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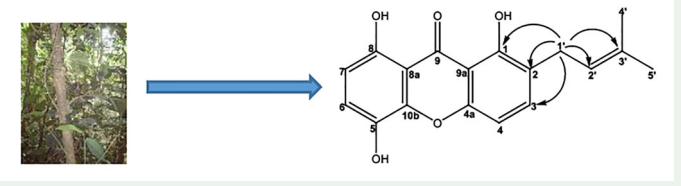
Antiproliferative activity of a new xanthone derivative from leaves of *Garcinia nobilis* Engl.

Hugues Fouotsa[a,b], Jean Paul Dzoyem[c,d], Alain Meli Lannang[e], Hans-Georg Stammler[f], Celine Djama Mbazoa[a], Michel Luhmer[g], Augustin Ephrem Nkengfack[a], Éric Allémann[d], Florence Delie[d], Franck Meyer[h] and Norbert Sewald[b]

[a]Department of Organic Chemistry, Faculty of Science, University of Yaounde I, Yaounde, Cameroon; [b]Department of Chemistry, Organic and Bioorganic Chemistry, Bielefeld University, Bielefeld, Germany; [c]Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon; [d]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, Geneva, Switzerland; [e]Department of Chemistry, Higher Teachers' Training College, University of Maroua, Maroua, Cameroon; [f]Inorganic and Structural Chemistry, Department of Chemistry, Bielefeld University, Bielefeld, Germany; [g]Centre d'Instrumentation en Résonance Magnétique (CIREM) Laboratoire de Résonance Magnétique Nucléaire Haute Résolution Université libre de Bruxelles (ULB), Brussels, Belgium; [h]Faculty of Pharmacy, Microbiology, Bioorganic and Macromolecular Chemistry Unit, Université Libre de Bruxelles, Brussels, Belgium

ABSTRACT

A new xanthone, mboudiexanthone (**1**), together with five known compounds, euxanthone (**2**), isogarcinol (**3**), garcinol (**4**), betulinic acid (**5**) and zeorin (**6**) were isolated from the leaves of *Garcinia nobilis* Engl**.** The structures were determined by 1D and 2D NMR techniques and X-ray diffraction for **6**. The *in vitro* antiproliferative properties of isolated compounds were evaluated against the human breast cancer cell line MCF-7. All compounds showed an antiproliferative activity with an IC_{50} value down to ~11 μM for isogarcinol.



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Garcinia nobilis Engl.; Guttiferae; xanthone; antiproliferative activity

1. Introduction

Plants of the genus *Garcinia* (family *Clusiaceae*), widely distributed in tropical Africa, Asia, New Caledonia and Polynesia, have yielded an abundance of biologically active and structurally intriguing natural products (Ampofo and Waterman 1986). Apart from

CONTACT Hugues Fouotsa fhugosuns@yahoo.fr, hugues.fouotsa@gmail.com
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its use as a preservative and food flavour, *Garcinia* extracts have been used in traditional medicine for treatment of ailments. A decoction of fruit rind is given as a purgative in the treatment of intestinal parasites, bilious digestive conditions, dysentery, rheumatism and in the treatment of tumours (Raina et al. 2016). Extracts are also used as a cardio-tonic to treat angina (CSIR 1956). In veterinary practice, extracts of *Garcinia* are used as a rinse for diseases of the mouth while the fruit is used in rickets and enlargement of spleen, and for healing of bone fractures (Khare 2007). *Garcinia* species are known to contain a wide variety of oxygenated and prenylated xanthones, as well as polyisoprenylated benzophenones such as guttiferones (Nguyen et al. 2005). Xanthones show a wide range of biological and pharmacological properties such as antioxidant, anti-inflammatory, antimicrobial, anticholinesterase, cytotoxic activities, antiallergy, antiulcer, antiparasitic and antihelminthic activities to help in human health and also weight loss and appetite-reducing properties (Chin et al. 2008; Louh et al. 2008). Guttiferones have been reported as anti-HIV, trypanocidal and cytotoxic agents (Gustafson et al. 1992; Komguem et al. 2005; Merza et al. 2006). Our previous studies of the chemistry of *Garcinia nobilis* led to the isolation of xanthones derivatives including the isolation from the leaves of d l-hydroxy-2,5-dimethoxyxanthone with cytotoxic activity against human cervix carcinoma cell line KB-3-1 (Fouotsa et al. 2014). We also isolated caroxanthone from the stem bark of *G. nobilis* which exhibited α-glucosidase and antibacterial activities but did not showed any α-chymotrypsin inhibitory activity (Fouotsa et al. 2012; 2013). As part of our ongoing research program on the identification of bioactive constituents from plants in the genus *Garcinia*, we have investigated the methanol extract of the leaves of *G. nobilis*. These have been subjected to petroleum ether liquid–liquid extraction, flash and column chromatography techniques that led to the separation of six compounds. In this article, we describe the isolation and characterisation of one new xanthone derivative (**1**) together with five known compounds (**2**–**6**). These compounds have been tested for their antipoliferative activity on breast cancer cell line, MCF-7.

