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A Novel Monoterpenoid Derivative Isolated from *Chloranthus serratus* Roots with Anti-inflammatory Activity

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Abstract: Eight compounds were isolated from the 95% ethanol extract of *Chloranthus serratus* roots, including two monoterpenoid derivatives (**1**, **2**), one pimarane-type diterpenoid (**3**), and five labdane-type diterpenoids (**4**-**8**). Compound **1** was identified as a previously undescribed camphene derivative, while compound **3** was a new natural product. Their structures and relative configurations were elucidated using HR-MS, NMR and ECD calculations. Compounds **1**, **2**, **5** significantly inhibited nitric oxide (NO) production in lipopolysaccharide (LPS)-induced RAW 264.7 cells, with IC_{50} values of 17.47±1.24, 14.92±1.17, and 30.48±1.48 μM, respectively.

Keywords: *Chloranthus serratus*; monoterpenoid; anti-inflammatory activity.

1. Plant Source

The roots of *Chloranthus serratus* were collected in Guiyang, Guizhou Province, People′s Republic of China, in November 2023. The plant material was authenticated by Prof. Ji-Xin Li from Guizhou University of Traditional Chinese Medicine. A voucher specimen (NO. 20231101) has been deposited at Anhui University of Chinese Medicine

2. Previous Studies

Chloranthus serratus (Chloranthaceae; *Chloranthus* genus) thrives in humid montane understories and streamside grasslands at elevations of 280–1800 m, with a wide distribution across southwestern and southeastern China [1]. In traditional medicine, it has been extensively used to treat traumatic injuries, rheumatic lumbago, leg pain, furuncles, abscesses, and venomous snake bites [2]. Lindenane-type sesquiterpenoids and their polymers are characteristic components of *Chloranthus* species, exhibiting significant anti-inflammatory, antitumor, and neuroprotective activities [3,4]. In addition to these compounds, *Chloranthus* plants contain diterpenoids, coumarins, and minor phenolic acids [5]. Compared to well-studied species such as *C. henryi*, *C. japonicus*, and *C. spicatus*, research on *C. serratus* remains relatively limited, potentially due to concerns regarding its hepatotoxicity [6].

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Nevertheless, its notable anti-inflammatory properties have facilitated clinical applications and sustained research interest[2,7-9]. Previous phytochemical investigations of *C. serratus* have revealed that while lindenane-type sesquiterpenoids are not predominant, eudesmane-type sesquiterpenoids [10] and labdane-type diterpenoids [11] are relatively abundant. To investigate the anti-inflammatory constituents of *C. serratus*, we isolated eight terpenoids from its 95% ethanol extract (Figure 1) and evaluated their anti-inflammatory activity.

3. Present Study

The air-dried roots of *Chloranthus serratus* (9.6 kg) were powdered and extracted three times with 95% EtOH under reflux (2 h × 3). The combined filtrate was concentrated under reduced pressure to yield a crude extract (256g). The extract was fractionated by silica gel column chromatography using a CH_2Cl_2–CH_3OH gradient (1:0–0:1, v/v) to obtain seven major fractions (A–K). Fraction B (19 g) was further separated by ODS column chromatography (CH_3OH–H_2O, 20:80–100:0) to afford 17 subfractions (B1–B17). Subfractions B8 and B9 (157.8 mg) were subjected to silica gel chromatography (petroleum ether–EtOAc, 25:1–1:1) followed by preparative HPLC (CH_3CN–H_2O, 65:35, 35 min) to yield compounds **4** (16.04 mg), **5** (6.41 mg), **6** (2.55 mg), **7** (6.09 mg), and **8** (3.10 mg). Subfraction B14 (43.0 mg) was purified by Sephadex LH-20 (CH_3OH) and preparative HPLC (CH_3CN–H_2O, 75:25, 33 min) to afford compounds **1** (7.60 mg) and **2** (58.01 mg). Subfraction B17 (103 mg) was processed through Sephadex LH-20 (CH_3OH) and preparative HPLC (CH_3CN–H_2O, 90:10-95:5, 48 min) to obtain compound **3** (3.13 mg).

Chloronin A (**1**): colorless oil; $[\alpha]_D^{24}$ +10° (c 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 312 (3.80) nm; ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 311 (−10.6) nm; ^{1}H and ^{13}C NMR data, see Table 1; HR-ESI-MS *m/z* 299.1662 $[M-H]^-$ (calcd. for $C_{19}H_{23}O_3$, 299.1647).

