

Short communication

Cytotoxic sesquiterpene lactones from *Artemisia anomala*

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ABSTRACT

Two new sesquiterpene lactones, 8 α -acetoxy-1,10 α -epoxy-2-oxo-guaia-3,11(13)-dien-12,6 α -olide (**1**) and 13-acetoxy-1-oxo-4 α -hydroxy-eudesman-2(11)-dien-12,6 α -olide (**2**), along with six known analogs (**3–8**), were isolated from the whole plant of *Artemisia anomala* S. Moore. Their structures were elucidated by extensive analysis of spectroscopic data. Compounds **6** and **7** exhibited *in vitro* moderate cytotoxicity against A549 cells with IC₅₀ values of 0.6 and 0.9 μ M, and HepG2 cells with IC₅₀ values of 5.4 and 3.0 μ M, respectively.

1. Introduction

The genus *Artemisia* belongs to the family of Compositae and comprises more than 500 species (Oberprieler et al., 2007). Many species of this genus have long been used as folk medicines in China for the treatment of diseases such as fever, malaria, hepatitis, and cancer. Artemisinin, a famous sesquiterpene isolated from *A. annua*, is now a well-known drug used to fight against malaria and saved millions of lives over the world (Tu, 2011).

A. anomala S. Moore, known as Nan-Liu-Ji-Nu in Chinese, is a perennial herbaceous plant that grows mainly on the roadside, hillside and forest edges with a distribution in most southern areas of China. Its whole plant has been commonly used for centuries as an analgesic, homeostatic, antibiotic and wound-healing agent. In recent years, phytochemical investigations of the title plant had revealed the existence of flavonoids, coumarins, and sesquiterpene lactones, some of which exhibited remarkable antitumor (Jakupovic et al., 1987; Marco et al., 1993; Lee et al., 1998, 2002, 2003; Zan et al., 2010; Zan et al., 2012a,b,c), anti-inflammatory (Hu et al., 2012; Turak et al., 2014; Zhang et al., 2014; Chi et al., 2016) and anti-HIV-1 protease (Ma et al., 2000) activities. In our further effort to search for bioactive sesquiterpene constituents, two new sesquiterpene lactones (**1** and **2**) (Fig. 1), along with six known analogs (**3–8**), were characterized from the whole plant of *A. anomala*. In this paper, we describe the isolation and structural elucidation of these compounds, and their cytotoxic

activity against human tumor cell lines A549 (human lung adenocarcinoma) and HepG2 (Human hepatocellular liver carcinoma) as well.

2. Results and discussion

Compound **1** possessed a molecular formula of C₁₇H₁₈O₆ as established by the HRESIMS ion at *m/z* 317.1021 [M-H]⁻ (calcd. 317.1031), implying nine degrees of unsaturation. The IR absorption band at 1765 cm⁻¹ indicated the presence of carbonyl groups. The ¹H NMR spectrum of **1** (Table 1) showed signals of three tertiary methyls at δ_{H} 1.78 (H-14), 2.13 (H-15), and 2.41 (H-2'), two oxygenated methine protons at δ_{H} 4.17 (H-6) and 5.15 (H-8), and three olefinic protons at δ_{H} 5.59 (H-13), 6.22 (H-13) and 6.23 (H-3). The ¹³C NMR spectrum (Table 1), in combination with HSQC and DEPT spectra, showed 17 carbon resonances ascribed to four olefinic (δ_{C} 122.1, 133.8, 135.9, 169.0), four oxygenated (δ_{C} 64.9, 65.2, 69.0, 77.5), two ester carbonyl (δ_{C} 169.6, 175.8), a ketone carbonyl (δ_{C} 200.1), three methyl (δ_{C} 18.7, 21.1, 21.2), one methylene (δ_{C} 41.2), and two methine (δ_{C} 48.5, 55.0) carbons. The aforementioned data showed high similarities to those of a known sesquiterpene lactone artemdubolide E (Huang et al., 2010), suggesting that **1** could possess a similar skeleton. Compared with artemdubolide E, additional signals of a methyl singlet at δ_{H} 2.41 and two carbon resonances at δ_{C} 175.8 and 21.1 were observed, indicative of an acetyl group present in **1**. The HMBC correlations from H-8 to C-1', C-2', C-7, and C-9 confirmed the location of the acetoxy group at C-8

