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A new dibenzofuran and other constituents from *Ligularia caloxantha*, a chinese medicinal plant

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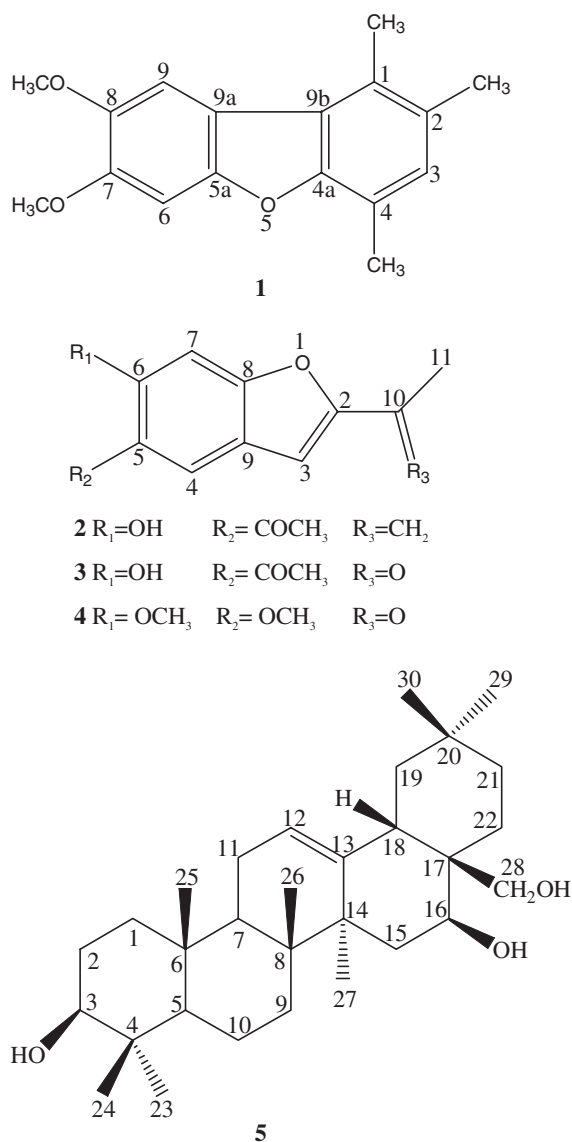
A new dibenzofuran named 1,2,4-trimethyl-7,8-dimethoxy-dibenzofuran (**1**), together with seven known compounds, euparin (**2**), 2,5-diacetyl-6-hydroxy-benzofuran (**3**), 2-acetyl-5,6-dimethoxy-benzofuran (**4**), gummosogenin (**5**), lupeol (**6**), stigmasterol (**7**) and (*E*)-2,5-dihydroxy-cinnamic acid (**8**), were isolated from the roots of *Ligularia caloxantha*, a Chinese medicinal plant. The structures of the compounds were elucidated by spectroscopic methods.

Keywords: *Ligularia caloxantha*; Compositae; Dibenzofuran; Benzofuran; Triterpene

1. Introduction

In our ongoing research on bioactive compounds from the genus *Ligularia* (Compositae) plants [1–5], we have investigated the roots of *Ligularia caloxantha* (Diels) Hand. -Mazz, collected in 2002 in mountainous areas of Southwestern China, which is traditionally used to cure injuries from falls and have an antiascarid activity in Lijiang area, Yunnan province [6]. The fresh plant of *L. caloxantha* was very recently reported to mainly contain triterpenes and benzofuran compounds [7]. By our phytochemical investigation of the dried underground parts of *L. caloxantha*, a new dibenzofuran along with seven known compounds were isolated and identified. The isolation and structural elucidation of the new dibenzofuran **1** and seven known

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Figure 1. Structures of Compounds **1–8** isolated from roots of *L. caloxantha*.

compounds **2** [7,8], **3** [9,10], **4** [10], **5** [11], **6** [12], **7** [13] and **8** [14] were reported in this article (figure 1). This is the first report on the presence of compounds **4**, **5** and **8** from *L. caloxantha*, a Chinese traditional medicinal plant.

