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Neo-clerodane diterpenoids from the whole plants of *Scutellaria formosana*

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ABSTRACT

Scuteformoids A-J, ten previously undescribed *neo*-clerodane diterpenoids along with one known analogue, were isolated from petroleum ether soluable fraction of the whole plants of *Scutellaria formosana*. The differences among these compounds are the substituents and stereochemistry at C-13. Their structures were elucidated by 1D and 2D NMR experiments, and the absolute configurations of Scuteformoids A, C, E, F, and I were further confirmed by single-crystal X-ray diffraction. Scuteformoids A, C, D, F, H, and I were evaluated for their inhibitory effects against HIV lytic replication and cytotoxic activities. All of them showed weak anti-HIV activities, with EC_{50} values ranging from 48.24 to 79.17 μg/mL.

1. Introduction

Scutellaria is an unique cosmopolitan genus of the subfamily Scutellarioideae belonging to the Lamiaceae (Labiatae) family. Approximately 360 species are found spread throughout the world, including Europe, North America, and East Asia (Bruno et al., 2002; Paton, 1990). However the majority grow in Asia. The use of species of *Scutellaria* in Chinese popular medicine has a long tradition. They are still used for the treatment of several human diseases, which include respiratory and gastrointestinal bacterial infections (Tang and Eisenbrand, 1992).

The genus *Scutellaria* is rich in flavonoids and diterpenoids, mainly *neo*-clerodane diterpenoids, with a variety of biological activities, such as anti-feedant (Raccuglia et al., 2010), anti-oxidant (Nguyen et al., 2009), cytotoxic (Kurimoto et al., 2015), anti-cancer (Wang et al., 2012), anti-influenzavirus FM1 (Gang et al., 2011), anti-EBV (Epstein-Barr virus) (Wu et al., 2015), and inhibition of nitric oxide production activities (Yeon et al., 2015). In the continuation of search for new *neo*-clerodanes from *Scutellaria* plants (Bozov et al., 1993; Bruno et al., 1993; de la Torre et al., 1992; Rodriguez et al., 1993; Rodriguez-Hahn et al., 1994; Wu et al., 2015; Yeon et al., 2015), we investigated *Scutellaria formosana* growing in southern China (Cui et al., 2010). In this paper, the isolation and structural elucidation of 10 previously undescribed *neo*-clerodane diterpenoids, scuteformoids A-J (**1**–**10**), and a known analogue, hastifolin A (**11**) were reported. In addition, compounds **1**, **3**, **4**, **6**, **8**, and **9** were evaluated for their inhibitory effects against HIV lytic replication and cytotoxic activities.

2. Results and discussion

An 85% EtOH extract of the whole plants of *Scutellaria formosana* was suspended in water and then partitioned successively with petroleum ether and EtOAc. As a result, 10 previously undescribed compounds (**1**–**10**) and a known compound, hastifolin A (**11**) (Fig. 1), were obtained from the petroleum ether soluable fraction. Their structures were elucidated on the basis of spectroscopic data interpretation, especially using 2D NMR (COSY, HSQC, HMBC, and NOESY) methods. The configurations of compounds **1**, **3**, **5**, **6**, and **9** were confirmed by single-crystal X-ray diffraction (Fig. 2).

Compound **1** was obtained as a white crystal. Its molecular formula was established as $C_{31}H_{38}O_{10}$ by its HRESIMS of the [M +

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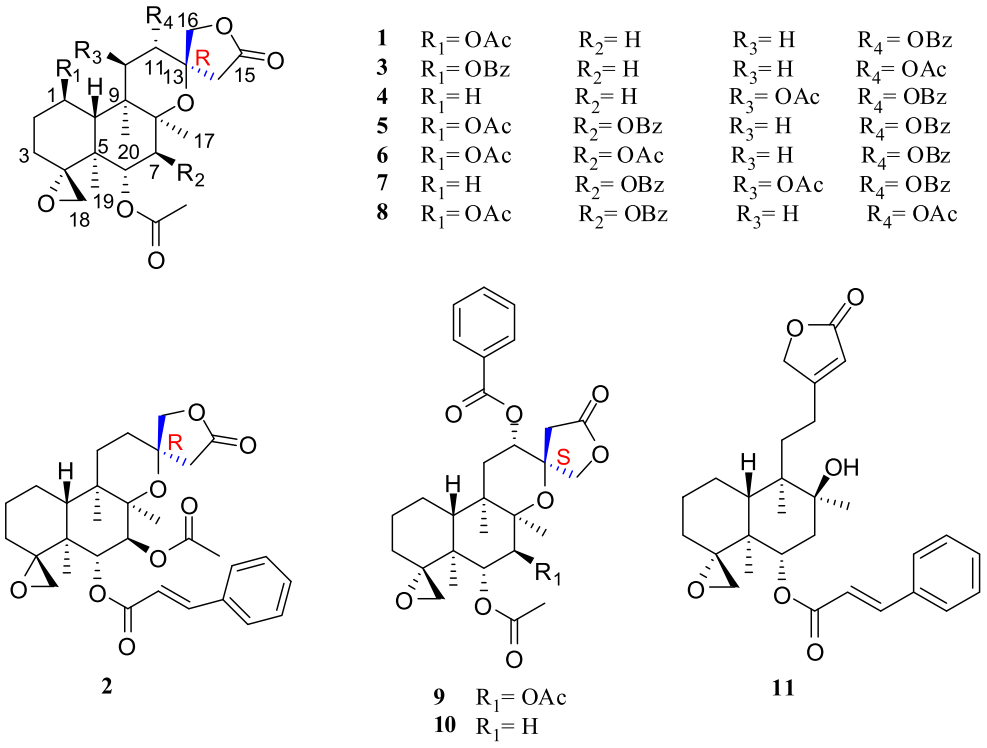

Fig. 1. Structures of compounds **1**–**11**.

