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Jatrophane and ingenane-type diterpenoids from *Euphorbia kansui* inhibit the LPS-induced NO production in RAW 264.7 cells

Jin Woo Lee [a], Qinghao Jin [a], Hari Jang [a], Dongho Lee [b], Sang Bae Han [a], Youngsoo Kim [a], Jin Tae Hong [a], Mi Kyeong Lee [a], Bang Yeon Hwang [a,*]

[a] College of Pharmacy, Chungbuk National University, Cheongju 28644, Republic of Korea
[b] College of Life Sciences and Biotechnology, Korea University, Seoul 02841, Republic of Korea

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ABSTRACT

Bioactivity-guided fractionation of the MeOH extract from the roots of *Euphorbia kansui* resulted in the isolation of two new jatrophane-type diterpenoids, kanesulones A (**1**) and B (**2**), together with six known jatrophane-type diterpenoids (**3**–**8**) and ten known ingenane-type diterpenoids (**9**–**18**). Their chemical structures were elucidated on the basis of spectroscopic data interpretation, especially 1D and 2D NMR such as HMQC, HMBC, COSY and NOESY, and HRESIMS data as well as CD analysis. Compounds **1**–**8** and **11**–**18** exhibited the inhibitory effects on LPS-induced nitric oxide production with IC_{50} values ranging from 0.7 to 46.5 μM in RAW 264.7 macrophages.

Euphorbia kansui L., belonging to Euphorbiaceae, distributed widely in Korea and China. The dried roots of this plant have been used as a traditional medicine for the treatment of asthma, edema, ascites, and cancer.[1] A number of structurally diverse diterpenoids such as jatrophane, ingenane, tigliane, daphnane, lathyrane, and casbane skeletons have been reported from the genus *Euphorbia*.[2,3] Some of these compounds have shown the wide range of biological activities including cytotoxic,[4–7] anti-fungal,[8,9] anti-viral,[10–12] anti-inflammatory,[13,14] and modulation of multidrug resistance effects.[15,16]

In a continuing search for plant-derived inhibitors of nitric oxide (NO) production from medicinal plant, two new jatrophane-type diterpenoids, kanesulones A and B (**1**–**2**), together with six known jatrophane-type diterpenoids (**3**–**8**) and ten known ingenane-type diterpenoids (**9**–**18**) were isolated from the roots of *E. kansui* using various column chromatographic separation techniques (Fig. 1).[17] The structures of these compounds were determined by 1D and 2D NMR such as HMQC, HMBC, COSY and NOESY, and HRESIMS data as well as CD analysis. All isolates were evaluated for their potential to inhibit LPS-induced nitric oxide production in RAW 264.7 cells.

Compound **1**[18] was obtained as a yellow powder, and gave a quasimolecular ion peak at *m*/*z* 707.2689 $[M+H]^+$ (calcd for $C_{38}H_{43}O_{13}$, 707.2698) in the positive-ion HRESIMS, corresponding to the molecular formula of $C_{38}H_{42}O_{13}$. The ^1H and ^{13}C NMR data (Table 1) of **1** were similar to those of esulone A (**8**), except for the presence of an additional OH group. Comparing ^1H NMR spectrum of **1** with those reported for esulone A (**8**), the H-1 proton signal was shifted from δ_H 2.47 (1H, ddd, J = 16.5, 1.5, 0.5 Hz, H-1) and 2.93 (1H, dd, J = 16.5, 1.0 Hz, H-1) in esulone A (**8**) to δ_H 4.42 (1H, d, J = 4.0 Hz, H-1) in **1**. In addition, in the ^{13}C NMR spectrum, the carbon signal for C-1 was shifted from δ_C 50.4 in esulone A (**8**) to δ_C 86.4 in **1** because of an additional OH group.[19] In the HMBC spectrum of compound **1**, the correlation between H-3 [δ_H 5.64 (1H, d, J = 4.5 Hz)] and acetoxy carbon [δ_C 168.8 (3-OAc)] established that an acetoxy group was located at C-3. However, no HMBC correlation between the remaining acetoxy carbon and the skeletal proton was suggested that the acetoxy group was attached to quaternary carbon of the jatrophane skeleton. The assignment of the acetoxy group at C-15 confirmed by comparison of the chemical shift value of C-15 in **1** (δ_C 96.2) with that in **2** (δ_C 84.8), which is a 15-hydroxy jatrophane-type diterpenoid. In addition, the HMBC correlations between H-5 (δ_H 5.90 (1H, m)] and benzoyloxy carbon [δ_C 165.5 (5-OBz)] and between H-7 [δ_H 6.03 (1H, br s)] and the other benzoyloxy carbon [δ_C 164.9 (7-OBz)] established that two benzoyloxy groups were located at C-5 and C-7 positions (Fig. 2). The absolute configuration of compound **1** was determined by comparison of its CD and NOESY data with those of esulone A (**8**), of which absolute configuration was determined by X-ray crystallographic analysis. The CD spectrum of compound **1** showed negative Cotton effects at 242 nm, and suggested the absolute configuration of 5*R* and 7*S*.

