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Four new flavonoids with DGAT inhibitory activity from *Psoralea corylifolia*

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ABSTRACT

Four new compounds, 3″-methoxy-bavacoumestan C (**1**), 6,7-furanbavachinone B (**2**), 3,4- furanbavachalcone A (**3**) and 4,5- furanbavachalcone A (**4**), together with seven known flavonoids were isolated from the *Psoralea corylifolia*. Their structures were determined by extensive spectroscopic and physicochemical analyses. All the compounds (**1–11**) were evaluated for *in vitro* inhibitory activity against DGAT. Among them, compounds **1, 6, 7, 10** and **11** were found to exhibit selective inhibitory activity on DGAT1with IC_{50} values ranging from 78.5 ± 1.7 to 153.4 ± 1.5 μM.

1. Introduction

Psoralea corylifolia L. (Leguminosae) is a well-known traditional Chinese medicine, and it has been widely used for the treatment of various diseases like bronchial asthma, leucopenia, vitiligo and psoriasis in East Asian countries (Zhang et al., 1990). Previous studies have reported that the major metabolites of *P. corylifolia* are coumarins, flavonoids, and meroterpenoids of the monoterpene phenol class (Haraguchi et al., 2002; Wang et al., 2001; Cho et al., 2001). In addition, these chemical constituents exhibited several therapeutic activities including antioxidant activities, stimulate osteoblast proliferation and hepatoprotective effect. Recent pharmacological and clinical studies showed that extract of *P. corylifolia* possess diverse bioactivities, such as antidermatophytic, antihyperglycemic, antiplatelet and antitumor activities (Tsai et al., 1996; Krenisky et al., 1999; Latha et al., 2000). Published article showed that the ethanol extract of *Psoralen* seed exhibit antihyperglycemic and antioxidative effects on the type 2 diabetes (Kamboj et al., 2011). Therefore, we explored more bioactive compounds of *P. corylifolia* to conduct a more in-depth study of *Psoralen* seed, and provide lead compounds for future treatment with diabetes.

Triacylglycerol (TG) is a kind of fat molecule which participate in the physiological metabolism. Excess TG accumulation would result in obesity and related diseases. So inhibiting TG synthesis may ameliorate obesity and its related medical consequences. DGAT is a key enzyme in TG synthesis and catalyzes the final step of the TG synthesis pathway by using diacylglycerol and fatty acyl CoA as substrates (Kim et al., 2013). DGAT1 and DGAT2 are two forms of DGAT, which have been identified and both enzymes are ubiquitously expressed especially in white adipose tissue, small intestine and liver (Turchetto-Zolet et al., 2011). However, only DGAT1 is regarded as a key enzyme that responsible for synthesis of TG. Thus, DGAT1 may be an important target to alter the energy equation. As a part of our research on seeking active compounds of inhibiting DGAT from the seed of *P. corylifolia*, we reported the isolation and structure elucidation of eleven flavonoid derivatives, of which **1–4** were new compounds, **9** was isolated from this plant for the first time. Their DGAT inhibitory activities were evaluated separately.

2. Results and discussion

Compound **1** was isolated as a yellow amorphous powder that gave a formula of $C_{21}H_{18}O_7$ by HREIMS at *m/z* 382.1049 $[M]^+$ (calcd. for $C_{21}H_{18}O_7$, 382.1053). The ^1H NMR spectrum revealed a set of signals including five aromatic signals at δ_H 8.06 (1H, s, H-2′), δ_H 7.78 (1H, d, J = 8.0 Hz, H-5), δ_H 7.20 (1H, s, H-8), δ_H 7.04 (1H, d, J = 8.0 Hz, H-6) and δ_H 6.95 (1H, s, H-5′); two oxymethine signals at δ_H 5.21 (1H, d, J = 2.5 Hz, H-3″) and δ_H 4.53 (1H, d, J = 2.5 Hz, H-2″); methoxy signal at δ_H 3.53 (3H, s, H-7″); two methyl signals at δ_H 1.34 (3H, s, H-5″) and δ_H 1.22 (3H, s, H-6″). Further observation of ^{13}C-NMR spectrum, it was found that compound **1** contained eleven quaternary carbons including a carbonyl carbon at δ 160.8, seven aromatic ring carbons at δ 165.1, δ 158.3, δ 157.5, δ 157.1, δ 126.7, δ 116.8 and δ 106.9; two olefinic carbons at δ 158.4 and δ 103.8 and a hydroxyl carbon at δ 71.1; four aromatic ring carbons at δ 122.0, δ 119.8, δ 115.0 and δ 99.5; two oxymethine carbons at δ 97.1 and δ 81.0. The NMR data of this compound were similar to those of Bavacoumestan C (Won et al., 2015), revealing the same coumestan feature. Moreover, the HMBC spectrum

