SHORT REPORT

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An Undescribed Zhepiresionol Analogue from *Ailanthus altissima*

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Abstract: This study involved the extraction, isolation, structural elucidation of a new analogue of zhepiresionol, as well as five lignans previously identified, from the plant *Ailanthus altissima* (Mill.) Swingle. The structural elucidation was accomplished through comprehensive analyses of various spectroscopic data, which included HRESIMS, UV, IR, and NMR, along with a comparison of ECD curves. At a concentration of 15 μM, Compound **1** showed the capacity to suppress IL-1β and IL-6 expression in RAW 264.7 cells that were Lipopolysaccharide-stimulated.

Keywords: *Ailanthus altissima*; zhepiresionol analogue; anti-inflammatory activity.

1. Plant Source

The bark of *Ailanthus altissima* (Mill.) Swingle used in this study was obtained from Sichuan Neautus Pharmaceutical Co., Ltd. Additionally, Prof. Guang-Zhi Wang at Chengdu University of Traditional Chinese Medicine, certified the authenticity of these specimens. The sample has been assigned the designation 20240909/CDCM/SCA and is currently preserved in the plant specimen chamber at the Herbarium of Chengdu University of Traditional Chinese Medicine (CDCM).

2. Previous Studies

A. altissima belongs to the Simaroubaceae family, which comprises over 170 species and is distinguished by the presence of quassinoids [1]. Research into the phytochemicals of *A. altissima* has uncovered a variety of natural substances that exhibit unique structural characteristics, such as

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quassinoids [2], terpenoids [3], lignans [4], coumarins [5], alkaloids [6], and an assortment of other compounds [7].

3. Present Study

A total of 50 kg of dried bark from *A. altissima* was powdered and subjected to extraction three times at room temperature using 95% methanol. The extract was then dried under reduced pressure, resulting a crude extract with a weight of 2.75 kg. The extract was fractionated on a normal-phase silica gel column (200-300 mesh). Initial elution with a petroleum ether and ethyl acetate gradient (30:1 to 4:1, v/v) removed lipid-soluble components. Subsequent gradient elution with dichloromethane and methanol (1:0 to 0:1, v/v) yielded 17 fractions (Fr.1 to Fr.17).

Fr.4 (75.67 g) was initially separated by normal-phase silica gel column chromatography using a gradient elution of petroleum ether and acetone (15:1 to 0:1), yielding ten fractions (Fr.4.1 to Fr.4.10). Subsequently, Fr.4.5 (23.0 g) and Fr.4.6 (4.86 g) were further purified by Sephadex LH-20 column chromatography with dichloromethane and methanol (1:1) as the mobile phase, resulting in five subfractions (Fr.4.5.1 to Fr.4.5.5) and nine subfractions (Fr.4.6.1 to Fr.4.6.9), respectively. Fr.4.5.5 (90.0 mg) was then purified utilizing semi-preparative HPLC with a solvent composition of methanol and water (38:62), resulting in compound **6** (2.3 mg, t_R = 32.5 min). In parallel, Fr.4.6.8 (148 mg) underwent semi-preparative HPLC (methanol-water, 48:52), yielding compound **2** (3.4 mg, t_R = 8.2 min). Fr.4.6.9 (175 mg) was separation and purified (methanol-water, 43: 57) by semi-preparative HPLC to obtain compound **4** (1.3 mg, t_R =29.7 min). Fr.4.8 (8.27 g) was eluted with dichloromethane and methanol (1:1) to give seven fractions (Fr.4.8.1 to Fr.3.8.7). Fr.4.8.4 (842.4 mg) was further purified by semi-preparative HPLC (methanol-water, 35∶65) to isolate compound **5** (22 mg, t_R =30.0 min).

