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Macdentichalcone, a unique polycyclic dimeric chalcone from *Macaranga denticulata*

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ABSTRACT

Macdentichalcone (**1**), an unprecedented polycyclic dimeric chalcone featuring a unique quinonoid moiety, was isolated from *Macaranga denticulata*, together with 1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one (**2**), a known monomeric chalcone proposed as a biosynthetic precursor of **1**. The structure of **1** was elucidated by extensive spectroscopic analysis including NMR and MS data, as well as calculation of ^{13}C NMR chemical shifts. Both compounds **1** and **2** showed inhibitory activity against PTP1B *in vitro*.

Chalcones are a class of polyphenolics abundant in higher plants, which show great potentials in therapeutic or preventive applications with biological properties associated with antioxidant, anti-inflammatory, anti-infective, and anti-diabetic activities [1]. Chalcone-containing oligomers featuring complex and diverse structures have gained greater attentions in the field of natural product chemistry in recent years [2]. They are usually formed by oligomerization of chalcones with flavonoids, benzofurans, stilbenes, and chalcones. In particular, oligomers produced by identical or different monomeric chalcones are limited, which have been found only in a few species from the families of Leguminosae [2a,2b], Anacardiaceae [2c], Moraceae [2d,2e], and Euphorbiaceae [2f,2g]. Euphorbiaceae is a large family comprising nearly 5000 species around the world with about 460 species in China [3]. The Euphorbiaceae plants are well known to produce alkaloids and diterpenoids [4], and only three species from the genera of *Drypetes*, *Mallotus*, and *Macaranga* have been reported to yield chalcones [2f,2g,5,6].

Macaranga denticulata (Bl.) Muell. Arg. (Euphorbiaceae) is a tree widely distributed in the tropical regions of Southeast Asia. It has rich resource in China and has been used as a Chinese folk medicine for the treatment of icteric hepatitis and epigastric pain [7]. Our previous study on this plant resulted in the isolation of *C*-methylated and isoprenylated chalcones, some of which showed inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) [6a]. As a continuing search for structurally and biologically interesting metabolites from *M. denticulata*, two additional chalcones, macdentichalcone (**1**) and 1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one (**2**) [2f,2i,8], were isolated and identified (Fig. 1). Compound **1** represents the first polycyclic chalcone dimer featuring a unique quinonoid motif, which could biogenetically originate from the known compound **2**. Both compounds showed *in vitro* inhibition on PTP1B.

Macdentichalcone (**1**) was obtained as yellow amorphous powder. Its IR spectrum showed typical absorption bands for hydroxyl (3419 cm^{-1}), carbonyl (1627 cm^{-1}), and aromatic (1600,1556, and 1449 cm^{-1}) moieties. The molecular formula was assigned as $C_{42}H_{40}O_9$ by HRESIMS with a $[M+H]^+$ ion at *m*/*z* 689.2757 (calcd 689.2745), suggesting 23 degrees of unsaturation. The ^{13}C NMR data (Table 1) revealed 42 resonances: 13 sp^2 quaternary carbons including three carbonyl groups and a hexasubstituted benzene (ring A), 14 sp^2 methines, five sp^3 quaternary carbons including a ketalized and three oxygenated ones, two sp^3 methines, two sp^3 methylenes, and six methyls, as evidenced by the DEPT and HSQC spectra. The ^{1}H NMR spectrum (Table 1) exhibited signals for a hydrogen-bonded hydroxyl group (δ_H 14.15, OH-2′), a hydroxyl group (δ_H 7.24, OH-4‴), two monosubstituted benzene rings (rings B and B′: δ_H 7.73, H-2, 6; 7.65, H-2″, 6″; 7.48, H-3, 5, 4, 4″, 3″, 5″), and two methyl singlets (δ_H 2.00, H$_3$-7′; 1.13, H$_3$-7‴). The ^{1}H and ^{13}C NMR signals for two isoprenoid groups both in the form of

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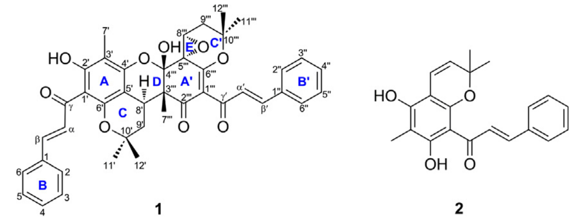

Figure 1. Structure of compounds **1**–**2**.

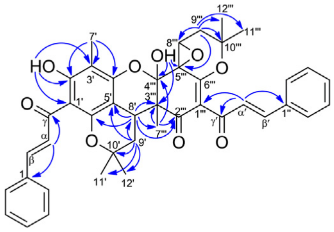

Figure 2. Key HMBC correlations for **1**.

2,2- dimethyl pyranoids (rings C and C′: δ_{H} 3.62, H-8′; 1.71, H-9′β; 1.62, H-9′α; 1.48, H_3-11′; 1.61, H_3-12′; 4.18, H-8‴; 2.32, H_2-9‴; 1.36, H_3-11‴; 1.38, H_3-12‴; δ_{C} 33.3, C-8′; 33.0, C-9′; 77.6, C-10′; 25.7, C-11′; 30.4, C-12′; 53.2, C-8‴; 34.3, C-9‴; 80.8, C-10‴; 29.2, C-11‴; 29.6, C-12‴) were differentiated. In addition, the NMR spectra showed signals for two sets of trans-olefinic moieties (δ_{H} 8.09, H-α; 7.74, H-β; 6.86, H-α′; 7.43, H-β′; δ_{C} 128.8, C-α, α′; 142.1, C-β; 145.8, C-β′) and two α,β-unsaturated keto carbonyl groups (δ_{C} 193.8, C-γ; 192.7, C-γ′), characteristic of two chalcone units. The aforementioned analyses indicated that **1** was a diprenylated chalcone dimer.

