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Anticomplement compounds from *Polygonum chinense*

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ABSTRACT

Five new compounds including two phenyldilactones (**1**, **2**), two coumarins (**3**, **4**) and a dimer of *N*-*E*-feruloyl tyramine (**5**) together with twenty-three known compounds (**6**–**28**) were isolated from a medicinal plant *Polygonum chinense*. The structures of the new compounds were established by detailed spectral analysis. The absolute configurations of **1** and **5** were elucidated by Mosher's method, $Mo_2(OAc)_4$-induced electronic circular dichroism (ECD) data, and ECD calculation. All the compounds were found to show potent anticomplement activity with CH_{50} and AP_{50} values ranging from 0.18 to 1.45 mM, and 0.26 to 2.80 mM, respectively. Phenyldilactones and phenylpropionic tyramines were firstly reported as anticomplement agents. The targets of compounds **1**, **3**, **5** and **10** in complement activation cascade were identified as well.

Complement is a part of the innate immune system which is responsible for host defense against pathogen invasion and clearance of potentially damaging cell debris. However, excessive complement activation may be detrimental because it can contribute to uncontrolled inflammatory responses and lead to tissue damage.[1] Hence, complement is an interesting and promising target for the treatment of diseases associated with excessive complement activation, including viral and bacterial infections,[2] inflammatory diseases and gastrointestinal disorders.[3–5]

Polygonum chinense Linn. (Huotanmu in Chinese) is a perennial plant widely distributed in the sub-tropical and warm temperate regions of Asia. It has been used as an herbal medicine for different purposes in these areas. In China, it is commonly used for the treatment of hepatitis, influenza, dysentery and enteritis.[6–8] In our research for anticomplement agents from traditional Chinese medicines, an ethanolic extract obtained from the herbs of *P. chinense*[9] was found to show strong anticomplement activity (CH_{50} 0.079 mg/mL). Bioactivity-guided fractionation of this extract was thus performed and led to the isolation[10] of five new (**1**–**5**) and twenty-three known (**6**–**28**) compounds with anticomplement activity. Herein, we report the isolation and structural elucidation of the new compounds and the anticomplement activity of all isolates.

Compound **1** was isolated as light brown amorphous powder. The molecular formula was determined to be $C_{15}H_{16}O_8$ according to the HRESIMS *m/z* 323.0912 $[M-H]^-$ (calcd for 323.0932).

The ^{13}C NMR and DEPT-135 spectroscopic data of **1** showed the presence of 15 carbons including two methylene carbons, seven methine carbons, six quaternary carbons, one δ-lactone carbonyl carbon (δ_C 173.5), and one γ-lactone carbonyl carbon (δ_C 176.6). The HMBC correlation of (Fig. 2) H-3/C-2, H-3/C-4a, H-4/C-4a, H-4/C-5 and H-7a/C-4a led us to propose a dilactone skeleton.[11] The ^1H NMR signals at δ_H 7.27 (H-3″/5″, d, 8.7 Hz) and δ_H 6.76 (H-2″/6″, d, 8.7 Hz) together with six aromatic carbon signals at δ_C 127.7 (C-1″), 116.5 (C-2″), 131.1 (C-3″), 158.5 (C-4″), 131.1 (C-5″), 116.5 (C-6″) indicated a *p*-hydroxyphenyl moiety. The attachment of the *p*-hydroxyphenyl moiety at the C-4 of the dilactone was based on the observed HMBC correlations from H-4 to C-1″ and C-2″/C-6″; and from H_a-3 to C-1″. Careful comparison of the NMR spectroscopic data (Table 1) of **1** with those of maysedilactone A isolated from *Maytenus senegalensis* indicated that they share the same planar structure.[12] The only difference was the specific rotation values ($[\alpha]_{25}^D = -6.5$ for 1, and $[\alpha]_{25}^D = +64$ for maysedilactone A).

The NOESY correlations (Fig. 3) between H-4 and H-7, H-4 and H-7a revealed that H-7a, H-7, and H-4 were cofacial. The absolute configuration of C-4a was established with convenient Mosher's method.[13,14] **1** was treated with(*R*)- and (*S*)-MTPA in CD_3OD at room temperature, to afford the (*S*)- and (*R*)-MTPA ester derivatives **1a** and **1b**, respectively. The negative $\Delta\delta_{S-R}$ values obtained for H-4 and H-7a, together with positive $\Delta\delta_{S-R}$ values obtained