Fr.5 (248.03 g) was subjected to normal-phase silica gel column chromatography using a mobile phase of dichloromethane and methanol (10:0 to 9:1) for elution, yielding ten fractions (Fr.5.1 to Fr.5.10). Fr.5.4 (57.05 g) was further separated by reversed-phase C18 column chromatography with methanol and water (60: 40) as the elution solvent, resulting in six subfractions (Fr.4.4.1 to Fr.4.4.6). Fr.5.4.1 (2.01 g) was purified via Sephadex LH-20 chromatography (dichloromethane-methanol, 1:1), affording seven fractions (Fr.5.4.1.1 to Fr.5.4.1.7). Fr.5.4.1.3 was further fractionated by normal-phase column chromatography (dichloromethane-methanol, 1:0 to 0:1), resulting in five subfractions (Fr.5.4.1.3.1 to Fr.5.4.1.3.4). Fr.5.4.1.3.1 (882.3 mg) was separated by semi-preparative HPLC, yielding twelve fractions (Fr.5.4.1.3.1.1 to Fr.5.4.1.3.1.12). Fr.5.4.1.3.1.1was further purified (methanol-water, 20:80) to obtain compound **1** (3.5 mg, t_R = 39.5 min). Fr.5.4.1.3.1.2 was further purified (methanol-water, 24:76) to yield compound **3** (5.0 mg, t_R = 49.9 min). The structures of the compounds are shown in Figure **1**.

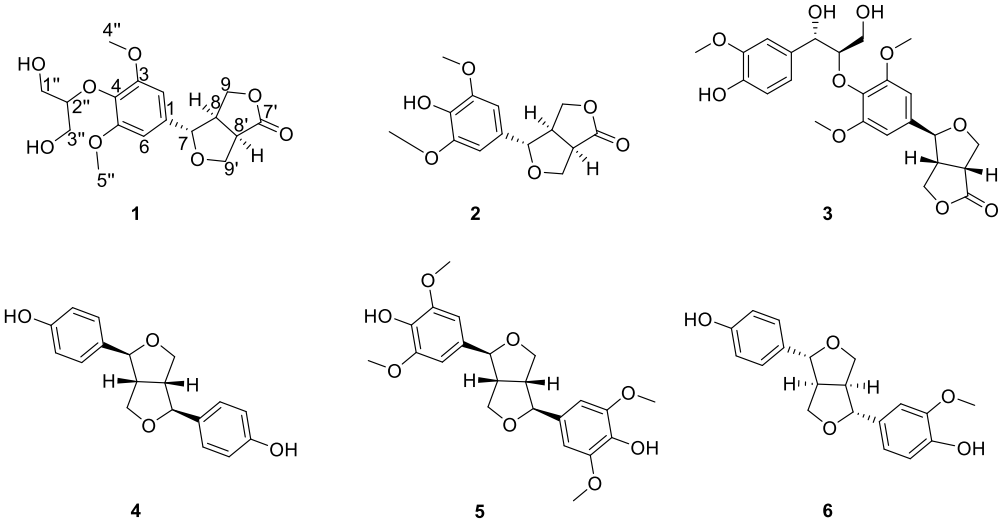

Figure 1. Structure of compounds **1-6**

*Compound **1**:* colorless oil; $[\alpha]_D^{20}$ = -8.63 (*c* = 0.139, MeOH); UV (MeOH) λ_{max} 207 (2.70), 227 (0.46); IR (KBr): 3442, 2944, 2885, 1766, 1595, 1507, 1461, 1420, 1379, 1333, 1235, 1129, 1036 cm^{-1}; CD (c 0.56 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 211(-1.60) , 224 （-0.88） nm; HRESIMS *m/z* 355.1373 $[M+H]^+$ (calcd. For $C_{17}H_{23}O_8$, 355.1388); For ^{1}H-NMR, ^{13}C-NMR data see Table 1.

