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Short communication

Monoterpene derivatives from the flowers of the *Hemerocallis minor* Mill.

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ABSTRACT

Three new monoterpene derivatives, named hemerolides A–C (**1**–**3**), one new phenol derivative hemeratrol A (**4**), along with thirteen known compounds (**5**–**17**) were isolated from the flowers of *Hemerocallis minor* Mill. The structures of the isolated compounds were determined by a combination of 1D and 2D NMR, HRESIMS, and CD spectroscopic data. All the isolates were evaluated their inhibitory activity against NF-κB activation in HeLa cells. Among them, compound **4** displayed a moderate inhibition of NF-κB activation with IC_{50} value of 41.7 μM.

1. Introduction

The genus *Hemerocallis* (Liliaceae), including about 14 different species distributed widely from southern Europe to the temperate zone of Asia, is a member of the lily family and commonly called day-lily. This genus is edible and ornamental plant and has been used for the treatment of a variety of diseases including inflammation, depression and insomnia (Uezu, 1998; Cichewicz and Nair, 2002). Previous investigations revealed its predominant chemical constituents including lactams (Inoue et al., 1994; Matsumoto et al., 2014, 2016), anthraquinones (He et al., 1982; Cichewicz et al., 2002), flavones (Cichewicz and Nair, 2002), terpenes (Yang et al., 2003; Zhang et al., 2004), steroidal saponins (Xiu et al., 1982; Konishi et al., 2001), and phenolic glycosides (Cichewicz and Nair, 2002). For the sake of exploring novel bioactive compounds from this genus, phytochemical research was conducted with the flowers of *H. minor* Mill. In our search, we have identified three new monoterpene derivatives, named hemerolides A–C (**1**–**3**), one new phenol derivative hemeratrol A (**4**), along with thirteen known compounds (**5**–**17**) from the flowers of *H. minor* Mill. (Fig. 1). Among them **5**–**13** were also monoterpene derivatives. In this paper, we describe the isolation, structure elucidation of the new isolates, and their NF-κB inhibitory activity in HeLa cells.

2. Results and discussion

Compound **1** was obtained as yellow oil. Its molecular formula was determined as $C_{23}H_{38}O_4$ on the basis of its positive HRESIMS pseudo-molecular ion peak at *m/z* 401.2672 $[M+Na]^+$ (calcd. for $C_{23}H_{38}O_4Na$, 401.2668), requiring five degrees of unsaturation. The ^1H and ^{13}C NMR spectroscopic data of **1** were very similar to those of loliolide (**5**) (Hodges and Porte, 1964; Tanaka and Matsunaga, 1989; Kimura and Maki, 2002). The ^{13}C, DEPT and HSQC NMR spectra of **1** showed the presence of 23 carbons: four methyls, twelve methylenes, one oxymethine (δ_C 68.3, C-3), one olefinic methine (δ_C 113.4, C-7), and four quaternary carbons, including two carbonyls at δ_C 171.4 (C-8) and 172.5 (C-1′) and one olefinic carbon at δ_C 181.2 (C-6) (Table 1). Compared with loliolide, **1** was 182 mass units and one degree of unsaturation more than loliolide, and **1** displayed signals of another methyl group at δ_H 0.87 (3H, t, J = 6.9 Hz, H-12′), a long-chain methylenes at δ_H 2.33 (2H, t, J = 7.6 Hz, H-2′), δ_H 1.64 (2H, m, H-3′), δ_H 1.25 (16H, m, H-4′ to H-11′), and a carbonyl group δ_C 172.5 (C-1′). The deshielding effect of the H-3 methine (δ_H 5.26) in relation to that of loliolide (δ_H 4.21) indicated that **1** was a loliolide derivative in which the OH group at C-3 was esterified by an additional twelve carbons chain fatty acid. The ^1H-^1H COSY correlations extended from H-2′ to H-12′ and the HMBC correlations of H-2′ to C-1′ demonstrated the presence of the long chain fatty acid (Fig. 2). The attached position of fatty acyl group was also elucidated by the HMBC correlations from H-3 to C-1′ (Fig. 2). The relative configuration of **1** was determined by the comparison of ^1H and ^{13}C chemical shifts with literature and further confirmed by NOESY spectrum (Junji and Noritsugu, 2002). The NOESY correlations of H-11 with H-9 proved that H-11 and H-9 occurred on the same side (α-orientations), while the cross peaks of H-3 with H-10 revealed that H-3 and H-10 were on the other side (β-orientations) (Fig. 3). The structure of loliolide had been determinned by X-ray diffraction analysis (Chen et al., 1997). Furthemore, **1** showed a negative specific rotation (−26.8) and a negative Cotton effect at 216 nm as same as loliolide (**5**) (Fig. 4). Thus, on the basis of these results, the structure of **1** was confirmed to be 3*S*, 5*R* and named hemerolide A.

