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Short communication

Three new compounds isolated from *Eleutherococcus senticosus* (Rupt. & Maxim.) Maxim

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ABSTRACT

Three new compounds, 3α, 2β-2-(3′-Hydroxy-4′-methoxy-phenyl)-1-(4″-hydroxy-5″-methoxyphenyl)-1-oxo-3-propanol (**1**), 1,6-Bis-(3,5-dimethoxy-4-hydroxyphenyl) hexane-1,6-dione (**2**) and 1-(3-Methoxy-4-hydroxyphenyl)-6-(3,5-dimethoxy-4-hydroxyphenyl) hexane-1,6-dione (**3**) along with six known compounds (**4**–**9**) were isolated from the EtOAc-soluble extract of *Eleutherococcus senticosus* (Rupt. & Maxim.) Maxim. Their structures were elucidated on the basis of spectroscopic and physicochemical analyses. All the isolates were evaluated for *in vitro* inhibitory activity against DGAT1 and DGAT2. Among them, compounds **2**–**7** were found to exhibit selective inhibitory activity on DGAT1 with IC_{50} values ranging from 62.1 ± 1.3 to 90.4 ± 1.3 μM.

1. Introduction

Obesity is defined as a chronic, costly disease because of the improvement in living standards and the increasing use of poor quality food. The US statistics for 2000 showed that 61% of Americans are overweight (Allison et al., 1999). In addition, it is predicted that the number of obese adults in the UK would reach 11 million by 2030, and the cost of treating related diseases estimated to increase by up to 2 billion dollar per annum. Such a trend will certainly increase the burden of obesity related diseases including atherosclerosis, type 2 diabetes and cardiovascular diseases (Angela and Charles, 2003). Therefore, studying a novel anti-obesity therapeutics is essential. One of potential therapeutics studied in recent years is inhibiting synthesis of triacylglycerol (TG). TG is a kind of fat molecules which participate in the physiological metabolism. However, excess TG accumulation would result in obesity and related diseases. So inhibiting TG synthesis may ameliorate obesity and its related medical consequences. Diacylglycerol acyltransferase (DGAT) is a key enzyme in TG synthesis, which 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 and further to treat obesity and related diseases.

Eleutherococcus senticosus (Rupt. & Maxim.) Maxim is a shrub, which is widely distributed in Northeast Asia and Siberia. It possesses a wide range of active compounds such as diterpenoids (Na et al., 2006), triterpenoids (Nhiem et al., 2011a,b), lignans (Choi et al., 2008), phenylpropanoids (Nhiem et al., 2011a, 2011b) and diphenyl ethers (Yang et al., 2010). In addition, it has been traditionally used as folk medicine for treating rheumatism, diabetes, and hepatitis (Nan et al., 2004). As a part of our research on seeking active compounds that inhibiting DGAT1 from the stem of *Eleutherococcus senticosus*, we isolated three new compounds along with six known compounds (Fig. 1), and evaluated their DGAT inhibitory activity.

2. Results and discussion

Compound **1** was obtained as pale yellow powder and its molecular formula of $C_{17}H_{18}O_6$ was established by HREIMS at *m/z* 318.1103 $[M]^+$. The ^1H NMR spectrum (Table 1) of **1** showed the characteristic signals for six aromatic protons. One aromatic proton at δ 7.61 (dd, J = 2.0, 8.5 Hz) was coupled with the protons at δ 7.54 (d, J = 2.0 Hz) and δ 6.76 (d, J = 8.5 Hz), and another aromatic proton at δ 6.76 (dd, J = 2.0, 8.0 Hz) with the protons at δ 6.89 (d, J = 2.0 Hz) and δ 6.72 (d, J = 8.0 Hz). The ^1H NMR spectrum also revealed the presence of two methoxy groups at δ 3.82 and δ 3.85 (each 3H, s), one methine at δ 4.75 (dd) and one methylene at δ 4.24/3.70 (dd). Its ^{13}C NMR spectrum