Assignment of the two chalcone units was accomplished by detailed interpretation of 2D NMR data. The HMBC correlation networks (Fig. 2) of OH-2′/C-1′, C-2′, C-3′; H_3-7′/C-2′, C-3′, C-4′; H-8′/C-5′, C-6′; and H_2-9′/C-5′, C-8′, C-10′, C-11′, C-12′ defined the presence of a benzo pyran moiety (rings A and C). In combination with the HMBC correlations of H-α/C-1, C-γ and the NOESY correlations of H-α/H_3-11′, H_3-12′ (Fig. 3), the substructure of one chalcone monomer was constructed. The HMBC correlations of OH-4‴/C-3‴, C-4‴, C-5‴; H_3-7‴/C-2‴, C-3‴, C-4‴; H_2-9‴/C-5‴, C-8‴, C-10‴, C-11‴, C-12‴; and H-α′/C-1″, C-γ′, C-1‴ established the conjunction of A′/C′ ring system and verified the substructure of another chalcone monomer, which contained a quinochalcone scaffold [9] as shown in **1**. These data accounted for 21 degrees of unsaturation, indicating the requirement of two additional rings in the structure of **1**. The existence of 5‴,8‴-oxirane ring (ring E) was supported by the chemical shifts of C-5‴ (δ_{C} 55.5) and C-8‴ (δ_{C} 53.2). Moreover, the HMBC correlations of H-8′/C-2‴, C-3‴, C-7‴ and the chemical shifts of C-4′ (δ_{C} 158.3) and C-4‴ (δ_{C} 98.8) implied the formation of a pyran ring (ring D) with a ketalized moiety at C-4‴. The planar structure of **1** was thus established to be a polycyclic dimeric chalcone bearing a quinonoid moiety.

The relative configuration of **1** was established by NOESY data (Fig. 3). The NOESY correlations of H-9′β/H_3-7‴, H_3-7‴/OH-4‴, OH-4‴/H-8‴, and H-8‴/H_3-12‴ (Fig. 3) indicated that H_3-7‴, OH-4‴, H-8‴, and H_3-12‴ were β-oriented and the 5‴,8‴-epoxy ring were thus α-oriented. The NOESY cross-peaks of H-9′α/H-8′ and H-8′/H_3-11′ assigned an α-orientation of H-8′ and H_3-11′. Furthermore, the structure of **1** was confirmed by calculation of the ^{13}C NMR shifts at the levels of MPW1PW91/6-31G(d,p) with the gauge-independent atomic orbital (GIAO) method (Supplementary data) [10]. Thus, the structure of **1** was identified and named macdentichalcone.

A plausible biogenetic origin for **1** could be tracked back to 1-(5,7-dihydroxy-2,2,6-trimethyl-2*H*-1-benzopyran-8-yl)-3-phenyl-2-propen-1-one (**2**), a known compound obtained in this study (Scheme 1). After isomerization, intermolecular Michael addition, **2** would yield the key intermediates of quinochalcone dimer (i and ii). Subsequent intramolecular nucleophilic reaction could lead to the formation of intermediate iii, which would undergo oxidation to produce **1**.

Compounds **1** and **2** were tested *in vitro* for the inhibition on PTP1B enzymatic activity. Both of them showed similar inhibitory activity with IC_{50} values of 21.0 ± 3.4 μM for **1** and 22.0 ± 3.9 μM for **2**, respectively. Oleanolic acid, an effective natural PTP1B inhibitor [11], was used as the positive control (IC_{50} = 2.6 ± 0.6 μM).

In conclusion, intensive chemical investigations on *M. denticulata* afforded macdentichalcone (**1**), the first example of polycyclic

Table 1
NMR data of **1** at 400 (^{1}H) and 100 (^{13}C) MHz in acetone-d_6

No.	**1**		No.	**1**	
	δ_{C}	δ_{H}		δ_{C}	δ_{H}
1	136.4		1″	135.4	
2, 6	129.0	7.73 (br d, 7.0)	2″, 6″	129.2	7.65 (dd, 7.3, 2.0)
3, 5	129.9[a]	7.48 (m)	3″, 5″	130.0[a]	7.48 (m)
4	131.0[b]	7.48 (m)	4″	131.5[b]	7.48 (m)
α	128.8	8.09 (d, 15.6)	α′	128.8	6.86 (d, 16.2)
β	142.1	7.74 (d, 15.6)	β′	145.8	7.43 (d, 16.2)
γ	193.8		γ′	192.7	
1′	106.6		1‴	123.4	
2′	164.3		2‴	195.8	
3′	103.1		3‴	51.6	
4′	158.3		4‴	98.8	
5′	96.7		5‴	55.5	
6′	155.2		6‴	163.5	
7′	7.4	2.00 (s)	7‴	8.8	1.13, s
8′	33.3	3.62 (dd, 12.5, 5.2)	8‴	53.2	4.18 (t, 2.8)
9′	33.0	α 1.62 (dd, 13.0, 5.2) β 1.71 (t, 13.0)	9‴	34.3	2.32 (d, 2.8)
10′	77.6		10‴	80.8	
11′	25.7	1.48 (s)	11‴	29.2	1.36 (s)
12′	30.4	1.61 (s)	12‴	29.6	1.38 (s)
OH-2′		14.15 (s)	OH-4‴		7.24 (s)

[a,b] Signals may be exchangeable.