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Four new sesquiterpene lactones from the stem bark of *Illicium burmanicum*

Doudou Huang [a], Huaping Deng [a], Wansheng Chen [b], Guanghui Huang [a], Cheng Chen [a], Lianna Sun [a,*]

[a] School of Pharmacy, Second Military Medical University, Guohe Road 325#, Shanghai 200433, People's Republic of China
[b] Department of Pharmacy, Changzheng Hospital, Second Military Medical University, Fengyang Road 415#, Shanghai 200003, People's Republic of China

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ABSTRACT

Four new sesquiterpene lactones (**1**), (**2**), (**3**), and (**4**), along with three known sesquiterene, namely, 6,7,10-trihydoxyisodaucane (**5**), 4β,10β-dihydroxyaromadendrane (**6**), and sescrassidiol (**7**) were isolated from the stem bark of *Illicium burmanicum*. The structures of the new compounds were determined using 1D and 2D NMR, and HRESIMS. The anti-inflammatory activities of these compounds were evaluated by measuring the enzymatic activity of luciferase in NF-κB reporters in a (Luc)-HEK 293 cell line treated with lipopolysaccharide (LPS).

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1. Introduction

The genus *Illicium* is composed of nearly 50 species worldwide, including approximately 28 species in China. They are mainly distributed in eastern and southern Asia. In China, *Illicium* has long been used in the traditional treatment of rheumatoid arthritis, traumatic injuries, and bleeding [1]. *Illicium burmanicum* was traditionally used as treating furunculosis and cataclasis in China [2]. Modern pharmacological research has demonstrated that this genus has neurotrophic, anti-inflammatory, anti-oxidative, cytotoxic, and anticancer activities [3–8]. Previous phytochemical studies have reported that *Illicium* is a rich source of prenylated C_6–C_3 compounds, neolignans and sesquiterpene [9–11]. It can also be used as a source of chemically and biologically useful secondary metabolites [12,13]. To identify effective and novel anti-inflammatory compounds, *I. burmanicum* Wils was selected for detailed study. *I. burmanicum*, which can grow into a shrub or tree, is mainly distributed in China's Yunnan Province and in Myanmar. Here, four sesquiterpene lactones were identified in the ethyl acetate-soluble fraction, all of which were firstly isolated in the present study.

These compounds were isolated and their structures were determined. Herein, biosynthetic pathways for compounds **2** and **4**, and their activity against lipopolysaccharide (LPS)-induced inflammation was evaluated using luciferase in NF-κB reporters (Luc)-HEK 293 cells (Fig. 1).

2. Experimental methods

2.1. General experimental procedures

Optical rotations were measured on a Perkin Elmer polarimeter (Serial No. 9903). IR spectra were recorded as KBr pellets on an Intelligent Fourier Nicolet FTIR 6700 Infrared Spectrometer. ^{1}H NMR (600 MHz), ^{13}C NMR (150 MHz) spectra and all 2D NMR spectra were determined on a Bruker Avance 600 NMR spectrometer (Bruker Co., Germany). HRESIMS were measured on an Agilent 6538 UHD Accurate-Mass Q-TOF LC/MSD trap mass spectrometer. Column chromatography was performed on Si gel (200–300 mesh, Yantai Jiang You Silica Gel Factory, China),

* Corresponding author at: School of Pharmacy, Second Military Medical University Guohe Road 325#, Shanghai 200433, People's Republic of China. Tel./fax: +86 21 8 187 1308.
E-mail address: sssnmr@163.com (L. Sun).

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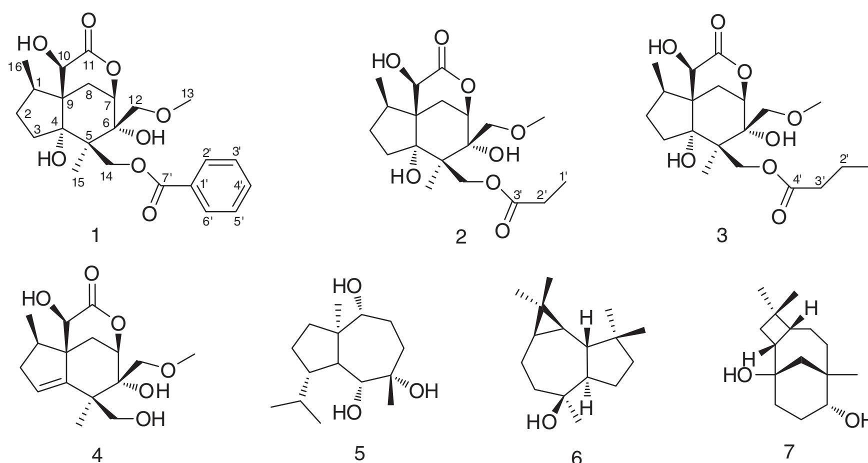

Fig. 1. Structures of the compounds isolated from *Illicium burmanicum*.

