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A new cytotoxic 2-(2-phenylethyl)chromone from Chinese eaglewood

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Abstract

A new compound 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one (**1**) was isolated from the Chinese eaglewood [*Aquilaria sinensis* (Lour.) Gilg]. Its structure was elucidated on the basis of spectral data. Compound **1** showed cytotoxicity against human gastric cancer cell line (SGC-7901) *in vitro* by MTT method with the IC_{50} value of 14.6 μg/mL.

Keywords: Chinese eaglewood; *Aquilaria sinensis*; Chromone; Cytotoxicity

Chinese eaglewood [*Aquilaria sinensis* (Lour.) Gilg] is distributed in Southern China such as Hainan, Guangxi, Guangdong, Fujian and Taiwan provinces. From ancient times, Chinese eaglewood was used as incense in the orient, it was also used as a sedative, analgesic, and digestive in traditional Chinese medicine [1]. Much attention has been paid to the chemical components of this plant in recent decades, and characteristic sesquiterpenes and chromone derivatives have been isolated [2,3]. In our screening for cytotoxic agents from tropical medicinal plants in Hainan, the ethanol extract of Chinese eaglewood [*A. sinensis* (Lour.) Gilg] showed inhibitory activity towards human gastric cancer cell line (SGC-7901), and the solvent–solvent partition of ethanol extract combined with bioassay revealed the water-soluble fraction was the active fraction. Further bioassay-guided fractionation of the active fraction led to the isolation of a new 2-(2-phenylethyl)chromone, its structure was unambiguously elucidated as 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one (**1**) by extensive spectroscopic analysis. Compound **1** showed cytotoxicity against human gastric cancer cell line (SGC-7901) *in vitro* by MTT method with the IC_{50} value of 14.6 μg/mL (Fig. 1).

Compound **1**, a white amorphous powder, mp 102–104 °C, $[\alpha]_{18}^{D}$ −17.9 (*c* 1.6, MeOH). Its HRESI-MS gave a quasi-molecular ion at 405.0720 $[M+Na]^+$ (calcd. For $C_{18}H_{19}O_7NaCl$: 405.0717) and a fragment ion at *m/z* 407 [M+Na+2], in which the relative abundance ratio for [M+Na]:[M+Na+2] was 3:1, indicating that **1** contains a chlorine atom. Its IR

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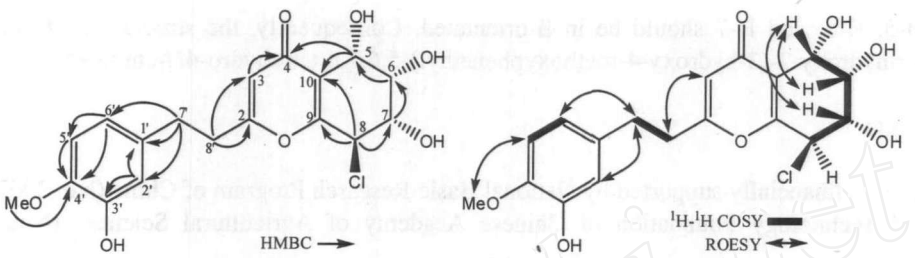

Fig. 1. Structure and correlations of compound **1**.

spectrum showed the presence of hydroxyl (3404 cm^{-1}), unsaturated carbonyl (1651 cm^{-1}), phenyl groups (1574, 1513 and 1451 cm^{-1}). ^{1}H NMR spectrum (Table 1) of **1** showed the presence of one methoxyl group at δ_H 3.79 (3H, s), four consecutive methine protons [δ_H 4.77 (d, 1H, J = 4.3 Hz, H-5), δ_H 4.05 (dd, 1H, J = 4.3, 1.8 Hz, H-6), δ_H 4.23 (dd, 1H, J = 7.5, 1.8 Hz, H-7) and δ_H 4.86 (d, 1H, J = 7.5 Hz, H-8)], and one 1,3,4-trisubstituted phenyl group at δ_H 6.63 (dd, 1H, J = 8.2, 1.5 Hz, H-6′), δ_H 6.68 (d, 1H, J = 1.5 Hz, H-2′) and δ_H 6.81 (d, 1H, J = 8.2 Hz, H-5′). The ^{13}C NMR spectrum (Table 1) of **1** showed the presence of two methylene groups at δ_C 33.1 and 36.3, one methoxyl at δ_C 56.6, four consecutive methine carbons (δ_C 66.5, 73.6, 73.5 and 58.0). One methine carbon appeared at higher field (δ_C 58.0) than the other three methines suggested this carbon was chlorinated. Based on the above evidence, compound **1** was presumed to be 2-(2-phenylethyl)chromone derivative. The ^{13}C NMR spectrum of **1** was very similar to that of 8-chloro-2-(2-phenethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydrochromone [4] except for the chemical shifts of aromatic carbons (δ_C 113.1, 116.4, 120.7, 133.9, 147.4 and 147.7) and an additional methoxyl signal at δ_C 56.6 in the phenylethyl moiety. Thus, it was inferred that compound **1** was the same 2-(2-phenethyl)chromone with additional hydroxyl and methoxyl group in the phenylethyl moiety. In the HMBC spectrum (Table 1), H-2′ (δ_H 6.68), H-6′ (δ_H 6.63) and H-OCH_3 (δ_H 3.79) are all correlated with C-4′ (δ_C 147.7), H-5′ (δ_H 6.81) correlated with C-3′ (δ_C 147.4), indicating that the methoxyl was located at C-4′, and the hydroxyl group at C-3′. Thus, the structure of **1** was determined as 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one.

The relative stereochemistry was determined by ^{1}H–^{1}H coupling constants and ROESY experiment. The relatively small coupling constants between H-5 and H-6, H-6 and H-7, revealed the *cis* relationships between these protons. While the relatively large coupling constants between H-7 and H-8 revealed the *trans* pseudoaxial–axial relationships between them. These results were supported by ROESY cross-signals from H-5 (δ_H 4.77) to H-7 (δ_H 4.23) and H-6 (δ_H 4.05). No cross-signals from H-8 (δ_H 4.86) to H-5 and H-6 were observed in ROESY spectrum. When H-8 was

Table 1
NMR data of **1** in CD_3OD (^{1}H: 400MHz; ^{13}C: 100 MHz; δ ppm, J Hz)

No.	δ_C	δ_H
2	171.5	
3	114.3	6.14 (1H, s)
4	181.6	
5	66.5	4.77 (1H, d, 4.3)
6	73.6	4.05 (1H, dd, 4.3, 1.8)
7	73.5	4.23 (1H, dd, 7.5, 1.8)
8	58.0	4.86 (1H, d, 7.5)
9	161.1	
10	122.8	
1′	133.9	
2′	116.4	6.68 (1H, d, 1.5)
3′	147.4	
4′	147.7	
5′	113.1	6.81 (1H, d, 8.2)
6′	120.7	6.63 (1H, dd, 8.2, 1.5)
7′	33.1	2.89 (2H, t, 7.1)
8′	36.3	2.88 (2H, t, 7.1)
4′-OCH_3	56.6	3.79 (3H, s)

α-orientated, H-5, H-6, and H-7 should be in β-orientated. Consequently, the structure of **1** was established as 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4*H*-chromen-4-one.

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