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Saururus chinensis

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Further Lignans from *Saururus chinensis*

Authors

Xiu Gao^{1,2}, Juan He¹, Xing-De Wu¹, Li-Yan Peng¹, Liao-Bin Dong^{1,2}, Xu Deng¹, Yan Li¹, Xiao Cheng¹, Qin-Shi Zhao¹

Affiliations

¹ State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming, People's Republic of China

² University of Chinese Academy of Sciences, Beijing, People's Republic of China

Key words

- *Saururus chinensis*
- Saururaceae
- lignans
- anti-inflammatory

Abstract

Three new sauchinone analogues, sauchinones B–D (1–3), together with sauchinone (4), were isolated from the aerial part of *Saururus chinensis*. Structures of the new compounds were determined by extensive spectroscopic data as well as X-ray analysis. Compounds 3 and 4 inhibited ni-

tric oxide production in lipopolysaccharide stimulated RAW 264.7 cells with IC₅₀ values of 13.0 and 14.2 μM, respectively.

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Introduction

Saururus chinensis (Lour.) Baill. (Saururaceae), a perennial herb widely distributed in China and southern Korea [1], has been used as folk medicine for the treatment of inflammation, jaundice, and gonorrhoea [2]. Previous chemical studies of *S. chinensis* have demonstrated the presence of lignans [3], aristolactams [4], flavonoids [4], furanoditerpenes [5], and C₁₃-norisoprenoids [6]. To date, a lot of lignans were isolated from *S. chinensis*, some of which exhibited diverse pharmacological effects including anti-inflammatory [5], hepatoprotective [6], antidiabetic [7], and antioxidant activities [8]. Among them, sauchinone, a known lignan with a unique structure (4), has attracted extensive interest because of its various activities such as attenuating oxidative stress-induced skeletal muscle myoblast damage through the downregulation of ceramide [9], reducing tumor necrosis factor- α production through the inhibition of c-raf/MEK1/2/ERK 1/2 pathway activation [10], and ameliorating allergen-induced airway inflammation, in part, by repressing GATA-3 activity for Th2 cell development [11]. Until now, only four sauchinone analogues (sauchinone (4) [12], sauchinone A, 1'-*epi*-sauchinone [13], and *ent*-sauchinone [14]) have been reported.

As part of our effort to discover naturally bioactive metabolites from the traditional medicine, a phytochemical investigation of the aerial parts of *S. chinensis* was carried out, which resulted in the

isolation of three new sauchinone analogues, sauchinones B–D (1–3) and the known compound sauchinone (4) (○ Fig. 1). Among them, compounds 3 and 4 showed nitric oxide production inhibition in lipopolysaccharide-stimulated RAW 264.7 cells. Reported herein are the isolation, structure elucidation, and nitric oxide (NO) production inhibition of the isolates.

Results and Discussion

The acetone extract of the aerial part of *S. chinensis* was partitioned between EtOAc and water. The EtOAc fraction was repeatedly subjected to column chromatography over silica gel, reverse-phase gel, and Sephadex LH-20, and subsequently recrystallized to afford three new sauchinone analogues, sauchinones B–D (1–3) (○ Fig. 1), together with the known compound sauchinone (4).

Sauchinone B (1), colorless crystals, had a molecular formula of C₂₀H₂₀O₇ as established on the basis of HREIMS at *m/z* 372.1205 [M]⁺ (calcd. 372.1209). Its IR spectrum showed the absorption bands of hydroxyl (3546 cm⁻¹), methylenedioxy (2916 cm⁻¹), conjugated carbonyl (1678 cm⁻¹), and aromatic ring (1651 and 1438 cm⁻¹) functionalities. The 1D NMR spectra (○ Table 1) displayed the presence of two aromatic protons (δ_{H} 6.48, 1H, s, H-3; δ_{H} 7.09, 1H, s, H-6), two methylenedioxy groups [δ_{C} 102.5, t, C-1" (δ_{H} 6.00, 5.98,

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Correspondence

Prof Qin-Shi Zhao
State Key Laboratory of Phytochemistry and Plant Resources in West China
132 Lanhei Road
Kunming 650201
P.R. China
Phone: + 86 871 6522 3058
Fax: + 86 871 6521 5783
qinshizhao@mail.kib.ac.cn

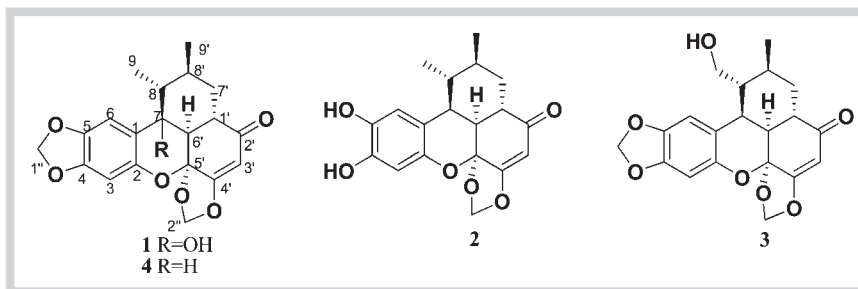


Fig. 1 Chemical structures of compounds 1–4 isolated from *S. chinensis*.