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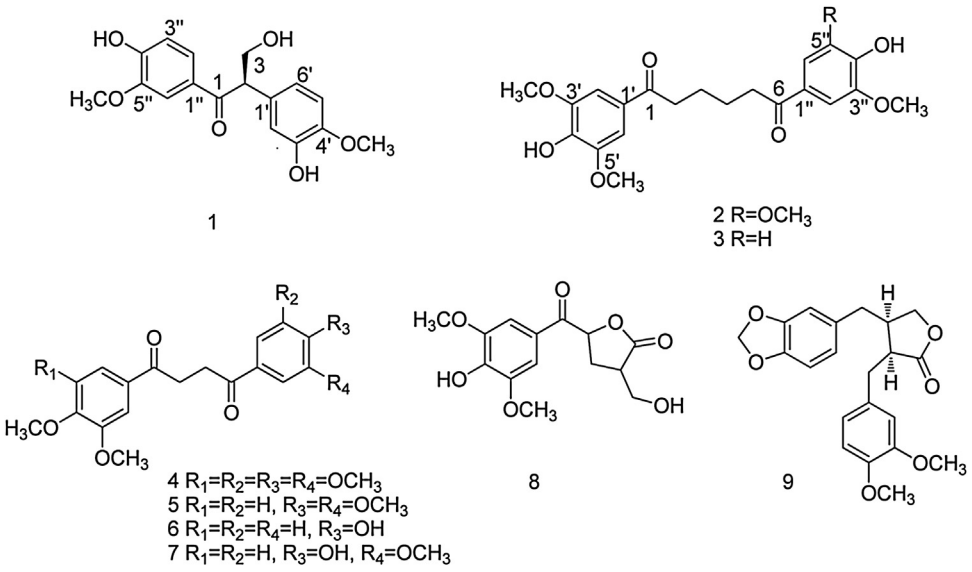

Fig. 1. Structures of compounds **1–9**.

Table 1
NMR data of compounds **1–3** in CD_3OD (^1H: 500 MHz, ^{13}C: 125 MHz).

Position	**1** δ_C δ_H, mult. (*J*, Hz)		**2** δ_C δ_H, mult. (*J*, Hz)		**3** δ_C δ_H, mult. (*J*, Hz)	
	δ_C δ_H (*J* in Hz)		δ_C δ_H (*J* in Hz)		δ_C δ_H (*J* in Hz)	
1	199.9		199.8		199.8	
2	56.4	4.75, dd (5.0, 8.5)	59.1	3.95, m	59.1	3.95, m
3	65.7	3.70, dd (5.0, 10.5) 4.24, dd (8.5, 10.5)	41.8	3.19, m	41.8	3.17, m
4			41.8	3.19, m	41.8	3.17, m
5			59.1	3.95, m	59.1	3.95, m
6			199.8		199.8	
1′	130.3		129.1		130.5	
2′	113.1	6.89, d (2.0)	107.5	7.32, s	107.4	7.32, s
3′	147.2		149.3		149.3	
4′	149.5		143.3		138.2	
5′	116.2	6.72, d (8.0)	149.3		149.3	
6′	122.4	6.76, dd (2.0, 8.0)	107.5	7.32, s	107.4	7.32, s
1″	129.8		129.1		130.5	
2″	125.6	7.61, dd (2.0, 8.5)	107.5	7.32, s	112.0	7.54, d (2.0)
3″	112.8	6.76, d (8.5)	149.3		149.3	
4″	155.0		143.3		154.0	
5″	149.5		149.3		116.0	6.85, d (8.0)
6″	116.8	7.54, d (2.0)	107.5	7.32, s	125.0	7.58, dd (2.0, 8.0)
3′-OCH_3			57.0	3.90, s	57.0	3.90, s
4′-OCH_3	56.5	3.82, s				
5′-OCH_3			57.0	3.90, s	57.0	3.90, s
3″-OCH_3			57.0	3.90, s	56.5	3.90, s
5″-OCH_3	56.6	3.85, s	57.0	3.90, s		

