Polyprenylated Xanthones and Benzophenones from the Bark of *Garcinia oblongifolia*

by **Wei-Guang Shan**, **Tian-Song Lin**, **Hai-Ning Yu**, **Yan Chen**, and **Zha-Jun Zhan***

College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, P. R. China (phone: +86-571-88871075; fax: +86-571-88320913; e-mail: zjnpr@zjut.edu.cn)

A new polyprenylated xanthone (=9*H*-xanthen-9-one) and a new polyprenylated benzophenone, namely oblongifolixanthone A (**1**) and garciniagifolone A (**2**), were isolated from the bark of *Garcinia oblongifolia*, together with five known compounds including the four xanthones **3**–**5** and **7** and a benzophenone **6**. The structures of **1** and **2** were established by detailed analysis of their spectroscopic data, especially 1D- and 2D-NMR spectra and HR-ESI-MS data. All these compounds were assayed for their cytotoxic activities against three human tumor cell lines (HeLa, SGC7901, and HepG2). The 1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one (**3**) was inactive, and the other compounds showed weak to moderate activity.

Introduction. – The genus of *Garcinia* belonging to the family Guttiferae is well known as a rich source of polycyclic prenylated acylphloroglucinols and xanthones (=9*H*-xanthen-9-ones) [1][2], which have been demonstrated to possess a wide range of biological activities including anti-inflammatory [3], antioxidant [4], antibacterial [5], antifungal [6], and cytotoxic activity [7]. *Garcinia oblongifolia*, a medium-sized shrub, is widely distributed in the south of China and north of Vietnam. In previous phytochemical studies of this plant, seven new polyprenylated benzoylphloroglucinol derivatives, oblongifolins A–G, three new xanthones, oblongixanthones A–C, four new prenylated biphenyl compounds, oblongifoliagarcinines A–D, and fourteen known compounds had been obtained [8–10]. Among these compounds, oblongifolin C was found to be a potent apoptotic inducer against HeLa-C3 cells [8]. The phytochemical investigation of this plant collected from Hainan Province of China has now resulted in the isolation of a new prenylated xanthone, oblongifolixanthone A (**1**) and a new polyprenyl-substituted benzophenone, garciniagifolone A (**2**) (*Fig. 1*). Their structures were determined by spectroscopic data, mainly the NMR and HR-ESI-MS data. In addition, the five known compounds **3**–**7** were also obtained from this plant (*Fig. 1*). The cytotoxic activities of all the isolates against three human-tumor cell lines (HeLa, SGC7901, and HepG2) were evaluated, and compounds **1**, **2**, and **4**–**7** showed moderate cytotoxicity against the tested tumor cell lines.

Results and Discussion. – Oblongifolixanthone A[1]) (**1**) was obtained as a yellow gum. Its molecular formula was determined as $C_{28}H_{33}O_6$ by HR-ESI-MS (*m*/*z* 465.2274 ($[M-H]^-$)). This elemental composition implied 12 degrees of unsaturation. The IR

