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Salviatalin A and salvitrijudin A, two diterpenes with novel skeletons from roots of *Salvia digitaloides* and anti-inflammatory evaluation

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ABSTRACT

Salviatalin A (**1**) and salvitrijudin A (**2**), two diterpenes with novel skeletons, were isolated from the roots of *Salvia digitaloides*. Their structures were determined using 1D, 2D NMR, and HRESI-MS spectroscopic analyses. Salviatalin A (**1**) from bioassay-guided fractionation showed a potent inhibitory effect on superoxide anion production in GMLP/CB-activated human neutrophils as well as other anti-inflammatory effects. A plausible biosynthetic pathway is also discussed.

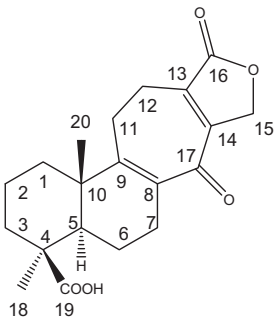
1. Introduction

Species of the genus *Salvia* (Labiatae) have been used worldwide in folk medicine from ancient times, because they exhibit various biological and pharmacological activities including antitumor,[1] antiallergic,[2] antioxidant,[3] antimicrobial,[4] and antiplatelet aggregation activities.[5] We previously reported a new antitumor agent, neotanshinlactone, which was isolated from *Salvia miltiorrhiza*,[6] and several notable new abietane diterpene alkaloids from *Schizothorsa yunnanensis*.[7]

Inflammation is a complex biological response of vascular tissues to harmful stimuli such as pathogens, damaged cells, or irritants. Inflammation can be classified as either acute or chronic. Although inflammation is a protective attempt by the organism to remove the injurious stimuli, chronic inflammation can also lead to a host of diseases such as hay fever, atherosclerosis, and rheumatoid arthritis. For this reason, inflammation is usually closely regulated. In our continuing investigation of *Salvia* species as anti-inflammatory agents, we recently investigated *S. digitaloides*, originally identified as the plant source of the traditional Chinese medicine 'Bai-Yun-Shen', later corrected to *Phlomis betonicoides* of the same plant family, from which a sweet glycoside named baiyunoside was isolated.[8] In the present study, we describe the isolation and the structure characterization of two new diterpenes, which have novel 6/6/7 and 6/5/3/7 tricyclic and tetracyclic skeletons, respectively, linked to a furan lactone ring, identified by using UV, IR, 1D and 2D NMR, and HRESI-MS spectroscopic analyses.

2. Results

The roots of *S. digitaloides* were extracted with MeOH. The concentrated extract was partitioned between water and chloroform. The chloroform extract (SDRC) was subjected to repeated silica gel chromatography to give salviatalin A (**1**) and salvitrijudin A (**2**).



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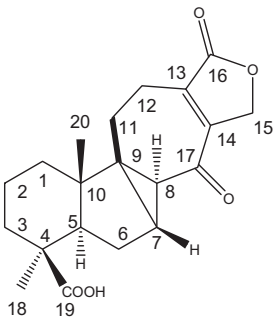

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Table 1
^{1}H (600 MHz), ^{13}C (150 MHz) NMR Data, and HMBC Correlations for **1** and **2** in $CDCl_3$

No.	**1**[a]			**2**[a]		
	δ_C (mult)	δ_H (mult, *J*, Hz)	HMBC	δ_C (mult)	δ_H (mult, *J*, Hz)	HMBC
1α	35.9 t	1.29 m	2, 5, 10, 20	33.6 t	1.21–1.26 m ovlp[b]	2, 5, 9, 10, 20
1β		2.03 br d (13.8)	9		1.62 dt (13.8, 4.2)	2, 3, 5, 10
2α	19.2 t	1.93 ddt (13.8, 13.8, 3.6)		19.8 t	1.74 ddt (13.8, 13.8, 4.2)	1
2β		1.62 dt (13.8, 3.6)			1.57–1.60 m ovlp[b]	3, 10
3α	37.0 t	2.24 dt (13.8, 3.6)	2, 4, 18, 19	36.8 t	0.90 dt (13.8, 4.2)	2, 4, 18
3β		1.04 ddd (13.8, 13.8, 3.6)			2.28 m	4, 5
4	43.7 s	—		43.3 s	—	
5	52.7 d	1.34 br d (13.0)	1, 4, 6, 7, 10, 19, 20	49.6 d	1.12 dd (12.9, 6.0)	1, 3, 4, 9, 10, 18, 20
6α	19.7 t	2.11 dd (13.0, 6.0)	5, 7, 10	26.5 t	1.93 dd (12.9, 6.0)	5, 7, 8, 9, 10
6β		1.73 ddd (13.0, 13.0, 6.0)	4, 5, 7, 10		2.26 m	4, 5, 7, 8
7α	27.9 t	2.01 m	6, 8, 9	31.4 d	2.17 t (3.0)	5, 17
7β		2.72 m	5, 8, 9, 17	—		
8	136.4 s	—		37.3 d	2.44 d (3.0)	6, 7, 10, 14, 17
9	157.4 s	—		47.4 s	—	
10	41.8 s	—		45.1 s	—	
11α	26.4 t	2.52 m	8, 9, 10, 12, 13	21.4 t	2.46 dt (14.8, 2.4)	7, 8, 9, 12, 13
11β		2.52 m			1.87 td (14.8, 2.4)	
12α	23.6 t	2.62 br dd (12.6, 1.2)	11, 13	25.1 t	2.26 m	
12β		2.39–2.47 m ovlp[b]	9, 11, 13		2.76 br d 19.8	
13	138.9 s	—		137.4 s	—	
14	152.5 s	—		151.0 s	—	
15α	70.1 t	4.82 ddd (18.0, 3.6, 1.2)	13, 14	69.8 t	4.71 dd (18.0, 3.0)	13, 14, 16
15β		4.98 dt (18.0, 3.6)	13, 14		4.98 dt (18.0, 3.0)	13, 14
16	173.9 s	—		173.6 s	—	
17	190.7 s	—		196.9 s	—	
18	28.5 q	1.29 s	2, 3, 4, 5, 19	28.9 q	1.19 s	3, 4, 5, 19
19	182.7 s	—		182.0 s	—	
20	16.7 s	0.98 s	1, 5, 9, 10	17.4 q	0.94 s	1, 5, 9, 10