(Table 1) displayed 17 carbon resonances, including twelve aromatic carbons at δ 112.8-155.0, one carbonyl carbon at δ 199.9 (C-1), one hydroxymethyl carbon at δ 65.7 (C-3), one methane carbon at δ 56.4 (C-2) and two methoxy carbons at 56.5 (4′-OCH_3) and 56.6 (5″-OCH_3). The structure of **1** was further demonstrated by the analysis of HMBC spectra (Fig. 2). In the HMBC spectrum, the methane proton at δ 4.75 exhibited correlations with the carbonyl carbon at δ 199.9 (C-1), methylene carbon at δ 65.7 (C-3), and three aryl carbons at δ 130.3 (C-1′), δ 113.1 (C-2′) and δ 122.4 (C-6′). The carbonyl carbon in turn showed correlations with the aromatic protons at δ 7.61 and δ 7.54. These correlations obviously indicated the presence of 1-oxo-3-propanol moiety attached to one aromatic group at C-2 and another aromatic group at C-1 which were in close agreement with those of 2-(4-hydroxy-3-methoxy-phenyl)-1-(2-hydroxy-5-methoxyphenyl)-1-oxo-3-propanol (Rahman and Moon, 2007). Otherwise, the methoxy group δ 3.82 (3H, s) was located at C-4′ by the HMBC correlations from δ 3.82 to δ 149.5 (C-4′), from δ 6.89 to δ 147.2 (C-3′) and 122.4 (C-6′), and from δ 6.76 to δ 149.5 (C-4′), and from δ 6.72 to δ 130.3 (C-1′) and δ 149.5 (C-4′). Another methoxy group δ 3.85 (3H, s) was attached to C-5″ by the HMBC correlations from δ 3.85 to δ 149.5 (C-5″), from δ 7.54 to δ 125.6 (C-2″), δ 155.0 (C-4″) and δ 149.5 (C-5″), and from δ 7.61 to δ 112.8 (C-3″) and δ 155.0 (C-4″), and from δ 6.76 to δ 129.8 (C-1″), δ 155.0 (C-4″) and δ 149.5 (C-5″). The presence of a $-CHCH_2OH$ moiety was inferred by the ABC type signals with a methine proton at δ 4.75 (1H, dd, J = 5.0, 8.5 Hz, H-β) together with two nonequivalent methylene protons at δ 3.70 (1H, dd, J = 5.0, 10.5 Hz, H-α) and δ 4.24 (1H, dd, J = 8.5, 10.5 Hz, H-α) which was determined by previous report (Wu et al., 1995). Hence, the structure of compound **1** was assigned as 3α, 2β-2-(3′-hydroxy-4′-methoxy-phenyl)-1-(4″-hydroxy-5″-methoxyphenyl)-1-oxo-3-propanol.

Compound **2** was obtained as pale yellow powder and exhibited an $[M]^+$ ion peak at *m/z* 418.1630 in the positive HREIMS corresponding to the molecular formula $C_{22}H_{26}O_8$. The ^1H NMR spectrum (Table 1) of **2** suggested four aromatic protons at δ 7.32 (4H, s) and four methoxy groups at δ 3.90 (12H, s). Its ^{13}C NMR spectrum (Table 1) displayed twelve aromatic carbons including four carbons at δ 107.5, four carbons at δ 149.3 and two carbons at δ 143.3, which indicated two symmetrical benzenes. Meanwhile, it also exhibited two carbonyl carbons at δ 199.8, four methane carbons at δ 57.0, two methylene carbons at δ 59.1 and two methylene carbons at 41.8, which similar to those of disyringoylpropan (Lipp et al., 1958). Above of the ^{13}C NMR spectrum, we could found **2** was a symmetrical structure. The structure of **2** was further demonstrated by analysis of HMBC spectra (Fig. 2). In the HMBC spectrum, the methylene proton at δ 3.95 exhibited correlations with the carbonyl carbon at δ 199.8 and methylene carbon at δ 41.8. The carbonyl carbon in turn showed correlations with the aromatic protons at δ 7.32. These correlations indicated the carbonyl carbon (δ 199.8) attached to C-1′ and another carbonyl carbon linked C-1″. In addition, methoxy group [δ 3.90 (12H, s)] were located at C-3′, 5′, 3″ and C-5″ by the HMBC correlations from δ 3.90 (12H, s) to δ 149.3, from δ 7.32 (4H, s) to δ 149.3, 143.3 and δ 129.1. All of the above, the structure of **2** was elucidated as 1,6-Bis-(3,5-dimethoxy-4-hydroxyphenyl) hexane-1,6-dione.