2. Results and discussion

Compound **1** was obtained as red crystals, m.p. 161–162°C. The IR spectrum of **1** indicated the presence of an aromatic group (1615, 1504 cm^{-1}) and an aromatic ether (1469 cm^{-1}). Its molecular formula, $\text{C}_{17}\text{H}_{18}\text{O}_3$, was determined by the molecular ion

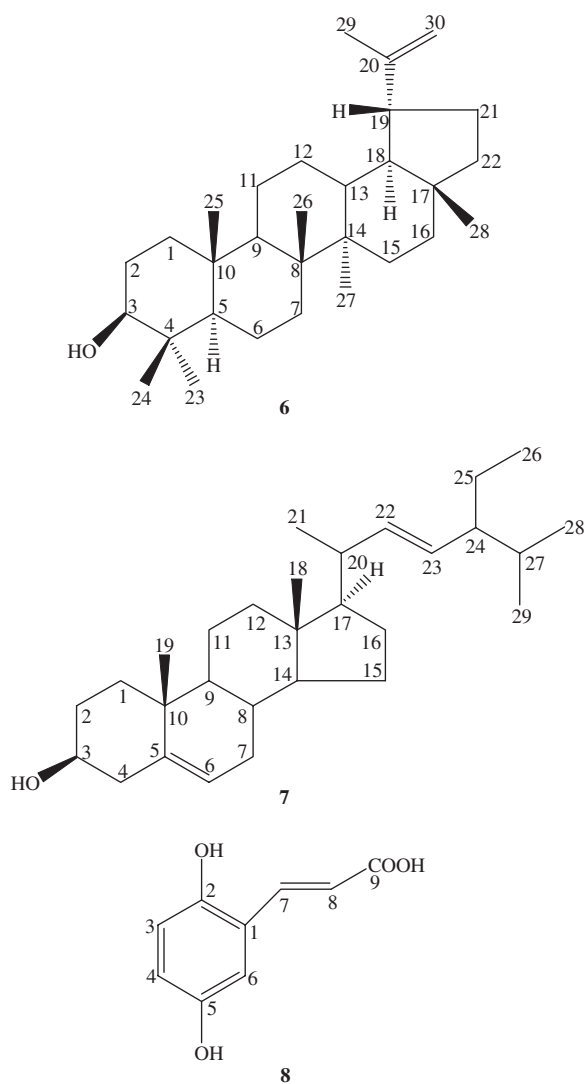


Figure 1. Continued.

peak $[M + Na]^+$ at m/z 293.1148 in the HR-ESI-MS. Moreover, the 1H NMR spectrum of **1** gave signals of five methyl groups and three aromatic protons. The corresponding ^{13}C NMR spectrum of **1** exhibited 12 aromatic carbons and five methyl carbons, indicating that **1** possessed a dibenzofuran skeleton [15]. Furthermore, the resonances of H-6 and H-9 appeared as broad singlets at δ_H 7.15 and δ_H 7.52, suggesting the *para* position of the two aromatic protons. Another aromatic proton H-3 could be found as a singlet at δ_H 6.99. Moreover, two signals at δ_H 3.98 (s, 3H), δ_H 4.01 (s, 3H) in the 1H NMR spectrum of **1**, together with two corresponding carbon resonances at δ_C 56.1 (q) and δ_C 56.7 (q) in the ^{13}C NMR spectrum indicated the presence of two methoxy groups in the molecule. In addition, the presence of three aromatic methyl groups could be

deduced from three singlets at δ_{H} 2.39 (s, 3H), δ_{H} 2.50 (s, 3H) and δ_{H} 2.66 (s, 3H) in the ^1H NMR spectrum of **1**, which were related to the corresponding carbon signals appearing at δ_{C} 14.7 (q), δ_{C} 15.6 (q) and δ_{C} 19.2 (q) in the ^{13}C NMR spectrum of **1**. Furthermore, NOE difference spectrum of **1** showed that H-3 was correlated to the methyl protons at δ 2.39 and δ 2.50, while the methoxyl at δ 3.98 exhibited correlations with H-6, and another methoxyl group at δ 4.01 showed correlations with H-9. All these data indicated that the two OMe groups were positioned at C-7 and C-8, while the position of three aromatic methyl groups on the dibenzofuran skeleton was proposed at the positions of C-1, C-2 and C-4. The structure of **1** was further supported by comparing its NMR signals with those of a known compound – ligumedia [16]. Finally, the structure of the previous unreported compound **1** was deduced as 1,2,4-trimethyl-7,8-dimethoxy-dibenzofuran.

