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Two new anthraquinone dimers from the stem bark of *Pentas schimperi* (Rubiaceae)

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ABSTRACT

Two new anthraquinone dimers, schimperiquinones A (**1**) and B (**2**), together with the known 2-hydroxymethylanthraquinone (**3**), cleomiscosin A (**4**), oleanolic acid (**5**) and sitosterol 3-*O*-β-D-glucoside (**6**) were isolated from the stem bark of *Pentas schimperi*. Their structures were elucidated on the basis of spectroscopic analysis and comparison with published data or by comparison with authentic samples. To the best of our knowledge, it is the first report of cleomiscosin A, a coumarinolignan from the genus *Pentas*. Compound 2 exhibited *in vitro* cytotoxicity (IC_{50} = 33.05 μM) against the human cancer cell the BGC-823.

1. Introduction

The genus *Pentas* consists of about 40 species and is widely distributed throughout tropical Africa (Troupin, 1985). Many representatives of this genus are used by local people as medicinal plants. Naphtoquinones and anthraquinones were found to be the major active principles of the studied species of this genus (Bukuru, 2003; Endale et al., 2013) while coumarins, iridoids and terpenoids have been isolated as minor constituents (Bukuru, 2003; Endale et al., 2012a,b; Puyvelde et al., 1998; Schripsema et al., 2007). In the course of our search for bioactive compounds from Cameroonian medicinal plants, we carried out the phytochemical investigation of *Pentas schimperi* (Hook f.) Verde which is a small tree growing in upland forest (Focho et al., 2009; Mesfin et al., 2009). In Cameroon, its leaves concoction with bark of *Masea lanceolata* (Myrsinaceae) is taken orally to treat hepatitis B liver infection (Ates and Erdogrul, 2003; Focho et al., 2009). In Ethiopia, fresh or dry root bark mixed with water is taken orally to treat epilepsy (Mesfin et al., 2009). To the best of our knowledge, it is the first report on the chemical constituents of the titled plant.

This paper describes the isolation and structural elucidation of two new anthraquinone dimers along with four known compounds from its stem bark, as well as the evaluation of their cytotoxic activity against three human tumor cells, A549, Hela, and BGC-823.

2. Results and discussion

The EtOAc-soluble fraction of the stem bark of *P. schimperi* was subjected to column chromatography over silica gel and Sephadex LH-20 to afford schimperiquinone A (**1**) and schimperiquinone B (**2**) along with the known 2-hydroxymethylanthraquinone (**3**), cleomiscosin A (**4**), oleanolic acid (**5**) and sitosterol 3-*O*-β-D-glucoside (**6**) (Fig. 1). To the best of our knowledge, it is the first report of compound **4** from this genus.

Schimperiquinone A (**1**) was obtained as yellow amorphous powder from *n*-hexane-EtOAc and gave positive ferric chloride test, characteristic of phenolic group. The molecular formula $C_{30}H_{18}O_6$ was deduced from the HRESIMS which displayed a pseudomolecular ion peak $[M+Na-2CH_3]^+$ at *m/z* 467.2733 (calcd for $C_{28}H_{12}O_6Na$: 467.0532) in conjunction with NMR data. The ESI spectrum showed peaks at *m/z* 413 $[M-CO-H_2O-CH_3]^+$ and *m/z* 390 $[M-3CO]^+$ indicative of the presence of hydroxyl, methyl and carbonyl groups. These fragmentations pattern are typical for