[a] s: singlet, d: doublet, t: triplet, m: multiplet.
[b] Overlapping peaks.

Salviatalin A (**1**) was obtained as a colorless syrup and had a positive rotation ($[\alpha]_D^{25}$ +107, *c* 0.05, MeOH). The HRESI-MS of **1** shows a quasimolecular ion peak at *m*/*z* 367.1523, which is consistent with the molecular formula of $C_{20}H_{24}O_5Na$. This formula implies nine degrees of unsaturation. The UV spectrum of **1** shows absorption maxima at 247 and 312 nm, indicating the presence of α,β-unsaturated ketone moiety in the molecule. The IR spectrum shows strong absorption peaks for OH (3580 cm^{-1}), carbonyl group of a carboxylic acid (1696 cm^{-1}), furan ring (756 cm^{-1}), and a carbonyl group of a conjugated α,β-unsaturated γ-lactone (1762 cm^{-1}). The ^{13}C NMR spectrum of **1** (Table 1) shows 20 carbon signals, including four quaternary olefinic (δ 157.4, 152.5, 138.9, and 136.4), three carbonyl (δ 190.7, 182.7, and 173.9), two quaternary (δ 43.7 and 41.8), one methine (δ 52.7), eight methylene (δ 70.1, 37.0, 35.9, 27.9, 26.4, 23.6, 19.7, and 19.2), and two methyl (δ 28.5 and 16.7) carbons. These results were confirmed by the HSQC spectrum. The ^{1}H NMR spectrum of **1** (Table 1) showed signals for two methyls (δ 1.29 and 0.98) and an oxygen-bearing methylene (H-15, δ 4.98, and 4.82), which are the typical lactone protons. H-15 revealed ^{4}J long-range coupling to H-12α (δ 2.62, *J* = 16.2, 1.2 Hz). The COSY spectrum showed the following proton–proton cross-peaks: H-11 (δ 2.52) to H-12 (δ 2.43 and 2.62), H-6 (δ 1.73 and 2.11) to H-7 (δ 2.01 and 2.72)/H-5, (δ 1.34), and H-2 (δ 1.62, 1.93) to H-1 (δ 1.29, 2.03)/H-3 (δ 1.04, 2.24). The HMBC spectrum of **1** showed the conjugated cross-peaks of H-15 to C-13 (δ 138.9)/C-14 (δ 152.5)/C-17 (δ 190.7) and H-11 (δ 2.52) to C-13 (δ 138.9). The seven-membered C-ring was established by the correlations of H-7 (δ 2.01, 2.72) and H-11α (δ 2.52) with C-8 (δ 136.4) and C-9 (δ 157.4), of H-7β with C-17 (δ 190.7), and of H-1β (δ 2.03) and H-20 (δ 0.98) with C-9 in the HMBC spectrum. The ^{3}J HMBC correlation of the methyl protons (H-18) at δ 1.29 with C-3 (δ 37.0), C-5 (δ 52.7), and C-19 (δ 182.7) indicated that the quaternary C-4 (δ 43.7) was substituted with both methyl and carboxylic acid groups. The stereochemistry was confirmed by a NOESY experiment, which showed correlation between H-5, Me-18, and H-6α (Fig. 1). Thus, the methyl substitu-

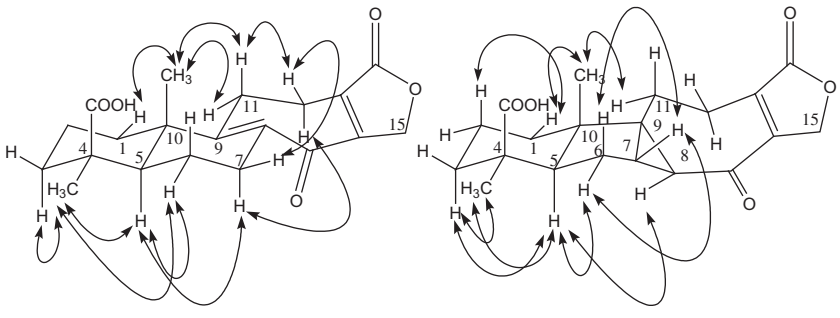

Figure 1. Selected NOESY correlations for **1** and **2**.