* Corresponding author. Tel.: +82 43 261 2814; fax: +82 43 268 2732.
E-mail address: byhwang@chungbuk.ac.kr (B.Y. Hwang).

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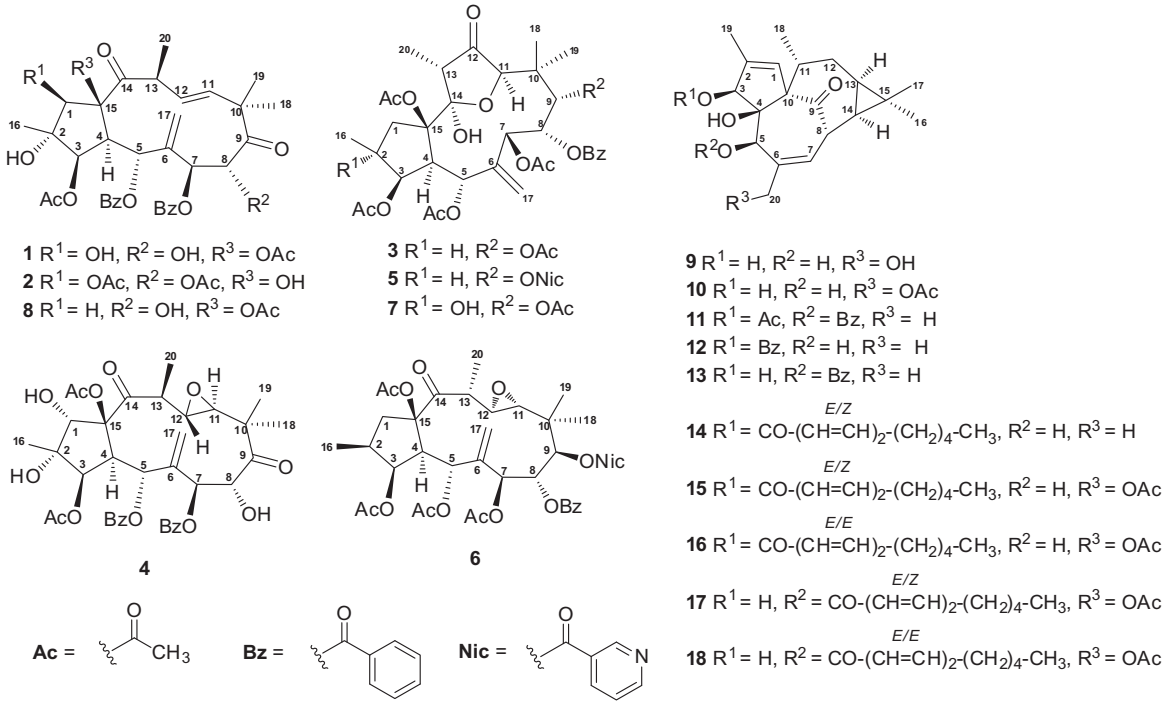

Figure 1. Structures of compounds **1**–**18**.

