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## Astrernestin, a novel aurone-phenylpropanoid adduct from the roots of *Astragalus ernestii*

Jin-Qiang Li\*, Chao-Jiang Xiao\*, Ye-Meng Li, Xin-Yan Tian, Xiang Dong and Bei Jiang

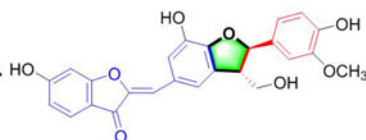
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### ABSTRACT

*Astragalus ernestii* has been used as a substitute for Radix Astragali (Huang-Qi) in southwest China. To better understand the chemical rationale for the medicinal usage, the phytochemistry of *A. ernestii* was recently studied. As a result, a novel aurone-phenylpropanoid adduct astrernestin (**1**), together with five known phenoloids calycosin-7-O- $\beta$ -D-glucopyranoside (**2**), 4,4'-dimethoxy-3'-hydroxy-7,9':7',9'-diepoxylicignan-3-O- $\beta$ -D-glucopyranoside (**3**), syringaresinol-4-O- $\beta$ -D-monoglucoside (**4**), hedyotol D 4''-O- $\beta$ -D-glucopyranoside (**5**) and trifolirhizin (**6**), were isolated from the roots of *A. ernestii*. The structure of compound **1** was elucidated by extensive spectroscopic analysis and optical rotation calculation.



*Astragalus ernestii*



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calculation

## 1. Introduction

The Radix Astragali has been used in China for over 2000 years, and known as 'Huang-Qi'. Traditionally, Radix Astragali is the dried root of *Astragalus membranaceus* (Fisch.) Bunge or *A. membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) P. K. Hsiao (Chinese Pharmacopeia Commission 2015). Huang-Qi is usually used to treat chronic illness and to increase overall vitality due to its various pharmacological effects, such as immunomodulatory, antihyperglycemic, antiinflammatory, antioxidant, anticancer, antiviral, liver protective and cardiovascular effects (Fu et al. 2014; Ionkova et al. 2014;

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Ng et al. 2014; Auyeung et al. 2016; Jung et al. 2016). *Astragalus ernestii* Comb. is a perennial flowering herb with thick and straight roots, which is mainly distributed in the southwest China. In Litang of Sichuan province, *A. ernestii* has been used as a substitute of Huang-Qi by local folk (The Compiler Group of Compilation of Chinese Herbal Medicine 1996). As previously reported, phytochemical investigation of the roots of *A. ernestii* led to several flavonoids and cycloartane triterpenoid saponins (Wang and He 1989; Wang et al. 1989; Sun et al. 2011; Tian et al. 2014). In order to find the chemical rationale for medicinal usage, *A. ernestii* was collected in Zhongdian (Yunnan province, China) for phytochemical exploration. As a result, a novel aurone-phenylpropanoid adduct astrernestin (**1**), together with five known phenoloids (**2–6**) were isolated from the roots of *A. ernestii*. Herein, this paper reports the isolation and structural determination of these compounds.

## 2. Results and discussion

A *n*-butanol soluble portion of the methanol extract from the roots of *A. ernestii* was subjected to normal and reverse phase silica gel column chromatography, Sephadex LH-20, macroporous adsorption resin and MCI gel column chromatography to give six phenoloids (**1–6**).

Compound **1** was obtained as a yellow amorphous powder, and assigned the molecular formula  $C_{25}H_{20}O_8$  (sixteen unsaturation degrees) from its HR-EI-MS and  $^1H$  and  $^{13}C$  NMR spectra (including DEPT, Table S1). The  $^1H$  NMR spectrum of **1** (Table S1) showed two ABX aromatic spin systems with protons at  $\delta_H$  7.64 (1H, d,  $J=8.5$  Hz, H-4), 6.75 (1H, d,  $J=1.7$  Hz, H-7) and 6.72 (1H, dd,  $J=8.5, 1.7$  Hz, H-5), and  $\delta_H$  7.01 (1H, d,  $J=1.9$  Hz, H-2''), 6.89 (1H, dd,  $J=8.1, 1.9$  Hz, H-6'') and 6.81 (1H, d,  $J=8.1$  Hz, H-5''), and other three olefinic proton singlets at  $\delta_H$  7.49, 7.38 and 6.76. In addition, one methoxyl at  $\delta_H$  3.85 (s) and four proton resonances from either methines or methylenes were also observed. Inspection of the  $^{13}C$  NMR spectrum with the aid of DEPT experiments (Table S1) revealed the existence of 25 carbon resonances including one carbonyl ( $\delta_C$  184.5), twenty olefinic carbons, one  $sp^3$  oxy-methylene ( $\delta_C$  64.8), two  $sp^3$  methines (including an oxy-methine at  $\delta_C$  89.7), and one methoxyl ( $\delta_C$  56.3). According to these spectroscopic data and the degree of unsaturation, **1** was assumed to be a flavone-phenylpropanoid adduct.