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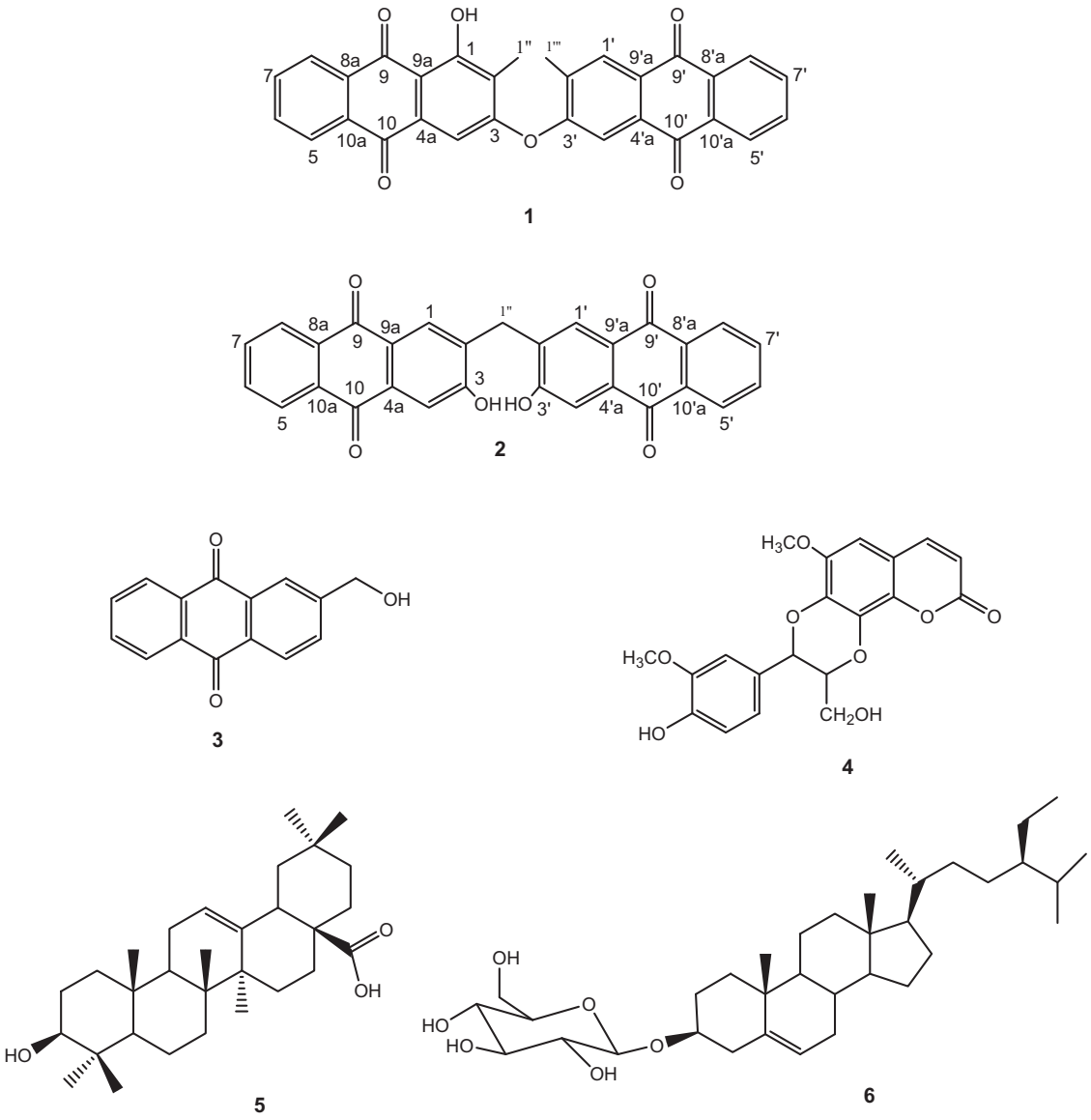

Fig. 1. Chemical structures of compounds **1**–**6**.