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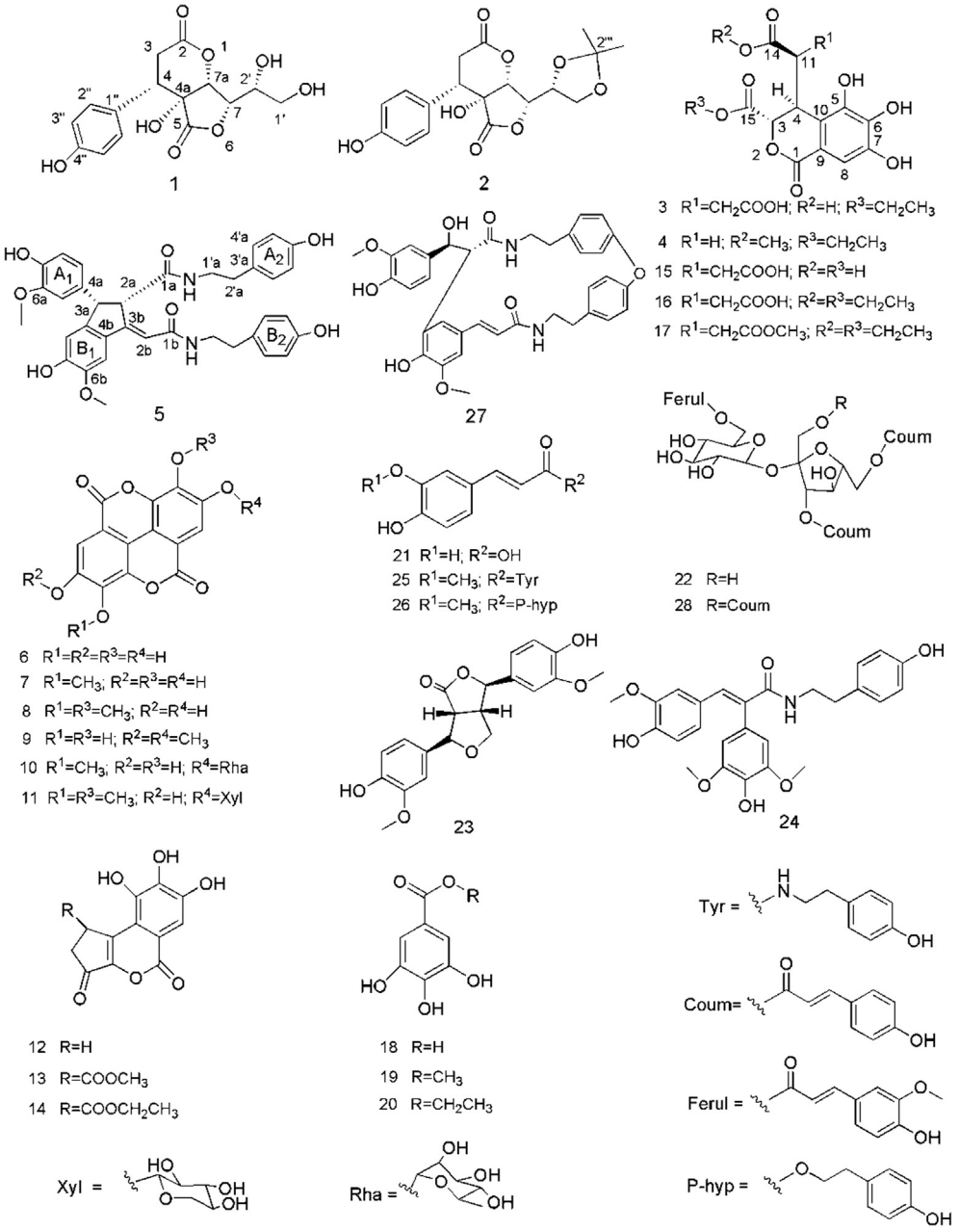

Fig. 1. Structures of compounds **1**–**28**.

for H-3_a and H-3_b (Fig. 4), indicated that the absolute configuration of C-4a is *R*. However, the Mosher ester procedure could not be used for assignment of the absolute configuration of C-2′ in the acylic 1′,2′-diol moiety, the Snatzke and Frelek's method was thus applied.[15,16] After mixing **1** with $Mo_2(OAc)_4$ in DMSO, a negative Cotton effect at approximately 310 nm (Fig. 5) was observed, indicating that the absolute configuration of C-2′ is *R*. To determine the absolute configurations at C-4, C-7a and C-7, the calculated ECD spectra (Fig. 6) of (4*S*, 4a*R*, 7a*R*, 7*S*, 2′*R*)-**1** and (4*R*, 4a*S*, 7a*S*, 7*R*, 2′*S*)-**1** were obtained at the B3LYP/6-311G (d,p) level, and the former was consistent with the experimental curve of **1**[ECD (c = 0.2, MeOH) λ_{max} ($\Delta\varepsilon$) 204 (+2.31), 219 (−8.65), 234 (+12.08), 277 (−0.92) nm.]. Compound **1** was thus established as the C-2′ epimer of maysedilactone A and named as (4*S*, 4a*R*, 7a*R*, 7*S*, 2′*R*) maysedilactone C.

Compound **2** was isolated as light brown amorphous powder. Its molecular formula was determined to be $C_{18}H_{20}O_8$ according to the HRESIMS m/z 363.1085 $[M-H]^-$ (calcd for 363.1077).

Comparison of the NMR spectroscopic data of **2** (Table 1) with those of compound **1** indicated the presence of same skeleton. The differences between **2** and **1** were that the presence of an additional double oxygenated quaternary carbon at δ_C 108.9, and two methyl carbons (δ_C 26.01, 25.37). The HMBC correlations from the protons (δ_H 2.04, 2.06) of two methyls to C-2‴ revealed that these two methyls were connected to C-2‴. While C-2‴ was linked with C-1′and C-2′ with oxygen bridges based on the HMBC correlations from H-1′ and H-2′ to C-2‴. The ECD curve of **2** (c = 0.2, MeOH) exhibited a negative cotton effect at 220, 273 nm and positive cotton effect at 205, 234 nm, in good agreement with **1**. Thus, compound **2** was identified as (4*S*, 4a*R*, 7a*R*, 7*S*, 2′*R*)