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

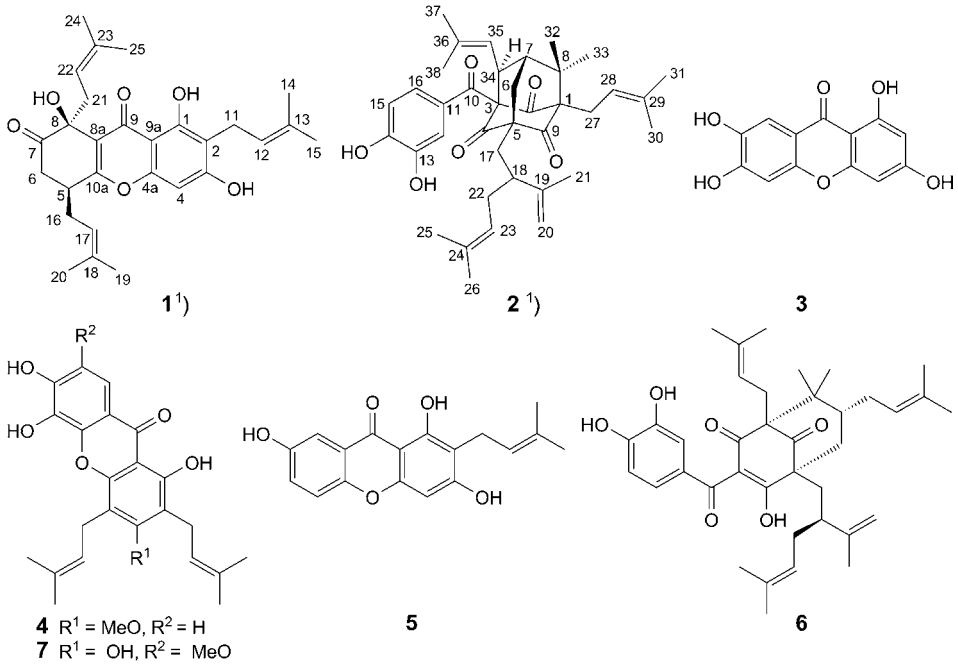

Fig. 1. *Compounds* **1**–**7**, *isolated from* Garcinia oblong ifolia

spectrum exhibited absorption bands for OH (3400 cm^{-1}) and C=O (1725 cm^{-1}) groups. Thirteen quaternary C-atoms (twelve sp^2 C-atoms including two C=O groups at δ(C) 180.7 and 206.8, resp.) and five CH (four sp^2 C-atoms), four CH_2, and six Me groups were found according to the ^{13}C-NMR and DEPT spectra (*Table 1*). The ^{1}H-NMR spectrum exhibited a signal for a chelated OH H-atom at δ(H) 12.92 (*s*, OH–C(1)) and an aromatic H-atom *s* at δ(H) 6.43. In addition, three olefinic H-atoms at δ(H) 5.26 (*t*, $J = 7.0$ Hz, CH(12)), 5.11 (*t*, $J = 7.0$ Hz, CH(17)), and 4.94 (br. *s*, CH(22)), six olefinic Me groups at δ(H) 1.57 (Me(25)), 1.60 (Me(20)), 1.64 (Me(24)), 1.71 (Me(19)), 1.74 (Me(15)), and 1.82 (Me(14)), and six allylic H-atoms at δ(H) 3.40 and 3.41 (2 *d*, $J = 7.0$ Hz, CH_2(11)), 2.16–2.21 and 2.46–2.50 (2*m*, CH_2(16)), and 2.75 and 2.92 (2 br. *s*, CH_2(21)) were observed in the ^{1}H-NMR spectrum, indicating the existence of three prenyl groups (= 3-methylbut-2-en-1-yl) in **1**. The data mentioned above showed that **1** was a tetrahydro-9*H*-xanthen-9-one bearing three prenyl groups. Analysis of the ^{1}H- and ^{13}C-NMR and HMQC spectra of **1** enabled us to assign all the H-atoms to their bonding C-atoms. The assemblage of all C-atoms, including quaternary C-atoms and heteroatoms was mainly made by an HMBC experiment (*Fig. 2*). One of the prenyl units was located at C(2) according to the correlations of the benzylic CH_2(11) to C(2), C(1) and C(3), and of OH–C(1) to C(2), C(9a), and C(1). The downfield shift of C(3) indicated the presence of an OH group at C(3), and the only aromatic H-atom at δ(H) 6.43 was assigned to H–C(4). The location of a second prenyl group (C(16)–C(20)) at C(5) was deduced by the correlations CH_2(6)/H–C(5)/CH_2(16)/H–C(17) in the ^{1}H,^{1}H-COSY plot and was confirmed by the HMBC cross-