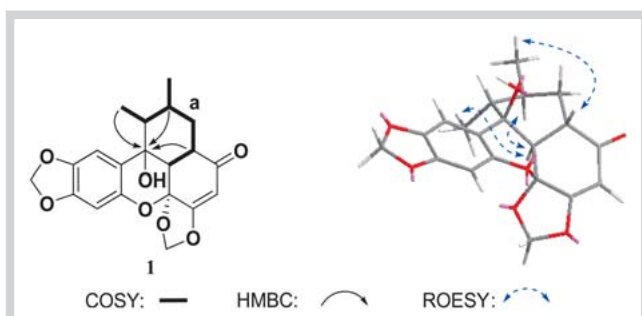


Fig. 2 Key 2D NMR correlations and X-ray structure of compound 1. (Color figure available online only.)

each 1H, s, H₂-1'"); δ_C 99.7, t, C-2'' (δ_H 5.80, 5.70, each 1H, s, H₂-2''), an enone group [δ_C 197.9, s, C-2'; δ_C 100.3, d, C-3' (δ_H 5.44, 1H, s, H-3'); δ_C 169.2, s, C-4'], and two secondary methyl groups [δ_C 17.2, q, C-9 (δ_H 1.25, 3H, d, J = 7.3 Hz, H₃-9); δ_C 20.7, q, C-9' (δ_H 0.58, 3H, d, J = 7.6 Hz, H₃-9')]. Detailed 2D NMR data analysis (► **Fig. 2**) indicated that **1** was a sauchinone analogue. The only difference was that **1** had one more hydroxy group which was connected to C-7 as deduced from the HMBC correlations of H-6 (δ_H 7.09, 1H, s), H-9 (δ_H 1.25, 3H, d, J = 7.3 Hz), H-6' (δ_H 2.64, 1H, d, J = 12.5 Hz), and H-8' (δ_H 2.02, m) with C-7 (δ_C 69.0, s).

The relative configurations of compound **1** were determined by a ROESY experiment (► **Fig. 2**). The ROESY correlations of H-8/Me-9', H-1'/Me-9', and Me-9/H-6' suggested that the relative configurations of H-8, H-1', H-6', and H-8' should be β , β , α , and α , respectively. To establish the configurations of C-7 and C-5', a single-crystal X-ray structure determination was undertaken (► **Fig. 3**) which ultimately established the structure of com-

ound **1** and the α -orientation of OH-7. Thus, the structure of **1** was concluded as 7 α -hydroxy-sauchinone, and the compound was named sauchinone B.

Compound **2** was isolated as colorless crystals. The molecular formula was determined as C₁₉H₂₀O₆ on the basis of HREIMS. The IR absorption bands at 3421, 2957, and 1639 cm⁻¹ indicated the presence of hydroxy, methylenedioxy, and carbonyl functionalities, respectively. The carbonyl band was almost 30 cm⁻¹ shifted compared to that of **1** due to an intramolecular hydrogen bond (see below). The ¹H and ¹³C NMR spectra of **2** resembled closely those of sauchinone. The sole difference was that **2** had only one methylenedioxy group, which was connected to C-4' and C-5' as deduced from the HMBC correlations of δ_H 5.76 (s, H-2'') and 5.68 (s, H-2'') with δ_C 169.7 (s, C-4') and 100.9 (s, C-5'). The ROESY correlations of H-7/H-9, H-7/H-6', and H-9'/H-1' demonstrated that H-7, H-9, and H-6' were β -oriented and H-9' and H-1' were α -oriented, which was confirmed by X-ray analysis (► **Fig. 3**). The X-ray determination also confirmed the existence of intramolecular H-bonding in **2**. Therefore, the structure of compound **2** was designated, and the compound was named sauchinone C.