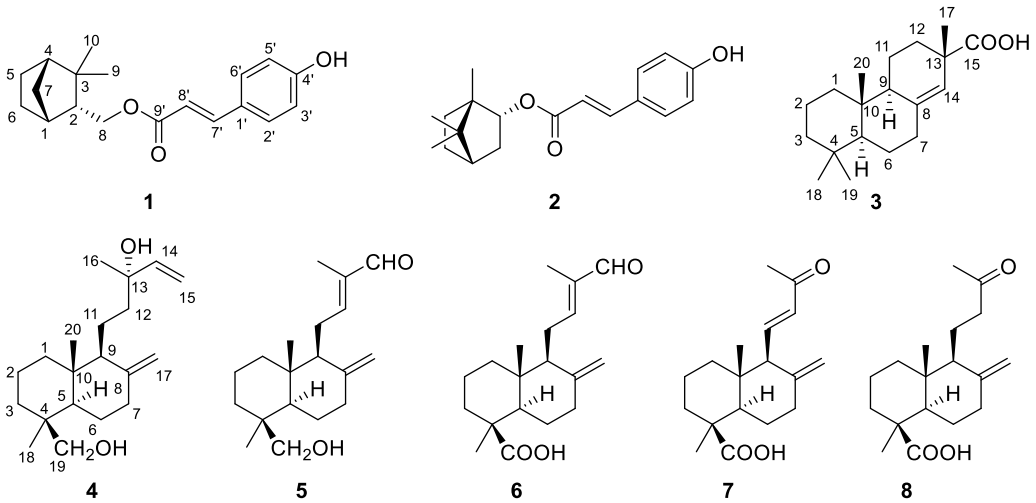

Figure 1. Structures of compounds **1-8**

Compound **1** was obtained as a colorless oil. Its molecular formula was determined as $C_{19}H_{24}O_3$ by HR-ESI-MS (*m/z* 299.1662 $[M-H]^-$, calcd for $C_{19}H_{23}O_3$, 299.1647), corresponding to eight degrees of unsaturation. The ^{1}H NMR spectrum of **1** (Table 1) revealed signals characteristic of an *ortho*-substituted benzene ring (δ_H 7.43, 2H, d, J = 8.6 Hz; 6.85, 2H, d, J = 8.6 Hz), a pair of *trans*-olefinic protons (δ_H 7.61, 1H, d, J = 16.0 Hz; 6.28, 1H, d, J = 16.0 Hz) , an oxygenated methylene (δ_H 4.20, 2H, m), and two methyl singlets (δ_H 1.03, 3H, s; 0.91, 3H, s). The ^{13}C NMR and HSQC spectra displayed 17 carbon signals, including two methyls, four methylenes (one oxygenated at δ_C 63.8), seven methines (four olefinic at δ_C 144.4, 130.1, 116.0, 116.0), and four quaternary carbons (a ester carbonyl at δ_C 167.8 and two olefinic at δ_C 157.8, 127.5). These data suggested the presence of a *p*-hydroxy-cinnamoyl moiety (δ_C 167.8, 157.8, 144.3, 130.1, 127.5, 116.0, 116.0), identical to that of the known compound pressafonin-A (**2**)[12]. This assignment was further supported by the HMBC

correlations (Figure 2) from H-7′ (δ_H 7.61) to C-1′ (δ_C 127.5), C-2′ (δ_C 130.1), C-9′ (δ_C 167.8), as well as from H-3′ (δ_H 6.85) to C-1′ and C-4′ (δ_C 157.8). Excluding the cinnamoyl group, the remaining C_{10} fragment with two degrees of unsaturation implied a bicyclic monoterpenoid structure. The spin systems (H-7/H-4/H-5/H-6/ H-1/H-2/H-8) observed in the ^{1}H-^{1}H COSY spectrum, along with the HMBC correlations from Me-10 (δ_H 1.03) to C-2 (δ_C 49.0), C-3 (δ_C 37.2), C-4 (δ_C 49.3), C-9 (δ_C 20.9), and from H-8 (δ_H 4.20) to C-1 (δ_C 40.6), C-2, and C-3, suggested a monoterpenoid scaffold closely resembling camphanol group, the aglycone of shionoside A [13]. Thus, compound **1** consists of two structural units: a camphanol group and a *p*-hydroxy-cinnamoyl group, linked via C-8 (as evidenced by the HMBC correlation between H-8 and C-9′). The structure of **1** was thereby elucidated as depicted in Figure 1 and designated chloronin A.

