

Short communication

Labdane and norlabdane diterpenoids from the aerial parts of *Leonurus japonicus*

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ABSTRACT

A new labdane diterpenoid, leojaponicin (**1**), a novel norlabdane, methyl 15,16-dinor-7-oxolabda-8-ene-14-oate (**2**), along with four known labdanes, hispanone (**3**), leoheteronins A (**4**) and B (**5**), 15-methoxyleoheteronin B (**6**), and three norlabdanes, 14,15,16-trinor-7-oxolabda-8-ene-13-oic acid (**7**), methyl 14,15,16-trinor-7-oxolabda-8-ene-13-oate (**8**), 14,15-dinor-8-labdene-7,13-dione (**9**), and a steroid, stigmast-4-ene-3-one (**10**), were isolated from a hexane extract of *Leonurus japonicus*. Their structures were determined using spectroscopic methods, mainly 1-D and 2-D NMR. Compounds **7** and **8** were previously semisynthesized but are reported here for the first time as naturally occurring compounds. In addition, α -glucosidase inhibitory activity of the isolated compounds was evaluated and compound **6** exhibited the strongest effect with IC_{50} value of 26.7 μ M (compared with the positive control acarbose, $IC_{50} = 214.5 \mu$ M).

1. Introduction

Leonurus japonicus Houtt. (Lamiaceae), synonym *L. heterophyllus* Sweet, is a herbal flowering plant which is confined to Asia, some countries of Africa and America (Vu, 2000). The species is used in traditional medicine for the treatment of female diseases such as post-partum bleeding (Do, 2005), menstrual disturbance, dysmenorrhea, amenorrhea, and menoxenia (Peng et al., 2013; Shang et al., 2014). In Viet Nam, extracts of a mixture of this species, *Artemisia vulgaris* and the rhizomes of *Cyperus rotundus* produce a popular remedy called “Cao Ich Mau” which has been long used as a blood tonic and menstruation regulation (Do, 2005).

Previous phytochemical studies showed that the *Leonurus* species biosynthesized mainly labdane-type diterpenoids (Gong et al., 2012; Hon et al., 1993; Liu et al., 2014; Phan et al., 2005a,b; Phan et al., 2005a,b; Romero-González et al., 2006). In addition, diterpenoids of other skeletons (Liu et al., 2014; Wu et al., 2015; Xiong et al., 2015a), triterpenoids (Ye et al., 2014), sesquiterpenoids (Xiong et al., 2013), flavonoids (Seo et al., 2010; Zhang et al., 2013), alkaloids (Shang et al., 2014), cyclic peptides (Morita et al., 1996, 1997, 2006), and steroids (Zhou et al., 2015), were also found. The labdane diterpenoids exhibited anti-platelet aggregation (Lee et al., 1991; Xiong et al., 2015b), anti-cholinesterase (Tran et al., 2011), anti-inflammatory (Khan et al.,

2012; Qin et al., 2014), and coagulant activities (Peng et al., 2013) whilst the other classes of compounds showed inhibitory activity against platelet aggregation (Xiong et al., 2013, 2015b; Zhou et al., 2015), cytotoxic (Jiang et al., 2015; Ye et al., 2014; Zhong et al., 2015), and antibacterial activities (Xiong et al., 2013). In this work, we chemically studied a hexane extract of the aerial parts of *L. japonicus* and evaluated α -glucosidase inhibitory activity of the extract and isolated compounds.

2. Results and discussion

Column chromatographies of the hexane extract on silica gel, RP-18 and Sephadex LH-20 led to the isolation of a new labdane, leojaponicin (**1**), a novel norlabdane, methyl 15,16-dinor-7-oxolabda-8-ene-14-oate (**2**), along with four known labdane diterpenoids, hispanone (**3**) (Phan et al., 2005a), leoheteronins A (**4**) and B (**5**) (Phan et al., 2005a), 15-methoxyleoheteronin B (**6**) (Qin et al., 2014), three norlabdanes, 14,15,16-trinor-7-oxolabda-8-ene-13-oic acid (**7**) (Perez-Sirvent et al., 1981), methyl 14,15,16-trinor-7-oxolabda-8-ene-13-oate (**8**) (Perez-Sirvent et al., 1981) and 14,15-dinor-8-labdene-7,13-dione (**9**) (Wahlberg et al., 1988), and a steroid, stigmast-4-ene-3-one (**10**) (Seca et al., 2000) (Fig. 1).