Table 1. *NMR Data of Compounds* **1** *and* **2**. δ in ppm, J in Hz

Position[1])	**1**[a])		Position[1])	**2**[a])	
	δ(H)	δ(C)		δ(H)	δ(C)
C(1)	–	159.2	C(1)	–	77.1
C(2)	–	110.6	C(2)	–	201.7
C(3)	–	161.6	C(3)	–	79.5
H–C(4)	6.43 (*s*)	94.0	C(4)	–	201.4
C(4a)	–	155.8	C(5)	–	68.4
H–C(5)	3.35–3.37 (*m*)	31.8	CH_2(6)	2.52, 2.37 (2*dd*,	44.1
CH_2(6)	2.81 (*dd*, J = 15.5, 7.5, H_α),	38.4		each J = 14.0, 3.0)	
	2.64 (*dd*, J = 15.5, 4.5, H_β)		H–C(7)	1.64–1.66 (*m*)	47.7
C(7)	–	206.8	C(8)	–	53.8
C(8)	–	75.7	C(9)	–	203.8
C(8a)	–	119.5	C(10)	–	192.3
C(9)	–	180.7	C(11)	–	128.1
C(9a)	–	104.6	H–C(12)	7.17 (br. *s*)	116.2
C(10a)	–	160.4	C(13)	–	142.9
CH_2(11)	3.41 (*d*, J = 7.0),	21.5	C(14)	–	148.7
	3.40 (*d*, J = 7.0)		H–C(15)	6.71 (*d*, J = 8.5)	114.1
H–C(12)	5.26 (*t*, J = 7.0)	121.2	H–C(16)	6.58 (*d*, J = 8.5)	124.6
C(13)	–	135.0	CH_2(17)	1.82, 2.10 (2 *dd*,	
Me(14)	1.82 (*s*)	17.9		each J = 14.0, 5.0)	33.2
Me(15)	1.74 (*s*)	25.9	H–C(18)	2.67–2.70 (*m*)	42.7
CH_2(16)	2.16–2.21, 2.46–2.50 (2*m*)	32.6	C(19)	–	148.7
H–C(17)	5.11 (*t*, J = 7.0)	120.5	CH_2(20)	4.62, 4.71 (2*s*)	112.7
C(18)	–	135.4	Me(21)	1.61 (*s*)	18.1
Me (19)	1.71 (*s*)	25.9	CH_2(22)	2.03–2.08 (*m*)	33.3
Me (20)	1.60 (*s*)	17.9	H–C(23)	5.03 (*t*, J = 7.0)	122.8
CH_2(21)	2.75, 2.92 (2 br. *s*)	36.5	C(24)	–	132.3
H–C(22)	4.94 (br. *s*)	115.7	Me(25)	1.59 (*s*)	18.1
C(23)	–	137.7	Me(26)	1.62 (*s*)	25.7
Me(24)	1.64 (*s*)	25.8	CH_2(27)	2.38, 2.50 (2*dd*,	23.1
Me(25)	1.57 (*s*)	17.9		each J = 13.0, 7.0)	
OH–C(1)	12.92 (*s*)	–	H–C(28)	4.87 (*t*, J = 7.0)	119.4
			C(29)	–	134.5
			Me(30)	1.72 (*s*)	18.2
			Me(31)	1.69 (*s*)	26.0
			Me(32)	1.20 (*s*)	22.7
			Me(33)	1.13 (*s*)	23.2
			H–C(34)	4.14 (*d*, J = 8.0)	51.1
			H–C(35)	4.97 (*d*, J = 8.0)	120.8
			C(36)	–	134.3
			Me(37)	1.68 (*s*)	25.9
			Me(38)	1.74 (*s*)	18.4

[a]) Data were recorded in $CDCl_3$ at 500 (^{1}H) and 125 MHz (^{13}C).

peaks of CH_2(16)/C(6), C(5), C(10a). The last prenyl unit was located at C(8) on the basis of the HMBC cross-peaks CH_2(21)/C(8), C(8a), and C(7), which also indicated the presence of a C=O group at C(7) and an OH group at C(8). Thus, the planar