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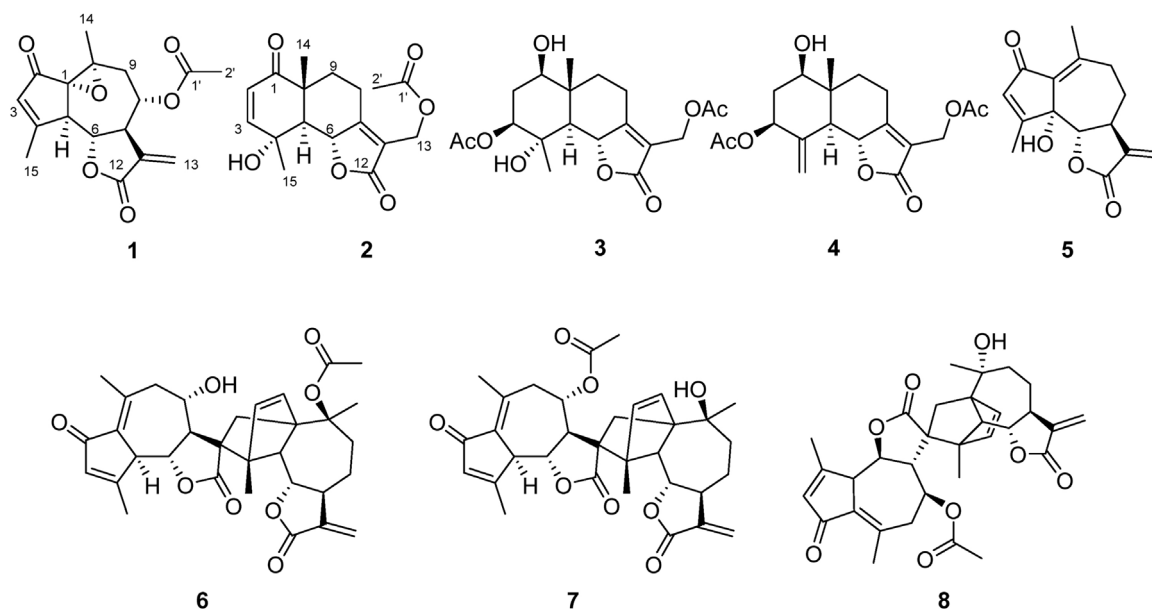


Fig. 1. Structures of compounds 1–8 isolated from *A. anomala*.

Table 1
 ^1H NMR (500 Hz) and ^{13}C NMR (125 Hz) data of compounds 1 and 2 in CDCl_3 .

No.	1		2	
	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)
1	64.9		200.5	
2	200.1		125.5	5.90 d (10.4)
3	133.8	6.23 br s	152.2	6.66 d (10.4)
4	169.0		70.1	
5	48.5	3.17 br d (10.5)	57.4	2.22 d (11.8)
6	77.5	4.17 dd (10.5, 10.5)	79.2	5.14 d (11.8)
7	55.0	2.82 m	168.1	
8	69.0	5.15 td (10.5, 3.0)	22.4	3.15 m 2.47 m 2.32 m 1.59 m
9	41.2	2.46 dd (15.0, 3.0) 2.29 dd (15.0, 10.5)	35.3	
10	65.2		45.1	
11	135.9		119.8	
12	169.6		171.2	
13	122.1	6.22 d (3.0) 5.59 d (3.0)	54.9	4.82 d (12.7) 4.80 d (12.7)
14	18.7	1.78 s	18.7	1.30 s
15	21.2	2.13 s	24.5	1.64 s
1'	175.8		170.7	
2'	21.1	2.41 s	20.9	2.08 s