Compound **1** was isolated as white needles, $[\alpha]_D^{25} + 23.5$ (c 1.0,

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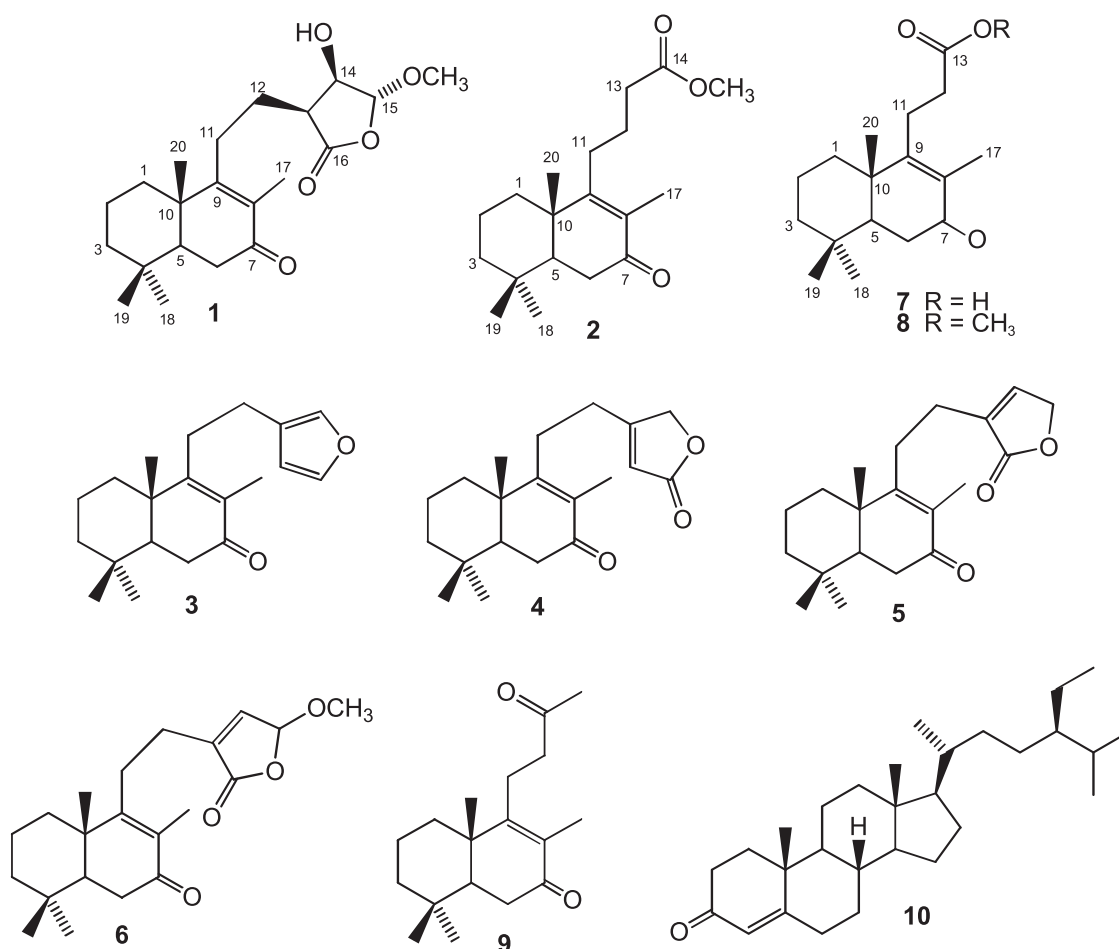


Fig. 1. Structures of 1–10.