Compound **3**, colorless powder, had a molecular formula of C₂₀H₂₀O₇ as deduced from the HREIMS (m/z 372.1210 [M]⁺, calcd. 372.1209). The ¹H and ¹³C NMR spectra showed signals for 20 carbons due to one methyl, four methylenes (two methylenedioxy groups, one oxygenated methylene), eight methines, and seven quaternary carbons. The above data suggested that compound **3** was a sauchinone analogue. The only difference was that the Me-9 in sauchinone was replaced by a hydroxymethyl in **3** as inferred from the HMBC correlations of δ_H 3.69 (2H, d, J = 7.5 Hz, H-9) with δ_C 30.0 (C-7, CH), 26.5 (C-8, CH), and 28.9 (C-8', CH). The ROESY correlations of H-7/H-9, H-7/H-6', and H-9'/H-1' indicated

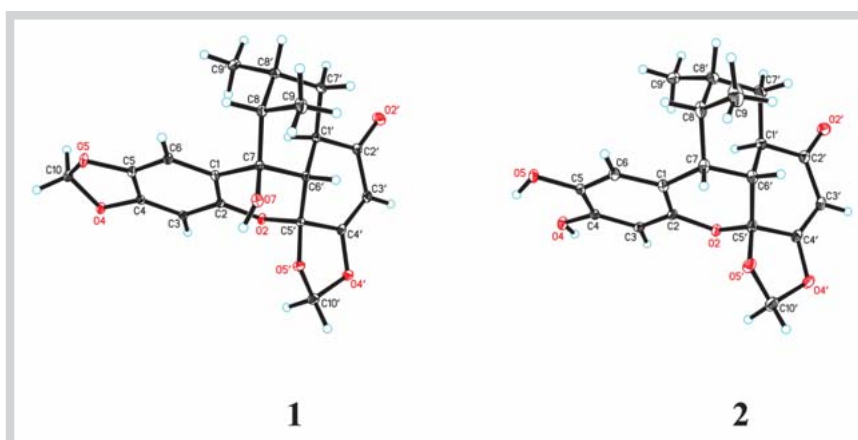


Fig. 3 X-ray structures of compounds 1 and 2. (Color figure available online only.)

that **3** had the same relative configuration as sauchinone. Therefore, compound **3** was designated as sauchinone D.

Considering the medical applications of *S. chinensis*, all isolates (purity >95%) from this plant material were evaluated for their inhibitory effects on NO release in the LPS-stimulated RAW 264.7 macrophage cell line and their cytotoxicity activity. The results showed that compounds **3** and **4** displayed NO production inhibitory activity with IC₅₀ values of 13.0 and 14.2 μM, respectively. However, none of them exhibited cytotoxic activity.

Materials and Methods

General experimental procedures

Melting points were obtained on an X-4 micromelting point apparatus. Optical rotations were measured on a JASCO-20C digital polarimeter. IR spectra were obtained on a Tensor 27 spectrometer with KBr pellets. UV spectra were recorded using a Shimadzu UV-2401A spectrophotometer. 1D and 2D NMR spectra were performed on DRX-500 and Avance III-600 spectrometers with TMS as an internal standard. Mass spectra were taken on a VG Auto Spec-3000 or API-Qstar-Pulsar instrument. X-ray diffraction was performed on a Bruker APEX DUO diffractometer using graphite-monochromated Mo K α radiation. Column chromatography (CC) was performed using silica gel (100–200 and 200–300 mesh; Qingdao Marine Chemical Co. Ltd.), MCI reverse-phase gel (75–150 μm; Mitsubishi Chemical Corporation), and Sephadex LH-20 (Amersham Pharmacia Biotech). TLC analysis was run on GF254 silica gel plates (10–40 μm; Qingdao).

