Phytochemistry Letters 26 (2018) 134–137

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Anti-inflammatory lignans from *Melodinus suaveolens*

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ARTICLE INFO

Keywords:
Melodinus suaveolens
Apocynaceae
Lignans
Anti-inflammatory activity

ABSTRACT

Three new lignans, melodinins A–C (**1**–**3**), together with four known analogues (**4**–**7**), were isolated from the stems of *Melodinus suaveolens*. Their structures including relative configurations were determined by spectroscopic methods, including 1D and 2D NMR, and HRESIMS. Their absolute configurations were unambiguously assigned by electronic circular dichroism (ECD) experiments, especially the application of ECD exciton chirality method. Anti-inflammatory evaluation revealed that compounds **1**, **2**, **4**, and **5** exhibited moderate inhibitory effects on β-glucuronidase release in rat polymorphonuclear leukocytes (PMNs) induced by platelet-activating factor, with IC_{50} values ranging from 1.68 to 9.56 μM.

1. Introduction

The genus *Melodinus* (Apocynaceae), comprising approximately 53 species, is mainly distributed in the tropical and subtropical areas of Asia, with 11 species occuring in China (Tsiang and Li, 1977). Previous phytochemical investigations have indicated that plants of this genus are rich sources of monoterpenoid indole alkaloids (MIAs) with diverse structural skeletons (Feng et al., 2009, 2010; Guo et al., 2017; He et al., 1994; Jiang et al., 2015; Liu et al., 2013; Zhang et al., 2017). The *Melodinus* MIAs have shown a variety of biological properties including antitumor, anti-inflammatory, and antibacterial activities (Au and Gray, 1969; Cai et al., 2011). However, the non-alkaloid components of *Melodinus* plants have been rarely investigated. As part of a continuous project for bioactive compounds from *Melodinus* plants (Fang et al., 2016; Zhou et al., 2017), we have recently investigated the non-alkaloid extract of *M. suaveolens*, a woody liana narrowly distributed in the south of China. Three new lignans, melodinins A–C (**1**–**3**) and four known analogues were obtained and structurally characterized in the present work. Compounds **1**–**3** are rare lignans with a 3,5-disubstituted C_6 unit. Herein, we report the isolation and structural elucidation of the new compounds, as well as determination of their absolute configurations through spectroscopic analyses and ECD data, especially the employment of exciton chirality method. The anti-inflammatory activity of **1**–**7** has also been assayed.

2. Results and discussion

Compound **1** was obtained as an amorphous white powder. The molecular formula was determined to be $C_{20}H_{22}O_7$ based on the HRESIMS peak at *m/z* 397.1254 $[M+Na]^+$. The ^1H NMR spectrum (Table 1) showed two singlet signals at δ_H 6.90 (2H, s, H-4, H-6) and 7.00 (1H, s, H-2) for a 1,3,5-trisubstituted benzene ring, signals of an ABX system at δ_H 6.88 (1H, d, J = 7.8, 1.8 Hz, H-6′), 6.96 (1H, d, J = 7.8 Hz, H-5′), and 6.98 (1H, d, J = 1.8, H-2′) for a 1,3,4-trisubstituted benzene ring, as well as two singlet signals at δ_H 3.90 (3H, s, 3-OCH_3) and 3.92 (3H, s, 3′-OCH_3) for two aromatic *O*-methyl groups. Additionally, two oxymethine protons at δ_H 4.86 (1H, d, J = 4.8 Hz, H-7) and 4.85 (1H, s, H-7′), two pairs of oxymethylene protons at δ_H 4.54 (1H, dd, J = 9.6, 7.8 Hz, H-9a), 3.84 (1H, dd, J = 9.6, 6.0 Hz, H-9b), 4.06 (1H, d, J = 9.6 Hz, H-9′a), and 3.91 (1H, d, J = 9.6 Hz, H-9′b), and a methine proton at δ_H 3.12 (1H, m, H-8) were also observed in the ^1H NMR spectrum, which indicated the existence of a 3,7-dioxabicyclo [3.3.0]octane moiety (Vo et al., 2012). The carbon signals in the ^{13}C NMR and DEPT spectra of **1** further confirmed the above units. The above NMR spectroscopic data suggested that **1** had a diepoxytetrahydrofuran lignan skeleton similar to that of pseuderesinol (Vo et al., 2012) except for the replacement of a 1,3,4,5-tetrasubstituted benzene ring by a 1,3,4-trisubstituted counterpart in **1**, as further confirmed by MS data. Analysis of the 2D NMR data (^1H–^1H COSY, HSQC, and HMBC) of **1** permitted the assignments of all proton and carbon resonances. Furthermore, the coupling constants of $J_{7,8}$ (4.8 Hz) and the

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https://doi.org/10.1016/j.phytol.2018.05.027
Received 25 March 2018; Received in revised form 13 May 2018; Accepted 17 May 2018

Table 1
^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) Data of Compounds **1–3** in $CDCl_3$.

