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A new secoiridoid glycoside and a new sesquiterpenoid glycoside from *Valeriana jatamansi* with neuroprotective activity

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ABSTRACT

A new secoiridoid glycoside, isopatrinioside (**1**) and a new sesquiterpenoid glycoside, valerianannoid F (**2**), together with nine known compounds, were isolated from the roots of *Valeriana jatamansi*. Their structures were elucidated on the basis of spectroscopic analysis. Compound **1** was an unusual monocyclic iridoid glycoside ring-opened between C-1 and C-2 produced by the cleavage of the pyran ring. Of the eleven isolates, compounds **1** and **4** exhibited 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 distributed widely in the southwest of China and India, which 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; Fernandez et al., 2004). Its root, as an important substitute of European *V. officinalis*, has been used to treat nervous disorders (Mathela et al., 2005; Fernandez et al., 2004). Previous chemical investigation of *V. jatamansi* revealed the presence of iriodoids, sesquiterpenoids, essential oil, flavone glycosides and lignans (Ming et al., 1997; Tang et al., 2003; Verma et al., 2011; Lin et al., 2010).

In the course of our continual search for bioactive natural products on nervous systems from *Valeriana* genus, eleven compounds were isolated from the roots of *Valeriana jatamansi* including a new secoiridoid glycoside, isopatrinioside (**1**) and a new sesquiterpenoid glycoside, valerianannoid F (**2**), together with nine known compounds. Isopatrinioside (**1**) is a monocyclic iridoid glycoside with pyran ring-opened between C-1 and C-2. To the best of our knowledge, the report about this type monocyclic iridoid from natural sources is still very rare (Wysokinska and Skrzypek, 1992; Dinda et al., 2007, 2009, 2011). Isopatrinioside(**1**) is so far another positional isomer of patrinioside isolated from *valeriana* (Kouno et al., 1995). Valerianannoid F(**2**) is one of the valerianannoid analogues which have been isolated from *V. jatamansi* (Ming et al., 1997; Dong et al., 2015). In this paper, we describe the isolation, structural elucidation of two new compounds and neuroprotective effects of the eleven compounds.

2. Results and discussion

Compound **1** was obtained as an amorphous powder. The IR spectrum showed typical absorption bands for hydroxy (3400 cm^{-1}), ester carbonyl (1713 cm^{-1}), and glycosyl (1077, 1047 cm^{-1}). The molecular formula was determined to be $C_{21}H_{36}O_{10}$ on the basis of the HRESIMS ($[M+Na]^+$ at m/z 471.2204, calcd. for 471.2206) with 4 degrees of unsaturation. The ^1H NMR (Table 1), DEPT combinated with HSQC spectra of **1** showed a doublet methyl signals at δ_C 22.8 and δ_H 0.96, methylene carbon signals (δ_C 45.3), a methine (δ_C 26.9), and a carbonyl carbon signal at δ_C 174.4, indicating an isovaleryloxyl ester moiety[δ_H 0.96 (6H, d, J = 6.6 Hz), 2.05 (1H, m), 2.16 (2H, m); δ_C 174.4, 45.3, 26.9, 22.8], the presence of which was confirmed by correlations in the

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Table 1
^{1}H and ^{13}C NMR Data (600 and 150 MHz, resp., MeOD-d_4) of **1** and **2** with J values (Hz) in parentheses.

