Antimalarial Compounds from the Root Bark of *Garcinia polyantha* Oliv.

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Abstract Eight compounds were isolated from the roots of *Garcinia polyantha*, and identified. Two of them, the xanthone garciniaxanthone I (**1**), and the triterpene, named garcinane (**2**), are reported as new natural products. The structures of the new compounds were elucidated on the basis of 1D and 2D NMR spectroscopic studies. The structure of compound **1** was confirmed by X-ray crystallography. Among the remaining six known compounds, three were known xanthones [smeathxanthone A (**3**), smeathxanthone B (**4**), and chefouxanthone (**5**)], one benzophenone [isoxanthochymol (**6**)], one triterpene [magnificol], and one sterol [β -sitosterol]. The *in vitro* antimalarial activity of isoxanthochymol (**6**) against *Plasmodium falciparum* shows strong chemosuppression of parasitic growth.

Keywords *Garcinia polyantha*, garciniaxanthone I, X-ray crystallography, xanthones; antimalarial activity

Introduction

The genus *Garcinia* of the Guttiferae family is well known to be a rich source of bioactive prenylated xanthones [1–3], triterpenes [4], and benzophenones [5, 6]. In continuation of our search for bioactive substances from

African medicinal plants, we investigated the methanol extract of the root bark of *Garcinia polyantha*, a tree distributed in the lowland tropical rainforest of West, East and Central Africa [7, 8]. In the current investigation we focused on minor constituents from *G. polyantha*, and one new xanthone (**1**), one new triterpene (**2**), and six known compounds (**3**–**6**, magnificol, and β -sitosterol), were isolated (Fig. 1). We report herein the structure elucidation of the eight natural products and their antimalarial activity.

Materials and Methods

General Experimental Procedures

Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. UV spectra were measured with a UV-210 PC UV. IR spectra were recorded on a SHIMADZU FTIR-8400S spectrometer in KBr disks. EI-MS (ionization voltage 70 eV) and HR-EI-MS mass spectra were recorded on Finnigan MAT double focusing spectrometer Model 8230. ^1H - and ^{13}C -NMR spectra were recorded with a Bruker Avance 500 MHz NMR spectrometer in CDCl_3 or $\text{CDCl}_3/\text{CD}_3\text{OD}$. Chemical shifts are recorded relative to TMS ($\delta=0$) internal standard and coupling constants J are reported in Hz. Optical rotation were recorded with a Perkin-Elmer 241

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Fig. 1 Structures of compounds **1**~**6** isolated from *Garcinia polyantha*.

polarimeter. Column chromatography (CC) was carried out on silica gel 60 F₂₅₄ (Merck) and silica 100 respectively. Precoated plates of silica gel 60 GF₂₅₄ were used for analytical purposes and the spots were detected with a UV lamp at 254 and 366 nm and by spraying with 50% H₂SO₄ or ceric sulfate followed by heating.

Plant Material

The roots of *Garcinia polyantha* were collected at Mt Kala, Central Province, Cameroon in August 2003, and identified by Mr. Nana Victor of the Cameroon National Herbarium (Yaoundé), where a voucher specimen (21337/SRF/Cam/Mt Kala) was deposited.

Extraction and Isolation

Air dried root bark of *G. polyantha* (5.2 kg) was extracted with MeOH at room temperature for two days. The extract was concentrated at reduced pressure to yield 100 g of crude extract. The methanolic extract was first subjected to silica gel flash chromatography, eluting with hexane-EtOAc of increasing polarity to afford fractions (A~D) and pure chefoxanthone (**5**, 73 mg) and isoxanthochymol (**6**, 1.2 g). Fractions A and B (2.3 g) were purified on a silica gel column with hexane-EtOAc with increasing order of polarity to yield magnificol (46 mg) and smeathxanthone B (**4**, 31 mg), respectively. Similarly, fraction C (5.4 g) was subjected to column chromatography (silica gel) eluting with hexane-EtOAc with increasing polarity to yield smeathxanthone A (**3**, 22 mg) and subfractions C₁ and C₂. Subfraction C₁ (1.1 g) was further purified by column chromatography (silica gel) eluting with hexane-EtOAc to give garciniaxanthone I (**1**, 11 mg). Finally, subfraction C₂ (1.7 g) was chromatographed (silica gel) with hexane-

EtOAc (7.8:2.2) yielding garcinane (**2**, 15 mg) and β -sitosterol (28 mg).

