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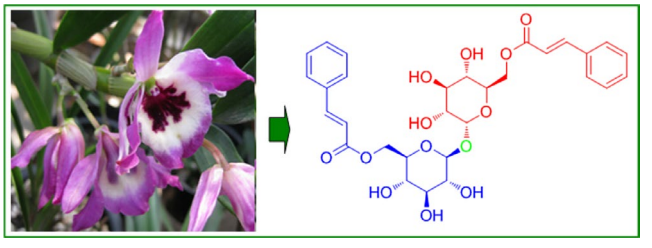
A new phenolic glycoside from the stem of *Dendrobium nobile*

Xue-Ming Zhou[a], Cai-Juan Zheng[a], Jia-Ting Wu[a], Guang-Ying Chen[a], Bin Zhang[a] and Chong-Ge Sun[b]

[a]Key Laboratory of Tropical Medicinal Plant Chemistry of Ministry of Education, College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou, People's Republic of China; [b]Hainan Boying Orchid Industrial Development Co Ltd., Haikou, People's Republic of China

ABSTRACT

A new phenolic glycoside dendroside (**1**), together with seven known compounds (**2**–**8**) were isolated from the stems of *Dendrobium nobile*. The structures of these compounds were elucidated using comprehensive spectroscopic methods. The inhibitory activities of all compounds against three cancer cell lines HeLa, MCF-7 and A549 were evaluated.



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KEYWORDS
Orchidaceae; *Dendrobium nobile*; glycoside; cytotoxic activity

1. Introduction

The genus *Dendrobium* (Orchidaceae) are mainly distributed throughout Asia, Europe and Australia. The stems of several *Dendrobium* species are used as a traditional medicine (Wang et al. 1985; Lee et al. 1995; Zhao et al. 2001, 2016; Zhang et al. 2007; Sun et al. 2014). *Dendrobium nobile*, widely distributed in China, is not only an ornamental but also a medicinal plant and many farmers grow *D. nobile* as an ornamental plant in China. Our previous study on *D. nobile* has led to the isolation of 23 phenanthrene derivatives and five bibenzyl derivatives, some of the isolated products showed cytotoxic or antifungal activities (Zhou, Zheng, Gan et al. 2016). In our ongoing investigation of natural cytotoxic products, a new phenolic glycoside dendroside (**1**) together with seven known compounds were isolated from the stems of *D. nobile*. All compounds were tested for their cytotoxic activities on three cancer cell lines.

CONTACT Guang-Ying Chen chgying123@163.com
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2. Results and discussion

Compound **1** was obtained as white amorphous powder, with the molecular formula $C_{30}H_{34}O_{13}$ from HRESIMS data combined with ^{1}H and ^{13}C NMR spectroscopic data (Supporting information, Table S1). The ^{1}H NMR data revealed four olefinic protons δ_H 7.72 (2H, d, 16) and δ_H 6.55 (2H, d, 16), 10 aromatic protons δ_H 7.61 (4H, m) and δ_H 7.41 (6H, m) together with many protons arising from sugar moiety. The ^{13}C NMR data showed 30 resonances, including 2 ester carboxyl carbons (δ_C 168.6 and 168.5), 4 olefinic carbons (δ_C 146.5, 146.4, 118.8 and 118.7), 12 benzene ring carbons and 12 oxygenated carbons. These data indicated that compound **1** was comprised of two trans-cinnamic acid subunits and two glucose subunits. The anomeric protons and carbons of glucose subunits at δ_H 5.11 (1H, d, 4.0), δ_C 94.0 and δ_H 4.51 (1H, d, 7.6), δ_C 98.3, respectively. These data suggested that the two glycosyl moieties were *α*-glucose and *β*-glucose, respectively. The location of the glycosyl moieties (C-6′ and C-6′a) at C-1 and C-1a were confirmed by the HMBC correlations between H-6′ and C-1, H-6′a and C-1a, respectively. The linkage of two glucose subunits was also confirmed by the HMBC correlation between H-1′ and C-1′a. Acid hydrolysis of **1** with 2 M HCl produced an *α*-glucose and a *β*-glucose (They were separated by the semi-preparative HPLC; MeOH/H_2O, 10:90). The *α*-glucose showed a positive optical rotation, $[\alpha]_D^{24}$ +44.8 (*c* 0.1, H_2O), and indicated that it was *α*-D-glucose. The *β*-glucose showed a positive optical rotation, $[\alpha]_D^{24}$ +19.2 (*c* 0.1, H_2O). These data indicated that it was *β*-D-glucose. Thus, compound **1** was identified as a new phenolic glycoside (Figure 1). And we named compound **1** as dendroside.

