Cytotoxic Xanthones from *Garcinia penangiana* Pierre

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Two new xanthones, characterized as 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**) and penangianaxanthone (**2**), with three known xanthones, cudratricusxanthone H (**3**), macluraxanthone C (**4**) and gerontoxanthone C (**5**), as well as friedelin and stigmaterol were isolated from the leaves of *Garcinia penangiana*. Their structures were elucidated by analysis of spectroscopic data and comparison of the NMR data with the literature ones. Significant cytotoxicity against DU-145, MCF-7 and NCI-H460 cancer cell lines was demonstrated by compounds **1**–**5**, with IC₅₀ values ranging from 3.5 to 72.8 μ M.

Key words: *Garcinia penangiana*, Cytotoxic Activity, Xanthones

Introduction

The medicinal properties of the species *Garcinia* (family Guttiferae) are well documented, both on their traditional use as well as the scientific basis for their biological activities (Burkill, 1966; Cao *et al.*, 1998; Chomnawang *et al.*, 2005; Grosvenor *et al.*, 1995; Tona *et al.*, 1999). Isolation of xanthones, benzophenones, triterpenes and biflavonoids has been reported (Ali *et al.*, 2000; Matsumoto *et al.*, 2003a; Peres *et al.*, 2000; Waterman and Husain, 1983). The constituents isolated from *Garcinia* exhibit various bioactivities, such as antitumour, anti-inflammatory (Lin *et al.*, 1997; Nakatani *et al.*, 2002) and antibacterial (Permana *et al.*, 2001; Rukachaisirikul *et al.*, 2003). Xanthones are especially noted as potential antitumour and chemopreventive agents (Chiang *et al.*, 2003; Ito *et al.*, 2003; Mackeen *et al.*, 2000; Matsumoto *et al.*, 2003b; Thoison *et al.*, 2000). In this report, the isolation of two new cytotoxic prenylated xanthones, 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**) and the furanoxanthone penangianaxanthone (**2**), is described. Three known xanthones, including cudratricusxanthone H (**3**), macluraxanthone C (**4**) and gerontoxanthone C (**5**), along with friedelin and stigmaterol were also isolated.

Results and Discussion

Compound **1** was isolated as a yellow amorphous solid with a melting point of 220–222 °C. The EIMS spectrum exhibited the HREIMS molecular ion peak ($[M^+]$) at m/z 328.3269 corresponding to the molecular formula C₁₈H₁₆O₆. The UV spectrum showed typical absorptions of the xanthone chromophore at 226, 256, 281 and 325 nm (Govindachari *et al.*, 1971). The absorption bands at 3392, 2922, 1585, and 1031 cm⁻¹ in the IR spectrum indicated the presence of hydroxy, alkyl, carbonyl, and allyl groups, respectively.

The ¹H NMR spectrum contained nine signals representing two chelated hydroxy groups [δ_H 12.26, 1H (s) and δ_H 11.18, 1H (s)], two *ortho*-coupled protons (δ_H 7.32, d, J = 9.0 Hz, H-6 and δ_H 6.64, d, J = 9.0 Hz, H-7), a set of four signals of the 1,1-dimethylallyl group [δ_H 6.58 (dd, J = 17.0, 10.0 Hz, H-2'), δ_H 5.11 (dd, J = 17.0, 1.5 Hz, H-*trans*-3'), δ_H 4.95 (dd, J = 10.0, 1.5 Hz, H-*cis*-3') and δ_H 1.76 (2CH₃, s, H-4' and H-5')], and one aromatic proton (δ_H 6.38, s, H-2).

The ¹³C NMR spectrum revealed the presence of 18 carbon atoms including one carbonyl carbon atom by a signal at δ_C 185.2 (C-9). Further inspection on the ¹³C NMR and HSQC spectra indicated

the presence of two aromatic rings with six oxygenated carbon atoms, corresponding to a tetrahydroxylated xanthone and one dimethylallyl group. In the HMBC spectrum, correlations were observed between the dimethyl signals (δ_{H} 1.76, $\text{CH}_3\text{-4'}/\text{CH}_3\text{-5'}$) with the carbon signal of C-4 (δ_{C} 112.5), thus allowing us to assign the connectivity of a dimethylallyl moiety at C-4.