Garciniaxanthone I (**1**)

Yellow crystals; mp 254~256°C; $[\alpha]_D^{20}$ -37.5 (*c* 0.8, CHCl₃+10% MeOH); UV (MeOH) $\lambda_{\max}$ (log ϵ): 205 (3.03), 220 (3.04), 297 (2.50), 337 (4.28), 335 (3.89); IR (KBr) $\nu_{\max}$: 3460, 3360, 1660, 1627 cm⁻¹; ¹H-NMR (CDCl₃, 500 MHz) δ 12.30 (1H, s, 1-OH), 11.33 (1H, s, 9-OH), 8.62 (1H, s, 5-OH), 7.24 (1H, d, *J*=8.8 Hz, H-6), 6.66 (1H, d, *J*=8.8 Hz, H-7), 6.38 (1H, s, H-2), 3.80 (1H, d, *J*=4.9 Hz, H-14), 3.90 (3H, s, OCH₃), 2.85 (1H, dd, *J*=14.5, 8.8 Hz, H-11a), 2.74 (1H, dd, *J*=14.5, 6.8 Hz, H-11b), 2.20 (1H, dd, *J*=8.8, 6.8 Hz, H-12), 1.94 (1H, m, H-15a), 1.68 (1H, m, H-15b), 1.53 (1H, m, H-16a), 1.44 (1H, m, H-16b), 1.27 (1H, s, H-21), 1.03 (1H, s, H-19), 0.97 (1H, s, H-20); ¹³C-NMR (CDCl₃, 125 MHz) δ 185.1 (C-9), 165.2 (C-3), 161.5 (C-1), 153.7 (C-8), 153.4 (C-4a), 143.7 (10a), 136.4 (C-5), 124.8 (C-6), 109.9 (C-7), 108.3 (C-8a), 107.2 (C-4), 103.3 (C-9a), 96.4 (C-2), 87.7 (C-17), 86.9 (C-14), 55.9 (OCH₃), 53.6 (C-12), 45.9 (C-13), 38.5 (C-16), 26.1 (C-15), 26.1 (C-20), 23.1 (C-19), 21.1 (C-11), 18.0 (C-21); EI-MS *m/z* (rel. int.): 426 [M⁺] (22), 408 (4), 341 (6), 315 (18), 287 (100), 274 (16), 257 (35), 97 (19); 44 (24); HREI-MS *m/z* 436.1686 (calcd. for C₂₄H₂₆O₇, 436.1679).

Garcinane (**2**)

White powder; mp 235~237°C; $[\alpha]_D^{20}$ +80 (*c* 0.25, CH₂Cl₂); IR (KBr) $\nu_{\max}$ 3730, 3460, 1660, 1627 cm⁻¹; ¹H-NMR (CDCl₃, 500 MHz) δ 5.20 (1H, t, *J*=4.0 Hz, H-12), 4.51 (1H, d, *J*=10.0 Hz, H-3), 3.80 (1H, ddd, *J*=12.5, 10.0, 4.5 Hz, H-2), 3.53 (1H, d, *J*=10.0 Hz, H-28a), 3.22 (1H, d,

