



Acylphloroglucinols from the leaves of *Callistemon viminalis*



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ARTICLE INFO

Article history:

Received 2 July 2016

Received in revised form 12 August 2016

Accepted 20 August 2016

Available online 24 August 2016

Keywords:

Callistemon viminalis

Acylphloroglucinols

Callistenones F–K

Antitumor

ABSTRACT

A phytochemical study on the leaves of *Callistemon viminalis*, a widely distributed ornamental and medicinal plant of agricultural importance in China, resulted in the isolation of eleven acylphloroglucinols, including six new ones named callistenones F–K (**1–6**), as well as five known congeners. Their structures were fully characterized using spectral data interpretation for the new structures and compared to published data for the known ones. All the isolated compounds were evaluated for *in vitro* antimicrobial activity and growth inhibitory activity against four tumor cell lines (MCF-7, NCI-H460, SF-268 and HepG-2).

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1. Introduction

The genus *Callistemon*, commonly known as “bottle brush” and well-known for its beautiful ever-green shrubs and small trees, was introduced from Australia to China decades ago and is now widely planted throughout the country due to its ornamental and medicinal properties. *C. viminalis* has been adopted into Chinese folk medicine and used to treat a variety of symptoms such as colds and arthralgia [1]. The accumulated phytochemical studies on the genus *Callistemon* have led to the isolation and characterization of flavonoids [2–3], triterpenoids [3–4], phloroglucinol derivatives [5–10], neolignans [11], essential oils, steroids and saponins [12]. Our previous investigation, which aimed to discover new antibacterial constituents from the family Myrtaceae, resulted in the discovery of a large batch of phloroglucinols possessing potent antibacterial activity and a variety of structural frames [13–15]. In a continuation to our efforts to search for more intriguing phloroglucinol derivatives, an extensive research on the constituents was launched on the ethanolic extract of *C. viminalis*. As a result, six new acylphloroglucinols, named callistenones F–K (**1–6**) (Fig. 1), along with five known analogous were isolated. Herein, the isolation, structural elucidation, and bioassay of these compounds are described.

2. Results and discussion

The separation of the *n*-hexane and EtOAc-soluble fractions from the antibacterial ethanolic extract of *C. viminalis* resulted in the isolation of eleven acylphloroglucinols (**1–11**), including six new ones named callistenones F–K (**1–6**) and five known acylphloroglucinols. The chemical structures of the known compounds (Fig. 1) were identified by direct spectral comparison to those reported for corresponding structures in literatures as pulverulentone A (**7**) [16], 2,6-dihydroxy-4-methoxyisovalerophenone (**8**) [16], aspidinol C (**9**) [17], aspidinol D (**10**) [17], and 2,6-dihydroxy-4-methoxy-3-methyl-isopropiophenone (**11**) [18].

Compound **1** was obtained as a yellowish oil. Its molecular formula was established as C₂₆H₃₄O₆ based on the high-resolution electrospray ionization mass spectroscopy (HRESIMS), wherein a protonated molecular ion [M + H]⁺ was detected at *m/z* 443.2417 (calcd 443.2428), which indicated ten indices of hydrogen deficiency. The resonances of three carbonyl carbons, nine quaternary carbons, four methine carbons, one methylene carbon, and eight methyl carbons were evident from the ¹³C, DEPT, and HSQC NMR data (Table 1). The ¹H NMR spectrum showed resonances of four tertiary methyl groups at δ_H 1.63 (H₃-10), 1.44 (H₃-11), 1.41 (H₃-12), and 1.38 (H₃-13). In the HMBC spectrum, H₃-10 and H₃-11 showed HMBC correlations with carbonyl carbons C-1 (δ_C 197.6) and C-3 (δ_C 212.0), whereas H₃-12 and H₃-13 showed correlations with the carbonyl carbon C-3 (δ_C 212.0) and an oxygenated vinylic carbon C-4a (δ_C 167.7). All of these observations collectively pointed to the presence of a β-triketone moiety [19–20].