NO.	**1**		**2**	
	δ_H	δ_C	δ_H	δ_C
1a	4.02 dd (9.6,4.0)	68.0	2.05 dd (14.0,7.6)	37.8
1b	3.50 dd (9.6,8.6)	–	1.60 dd (14.0,6.7)	–
2	–	–	3.96 ddd (7.6,6.7,1.2)	80.4
3a	5.28 d (1.1)	110.2	1.48 t (5.9)	46.0
3b	4.98 bs	–	–	–
4	–	150.7	–	40.0
5	2.97 br q (9.1)	40.2	–	76.6
6a	2.12 ddd (14.5,6.8,1.9)	37.1	1.73 dd (14.3,5.2)	32.8
6b	1.72 ddd (14.5,8.6,3.6)	–	1.54 m	–
7a	4.49 dd (6.8,3.6)	76.7	1.52 m	29.6
7b	–	–	1.38 m	–
8	–	93.1	1.96 m	29.0
9	2.57 td (8.6,4.0)	51.4	1.36 m	44.3
10	1.6 s	19.2	–	41.5
11a	4.10 br d (14.5)	66.7	1.55 m	25.0
11b	4.00 br d (14.5)	–	1.32 m	–
12	–	–	0.81 d (6.7)	19.3
13	–	–	1.09 s	25.7
14	–	–	1.17 s	28.9
15	–	–	0.89 s	21.0
Glc-1	4.13 d (7.8)	104.6	4.33 d (7.8)	103.3
Glc-2	3.13 dd (8.8,7.9)	75.2	3.15 dd (8.8,7.9)	75.3
Glc-3	3.33 br t (8.8)	78.1	3.35 br t (8.8)	77.8
Glc-4	3.27 br t (9.5)	71.6	3.29 m	71.8
Glc-5	3.23 m	77.8	3.24 m	76.6
Glc-6a	3.85 dd (11.9,2.3)	62.7	3.86 dd (11.9,2.3)	62.9
Glc-6b	3.66 dd (11.9,5.6)	–	3.67 dd (11.9,5.6)	–
1′	–	174.4	–	–
2′	2.16 m	45.3	–	–
3′	2.05 m	26.9	–	–
4′	0.96 d (6.6)	22.8	–	–
5′	0.96 d (6.6)	22.8	–	–

^{1}H-^{1}H COSY and HSQC spectrum. In addition, the presence of a β-glycosyl moiety was established by an anomeric proton [δ_H 4.13 (1H, d, J = 7.8 Hz)] and partially overlapped signals attributed to oxymethylene and oxymethine protons between δ_H 3.13 and 3.85. Acid hydrolysis afforded D-glucose as the sole sugar, identified by TLC comparison and the positive optical rotation $[\alpha]_D^{20} + 47.0^{\circ}$ (Gan et al., 2008; Hudson and Dale, 1917). Five of the remaining 10 carbon signals were ascribable to a methyl (δ_C 19.2), *exo*-methylene (δ_C 150.7 and 110.2), and two oxy-methylene (δ_C 66.7 and 68.0).

The connectivities of the proton coupling sequence for the C-1-C-9-C-5-C-6-C-7 fragment in an iridoid skeleton were observed in the ^{1}H-^{1}H COSY spectrum (Fig. 1). The absence of HMBC correlations between H-3 (δ_H 5.28 and 4.98) and C-1 (δ_C 68.0) and/or between H-1 (δ_H 4.02 and 3.50) and C-3 (δ_C 110.2) showed that **1** was a monocyclic iridoid ring-opened. ^{1}H and ^{13}C NMR spectroscopic data showed the compound gross structure was closely similar to jatamanin J except for the absence of one hexose and isovaleryl moiety (Lin et al., 2010). Detailed analysis of 2D NMR data verified the location of the substitutents. The HMBC correlations (Fig. 1) between the Glc anomeric proton at δ_H 4.13 (1H, d, J = 7.8 Hz) and C-1 (δ_C 68.0) indicated that the glucose moiety was linked to C-1 (δ_C 68.0) of the aglycone. In the HMBC spectrum (Fig. 1), the position of the isovaleryloxyl ester group was determined as C-8 (δ_C 93.1) on the basis of weak correlation of H-10 (δ_H 1.6) and the ester carbonyl of the isovaleroxyl moiety. The stereo-structure was examined by a NOESY experiment. The NOESY correlations of H-9 (δ_H 2.57) with H-5 (δ_H 2.97) and H-10 (δ_H 1.6), H-7 (δ_H 4.49) with H-6α (δ_H 2.12), H-5 (δ_H 2.97) with H-6β (δ_H 1.72) showed that the H-5 (δ_H 2.97) and H-9 (δ_H 2.57) possess a *cis*-configuration and indicated 7β-OH, 8α-isovaleroxyl groups. Comparisions of NOESY NMR data for **1** with those from jatamanin J allowed the relative configurations at C-5 (δ_C 40.2), C-7 (δ_C 76.7), C-8 (δ_C 93.1), and C-9 (δ_C 51.4) to be identically assigned (Lin et al., 2010). The above data strongly suggested that **1** is a position isomer of patrinioside with an isovaleroxyl group at C-8 (δ_C 93.1) and sugar moiety at C-1 (δ_C 68.0). Thus, the structure of **1** was established as 8-*O*-isovaleroxyl-1-*O*-β-D-glucopyranosyl jatamanin J and named isopatrinioside.