Position	1		2		3	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		132.5		132.4		133.4
2	7.00 (s)	109.2	6.99 (s)	109.2	7.02 (s)	108.9
3		146.8		146.9		146.9
4	6.90 (s)	114.4	6.89 (s)	114.4	6.87 (s)	114.2
5		146.2		145.6		145.6
6	6.90 (s)	119.8	6.89 (s)	119.8	6.87 (s)	119.8
7	4.86 (d, 4.8)	86.0	4.86 (d, 4.8)	86.0	4.68 (d, 7.2)	84.4
8	3.12 (m)	60.2	3.11 (m)	60.1	2.58 (m)	56.4
9	4.54 (dd, 9.6, 7.8)	71.8	4.53 (dd, 9.6, 7.8)	71.8	4.36 (dd, 11.4, 6.6)	62.6
	3.84 (dd, 9.6, 6.0)		3.84 (dd, 9.6, 6.0)		4.20 (dd, 11.4, 6.6)	
1′		127.1		126.2		127.9
2′	6.98 (d, 1.8)	109.5	6.64 (s)	103.6	6.78 (d, 1.80)	122.8
3′		147.1		147.5		146.7
4′		145.6		135.1		145.0
5′	6.96 (d, 7.8)	114.8		147.5	6.96 (d, 7.8)	114.7
6′	6.88 (dd, 7.8, 1.8)	119.7	6.64 (s)	103.6	6.74 (dd, 7.8, 1.8)	112.7
7′	4.85 (s)	88.0	4.81 (s)	88.1	2.96 (d, 13.8)	39.6
					2.85 (d, 13.8)	
8′		91.8		91.6		81.4
9′	4.06 (d, 9.6)	74.8	4.04 (d, 9.6)	74.7	3.88 (d, 9.6)	77.8
	3.91 (d, 9.6)		3.90 (d, 9.6)		3.70 (d, 9.6)	
OH-5	5.68 (s)		5.87 (brs)		5.60 (s)	
OH-4′	5.63 (s)		5.80 (brs)		5.57 (s)	
OMe-3	3.90 (s)	56.1	3.89 (s)	56.1	3.89 (s)	56.0
OMe-3′	3.92 (s)	56.2	3.90 (s)	56.5	3.90 (s)	56.1
OMe-5′			3.90 (s)	56.5		
OAc						171.0
					2.04 (s)	21.0

shifts of H-7/H-7′, H-8 and C-8/C-8′ indicated that the aryl moieties were pseudoequatorial and *cis*-oriented with H-8 and H-8′ in **1** (Greger and Hofer, 1980; Kim et al., 2010), which was also confirmed by the chemical shift differences of H_2-9 and H_2-9′ ($\Delta\delta_{H\text{-}9} = 0.7$, $\Delta\delta_{H\text{-}9'} = 0.15$) (Shao et al., 2018). In addition, a positive Cotton effects at 211 nm in ECD spectra and the specific rotation ($[\alpha]_D^{25}$ +16.0 (*c* 0.05, MeOH)) of **1** suggested the *7S,7′R,8R,8′S* configuration (Xiong et al., 2011). Accordingly, the structure of **1** was elucidated as (*7S,7′R,8R,8′S*)-5,4',8'-trihydroxy-3,3'-dimethoxy-7,9':7',9-diepoxylignane and was named melodinin A (Fig. 1).

Compound **2** was isolated as a white amorphous powder, and its molecular formula was deduced to be $C_{21}H_{24}O_8$ from its positive HRESIMS data (*m/z* 405.1548 $[M+H]^+$). The ^{1}H and ^{13}C NMR spectra of **2** were very similar to those observed for **1** (Table 1), except for the disappearance of H-5′ signal and the appearance of an additional *O*-methyl group (δ_H 3.90). The location of the *O*-methyl group was confirmed by the HMBC correlations from its proton signals (δ_H 3.90, 3H, s) to C-5′ (δ 147.5) (Fig. 2). The relative configuration of **2** was also supported by the ^{1}H NMR coupling constants of $J_{7,8}$ (4.8 Hz), the shifts of H-7/H-7′, H-8 and C-8/C-8′, and the chemical shift differences of H_2-9 and H_2-9′. Furthermore, the ECD spectrum of **2** was similar to **1**. On the basis of the above data, the structure of **2** was assigned as (*7S,7′R,8R,8′S*)-5,4',8'-trihydroxy-3,3',5'-trimethoxy-7,9':7',9-diepoxylignane and was named melodinin B.

