were obtained. The extract was further fractionated using silica gel column chromatography (CC). It was first eluted with petroleum ether to remove lipophilic components, followed by a gradient of dichloromethane-methanol (from 1: 0 to 0: 1, v/v), resulting in 16 fractions (Fr.1–Fr.16).

Fr. 4 (75.67 g) was subjected to silica gel column chromatography with gradient elution [petroleum ether/acetone (15: 1 → 1: 1, v/v)] to afford ten subfractions (Fr. 4.1–Fr. 4.10). Fr. 4.6 (4.86 g) was chromatographed over Sephadex LH-20 [dichloromethane/methanol (1: 1, v/v)] to yield nine fractions (Fr. 4.6.1–Fr. 4.6.9). Fr. 4.6.8 (148 mg) was purified by semi-preparative HPLC [methanol/water (48: 52, v/v)] to give seven subfractions (Fr. 4.6.8.1–Fr. 4.6.8.7). Fr. 4.6.8.5 (11.7 mg) was further purified by semi-preparative HPLC [methanol/water (42: 58, v/v)] to obtain compound **2** (2.2 mg, t_R = 27.52 min) (Figure 1). Fr. 4.6.8.7 (6.8 mg) was further purified by semi-preparative HPLC [methanol/water (42: 58, v/v)] to obtain compound **3** (1.8 mg, t_R = 38.24 min). Fr. 4.7 (5.53 g) was chromatographed over Sephadex LH-20 [dichloromethane/methanol (1: 1, v/v)] to yield six fractions (Fr. 4.7.1–Fr. 4.7.6). Fr. 4.7.6 (490 mg) was further separated by silica gel column chromatography [dichloromethane/methanol (1: 1, v/v)] to give eight subfractions (Fr. 4.7.6.1–Fr. 4.7.6.8). Fr. 4.7.6.3 (115.1 mg) was purified by reversed-phase C18 column chromatography [acetonitrile/water (25: 75, v/v)] to afford eight subfractions (Fr. 4.7.6.3.1–Fr. 4.7.6.3.8). Fr. 4.7.6.3.6 was identified as compound **4** (7.6 mg, t_R = 24.42 min).

Fr.9 (96.64 g) was subjected to reversed-phase C18 column chromatography and eluted with a gradient of 60%,

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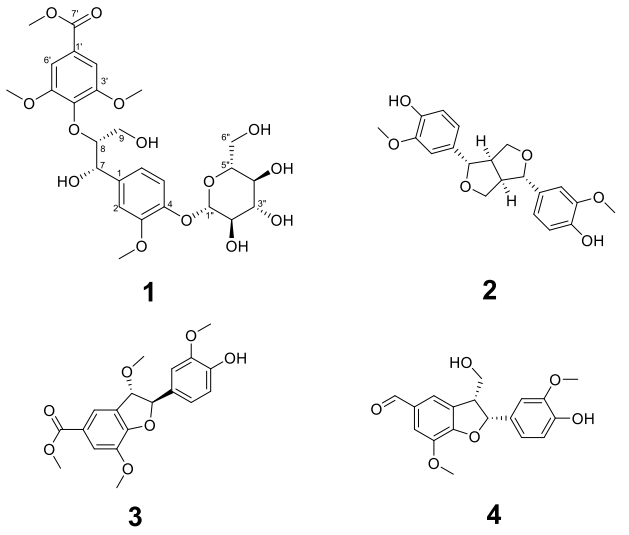

Figure 1. Structure of compounds **1**–**4**

70%, and 100% methanol to afford five fractions (Fr.9.1–Fr.9.5). Fr.9.2 (30.4 g) was separated by Sephadex LH-20 column chromatography (dichloromethane: methanol = 1: 1) to yield five fractions (Fr.9.2.1–Fr.9.2.5). Fr.9.2.3 (14.9 g) was chromatographed on a normal-phase silica gel column with a gradient elution of dichloromethane-methanol (1: 0 → 0: 1) to give 14 subfractions (Fr.9.2.3.1–Fr.9.2.3.14). Fr.9.2.3.8 (8.02 g) was further separated on an MCI column using methanol-water as the mobile phase to yield 15 fractions (Fr.9.2.3.8.1–Fr.9.2.3.8.15). Fr.9.2.3.8.12 (546.9 mg) was purified by semi-preparative HPLC (acetonitrile: water = 15: 85) to obtain compound **1** (5.7 mg, t_R = 31.67 min).