ODS (40–70 μm, Osaka, Japan), and Sephadex LH-20 (Pharmacia Biotech, Sweden). TLC was performed using glass plates precoated with silica gel F_{254} (Yantai Jiang You Silica Gel Factory, China) and RP-18 F_{254s} plates (Merck Co., Germany). Spots were visualized under UV light or by spraying with 10% H_2SO_4 in 95% EtOH. This was followed by heating.

2.2. Plant material

Stem bark of *I. burmanicum* was collected in Yunnan Province during July 2010. The plant was identified by Prof. Wan-sheng Chen of the Shanghai Changzheng Hospital. A voucher specimen (No. IT100629) was deposited in the herbarium of the Department of Pharmacognosy of the Second Military Medical University.

2.3. Extraction and isolation

Stem bark of *I. burmanicum* (5.0 kg) was dried, chopped, extracted with 80% MeOH (3 × 2 h) under reflux, and filtered. The filtrate was evaporated under vacuum to obtain a crude MeOH extract (750 g), which was suspended in distilled H_2O (5.0 L) and partitioned successively with petroleum ether, ethyl acetate, and *n*-BuOH, yielding 35.6, 230.4, and 361.4 g fractions, respectively. The ethyl acetate fraction was subjected to silica gel column chromatography, eluted with petroleum ether/ethyl acetate (50:1, 30:1, 20:1, 10:1, 5:1, v/v) and ethyl acetate, to yield fractions E1–E4. Fraction E1 extract (4.2 g) was passed through silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (6:1 → 1:1 v/v) to yield fractions E1-1 and E1-2. These were then passed through silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (E1-1, 6:1 and E1-2, 5:1) and Sephadex LH-20 CC (CH_2Cl_2/MeOH, 1:1, repeated several times) to produce compounds **1** (18.2 mg) and **3** (16.1 mg) from E1-1 and **4** (21.6 mg) from E1-2. Fraction E2 (7.2 g) yielded compound **2** (21.3 mg) through silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (5:1). Fraction E3 (9.1 g) yielded **5** (18.1 mg) and **6** (15.1 mg) via Sephadex LH-20 CC (CH_2Cl_2/MeOH, 1:1) and silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (5:1). Fraction E4 (12.0 g) yielded E4-1, E4-2, and E4-3 through silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (6:1 → 3:1). Fraction E4-1 yielded compound **7** (25.2 mg) via silica gel CC (200–300 mesh) eluted with petroleum ether/ethyl acetate (5:1).

Burmanicumolide A: Colorless oil; $[\alpha]^{22}_D$ −23.9 (c 0.91, $CHCl_3$); IR (KBr) ν_{max} 3386, 2960, 2922, 2850, 1654, 1602, 1460, 1383, 1261, 1095, 1022, and 800 cm^{-1}; ^{1}H-NMR and ^{13}C-NMR dates, see Table 1; HRESIMS *m/z* 452.2285 $[M + NH_4]^+$ (calculate. for $C_{23}H_{34}NO_8$, 452.1974).

Burmanicumolide B: Colorless oil; $[\alpha]^{22}_D$ −15.1(c 0.22, $CHCl_3$); IR(KBr) ν_{max} 3384, 2960, 2921, 2850, 2724, 1739, 1459, 1376, 1261, 1095, 1020, 800, 727, and 684 cm^{-1};

Table 1
^{1}H (600 MHz) and ^{13}C (150 MHz) NMR data for compound **1** (in $CDCl_3$).

No.	1	
	δ_H mult (*J* in Hz)	δ_C
1	2.47 (1H, m)	40.3
2α	2.02 (1H, m)	31.1
2β	1.48 (1H, m)	
3α	2.48 (1H, m)	32.2
3β	1.69 (1H, m)	
4	–	89.8
5	–	47.5
6	–	79.1
7	4.73 (1H, dd, *J* = 2.4, 3.6)	78.7
8β	2.43 (1H, dd, *J* = 1.8, 15.0Hz)	28.2
8α	1.93 (1H, dd, *J* = 3.6, 15.0Hz)	
9	–	51.1
10	4.28 (1H, s)	71.9
11	–	177.6
12a	3.83 (1H, d, *J* = 12.0)	73.3
12b	3.65 (1H, d, *J* = 12.6)	
13	3.45 (3H, s)	59.8
14a	4.45 (1H, d, *J* = 12.0)	67.0
14b	4.38 (1H, d, *J* = 12.0)	
15	1.38 (3H, s)	16.3
16	1.06 (3H, d, *J* = 7.2)	14.4
1′	–	131.3
2′, 6′	8.03 (2H, dd, *J* = 1.2, 8.4)	130.5
3′, 5′	7.52 (2H, t, *J* = 7.8)	129.7
4′	7.65 (1H, t, *J* = 7.2)	134.4
7′	–	167.5

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