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Three new 2-(2-phenylethyl)chromone derivatives from artificial holing agarwood of *Aquilaria sinensis*

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ABSTRACT

Three new 2-(2-phenylethyl)chromone derivatives (**1–3**) were obtained from the artificial holing agarwood originating from *Aquilaria sinensis*. Their structures were unambiguously deduced by detailed spectroscopic analysis and the absolute configurations were determined by ECD calculations. Compounds **1–3** displayed acetylcholinesterase (AChE) inhibitory activity with the inhibition ratios in the range of 30%–45% at a concentration of 50 μg/ml.

1. Introduction

Agarwood is an aromatic dark resin produced from the heartwood of various Aquilaria and *Gyrinops* species of the family Thymelaeaceae when suffering natural or artificial injury (Chen et al., 2012b; Naef, 2011; Yang et al., 2016). *Aquilaria sinensis* (Lour.) is a peculiar plant resource of Chinese agarwood (Mei et al., 2013). Natural agarwood is extremely rare and very precious, but still popular used in incenses, high-grade perfumes, medicines and some other products (Dai et al., 2010). 2-(2-Phenylethyl)chromone derivatives and sesquiterpenes as two of diagnostic components of agarwood quality, are widely distributed in agarwood (Huo et al., 2015; Li et al., 2015; Liao et al., 2017). So far more than one hundred and thirty 2-(2-phenylethyl) chromone derivatives have been identified from sorts of agarwood, which are classified as four main types: tetrahydro-2-(2-phenylethyl) chromones (THPECs), epoxy-tetrahydro-2-(2-phenylethyl)chromones (EPECs), flidersia type 2-(2-phenylethyl)chromones (FTPECs) and 2-(2-phenylethyl)chromones polymers (Dai, 2017; Ding et al., 2015). However, no more than forty THPECs have been reported since the first one named agarotetrol was found in 1978 (Yoshii et al., 1978). and few reports about 5-dehydroxyl THPECs can be found (Dai, 2017). 2-(2-Phenylethyl)chromone derivatives are reported to show various biological activities including AChE inhibition, α-glucosidase inhibition, antineuroinflammatory and antidepressant in modern pharmacological researches (Chen et al., 2012a, 2012b; Li et al., 2014; Liao et al., 2016; Liao et al., 2017; Ma et al., 2017).

Previous phytochemical studies on the EtOAc extract of artificial holing agarwood originating from *A. sinensis* contributed to a serials of sesquiterpenes and 2-(2-phenylethyl)chromone derivatives (Li et al., 2014, 2015; Liao et al., 2016; Liao et al., 2017; Xiang et al., 2017), and the ongoing studies were focused on n-BuOH extract, that led to isolation and identification of three new chromones including two 5-dehydroxyl THPECs (**1–2**) (Fig. 1). This paper described the structural elucidation of the new compounds and their AChE inhibitory activity.

2. Result and discussion

Compound **1** was obtained as yellow oil, and its molecular formula was assigned to be $C_{18}H_{20}O_7$ with nine degrees of unsaturation according to its negative HRESIMS data (*m/z* 347.1128 $[M-H]^-$, calcd. 347.1136 for $C_{18}H_{19}O_7$) and ^{13}C NMR data. The IR spectrum showed the presence of hydroxyl (3306 cm^{-1}) and α, β-unsaturated carbonyl groups (1657 cm^{-1}). The ^1H and ^{13}C NMR data (Tables 1 and 2) exhibited one methoxyl group [δ_H 3.79 (3H, s)/δ_C 56.2], a characteristic ABX coupling aromatic system [δ_H 6.74 (1H, d, J = 1.9 Hz, H-2′), 6.69 (1H, d, J = 8.0 Hz, H-5′), 6.64 (1H, dd, J = 8.0, 1.9 Hz, H-6′); δ_C 113.2 (C-2′), 116.2 (C-5′), 121.9 (C-6′), 132.7 (C-1′), 148.9 (C-3′), 146.1 (C-4′)], a pyrone fragment [δ_H 6.06 (1H, s, H-3); δ_C 171.3 (C-2), 113.1 (C-