Compound **1**: oil; $[\alpha]_D^{25}$ = −18.60 (c = 0.040, MeOH); IR (KBr): 3391.6, 2921.2, 1715.5, 1593.1, 1508.5, 1461.4, 1418.2, 1338.1, 1263.3, 1223.6, 1187.4, 1126.6, 1074.1, 1035.6, 764.4 cm^{-1}; UV (MeOH) λ_max 214 (3.61), 271 (3.08) nM; CD (351 μM, MeOH) λ_max (Δε) 205 (−8.54), 236 (+2.22), 276 (−1.92) nM; HRESIMS *m/z* 593.1841 $[M + Na]^+$ (calcd. 593.1841). For details on the ^1H and ^{13}C NMR data, see Table 1.

Compound **1** was obtained as an oil. Its molecular formula was established as $C_{26}H_{34}O_{14}$ by HR-ESI-MS (*m/z* 593.1841 [M + Na] $^+$, calcd for $C_{26}H_{34}O_{14}$, 593.1841), corresponding to 10 degrees of unsaturation. The IR bands indicated the presence of hydroxyl (3391.6 cm^{-1}) and carbonyl (1715.5 cm^{-1}) groups. The ^1H NMR spectrum (Table 1) displayed two aromatic proton signals at δ_H 7.30 (H-6′, *s*) for a 1′,3′,4′,5′-tetrasubstituted benzene ring, indicating a symmetric meta relationship. Another 1,3,4-trisubstituted benzene ring exhibited an ABX coupling system with proton signals at δ. $_H$6.91 (*dd*, *J* = 8.4, 2.1 Hz), 7.07 (*d*, *J* = 2.1 Hz), and 7.10 (*d*, *J* = 8.4 Hz). Characteristic signals further revealed four methoxy groups at δ_H 3.89 (3H, *s*) and 3.83 (3H, *s*), where the latter comprises three overlapping aromatic methoxy singlets and the former corresponds to a carbomethoxy group. The anomeric proton signal at δ_H 4.85 (1H, *d*, *J* = 7.5 Hz), together with a set of sugar proton multiplets at δ_H 3.39 (H-4″), 3.39 (H-5″), 3.46 (H-3″), and 3.48 (H-2″), indicated the presence of a glycosyl moiety. The two diastereotopic methylene protons at C-6″ of the sugar unit resonated as a pair of double doublets at δ_H 3.69 (H-6″) and 3.87 (H-6″) due to the adjacent chiral center. Additional signals included an oxygenated methylene at δ_H 3.92 (1H, *dd*, *J* = 12.0, 5.1 Hz) and δ_H 3.65 (1H, *dd*, *J* = 12.0, 3.5 Hz), and three oxygenated methine protons at δ_H 4.43 (1H, *td*, *J* = 5.4, 3.5 Hz), 4.93 (1H, *d*, *J* = 5.6 Hz), 4.84 (1H, *s*), suggesting the presence of oxygenated methine functionalities within the lignan skeleton. The ^{13}C NMR spectrum (Table 1) exhibited 26 carbon resonances, which could be assigned to one phenylpropanoid C_6–C_3 unit (δ_C 137.5, 112.5, 150.4, 147.3, 117.5, 120.9, 87.2, 73.9, 61.8). The anomeric carbon at δ_C 102.9 and other sugar carbon signals (δ_C 78.2, 77.8, 74.9, 71.3, 62.5) indicated a pyranoside. An aromatic ring was observed (δ_C 126.4, 107.9, 154.2, 141.4, 154.2, 107.9). A carbonyl carbon was observed at δ_C 168.1. Four methoxy carbon signals (δ_C 56.7, 56.7, 56.7, 52.8) corresponded to the methoxy protons. The above data revealed that compound **1** was a lignan glycoside.