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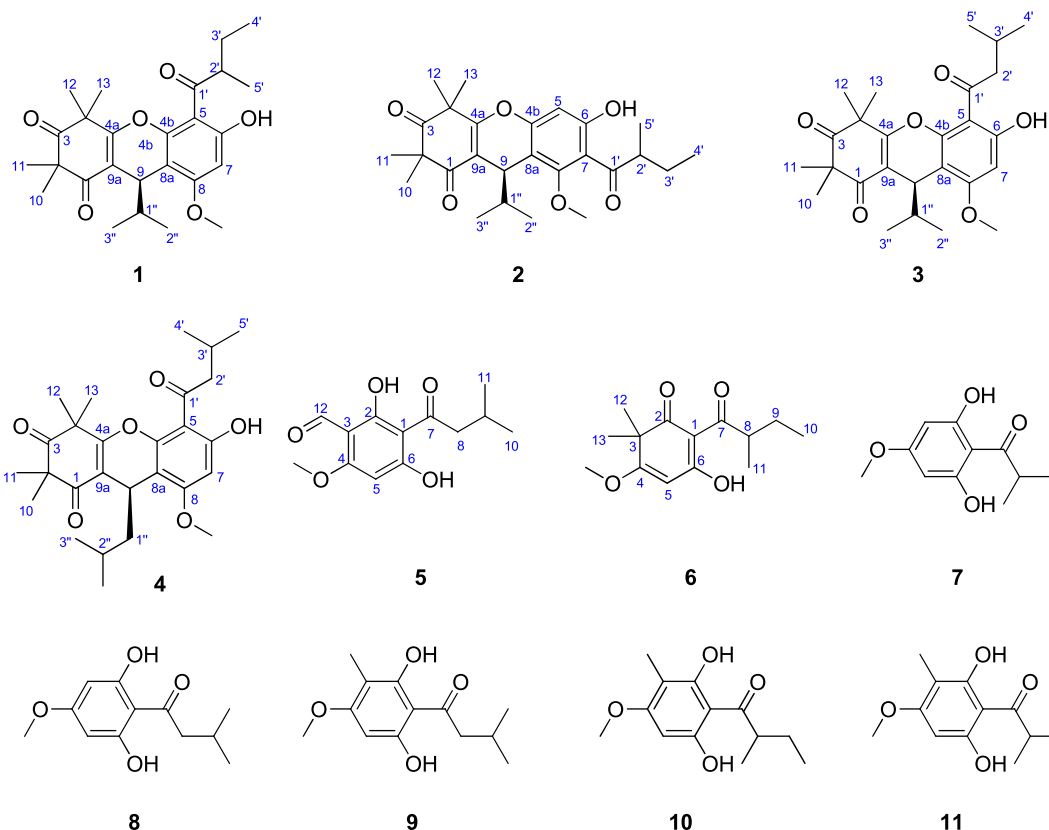


Fig. 1. Structures of compounds 1–11.

The six ^{13}C signals (164.9, 162.4, 153.0, 105.1, 104.8, 96.4), including five quaternary carbons and one methine carbon in the aromatic region, could be readily assigned to a di-C-substituted phloroglucinol moiety.

Table 1

^1H (500 MHz) and ^{13}C (125 MHz) NMR data of **1** and **2** in CDCl_3 .