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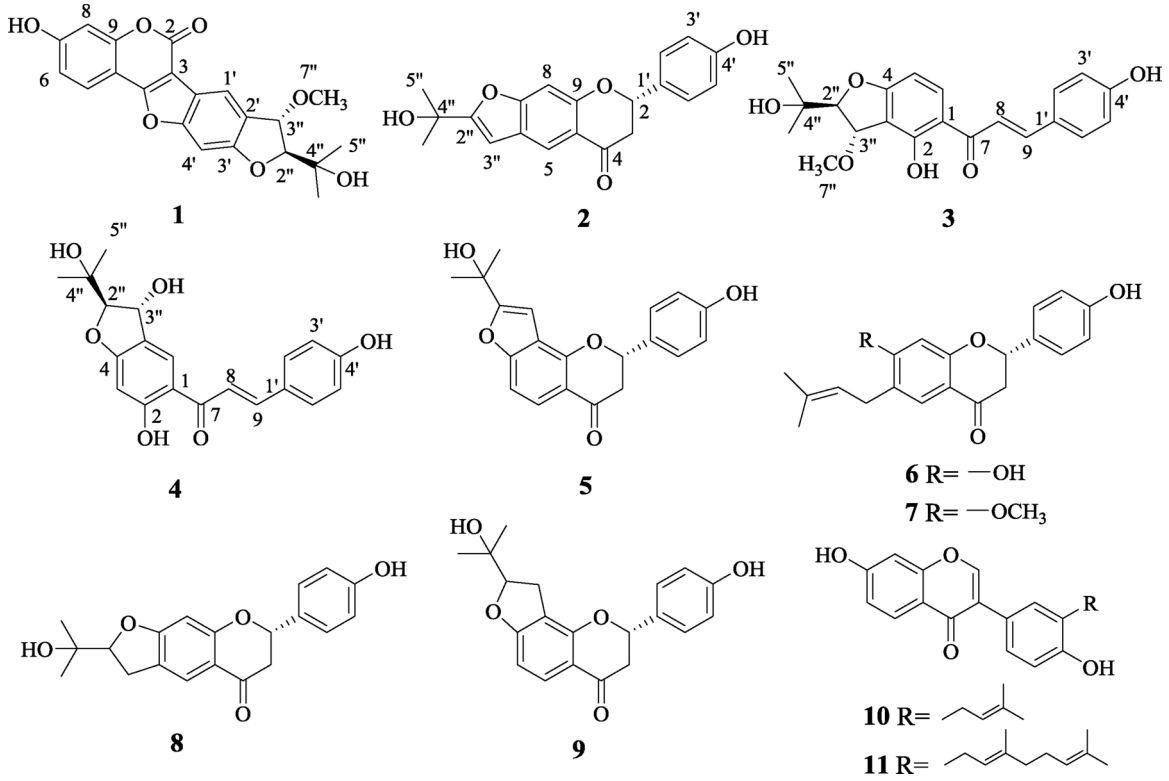

Fig. 1. Structures of compounds.**1–11.**

showed that the proton on the methoxyl (δ 3.53) correlated with C-3″ (δ 81.0) and the proton on the oxygenated methylene (δ 5.21) correlated with C-2′ (δ 126.7), C-3′ (δ 165.1), C-4″ (δ 71.1) and C-7″ (δ 56.1). Accordingly, the placement of the methoxyl (δ_C 56.1, δ_H 3.53) at this position was confirmed by the HMBC. The relative configuration at the C-2″ and C-3″ asymmetric carbon centers in **1** was determined as *trans* from the small vicinal proton–proton coupling constant ($J2'',3''$ = 2.5 Hz). Owing to the spatial crowding between the C-3″ methoxy and bulky C-2″ hydroxyisopropyl groups, however, several attempts to modify **1** to form derivatives suitable for spectroscopic measurements, e.g., esterification using Mosher's method and CD measurement, were unsuccessful. On the basis of the isoflavone homologues that have biogenetic considerations (Song et al., 2013), the absolute configuration at C-2″ of **1** were proposed as *S* from its biogenetic relationship with bavacoumestan C. Thus, the structure of **1** was assigned as 3″-methoxy-bavacoumestan C.