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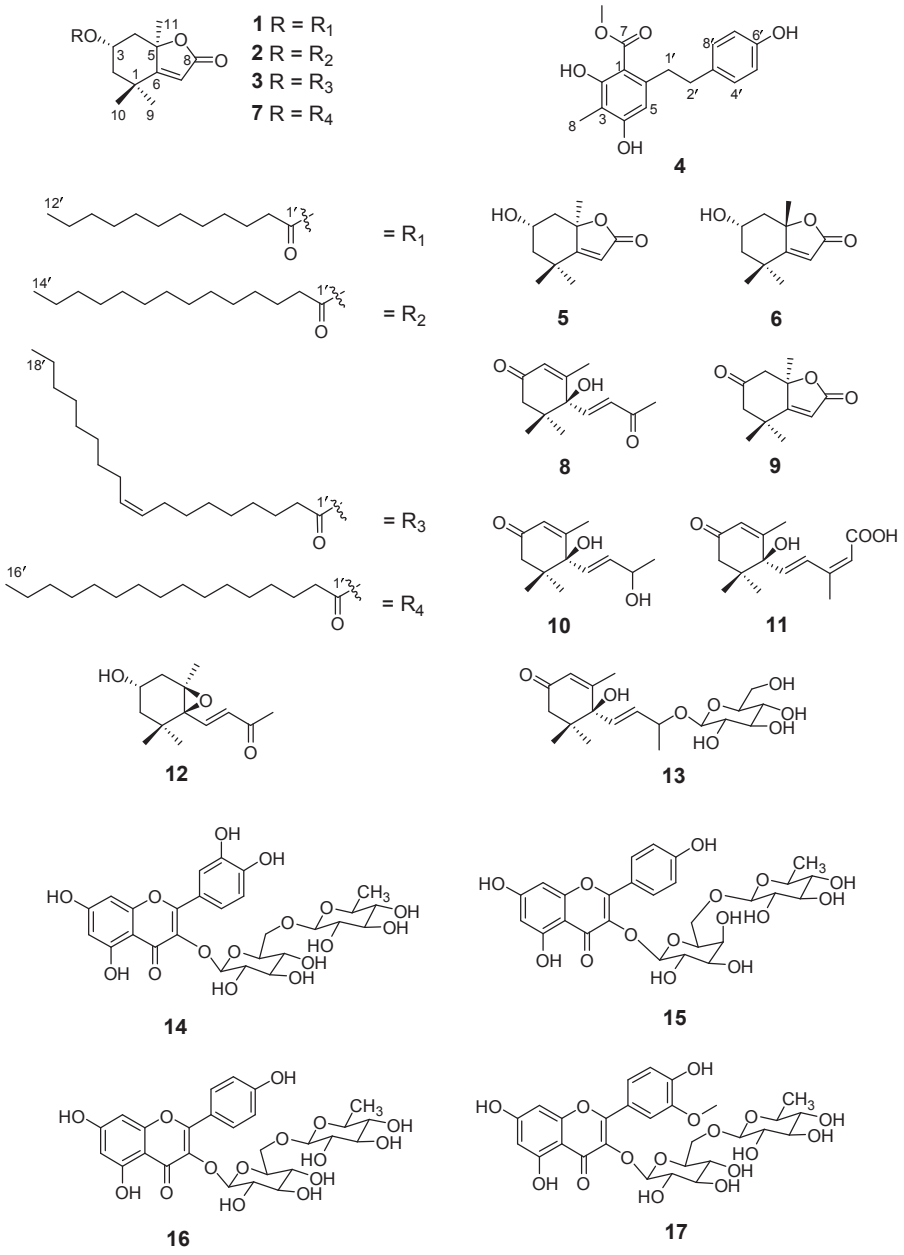