Compound **1** was subjected to acid hydrolysis followed by chiral derivatization, and subsequent HRESIMS analysis identified the sugar moiety as D-glucose, consistent with the method for determining the absolute configuration of monosaccharides (Tanaka et al., 2007; Chen et al., 2023). The large coupling constant (7.5 Hz) of the anomeric proton (δ 4.85) supported a β-configuration for the glucopyranosyl linkage, in accordance with the established $J_{1,2}$ criteria for β-glucopyranosides (Chen et al., 2023; Li et al., 2025). In the HMBC spectrum, a key long-range correlation from H-1″ to C-4 (δ 147.3) confirmed the attachment of the glucosyl moiety at the C-4 position of the aglycone. Additionally, an HMBC cross-peak between H-8 and C-4′ (δ 141.4) verified the 8-*O*-4′ neolignan connectivity. Based on ^1H–^1H COSY and HMBC analyses, the structure of was elucidated as 3,3′,5′-trimethoxy-8-*O*-4′-neolignan-7′-oic acid methyl ester 4-*O*-β-D-glucopyranoside. This allowed for the determination of the planar structure of compound **1** (Figure 2). The coupling constant between H-7 and H-8 of compound **1** is $J_{7,8}$ = 5.6 Hz, and the chemical shift difference between the two methylene protons at C-9 is Δδ (H9a–H9b) = 0.27 ppm (δ 3.92 and 3.65). According to the empirical rule for the configuration of 8-O-4′ neolignans—where $J_{7,8}$ values of approximately 5–6 Hz correspond to the erythro configuration, and 7–8 Hz correspond to the threo configuration—the above NMR data indicate that the relative configuration of C-7 and C-8 in this compound is erythron (Fang et al., 2010; Zhao et al., 2023). The C7-aryl and C8-methyl benzoate groups in the molecule serve as strong $\pi \rightarrow \pi^*$ transition chromophores, generating exciton coupling in the UV region. The CD spectrum of **1** exhibits a positive Cotton effect at 236 nM (+) and a negative Cotton effect at 276 nM (−) (Figure 3). According to the exciton chirality rule and conformational analysis, this characteristic Cotton effect is consistent with the absolute configuration of 7S, 8R (Pescitelli, 2022), which is further confirmed by subsequent ECD calculations.

According to the SciFinder database, compound **1** was isolated as new natural products (Figure S2). In addition,

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Table 1. The NMR data[a] of compound **1**

Position	δ_C	δ_H (*J*, Hz)	HMBC
1	137.5		
2	112.5	7.07 (*d*, *J* = 2.1 Hz, 1H)	C-1,3,4,6,7
3	150.4		
4	147.3		
5	117.5	7.10 (*d*, *J* = 8.4 Hz, 1H)	C-1,3,4
6	120.9	6.91 (*dd*, *J* = 8.4, 2.1 Hz, 1H)	C-2,4,5,7
7	73.9	4.93 (*d*, *J* = 5.6 Hz, 1H)	C-1,2,6,8,9
8	87.2	4.43 (*td*, *J* = 5.4, 3.5 Hz, 1H)	C-1,4',7,9
9	61.8	3.92 (*dd*, *J* = 12.0, 5.1 Hz, 1H) 3.65 (*dd*, *J* = 12.0, 3.5 Hz, 1H)	C-7,8
1′	126.4		
2′	107.9	7.30 (*s*, 2H)	C-1′,3′,4′,6′,7′
3′	154.2		
4′	141.4		
5′	154.2		
6′	107.9	7.30 (*s*, 2H)	C-1′,2′,4′,5′,7′
7′	168.1		
3-OCH_3	56.7	3.83 (*s*, 3H)	C-3
5′-OCH_3	56.7	3.83 (*s*, 3H)	C-5′
3′-OCH_3	56.7	3.83 (*s*, 3H)	C-3′
7′-OCH_3	52.8	3.89 (*s*, 3H)	C-7′
1″	102.9	4.85 (*d*, *J* = 7.5 Hz, 1H)	C-4,5″
2″	74.9	3.48 (*m*, 1H)	C-1″,3″
3″	77.8	3.46 (*m*, 1H)	C-2″,4″
4″	71.3	3.39 (*m*, 1H)	C-5″,6″
5″	78.2	3.39 (*m*, 1H)	C-4″,6″
6″	62.5	3.69 (*m*, 1H) 3.87 (*d*, *J* = 1.9 Hz, 1H)	C-4″,5″

Note: [a] Measured in CD_3OD using a 600 MHz NMR instrument.