Compound **2** was obtained as a yellow amorphous solid, which molecular formula was determined to be $C_{20}H_{18}O_5$ by HREIMS at *m/z* 338.1149 $[M]^+$ (calcd. for $C_{20}H_{18}O_5$, 338.1154). The ^{1}H-NMR spectrum revealed the presence of two aromatic signals at δ_H 8.05 (1H, s, H-5), δ_H 7.08 (1H, s, H-8); a methyl signal at δ_H 1.60 (6H, s, H-5″, 6″); an olefinic signal at δ_H 6.70 (1H, s, H-3″). It's ^{1}H-NMR spectra indicated an ABX-type system at δ_H 5.51 (1H, dd, J = 3.0 Hz, 13.0 Hz), δ_H 2.80 (1H, dd, J = 3.0 Hz, 17.0 Hz, H-3_{eq}) and δ_H 3.16 (1H, dd, J = 13.0 Hz, 17.0 Hz, H-3_{ax}). The ^{13}C NMR showed an oxygenated carbon resonance at δ 80.8 (C-2), a methylene resonance at δ 45.1 (C-3), and a carbonyl resonance at δ 192.1 (C-4). All of these observations were indicative of a flavanone skeleton for **2**. The flavanone nature of this compound was supported by a comparison of its NMR data with those of bavachinone B (Won et al., 2015), which indicated that there was a 2-(2-hydroxypropan-2-yl) furan ring. Its HMBC spectrum suggested that H-3″ (δ 6.70) proton and neighboring C-5 (δ 120.2), C-6 (δ 124.7), C-7 (δ 160.5), C-2″ (δ 167.1) and C-4″ (δ 69.0) carbons, H-8 (δ 7.08) proton and neighboring C-5, C-6, C-7 and C-10 (δ 119.1) carbons were observed clearly. The configuration at C-2 was inferred to be *S* by the CD spectrum, which showed two maxima of positive and negative Cotton effects at 327 and 286 nm, respectively. Therefore, the structure of the new compound **2** was determined as 6,7-furanbavachinone B.

Compound **3** was obtained as a yellowish solid that determined to be $C_{21}H_{22}O_6$ by HREIMS. The ^{1}H-NMR spectrum of **3** showed two singlet protons at δ_H 7.79 (1H, d, J = 15.5 Hz) and δ_H 7.85 (1H, d, J = 15.5 Hz), and AA'XX'-type aromatic protons at δ_H 7.75(2H, d, J = 8.0 Hz) and δ_H 6.93 (2H, d, J = 8.0 Hz). The ^{13}C-NMR and HMBC patterns revealed a carbonyl signal at δc 193.5, and two olefinic carbons at δc 118.5 and δc 145.7. All of this suggested a chalcone for compound **3**. Additionally, there was a hydroxyisopropenyl-dihydrofuran ring similar to **1**. The location of the methoxyl was determined at C-3″ (δ 80.0) by the observation of the HMBC correlations between H-3″ (δ 5.17) proton and C-5 (δ 115.3), C-6 (δ 169.2), C-4″ (δ 71.0), C-7″ (δ 57.1). In the NMR data comparison of **3** and **1**, it was found that the dihydrofuran ring had the same substituent and the coupling constants ($J2'',3''$ = 2.5 Hz) were the same. Then based on the positive signs of both the specific rotation ([α]eq \o(\s\up 6(25),\s\do 2(D)) +4.1), the absolute configuration at C-2″ of **3** were proposed as *S*. Thus, the structure of **3** was assigned as 3,4- furanbavachalcone A.

The HREIMS data of compound **4** gave a molecular ion peak at *m/z* 356.1256 (calcd. for $C_{20}H_{20}O_6$, 356.1260), which corresponds to the molecular formula $C_{20}H_{20}O_6$. Compound **4** was isolated as a yellowish amorphous powder. The ^{1}H-NMR spectrum of **4** showed two singlet protons at δ_H 7.79 (1H, d, J = 15.5 Hz) and δ_H 7.86 (1H, d, J = 15.5 Hz), and AA'XX'-type aromatic protons at δ_H 7.75(2H, d, J = 8.0 Hz) and δ_H 6.93 (2H, d, J = 8.0 Hz). The ^{13}C-NMR and HMBC patterns revealed a carbonyl signal at δc 193.0, and two olefinic carbons at δc 118.4 and δc 145.5. The NMR data of this compound were similar to those of compound **3**, revealing the same chalcone structure of compound **4**. By carefully observation of the NMR spectrum of compound **4**, it was found that the hydroxyl group of **4** replaced the methoxy group of **3**. At the same time, by analyzing the HMBC spectrum found that H-3″ (δ 5.35) correlated with C-1 (δ 124.0), C-2 (δ 128.8), C-4″ (δ 71.1) and H-2″ (δ 4.39) correlated with C-4 (δ 168.0),