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Antiplasmodial anthraquinones and hemisynthetic derivatives from the leaves of *Tectona grandis* (Verbenaceae)

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ABSTRACT

Chemical investigation of the methanol extract of the leaves of *Tectona grandis* led to the isolation of one new anthraquinone derivative, grandiquinone A (3-acetoxy-8-hydroxy-2-methylanthraquinone) (**1**), along with nine known compounds: 5,8-dihydroxy-2-methylanthraquinone (**2**), hydroxysesamone (**3**), 3-hydroxy-2-methylanthraquinone (**4**), quinizarine (**5**), betulinic acid (**6**), ursolic acid (**7**), tectograndone (**8**), corosolic acid (**9**) and sitosterol 3-*O*-β-D-glucopyranoside (**10**). Compounds **2** and **3** were isolated for the first time from the leaves of this plant, while **5** has never been reported from the genus *Tectona*. Hydroxysesamone (**3**) and tectograndone (**8**) were subjected to cyclisation and acetylation reactions to afford two hemisynthetic derivatives, 6,9-dihydroxy-2,2-(dimethyldihydropyrano)-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (**11**) and acetyltectograndone (**12**) respectively, which are reported here for the first time. The ethyl acetate-soluble portion, some of the isolated compounds and hemisynthetic derivatives were evaluated for their antiplasmodial activity against the multidrug-resistant Dd2 strain of *Plasmodium falciparum*. Compound **3** showed a prominent activity, while **2**, **8**, **9**, **11** and **12** showed significant *in vitro* anti-malarial activity. Compound **1** was weakly active in this test. The structures of the compounds were elucidated by spectroscopic methods and comparison of the data with the literature.

1. Introduction

Tectona grandis Linn. is a large tree from southeast Asia which grows up to 50 m in height. It is commonly known as sagwan or teak and is the most important of the three species that belong to the genus *Tectona* (Macias et al., 2008). This plant is widely used in Asian countries in the treatment of diabetes, lipid disorders, ulcers, inflammation, bronchitis, cancer, skin diseases, malaria and tuberculosis (Rajuri et al., 2010; Warrier, 1994). In Cameroon, it is locally used in the treatment of fever. Previous phytochemical investigation on *T. grandis* has led to the isolation of triterpenoids, flavonoids (Ragasa et al., 2008a), chromomoric acid derivatives (Ragasa et al., 2008b), anthraquinones (Sumthong et al., 2006, 2008), naphthoquinones (Pradeep and Pahup, 2004; Lacret et al., 2011), anthraquinone-naphthoquinones (Aguinaldo et al., 1993; Lacret et al., 2011), apocarotenoids (Macias et al., 2008), lignans (Lacret et al., 2012). Some of these metabolites showed anti-mycobacterial, antifungal and allelopathic activities (Sumthong et al., 2006, 2008; Pradeep and Pahup, 2004; Aguinaldo et al., 1993; Macias et al., 2008; Lacret et al., 2011). In the course of our search for potent biological antiplasmodial compounds from Cameroonian medicinal plants (Zofou et al., 2011a), we carried out the chemical investigation of the leaves of the title plant and report herein the isolation and structure elucidation of a new anthraquinone named grandiquinone A (**1**), as well as the antiplasmodial activity of the ethyl acetate-soluble fraction and some isolated constituents. The hemisynthesis of one naphthoquinone and one anthraquinone-naphthoquinone were carried out and the evaluation of the antiplasmodial activity of the obtained derivatives is also reported.

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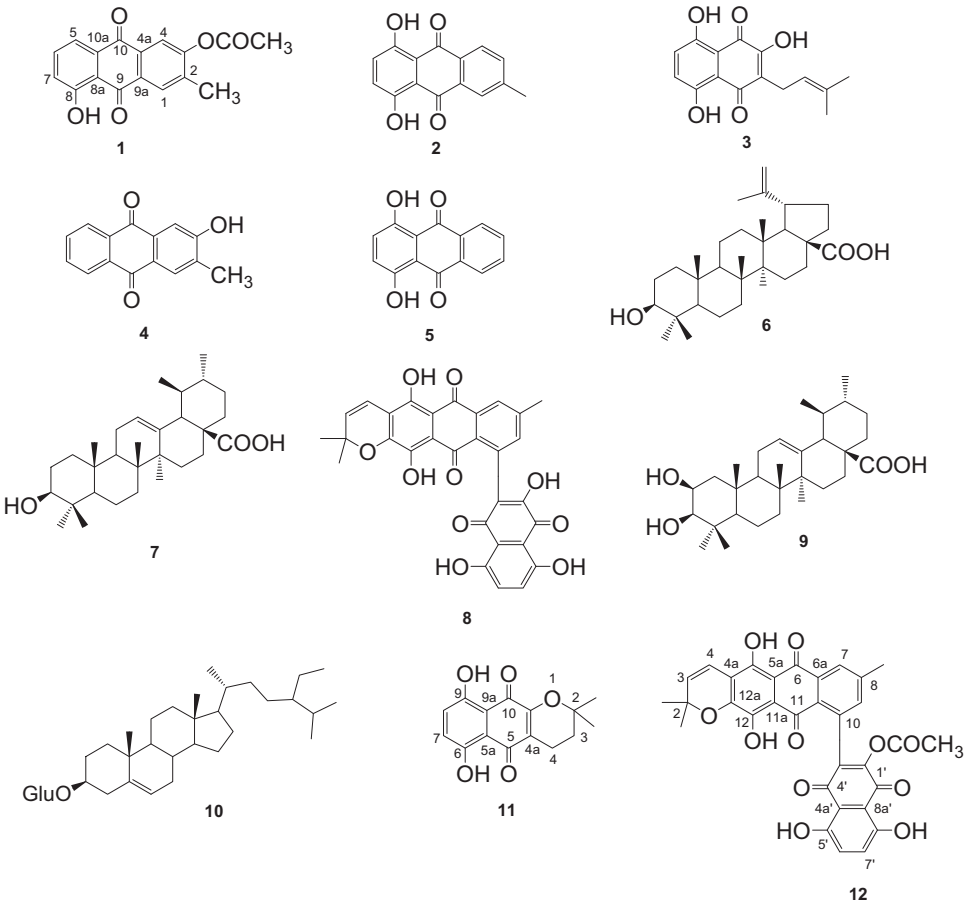