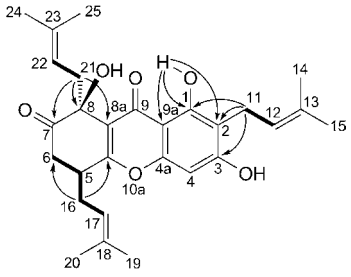

Fig. 2. *Selected* $^1H,^1H$*-COSY* (—) *and HMBC* (H → C) *features of* **1**[1])

structure of **1** was established. The relative configuration of **1** was deduced by the NOESY analysis. The NOESY correlations H_α–C(6)/H–C(5) and H–C(21) indicated that H_α–C(6), H–C(5), and the prenyl group at C(8) were on the same side of the molecular plane, tentatively assumed as α-side. As a consequence, OH–C(8) and the prenyl group at C(5) were in β-orientation. Complete ^{1}H- and ^{13}C-NMR assignments (*Table 1*) were achieved by a combination of two-dimensional NMR techniques, including $^1H,^1$H-COSY, HMQC, HMBC, and NOESY experiments. Thus, the structure of oblongifolixanthone A was established as **1**, which contained an unusual tetrahydro-9*H*-xanthen-9-one core.

Garciniagifolone A[1]) (**2**) was obtained as a pink amorphous solid. Compound **2** was assigned the molecular formula $C_{38}H_{48}O_6$ (15 degrees of unsaturation) which was based on the negative-ion-mode HR-ESI-MS (*m/z* 599.3379 ($[M-H]^-$)). The IR spectrum of **2** showed signals for OH (3400 cm^{-1}), C=O (1740 and 1694 cm^{-1}), and aromatic groups (1598, 1521, and 1439 cm^{-1}). On the basis of NMR evidences (*Table 1*) and the data mentioned above, **2** had a trioxygenated benzophenone-derived skeleton [11][12]. Furthermore, the appearance of ^{13}C-NMR signals at δ(C) 203.8, 201.7, and 201.4 implied that the trioxygenated ring was nonaromatic and had three nonconjugated keto moieties [11][12]. Apart from a dioxygenated benzoyl group, the NMR data also showed the existence of five additional five-C-atom units: a 2-isopropenyl-2-prenylethyl group made up of a 3-methylbut-2-en-1-yl unit (C(22) to C(26)) and a 3-methylbut-3-en-1-yl unit (C(17) to C(21)), two individual 3-methylbut-2-en-1-yl groups (C(27) to C(31) and C(34) to C(38)), and a geminal dimethyl group (C(32), and C(33)) attached to the quaternary C(8), in turn connected to the CH(7) group (linked to the CH_2(6) group). Only 3 of the 15 required degrees of unsaturation were not assigned. Furthermore, the absence of additional signals for sp^2 C-atoms indicated the presence of a tricyclic moiety in **2**. The NMR data of **2** was superimposing on those of garcinialiptone A, except for signals for a 3-methylbut-2-en-1-yl unit (C(22) to C(26)) in **2** rather than a 3-methylbut-3-en-1-yl unit in garcinialiptone A (= *rel*-(1*R*,3*S*,5*R*,7*S*,8*R*)-1-(3,4-dihydroxybenzoyl)-6,6-dimethyl-5-(3-methylbut-2-en-1-yl)-3-[5-methyl-2-(1-methylethenyl)hex-5-en-1-yl]-8-(2-methylprop-1-en-1-yl)tricyclo[3,3,1,$1^{3,7}$]-decane-2,4,9-trione) [12]. The conclusion was confirmed by the $^1H,^1$H-COSY and HMBC experiments. The interpretation of ^{1}H-NMR data including coupling constants indicated that the relative configuration of **2** was the same as that of garcinialiptone A, which was confirmed by the NOESY plot. The NOEs H–C(7)/H–C(34), H–C(7)/Me(33), and H–C(34)/Me(33) showed that H–C(7), H–C(34), and Me(33) were on the same side of the molecular plane. As a result, the NOEs Me(32)/H–C(6) and

H–C(6)/H–C(35) revealed that the H–C(6), Me(32), and H–C(35) were on the opposite face to H–C(7) and H–C(34). Thus, the structure of garciniagifolone A was determined as **2**.