$J=10.0$ Hz, H-28b), 2.14 (1H, s, CH_3COO), 2.07 (1H, dd, $J=12.5$, 4.5 Hz, H-1a), 2.00 (1H, dd, $J=14.0$, 5.0, H-18), 1.90 (1H, m, H-16a), 1.90 (1H, m, H-11), 1.90 (1H, m, H-16b), 1.63 (1H, dd, $J=11.0$, 7.8 Hz, H-9), 1.63 (1H, dd, $J=11.0$, 5.0 Hz, H-19a), 1.54 (1H, m, H-6a), 1.54 (1H, m, H-7a), 1.54 (1H, br dd, $J=14.0$, 4.0 Hz, H-22a), 1.41 (1H, m, H-6b), 1.36 (1H, br dd, $J=14.0$, 3.0 Hz, H-22b), 1.34 (1H, m, H-7b), 1.31 (1H, br dd, $J=14.0$, 4.0 Hz, H-21a), 1.19 (1H, br dd, $J=14.0$, 3.0 Hz, H-21b), 1.16 (1H, s, H-27), 1.09 (1H, dd, $J=14.0$, 11.0 Hz, H-19b), 1.06 (1H, m, H-15a), 1.01 (1H, s, H-25), 0.98 (1H, m, H-1b), 0.98 (1H, m, H-15b), 0.94 (1H, s, H-30), 0.93 (1H, br t, $J=2.0$, H-5), 0.90 (1H, s, H-24), 0.89 (1H, s, H-23), 0.88 (1H, s, H-29), 0.87 (1H, s, H-26); ^{13}C -NMR (CDCl_3 , 125 MHz) δ 172.4 (CH_3CO_2), 144.3 (C-13), 122.1 (C-12), 84.9 (C-3), 69.7 (C-28), 67.6 (C-2), 55.1 (C-5), 47.9 (C-1), 47.5 (C-9), 46.4 (C-19), 42.3 (C-18), 41.8 (C-14), 39.9 (C-8), 38.1 (C-4), 38.0 (C-10), 36.9 (C-17), 34.1 (H-21), 33.1 (C-29), 32.4 (C-7), 31.0 (C-22), 30.9 (C-20), 28.5 (C-23), 25.9 (C-27), 23.5 (C-30), 21.0 (CH_3CO_2), 18.3 (C-6), 25.5 (C-15), 23.6 (C-11), 22.0 (C-16), 16.7 (C-26), 17.6 (C-24), 16.6 (C-25); EI-MS m/z (rel. int.): 500 [M^+] (4); 470 (72), 234 (79), 203 (100), 189 (61), 119 (56), 69 (51), 43 (59); HREI-MS m/z 500.3869 (calcd. for $\text{C}_{32}\text{H}_{52}\text{O}_4$, 500.3866).

X-Ray Crystal Structure Analysis of Garciniaxanthone I (1)

$\text{C}_{24}\text{H}_{26}\text{O}_7$ ($M_r=426.45$), orthorhombic, space group $P2_12_12_1$ with $a=7.0837(18)$ Å, $b=13.148(3)$ Å, $c=21.674(6)$ Å, $V=2018.6(9)$ Å³, $Z=4$, $D_{\text{calcd}}=1.403$ g/cm³, $\lambda=0.71073$ Å. Yellow prismatic crystal, size $0.20\times 0.08\times 0.04$ mm. Intensity data were measured on a Bruker-AXS SMART APEX CCD diffractometer. A total of 18152 reflections were collected to a maximum 2θ value of 55.7° at 120(2) K. Data reduction and semi-empirical absorption correction from equivalents with the Bruker package [9]. The structure was solved by direct methods and refined by full matrix least-squares procedure [10]. The title compound crystallizes in the non-centrosymmetric space group $P2_12_12_1$; however, in the absence of significant anomalous scattering effects, the Flack parameter is essentially meaningless. Accordingly, Friedel pairs were merged. All non-hydrogen atoms were given anisotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined at idealized positions riding on their parent atoms. The refinement converged at $R(I>2\sigma(I))=0.057$, $wR2$ (all data)=0.087 for 2764 independent reflections and 284 variables. Crystallographic data for the structure of **1** have been deposited with the Cambridge Crystallographic Data Center, deposition No. CCDC-680049. Data can be obtained free of charge

from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Antimalarial Test

Compounds **1**~**6** were dissolved in water+DMSO 0.02% v/v [11]. The compounds were administered over a period of four days to the culture and the number of parasites was determined daily. Control experiments were performed either without treatment or with administration of $0.032\text{ }\mu\text{M}$ chloroquine in the same solvent.

