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Sesquiterpenoids from the seeds of *Sarcandra glabra* and the potential anti-inflammatory effects

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ABSTRACT

Five new sesquiterpenoids, including two linderanes (**1**–**2**) and three eudesmanes (**3**–**5**) were isolated from the seeds of *Sarcandra glabra*. Their structures and relative configurations were established by spectroscopic data analysis. **1** was a rare linderane derivative having an 18-membered triester ring which is a common characteristic in linderane dimers. Compounds **1**–**5** were investigated for their inhibitory effects on NO production in LPS-induced macrophages and **1** showed moderate bioactivity.

1. Introduction

The whole plant of *Sarcandra glabra* (Thunb.) Nakai (Chloranthaceae) has been used as a Traditional Chinese Medicine (TCM) for the treatment of inflammation and traumatic injuries in China for thousands of years [1]. Modern pharmacological research has also confirmed the traditional applications and curative effects of *S. glabra* recorded in the ancient books on TCMs [2]. However, there are only a few chemical investigations on the bioactive compounds responsible for the pharmacological effects in *S. glabra*. Sesquiterpenoids, linderanes and eudesmanes mostly, are reported to be the most important metabolites in *S. glabra* [2–3]. Particularly, linderane dimers isolated from *S. glabra* and other plants of the Chloranthaceae family, have attracted a lot more attention of medicinal chemists due to their complex structures and significant bioactivities [4–7]. For instance, some linderane dimers with novel structures and anti-inflammatory activities were isolated from *S. glabra* in our previous research [8]. In the subsequent investigation of sesquiterpenoids in *S. glabra*, five new sesquiterpenoid monomers, including two linderanes (**1**–**2**) and three eudesmanes (**3**–**5**) were isolated from the seeds of *S. glabra*. Compound **1**, named as sarglabolide L, was a rare linderane derivative having an 18-membered triester ring which is common in linderane dimers [2–3], and also exhibited moderate inhibitory effect on NO production in LPS-induced macrophages. Herein, we report the isolation, structural elucidation and bioassay of the new compounds.

2. Experimental

2.1. General

Optical rotations were measured on a JASCO P-1020 polarimeter. HRESIMS experiments were performed using an Agilent UPLC-Q-TOF-MS (6520B) spectrometer. UV and IR spectra were recorded on a Shimadzu UV-2450 spectrometer and a Bruker Tensor 27 spectrometer, respectively. NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker AV-500 NMR instrument at 500 MHz (^1H) and 125 MHz (^{13}C). Silica gel (Qingdao Marine Chemical Co., Ltd., China), ODS (FuJi, Japan), MCI gel (Mitsubishi Chemical, Japan), and Sephadex LH-20 (Pharmacia, Sweden) were employed for separation by column chromatography. MPLC was carried out on a Quiksep system (H&E Co., Ltd., China). Preparative HPLC was performed on a Shimadzu LC-6A instrument with a SPD-10A detector and a shim-pack RP-C18 column (20 × 200 mm, 10 μm). Analytical HPLC was performed on an Agilent 1200 series instrument using a DAD detector and a shim-pack VP–ODS column (150 × 4.6 mm, 5 μm). Authentic L- and D-malic acid samples were purchased from J&K Chemical Ltd., (China). All solvents and reagents were of analytical grade.

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Table 1
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) data of compounds 1–3.

	1[a]		2[b]		3[a]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	1.74, m	27.9	1.35, td (7.7, 3.4)	28.6	3.82, dd (12.4, 5.7)	73.5
2α	0.85, ddd (9.1, 8.5, 6.0)	12.4	0.81, m	16.8	2.71, dd (17.1, 5.7)	42.6
2β	1.46, m		0.96, m		2.64, dd (17.1, 12.4)	
3	1.51, m	28.4	1.93, m	24.1		197.7
4		78.6		152.0		128.7
5	2.40, dd (13.7, 3.4)	64.2	2.48, m	66.8		154.6
6	2.63, ddd (17.2, 13.7, 1.6)	22.1	2.45, m	25.3	6.70, br. d (1.6)	116.3
	2.96, dd (17.2, 3.4)		2.67, d (13.1)			
7		154.5		163.9		156.3
8		148.8		107.6	2.35, m	22.3
9	6.37, s	124.5	1.87, d (13.1)	49.6	2.17, m	32.7
			2.67, d (13.1)			
10		43.3		39.1		38.5
11		120.1		124.0		73.5
12		169.0		173.7	1.42, s	29.3
13	5.02, br.d (13.3)	56.4	1.83, s	8.2	1.42, s	29.1
	4.73, d (13.3)					
14	1.19, s	22.8	0.93, s	17.9	1.04, s	15.1
15	4.14, d (11.8)	72.3	4.80, s	106.2	1.85, s	10.5
	4.71, d (11.8)		4.97, s			
1'		166.9	4.04, d (7.8)	97.6		
2'		130.5	3.28, br.d (8.9)	78.2		
3'	6.66, td (5.8, 1.1)	135.1	3.23, m	74.4		
4'	4.60, dd (15.0, 5.7)	62.2	3.21, m	71.6		
	5.31, dd (15.0, 5.5)					
5'	1.92, d (1.1)	13.2	2.97, ddd (9.5, 6.0, 2.2)	78.4		
6'			3.55, dd (11.9, 6.0)	62.6		
			3.75, dd (11.9, 2.2)			
1"		173.1				
2"	4.48, dd (5.8, 3.4)	67.2				
3"	2.86, dd (16.7, 5.8)	38.3				
	3.02, dd (16.7, 3.4)					
4"		170.5				