The structures of known compounds, isorhamentin-3-*O*-*β*-D-rutinoside (**2**) (Comte et al. 1996), adenosine (**3**) (Lai & Lee 2013), 4-methoxy-2,5,9*R*-trihydroxy-9,10-dihydrophenanthrene 2-*O*-*β*-D-glucopyranoside (**4**) (Lin et al. 2013), (7S,8R) dehydrodiconiferyl alcohol

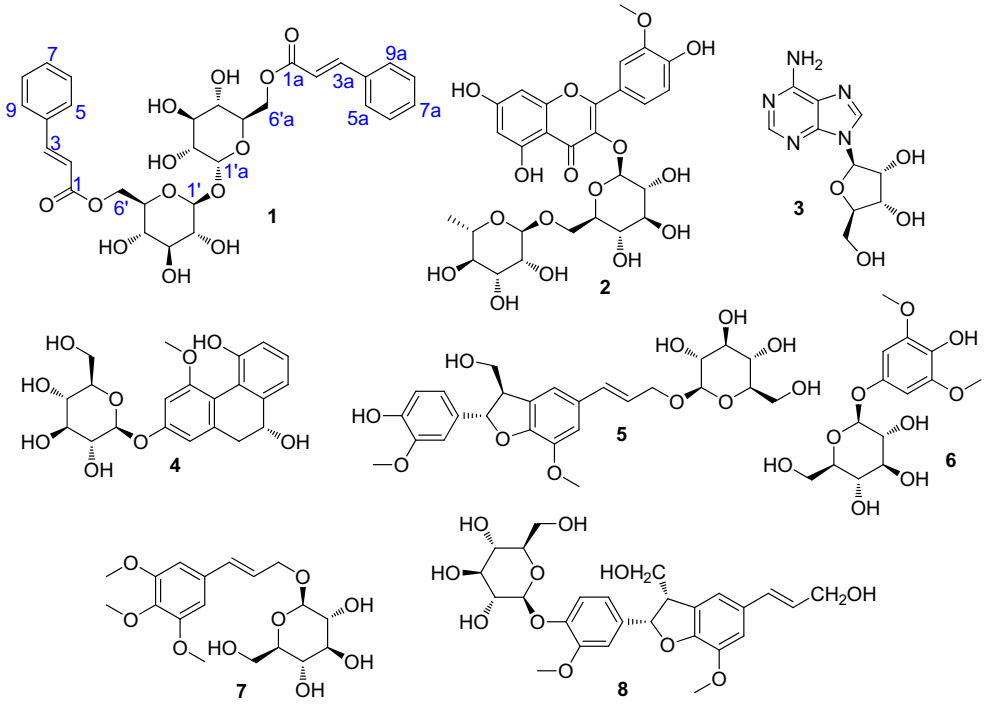

Figure 1. Structures of compounds **1**–**8** isolated from *D. nobile*.

Table 1. The cytotoxic activities of isolated compounds.

Compounds	IC_{50} (μM)		
	HeLa	MCF-7	A549
1	16.8	22.3	19.8
2	22.5	26.8	23.3
3	>100	>100	89.5
4	38.9	>100	42.3
5	40.8	53.1	49.6
6	>100	>100	>100
7	>100	>100	>100
8	37.0	51.1	46.7
Epirubicin[a]	0.5	0.8	1.0

[a]Epirubicin was used as a positive control.

9′-*β*-glucopyranoside (**5**) (Jiang et al. 2001), koaburaside (**6**) (Kosuge et al. 1994; Zhou, Zheng, Song et al. 2016), juniperoside (**7**) (Comte et al. 1996), and dehydrodiconiferyl-alcohol-4-*β*-D-glucoside (**8**) (Arens et al. 1985) were identified by comparison of their spectroscopic data with those in the literature.

All compounds were tested for cytotoxic activities against HeLa, MCF-7 and A549 cells (Table 1). Compounds **1** and **2** showed moderate inhibitory effects on HeLa, MCF-7 and A549 cells with IC_{50} values ranging from 16.8 to 26.8 μM.

3. Experimental

3.1. General

Optical rotations were measured on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Nicolet 6700 spectrophotometer. NMR spectra were recorded on a Bruker AV spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). TMS was used as an internal standard. HRESIMS spectra were measured on a Q-TOF Ultima Global GAA076 LC mass spectrometer. Semi-Preparative HPLC was performed on an Agilent 1260 LC series with a DAD detector using an Agilent Eclipse XDB-C18 column (9.4 × 250 mm, 5 μm). Silica gel (Qing Dao Hai Yang Chemical Group Co; 200–300 mesh), octadecylsilyl silica gel (YMC; 12 nm–50 μm) were used for column chromatography (CC). Precoated silica gel plates (Yan Tai Zi Fu Chemical Group Co; G60, F-254) were used for thin layer chromatography.