The assignment of a hydroxy group at C-1 was based on the HMBC correlation of the chelated hydroxy signal at δ_{H} 12.26 with the carbon signals at δ_{C} 161.3 (C-1), δ_{C} 99.8 (C-2) and δ_{C} 102.2 (C-9a). The correlation of the proton signal at δ_{H} 6.38 with the carbon signals at δ_{C} 161.3 (C-1), δ_{C} 165.5 (C-3), δ_{C} 112.5 (C-4) and δ_{C} 102.2 (C-9a) confirmed the assignment of an aromatic methine carbon atom of C-2. The chelated hydroxy group at δ_{H} 11.18 correlated with the carbon signals at δ_{C} 153.1 (C-8), δ_{C} 107.4 (C-8a) and δ_{C} 109.3 (C-7) in the HMBC spectrum, thus suggesting that the OH group was located at C-8. The assignment of the *ortho*-coupled H-6 proton (δ_{H} 7.32) was based on its correlations with the carbon signals at δ_{C} 153.1 (C-8), δ_{C} 137.6 (C-5) and δ_{C} 144.0 (C-10a), whereas, the assignment of the H-7 proton (δ_{H} 6.64) was based on its correlations with the signals at δ_{C} 153.1 (C-8), δ_{C} 107.4 (C-8a) and δ_{C} 137.6 (C-5). Based on these observations, the compound was concluded to be 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**, Fig. 1). The ^1H NMR, ^{13}C NMR and HMBC data for **1** are summarized in Table I.

Fig. 1. Compounds isolated from *G. penangiana* leaves: 4-(1,1-dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (**1**), penangianaxanthone (**2**), cudraticusxanthone H (**3**), macluraxanthone C (**4**), and gerontoxanthone C (**5**).

Penangianaxanthone (**2**) was isolated as yellow fluffy crystals with a melting point of 216–218 °C. The HREI mass spectrum of this compound showed the molecular ion peak at m/z 352.0960,

C	^{13}C chemical shift (ppm)	^1H chemical shift (integration of proton, multiplicity, J in Hz)	HMBC correlations (H to C)
C-1	161.3	12.26 (1H, s, OH-1)	C-1, C-2, C-9a
C-2	99.8	6.38 (1H, s)	C-1, C-3, C-4, C-9a
C-3	165.5		
C-4	112.5	155.0	
C-5	137.6		
C-6	123.3	7.32 (1H, d, $J = 9.0$)	C-8, C-5, C-10a
C-7	109.3	6.64 (1H, d, $J = 9.0$)	C-8a, C-5
C-8	153.1	11.18 (1H, s, OH-8)	C-7, C-8, C-8a
C-8a	107.4		
C-9	185.2		
C-9a	102.2		
C-10a	144.0		
C-1'	41.3		
C-2'	151.6	6.58 (1H, dd, $J = 17.0, 10.0$)	C-4, C-1', C-2', C-5'
C-3'	107.4	5.11 (1H, dd, $J = 17.0, 1.5$)	C-4, C-1', C-2', C-4'
		4.95 (1H, dd, $J = 10.0, 1.5$)	C-1', C-4', C-5'
C-4'	28.8	1.76 (3H, s)	C-1', C-2'
C-5'	28.8	1.76 (3H, s)	C-1'

Table I. NMR spectroscopic data (^{13}C at 125 MHz and ^1H at 500 MHz, acetone- d_6) of compound **1**.

corresponding to the molecular formula $C_{20}H_{16}O_6$. The UV spectral data is consistent with the xanthone chromophore with absorption maxima at 258, 280, 326 and 381 nm. The IR spectrum showed the presence of carbonyl and OH functionalities by absorption bands at 1582 and 3427 cm^{-1} , respectively.

