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Three new nortriterpenoids from the rattan stems of *Schisandra chinensis*

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ABSTRACT

Three new nortriterpenoids, schindilactones L and M (**1–2**) and wuweizidilactone S (**3**), along with five known nortriterpenoids, schindilactone G (**4**), wuweizidilactone A (**5**), wuweizidilactone L (**6**), wuweizidilactone C (**7**) and pre-schisanartanin (**8**), were isolated from the rattan stems of *Schisandra chinensis*. The structure of the new compounds were elucidated by spectroscopic methods, including one and two-dimensional NMR as well as high-resolution mass spectrometry. All of the compounds were evaluated for their cytotoxicities against human Hela cancer cell lines *in vitro*; none of them showed significant activities.

1. Introduction

Schisandra chinensis (Turcz.) Baill., is a climbing plant that is endemic to the northeast regions of China, the Russian Far East, Korea, and Japan (Panossian and Wikman, 2008; Hancke et al., 1999). The stems of this plant are listed officially as a food and herbal medicine in the Chinese Pharmacopoeia Commission, and they have been widely added to functional foods (Zhu et al., 2015). The extracts from the stems of this plant have some important pharmacological effects that include liver-protective (Meng et al., 2013; Hu and Yu, 2011), antioxidant (Gao et al., 2016; Li et al., 2012), antifatigue (Gao et al., 2016), anti-HIV-1 (Shi et al., 2014a,b), anti-HSV-2 (Song et al., 2013) and cytotoxicity (Zhu et al., 2015; Hu and Yu, 2011) activities, and they have been used for the treatment of frostbite, influenza, and gastrointestinal dysfunction in China (Zhang et al., 2005). In previous studies, the rattan stems of this plant have yielded a series of chemical constituents, such as monoterpenes (Yang et al., 2016a,b), nortriterpenoids (Shi et al., 2011; Song et al., 2013) and dibenzocyclooctadiene lignans (Shi et al., 2014a,b; Yang et al., 2016a,b). Motivated by the discovery of new and bioactive natural products from this plant, our group has phytochemically studied the stems of *S. chinensis*, isolating three new compounds, including two schisanartane nortriterpenoids, schindilactones L–M (**1–2**), and a 18-nor-schiartane nortriterpenoid, wuweizidilactone S (**3**), together with five known ones (Fig. 1). All of the compounds were evaluated for their cytotoxicities.

2. Results and discussion

Compound **1** was obtained as a white powder, and its molecular formula was determined to be $C_{29}H_{36}O_{11}$ by HRESIMS *m/z* 561.2339 $[M + H]^+$ (calcd for $C_{29}H_{37}O_{11}$, 561.2336) and ^{13}C NMR spectroscopic data, requiring 12° of unsaturation. The ^1H NMR spectrum of **1** (Table 1) exhibited five methyl groups at δ_H 1.40 (3H, s, H_3-29), 1.31 (3H, s, H_3-30), 0.92 (3H, s, H_3-18), 1.13 (3H, d, J = 5.9 Hz, H_3-21), and 1.43 (3H, d, J = 7.2 Hz, H_3-27). Analysis of the ^{13}C NMR and DEPT spectra showed the presence of six methylenes (δ_C 19.5, 32.0, 33.2, 37.0, 39.6, and 43.1), and two ester carbons (δ_C 173.4 and 177.7), two ketone carbons (δ_C 214.8 and 220.2), and six oxygenated quaternary carbons (δ_C 83.9, 84.3, 77.9, 97.2, 97.9, and 108.5). This indicated that compound **1** required the presence of eight rings to satisfy the observed indices of hydrogen deficiency and possessed a highly oxygenated nortriterpenoid with a schisanartane skeleton (Shi et al., 2015). Two pairs of AB-type methylenes (δ_H 3.15, 3.06, both d, J = 17.7 Hz, H_2-2), (δ_H 2.54, 2.98, both d, J = 16.4 Hz, H_2-19) in the ^1H NMR spectra (Table 1) together with key HMBC correlations of H-30 (δ_H 1.12, s) with C-4, C-5 and C-29; H-19a (δ_H 2.54, d, J = 16.4 Hz) with C-8, C-9, C-10, C-5, and C-1; and H-7 (δ_H 2.10, m) with C-8 and the ^1H-^1H COSY correlation of H-5/H_2-6/H_2-7 (Fig. 2) were found. This information shows that compound **1** possessed the representative 5/5/7 membered A-C rings of Schisandra nortriterpenoids (Li, R.T., 2005). The correlations of H_2-11/H-12 and H_3-21/H-20/H-22/H-16/H-23/H-24/H-25/H-27 in ^1H-^1H COSY (Fig. 2), along with key HMBC correlations from H-18 to C-12, C-16, and C-17; from H-16 to C-15; and from H_3-27 to C-26 showed that compound **1** had a similar structure to that of sphenadilactone F (He et al., 2012). The main differences between **1** and sphenadilactone F were observed in the absence of a hydroxyl group at C-20 and the presence of a hydroxyl group at C-1 in **1**. This was deduced by the upfield chemical shifts of C-20 from δ_C 75.0 in sphenadilactone F to δ_C 44.8 of compound **1** and the downfield chemical shifts of C-1 from δ_C 81.9 in sphenadilactone F to δ_C 108.5 of compound **1**. These notable