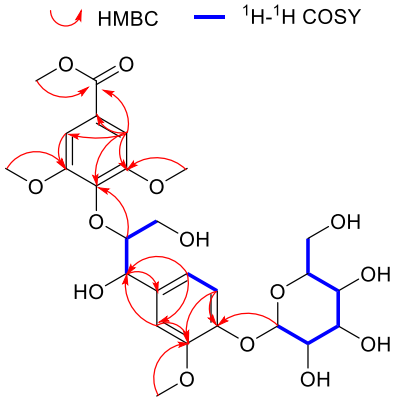

Figure 2. The key HMBC and ^{1}H-^{1}H COSY correlations of **1**

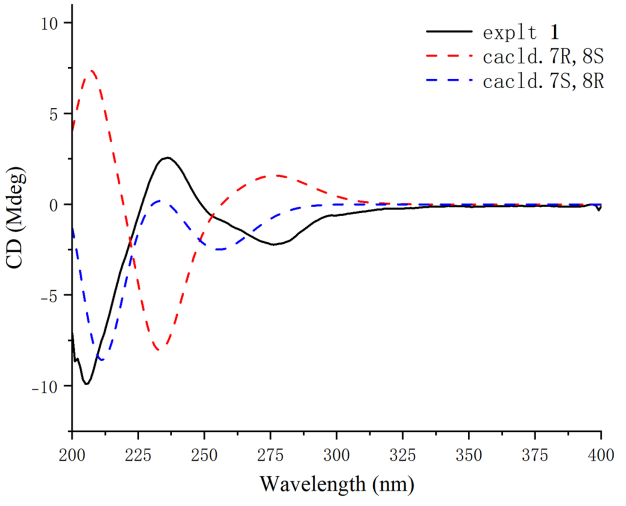

Figure 3. CD spectrum of compound **1**

compounds **2**–**4** were identified as pinoresinol (Wang et al., 2012), curlignan (Chang & Lee, 1998), ficusal (Li & Kuo, 2000).

Cytotoxicity assay (Zuo et al., 2025) results indicate that compound **1** exhibits no toxic effects on RAW 264.7 cells at a concentration of 15 μM (Figure 4). Therefore, three concentrations of 3.75, 7.5 and 15 μM were selected for follow-up anti-inflammatory assays using dexamethasone (DXM) at the concentration of 30 μM as a positive control (Liu

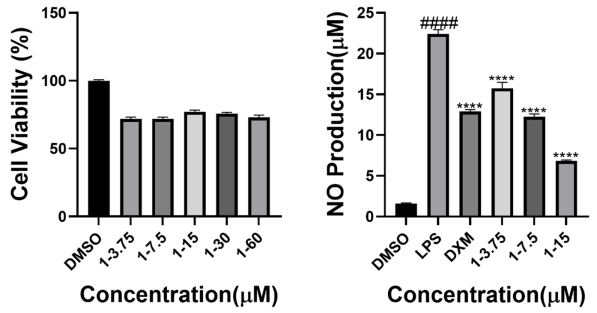

Figure 4. Cytotoxicity and NO production assay results of **1** in RAW 264.7 cells. A: Cell viability results for **1**. B: NO results for **1**. Data are expressed as the mean ± SD. $^{####}p < 0.0001$, compared with the normal control group. $^{*}p < 0.05$, $^{**}p < 0.01$ and ****p<0.0001, compared with the LPS group

et al., 2026; Zhang et al., 2026). The results demonstrated that compounds **1** at 3.75, 7.5, and 15 μM effectively and dose-dependently reduced nitric oxide (NO) levels in LPS-stimulated RAW 264.7 macrophages.

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Author Contributions

Xiang Guo: Writing—original draft, Investigation, Data curation, Li Huang: Investigation, Data curation. Li-Lian Zhao: Data curation. Jie Li: Data curation. Da-Le Guo: Supervision. Yu You: Supervision, Validation, Writing—review & editing, Funding acquisition.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

Supplementary data to this article can be found online at http://www.acgpubs.org/journals/records-of-natural-products.

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