In the ^1H NMR spectrum, the presence of a 1,1-dimethylallyl group was noted by the presence of proton signals at δ_{H} 6.48 (dd, $J = 17.0, 10.0\text{ Hz}$, H-2''), δ_{H} 5.03 (d, 17.0 Hz , H-3''*trans*), δ_{H} 4.95 (d, $J = 10.0\text{ Hz}$, H-3''*cis*) and two overlapping methyl peaks at δ_{H} 1.77. In the ^1H - ^1H COSY experiment (Table II) the proton signal at δ_{H} 6.48 (H-2'') was correlated with proton signals at δ_{H} 5.03 (H-3''*trans*) and δ_{H} 4.95 (H-3''*cis*), which further supported the presence of an allylic system. The HSQC spectrum showed the correlation between the allylic methine proton signal at δ_{H} 6.48 with the carbon signal at δ_{C} 148.1 (C-2''), while terminal allylic methylene proton signals at δ_{H} 5.03 and δ_{H} 4.95 correlated with a carbon signal at δ_{C} 109.1 (C-3''). The HMBC spectrum further showed the correlation of a dimethyl proton signal at δ_{H} 1.77 (H-4'' and H-5'') with the allylic carbon atom (δ_{C} 148.1, C-2''). Correlation of dimethyl allyl proton signals at δ_{H} 1.77 (CH_3 -4'' and CH_3 -5'') with the carbon signal at δ_{C} 113.5 (C-2) suggested the connectivity of the 1,1-dimethylallyl moiety to the xanthone

skeleton through C-2. In the ^1H NMR low field region, a chelated hydroxy proton signal at δ_{H} 13.94 (OH-1), which correlated with the carbon signals at δ_{C} 158.3 (C-1), δ_{C} 113.5 (C-2) and δ_{C} 104.9 (C-9a), was observed in the HMBC spectrum, thus confirming the position of the chelated hydroxy group at C-1.

The presence of two methine protons in the fused furan ring was noted from the ^1H NMR spectrum by the signals at δ_{H} 7.38 (d, $J = 2.0\text{ Hz}$, H-3') and δ_{H} 7.86 (d, $J = 2.0\text{ Hz}$, H-2'), which mutually correlated in the ^1H - ^1H COSY spectrum. The HSQC spectrum further allowed the assignment of the furanyl carbon signals at δ_{C} 103.9 and δ_{C} 144.1 to C-3' and C-2', respectively. The connectivity of the fused furan ring to the xanthone skeleton was further determined by the HMBC spectrum. The correlations between H-3' (δ_{H} 7.38) with the carbon signals at δ_{C} 148.7 (C-4a), δ_{C} 158.7 (C-3) and δ_{C} 144.1 (C-2') and the other methine proton, H-2' (δ_{H} 7.86), with the carbon signals at δ_{C} 158.7 (C-3), δ_{C} 109.3 (C-4) and δ_{C} 103.9 (C-3') suggested that the connection of the fused furan ring was at C-4 and C-3 of the xanthone skeleton.

In the ^1H NMR spectrum, two *ortho*-coupled aromatic proton signals (AB system) at δ_{H} 7.77 (d, $J = 8.5\text{ Hz}$) and δ_{H} 7.09 (d, $J = 8.5\text{ Hz}$) were observed. The former was assigned to H-8 due to its HMBC correlation with the carbon signals at δ_{C}

Table II. NMR spectroscopic data (^{13}C at 125 MHz and ^1H at 500 MHz, acetone- d_6) of compound **2**.

C	^{13}C chemical shift (ppm)	^1H chemical shifts (integration of proton, multiplicity, J in Hz)	COSY	HMBC correlations (H to C)
C-1	158.3			
C-2	113.5			C-1, C-2, C-9a
C-3	158.7			
C-4	109.3			
C4a	148.7			
C-5	132.6			
C-6	146.0			
C-7	113.7	7.09 (1H, d, $J = 8.5$)	H-8	C-8a, C-5
C-8	117.1	7.77 (1H, d, $J = 8.5$)	H-7	C-9, C-6, C-10a, C-8a
C-8a	114.4			
C-9	182.0			
C-9a	104.9			
	152.0			
C-1''	40.9			
C-2''	148.1	6.48 (1H, dd, $J = 17.0, 10.0$)	H-3'' <i>cis</i> , H-3'' <i>trans</i>	C-2, C-1'', C-4'', C-5''
C-3''	109.1	5.03 (1H, d, $J = 17.0$) 4.95 (1H, d, $J = 10.0$)	H-2'' H-2''	C-2'', C-1'' C-1''
C-4''	28.1	1.77 (3H, s)		C-2, C-2'', C-1'', C-4'', C-5''
C-5''	28.1	1.77 (3H, s)		C-2, C-2'', C-1'', C-4'', C-5''
C-2'	144.1	7.86 (1H, d, $J = 2.0$)	3'	C-3', C-4, C-3
C-3'	103.9	7.38 (1H, d, $J = 2.0$)	2'	C-4a, C-3, C-2'