Table 1
^{1}H and ^{13}C NMR data of compound **1**

Position	δ_H[a,b]	δ_C[a,c]	Position		δ_H[a,b]	δ_C[a,c]
1	4.42 (d, 4.0)	86.4 d	3-OAc	1	—	168.8 s
2	—	78.5 s		2	1.92 (s)	20.5 q
3	5.64 (d, 4.5)	78.0 d	15-OAc	1	—	172.3 s
4	3.87 (dd, 10.0, 5.0)	45.1 d		2	2.28 (s)	21.5 q
5	5.90 (m)	73.5 d				
6	—	137.7 s	5-OBz	1	—	128.6 s
7	6.03 (br s)	65.2 d		2/6	6.90–7.70	129.5 d
8	4.81 (m)	71.5 d		3/5	6.90–7.70	127.8 d
9	—	211.1 s		4	6.90–7.70	132.7 d
10	—	48.2 s		7	—	165.5 s
11	6.13 (d, 16.0)	134.7 d				
12	5.76 (dd, 16.0, 10.0)	134.9 d	7-OBz	1	—	128.7 s
13	4.47 (m)	43.6 d		2/6	6.90–7.70	129.4 d
14	—	204.6 s		3/5	6.90–7.70	127.8 d
15	—	96.2 s		4	6.90–7.70	132.9 d
16	1.35 (s)	20.7 q		7	—	164.9 s
17	5.92 (m), 5.74 (m)	123.7 t				
18	1.37 (s)	23.6 q	1-OH		3.78 (d, 3.5)	—
19	1.22 (s)	25.9 q	2-OH		2.60 (s)	—
20	1.33 (d, 6.5)	18.9 q	8-OH		3.28 (d, 9.0)	—

Assignments were confirmed by the HMQC and HMBC experiments.
[a] Measured in $CDCl_3$.
[b] Recorded at 500 MHz.
[c] Recorded at 125 MHz.

The interaction of two benzoates between C5—O and C7—O bonds in **1** cause a negative Cotton effect at 242 nm.[19] Furthermore, in the NOESY spectrum, the correlations between H-4 and H-1, OH-2, H-3, H-7, and H-13 indicated the α-orientation of H-1, OH-2, H-3, H-4, and H-13. In contrast, NOE correlations between H-8 and H-5 indicated the β-orientation of H-8 (Fig. 3). Therefore, the structure of compound **1** was determined as (1*R*,2*R*,3*R*,4*S*,5*R*,7*S*,8*R*,13*S*,15*S*)-3,15-diacetoxy-5,7-dibenzoyloxy-1,2,8-trihydroxyjatropha-6(17),11(12)-diene-9,14-dione, and give the trivial name kanesulone A.

Compound **2**[20] was obtained as a yellow powder, showed a quasimolecular ion peak at *m*/*z* 771.2607 [M+Na]$^+$ (calcd for $C_{40}H_{44}O_{14}Na$, 771.2623) in the positive-ion HRESIMS, corresponding to the molecular formula of $C_{40}H_{44}O_{14}$. The ^{1}H and ^{13}C NMR data analysis suggested that **2** shares an identical jatrophane skeleton with **1**,[19,21] except for the presence of an additional acetyloxy group. The ^{1}H and ^{13}C NMR data (Table 2) of compound **2** showed three acetyloxy groups [δ_H 2.14 (3H, s, 1-OAc), 2.13 (3H, s, 3-OAc), 1.94 (3H, s, 8-OAc); δ_C 170.4 and 21.5 (1-OAc), δ_C 169.9 and 21.5 (3-OAc), δ_C 169.9 and 21.4 (8-OAc)]. In the HMBC spectrum of compound **2**, the correlation from H-1 [δ_H 4.93 (1H, s)], H-3 [δ_H 5.50 (1H, d, J = 4.8 Hz)], and H-8 [δ_H 5.54 (1H, s)] to three acetoxy carbons [δ_C 170.4 (1-OAc), δ_C 169.9 (3-OAc), δ_C 169.9 (8-OAc)], respectively, established that three acetoxy groups were located at