Fig. 1. Structures for compounds **1–17**.

Compound **2** was obtained as yellow oil with a molecular formula $C_{25}H_{42}O_4$ determined by its HRESIMS pseudo-molecular ion peak at *m/z* 429.2981 $[M+Na]^+$ (calcd. for $C_{25}H_{42}O_4Na$, 429.2981). Compound **2** is 28 mass units more than **1**. The 1D and 2D NMR data indicated that the structure of **2** was exactly similar to those of **1**, but the signals for multiple aliphatic protons at δ_H 1.25 (20H, m, H-4′ to H-13′) and the presence of 25 carbons including fourteen methylenes, suggesting the presence of two additional methylenes in the long chain fatty acid moiety (Table 1). The NOESY spectrum of **2** was very simiar to **1**. Moreover, **2** also displayed a negative specific rotation (−28.3) and a negative Cotton effect at 216 nm (Fig. 4). So the chemical structure of **2** was also proved to be 3*S*, 5*R* and named hemerolide B.

Compound **3** was isolated as yellow oil. Its HRESIMS exhibited a quasi-molecular ion peak at *m/z* 483.3465 $[M+Na]^+$ (calcd. for $C_{29}H_{48}O_4Na$, 483.3450), corresponding to the molecular formula $C_{29}H_{48}O_4$. Compound **3** is 82 mass units more than **1**. The ^1H and ^{13}C NMR data were also very similar to those of **1** except new signals for two olefinic methines (δ_C 129.6, C-9′; δ_C 129.4, C-10′) and the signals for multiple aliphatic protons at δ_H 1.31 (20H, m, H-4′ to H-7′, H-12′ to H-17′), δ_H 2.04 (4H, m, H-8′, H-11′), suggesting compound **3** has four more methylenes and one double bond than **1** in the long chain fatty acid moiety (Table 1). The long chain fatty acid was assigned as oleoyl group by the EIMS fragment ions at *m/z* 265, 180,165, 151, 138, 125, 111, 97, 83, 69, 55, and 41. The NOESY spectrum of **3** was also extremely simiar to **1**. And **3** also displayed a negative specific rotation (−18.7) and a negative Cotton effect at 216 nm (Fig. 4). From the above evidence, the structure of **3** was determined to be 3*S*, 5*R* and named hemerolide C.

Compound **4** was obtained as yellow gum. Its molecular formula was assigned as $C_{17}H_{18}O_5$ on the basis of its positive HRESIMS peak at *m/z* 325.1052 $[M+Na]^+$ (calcd. for $C_{17}H_{18}O_5Na$, 325.1052), indicating nine degrees of unsaturation. The NMR data of **4** revealed that two phenyl moieties account for eight units of unsaturation. The last one degree of unsaturation was attributed to the carbonyl. The ^{13}C, DEPT and HSQC spectra of **4** displayed resonances for 17 carbon signals: one methyl, one methoxy (δ_C 50.8, 7-OCH_3), two methylenes, five methines, and eight quaternary carbons, including a carbonyl at δ_C 170.7 (C-5), three oxygen-bonded aromatic carbons at δ_C 162.7 (C-2),