Compound **2** was obtained as a white, amorphous powder. **2** had the molecular formula $C_{21}H_{36}O_7$, which was determined by HRESIMS ($[M+Na]^+$ at m/z 423.2352, calcd. for 423.2359), requiring 4 unsaturation. The IR spectrum of **2** displayed the presence of the hydroxyl (3414 cm^{-1}) and glycosyl (1074,1045 cm^{-1}). The ^{1}H NMR spectrum (Table 1) of **2** exhibited four methyls [δ_H 0.81 (3H, d, J = 6.7 Hz), 1.17 (3H, s), 1.09 (3H, s), 0.89 (3H, s)], and anomeric proton signal of β-glycosyl group at δ_H 4.33 (1H, d, J = 7.8 Hz), which gave correlation in the HMQC spectrum at δ_C 103.3. The ^{13}C NMR (Table 1) and DEPT spectroscopic data, in combination with HMQC spectrum, revealed the existence of one tricyclic sesquiterpenoid skeleton, including four methyls [δ_H 1.17 (1H, s), 1.09 (1H, s), 0.89 (1H, s), 0.81 (1H, d, J = 6.7 Hz); δ_C 28.9, 25.7, 21.0, 19.3]; four methylenes [δ_H 2.05 (1H, dd, J = 14.0, 7.6 Hz), 1.60 (1H, dd, J = 14.0, 6.7 Hz), 1.73 (1H, dd, J = 14.3, 5.2 Hz), 1.54 (1H,m), 1.52 (1H,m), 1.38 (1H,m), 1.55 (1H, m), 1.32 (1H, m); δ_C 37.8, 32.8, 29.6, 25.0], four methines [δ_H 3.96 (1H, ddd, J = 7.6, 6.7, 1.2 Hz), 1.48 (1H, t, J = 5.9 Hz), 1.36 (1H,m), 1.96 (1H,m); δ_C 80.4, 46.0, 44.3, 29.0] as well as three quaternary carbons [δ_C 40.0, 41.5, 76.6], which according to remaining three unsaturated degree. A careful comparison of the NMR data of **2** with those of the known compound valerianandid B (Mathela et al., 2005) indicated that they were structural analogues. The only difference was absence the β-D-glucose moiety in valerianandid B. The position of β-D-glucose at C-2 (δ_C 80.4) was confirmed based on the HMBC

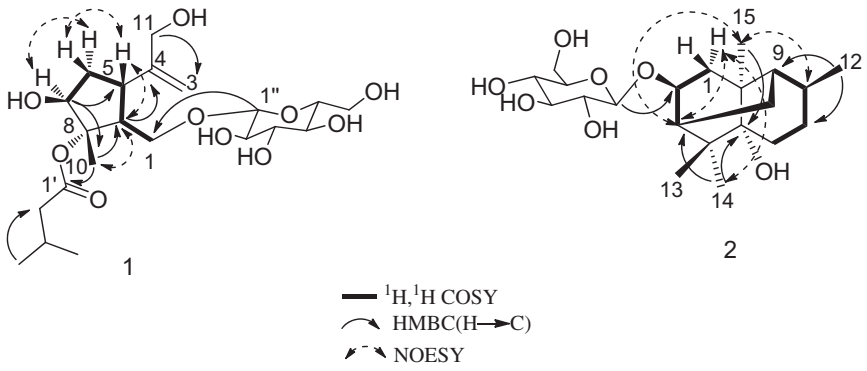

Fig. 1. Key ^{1}H, ^{1}H COSY, HMBC and NOSEY correlations of compound **1** and **2**.

correlation (Fig. 1) from anomeric proton δ_H 4.33 (1H, d, J = 7.8 Hz) to C-2 (δ_C 80.4). A detailed analysis of HMQC, HMBC and ^{1}H-^{1}H COSY spectrum (Fig. 1) supported the assignment of all protons and carbon signals. The relative configuration of **2** was established by the NOESY experiment. The NOESY correlations of H-1α (δ_H 2.05) with H-3 (δ_H 1.48), H-15 (δ_H 0.89) with H-3 (δ_H 1.48), H-8 (δ_H 1.96) with H-15 (δ_H 0.89) and H-14 (δ_H 1.17) with H-1α (δ_H 2.05). The relative configuration of **2** was the same as that of valerianananoid B and detailed comparison of the ^{1}H NMR coupling constants of **2** with valerianananoid B (Mathela et al., 2005). Consequently, **2** was defined and named as valerianananoid F.