The structures of the known compounds were identified as 1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one (**3**) [13][14], dulxanthone B (**4**) [15], 1,3,7-trihydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**5**) [16], camboginol (**6**) [17], and xanthone V_{2a} (**7**) [15][18] by comparison of their spectroscopic data with literature data. Among these known isolates, compounds **3**, **4**, **5**, and **7** were isolated from this plant for the first time.

Three human-tumor cell lines (HeLa, SGC7901, and HepG2) were used to evaluate the cytotoxic activities of all the isolates (*Table 2*) with etoposide as positive control. While 1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one (**3**) was inactive, the prenylated compounds **1**, **2**, and **4**–**7** showed moderate to weak cytotoxicity against the tested human cancer cell lines with IC_{50} values ranging from 9.7 to 80.0 μM. Compound **2** exhibited the strongest activity against SGC7901 ($IC_{50} = 9.7$ μM). The results of the cytotoxic assay established that the existence of prenyl groups may contribute to the cytotoxic activity of these metabolites.

Table 2. *Cytotoxic Data of Compounds* **1**, **2**, *and* **4**–**7** *by the MTT Method*[a])

Compound	Cell Line[b])		
	HeLa	HepG2	SGC7901
1	24.5 ± 0.9	42.8 ± 0.8	22.5 ± 0.6
2	25.3 ± 0.3	40.0 ± 0.3	9.7 ± 0.4
3[c])	–	–	–
4	28.7 ± 0.4	52.7 ± 0.8	14.0 ± 0.7
5	80.0 ± 0.6	55.0 ± 0.4	75.8 ± 0.8
6	30.4 ± 0.8	> 100	28.6 ± 0.6
7	44.9 ± 0.7	28.8 ± 0.5	44.9 ± 0.8
Etoposide[d])	18.0 ± 0.6	26.7 ± 0.7	37.7 ± 0.9

[a]) Results are expressed as IC_{50} values ± standard deviation in μM. [b]) HeLa, cervical carcinoma; HepG2, hepatoblastoma; SGC7901, human gastric cancer. [c]) Compound **3** was inactive against all cancer cell lines ($IC_{50} > 100.0$ μM). [d]) Etoposide was used as positive control.

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Experimental Part

General. Solvents were of anal. grade (*Shanghai Chemical Plant*). Culture medium from *KeyGEN BioTECH* and fetal bovine serum from *HyClone* were used. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh; *Qingdao Haiyang Chemical Co., Ltd.*), *MCI-CHP20P* gel (75–150 μm; *Mitsubishi Chemical Industries Ltd.*), *RP-C_{18}* silica gel (SiO_2, 50 μm; *YMC Co., Ltd.*), and *Toyopearl HW-40C* gel (50–100 μm; *Tosoh*). TLC: precoated silica gel *GF_{254}* plates (*Qingdao Haiyang Chemical Co., Ltd.*); visualization with UV light (254 and/or 366 nm) and 10% H_2SO_4/EtOH. Optical rotations: *Perkin-Elmer-341* polarimeter. UV Spectrum: *Shimadzu-UV-2450* spectrometer; λ_{max} (log ε) in nm. IR Spectrum: *Thermo-Nicolet-6700* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-AM-400* and *Bruker-AM-500* apparatus; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI-MS: *Agilent-6210-Lc/Tof* mass spectrometer; in *m*/*z*.

Plant Material. The barks of *Garcinia oblongifolia* (5.5 kg) were collected from Hainan Province, P. R. China, in January 2011, and identified by Prof. *Shi-Man Huang*, Department of Biology, Hainan University, P. R. China. A voucher specimen (GO-1103) was deposited with Zhejiang University of Technology.