182.0 (C-9), δ_C 146.0 (C-6) and δ_C 152.0 (C-10a), while the latter was assigned to H-7 due to its HMBC correlation signals at δ_C 114.4 (C-8a) and δ_C 132.6 (C-5). Comparison of respective data for proton and carbon signals in previously isolated xanthone compounds, containing a fused furanyl system in subelliptenone C and D (Iinuma *et al.*, 1995, 1996), supported the assignments. Based on these observations (see Table II), compound **2** was assigned as penangianaxanthone or 1,5,6-trihydroxy-2-(1',1'-dimethylallyl)furano(4',5':3,4)xanthone (Fig. 1).

From the biogenetic point of view, compounds **2**, **3** and **5** may have the common origin of compound **4**. Intramolecular cyclization of 3-OH with the 2-prenyl moiety led to compound **5**, while cyclization of 3-OH with an epoxidized 4-prenyl moiety led to pyranoxanthone **3** or a furanoxanthone intermediate which underwent further elimination of the isopropyl moiety to penangianaxanthone (**2**).

The cytotoxic activity test of the isolates against three cell lines, MCF-7 (hormone-dependent breast cancer), NCI-H460 (non-small lung cancer) and DU-145 (non-hormone-dependent prostate cancer), was conducted and the results are presented in Table III. All compounds except for friedelin and stigmasterol showed strong to weak activity towards MCF-7 cell lines. Xanthenes **2–5** showed strong cytotoxic activity towards MCF-7, NCI-H460 and DU-145 cell lines, with IC_{50} values ranging between 3.5 to 16.4 μM , while **1** showed only weak activity towards MCF-7 and NCI-H460, with IC_{50} values of 72.8 μM and 40.8 μM , respec-

tively. Compound **4** seemed to be the most cytotoxic among the isolates.

The most obvious structural difference between compounds **1** and **2–5** is the location of two hydroxy groups in ring B. While compound **1** has two hydroxy groups located *para* to each other (C-5 and C-8), the hydroxy groups in compounds **2–5** are located *ortho* (C-5 and C-6) to each other. This factor may therefore be responsible for the cytotoxic activity of these compounds. The presence of *ortho*-dihydroxy groups in the aromatic system of antioxidative compounds such as curcuminoids, cinnamonooids and feruloids has been emphasized in previous reports (Cai *et al.*, 2006; Kanski *et al.*, 2002; Mansouri *et al.*, 2005; Notarbartolo *et al.*, 2005; Sen *et al.*, 2005). The principle of antioxidative compounds in expressing cytotoxic activity has also been proposed for example in the case of curcumin (Notarbartolo *et al.*, 2005; Sen *et al.*, 2005). The presence of one or two prenyl moieties in ring A, either cyclized into furanyl or pyranyl rings, did not seem to affect the cytotoxic activity.

Experimental

General experimental procedures

NMR spectra were recorded on a Varian Unity 500 spectrometer using CD_3OD , $CDCl_3$ and acetone- d_6 as solvents. Chemical shifts are recorded in δ (ppm) with tetramethylsilane (TMS) as an internal reference. All mass spectra were taken under EI condition, using a PolarisQ mass spectrometer and a Finnigan MAT95XL-T HREIMS instrument. UV spectra were recorded on a CARY Conc 100 spectrometer in MeOH and IR spectra on an FTIR Perkin Elmer spectrometer 1650 in KBr disc.