In addition to the two new compounds **1** and **2**, the known iridoids and sesquiterpenoid were identified by comparison of spectroscopic data with those reported in the literature as 8-methoxy-3-methoxy-10-methylene-2,9-dioxatricyclo[4.3.1.0^{3,7}] decan-4-ol (**3**) (Inouye et al., 1974), vibutinal (**4**) (Liu et al., 2010), baldrinal (**5**) (Chen et al., 2005), 11-ethoxyviburtinal (**6**) (Boros and Stermitz, 1991), jatamanvaltrate E (**7**) (Lin et al., 2009), jatamanvaltrate A (**8**) (Lin et al., 2009), jatamanvaltrate F (**9**) (Lin et al., 2009), valeriotetrate C (**10**) (Lin et al., 2010), chlorovaltrate A (**11**) (Lin et al., 2013).

The neuroprotective effects of the compounds against $CoCl_2$-induced neuronal cell death in PC12 cells were investigated by an established CCK-8 assay. At the concentrations of 0.1 μM, 1 μM, 10 μM, compound **1** and **4** showed potent neuroprotective effects. Compound **1** increased the cell viability from 56.1% to 60.9%, 63.4% and 65.4%, respectively. For compound **4**, the weak neuroprotective activities were exhibited with the viability by 60.4% only with the concentrations of 10 μM. However, the other compounds were inactive even at the high concentrations of 10 μM. CCK-8 assay indicated that all of the compounds had no significant cytotoxicity to the PC12 cells at their effective concentration required for neuroprotective effects (data not shown).

In the course of our survey on pharmacologically active substances in Chinese herb medcine, much attention has been paid to the occurrence of compounds with neuroprotective effects, since these compounds are expected to be potentially useful for the treatment and prevention of Parkinson's disease (PD). During our search for new types of natural products possessing neuroprotective activities, we investigated the chemical constituents of the roots of *V. jatamansi*, of which the ethylacetate fractions showed moderate neuroprotective effects. By bioactivity-guided isolation, we isolated and identified a new secoiridoid glycoside (**1**) and a new sesquiterpenoid glycoside (**2**) and nine known (**3**–**11**) compounds successfully from the roots of *V. jatamansi*. This study discovered secoiridoid and sesquiterpenoid glycoside from *Valeriana* and first reported the activity of these compounds against PC12 cell damage. It can be seen that secoiridoid glycoside was bioactive component in *V. jatamansi*, which has been used as neurological disorder drug for thousands of years in East Asia. Of course, the neuroprotective effect of the secoiridoid aglycone is also worth of our concern in the further research.

3. Experimental

3.1. General experimental procedures

NMR measurements were performed on a Bruker-AVII-600 spectrometer. HRESIMS were obtained using Waters Synapt G_2HDMS. IR spectra were measured by PerkinElmer one FT-IR spectrometer (KBr). UV spectra were obtained on a Shimadzu UV-260 spectrophotometer. Optical rotations were measured with Anton Paar MCP 200. Preparative HPLC was performed on Shimadazu LC-10AT instrument with an SPD-10AVP detector and a YMC-Pack ODS-A column (250 mm × 10 mm, 5 μm). Preparative TLC was conducted with glass plates precoated silica gel GF_{254} (Yantai). TLC was carried out with GF_{254} plates (Qingdao Marine Chemical Factory). Spots were visualized by spraying with 10% H_2SO_4 in 95% EtOH followed by heating. Column chromatography (CC) was performed with silica gel and Sephadex LH-20. All the solvent used were of analytical grade.

3.2. Plant material

The root of *Valeriana jatamansi* Jones was collected in June of 2014 from the medicinal herbs market in Chengdu, Sichuan Province, China. The medical material identity was verified by Prof. Min Li (Chengdu University of TCM, Sichuan, China). A voucher specimen (ZZX-1407) was deposited at the School of Pharmacy, Chengdu University of TCM, Chengdu, China.