Fig. 1. Chemical structures of compounds isolated from *T. grandis* (**1**–**10**) and of cyclised and acetylated derivatives (**11**–**12**).

2. Results and discussion

The ethyl acetate-soluble fraction of the leaves of *T. grandis* was fractionated by silica gel column chromatography followed by gel permeation over Sephadex LH-20 to afford the new anthraquinone derivative, grandiquinone A (**1**), along with the known 5,8-dihydroxy-2-methylanthraquinone (**2**) (Hua et al., 2004), hydroxysesamone (**3**) (Hasan et al., 2001), 3-hydroxy-2-methylanthraquinone (**4**) (Da Silva et al., 2008), quinizarine (**5**) (Hua et al., 2004), betulinic acid (**6**) (Shukla et al., 2010), ursolic acid (**7**) (Shukla et al., 2010), tectograndone (**8**) (Aguinaldo et al., 1993), corosolic acid (**9**) (Mohammed et al., 1991), and sitosterol 3-*O*-*β*-D-glucopyranoside (**10**) (Singh et al., 2010). Two hemisynthetic compounds, 6,9-dihydroxy-2,2-(dimethyldihydropyrano)-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (**11**) and acetyl tectograndone (**12**) were newly reported. Structures of the compounds (Fig. 1) were elucidated by 1D and 2D NMR spectroscopy, ESI and EI-MS and comparison of the data with those reported in the literature.

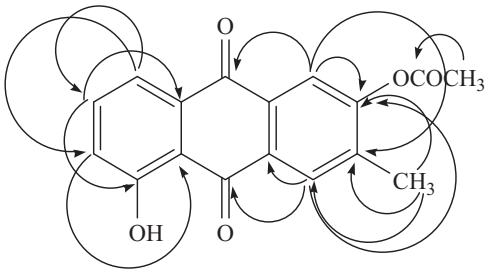

Fig. 2. HMBC (^{1}H–^{13}C) correlations for **1**.

Compound **1** was obtained as an orange powder from petroleum ether. The molecular formula was determined as $C_{17}H_{12}O_5$ by HR-ESI-TOF-MS, which showed the pseudo-molecular ion peak at *m/z* 297.0762 (calcd. 297.0763 for $[M+H]^+$), in conjunction with NMR data, indicating 12 degrees of unsaturation. Its UV spectrum showed maxima at λ_{max} 216, 226, 262, 336 and 407 nm. The IR spectrum exhibited absorption bands at ν_{max} 3047, 1757 and 1670 cm^{-1}, indicating the existence of hydroxyl, acetyl and ketone functionalities respectively. The ^{1}H NMR spectrum (Table 1) exhibited two different aromatic proton spin systems: three protons of a 1,2,3-substituted aromatic ring at δ 7.82 (1H, dd,

Table 1
^{1}H and ^{13}C NMR data for compound **1** (500 and 125 MHz, in $CDCl_3$), δ in ppm, *J* in Hz.

Position	δ_H	δ_C	HMBC (H → C)
1	8.20, 1H, s	130.5	C-3, C-9, C-9a
2	–	137.9	–
3	–	154.4	–
4	7.94, 1H, s	121.1	C-2, C-3, C-4a, C-10
4a	–	130.8	
5	7.82, 1H, dd (12.0, 6.0)	119.6	C-6, C-7
6	7.67, 1H, t (12.0)	136.7	C-8, C-10a
7	7.31, 1H, dd (12.0, 6.0)	124.5	C-5, C-8a
8	–	162.6	
8a	–	116.0	
9	–	188.0	
9a	–	133.6	
10	–	181.6	
10a	–	133.4	
CH_3OC=O	–	168.3	
$OCOCH_3$	2.40, 3H, s	20.7	
2-CH_3	2.37, 3H, s	16.8	C-2, C-3, C-1
8-OH	12.59, 1H, s	–	