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Iridoids and sesquiterpenoids from the roots of *Valeriana jatamansi* Jones

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ABSTRACT

Three new iridoids, jatamanvaltrates R–S (**1**–**2**) and jatamanin Q (**3**), as well as three new sesquiterpenoids, valerianannoids D–E (**4**, **5**) and clovane-2β-isovaleroxy-9α-ol (**6**), together with nine known compounds were isolated from the roots of *Valeriana jatamansi* Jones. Compound **2** was the first reported iridoid with fatty acid esters in the Valerianaceae family. The structures of new compounds were established on the basis of extensive spectroscopic analysis. Moreover, all the isolates were evaluated for inhibitory activity on acetylcholinesterase (AChE).

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1. Introduction

Valeriana jatamansi Jones (Valerianaceae family), also named as *Valeriana wallichii* DC., an annual herb of the 200 species in genus *Valeriana*, is mainly distributed in China and mainland India [1]. The roots and rhizomes of the plant were used as a traditional Chinese medicine (TCM) for the treatment of various diseases, including insomnia, epilepsy, insanity, and nervous disorders [2–5]. Previous phytochemical investigations on this specie resulted in the isolation of sesquiterpenoids [5,6], essentials oils [5,7,8], flavone glycosides [9], valepotriates and acylated iridoids [10–19]. In the course of our continual search for bioactive natural products on nervous systems from genus *Valeriana* [20–23], the roots of *V. jatamansi* were investigated and got six new compounds, including three iridoids jatamanvaltrates R–S (**1**–**2**) and jatamanin Q (**3**), three sesquiterpenoids, valerianannoids D–E (**4**, **5**) and clovane-2β-isovaleroxy-9α-ol (**6**), together with nine known compounds. Compound **2** was the first reported iridoid with fatty acid esters in the Valerianaceae family. In view of traditional usage of *V. jatamansi* at nervous disorders, and it is reported that the chloroform and ethylacetate fractions, the essential oils of *V. jatamansi* and the related species of genus *Valeriana* exhibited activity against acetylcholinesterase (AChE) [22–27], which involves in learning, memory, Alzheimer's, and Parkinson's disease [28–31]. Thus, all the isolates were evaluated to know whether these compounds were the effective constituents on acetylcholinesterase (AChE) inhibitory activity of this plant (Fig. 1).

Herein, we describe the isolation, structural elucidation of these new compounds and the AChE inhibitory activities of the 15 isolates.

2. Experimental

2.1. General experimental procedures

Optical rotations were recorded on a JASCO model 1020 polarimeter (Horiba, Tokyo, Japan). ESIMS and HRESIMS were

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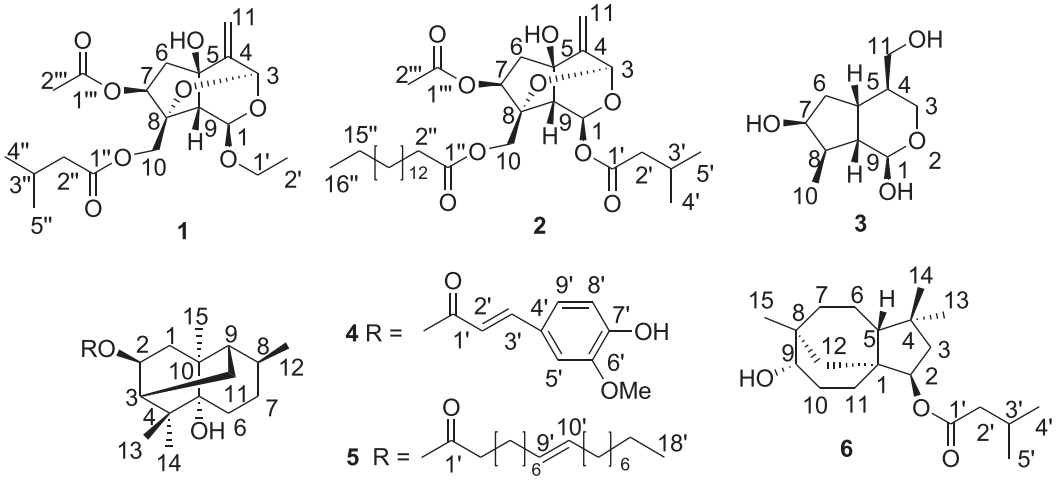

Fig. 1. Structures of compounds **1**–**6**.