Plant material

The plant material was collected from the Fraser Hill Forest Reserve (elevation: 1100 m above the sea level) in Pahang, Malaysia, and was classified by Mr. Shamsul Khamis, a resident botanist of the Institute of Bioscience, University Putra Malaysia. The sample (SK 95/01) was deposited in the herbarium of the Institute of Bioscience, University Putra Malaysia.

Extraction

The air-dried (1.5 kg) leaves of *G. penangiana* were ground to powder and soaked in methanol

Table III. Cytotoxic activity of compounds isolated from *G. penangiana*.

Compound	IC_{50} [μM] ^a		
	MCF-7	NCI-H460	DU-145
1	72.8 $\pm$ 2.6	40.8 $\pm$ 1.1	nd
2	16.4 $\pm$ 1.2	12.7 $\pm$ 1.4	12.2 $\pm$ 0.4
3	9.8 $\pm$ 0.8	12.6 $\pm$ 1.2	11.7 $\pm$ 0.2
4	7.8 $\pm$ 0.1	3.5 $\pm$ 0.9	6.6 $\pm$ 0.6
5	7.6 $\pm$ 0.2	5.0 $\pm$ 0.7	7.6 $\pm$ 0.4
Friedelin	na	nd	nd
Stigmasterol	na	nd	nd

^a Results are expressed as IC_{50} values $\pm$ SD of three experiments performed in four replicates; MCF-7, human breast cancer (Re+); NCI-H460, non-small human lung cancer; DU-145, human prostate cancer; na, not active; nd, not determined.

(MeOH) for 2 d at room temperature and the extract was filtered. The solvent was removed under reduced pressure. The extraction was repeated for 3 times and the combined MeOH extract (77 g) was partitioned into hexane, DCM, EA and butanol to yield 4.2 g, 12.3 g, 5.2 g and 35.9 g, respectively, of the dried fractionated extracts.

Isolation of compounds **1**, **2**, **3**, **4** and **5**

Approx. 4.2 g of the hexane-fractionated extract was subjected to gel permeation chromatography (Sephadex LH-20, 2.5 cm $\phi \times 40$ cm) with methanol/chloroform (1:1) as an eluant, to give eight (20 ml) fractions. Fractions 1–3 were combined and further purified to yield 10 mg of friedelin and 2 mg of stigmasterol. The combined fractions 4–8 (1.8 g) were subjected to silica gel column chromatography (2 cm $\phi \times 40$ cm) and eluted with hexane/EA/MeOH mixtures, in ascending polarity manner, to give 30 (10 ml) fractions. The fractions were combined into 4 fractions based on their TLC profile. Fraction 3 (96.9 mg) was subjected to further silica gel column chromatography (1 cm $\phi \times 30$ cm) eluting with hexane/EA (8:2) to yield 4 mg of **1**. Fraction 4 (41.5 mg) was subjected onto a C-18 reverse phase silica column and eluted with MeOH/water mixtures to give **3** (8.3 mg).

The DCM fraction (12.3 g) was subjected to a silica gel column (10 cm $\phi \times 30$ cm) and eluted in ascending polarity manner with hexane/DCM/EA/MeOH mixtures to give 9 combined fractions (A–I) based on their TLC pattern. Fraction E (6.8 g) was subjected to gel permeation column chromatography (Sephadex LH-20, 2.5 cm $\phi \times 30$ cm) with a methanol/chloroform (1:1) mixture as eluant to give fifteen (20 ml) fractions. The combined fractions 9–15 (408 mg) were subjected to C-18 reverse phase column chromatography (2.5 cm $\phi \times 30$ cm) using MeOH/water as eluant to afford 20.4 mg of compound **2**. The combined fractions 4–8 (4 g) were subjected to reverse phase column chromatography (4.0 cm $\phi \times 30$ cm) and eluted with a MeOH/water mixture in descending manner to afford compounds **2** (40 mg) and **5** (80 mg). Fraction D (1.7 g) was also subjected to C-18 reverse phase column chromatography (2 cm $\phi \times 30$ cm) and eluted with MeOH/water to afford 67.7 mg of the yellow amorphous solid of compound **4**.

