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Iridoids from the roots of *Valeriana jatamansi* Jones

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ABSTRACT

Five iridoids, named as chlorovaltrate P-T, together with six known analogues, (4β,8β)-8-methoxy-3-methoxy-10-methylene-2,9-dioxatricyclo[4.3.1.0^{3,7}]decan-4-ol, chlorovaltrate A, (1*R*,3*R*,5*R*,7*S*,8*R*,9*S*)-3,8-epoxy-1-*O*-ethyl-5-hydroxyvalechlorine, 8-methoxy-4-acetoxy-3-chlormethyl-10-methylen-2,9-dioxa-tricyclo[4.3.1.0^{3,7}]decan, (1*S*,3*R*,5*R*,7*S*,8*R*,9*S*)-3,8-epoxy-1-*O*-ethyl-5-hydroxyvalechlorine, (1*R*,3*R*,5*R*,7*S*,8*R*,9*S*)-3,8-epoxy-1-*O*-methyl-5-hydroxyvalechlorine were isolated from the roots of *Valeriana jatamansi* (syn. *Valeriana wallichii*). Their structures were elucidated by extensive analysis of 1D, 2D NMR and HRESIMS spectroscopic. The absolute configuration of chlorovaltrate P-T were established by comparing their experimental and calculated electronic circular dichroism (ECD) spectra. 3,8-epoxy iridoids exhibited weak cytotoxicity against the lung adenocarcinoma (A 549) and gastric carcinoma cells (SGC 7901). Some also showed moderate neuroprotective effects against $CoCl_2$-induced neuronal cell death in PC12 cells.

1. Introduction

Valeriana jatamansi Jones belongs to the family Caprifoliaceae, an annual herb mainly distributed in China and India (Mathela et al., 2005). It is well known as traditional Chinese medicine with tranquilizing hypnotic, nervous disorders, epilepsy, insanity, snake poisoning and skin diseases (Ming et al., 1997; Mathela et al., 2005; Fernández et al., 2004). Its root, as an important substitute of European *V. officinalis*, has been used to treat nervous disorders (Mathela et al., 2005; Fernández et al., 2004). Previous chemical investigation of *V. jatamansi* revealed the presence of iridoids, sesquiterpenoids, essential oil, flavone and lignans (Ming et al., 1997; Tang et al., 2002; Verma et al., 2011; Lin et al., 2010a,b; Tan et al., 2016; Xu et al., 2011a,b). Valepotriates, a family of iridoid esters exhibiting potent cytotoxic and antitumor activities, have been attracting great interest in natural products (Yu et al., 2005; Tang et al., 2002; Becker et al., 1984; Bounthanh et al., 1981). What is worth mentioning, volvaltrate B induced a significant percentage of definitive remissions of ovarian tumors in the female mice (Zhang et al., 2010). As a part of our ongoing efforts to search for bioactive natural products on antineoplastic and neuroprotective agent from *Valeriana* genus, we herein report five iridoids, named chlorovaltrate P-T (**1**–**5**) and six known analogues (**6**–**11**) (see Fig. 1). Reported herein are the isolation, structure elucidation and biological activities including cytotoxicity and neuroprotective effects of the isolates.

2. Results and discussion

Chlorovaltrate P **(1)**, molecular formula $C_{11}H_{15}ClO_4$ by HRESIMS (*m*/*z* 269.0499 [M (^{35}Cl)+Na]$^+$, calcd for $C_{11}H_{15}ClO_4Na$, 269.0557). The 1D NMR spectrum in combination with HSQC spectroscopic data of **1** showed one methoxyl, three methylenes, five methines (three oxygenated) and two quaternary carbons. The NMR spectroscopic data suggested that compound **1** possessed an iridoid-

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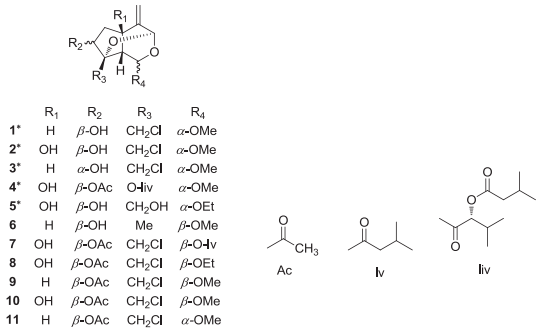

