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Two New Dibenzofurans from the Underground Parts of *Ligularia intermedia*

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Abstract: Two new dibenzofurans, 7,8-dimethoxy-4-methyldibenzofuran-1-carboxaldehyde, named ligumedial (**1**) and 7,8-dimethoxy-4-methyldibenzofuran-1-carboxylic acid, named ligumediaoic acid (**2**), have been isolated from the underground parts of *Ligularia intermedia*. Their structures were elucidated by spectroscopic methods.

Keywords: *Ligularia intermedia*, Compositae, Chinese herbs, dibenzofuran, ligumedial, ligumediaoic acid.

Ligularia intermedia Nakai (Compositae) is a perennial herbaceous plant widely distributed in China. Its roots and rhizomes, commonly known as *Shanziwan*, are used as an antitussive and phlegm-expelling remedy in Chinese traditional medicine. The fresh plants of *L. intermedia* mainly contain sesquiterpene and benzofuran compounds[1]. We have investigated the dried underground parts of *L. intermedia* and isolated two new dibenzofurans, besides 5 known compounds, friedelin, euparin, lupeol, β-sitosterol and daucosterol[2]. This paper reports the structure elucidation of two new dibenzofurans, named ligumedial (**1**) and ligumediaoic acid (**2**). Naturally occurring dibenzofurans are noted for their biological, particularly antibiotic, activities[3].

Compound **1** was obtained as red powder. The molecular formula of **1** was assigned as $C_{16}H_{14}O_4$ from HRMS (*m/z* 270.0898, calcd. 270.0892). The IR spectrum displayed peaks at 1685 (aldehyde group), 1630, 1610 (aromatic residue) and 1300 cm^{-1} (aromatic ether). The ^{13}C NMR spectrum (**Table 1**) showed 12 aromatic carbons, one carbonyl carbon and three methyl carbons, indicating that **1** possessed a dibenzofuran skeleton[4]. The ^1H NMR spectrum showed a singlet at δ 10.22 attributed to an aldehyde proton. The ortho-coupled H-2 and H-3 protons appeared as doublets at δ 7.71 (J=7.6 Hz) and δ 7.33 (J=7.6 Hz). The other two aromatic protons, H-6 and H-9, gave singlets at δ 7.15 and 8.55 respectively. Two signals at δ_H 4.01 (s, 3H), δ_H 4.08 (s, 3H) in the ^1H NMR spectrum and two signals at δ_C 56.2 (q) and δ_C 56.4 (q) in the ^{13}C NMR spectrum indicated the presence of two methoxy groups. In addition, the presence of an aromatic

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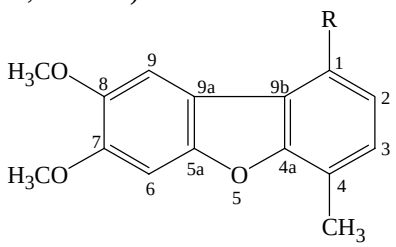
methyl group was apparent from a singlet at δ_H 2.66 (s, 3H) and from a quartet at δ_C 15.8.

The positions of the four substituent groups on the dibenzofuran skeleton were determined unambiguously from the analysis of the NOESY, HMQC, HMBC and COLOC spectra.

The NOESY spectrum of **1** showed that the CHO proton signal correlated to both the H-2 and the H-9. The aromatic methyl protons correlated to the H-3. The methoxy protons at δ 4.08 showed correlation with the H-9, and another methoxy protons showed correlation with the H-6. These NOESY interactions indicated that the two OMe substituents should be at positions 7 and 8, and the CHO and CH_3 substituents at positions 1 and 4 respectively.

In the COLOC experiment of **1,** the CHO proton showed connectivity to the C-9b and C-2 carbons, while the methyl protons showed connectivity to the C-3 and C-4a carbons. The methoxy protons at δ 4.08 showed connectivity to C-8, and the methoxy protons at δ 4.01 correlated to C-7. The H-6 signal showed long range correlation to C-8 and C-9a, while H-9 correlated to C-7 and C-5a, respectively. HMQC and HMBC experiments provided further information about the structure of **1**. Therefore, **1** was identified as 7,8-dimethoxy-4-methyldibenzofuran-1-carboxaldehyde, named ligumedial.