In the  $^1H$ - $^1H$  COSY spectrum, three spin coupling systems H-4/H-5, H-5''/H-6'' and H-7''/H-8''/H<sub>2</sub>-9'' (Figure S1) were unambiguously observed. According to HMBC spectrum (Figure S1), long-range correlations between H-4 and C-3 ( $\delta_C$  184.5), and H-10 ( $\delta_H$  6.76, brs) to C-3, C-2' ( $\delta_C$  120.2) and C-6' ( $\delta_C$  121.6) indicated that **1** should possess an aurone moiety. Then, *Z*-configuration of the aurone was determined by comparing chemical shift value of C-10 with those of previously reported (Pelter et al. 1979; Xiao et al. 2014). H-7'' ( $\delta_H$  5.65, d,  $J=6.2$  Hz) correlated to C-2'' ( $\delta_C$  110.4) and C-6'' ( $\delta_C$  119.8), which suggested a phenylpropanoid moiety should be present in **1**. The methoxyl ( $\delta_H$  3.85) correlated to C-3'' ( $\delta_C$  149.2) suggesting it connect to C-3''. HMBC correlations of H-7'' correlated to C-4' ( $\delta_C$  151.0) and C-5' ( $\delta_C$  131.0), and H<sub>2</sub>-9'' ( $\delta_H$  3.90, m) to C-5', which confirmed **1** to be an aurone-phenylpropanoid adduct fusing by a dihydrofuran.

The observation of ROESY correlation between H-7'' and H<sub>2</sub>-9'' indicated that H-7'' was in the opposite direction to H-8'' ( $\delta_{\text{H}}$  3.60, q-like,  $J = 5.9$  Hz). Namely, there were two possibilities (7''S,8''R or 7''R,8''S) for the stereochemical configuration of **1**. To determine the absolute configuration of **1**, the time-dependent density functional theory (TD-DFT) method for quantum mechanical calculation of optical rotation was adopted (Baranowska-Łączkowska et al. 2016). Comparing the experimental specific rotation data (+172.3,  $c$  0.09, MeOH) of **1** with those of computational values (Table S2), the stereochemical configuration of C-7 and C-8 was confirmed as 7''R/8''S. Therefore, the structure of compound **1** was finally identified to be a novel adduct of an aurone and a phenylpropanoid, and named astrernestin (Figure 1).

By comparing the spectroscopic data with those reported in the literature, the five known compounds obtained in this study were identified as calycosin-7-O- $\beta$ -D-glucopyranoside (**2**) (Luan et al. 2016), 4,4'-dimethoxy-3'-hydroxy-7,9':7',9'-diepoxylignan-3-O- $\beta$ -D-glucopyranoside (**3**) (Li et al. 2003), syringaresinol-4-O- $\beta$ -D-monoglucoside (**4**) (Meng et al. 2013), hedyotol D 4''-O- $\beta$ -D-glucopyranoside (**5**) (Miyachi & Tomimori 1998), and trifolirhizin (**6**) (Zhao et al. 2009), respectively.

### 3. Experimental

#### 3.1. General experimental procedures

1D and 2D NMR spectra were recorded on a Bruker Avance III-400 (Bruker, Faellanden, Switzerland) with TMS as an internal standard. The HR-ESI-MS and EI-MS data were obtained on a Waters AutoSpec Premier P776 mass spectrometer (Waters Co., Milford, MA, USA). UV spectra were recorded with UV2401PC UV/Vis spectrophotometer (Shimadzu, Kyoto, Japan). Optical rotations were determined on a SGW-3 automatic polarimeter (Shanghai INESA Physico optical instrument Co., Ltd, Shanghai, P. R. China). Column chromatography (CC) was performed on silica gel (200–300 or 300–400 mesh, Qingdao Marine Chemical Ltd., Qingdao, P. R. China), C-18 reversed phase silica gel (40  $\mu\text{m}$ ; J. T. Baker, Phillipsburg, NJ, USA), D101 macroporous adsorption resin (Tianjin Bohong Resin Technology Co., Ltd., Tianjin, China), MCI gel (75–150  $\mu\text{m}$ ; Mitsubishi Chemical Corp., Tokyo, Japan) and Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden). Thin layer chromatography (TLC) was performed on precoated silica gel GF<sub>254</sub> plates (Qingdao Marine Chemical Ltd.).