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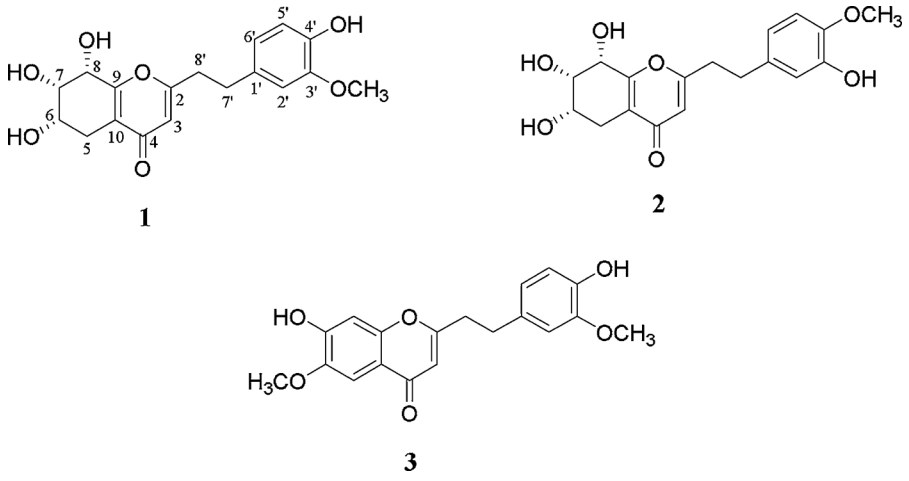

Fig. 1. Structures of compounds **1–3**.

Table 1
^{1}H NMR spectroscopic data for compounds **1–3** (500 MHz, δ in ppm, J in Hz, measured in CD_3OD).

position	1	2	3
3	6.06, s	6.08, s	5.93, s
5	2.51, dd (17.1, 7.3)	2.51, dd (17.1, 7.4)	7.24, s
	2.67, dd (17.1, 5.1)	2.67, dd (17.1, 5.0)	
6	4.11, ddd (7.3, 5.1, 2.2)	4.11, ddd (7.3, 5.0, 2.1)	
7	3.90, dd (5.0, 2.2)	3.90, dd (5.0, 2.1)	
8	4.51, d (5.0)	4.50, d (5.0)	6.60, s
2′	6.74, d (1.9)	6.67, d (2.1)	6.72, d (1.8)
5′	6.69, d (8.0)	6.81, d (8.2)	6.68, d (8.0)
6′	6.64, dd (8.0, 1.9)	6.63, dd (8.2, 2.1)	6.63, dd (8.0, 1.8)
7′	2.95, m	2.90, m	2.96, t (7.0)
8′	2.88, m	2.87, m	2.88, t (7.0)
6-OCH_3			3.86, s
3′-OCH_3	3.79, s		3.72, s
4′-OCH_3		3.80, s	

Table 2
^{13}C NMR spectroscopic data for compounds **1–3** (125 MHz, δ in ppm, measured in CD_3OD).

position	1	2	3
2	171.3, C	171.3, C	169.1, C
3	113.1, CH	113.0, CH	109.1, CH
4	182.0, C	182.0, C	179.8, C
5	26.5, CH_2	26.5, CH_2	102.8, CH
6	67.3, CH	67.3, CH	150.2, C
7	75.0, CH	75.0, CH	155.1, C
8	71.2, CH	71.2, CH	103.9, CH
9	163.1, C	163.0, C	163.6, C
10	120.9, C	120.9, C	111.8, C
1′	132.7, C	134.1, C	133.0, C
2′	113.2, CH	116.5, CH	113.1, CH
3′	148.9, C	147.8, C	148.8, C
4′	146.1, C	147.7, C	145.9, C
5′	116.2, CH	112.9, CH	116.2, CH
6′	121.9, CH	120.5, CH	121.8, CH
7′	33.5, CH_2	33.2, CH_2	33.9, CH_2
8′	36.8, CH_2	36.5, CH_2	37.3, CH_2
6-OCH_3			55.9, CH_3
3′-OCH_3	56.2, CH_3		56.2, CH_3
4′-OCH_3		56.4, CH_3	