2. Results and discussion

Two hundred and fifty grams of the methanolic extract of the leaves of *G. nobilis* were partitioned with petroleum ether and ethyl acetate (EtOAc). The petroleum ether extract (78.8 g) was then subjected to successive flash and column chromatography techniques over silica gel and Sephadex to obtain a new xanthone derivative named mboudiexanthone (**1**), along with six known molecules identified as euxanthone (**2**), isogarcinol (**3**), garcinol (**4**), betulinic acid (**5**) and zeorin (**6**) (Figure 1).

Compound **1** was isolated as a yellow powder. Its molecular formula $C_{18}H_{15}O_5$ was determined by HR-ESI-MS. A positive ferric chloride test revealed its phenolic nature.

The UV spectrum showed absorption bands at λ_{max} 352, 264, 241 and 201 nm, indicating a xanthone derivative. The IR spectrum showed absorptions at 3730, 3370, 2922, 1739 and 1622 cm^{-1} suggesting a carbonyl group in the xanthone skeleton (Meli et al. 2005). The ^{1}H NMR spectrum of xanthone **1** showed signals at δ 3.39 (2H, d, $J = 7.3$ Hz, H-1′), 5.32 (1H, t, $J = 7.3$ Hz, H-2′), 1.74 (3H, s, H-4′) and 1.75 (3H, s, H-5′) suggesting the presence of a 3-methyl-2-butenyl moiety, which was connected to C-2