[a] Recorded in $CDCl_3$.
[b] Recorded in CD_3OD.

2.2. Plant material

The fresh seeds of *S. glabra* were collected in Ganzhou, Jiangxi province, PR China in November 2013. The plant material was authenticated by Prof. Mian Zhang, Department of Medicinal Plants, China Pharmaceutical University. A voucher specimen, (No. CSH201311) was deposited in the Department of Natural Medicinal Chemistry, China Pharmaceutical University.

2.3. Extraction and isolation

The fresh seeds of *S. glabra* (10 kg) were air dried and roughly ground. The ground seeds were then extracted with 95% EtOH (3 L) under reflux (4 × 2 h) and the solvent was removed under reduced pressure to afford a brown and odorous crude extract (460 g). This extract was suspended in 2.0 L water and successively extracted with petroleum ether (4 × 2 L) and ethyl acetate (3 × 2 L).

The ethyl acetate extract (70 g) was subjected to a silica gel column and eluted with CH_2Cl_2/MeOH (50:1, 25:1, 10:1, 0:1, *v*/*v*), affording four fractions (Fr. 1–4). Fr. 2 (27 g) was further applied to a silica gel column eluted with a continuous gradient of petroleum ether/acetone (3:1 to 1:1, *v*/*v*) to afford 30 subfractions (Fr. 2.1–30). Frs. 2.1–15 were combined and chromatographed on an MCI gel column eluted with 60%, 80% and 100% methanol. The 60% methanol eluate was further separated on a reversed-phase MPLC and Sephadex LH-20 gel columns, and purified by preparative HPLC to obtain **1** (2.1 mg) and **5** (3.0 mg). Frs. 2.19–26 were combined and subjected to an MCI gel column eluted with 60%, 80% and 100% methanol. The 60% methanol eluate was further applied to a Sephadex LH-20 gel column, and purified by preparative HPLC to afford **3** (15.2 mg) and **4** (6.6 mg). Fr. 3 (12 g) was also subjected to an MCI gel column and eluted with 40%, 60%, 80% and 100% methanol to afford fractions Fr. 3.1–4. Fr. 3.2 was further chromatographed on an ODS column and purified by preparative HPLC to afford **2** (10.5 mg).

Table 2
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) data of compounds **4**–**5** in $CDCl_3$.

	4		5	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	1.14, m	40.7	1.26, t (11.9)	49.5
	1.57, m		1.87, br. d (13.3)	
2	1.53, m	17.0	3.92, m	67.0
	1.89, dt (13.5, 3.5)			
3	1.33, m	36.2	1.99, t (11.8)	46.0
	1.75, m		2.72, dd (12.4, 4.9)	
4		73.2		145.4
5	1.21, m	49.3	1.93, dd (12.8, 3.7)	49.9
6	2.38, t (14.0)	23.4	2.84, dd (13.9, 12.8)	25.4
	2.86, dd (14.5, 3.5)		2.77, dd (13.9, 3.7)	
7		163.2		161.9
8	4.86, dd (11.5, 6.3)	78.2	4.84, dd (10.8, 6.8)	77.7
9	1.00, t (11.8)	49.9	1.16, t (11.8)	47.1
	2.14, dd (12.0, 6.3)		2.35, dd (12.2, 6.3)	
10		35.2		36.8
11		120.4		120.9
12		175.1		174.7
13	1.80, s	8.4	1.83, s	8.4
14	1.22, s	19.2	0.92, s	17.6
15	3.43, d (10.4)	70.0	4.72, s	109.7
	3.60, d (10.4)		4.99, s	