#### 3.2. Plant material

The roots of *Astragalus ernestii* were collected from Zhongdian, Yunnan, P. R. China in July 2012. The plant material was identified to be *Astragalus ernestii* Comb. by

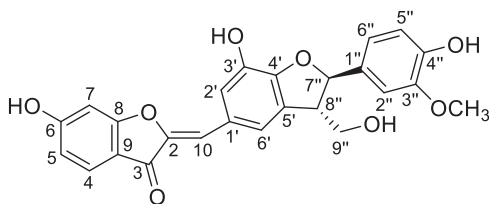


Figure 1. Structure of compound **1** isolated from the roots of *A. ernestii*.

Dr. De-Quan Zhang at the College of pharmacy and chemistry, Dali University, P. R. China. A voucher specimen (NO. 20120716-4-A) has been deposited at Institute of Materia Medica, Dali University.

### 3.3. Extraction and isolation

The dried and powdered roots of *A. ernestii* (1.26 kg) were extracted six times with methanol at room temperature ( $6 \times 6.5$  L, each for 24 h). After evaporation of the solvent *in vacuo*, the residue (168 g) was suspended in water and partitioned successively with ethyl acetate and *n*-butanol. The *n*-butanol soluble portion (32.1 g) was subjected to D101 macroporous adsorption resin with MeOH-H<sub>2</sub>O gradient solvent system (0:100→100:0) to give five fractions (Fr.A – Fr.E). Fr.C was subjected to a C-18 reversed phase silica gel CC (MeOH/H<sub>2</sub>O 5:5), a Sephadex LH-20 CC (MeOH) and repeated silica gel CC (CHCl<sub>3</sub>/MeOH 50:1) to give compounds **2** (2.3 mg), **3** (4.5 mg), **4** (21.1 mg) and **5** (3.1 mg). Fr.D was purified by a MCI gel CC (MeOH/H<sub>2</sub>O 6:4) and repeated silica gel CC (CHCl<sub>3</sub>/MeOH 60:1) to give compound **6** (25.0 mg). Fr.E was separated by a MCI gel CC (MeOH/H<sub>2</sub>O 6:4) and repeated silica gel CC (petroleum ether/acetone 4:1) to give compound **1** (3.9 mg).

### 3.4. Astrernestin (1)

Yellow amorphous powder;  $[\alpha]_D^{27} +172.3$  ( $c = 0.09$ , MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ): 203 (4.5), 254 (4.0), 280 (3.9), 401 (4.2) nm. <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data see Table S1; EI-MS  $m/z$  (rel. int. %): 448 [M]<sup>+</sup> (20), 431 (40), 430 (100), 418 (35), 270 (30), 137 (80), 121 (27); HR-EI-MS  $m/z$ : 448.1151 [M]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>20</sub>O<sub>8</sub>, 448.1158).

### 3.5. Optical rotation calculation

The CONFLEX 7 (CONFLEX Corporation, Tokyo, Japan) searches based on molecular mechanics with MMFF94S force field was performed for **1**, which gave 5 stable conformers for 7''S,8''R and 4 stable conformers for 7''R,8''S. Selected conformers with distributions higher than 1% were further optimized by the density functional theory (DFT) method at the B3LYP/6-31G+(d, p) level in Gaussian 09 program package (Gaussian, Inc., Wallingford, CT, USA, 2013). The specific rotations of the all conformers were then calculated by the TD-DFT method at the B3LYP/6-31G+(d, p) level in the gas phase or with the CPCM model in methanol solution. Optical rotation calculation at the wavelength of the sodium D line,  $\lambda = 589$  nm, used in the experimental measurement.

## 4. Conclusions

Our phytochemical study on the roots of *A. ernestii* has led to the isolation of a novel aurone-phenylpropanoid adduct astrernestin (**1**), together with five known phenoloids (**2–6**). Flavone-phenylpropanoid adducts are common in the literature, but the aurone-phenylpropanoid dimer was discovered in nature for the first time.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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