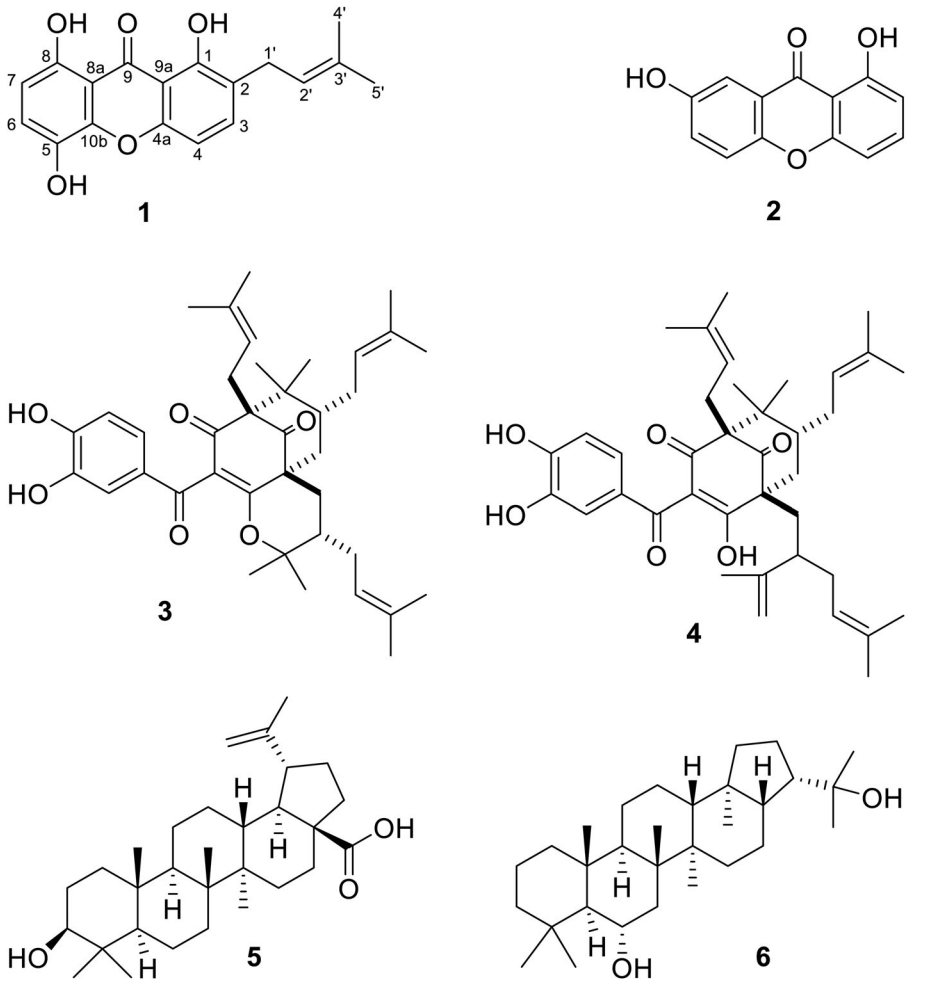

Figure 1. Structures of isolated compounds **1–6**.

(δ_C 124.2) on the basis of HMBC correlations (Supplementary information). The protons H-1′ showed HMBC correlations with C-1 (δ_C 158.9), C-2 (δ_C 124.2) and C-3 (δ_C 137.8). The analysis of an aromatic AB system at δ 7.52 (1H, d, $J = 8.5$ Hz, H-3) and 6.90 (1H, d, $J = 8.5$ Hz, H-4) on one hand, and δ 7.30 (1H, d, $J = 8.9$ Hz, H-6) and 6.71 (1H, d, $J = 8.6$ Hz, H-7) on the other hand, suggested the presence of two different *ortho*-protons in the skeleton. H-3 attached to C-3 showed HMBC correlations with C-1 (δ_C 158.9), C-1′ (δ_C 27.2) and C-4a (δ_C 154.0), H-4 attached to C-4 showed long range correlations with C-2 (δ_C 124.2), C-9a (δ_C 107.8), and C-4a (δ_C 154.0). Likewise, H-6 correlated with C-10a (δ_C 143.2), C-5 (δ_C 135.9) and C-8 (δ_C 154.0), while H-7 correlated with C-8a (δ_C 107.3), C-8 (δ_C 154.0) and C-5 (δ_C 135.9). The signals at δ_C 186.4 (C-9), δ_H 12.16 (1H, s, 1-OH) and 11.17 (1H, s,8-OH) indicated the presence of chelated carbonyl and hydroxyl groups in product **1**. The HMBC spectrum highlighted a correlation between proton 1-OH (δ_H 12.16) and carbons C-9a (δ_C 107.8), C-1 (δ_C 158.9), and C-2 (δ_C 124.2). The signal at δ_H 11.17 (8-OH) showed cross peaks with the signals at δ_C 154.0 (C-8), 109.9 (C-7) and 107.3 (C-8a). From these spectral data, compound **1** was

confirmed as a trioxygenated xanthone which was named mboudiexanthone (1,5,8-trihydroxy-2-(3-methyl-2-butenyl)xanthone) (Figure 1).