	R_1	R_2	R_3	R_4
1*	H	β-OH	CH_2Cl	α-OMe
2*	OH	β-OH	CH_2Cl	α-OMe
3*	H	α-OH	CH_2Cl	α-OMe
4*	OH	β-OAc	O-Iiv	α-OMe
5*	OH	β-OH	CH_2OH	α-OEt
6	H	β-OH	Me	β-OMe
7	OH	β-OAc	CH_2Cl	β-O-Iv
8	OH	β-OAc	CH_2Cl	β-OEt
9	H	β-OAc	CH_2Cl	β-OMe
10	OH	β-OAc	CH_2Cl	β-OMe
11	H	β-OAc	CH_2Cl	α-OMe

Fig. 1. Structures of compounds **1**–**11**.

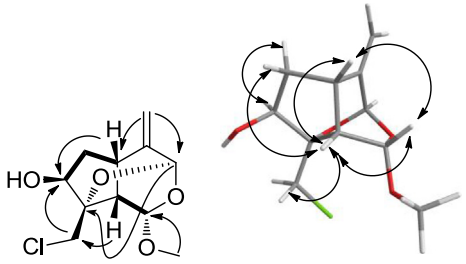

Fig. 2. Selected COSY, HMBC and NOESY correlations of compound **1**.

type skeleton with a methoxyl group. The NMR data of **1** were identical to those of (1*S*,3*R*,5*R*,7*S*,8*R*,9*S*)-3,8-epoxy-1-*O*-methyl-5-hydroxyvalechlorine (Lin et al., 2010b). The only differences that could be discerned was the absence of a hydroxyl group at C-5 and hydroxyl group at C-7 instead of acetoxy in **1**, which was supported by the HRESIMS. Interpretation of their 2D NMR data established the same overall structure. According to the HMBC spectrum (see Fig. 2), the correlations from H-1' (δ_H 3.34, s) to C-1(δ 98.0) indicated that methoxyl was attached at C-1. Further analysis of the 2D NMR data led to the assignment of all the proton and carbon signals for **1** (Table 1). The relative configuration of **1** was established by the NOESY experiment (see Fig. 2). Generally, naturally occurring iridoids display the oxo-bridge from C-3 to C-8 could only be α-oriented, and the H-5 and H-9 could only be β-oriented (Xu et al., 2011a; Li et al., 2013; Lin et al., 2013). NOESY correlations observed for H-7/H-6α, H-9/H-6β, H-9/H-5, H-9/H-1, H-5/H-1 and H-9/H_2-10, indicated a β-configuration for the hydroxyl at C-7 and α-configuration for the methoxyl group at C-1. Therefore, the relative configuration of **1** was assigned as 1S^*,3R^*,5R^*,7S^*,8R^* and 9S^*. The absolute configuration of **1** was determined by the experimental and calculated ECD data. Comparison of the experimental ECD data of **1** with the calculated data for the model molecules indicated **1** be in agreement with the 1*S*, 3*R*,5*R*,7*S*,8*R* and 9*S* configuration (see Fig. 3).

Chlorovaltrate Q **(2)**, molecular formula $C_{11}H_{15}ClO_5$ by HRESIMS (*m*/*z* 285.0490 [M (^{35}Cl)+Na]$^+$, calcd for $C_{11}H_{15}ClO_5Na$ 285.0506). Analysis of its 1D and 2D NMR indicated that **2** was similar to those of **1** (Table 1), suggesting that they were structural analogues except for the presence of hydroxyl group in **2**. This assumption was corroborated by the interpretation of 2D NMR spectra (Fig. S2 in Supplementary Information). The NOESY correlations of H-7/H-6α, HO-5β/H-6β, H-9/H-1 and HO-5β/H-1 indicated a β-configuration for the hydroxyl at C-7 and α-configuration for the methoxyl group at C-1 (Fig. S3 in Supplementary Information), which was the same as compound **1**. The calculated ECD spectrum of **2** showed a weak negative Cotton effect at 213 nm, but no conspicuous negative Cotton effect at 218 nm in experimental ECD spectrum (Fig. S4 in Supplementary Information). The similar NOESY correlations and biogenetic considerations assumed the assignment of the absolute configuration of **2** to be the same as that of **1**.