hydroxyanthraquinones (Eyong et al., 2005). This assumption was supported by the IR spectrum which exhibited absorption bands due to anthraquinone nucleus at 1668 and 1581 cm^{-1} and phenolic hydroxyl groups at 3407 cm^{-1} (Singh et al., 2006). The UV spectrum also displayed a pattern characteristic of an anthraquinone skeleton with absorption maxima at 410, 340, 323 and 293 nm (Williams and Fleming, 1995). The ^{1}H NMR spectrum of **1** (Table 1) showed characteristic signals of two 1,2-disubstituted aromatic rings at δ_H 8.14 (1H, m, H-5), 7.68 (1H, m, H-7), 7.70 (1H, m, H-6) and 8.22 (1H, dd, J = 1.2, 7.6 Hz, H-8) and at δ_H 7.69 (1H, m, H-7′), 7.72 (1H, dd, J = 1.3, 7.4 Hz, H-6′), 8.16 (1H, m, H-5′) and 8.19 (1H, dd, J = 1.4, 7.5 Hz, H-8′), three other aromatic protons at δ_H 7.43 (1H, s, H-4′), 7.98 (1H, s, H-1′) and 7.15 (1H, s, H-4), one chelated hydroxyl group at δ_H 13.10 and two aromatic methyl groups at δ_H 2.14 (H-1″) and 2.30 (H-1‴), respectively. The ^{13}C NMR spectrum (Table 1) of **1** exhibited thirty signals of two aromatic methyl groups at δ_C 8.0 (C-1″) and 16.8 (C-1‴), 11 methines, seventeen quaternary carbons including four carbonyl groups at δ_C 183.5 (C-10), 186.6 (C-9), 182.5 (C-9′) and 184.2 (C-10′), and three oxygenated aromatic carbons at δ_C 162.7 (C-3), 163.4 (C-1) and 161.4 (C-3′). The presence of four carbonyl groups and only one hydroxyl group for three oxygenated aromatic carbons strongly suggested that **1** was a dimer of anthraquinone linked by an oxygenated bridge. This bridge was located at C-3/C-3′ from the interpretation of the HMBC spectrum (Fig. 2) which showed pertinent correlations from observed between the protons of H-4 (δ_H 7.15) to C-3 (δ_C 162.7) and from H-4′ (δ_H 7.43) to C-3′ (δ_C 161.4). In this spectrum, correlations observed between the proton of the hydroxyl group and C-1, C-2 and C-9a gave evidence of the attachment of this function at C-1 (Zaman et al., 2011). The long ranges correlations observed between H-6 (δ_H 7.70) and C-10a (δ_C 131.8) and C-8 (δ_C 126.7) and between H-7 (δ_H 7.68) and C-8a (δ_C 133.4) allow assignments of these aromatic protons to C-6 and C-7, respectively. The heteronuclear connectivities revealed between H-7′ (δ_H 7.70) and C-5′ (δ_C 126.8) is indicative of his attachment to C-7′. Further connectivities were established and the important correlations are shown in Fig. 2. The position of the two aromatic methyl at C-2 and C-2′ was established from the long-range correlations between the methyl protons at δ_H 2.14 and the carbons C-1 (δ_C 163.4), C-2 (δ_C 119.1) and C-3 (δ_C 162.7) as well as between the methyl protons at δ_H 2.30 and the carbons C-1′ (δ_C 125.9), C-2′ (δ_C 132.8) and C-3′ (δ_C 161.4).Therefore, compound **1** was characterized as a new bianthraquinone derivative trivially named schimperiquinone A.

Table 1
NMR data of schimperiquinone A (**1**) and schimperiquinone B (**2**) (600 MHz for ^{1}H and 150 MHz for ^{13}C), δ in ppm, J in Hz.

Position	**1**[a]		**2**[b]	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	163.4	–	126.3	8.31, s
2	119.1	–	136.5	–
3	162.7	–	159.7	–
4	107.8	7.15, s	111.3	7.51, s
4a	131.8	–	133.2	–
5	127.0	8.14, ov. m	126.7	7.91, ov. m
6	134.1	7.70, ov. m	134.1	7.75, ov. m
7	133.4	7.68, ov. m	134.6	7.78, ov. m
8	126.7	8.22, dd (1.2, 7.6)	126.7	8.21, ov. m
8a	133.4	–	135.5	–
9	186.6	–	181.7	–
9a	109.7	–	125.1	–
10	183.5	–	182.8	–
10a	131.8	–	133.5	–
1′	125.9	7.98, br s	126.3	
2′	132.8		136.5	
3′	161.4		159.7	
4′	111.6	7.43, s	111.3	8.31, s
4a′	133.6	–	133.2	7.51, s
5′	126.8	8.16, ov. m	126.7	7.91, ov. m
6′	134.2	7.72, dd (1.3, 7.4)	134.1	7.75, ov. m
7′	133.7	7.69, ov. m	134.6	7.78, ov. m
8′	130.6	8.19, dd (1.4, 7.5)	126.7	8.21, ov. m
8a′	133.5	–	135.5	–
9′	182.5	–	181.7	–
9a′	125.1	–	125.1	–
10′	184.2	–	182.8	–
10a′	133.8	–	133.5	–
1″	8.0	2.14, s	–	–
1‴	16.8	2.30, s	–	–
1-OH	–	13.10, s	–	–
1″	–	–	57.9	4.59, s

ov, overlapped.
[a] $CDCl_3$-MeOD.
[b] DMSO-d_6.