3.3. Extraction, isolation and characterization of compounds

The air-dried roots of *Valeriana jatamansi* Jones (5 kg), was powdered and exhaustively extracted using by percolating with 75% EtOH (3 × 30 L). The combined extract was concentrated under reduced pressure to dryness. The residue was suspended in water (2 L) and then the successively partitioned with Petroleum Ether (3 × 2 L), EtOAc (3 × 2 L)and *n*-BuOH (3 × 2 L). The EtOAc extract (170 g) was subjected to CC over silica gel and eluted with a gradient of $CHCl_3$-MeOH [95:5; 90:10; 85:15; 80:20; 75:25; 70:30; 60:40; 50:50; MeOH] to afford nine fractions A-I. Fraction D (3 g) and E (4 g) were separated by MHPLC (3.6 cm × 46 cm, ODS, 10 mL/min, 6 h), eluted with 40%, 50%, 60%, 70%, 80%, 90%, 100% MeOH-H_2O to afford about 7 subfractions respectively. The fraction D_4 (847 mg) was chromatographed over Sephadex LH-20 eluted with MeOH as mobile phase to give three subfractions. Successive separation of the $D_{4\text{-}2}$ (85 mg) by preparative TLC with $CHCl_3$-MeOH (4:1, v/v) to yield **1** (11.5 mg). The subfraction $D_{4\text{-}3}$ (127 mg) was separated by preparative TLC with Pe-EtOAc (15:1, v/v) to yield **4** (15.4 mg) and **5** (10.7 mg). Fraction D_5 (215 mg)was further purified by CC over Sephadex LH-20 eluted with MeOH-H_2O (9:1, v/v) as mobile phase to give five subfractions. The subfraction $D_{5\text{-}2}$ (58 mg) was purified by preparative TLC with petroleum ether-EtOAc (20:1, v/v) to **7** (11.2 mg). The Fraction $D_{5\text{-}3}$ (48 mg)was purified by preparative HPLC using 75% MeOH-H_2O (3 mL/min) as mobile phase to afford **2** (8.8 mg) and **6** (6.7 mg). At last, Fraction $D_{5\text{-}4}$ (45 mg) was purified by preparative HPLC using 70% MeOH-H_2O (3 mL/min) as mobile phase to afford **10** (10.5 mg), **11**(8.5 mg). Fraction E_3 (86 mg) was purified by preparative HPLC using 75% MeOH-H_2O (3 mL/min) as mobile phase to yield **3** (7.5 mg) and **8** (10.5 mg). The fraction E_4 (118 mg) was chromatographed over Sephadex LH-20 eluted with MeOH as mobile phase to give four subfractions. The subfraction $E_{4\text{-}3}$ (50 mg) was purified by preparative TLC with petroleum ether-EtOAc (10:1,v/v) to yield **9** (12.5 mg).

3.3.1. Isopatrinioside (*1*)

Amorphous powder; $[a]_D^{20}$ − 15.6° (c = 0.02, MeOH); UV (MeOH) λ_{max} (log ε): 206 (3.87), 220 (3.77); IR (KBr) ν_{max} cm^{-1}: 3400, 2958, 1713, 1605, 1077, 1047; HRESIMS *m/z*: 471.2204 [M+Na]$^+$ (calcd for C_{21} H_{36} O_{10}Na 471.2206); ^{1}H and ^{13}C NMR data see Table 1.

3.3.2. Valerianananoid F(*2*)

Amorphous powder; $[a]_D^{20}$ − 18.6° (c = 0.05, MeOH); UV (MeOH) λ_{max} (logε): 209 (3.27), 220 (3.14), 228 (3.16); IR (KBr) ν_{max} cm^{-1}: 3414, 2926, 2870, 1574, 1416, 1074, 1045; HRESIMS *m/z*: 423.2352 [M+Na]$^+$ (calcd for $C_{21}H_{36}O_7Na$ 423.2359); ^{1}H and ^{13}C NMR data see Table 1.

3.4. Acid hydrolysis

A solution of each compound (2.0 mg) in 2 N aqueous HCl (5 mL) was refluxed for 3 h. The residue was partitioned between H_2O (10 mL) and EtOAc (3 × 5 mL). The aqueous phase was evaporated under reduced pressure to give the sugar residue which could be identified as D-glucose by the sign of its optical rotation ($[\alpha]_D^{20}$ + 47.0°, c 0.05, H_2O). Similarly, compound **2** was hydrolyzed to afford the same sugar.

3.5. Neuroprotective effect assay

Rat pheochromocytoma cell line (PC12) were cultured in 96-well plates with DMEM supplemented with 10% (v/v) inactivated fetal bovine serum, and 100 U/mL penicillin/streptomycin. The cells were maintained at 37 °C in 5% CO_2 and 95% humidified air incubator. The cells were subcultured every three days. At 24 h before experiments, the medium was substituted by serum-deprived medium. Cells were pre-treated for 2 h with various concentrations (0.01, 0.1, 1.0, 10 μM) of compounds before incubation in a medium containing 300 μM $CoCl_2$. After incubation for 4 h, 10 μL CCK-8 solution was added. Absorbance was measured at 450 nm using a microplate reader.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2016.07.020.

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