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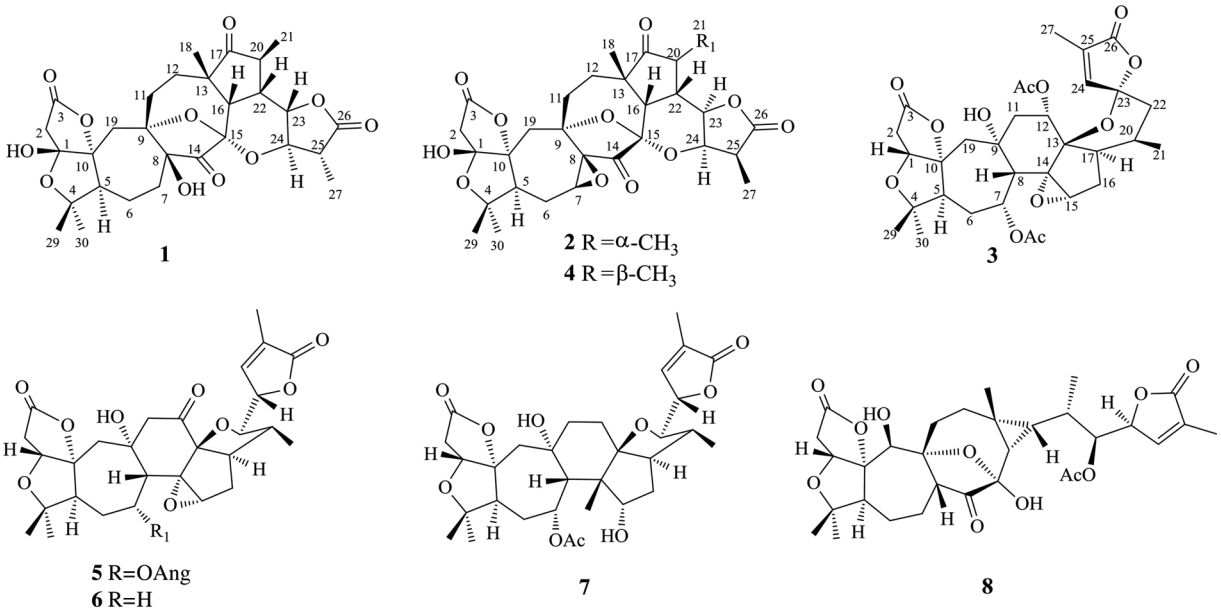

Fig 1. Structures of compounds **1–8**.

changes were determined by the HMBC spectrum (Fig. 2). Correlations were evident from H-2a (δ_H 3.06, d, J = 17.7 Hz) and H-19a (δ_H 2.54, d, J = 16.4 Hz) to an oxygenated quaternary carbon (δ_C 108.5, C-1) and correlations from H-16 (δ_H 2.55, d, J = 8.4 Hz), H-22 (δ_H 2.86, m) and H-23 (δ_H 4.74, br. s) to a methine (δ_C 44.8, C-20). Moreover, the ^{1}H-^{1}H COSY correlations of H_3-21/H-20/H-22/H-23/H-24 observed in compound **1** (Fig. 2) also supported the above conclusion. Thus, the planar structure of **1** was established as shown.

The relative configuration of compound **1** was determined by comparing the spectroscopic data with sphenadilactone F and by use of the NOESY experiment. The ^{13}C NMR chemical shift of C-20 was approximately 45; hence, the orientation of Me-21 was determined to be *β* (Huang et al., 2007a,b). NOESY correlations (Fig. 3) for Me-21/H-16/H-22, H-22/H-18, Me-21/H-23, H-23/H-25, and Me-27/H-24 indicated that H-16, H-22, H-18, H-23, and H-25 possessed the same *β*-orientation, whereas Me-27 and H-24 were in an α-orientation. The other configurations of **1** were determined to be the same as those of sphenadilactone F (He et al., 2012). Therefore, compound **1** was determined and named schindilactone L.