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data of **1** ($CDCl_3$, *J* in Hz)

No	δ_H (*J* in Hz)	δ_C
1	2.27, br s	40.6
2	1.80, m*	49.0
3		37.2
4	1.79, m*	49.3
5*α*	1.31, m*	24.7
5*β*	1.62, m	
6*α*	1.31, m*	20.7
6*β*	1.39, m	
7a	1.23, br d (9.7)	37.4
7b	1.68, br d (9.7)	
8	4.20, m	63.8
9	0.91, s	20.9
10	1.03, s	32.6
1′		127.5
2′	7.43, d (8.6)	130.1
3′	6.85, d (8.6)	116.0
4′		157.8
5′	6.85, d (8.6)	116.0
6′	7.43, d (8.6)	130.1
7′	7.61, d (16.0)	144.4
8′	6.28, d (16.0)	116.0
9′		167.8

*overlapped

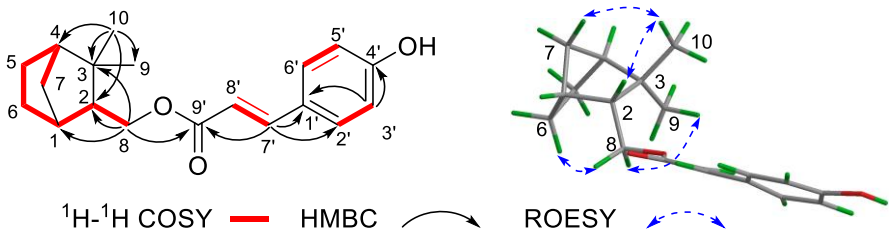

Figure 2. Key 2D NMR correlations of compounds **1**

In the ROESY spectrum, the cross-peaks of H-8/Me-9/H-6*α* suggested that these protons were on the same side, assigned as *α*-orientation. Similarly, Me-10, H-2 and H-7b were established as *β*-oriented by the cross-peaks of H-2/Me-10/H-7b. Given the chemical shifts of C-9 (δ_C 20.4) and C-10 (δ_C 30.5) reported for *endo*-camphanol in the literature [11], the camphanol fragment in compound **1**

was determined to adopt the *endo* configuration. Furthermore, the absolute configurations of **1** was assigned as 1*R*, 2*R*, 4*S* by ECD calculations (Figure 3).

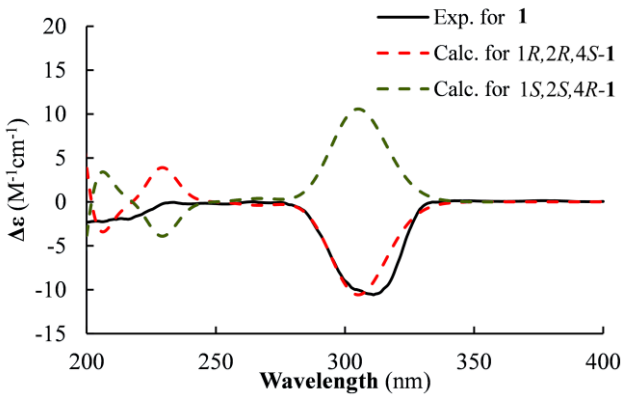

Figure 3. Experimental and computational ECD spectra of chloronin A (**1**)

Additionally, seven known compounds were isolated and identified as pressafonin-A (**2**)[12], (5*S*,9*R*,10*S*,13*S*)-16-norpimar-8(14)-en-15-oic acid (**3**)[14], 13-*epi*-torulosol (**4**)[15], 5-nor-14-oxolabda-8(17),12*E*-dien-19-ol (**5**)[16], 15-nor-14-oxolabda-8(17),12*E*-dien-19-oic acid (**6**)[16], 15,16-bisnor-13-oxo-8(17),11*E*-labdadien-19-oic acid (**7**)[17], 14,15-dinor-13-oxo-8(17)-labden-19-oic acid (**8**)[18], and compound **3** was a new natural product.

In this study, all compounds were evaluated for their inhibitory effects on NO production in LPS-stimulated RAW264.7 macrophages, using L-NMMA as a positive control (IC_{50} = 45.70±1.33 μM). Among the tested compounds, **1**, **2**, and **5** demonstrated significant anti-inflammatory activity, with IC_{50} values of 17.47±1.24, 14.92±1.17, and 30.48±1.48 μM, respectively.

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Supporting Information

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