Culturing of *Plasmodium falciparum* NF54 Strain

Plasmodium falciparum isolate NF54 was maintained in small Petri dishes (5.0 cm) according to a protocol from Moloney [12] and Trager [13] in a gaseous phase of 90% N_2 , 5.0% CO_2 and 5.0% O_2 . Parasites were cultured in human erythrocytes (blood group A⁺) in RPMI640 medium (Sigma) supplemented with $25\text{ }\mu\text{M}$ HEPES, 20 mM sodium bicarbonate, and 10% heat inactivated human A+ plasma at 10% (v/v) hematocrit. The parasitemia of infected erythrocytes was determined by light microscopy and estimated by Giemsa-stained smears. Parasitemia detected in the cultures was scored visually with a 100-fold oil immersion objective, counting at least 1000 infected erythrocytes to determine the parasitemia.

Inhibitor Experiments by Monitoring Multiplication and Growth of Plasmodia

Cultures were adjusted to a parasitemia of 0.5%. Aliquots were diluted 1:10-fold in RPMI-medium, dispensed into 12-well microculture trays and incubated at 37°C in a candle jar. Thereafter, growth medium was changed once a day for four days and inhibitors were added to the media in a concentration of $10\text{ }\mu\text{M}$ as indicated. Each substance was analyzed in four independent wells of the microculture tray. Parasitemia was estimated as triplicates daily in each of the four independent wells from Giemsa-stained smears by counting 1000 erythrocytes. To determine the IC_{50} values, we performed growth experiments with $10\text{ }\mu\text{M}$, $5.0\text{ }\mu\text{M}$ and $2.5\text{ }\mu\text{M}$ of each compound. The data obtained in these experiments were computed into plots with linear regression analysis from y axis (inhibition %) to x axis (inhibitor concentration in μM) [14].

Results and Discussion

Physico-chemical Properties

The physico-chemical properties of garciniaxanthone I (**1**) and garcinane (**2**) are summarized in Experimental section. Compound **1**, garciniaxanthone I, was obtained as yellow

crystals reacting positively with FeCl_3 , suggesting its phenolic nature. The $[\text{M}]^+$ at m/z 426.1686 in the HREI-MS corresponded to the molecular formula $\text{C}_{24}\text{H}_{26}\text{O}_7$. The UV spectrum showed absorption bands at λ_{max} 335, 297, and 205 nm, indicating the presence of a 1,3,5,8-oxygenated xanthone nucleus [3]. The absorption bands at 3460, 1660, and 1627 cm^{-1} in the IR spectrum suggested a xanthone skeleton with a chelated hydroxyl group [15].

Similarly, garcinane (**2**) was obtained as a white powder, mp $235\sim 237^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} +80$ (c 0.25, CH_2Cl_2), and reacted positive in the Lieberman Burchard test for triterpenoids. The molecular formula was deduced as $\text{C}_{32}\text{H}_{52}\text{O}_4$ through HREI-MS which showed the M^+ peak at m/z 500.3869 (calcd. for $\text{C}_{32}\text{H}_{52}\text{O}_4$, 500.3866). The IR spectrum showed absorption bands for hydroxyl groups at 3730 cm^{-1} and a double bond at 1627 cm^{-1} .