3.2. Plant material

The stems of *D. nobile* were provided by the Hainan Boying Orchid Industrial Development Co, Ltd in June 2014. A voucher specimen (No. GFM20140612) has been deposited at the Key Laboratory of Tropical Chemistry of Medicinal Plant of Ministry of Education, Hainan Normal University (Hainan, China).

3.3. Extraction and isolation

The air-dried and powdered stems (5 kg) of *D. nobile* were extracted with 70% EtOH (3 × 20 L, 5 days each) at room temperature. After concentration under reduced pressure, the water-soluble residue was partitioned successively with petroleum ether and EtOAc. The EtOAc extract

(95 g) was separated using a silica gel CC (petroleum ether, EtOAc, MeOH v/v, gradient) to generate seven fractions (Frs. 1–7). Frs. 7 (20 g) was applied to silica gel CC eluted with EtOAc–MeOH (from 20:1 to 1:1) to afford three subfractions (3a–3c). Subfraction 3a was further purified by using octadecylsilyl silica gel (10% MeOH/H_2O) to obtain **4** (8 mg), **6** (12 mg) and **7** (21 mg). Subfractions 3b and 3c were further separated by semi-preparative HPLC (CH_3CN/H_2O, 10:90 and 7:93 v/v) to obtain **3** (31 mg), **5** (13 mg), and **8** (18 mg); **1** (6 mg) and **2** (22 mg), respectively.

3.4. *Dendroside* (1)

White amorphous powder; $[\alpha]_D^{24}$ +52.8 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3425, 2928, 1712, 1638, 1577 and 1496 cm^{-1}; HR-ESI-MS *m/z* 601.1918 $[M - H]^-$ ($C_{30}H_{33}O_{13}$; calcd 601.1921); ^1H NMR (MeOD-d_4, 400 MHz) δ: 7.72 (2H, d, J = 16.0 Hz, H-3/3a), 7.61 (4H, m, H-5/9/5a/9a), 7.41 (6H, m, H-6/7/8/6a/7a/8a), 6.55 (2H, d, J = 16 Hz, H-2/2a), 5.11 (1H, d, J = 4.0 Hz, H-1′a), 4.51 (1H, d, J = 7.6, H-1′), 4.29–4.55 (4H, m, H-6′/6′a), 4.05 (1H, m, H-5′a), 3.70 (1H, m, H-3′a), 3.54 (1H, m, H-2′), 3.33–3.40 (4H, m, H-3′/4′/2′a/4′a), 3.17 (1H, m, H-5′); ^{13}C NMR (MeOD-d_4,100 MHz) δ: 168.6 (C-1), 168.5 (C-1a), 118.8 (C-2), 118.7 (C-2a), 146.5 (C-3), 146.4 (C-3a), 135.7 (C-4/4a), 129.2 (C-5/9/5a/9a), 130.1 (C-6/8/6a/8a), 131.6 (C-7/7a), 98.3 (C-1′), 75.4 (C-2′), 78.0 (C-3′), 72.0 (C-4′), 76.2 (C-5′), 65.1 (C-6′), 94.0 (C-1′a), 73.8 (C-2′a), 74.8 (C-3′a), 71.8 (C-4′a), 70.8 (C-5′a), 65.0 (C-6′a).

3.5. *Hydrolysis of compound* 1

Acid hydrolysis of compound **1**: A solution of **1** (5 mg) in 2 M HCl (2 mL) was heated under reflux for 4 h, and then evaporated to dryness. The mixture of **1** was extracted with EtOAc (4 mL × 3). Finally, trans-cinnamic acid (2.2 mg) was obtained. The aqueous layer was further separated by the semi-preparative HPLC (MeOH/H_2O, 10:90) to obtain an α-glucose (1.2 mg) and a β-glucose (1 mg).

3.6. *Biological assays*

Cytotoxic activity was evaluated by the MTT method as described previously (Scudiero et al. 1988). HeLa, MCF-7 and A549 were provided by College of Pharmacy, Hebei University and maintained in DMEM medium (Gibco) containing 5% foetal bovine serum (Gibco) at 37 °C in air with 5% CO_2. Compounds **1**, **2**, **5** and **8** showed moderate inhibitory effects on HeLa, MCF-7, and A549 cells. The IC_{50} values of other compounds higher than 100 μM were regarded as inactive.

Disclosure statement

No potential conflict of interest was reported by the authors.

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