Plant material

The aerial part of *S. chinensis* was collected in BoZhou, Anhui Province, People's Republic of China, in May 2010, and the plant was identified by Prof. Xiao Cheng. A voucher specimen (200908 M) was deposited with 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 and leaves of *S. chinensis* (20 kg) were extracted with acetone (3 × 100 L), each for 48 h, at room temperature and concentrated under reduced pressure to give the crude extract. The extract was partitioned between H₂O and EtOAc. The EtOAc portion (737 g) was chromatographed on silica gel column (4 kg, 100–200 mesh, 10 × 200 cm) eluting with a gradient of petroleum ether-acetone (1 : 0, 9 : 1, 8 : 2, 7 : 3, 3 : 2, and 0 : 1) to then afford three fractions (fr. A–D). Fraction A (80 g) was chromatographed on silica gel column (300 g, 100–200 mesh, 5 × 60 cm) eluting with a gradient of petroleum ether-EtOAc (from 90 : 10 to 80 : 20) to afford **4** (12 g). Fraction B (128 g) was fractionated by MPLC (MCI reverse-phase gel 15.0 × 110.0 cm, 1 kg) eluting with MeOH-H₂O (from 30% to 100%) to provide five subfractions (B₁–B₅). Subfraction B₂ (12 g) was chromatographed repeatedly over silica gel CC (200–300 mesh, 3 × 50 cm), eluting with CHCl₃-Me₂CO (50 : 1) to afford B_{2.1}–B_{2.3}. Subfraction B_{2.2} was recrystallized to afford **1** (45 mg). Subfraction B_{2.3} (235 mg) was chromatographed over silica gel CC (20 g, 200–300 mesh 1 × 40 cm) and eluted with petroleum ether-EtOAc (7 : 3) to afford **2** (4 mg). Subfraction B₃ (23 g) was chromatographed over silica gel CC (200–300 mesh, 4 × 50 cm), eluting with CHCl₃-Me₂CO (from 50 : 1 to 95 : 5) and then by Sephadex LH-20 (1.0 × 150 cm, MeOH, 500 mL) to give **3** (8 mg).

Isolates

Sauchinone B (1): colorless crystal; mp 155–158 °C; [α]_D²⁵ – 45 (c 0.08, MeOH); UV (MeOH) λ_{\max} (log ϵ): 296 (2.98), 240 (3.47); IR (KBr) ν_{\max} 3546, 2916, 1678, 1651, 1504, 1438, 1307, 1280, 1207, 1182, 1109 cm⁻¹; ¹H and ¹³C NMR data, see **Table 1**; positive ESIMS *m/z* 395 [M + Na]⁺; HREIMS *m/z* 372.1205 [M]⁺ (calcd. for C₂₀H₂₀O₇, 372.1209).

Crystal data for sauchinone B (1): C₂₀H₂₀O₇, *M* = 372.36; orthorhombic, space group *P*2₁2₁2₁; *a* = 10.7319 (9) Å, *b* = 11.1595 (10) Å, *c* = 14.0422 (12) Å, α = 90.00, β = 90.00, γ = 90.00, *V* = 1681.7 (3) Å³, *Z* = 4, μ (MoK α) = 0.112 mm⁻¹, a crystal dimension of 0.62 × 0.48 × 0.44 mm was used for measurement on a Bruker APEX DUO diffractometer using graphite-monochromated Mo K α radiation. The total number of reflections measured was 17912, of which 4779 were observed, *I* > 2 σ (*I*). Final indices: *R*₁ = 0.0289, *wR*₂ = 0.0773. Crystallographic data for the structure of **1** have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 930553). Copies of the data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk.

Sauchinone C (2): colorless crystal; mp 150–153 °C; [α]_D²⁵ – 76 (c 0.08, MeOH); UV (MeOH) λ_{\max} (log ϵ): 296.5 (2.1), 240.5 (3.5); IR (KBr) ν_{\max} 3427, 2957, 2923, 2854, 1708, 1639, 1551, 1411, 1273, 1187, 1102, 1046 cm⁻¹; ¹H and ¹³C NMR data, see **Table 1**; positive ESIMS *m/z* 367 [M + Na]⁺; HREIMS *m/z* 344.1262 [M]⁺ (calcd. for C₁₉H₂₀O₆, 344.1260).

Crystal data for sauchinone C (2): C₁₉H₂₀O₆ · H₂O, *M* = 362.37; orthorhombic, space group *P*2₁2₁2₁; *a* = 8.1498 (10) Å, *b* = 11.7904 (14) Å, *c* = 17.831 (2) Å, α = 90.00, β = 90.00, γ = 90.00, *V* = 1713.3 (4) Å³, *Z* = 4, μ (MoK α) = 0.107 mm⁻¹, a crystal dimension of 0.30 × 0.12 × 0.11 mm was used for measurement on a Bruker APEX DUO diffractometer using graphite-monochromated Mo K α radiation. The total number of reflections measured was 16946, of which 4261 were observed, *I* > 2 σ (*I*). Final indices: *R*₁ = 0.0403, *wR*₂ = 0.0776. Crystallographic data for the structure of **2** have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 930554). Copies of the data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk.

Sauchinone D (3): colorless powder; [α]_D²⁵ – 33 (c 0.01, MeOH); UV (MeOH) λ_{\max} (log ϵ): 296.5 (2.52), 240.5 (2.96); IR (KBr) ν_{\max} 3433, 2923, 1638, 1482, 1410, 1273, 1188, 1156, 1102, 1046 cm⁻¹; ¹H and ¹³C NMR data, see **Table 1**; positive ESIMS *m/z* 395 [M + Na]⁺; HREIMS *m/z* 372.1210 [M]⁺ (calcd. for C₁₉H₂₀O₆, 372.1209).