Schimperiquinone B (**2**) was isolated as a yellowish powder from *n*-hexane-EtOAc, m.p. 264–265 °C. It gave a positive ferric chloride test, characteristic of phenolic group. The HREIMS displayed a molecular ion peak at *m/z* 460.1019 (Calcd for $C_{29}H_{16}O_6$: 460.0947), implying the molecular formula $C_{29}H_{16}O_6$ for **2**. The UV and IR data of **2** were similar to those of **1**, suggesting the presence of a hydroxylated 9,10-anthraquinone moiety (Ismail et al., 2012). The ^{1}H NMR spectrum (Table 1) revealed the presence of a 1,2-disubstituted aromatic ring between δ_H 7.91–8.21 (4H, H-5/H-5′ and H-8/H-8′) and δ_H 7.75–7.78 (4H, H-6/H-6′ and H-7/H-7′) (Singh et al., 2006). This spectrum also showed signals of four additional aromatic protons at δ_H 8.31 (2H, s, H-1/H-1′) and 7.51 (2H, s, H-4/H-4′) and of a benzylic methylene at δ_H 4.59 (2H, s, H-1″). The ^{13}C NMR spectrum (Table 1) showed signals of one benzylic methylene at δ_C 57.9 (H-1″), four conjugated carbonyls at δ_C 182.8 (C-10/C-10′) and δ_C 181.7 (C-9/C-9′) and two oxygenated aromatic carbon at δ_C 159.7 (C-3/C-3′). The appearance of only fifteen signals on the ^{13}C NMR spectrum, including one benzylic methylene, suggested that compound **2** must be a symmetric dimer of anthraquinone. Moreover, the presence of both one oxygenated sp^2 carbon bearing a hydroxyl group and one relatively deshielded benzylic methylene (δ_H/δ_C 4.59/57.9) showed that the two-anthraquinone units were connected through a carbonated bridge. A careful examination of the HMBC spectrum (Fig. 2) revealed pertinent correlations between H-1 (δ_H 8.31) and C-3 (δ_C 159.7), C-2 (δ_C 136.5) and C-9a (δ_C 125.1). Cross peaks observed between H-1 and the carbon at δ_C 57.9 as well as from the methylene protons at δ_H 4.59 and C-2 (δ_C 136.5), C-3 (δ_C 159.7) and C-1 (δ_C 126.3) were indicative of the attachment of the methylene bridge at C-2/C-2′. The above correlations and those observed between H-4 (δ_H 7.51) and C-10, C-3, C-2 and C-9a were indicative of the hydroxyl group to be at C-3. Compound 2 was thus characterized as a new anthraquinone dimer named schimperiquinone B.

The cytotoxic activities of compounds **1**–**4** were evaluated against three human tumor cells (A549, Hela and BGC-823). A549 and Hela cell lines were not sensitive to all tested compounds. The new compound, schimperiquinone B (**2**) was found to be active, against BGC-823 cell line (IC_{50} = 33.05 μM). Cytotoxicity of several anthraquinones dimers have previously been reported (Li et al., 2013; Zheng et al., 2012). Compound **1**, structurally related to compound **2** was not active; this suggested that the activity of **2** could be due to the free hydroxyl groups present in its structure. It was shown that the wide range of biological activities of several heterocyclic compounds such as polyhydroxylated xanthones, flavonoids and anthranoids is due to the number and position of hydroxyl groups on their basic skeleton (Gopalakrishnan et al., 1997; Heim et al., 2002; Pinto et al., 2011). Their activities can be considerably weaken or lost when some of these hydroxyl groups form chelating complexes with a carbonyl function (Pinto et al., 2011). The inactivity of compound **3** could be associated to the absence of hydroxyl group on the anthraquinone nucleus. Compounds **3** and **4** did not display any cytotoxicity.

3. Experimental

3.1. General experimental procedures

Melting points were determined on Electrothermal IA9000 series digital melting point apparatus and are uncorrected. UV spectra were recorded on UV-570/VIS/NIR and Shimadzu UV-2401A double-beam spectrophotometers. IR spectra were recorded on Shimadzu FTIR-8400S spectrophotometer. ESIMS and HRESIMS analyses were performed using benchtopquadrupoleorbitrapmass spectrometer (Q Exactive; Thermo Fisher Scientific, Bremen, Germany) and on a API-Qstar-Pulsar Bruker instrument, while Waters AutoSpec Premier P776 was used to record EIMS and HREIMS spectra. NMR spectra were recorded at room temperature, on Bruker AVANCE DMX 600, Bruker-DRX-600 and Bruker-DRX-500 instruments with solvent signals or TMS as internal references (δ in ppm and J in Hz).

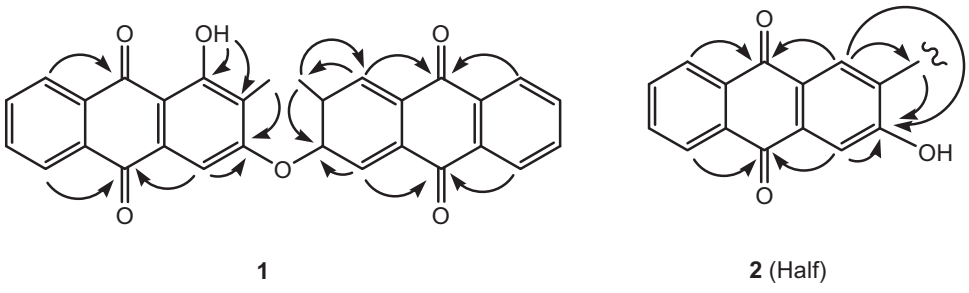

Fig. 2. Key HMBC ($^{1}H \rightarrow {}^{13}C$) correlations for **1** and **2** (half).