Extraction and Isolation. The air-dried barks of *G. oblongifolia* were powdered and then extracted with 95% EtOH three times (30 l, 7 d each) at r.t. After evaporation, the EtOH extract (0.6 kg) was suspended in H_2O and partitioned successively with petroleum ether (3 l), $CHCl_3$ (9 l), and BuOH (9 l). The $CHCl_3$ fraction (80 g) was then subjected to CC (SiO_2, petroleum ether/Me_2CO 7:1, 5:1, 3:1, 1:1, 0:1): *Frs. A–C. Fr. A* (11.4 g) was subjected to CC (*MCI* gel, MeOH/H_2O 4:6 → 100:0), then to CC (*RP-C_{18}*, MeOH/H_2O 8:2 → 85:15): **1** (34.4 mg) and **2** (4.5 mg). *Fr. B* (5 g) was subjected to CC (SiO_2, petroleum ether/Me_2CO 5:1 → 2:1): *Frs. B1* and *B2*. *Fr. B1* (100 mg) was subjected to CC (*RP-C_{18}*, MeOH/H_2O 8:2): **7** (3 mg). *Fr. B2* (600 mg) was applied to CC (*Toyopearl HW-40C*, MeOH) and then purified by CC (*RP-C_{18}*, MeOH/H_2O, 65:35 → 9:1): **4** (19 mg), **5** (3.1 mg), and **6** (300 mg). *Fr. C* (600 mg) was subjected to CC (SiO_2, petroleum ether/Me_2CO 2:1): **3** (12.3 mg).

Oblongifolixanthone A (= rel-*(1*R,*4*R*)-3,4-Dihydro-1,6,8-trihydroxy-1,4,7-tris(3-methylbut-2-en-1-yl)-1*H*-xanthene-2,9-dione;* **1**): Yellow gum. $[\alpha]_D^{25} = +89.8$ ($c = 0.51$, MeOH). IR (KBr): 3400, 2970, 2920, 1725, 1640, 1419, 1367, 1178, 1071, 819. UV (MeOH): 303 (3.46), 259 (3.76), 233 (3.75). ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS (neg.): 465.2 ($[M-H]^-$). HR-ESI-MS (neg.): 465.2274 ($[M-H]^-$, $C_{28}H_{33}O_6^-$; calc. 465.2277).

Garciniagifolone A (= rel-*(1*R,*3*S,*5*R,*7*S,*8*R*)-1-(3,4-Dihydroxybenzoyl)-6,6-dimethyl-5-(3-methylbut-2-en-1-yl)-3-[5-methyl-2-(1-methylethenyl)hex-4-en-1-yl]-8-(2-methylprop-1-en-1-yl)tricyclo[3,3,1,1^{3,7}]decane-2,4,9-trione;* **2**): Pink amorphous solid. $[\alpha]_D^{25} = +7.0$ ($c = 0.09$, MeOH). IR (KBr): 3400, 2964, 2920, 2858, 1740, 1694, 1598, 1520, 1439, 1375, 1285, 1193, 1112, 892, 772. UV (MeOH): 313 (2.35), 278 (2.48), 227 (2.86). ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS (neg.): 599.3 ($[M-H]^-$). HR-ESI-MS (neg.): 599.3379 ($[M-H]^-$, $C_{38}H_{47}O_6^-$; calc. 599.3373).

Cytotoxicity Assay. Compounds **1**–**7** were evaluated for cytotoxicity against HeLa, HepG2, and SGC7901 cells (provided by Wuhan University) by means of the MTT (= 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) assay following a standard protocol [19]. HeLa and HepG2 cells were cultured in *Dulbecco*'s modified *Eagle*'s medium (DMEM, high glucose) containing 10% fetal bovine serum, 100 U/ml of penicillin, and 100 mg/ml of streptomycin. SGC7901 cells were maintained in *RPMI-1640* medium containing 10% fetal bovine serum. Before the addition of the compounds, the cells were transferred into 96-well plates, and incubated overnight at 37°. Compounds were dissolved in DMSO, diluted with culture medium at the designed concentration, and incubated with the cells for 44 h. MTT soln. (20 µl, 5 mg/ml) was added into each well, and the plates were incubated for an additional 4 h. After removing the old medium, DMSO (150 µl) was added to dissolve the formazan produced from MTT by viable cells. Absorbance at 570 nm is proportional to the live cell count. The linear dependence between the percent cell survival and the *OD* value were calculated with Excel (*Microsoft*), and the IC_{50} values were determined graphically as described in [20].

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