3), 182.0 (C-4)], three methylene groups [δ_H 2.95 (2H, m, H-7′)/δ_C 33.5; δ_H 2.88 (2H, m, H-8′)/δ_C 36.8; δ_H 2.67 (1H, dd, J = 17.1, 5.1 Hz, H-5a), 2.51 (1H, dd, J = 17.1, 7.3 Hz, H-5b)/δ_C 26.5], in addition to three oxymethines [δ_H 4.11 (1H, ddd, J = 7.3, 5.1, 2.2 Hz, H-6)/δ_C 67.3; δ_H 3.90 (1H, dd, J = 5.0, 2.2 Hz, H-7)/δ_C 75.0; δ_H 4.51 (1H, d, J = 5.0 Hz, H-8)/δ_C 71.2], which were supported by HSQC spectrum. Above data were allowed to assign **1** to be a 2-(2-phenylethyl)-4*H*-chromone derivative (Meng et al., 2016; Wu et al., 2012), which was further confirmed by ^{1}H-^{1}H COSY and HMBC correlations (Fig. 2). By comparison, it revealed that the structure of **1** was identical with that of aquilarone E (Chen et al., 2012a) except for the missing of 5-hydroxy in **1**, which was confirmed by HMBC correlations from the methylene CH_2-5 (δ_H 2.67 and 2.51) to the carbonyl carbon (δ_C 182.0), and supported by three consecutive oxymethine groups connected with CH_2-5, as clarified by the cross-peaks of H_2-5/H-6/H-7/H-8 in the ^{1}H-^{1}H COSY spectrum. The relative stereochemistry of **1** was determined by analyses of the J coupling constants and NOE spectra. The significant NOE interaction (Fig. S7) between H-6 and H-8 suggested their cis diaxial orientations, while the small J value (2.2 Hz) of H-6/H-7 revealed the equatorial orientation of H-7. Thus, all of these three protons were cofacial, which was different with the known aquilarone E. In order to determine the absolute configuration of compound **1**, the ECD of (6*S*,7*S*,8*S*)-**1** was calculated by the TDDFT method at the B3LYP/6-31G(d) level (Kong et al., 2017). The calculated ECD spectrum fit well with the measured one (Fig. 3), indicating 6*S*, 7*S* and 8*S* configurations of **1**. Thus, the structure of compound **1** was elucidated as (6*S*,7*S*,8*S*)-6,7,8-trihydroxyl-2-(4-hydroxyl-3-methoxylphenylethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one.

Compound **2** was obtained as yellow oil, and its molecular weight was found to be the same with that of **1**. By comparison, the ^{1}H and ^{13}C NMR data (Tables 1 and 2) showed high similarity between these two compounds, with the only subtle difference in the chemical shifts of the proton resonances on the aromatic system. Further detailed analysis of 1D and 2D NMR, the positions of the methoxyl and hydroxyl groups at the aromatic system were found to be opposite with those in **1**, that was confirmed by the ROESY correlation from the methoxyl group (δ_H 3.80) to H-5′ [δ_H 6.81 (1H, d, J = 8.2 Hz)]. Moreover, the similar CD spectrum and the same sign of optical rotation with those of compound **1** indicated the same absolute configurations of both compounds. As a consequence, the structure of **2** was elucidated as (6*S*,7*S*,8*S*)-6,7,8-trihydroxyl-2-(3-hydroxyl-4-methoxylphenylethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one.

Compound **3** was isolated as yellow oil. Its molecular formula was determined to be $C_{19}H_{18}O_6$ from the molecular ion peak at m/z 365.1004 $[M+Na]^+$ (calcd. 365.0996 for $C_{19}H_{18}O_6Na$) in the HRESIMS spectrum. The IR spectrum indicated the presence of hydroxyl (3432 cm^{-1}) and α, β-unsaturated carbonyl groups (1634 cm^{-1}). The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) showed the presence of two methoxyl groups [δ_H 3.86 (3H, s)/δ_C 55.9; δ_H 3.72 (3H, s)/δ_C 56.2], two methylene groups [δ_H 2.96 (2H, t, J = 7.0 Hz, H-7′)/δ_C 33.9; δ_H 2.88 (2H, t, J = 7.0 Hz, H-8′)/δ_C 37.3], α, β-unsaturated