The *in vitro* antiproliferative properties of isolated compounds were screened against the human breast cancer cell line MCF-7. Dose-response curves as well as IC_{50} values are given in Supplementary information. All molecules showed an antiproliferative activity with a growth inhibition higher than 50% at 20 μM − 50 μM, except for compound **6** that reached 111.45 μM. Isogarcinol (**3)** was the most active with an IC_{50} value of 10.76 μM. Garcinol (**4**) also showed a significant activity with an IC_{50} value of 13.77 μM. Both compounds **3** and **4** are polyisoprenylated benzophenones and previous studies revealed that substrates belonging to the benzophenone family exhibit an antiproliferative activity against several tumour cell lines in different experimental models (Wu et al. 2014). A significant activity was also observed with betulinic acid (**5**) (IC_{50} values of 19.52 μM). Betulinic acid has been reported as one of the most active agents against cancer development in the group of pentacyclic triterpenoids (Paduch and Kandefer-Szerszen 2014). However, zeorin **6**, another pentacyclic triterpenoid, was the least active compounds tested in this work, showing an IC_{50} value of 111.45 μM. Mboudiexanthone (**1**) and euxanthone (**2**), two xanthonoid derivatives exhibited an antiproliferative activity with IC_{50} values of 35.26 and 32.91 μM, respectively. These findings are in agreement with previous studies on the anticancer properties of xanthonoids, considering that several traditionally used medicinal plants contain xanthones as active constituents (Anantachoke et al. 2012). Structure–activity relationship analysis of xanthones derivatives such as mangostin indicates that the maintenance of the isopentene group at C-8 is essential for the cytotoxic activity (Chi et al. 2018). This may justify the moderate activity observed with the isolated new compound mboudiexanthone. The overall antiproliferative properties of compounds isolated in this work are consistent with the literature which reports that xanthonoids, triterpenoids and benzophenones are generally responsible for the pharmacological activity of *Garcinia* species (Hemshekhar et al. 2011).

3. Experimental

3.1. General procedures

IR spectra were recorded on a JASCO A-302 IR spectrophotometer (JASCO, Gross-Umstadt, Germany). The ^{1}H, ^{13}C and 2D NMR spectra were recorded on a Bruker AMX-500 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) using $CDCl_3$ as solvent. Homonuclear ^{1}H-^{1}H connectivities were determined by using the COSY 458 experiment. One-bond ^{1}H-^{13}C connectivities were determined by HMQC. Two and three-bond ^{1}H-^{13}C connectivities were determined by HMBC experiments. Proton chemical shifts are reported in δ (ppm) with reference to the residual $CDCl_3$ signal at δ 7.26, and ^{13}C NMR spectra are referenced to the central peak of $CDCl_3$ at δ 77.0. Coupling constants (*J*) were measured in Hz. The HR-ESI-MS were recorded on a JEOL HX 110 mass spectrometer. Column chromatography was carried out on silica gel 60 (70–230 and 240–300 mesh, E. Merck,), and with Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden). Preparative thin layer chromatography (PTLC) was done on F254 PTLC plates (E. Merck, Darmstadt, Germany). Precoated silica gel TLC

was used to check the purity of compounds, and ceric sulphate spray reagent was used to visualise compounds on TLC.

3.2. Plant material

Garcinia nobilis Engl. was collected from Okola, Central Province, Cameroon in April 2010, and identified by Mr. Victor Nana of the Cameroon National Herbarium (Yaoundé) where a voucher specimen (50779/HNC/Cam/Mt Zamangoué) was deposited.