Compound **2** was isolated as a white solid, and the molecular formula of $C_{29}H_{34}O_{11}$ was determined by the HRESIMS ion at *m/z* 559.2156 $[M + H]^+$ (calcd for 559.2179) and ^{13}C NMR data, which indicated 13 indices of hydrogen deficiency. Analysis of the ^{1}H and ^{13}C NMR spectra of **2** (Table 1) showed the presence of two ester carbonyls (δ_C 173.2 and 177.9), two ketone carbonyls (δ_C 208.3 and 221.4), and six oxygenated quaternary carbons (δ_C 61.4, 80.0, 84.5, 97.1, 97.3 and 108.7), which are characteristic signs of a schisanartane nucleus with eight rings and one hydroxyl. Two pairs of AB-type in the ^{1}H NMR spectra (Table 1) suggested that compound **2** had A-C rings, and key HMBC correlations of H-18 with C-12, C-16 and C-17; H_3-21 with 17; H_2-11 with C-9; H-16 with C-15; and H_3-27 with C-26, together with the correlations of H_2-11/H-12 and H_3-21/H-20/H-22/H-16/H-23/H-24/H-25/H-27 in ^{1}H-^{1}H COSY (Fig. 2) indicated that molecule **2** possessed the same skeleton as schindilactone G (**4**) (Huang et al., 2008) and that they might be a pair of diastereomers. This deduction was shown by the upfield chemical shift for C-20 from δ_C 45.4 in **4** to δ_C 41.3 in **2** and by the ROESY correlation (Fig. 3) of Me-21 (δ_H 1.37, 3H, d, J = 7.8 Hz) with H-23 (δ_H 4.76, br. s). Thus, Me-21 in **2** was α-oriented, and compound **2** was the C-20 epimer of **4**. Combined with 2D NMR analysis and the molecular formula, the planar structure of **2** was elucidated as shown in Fig. 2. The relative stereochemistry of **2** was determined to be the same as that of **4** by comparison of the carbon and proton chemical shifts, coupling constants and ROESY spectrum. Thus, the complete structure of **2** was established and named schindilactone M.

Compound **3** was isolated as a white solid, and it had a molecular formula of $C_{32}H_{40}O_{12}$ by the positive HRSEIMS found at 617.2590$[M + H]^+$ (calcd for 617.2598), requiring 12 ° of unsaturation. Four groups of ^{1}H-^{1}H COSY spin systems, H-1/H_2-2, H-5/H_2-6/H-7/H-8, H_2-11/H-12, and H-15/H_2-16/H-17/H-20/H_3-21/H-22 coupled with key HMBC correlations from H_2-11 to C-9, H-8 to C-9 and C-14, H-12 to C-13, H-16 to C-13, and from H_2-27 to C-24 and C-26 accomplished the planar structure of **3**, and a comparison of the spectral data with those of propindilactone Q (Lei et al., 2010) revealed that the structure of **3** had the same core structure to that of propindilactone Q, except for an additional acetyl group (δ_C 169.7, 20.9). The HMBC cross-peak (Fig. 2) of H-7 (δ_H 5.47, br. d, J = 8.6 Hz) with the carbonyl carbon at δ_C 169.7 showed that the acetyl group was located at C-7. The relative stereochemistry of **3** was mainly established by means of ROESY experiments and by a comparison of its spectroscopic data with propindilactone Q. The ROESY spectrum of **3** (Fig. 3) exhibited correlations between H-5/H_3-30, H_3-29/H-1, H-1/H_2-19, H_2-19/H-7/H-8, H-7/H-15, H-15/H-16*β*, H-16*β*/H_3-21/H-22*β*, H-22α/H-17 and H-12/H-17/H-20, indicating that H-1, H-8, H_3-21 and the acetyl group attached at C-12 were *β*-oriented, whereas the other acetyl group attached at C-7 and the 14, 15-epoxy-ring were on the α-face of the molecule. The other chiral centers in compound **3** were found to be the same as propindilactone Q. Thus, the structure of **3** was determined as shown and given the name wuweizidilactone S.

Compounds **1–3** were not obtained as single crystals to determine the absolute configurations. The structures of compounds **4–8** were determined as schindilactone G (**4**) (Huang et al., 2008), wuweizidilactone A (**5**) (Huang et al., 2007a,b), wuweizidilactone L (**6**) (Shi et al., 2014a,b), wuweizidilactone C (**7**) (Huang et al., 2007a,b) and preschisanartanin (**8**) (Huang et al., 2007a,b) by comparing with their experimental and reported physical data (Table 2).

The cytotoxicities of compounds **1–8** *in vitro* against Hela cancer cell lines obtained from the China Center for Type Culture Collection were tested using an MTT assay with cisplatin as a positive control (He et al., 2012), but they showed no obvious cytotoxicity with IC_{50} values of over 100 μM (Table 3).