Structure Elucidation

Inspection of a part of the ^1H -NMR spectrum (see Experimental) of garcini-xanthone I (**1**) showed an AB spin system for aromatic type protons at δ 7.24 (1H, d, $J=8.8\text{ Hz}$, H-6) and 6.66 (1H, d, $J=8.8\text{ Hz}$, H-7), typical for the presence of *ortho* protons. A shielded isolated proton at δ 6.38 (1H, s, H-2) was in agreement with a pentasubstituted aromatic ring (ring A), and the presence of a methoxy group was evidenced from the three proton singlet at δ 3.90. The signal at δ 185.5 (C-9) in the ^{13}C -NMR and signals at δ 12.30 (1H, s, 1-OH) and 11.33 (1H, s, 8-OH) in the ^1H -NMR spectrum indicated the presence of a conjugated carbonyl and two chelated hydroxyl groups. A free hydroxyl group is suggested by the signal at δ 8.62 (1H, s, 5-OH). The ^{13}C -NMR spectrum (see Experimental) showed 24 signals, which could be attributed to four CH_3 , three CH_2 , five CH, and twelve quaternary carbons including seven oxygenated carbons, as evidenced by the respective DEPT spectra. The long range correlation (Fig. 2) between δ 12.30 (1-OH) with C-1, C-2, and C-9a, and correlations of the signal at δ 6.38 (H-2) with C-1, C-3, C-4 and C-9a, and that of a methoxy signal at δ 3.90 (3- OCH_3) with C-3 allowed an unequivocal assignment of ring A in the xanthone moiety. In ring B, the correlation of the signal at δ 11.33 (8-OH) with C-8, C-7 and C-8a; 7.24 (H-6) with C-6, C-7, C-8, and the signal at δ 6.66 (H-7) with C-8, C-8a, (C-5) and C-5 established the free hydroxyl position at C-5 along with the other assignments of ring B. These data established the xanthone substructure of our compound **1** to be related to the xanthone bellidifolin [16], however with a substituent at C-4.

The absence of carbon resonances below 90 ppm suggested the presence of a saturated C_{10} side chain at C-4. From the twelve degrees of unsaturation, calculated from

the formula of **1**, ten were attributed to the xanthone nucleus and the other two to rings in the side chain. These two rings consist of a 7-oxo-[2.2.1]-system, as determined by ^1H - ^1H COSY and HMBC spectroscopy (Fig. 2). This was further confirmed by comparison of the NMR data with those of the 7-oxo-[2.2.1]-system in the related parvixanthone I [17]. The C-14/C-15/C-16 connectivity was deduced from the ^1H - ^1H COSY cross-peaks between H-14/H-15 and H-15/H-16. From this partial structure, the six-membered ring from C-12 to C-17 could be confirmed from the following HMBC correlations: Me-19/C-12,13,17,20; Me-20/C-12,13,17,19; and Me-21/C-12,16,17. The C-14 and C-17 positions were further deduced to be connected by an oxygen bridge (O-18) by the important HMBC correlation of H-14/C-17 and the fact that both C-14 (δ 86.9) and C-17 (δ 87.7) were oxygenated. Thus, a

Fig. 2 Selected ^1H - ^1H COSY and HMBC correlations for compound **1**.

Fig. 3 Molecular structure of **1**.

Ellipsoids are drawn at the 50% probability level.

Fig. 4 Antiplasmodial activity of compound **6**^a.

^aGrowth curves of *P. falciparum* strain NF54 after treatment with different concentrations of compound **6** are shown. Inhibitor treatment was started at a parasitemia of 0.5% and monitored for 96 hours.

monoterpenoid substitution in **1** was determined as a 7-oxo-[2.2.1]-system, which was linked to position C-4 of the xanthone nucleus, as indicated by the HMBC correlations between H-11/C-4,3,4a. Finally, the detailed structure and relative stereochemistry of **1** were confirmed unambiguously from single-crystal X-ray analysis (ORTEP drawing in Fig. 3). Compound **1** was given the trivial name garciniaxanthone I, and assigned as 1,5,8-trihydroxyl-3-methoxy-4-(1,3,3-trimethyl-7-oxabicyclo[2.2.1]hept-2-ylmethyl)xanthone.