3.3. Extraction and isolation

The air-dried and ground leaves of *G. nobilis* (1.3 kg) were extracted three times with MeOH (10 L) at room temperature. The resulting extract was concentrated under reduce pressure to obtain a crude extract (250.0 g). The obtained extract was partitioned with petroleum ether (35.0 g) and ethyl acetate (17.0 g). 33.0 g of petroleum ether fraction were submitted to vacuum liquid chromatography (VLC; 25–40 μm, 8 cm × 60 cm, 300 g), eluting with n-hexane/ethyl acetate (EtOAc) of increasing polarity (10:0 1 L; 8:2 1 L, 6:4 750 mL, 4:6 500 mL, 0:10 500 mL), which were collected into 300 mL fractions and subsequently combined based on their thin layer chromatography (TLC) profile into four fractions A–D. Fraction B (3.0 g) was subjected to column chromatography on silica gel (25–40 μm, 4.0 × 60 cm) and eluted with petroleum ether/EtOAc by increasing polarity, 25 mL of each fraction were collected and subsequently combined on the basis of similar TLC into four fractions B1–B4. Fraction B1 was further purified using silica gel and column chromatography (25–40 μm; 4.0 × 60 cm) eluting with mixture of petroleum ether/EtOAc (2:8) and washing with methanol after condensation to afford betulinic acid (**5**, 10 mg) and zeorin (**6**, 5 mg). Isogarcinol (**3**, 32 mg) and garcinol (**4**, 7.5 mg) were obtained from fraction B2 by using preparative thin layer chromatography (PTLC) followed by further purification on silica gel chromatography (25–40 μm; 3.0 × 15 cm) eluting with petroleum ether/acetone solvent system by increasing the polarity.

B3 (2 g) was further purified by silica gel in the same column chromatography using petroleum ether/CH_2Cl_2/MeOH by increasing polarity and Sephadex LH-20 to afford 1,5,8-trihydroxy-2-prenylxanthone (**1**, 11 mg), Euxanthone (**2**, 17 mg). due to the TLC profile, B4 was kept.

Mboudiexanthone (**1**): Yellow powder; $C_{18}H_{15}O_5$; UV (MeOH) λ_{max} (nm) 352, 264, 241; 201. IR(KBr) $\nu_{max}(cm^{-1})$ 3730, 3370, 2922, 1739 and 1622. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.52(d; $J = 8.5$ Hz; 1H; H-3), 6.90(d; $J = 8.5$ Hz; 1H; H-4), 7.30(d; $J = 8.9$ Hz; 1H; H-6), 6.70(d; $J = 8.9$ Hz; 1H; H-7); 3.39(2H, H-1′), 5.32(1H, H-2′), 1.76(H-4′), 1.74(H-5′), 12.16(s; 1H; 1-OH), 11.17(s; 1H; 8-OH) and ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.9(C-1), 124.2(C-2), 137.8(C-3), 106.3(C-4), 135.9(C-5), 123.9(C-6), 109.9(C-7), 154.1(C-8), 186.4(C-9), 154.0(C-4a), 107.3(C-8a), 107.8(C-9a), 143.2(C-10a), 27.2(C-1′), 121.5 (C-2′), 133.9 (C-3′), 26.0 (C-4′), 26.0 (C-5′). HR-ESI-MS: *m/z* 311,0932 [$M - 1$] (calcd. for $C_{18}H_{15}O_5$ −1, 311,0925).

Euxanthone (**2**): Yellow needles; EI-MS: *m/z* 228 M $^{+}$, $C_{13}H_8O_4$; mp 231–232 °C. UV λ_{max} (nm):(log ε): 387, 288, 259, 235, 202. IR (KBr)υ_{max} (cm^{-1}): 3300, 1640, 1600, 1580, 1480. ^{1}H NMR and ^{13}C NMR are consistent with published data (Wenkui et al. 1998).

Isogarcinol (**3**): Brown crystal, ESI-MS: *m/z* 603.37 [M + H] $^{+}$, $C_{38}H_{50}O_6$; mp 251 °C; UV λ_{max} (nm):(log ε): 317 (3.82), 277 (4.14), 233 (4.07); IR (KBr)υ_{max} (cm^{-1}): 3290, 2920, 2850, 1730, 1670, 1590, 1520, 1440, 1370, 1290, 1170. ^{1}H NMR and ^{13}C NMR are consistent with published data (Jaideep et al. 2013).