Compound **1** was identified as a colorless oil. Its molecular formula was established as $C_{17}H_{22}O_8$, with seven degrees of unsaturation at *m/z* 355.1373 $[M+H]^+$ (calcd. 355.1388). The infrared (IR) spectrum displayed absorption bands typical of hydroxyl (3442 cm^{-1}), methyl (2944 cm^{-1} and 2885 cm^{-1}), and carbonyl (1766 cm^{-1}) groups. An extensive evaluation of the ^{1}H NMR, ^{13}C NMR (refer to Table 1), and HSQC spectra of compound **1** demonstrated the identification of one carbonyl group; an aromatic ring; four oxygenated methylene signals; four methine signals; and two methoxy groups. The ^{1}H-^{1}H COSY correlations of H-7/H-8/H-9, of H-8/H-8'/H-9', and of H-1"/H-2"/H-3", in addition to the HMBC correlations from H-4" to C-3, H-5" to C-5, H-2" to C-4, from H-6 to C-1, C-4, C-5, and C-7, from H-7 to C-9" as well as from H-9, H-8" to C-7" established the planar structure of compound **1**, which is a benzene-reducing lignin containing a dioxabicyclo[3.3.0]octan-2-one moiety, as illustrated in Figure 2.

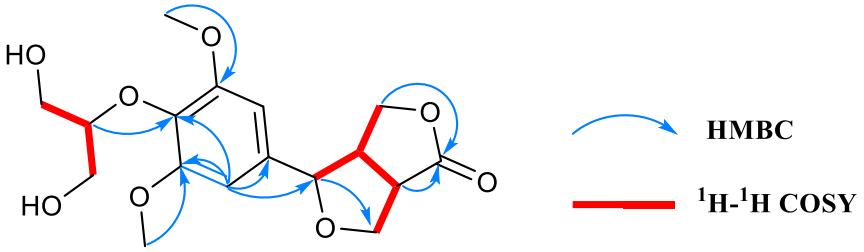

Figure 2. The key ^{1}H-^{1}H COSY, HMBC correlations of **1**

The relative configuration of compound **1** was determined as 7*R**,8*S**,8"*S** based on NOESY correlations (Figure **3**) between H-7 and H-9a, as well as NOESY coupling signals between H-8 and H-8"/H-9b.

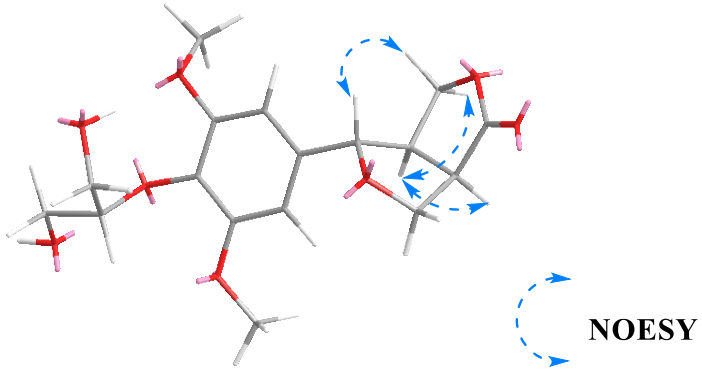

Figure 3. The key NOESY correlations of **1**

In order to confirm the absolute configuration of compound **1**, both measurements and calculations of ECD were performed [8-9]. The results revealed a significant alignment between the calculated ECD curve for 7R, 8S, 8"S-1 and the experimental curve associated with compound 1 (Figure 4), thus validating the absolute configuration of **1**.

Table 1. ^{1}H (700 MHz) and ^{13}C NMR (175 MHz) Data for compound **1** in CD_3OD.

pos	δ_C, type	δ_H (*J* in Hz)
1	137.6, C	
2	104.3, CH	6.75, s
3	154.8, C	
4	136.7, C	
5	154.8, C	
6	104.3, CH	6.75, s
7	87.6, CH	4.75, d, *J* = 6.4 Hz
8	49.8, CH	3.22, dtd, *J* = 8.9, 6.7, 2.1 Hz
9	71.9, CH_2	4.57, dd, *J* = 9.6, 6.8 Hz 4.46, dd, *J* = 9.7, 2.0 Hz
7'	180.9, C	
8'	47.6, CH	3.57, td, *J* = 8.7, 3.4 Hz
9'	71.3, CH_2	4.34, dd, *J* = 9.2, 8.3 Hz 4.14, dd, *J* = 9.1, 3.4 Hz
1"	62.1, CH_2	3.76, dd, *J* = 5.0, 0.9 Hz
2"	84.8, CH	4.01, p, *J* = 5.0 Hz
3"	62.1, CH_2	3.76, dd, *J* = 5.0, 0.9 Hz
4"	56.7, CH_3	3.88, s
5"	56.7, CH_3	3.88, s