No.	1		2	
	δ_{H}	δ_{C}	δ_{H}	δ_{C}
1		197.6, C		198.0, C
2		47.3, C		47.2, C
3		212.0, C		205.1, C
4		56.2, C		56.2, C
4a		167.7, C		167.5, C
4b		152.8, C		152.8, C
5	6.32, s	96.5, CH		103.8, C
6		164.8, C		165.7, C
7		104.7, C	6.33, s	96.7, CH
8		162.3, C		162.3, C
8a		104.9, C		104.7, C
9	4.31, d, 3.6	31.4, CH	4.31, m	31.2, CH
9a		112.1, C		113.8, C
10	1.63, s	25.2, CH_3	1.63, s	25.0, CH_3
11	1.41, s	24.8, CH_3	1.45, s	25.1, CH_3
12	1.44, s	25.0, CH_3	1.44, s	24.7, CH_3
13	1.38, s	24.1, CH_3	1.38, s	24.3, CH_3
1'		209.3, C		208.7, C
2'	3.92, m	45.4, CH	3.79, m	46.8, CH
3'	1.86, m	28.6, CH_2	1.99, m	24.8, CH_2
	1.55, m		1.51, m	
4'	0.85, t, 7.5	11.2, CH_3	0.99, t, 7.5	12.2, CH_3
5'	1.27, d, 6.7	15.7, CH_3	1.23, d	18.9, CH_3
1''	1.87, m	34.6, CH	1.86, m	34.6, CH
2''	0.78, d, 6.7	18.9, CH_3	0.76, d, 6.8	18.8, CH_3
3''	0.78, d, 6.7	18.6, CH_3	0.76, d, 6.8	18.7, CH_3
OMe	3.87, s	55.8, CH_3	3.87, s	55.8, CH_3
6-OH	13.6, s		13.7, s	

This deduction was further confirmed by the HMBC correlations observed from the aromatic proton H-7 to C-5 and C-8a, and from 6-OH to C-5 and C-7. The methoxy group in the phloroglucinol moiety was concluded to be attached at the C-8 position based on the HMBC correlation between δ_{H} 3.87 and C-8. Moreover, the COSY correlations of **1** indicated the presence of the spin system $\text{H}_3\text{-4'}/\text{H-3'}/\text{H-2'}/\text{H}_3\text{-5'}$. Coupled with the triplet appearance of $\text{H}_3\text{-4'}$, as well as HMBC correlations from H-2' and H-3' to the carbonyl carbon at δ_{C} 209.3, this result indicated the presence of a 2-methylbutanoyl moiety in this molecule. It was worth mentioning that the phenolic proton (6-OH) resonated significantly downfield, suggesting the existence of a strongly intramolecular hydrogen bond effect and indicating that the 2-methylbutanoyl group should be linked at the carbon *ortho* to the phenolic proton [21]. The fulfillment of molecular formula for **1** required an ether linkage presented between C-4a and C-4b. Thus, **1** was assigned as 6-hydroxy-9-isopropyl-8-methoxy-2,2,4,4-tetramethyl-5-(2-methylbutanoyl)-4,9-dihydro-1*H*-xanthene-1,3(2*H*)-dione, and was given the trivial name callistenone F. Unfortunately, the absolute configuration at C-9 in **1** could not be determined due to a paucity of natural samples.

Compound **2** was also isolated as a yellowish oil. Its molecular formula was determined as $\text{C}_{26}\text{H}_{34}\text{O}_6$ based on the HRESIMS pseudo-molecular peak observed at m/z 443.2423 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{26}\text{H}_{34}\text{O}_6$, 443.2428). The ^1H and ^{13}C NMR data of **2** (Table 1) were similar to those of **1** with the only significant difference being that the methine signals assignable to the 2-methylbutanoyl groups in **2** were observed at δ_{H} 3.79 (m, H-2') and δ_{C} 46.8 (C-2'), while they were observed at 3.92 (m, H-2') and δ_{C} 45.4 (C-2') in **1**. This difference suggests that **2** is a regioisomer of **1**. The HMBC correlations (Fig. 2) observed from H-5 to C-7, C-8a, and that of 6-OH to C-5, C-6, were consistent with the assignment wherein the aromatic proton was bonded to C-5 and the 2-methylbutanoyl group was attached at C-7. Compound **2** was thus established as 6-hydroxy-9-isopropyl-8-methoxy-2,2,4,4-

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