Garcinol (**4**): Yellow crystal; ESI-MS: *m/z* 603.37 [M + H] $^{+}$, $C_{38}H_{50}O_6$; mp 132^{0}C; UV λ_{max} (nm):(log ε): 279 (4.18), 232 (4.04); IR (KBr)υ_{max} (cm^{-1}): 3300, 2920, 1720, 1640, 1590, 1440, 1370, 1290, 1190. ^{1}H NMR and ^{13}C NMR are consistent with published data (Jaideep et al. 2013).

Betulinic acid (**5**): Colourless amorphous powder; MS *m/z* 456 M $^{+}$m.p 297 °C; UV: 206 nm; IR (KBr)υ_{max} (cm^{-1}): 3473, 3063, 2953, 2887, 2712, 1682, 1643, 1457, 1375, 1221, 1194, 1106, 1035, 980, 876, 871, 789. ^{1}H NMR and ^{13}C NMR are consistent with published data (Eder et al. 2008).

Zeorin (**6**): MS *m/z* 444 M $^{+}$, $C_{30}H_{52}O_2$; m.p. 237–240 °C. IR (KBr)υ_{max}(cm^{-1}): 3385, 2980, 1465, 1380, 1260, 1250, 1210, 1160, 1140, 1044, 1020, 980, 965, 875, 830, 760, 730, 710, 690. ^{1}H NMR and ^{13}C NMR are consistent with published data (Konig and Wright 1999).

3.4. X-ray crystallographic study of 6

Crystal data for **6**. ($C_{30}H_{52}O_2$) x 0.5 CH_2Cl_2. $M = 444$, hexagonal, space group $P6_122$ (no. 178), $a = 16.76179(13)$ Å, $c = 68.9708(6)$ Å, $V = 16781.7(3)$ Å^3, $Z = 24$, $T = 100.0(1)$ K, μ(CuKα) = 0.927 mm^{-1}, D_{calc} = 1.107 g/cm^3, 283,999 reflections measured ($6.088° \leq 2\Theta \leq 151.65°$), 11,582 unique ($R_{int}$ = 0.0926, R_{sigma} = 0.0230) which were used in all calculations. The final R_1 was 0.0562 for 10773 reflections with $I > 2\sigma(I)$ and wR_2 was 0.1373 for all data. CCDC 1970901 contains the supplementary crystallographic data for this article (Supplementary information). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html.

3.5. Antiproliferative activity assay

3.5.1. Cell culture and treatment

The breast carcinoma cell line MCF-7 was cultured in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with 10% FCS and 1% antibiotics comprising 100 IU/mL penicillin and 100 µL/mL streptomycin. Cells were maintained at 37 °C in a humidified atmosphere containing 5% CO_2.

3.5.2. WST-1 assay for cell proliferation inhibition

Cell proliferation was evaluated using reagent WST-1 [2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium] (Roche Diagnostics, Germany) as described by Delie et al. (2013). Cells at a density of 10^4 per well were seeded in 96-well plates and incubated overnight. The next day, they were exposed to different

concentrations (5–100 μM or 20–200 μM) in triplicate of compounds solubilised in DMSO and incubated for 48 h. Then the medium in each well was aspirated, WST-1 solution was diluted 1:10 with fresh medium, added to each well and the plates were incubated at 37 °C for 45 min. The absorbance was recorded at 450 nm/690 nm using Synergy Multi-Mode Microplate Reader (BioTek). Results were expressed as percentage of inhibition of cell proliferation relatively to the control without treatment. Concentration-response analysis was performed to determine the compound concentrations required to inhibit the growth of cancer cells by 50% (IC_{50}) using GraphPad Prism 8.00 software.

4. Conclusion

The present work indicated that *G. nobilis* is a good source of bioactive xanthones and benzophenones. All molecules showed an antiproliferative activity with a growth inhibition higher than 50% at 20–50 μM, except for compound **2** that reached 200 μM. Their cytotoxicity provided baseline information for their possible use for the control of cancer diseases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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