4-(1,1-Dimethylprop-2-enyl)-1,3,5,8-tetrahydroxyxanthone (1): Yellow amorphous solid, m.p. 220–

222 °C. – IR (KBr): $\nu_{\max}$ = 3392 (OH stretching), 2922 (CH stretching), 2848 (sp^3 CH stretching), 1585 (carbonyl stretching), 1031 cm^{-1} (out of plane bending of alkene). – UV (MeOH): $\lambda_{\max}$ (log ϵ) = 226 (3.88), 256 (3.94), 281 (3.76), 325 nm (3.59). – HREIMS: m/z = 328.3269 (calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_6$: 328.3246). – MS: m/z = 328 [M^+] (32), 313 [M^+ -methyl] (100), 285 (46), 273 (26), 257 (38), 244 (18), 149 (24), 129 (22), 105 (18), 91 (36), 83 (68), 76 (28), 56 (24), 46 (34), 44 (79). – ^1H NMR (acetone- d_6 , 500 MHz) and ^{13}C NMR (acetone- d_6 , 125 MHz): see Table I.

Penangianaxanthone (2): Yellow fluffy crystals, m.p. 216–218 °C. – IR (KBr): $\nu_{\max}$ = 3427 (OH stretching), 2900 (CH stretching), 2830 (CH stretching), 1582 (carbonyl stretching), 1414, 1332, 1314, 1284, 1239, 1215, 1174, 1132, 1095 cm^{-1} . – UV (MeOH): $\lambda_{\max}$ (log ϵ) = 258 (4.25), 280 (4.05), 326 (3.82), 381 (3.55). – HREIMS: m/z = 352.0960 (calcd. for $\text{C}_{20}\text{H}_{16}\text{O}_6$: 352.0946). – MS: m/z = 352 [M^+] (42), 336 [352-methyl-H] (100), 318 [336- H_2O] (56), 297 (90), 280 (26), 253 (6), 189 (6), 153 (6), 147 (10), 97 (16), 81 (22), 57 (24). – ^1H NMR (acetone- d_6 , 500 MHz) and ^{13}C NMR (acetone- d_6 , 125 MHz): see Table II.

Cudratricusxanthone H (3): Yellow needles, m.p. 174–176 °C (lit. m.p. 175 °C (Kanski *et al.*, 2002)). – MS, ^1H NMR, ^{13}C NMR data are consistent with cudratricusxanthone H (Zou *et al.*, 2004).

Macluraxanthone C (4): Yellow amorphous solid, m.p. 204 °C (lit. m.p. is not available). – MS, ^1H NMR, ^{13}C NMR data are consistent with macluraxanthone C (Groweiss and Boyd, 2000).

Gerontoxanthone C (5): Yellow amorphous solid, m.p. 205–207 °C (lit. m.p. 204–206 °C). – MS, ^1H NMR, ^{13}C NMR data are consistent with gerontoxanthone C (Chang *et al.*, 1989).

Friedelin: White needles, m.p. 260–262 °C (lit. m.p. 262–265 °C). – MS, ^1H NMR, ^{13}C NMR data are consistent with friedelin (Queiroga *et al.*, 2000).

Stigmasterol: White needles, m.p. 168–170 °C (lit. m.p. 170 °C) (Forgo and Kover, 2004).

In vitro test for cytotoxic activity (MTT assay)

Three types of human tumour cell lines, DU-145, MCF-7 and NCI-H460, were used in the cytotoxicity study. Crude extracts or compounds were tested at 0.1 µg/ml, 1 µg/ml, 10 µg/ml and 100 µg/ml concentrations and each concentration was performed in 4 replicates. The assay was conducted according to the previously described protocol (Stanslas *et al.*, 2000).