(Fig. 2a). The ^1H – ^1H COSY spectrum implied the presence of a partial structure (C5–C9) shown as a bold line in Fig. 2a. The relative configuration of 1 was inferred from the ROESY experiment. The ROESY correlations of Me-14/H-9 β , H-9 β /H-8, and H-8/H-6 indicated that Me-14, H-8 and H-6 were co-facial and β -oriented, while the cross-peaks of H-7/H-9 α and H-7/H-5 suggested that H-5 and H-7 were on the other face and α -oriented (Fig. 2a). The distinction of relative configuration of 1 and artemdubolide E lied in the orientation of C-14 and the epoxy functionality. The Me-14 was placed in a β -orientation in 1, which was evident from the aforementioned ROESY correlations, while Me-14 of artemdubolide E was in an α -orientation as reported (Huang et al., 2010). The different chemical shifts of C-1, C-10 and C-14 (δ_{C} 64.9, 65.2 and 18.7 in 1 vs δ_{C} 66.7, 66.7 and 21.3 in artemdubolide E) also supported that they might have different configurations on these positions. The orientation of C-14 influenced the migration of the chemical shifts of the close carbons. Therefore, compound 1 was established as 8 α -acetoxy-1,10 α -epoxy-2-oxo-guaia-3,11(13)-dien-12,6 α -olide.

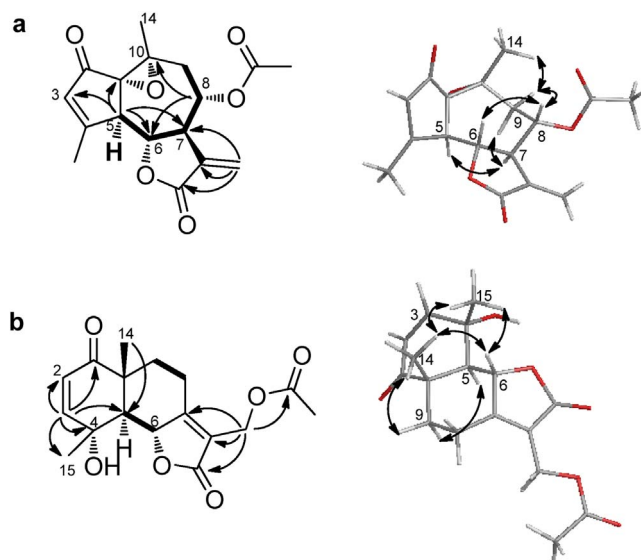


Fig. 2. Selected HMBC (H \rightarrow C), ^1H – ^1H COSY (H–H), ROESY (H \leftrightarrow H) correlations for compounds 1 and 2.

Compound 2 had a molecular formula of $\text{C}_{17}\text{H}_{20}\text{O}_6$ determined by the HRESIMS ion at m/z 319.1182 [$\text{M}-\text{H}$] $^-$ (calcd. 319.1187), corresponding to eight degrees of unsaturation. The IR spectrum showed absorption bands for hydroxyl group (3437 cm^{-1}), carbonyl group (1768 cm^{-1}) and double bands (1641 cm^{-1}). The NMR data, similar to those of the known compound 3 β ,13-diacetoxy-1 β ,4 α -dihydroxyeu-desm-7(11)-en-12,6 α -olide (3) (Barrero et al., 2013), suggested that they shared the same skeleton. The ^{13}C NMR spectrum of compound 2 (Table 1) revealed the characteristic signals of two olefinic carbon resonances at δ_{C} 125.5, 152.2 and a ketone carbonyl resonance at δ_{C} 200.5, which suggested the presence of an α , β -unsaturated ketone carbonyl group, rather than those of two oxygenated (δ_{C} 70.4, 76.1) and a methylene (δ_{C} 37.1) carbon reported for compound 3. In the HMBC spectrum, the long range correlations from H-3 (δ_{H} 6.66, d, $J = 10.4$ Hz) to C-1, C-2, C-4 and C-15, and from H-2 (δ_{H} 5.90, d, $J = 10.4$ Hz) to C-10, C-1, C-3, and C-4 confirmed a double bond occurring between C-2 and C-3 (Fig. 2b). The ROESY correlations of Me-15/Me-14, H-6/Me-14, H-6/Me-15, H-9 β /Me-14, and H-5/H-9 α

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