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NOTE

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

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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. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker Avance 500 MHz NMR spectrometer in $CDCl_3$ or $CDCl_3/CD_3OD$. Chemical shifts are recorded relative to TMS (δ=0) internal standard and coupling constants J are reported in Hz. Optical rotation were recorded with a Perkin-Elmer 241

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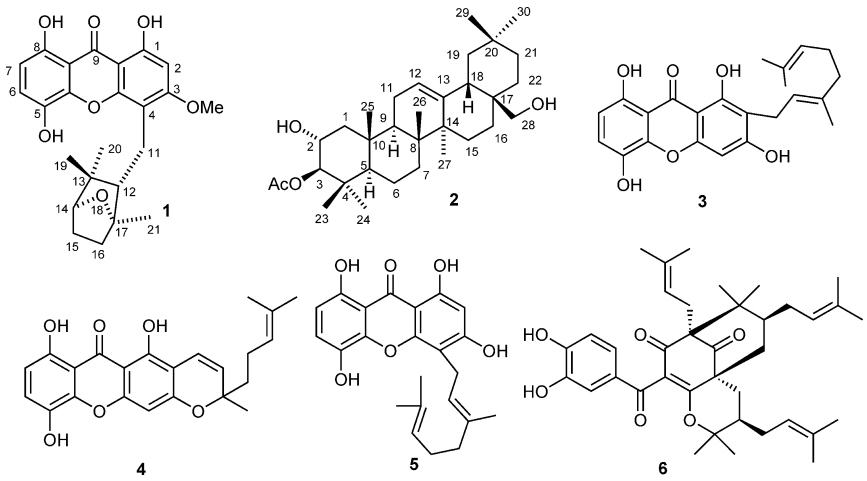

Fig. 1 Structures of compounds **1**∼**6** isolated from *Garcinia polyantha*.

polarimeter. Column chromatography (CC) was carried out on silica gel 60 F_{254} (Merck) and silica 100 respectively. Precoated plates of silica gel 60 GF_{254} were used for analytical purposes and the spots were detected with a UV lamp at 254 and 366 nm and by spraying with 50% H_2SO_4 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 chefouxanthone (**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 C_1 and C_2. Subfraction C_1 (1.1 g) was further purified by column chromatography (silica gel) eluting with hexane - EtOAc to give garciniaxanthone I (**1**, 11 mg). Finally, subfraction C_2 (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, $CHCl_3$+10% MeOH); UV (MeOH) λ_{max} (log ε): 205 (3.03), 220 (3.04), 297 (2.50), 337 (4.28), 335 (3.89); IR (KBr) ν_{max}: 3460, 3360, 1660, 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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, OCH_3), 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); ^{13}C-NMR ($CDCl_3$, 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 (OCH_3), 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 $C_{24}H_{26}O_7$, 436.1679).

Garcinane (2)

White powder; mp 235∼237°C; $[\alpha]_D^{20}$ +80 (*c* 0.25, CH_2Cl_2); IR (KBr) ν_{max} 3730, 3460, 1660, 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 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 $C_{32}H_{52}O_4$, 500.3866).

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

$C_{24}H_{26}O_7$ (Mr=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) Å^3, Z=4, D_{calcd}=1.403 g/cm^3, λ=0.71073 Å. Yellow prismatic crystal, size 0.20×0.08×0.04 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 $R1$(I>2σ(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 μM 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 RPM1640 medium (Sigma) supplemented with 25 μM 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 μM 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 μM, 5.0 μM and 2.5 μM 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 $[M]^+$ at *m/z* 426.1686 in the HREI-MS corresponded to the molecular formula $C_{24}H_{26}O_7$. 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 235~237°C, $[\alpha]_D^{20}$ +80 (*c* 0.25, CH_2Cl_2), and reacted positive in the Lieberman Burchard test for triterpenoids. The molecular formula was deduced as $C_{32}H_{52}O_4$ through HREI-MS which showed the M^+ peak at *m/z* 500.3869 (calcd. for $C_{32}H_{52}O_4$, 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 ^{1}H-NMR spectrum (see Experimental) of garciniaxanthone I (**1**) showed an AB spin system for aromatic type protons at δ 7.24 (1H, d, *J*=8.8 Hz, H-6) and 6.66 (1H, d, *J*=8.8 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 ^{1}H-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 ^{1}H-^{1}H 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 ^{1}H-^{1}H 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