Compound **2** has the molecular formula $C_{16}H_{14}O_5$ assigned from the HRMS analysis (*m/z* 286.0824, calcd. 286.0841), which differed from compound **1** by having one more oxygen, suggesting that **2** was likely to be the oxidized product of **1**. It gave very similar ^{1}H NMR and ^{13}C NMR spectra to **1**, a significant difference was only for the carbonyl carbon at δ_C 167.7, which was a characteristic carboxylic acid carbon instead of the aldehyde carbon at δ_C 192.4 of **1**. Further more, the absence of CHO proton in the ^{1}H NMR spectrum of **2** also gave evidence for the structure confirmation. Therefore **2** was identified as 7,8-dimethoxy-4-methyldibenzofuran-1-carboxylic acid, named ligumediaoic acid, and the structure was further confirmed by 2D NMR experiments (^{1}H-^{1}H COSY, HMQC, HMBC, NOESY).



1: R = CHO
2: R = COOH

Ligumedial (7,8-dimethoxy-4-methyldibenzofuran-1-carboxaldehyde) (**1**). Red powder. IR ν (KBr) cm^{-1}: 1690(C=O), 1635, 1610, 1570, 1370. MS *m/z* (rel. int): 270.0898 $[M]^+$ (92) (calcd for $C_{16}H_{14}O_4$: 270.0892), 255 [270-Me](39), 227 [255-CO](13), 212(3), 184(46), 167(2), 155(10), 135(3), 128(13), 102(5), 77(6), 69(5). ^{1}H NMR (400MHz, $CDCl_3$) δ: 10.22 (s, 1H, 1-CHO), 8.55 (s, 1H, H-9), 7.71 (d, 1H, J = 7.6 Hz, H-2), 7.33 (d, 1H, J = 7.6 Hz, H-3), 7.15 (s, 1H, H-6), 4.08 (s, 3H, 8-OMe), 4.01 (s, 3H, 7-OMe), 2.66 (s, 3H, 4-Me). ^{13}C NMR data are listed in **Table 1**.

Ligumediaoic acid (7,8-dimethoxy-4-methyldibenzofuran-1-carboxylic acid) (**2**). Yellowish-brown solid. IR ν (KBr) cm^{-1}: 3300~2500, 1680(C=O), 1610, 1590, 1480, 1460, 1440. MS *m/z* (rel. int): 286.0824 $[M]^+$ (98) (calcd for $C_{16}H_{14}O_5$: 286.0841), 271 [286-Me](32), 243 [271-CO](8), 225(36), 207(8), 197(24), 184(22), 144(8), 115(10). ^{1}H NMR (400MHz, DMSO-d_6) δ: 8.40 (s, 1H, H-9), 7.86 (d, 1H, J = 7.8 Hz, H-2), 7.43 (s, 1H, H-6), 7.32 (d, 1H, J = 7.8 Hz, H-3), 3.90 (s, 3H, 8-OMe), 3.85 (s, 3H, 7-OMe), 2.59 (s, 3H, 4-Me). ^{13}C NMR data are listed in **Table 1**.

Table 1 ^{13}C NMR spectral data of ligumedial (**1**) and Ligumediaoic acid (**2**) (δ ppm)

No. of Carbon	**1**	**2**	No. of Carbon	**1**	**2**
1	129.1 (*s*)	125.9 (*s*)	8	145.8 (*s*)	145.3 (*s*)
2	130.2 (*d*)	125.8 (*d*)	9	107.5 (*d*)	108.0 (*d*)
3	125.8 (*d*)	125.6 (*d*)	9a	115.3 (*s*)	114.1 (*s*)
4	128.6 (*s*)	123.6 (*s*)	9b	123.2 (*s*)	122.4 (*s*)
4a	155.4 (*s*)	154.7 (*s*)	4-Me	15.8 (*q*)	15.1 (*q*)
5a	152.4 (*s*)	151.5 (*s*)	7-OMe	56.2 (*q*)	55.8 (*q*)
6	94.5 (*d*)	95.3 (*d*)	8-OMe	56.4 (*q*)	55.9 (*q*)
7	151.1 (*s*)	150.6 (*s*)	CHO	192.4 (*d*)	
			COOH		167.7 (*d*)

δ values of **1** and **2** were measured in $CDCl_3$ and DMSO-d_6 respectively.

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