To the best of our knowledge, Compound **1**, along with Compounds **2** and **3**, contains a 3,7-dioxabicyclo[3.3.0]octan-2-one moiety, which is reported here for the first time in the genus *Ailanthus*.

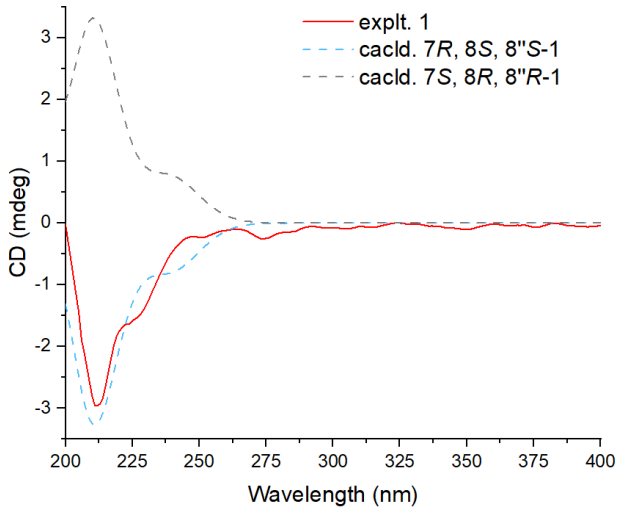

Figure 4. Comparison of the calculated ECD spectra with the experimental spectra of **1** in CH_3OH

In addition, compounds **2-6** were identified as zhebeiresinol [10], forsysesquinorlignan [11], (+)-(1R, 2S, 5R, 6S)-2, 6-di(4'-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0]octane [12], (+)-syringaresinol [13], and (1R, 2S, 5R, 6S)-2-(4-hydroxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3, 7-dioxabicyclo [3.3.0]octane [14] by comparing NMR spectroscopic data with relevant literature sources.

In a series of anti-inflammatory assays [15], it was observed that gene (IL-1β, IL-6) expression were markedly reduced in RAW 264.7, with the lipopolysaccharide stimulation at a concentration of 15 μM (see Figure 5).

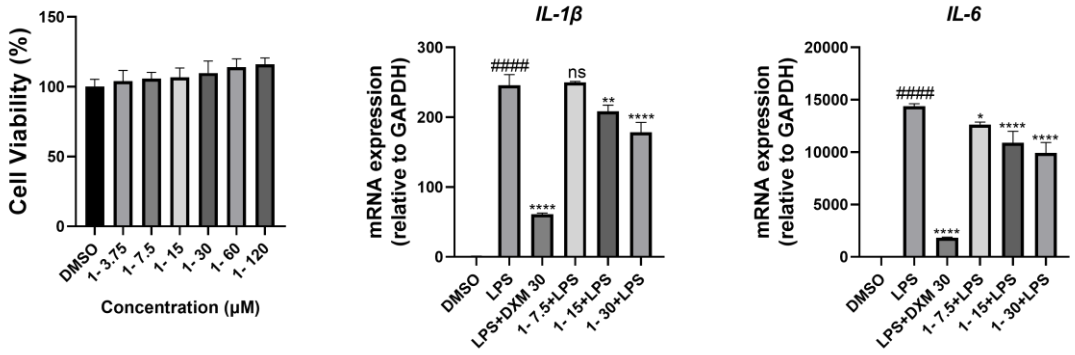

Figure 5. Anti-inflammatory assay of **1** using macrophages RAW 264.7.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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