Compound **2** was obtained as a white powder. The broad band and DEPT ¹³C-NMR spectra (see Experimental) of garcinane (**2**) displayed 32 carbon signals comprising of eight quaternary, six methine, ten methylene and eight methyl carbons. The carbonyl of the ester moiety resonated at δ 172.4 (CH₃CO₂) while the olefinic carbons were observed at δ 144.3 (C-13) and 122.1 (C-12). Three oxygenated carbons resonated at δ 84.4 (C-3), 67.6 (C-2), and 69.7 (C-28). In the ¹H-NMR spectrum (see Experimental), signals were observed for one olefinic proton at δ 5.20 (t, $J=4.0$ Hz), two oxymethine protons [δ 4.51 (d, $J=10.0$ Hz), 3.80 (ddd, $J=12.5, 10.0, 4.5$ Hz)], an AB system of methylene protons on a carbon bonded to an oxygen at δ 3.53 (d, $J=10.0$ Hz) and 3.80 (ddd, $J=12.5, 10.0, 4.5$ Hz), seven tertiary methyl groups (δ 0.87, 0.88, 0.89, 0.90, 0.94, 1.01, and 1.16), and one acetate methyl singlet at δ 2.14. The attachment of the acetate group at C-3 (δ 84.9) was confirmed by long-range correlation between H-3 and the carbonyl group at δ 172.4 (CH₃CO₂). On the basis of the molecular formula and NMR (¹H-, ¹³C-NMR) data analysis [C-12 (122.1) and C-13 (C-144.3) in ¹³C-NMR], and an intense fragment ion peak at m/z 203 it was concluded that compound **2** was an Δ^{12} -oleanane-type triterpene [18–20]. From the ¹H-NMR data it was

concluded that the OH groups at positions C-2 and C-3 must be equatorial, since the coupling constants of H-2 ($J_{2ax,1ax}=12.5, J_{2ax,3ax}=10$ Hz) and H-3 ($J_{3ax,2ax}=10$ Hz) were consistent with axial configurations for both protons. The $2\alpha,3\beta$ relative configuration was further confirmed by comparison of the ¹H-NMR coupling constants with those reported for related compounds [21, 22]. The hydrolysis of **2** with K₂CO₃ in MeOH at room temperature afforded 2 α -hydroxyerythrodil [23]. Therefore, garcinane (**2**) was assigned as a new compound, 3 β -O-acetyl-2 α -hydroxyolean-12-en-28-ol.

Smeathxanthone A (**3**) and B (**4**) [3], chefoxanthone (**5**) [24], isoxanthochymol (**6**) [5], magnificol [25], and β -sitosterol [26] were identified by comparison with published data.

Biological Activity

Compounds **1**–**6** were tested against *Plasmodium falciparum* *in vitro*. Among these compounds, **6** showed good activity against *Plasmodium falciparum* *in vitro* and less so for compounds **1**–**5**. Compound **6** exhibited antimalarial activity with an IC₅₀ of 2.21 μ M (Fig. 4). This was lower than the IC₅₀ of the other five compounds, which ranged from 2.5–4.1 μ M.

In summary, the structure of a new xanthone (**1**) with the very rare cyclization of a geranyl residue to a 7-oxo-[2.2.1]-system was elucidated and confirmed by X-ray single crystal analysis. The entire set of prenylated xanthones **1** and **3**–**6** showed a remarkable variety in attachment and cyclization modes of prenyl and geranyl side chains thus increasing the diversity of this class of plant metabolites. In addition, the *in vitro* activity against *Plasmodium falciparum* of isoxanthochymol (**6**) with an interesting bridged ring system was established.

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