Column chromatography was run on Merck silica gel 60 (0.063–0.200 mm) and Sephadex LH-20 while TLC was carried out on silica gel GF_{254} pre-coated plates with detection accomplished by visualizing with a UV lamp at 254 and 365 nm, followed by spraying with 50% H_2SO_4 and then heating at 100 °C.

3.2. Plant material

The stem bark of *P. schimperi* (Hook f.) Verde was collected at Mount Bamboutos, West Region, Cameroon, in February 2011. The plant material was identified by Mr. Tadjouteu Fulbert of the Cameroon National Herbarium, Yaoundé, where a voucher specimen (No 22547 SRF/Cam) is deposited.

3.3. Extraction and isolation

Dried and powdered stem bark of *P. schimperi* (3.2 kg) was extracted with EtOH (3 × 10 L) at room temperature to yield a crude extract (142 g) after evaporation under vacuum. This extract was dissolved in water and successively extracted with EtOAc (3 × 2 L) and *n*-butanol (3 × 1.5 L) to give an EtOAc-soluble fraction (36 g) and an *n*-butanol portion (62 g) after evaporation under reduced pressure. The EtOAc fraction (36 g) was subjected to column chromatography over silica gel eluting with gradients of petroleum ether-EtOAc and EtOAc–MeOH to afford 77 fractions of 300 mL each. These fractions were combined on the basis of their TLC profiles into five major fractions: A (4.0 g, 1–13), B (3.8 g, 14–22), C (6.3 g, 23–44), D (9.6 g, 45–66) and E (12.3 g, 67–77). Fractions A and B contained mostly fats and mixture of phytosterols. Fraction C was purified by silica gel column chromatography with a gradient of *n*-hexane-EtOAc to afford four main subfractions (C_1 to C_4). Compound **3** (13 mg) crystallized from subfraction C_3 (*n*-hexane-EtOAC, 8:2). Subfraction C_4 was further separated by prep. TLC (*n*-hexane-EtOAC, 7:3) followed by column chromatography on Sephadex LH-20 (CH_2Cl_2–MeOH, 1:1) to yield **2** (18 mg). Fraction D was subjected to column chromatography over silica gel, eluted with a gradient of *n*-hexane-EtOAc to give six subfractions. Compound **1** (14 mg) was obtained from subfraction D_3. Oleanolic acid (**5**, 40 mg) was filtered from subfraction D_6. Fraction E was chromatographed over silica gel with a gradient of CH_2Cl_2–MeOH as solvent system, to afford four subfractions. Compound **4** (11 mg) crystallized from subfraction E_4. Compound **6** (23 mg) crystallized from E_3.

3.4. Schimperiquinone A (*1*)

Yellow amorphous powder; UV (MeOH) λ_{max} nm (log ε) 410 (3.19), 340 (3.12), 323 (2.75) and 293 (3.30); IR υ_{max} (KBr) 3407, 3080, 2960, 2921, 2880, 1668, 1630, 1581, 1433, 1122, 867 and 711 cm−1; ^{1}H and ^{13}C NMR data, see Table 1; ESIMS, *m/z* (rel. int.): 467 (6), 413 (4) and 390 (12); HRESIMS: *m/z* 467.2733 (calcd for $C_{28}H_{12}O_6Na$, 467.0532).

3.5. Schimperiquinone B (*2*)

Yellow powder; m.p. 264–265 °C; UV (MeOH) λ_{max} nm (log ε) 368.5 (0.99), 275.5 (1.94), 244.5 (1.71), 203.5 (1.79); IR υ_{max} (KBr) 3379, 3278, 3076, 2920, 2848, 1670, 1652, 1583, 1500, 1429, 1338, 1045, 968 and 709 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS, 70 eV, *m/z* (rel. int.): 442 $[M-H_2O]^+$(10), 426 $[M-2OH]^+$(15); HREIMS: *m/z* 460.1019 (calcd for $C_{29}H_{16}O_6$, 460.0947).

3.6. Cytotoxic activity

The cytotoxic activities of compounds **1**–**4** against three human tumor cancer cells, A549, Hela, and BGC-823 were tested by the SRB method as previously described by Xu et al. (2011). Taxol was used as a positive control.

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