Inhibition of NO production

Inhibition of NO production and cell viability of LPS-stimulated RAW 264.7 macrophage cells were determined. The NO production assay was carried out according to the method described before [15]. The murine monocytic RAW 264.7 macrophages were dispensed into 96-well plates (2 × 10⁵ cells/well) containing RPMI 1640 medium (Hyclone, Logan, USA) with 10% FBS under a humidified atmosphere of 5% CO₂ at 37 °C. After 24 h of preincubation, cells were treated with serial dilutions of compounds **1–4** with the maximum concentration of 25 μM in the presence of 1 μg/mL LPS for 18 h. Each compound (purity >95%) was dissolved in DMSO and further diluted in the medium to produce different concentrations. NO production in each well was assessed by adding 100 μL of Griess reagents A and B to 100 μL of each supernatant from LPS or the compound-treated cells in triplicate. After 5 min of incubation, the absorbance was measured at 570 nm with a 2104 Envision multilabel plate reader (Perkin-El-

Table 1 ^1H and ^{13}C -NMR spectroscopic data for compounds **1–3** (δ in ppm, J in Hz).

No.	1^a		2^a		3^b	
	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	$\delta_{\text{H}}^{\text{c}}$
C-1	120.5 s		115.0 s		115.3 s	
C-2	145.5 s		144.4 s		145.4 s	
C-3	99.7 d	6.48 (s)	104.9 d	6.37 (s)	99.5 d	6.35 (s)
C-4	144.2 s		141.3 s		143.5 s	
C-5	149.1 s		145.3 s		146.9 s	
C-6	107.1 d	7.09 (s)	114.6 d	6.92 (s)	106.5 d	6.77 (s)
C-7	69.0 s		35.0 d	3.02 (d, 5)	30.0 d	3.36 (d, 6)
C-8	41.0 d	2.58 (m)	35.3 d	2.52 (m)	26.5 d	1.42 (m)
C-9	17.2 q	1.25 (3H, d, 7.3)	21.4 q	1.23 (3H, d, 7.3)	65.3 t	3.69 (2H, d, 7.5)
C-1'	41.0 d	2.41 (td, 6.0, 12.0)	38.2 d	2.41 (td, 3.7, 12.3)	37.5 d	2.52 (td, 3.8, 12.4)
C-2'	197.8 s		198.9 s		199.7 s	
C-3'	100.3 d	5.44 (s)	99.9 d	5.38 (s)	99.5 d	6.35 (s)
C-4'	169.2 s		169.7 s		168.8 s	
C-5'	101.7 s		100.9 s		100.1 s	
C-6'	45.1 d	2.64 (d, 12.5)	38.2 d	2.55 (d, 5.7)	38.3 d	2.35 (d, 5.9)
C-7'	25.2 t	1.72, 1.74 (2H, m)	26.2 t	1.63 (2H, ddd, 4.1, 4.7, 4.8) 1.81 (m)	26.6 t	1.42 (ddd, 3.8, 4.9, 4.4) 1.92 (m)
C-8'	35.7 d	2.02 (m)	34.4 d	1.87 (m)	28.9 d	2.07 (m)
C-9'	20.7 q	0.58 (3H, d, 7.6)	21.3 q	0.72 (3H, d, 7.3)	21.0 q	0.71 (3H, d, 7.3)
C-1''	102.6 t	6.00 (s) 5.98 (s)			101.4 t	5.84 (s) 5.88 (s)
C-2''	99.7 t	5.80 (s) 5.71 (s)	99.6 t	5.76 (s) 5.68 (s)	98.8 t	5.57 (s) 5.70 (s)

^a Assignments are based on 1D and 2D NMR experiments. In acetone- d_6 , 500 MHz for ^1H and 125 MHz for ^{13}C ; ^b Assignments are based on 1D and 2D NMR experiments. In CDCl_3 , 600 MHz for ^1H and 150 MHz for ^{13}C

mer Life Sciences, Inc.). Cytotoxicity was determined by the MTT assay. MG-132 (Sigma–Aldrich, purity ≥ 99 , IC_{50} value = 0.15 μM) was used as a positive control.

Supporting information

1D and 2D NMR spectra, as well as HREIMS spectra of the three new compounds are available as Supporting Information.

Acknowledgments

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Conflict of Interest

None of the authors have conflicts of interest in this study.

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