MeOH), UV (EtOH) λ_{\max} 256 nm, IR (ν_{\max}) 3491 cm^{-1} (O–H), 1774 cm^{-1} (C=O of γ -lactone), 1658 cm^{-1} (conjugated C=O), 1072 cm^{-1} (C–O). HRESIMS revealed the molecular formula to be $\text{C}_{21}\text{H}_{32}\text{O}_5$ (m/z 365.2328 [M+H]⁺); *i.e.* the molecule had six degrees of unsaturation. The ¹H and ¹³C NMR spectra of **1** (Table 1) contained resonances for twenty one carbons consisting of an α,β -unsaturated carbonyl group [δ_{C} 200.4 (s, C-7), 166.9 (s, C-9) and 130.9 (s, C-8)], a carbonyl carbon of a carboxylic acid or ester [δ_{C} 176.6 (C-16)], a hemiacetal methine [δ_{H} 5.19 (1H, s, H-15); δ_{C} 107.9 (C-15)], a secondary alcohol [δ_{H} 4.35 (1H, d, J = 5.1 Hz, H-14); δ_{C} 73.0 (C-14)], a methoxyl [δ_{H} 3.51 (3H, s, 15-OMe); δ_{C} 56.9 (15-OMe)], an allylic methyl [δ_{H} 1.79 (3H, s, H₃-17); δ_{C} 11.7 (C-17)], three tertiary methyls [δ_{H} 1.09 (3H, s, H₃-20), 0.92 (3H, s, H₃-19) and 0.88 (3H, s, H₃-18); δ_{C} 32.7, 21.5 and 18.4 (C-18, C-19 and C-20)], two methines [δ_{C} 50.5 (C-5) and 43.8 (C-13)], six methylenes [δ_{C} 41.5, 36.2, 35.4, 27.5, 23.0, 18.8] and two quaternary carbons [δ_{C} 41.0 (C-10) and 33.3 (C-4)]. The spectral data were similar to those of 15-methoxyleoheteronin B (**6**) previously isolated from the same species (Qin et al., 2014), except that signals for a trisubstituted carbon–carbon double bond were replaced by resonances for a methine and an oxymethine group. In the HMBC spectrum (Fig. 2), two tertiary methyls of the A ring (δ_{H} 0.92 and 0.88) correlated with each other, revealing that they were the 18- and 19-methyls [δ_{H} 0.88 (H₃-18) to δ_{C} 21.5 (C-19) and δ_{H} 0.92 (H₃-19) to δ_{C} 32.7 (C-18)]. In addition, the methyls showed correlations to a methylene group (δ_{C} 41.5, C-3), a quaternary carbon (δ_{C} 33.3, C-4), and a methine group (δ_{C} 50.5, C-5). The remaining tertiary methyl protons (δ_{H} 1.09, H₃-20) showed a cross-peak with C-5, a quaternary carbon (δ_{C} 41.0, C-10), a methylene (δ_{C} 36.2, C-1), and a fully substituted olefinic carbon (δ_{C} 166.9, C-9). Meanwhile, protons of the allylic methyl group

(δ_{H} 1.79, H₃-17) showed correlations to C-9, a disubstituted olefinic carbon (δ_{C} 130.9, C-8) and a carbonyl carbon (δ_{C} 200.4, C-7). The allylic methylene protons at δ_{H} 2.30 and 2.46 correlated with C-8, C-9 and C-10, and were thus attached to C-11. In addition, proton H₂-11 showed correlations to a methylene (δ_{C} 23.0, C-12) and a methine (δ_{C} 43.8, C-13) whilst protons H₂-12 correlated with C-13, the secondary alcoholic carbon (δ_{C} 73.0, C-14) and the remaining carbonyl carbon (δ_{C} 176.5, C-16). On the other hand, the hemiacetal proton (δ_{H} 5.19) gave cross-peaks to C-13, C-14, C-16 and the methoxyl carbon (δ_{C} 56.9), indicating that it was bonded to both C-15 which carried the methoxyl group, and to C-16 through an oxygen atom to form a lactone ring. Observation of correlations in the COSY spectrum agreed with the bond establishment. The relative stereochemistry of the lactone ring was identified by analysis of the coupling constants and patterns of H-14 and H-15. In the ¹H NMR spectrum, proton H-14 appeared as a doublet (δ_{H} 4.35, d, J = 5.1 Hz) whilst H-15 had a singlet pattern (δ_{H} 5.19, s). Since C-14 and C-15 carried electronegative substituents, the zero coupling constant of H-15 meant that H-14 and H-15 were oriented *trans* while the large coupling constant of H-14 with H-13 (J = 5.1 Hz) indicated a *cis* stereochemical relationship (Ravi and Wells, 1982). In the NOESY spectrum, H-13 (δ_{H} 2.75) correlated with H-14 (δ_{H} 4.35) whilst no correlation was observed between H-14 and H-15 (δ_{H} 5.19), being consistent with the relative stereochemistry. The compound was therefore assigned as 15,16-epoxy-14-hydroxy-15-methoxy-7,16-dioxolabda-8-ene or 14-hydroxy-15-methoxy-7-oxolabda-8-ene-16,15-olide (**1**), which we named leojaponicin.

Compound **2** was obtained as white needles, $[\alpha]_{\text{D}}^{25}$ – 20.5 (c 0.3, MeOH), UV (EtOH) λ_{\max} 249 nm, IR: (ν_{\max}) 1735 and 1655 cm^{-1} (C=O), $\text{C}_{19}\text{H}_{30}\text{O}_3$ (m/z 329.2099 [M+Na]⁺); *i.e.* the molecule had five

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