Other isolated compounds such as euparin (**2**), 2,5-diacetyl-6-hydroxy-benzofuran (**3**), 2-acetyl-5,6-dimethoxy-benzofuran (**4**), gummosogenin (**5**), lupeol (**6**), stigmasterol (**7**) and (*E*)-2,5-dihydroxy-cinnamic acid (**8**) were identified by comparisons of their NMR spectral data with those of the known compounds and by direct comparison (TLC) with authentic samples.

3. Experimental

3.1. General

Silica gel (200–300 mesh) used for column chromatography (CC) and silica GF₂₅₄ (10–40 μm) for TLC were supplied by the Qingdao Marine Chemical Factory, Qingdao, China. Sephadex LH-20 (Pharmacia) and RP-18 material used for separation were purchased from Beijing Green Herbs Science and Technology Development Co., China. Melting points were obtained in an X-4 digital melting point instrument and were uncorrected. Optical rotations were measured on a Polax-2L polarimeter. Infrared spectra were obtained with a Bruker Vector-22 spectrometer. High-resolution ESI mass spectra were recorded on a Bruker Bio Apex 70eV FT-ICR (Bruker Daltonics, USA) instrument. ^1H -NMR (400 MHz), ^{13}C -NMR (100 MHz) and 2D-NMR spectra were recorded on an INOVA NMR spectrometer with TMS as internal standard.

3.2. Plant materials

The roots of *L. caloxantha* were collected in Lijiang County, Yunnan Province, P. R. China, in August 2002 and were identified by Prof. Xun Gong from Kunming Institute of Botany, Chinese Academy of Sciences, where a voucher specimen (200208ZY004) is deposited.

3.3. Extraction and isolation

The air-dried roots of *L. caloxantha* (2.8 kg) was pulverized and extracted at room temperature with ethanol (3 L \times 3 times). The solutions were combined and evaporated to dryness (317 g). The residue was suspended in H_2O and partitioned with petroleum ether (PE) and EtOAc. The PE extracts (35 g) were subjected to repeat chromatography on a silica gel column (200–300 mesh, 400 g), eluted with a gradient of

PE (60–90°C)–EtOAc (100:1–0:1). According to the guidance of TLC, 8 crude fractions were obtained. Fraction 3 (8 g) was chromatographed on a silica gel column and eluted with PE–EtOAc (80:1) to produce compound **2** (3 g). Fractions 4 (800 mg) and 5 (3.9 g) were further purified by recrystallization to afford **1** (21 mg) and **6** (650 mg). Fraction 6 (2.5 g) was chromatographed on a silica gel column and eluted with PE–EtOAc (5:1) to give **7** (930 mg). Fraction 8 (1 g) was chromatographed on sephadex LH-20 (CHCl₃: MeOH = 1:1) to afford **3** (100 mg) and **5** (4 mg). The EtOAc extract (45 g) was chromatographed on RP-18 column (200 g) and eluted with a gradient of MeOH–H₂O (0:1–1:0) to give **4** (27 mg), **7** (46 mg) and **8** (53 mg).

1,2,4-trimethyl-7,8-dimethoxy-dibenzofuran (1) Red crystals; m.p. 161–162°C; IR (KBr, ν_{\max} cm⁻¹): 2917, 2832, 1615, 1504, 1469, 1249, 1039; HR-ESI-MS m/z ([M + Na]⁺): 293.1144; ¹H NMR (400 MHz, CDCl₃) δ 2.39 (3H, 4-CH₃, s), 2.50 (3H, 2-CH₃, s), 2.66 (3H, 1-CH₃, s), 3.98 (3H, 7-OCH₃), 4.01 (3H, 8-OCH₃), 6.99 (1H, H-3, s), 7.15 (1H, H-6, br s), 7.52 (1H, H-9, br s); ¹³C NMR (100 MHz, CDCl₃) δ 14.7 (4-CH₃), 15.6 (2-CH₃), 19.2 (1-CH₃), 56.1 (7-OCH₃), 56.7 (8-OCH₃), 95.2 (C-6), 104.8 (C-9), 116.8 (C-9a), 118.0 (C-9b), 123.0 (C-4), 127.2 (C-2), 128.6 (C-1), 129.9 (C-3), 145.5 (C-8), 149.0 (C-7), 151.2 (C-5a), 153.5 (C-4a).

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