Compound **3** was obtained as a white amorphous powder, and its molecular formula of $C_{22}H_{26}O_8$ was established by HRESIMS at *m/z* 441.1517 $[M+H]^+$. The ^{1}H NMR data (Table 1) indicated the presence of a 1,3,5-trisubstituted benzene ring [δ_H 6.87 (2H, s, H-4, H-6) and 7.02 (1H, s, H-2)], a 1,3,4-trisubstituted benzene ring [δ_H 6.74 (1H, d, J = 7.8, 1.8 Hz, H-6′), 6.96 (1H, d, J = 7.8 Hz, H-5′), and 6.78 (1H, d, J = 1.8, H-2′)], two methylene groups [δ_H 4.36 (1H, dd, J = 11.4, 6.6 Hz, H-9a), 4.20 (1H, dd, J = 11.4, 6.6 Hz, H-9b), 2.96 (1H, d, J = 13.8 Hz, H-7′a), and 2.85 (1H, d, J = 13.8 Hz, H-7′b)], and two *O*-methyl groups [δ_H 3.89 (3H, s, 3-OCH_3), and 3.90 (3H, s, 3′-OCH_3)]. Besides, the ^{1}H NMR together with ^{13}C NMR revealed an acetoxyl group [δ_H 2.04 (3H, s); δ_C 21.0 and 171.0], as well as a tetrahydrofuran ring [δ_H 4.68 (1H, d, J = 7.2 Hz, H-7), 2.58 (1H, m, H-8), 3.88 (1H, d, J = 9.6 Hz, H-9′a), and 3.70 (1H, d, J = 9.6 Hz, H-9′b); δ_C 84.4 (C-7), 56.4 (C-8), 81.4 (C-8′) and 77.8 (C-9′)]. The above observations revealed that **3** possessed a tetrahydrofuran lignan skeleton (Liao et al., 2006). In the HMBC spectrum, the long-range correlations from H-7 and H-8 to C-9′, from H-9 to C-7, from H-7′ to C9′, and from H-9 to C-10 confirmed the presence of the tetrahydrofuran ring with an acetoxyl group linked to C-9 (Fig. 2). In addition, the HMBC correlations between the methoxyl signals at δ_H 3.89 and C-3 and those at δ_H 3.90 and C-3′ revealed that the two *O*-methyl groups were attached at C-3 and C-3′, respectively. Thus, the gross structure of **3** was established as shown. The chemical shift of H-7 at *ca.* δ_H 4.68 and the coupling constants of $J_{7,8}$ (7.2 Hz) in the ^{1}H NMR spectrum established the 7,8-*trans*

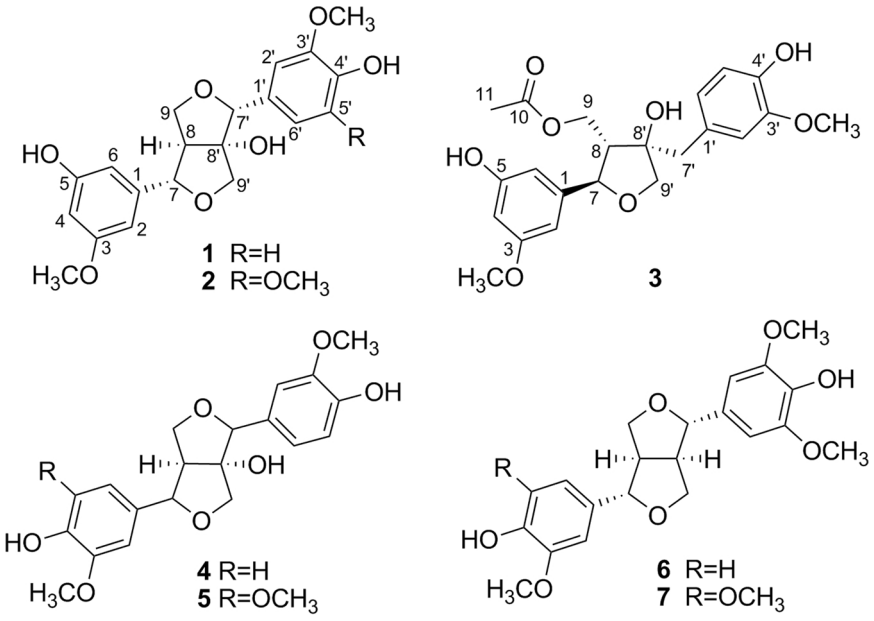

Fig. 1. Structures of compounds **1–7**.