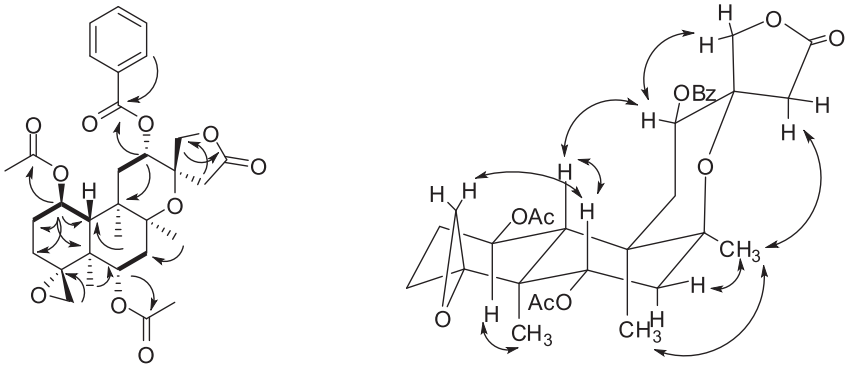

Fig. 2. The Key $^{1}H-^{1}H$ COSY (▬), HMBC (→) and NOESY (↔) correlations of compound **1**.

Na]$^{+}$ peak at *m/z* 593.2366. The IR spectrum showed absorption signals for epoxide group (3001 cm^{-1}), γ-lactone group (1785 cm^{-1}), ester carbonyl (1714 cm^{-1}), phenyl (1597 cm^{-1}), and acetoxyl (1248 cm^{-1}) functionalities. The ^{1}H NMR spectrum of **1** also revealed the presence of a benzoyloxy moiety [δ_H 7.92 (2H, d, J = 7.2 Hz, H-3′ and H-7′), 7.57 (1H, t, J = 7.2 Hz, H-5′), 7.44 (2H, t, J = 7.2 Hz, H-4′ and H-6′)], and acetoxyl groups [δ_H 1.98, s, (3H × 2)]. The ^{13}C NMR data of **1** revealed the presence of two acetoxyls (δ_C 170.1, 21.7 and 170.4, 21.4) and a benzoyloxy [δ_C 165.4 (PhCOO); 129.0 (C-2′); 129.8 (C-3′ and C-7′); 128.8 (C-4′ and C-6′) and 133.8 (C-5′)] group. In addition to the acetoxyl and benzoyloxy groups, the ^{1}H and ^{13}C NMR spectra of **1** showed 20 carbon signals including three tertiary methyl groups [δ_H 0.96 (s, H_3-20), 1.31 (s, H_3-17), 1.37 (s, H_3-19); δ_C 20.9 (C-20), 24.4 (C-17), 14.9 (C-19)], an epoxide methylene proton [δ_H 3.18 (br s, H_a -18), 2.46 (d, J = 4.0 Hz, H_b-18); δ_C 51.7 (C-18), and 65.5 (C-4)], an oxygen bearing methylene group [δ_H 4.42 (d, J = 9.6 Hz, H_a-16), 4.32 (d, J = 9.6 Hz, H_b-16); δ_C 78.5 (C-16)], an isolated methylene group [δ_H 2.78 (d, J = 16.8 Hz, H_a-14), 3.07 (d, J = 16.8 Hz, H_b-14); 38.3 (C-14)], and two oxygen-bearing quaternary carbons [δ_C 78.4 (C-13) and 80.7 (C-8)], which are characteristic signals for a *neo*-clerodane diterpenoid with a 4α,18; 8β,13-diepoxy-15,16-γ-lactone moiety (Raccuglia et al., 2010). The locations of the substituents of the acetoxyls and benzoyloxy in **1** were established from the key HMBC correlations from H-1 (δ_H 5.36) to C-1″ (δ_C 170.1), H-6 (δ_H 5.06) to C-1‴ (δ_C 170.4), and H-12 (δ_H 5.60) to C-1′ (δ_C 165.4). Furthermore, the HMBC correlations of H-12 with C-13 and C-16, H-14 with C-13, C-15, and C-16, and H-16 with C-15 supported the proposed 13-spiro-15,16-γ-lactone skeleton of **1** (Fig. 2). The NOESY experiment (Fig. S8, Supporting Information) of **1** showed clear correlation peaks between Me-17 with H-14, indicating 13*R** stereochemistry, and also between H-6 and H-18a, which confirmed, as in hastifolin B (Raccuglia et al., 2010), a 4*R* configuration. NOESY correlations were also observed between H-1 and Me-19, and between H_2-7 and Me-