run on an API QSTAR time-of-flight (AB-MDS Sciex, Concord, ON, Canada) or a Shimadzu LCMS-IT-TOF mass spectrometer (Shimadzu, Kyoto, Japan) or an Agilent G6230 TOF MS (Agilent Technologies, Palo Alto, USA), while EIMS and HREIMS were carried out on an Waters AutoSpec Premier p776 spectrometer (Waters, Millford, MA, USA). IR (KBr) spectra were obtained using a Tenor 27 spectrophotometer (Bruker Optics GmbH, Ettlingen, Germany). UV spectra were measured on a Shimadzu UV-2401PC spectrophotometer (Shimadzu, Kyoto, Japan). 1D and 2D NMR spectra were performed on a Bruker AM-400, DRX-500, AV 600 and an Avance III 600 spectrometer (Bruker, Bremerhaven, Germany) with TMS as the internal standard. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. MPLC was performed on a Dr-Flash-S MPLC system (Lisui, Suzhou, China). Silica gel (200–300 mesh) for column chromatography (CC) and TLC was obtained from Qindao Marine Chemical Factory, Qingdao, China. Sephadex LH-20 was purchased from Amersham Biosciences, Sweden; RP-C_{18} gel (40–63 μm, Merck, Darmstadt, Germany), MCI gel (75–150 μm, Mitsubishi Chemical Corporation, Japan). Fractions were monitored by TLC, and spots were visualized by UV light and sprayed with 5% sulfuric acid in EtOH, followed by heating.

2.2. Plant material

The roots of *V. jatamansi* were purchased in July 2012 from Yunnan Hongxiang Yixintang Pharmaceutical Co., Ltd. and identified by Dr. Zhi-Kun Wu. A voucher specimen (KUN No. 0864803) has been deposited at Herbarium of Kunming Institute of Botany, the Chinese Academy of Sciences, Kunming, China.

2.3. Extraction and isolation

The roots of *V. jatamansi* (32.5 kg) were powdered and extracted with 95% EtOH (60 L) at room temperature (28 h) for 3 times. The combined extracts were concentrated under reduced pressure to afford a crude residue (3.65 kg) and then suspended in water (4.0 L) and partitioned with EtOAc (4.0 L × 5). The EtOAc layer (1.72 kg) was subjected to silica gel column chromatography (CC, 200–300 mesh), then eluted with a gradient of petroleum ether/acetone (1:0–0:1) to afford 7 fractions (Fr.1–Fr.7). Fraction 1 (192.4 g) was passed through silica gel CC (petroleum ether/acetone gradient, 1:0–10:1) to give 7 subfractions (Fr.1.1–Fr.1.7). Fr.1.2 (49.5 g) was separated by repeated silica gel CC (petroleum ether/acetone, 1:0–50:1), then passed through Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1) to yield compound **5** (17.0 mg). Fr.1.5 (4.2 g) was chromatographed on Sephadex LH-20 column and eluted with MeOH to obtain 7 subfractions (Fr.1.5.1 Fr.1.5.7). Fr.1.5.4 (312 mg) was subjected to Sephadex LH-20 column (MeOH), then followed by RP-$_{18}$ (MeOH/H_2O gradient, 50:50–90:10) to give compounds **6** (14.0 mg), **7** (14.0 mg) and **13** (94.0 mg). Fraction 3 (55.5 g) was subjected to MCI gel (MeOH/H_2O, 70:30–95:5) to give 5 subfractions. Fr.3.2 (5.45 g) was further separated by MPLC (MeOH/H_2O gradient, 40:60–60:40), followed by a silica gel (petroleum ether/acetone, 20:1–15:1) and then passed through Sephadex LH-20 column ($CHCl_3$/MeOH, 1:1) to yield compound **1** (34.0 mg). Fraction 4 (100.3 g) was chromatographed on silica gel CC (200–300 mesh) (petroleum ether/acetone, 50:1–1:1) to yield 4 fractions (Fr.4.1–Fr.4.4). Fraction 4.2 (28.3 g) was applied to a MCI gel (MeOH/H_2O gradient, 60:40–85:15) to afford 3 subfractions (Fr.4.2.1–Fr.4.2.3). Fr.4.2.2 (9.0 g) by repeated silica gel CC (petroleum ether/acetone, 20:1–5:1), then followed by RP-$_{18}$ (MeOH/H_2O gradient, 50:50–85:15) and Sephadex LH-20 (MeOH) to yield compounds **2** (5 mg) and **8** (53 mg). Fraction 6 (193.7 g) was separated over silica gel CC, eluted with petroleum ether/acetone (20:1–0:1), to afford 8 fractions ((Fr.6.1–Fr.6.8). Fr.6.4 (16.3 g) was subjected to MCI gel (MeOH/H_2O gradient, 30:70–100:0) to obtain 7 subfractions (Fr.6.4.1–Fr.6.4.7). Fr.6.4.2 (4.16 g) was purified by Sephadex LH-20 (MeOH) to give **12** (96 mg). Fr.6.5 (70.4 g) was chromatographed on repeated silica gel CC (petroleum ether/acetone, 10:1–0:1) to afford 8 subfractions (Fr.6.5.1–Fr.6.5.8). Fr.6.5.4 (33.6 g) was successively separated by MPLC (MeOH/H_2O gradient, 20:80–85:15) and repeated silica gel CC (petroleum ether/EtOAc, 5:1–1:1), followed by RP-$_{18}$ (MeOH/H_2O gradient, 30:70–75:25) and purified by

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