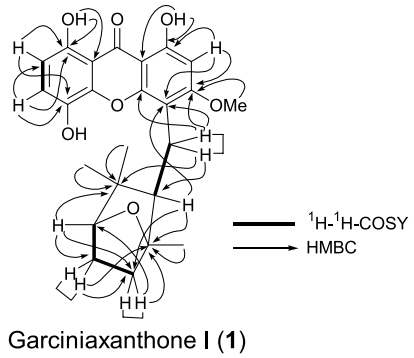

Fig. 2 Selected ^{1}H-^{1}H COSY and HMBC correlations for compound **1**.

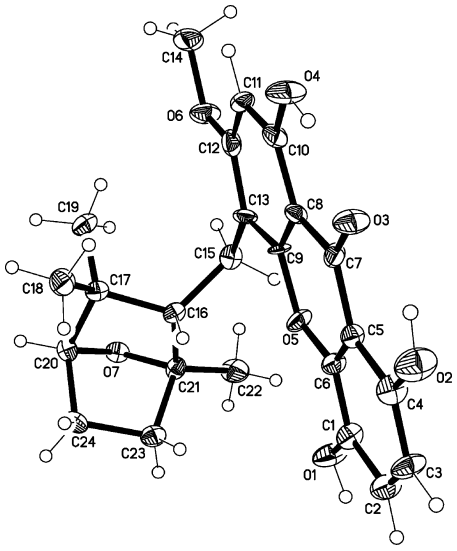

Fig. 3 Molecular structure of **1**.

Ellipsoids are drawn at the 50% probability level.

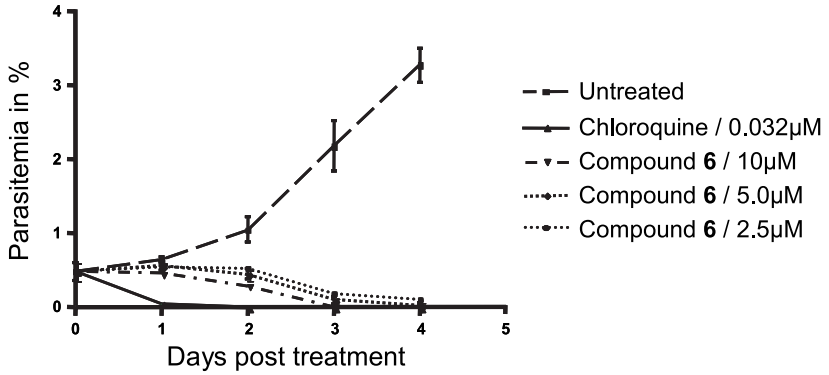

Fig. 4 Antiplasmodial activity of compound **6**[a].

[a] Growth 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 ^{13}C-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 (CH_3CO_2) 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 ^{1}H-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 (CH_3CO_2). On the basis of the molecular formula and NMR (^{1}H-, ^{13}C-NMR) data analysis [C-12 (122.1) and C-13 (C-144.3) in ^{13}C-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 ^{1}H-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 2α,3β relative configuration was further confirmed by comparison of the ^{1}H-NMR coupling constants with those reported for related compounds [21, 22]. The hydrolysis of **2** with K_2CO_3 in MeOH at room temperature afforded 2α-hydoxyerythrodiol [23]. Therefore, garcinane (**2**) was assigned as a new compound, 3β-*O*-acetyl-2α-hydroxyolean-12-en-28-ol.

Smeathxanthone A (**3**) and B (**4**) [3], chefouxanthone (**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 IC_{50} of 2.21 μM (Fig. 4). This was lower than the IC_{50} of the other five compounds, which ranged from 2.5～4.1 μM.

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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