Chlorovaltrate R **(3)**, molecular formula $C_{11}H_{15}ClO_4$ by HRESIMS (*m*/*z* 269.0486 [M+Na]$^+$, calcd for $C_{11}H_{15}ClO_4Na$, 269.0557), showed NMR data similar to those of compound **1** (Table 1). Comparison of the spectroscopic data and key NOESY correlations with compound **1**, the relative configurations at C-1, C-3, C-5, C-8 and C-9 in compound **3** were same to **1** (see Fig. 4). Moreover, the NOESY cross peaks of H-7/H-9 and H-7/H-5, but not of H-7/H-9 and H-7/H-5 for compound **1** indicated β-orientation of H-7 in compound **3**, which was unambiguous difference between compound **1** and **3.** In regard to the absolute configuration of the hydroxyl group at C-7, the ECD spectra of the molecules for (1*S*, 3*R*, 5*R*, 7*R*, 8*R* and 9*S*)-**3** and its enantiomer were calculated using the quantum chemical TDDFT method. Comparison of the experimental cotton effect (CE) of **3** (positive CE at 208 nm and negative CE at 226 nm) with the calculated data for the model molecule assigned **3** have the 1*S*, 3*R*, 5*R*, 7*R*, 8*R* and 9*S* configuration (see Fig. 5).

Chlorovaltrate S (**4**) was assigned as $C_{23}H_{34}O_{10}$ on the basis of HRESIMS (*m*/*z* 493.2050 [M+Na]$^+$, calcd for $C_{23}H_{34}O_{10}Na$, 493.2050). The 1D NMR spectrum in combination with HSQC exhibited twenty three carbon signals, including one methoxyl, five

Table 1
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of 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	δ_H
1	98.0 CH	4.93 br.s	96.7 CH	5.00 br.s	96.3 CH	4.92 d (2.3)
3	92.1 CH	5.14 s	93.2 CH	5.19 s	93.9 CH	5.13 s
4	148.7 C		152.2 C		148.3 C	
5	38.9 CH	2.97 m	76.1 C		37.0 CH	3.21 m
6a	42.6 CH_2	1.84 ddd (13.7, 7.3, 2.9)	49.7 CH_2	1.85 dd (13.4, 3.0)	41.4 CH_2	1.90 ddd (14.0, 7.4, 3.1)
6b		1.94 m		2.25 dd (13.4, 7.1)		2.14 dd (14.0, 7.4)
7	75.1 CH	3.81 s	71.6 CH	3.65 m	77.1 CH	4.26 dd (7.3, 2.9)
8	82.9 C		83.2 C		83.1 C	
9	41.7 CH	2.27 br.d (5.0)	47.9 CH	2.22 br.s	42.2 CH	2.44 dd (4.8, 3.1)
10a	47.7 CH_2	3.79 d (11.0)	47.7 CH_2	3.82 d (11.1)	47.5 CH_2	3.85 d (11.2)
10b		4.13 d (11.0)		4.09 d (11.1)		3.92 d (11.2)
11a	107.7 CH_2	4.81 br.s	107.2 CH_2	5.03 br.s	108.1 CH_2	4.83 d (1.0)
11b		4.91 br.s		5.13 br.s		4.92 d (1.0)
1′	55.5 CH_3	3.34 s	55.8 CH_3	3.34 s	55.3 CH_3	3.39 s

The ^{1}H NMR data of the hydroxy at C-5 of **2**: δ_H 5.69 (1H, br.s, H-HO-5).
[a] Recorded in DMSO-d_6.
[b] Recorded in $CDCl_3$.