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- Ali S., Goundar R., Sotheeswaran S., Beaulieu C., and Spino C. (2000), Benzophenones of *Garcinia pseudo-guttifera* (Clusiaceae). *Phytochemistry* **53**, 281–284.
- Burkill I. H. (1966), A Dictionary of the Economic Products of the Malay Peninsula. Ministry of Agriculture and Cooperation, Kuala Lumpur, Malaysia.
- Cai Y.-Z., Mei S., Jie X., Luo Q., and Corke H. (2006), Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. *Life Sci.* **78**, 2872–2888.
- Cao S. G., Wu X. H., Sim K. Y., Tan B. K. H., Pereira J. T., Wong W. H., Hew N. F., and Goh S. H. (1998), Cytotoxic caged tetraprenylated xanthonoids from *Garcinia gaudichaudii* (Guttiferae). *Tetrahedron Lett.* **39**, 3353–3356.
- Chang C.-H., Lin C.-C., Hattori M., and Namba T. (1989), Four prenylated xanthonoids from *Cudrania cochinchinensis*. *Phytochemistry* **28**, 595–598.
- Chiang Y. M., Kuo Y. H., Oota S., and Fukuyama Y. (2003), Xanthonoids and benzophenones from the stems of *Garcinia multiflora*. *J. Nat. Prod.* **66**, 1070–1073.
- Chomnawang M. T., Surassmo S., Nukoolkarn V. S., and Gritsanapan W. (2005), Antimicrobial effects of Thai medicinal plants against acne-inducing bacteria. *J. Ethnopharmacol.* **101**, 330–333.
- Forgo P. and Kover K. E. (2004), Gradient enhanced selective experiments in the ¹H NMR chemical shift assignment of the skeleton and side-chain resonances of stigmasterol, a phytosterol derivative. *Steroids* **69**, 43–50.
- Govindachari T. R., Kalyanaraman P. S., Muthukumaraswamy N., and Pai B. R. (1971), Xanthonoids of *Garcinia mangostana* Linn. *Tetrahedron* **27**, 3919–3926.
- Grosvenor P. W., Gothard P. K., McWilliam N. C., Supriyono A., and Gray D. O. (1995), Medicinal plants from Riau Province, Sumatra, Indonesia. Part 1: Uses. *J. Ethnopharmacol.* **45**, 75–95.
- Groweiss A. and Boyd M. R. (2000), HIV-inhibitory prenylated xanthonoids and flavones from *Maclura tinctoria*. *J. Nat. Prod.* **63**, 1537–1539.
- Iinuma M., Hedeki T., Toshiyuki T., Fujio A., and Ryoyu S. (1995), Two new xanthonoids from the root bark of *Garcinia subelliptica*. *Heterocycles* **40**, 279–284.
- Iinuma M., Ito T., Tosa H., Tanaka T., and Riswan S. (1996), Five new xanthonoids from *Garcinia dulcis*. *J. Nat. Prod.* **59**, 472–475.
- Ito C., Itoigawa M., Takakura T., Ruangrunsi N., Enjo F., Tokuda H., Nishino H., and Furukawa H. (2003), Chemical constituents of *Garcinia fusca*: Structure elucidation of eight new xanthonoids and their cancer chemopreventive activity. *J. Nat. Prod.* **66**, 200–205.
- Kanski J., Aksenova M., Stoyanova A., and Butterfield D. A. (2002), Ferulic acid antioxidant protection against hydroxyl and peroxy radical oxidation in synaptosomal and neuronal cell culture systems *in vitro*: structure-activity studies. *J. Nat. Biochem.* **13**, 273–281.
- Lin Y. M., Anderson H., Flavin M. T., Pai Y. H. S., Mata-Greenwood E., Pengsuparp T., Pezzuto J. M., Schinazi R. F., Hughes S. H., and Chen F. C. (1997), *In vitro* anti-HIV activity of biflavonoids isolated from *Rhus succedanea* and *Garcinia multiflora*. *J. Nat. Prod.* **60**, 884–888.
- Mackeen M. M., Ali A. M., Lajis N. H., Kawazu K., Hassan Z., Amran M., Habsah M., Mooi L. Y., and Mohamed S. M. (2000), Antimicrobial, antioxidant, anti-tumour-promoting and cytotoxic activities of different plant part extracts of *Garcinia atroviridis* Griff. ex T. Anders. *J. Ethnopharmacol.* **72**, 395–402.
- Mansouri A., Makris D. P., and Kefalas P. (2005), Determination of hydrogen peroxide scavenging activity of cinnamic and benzoic acids employing a highly sensitive peroxyoxalate chemiluminescence-based assay: Structure-activity relationships. *J. Pharm. Biomed. Anal.* **39**, 22–26.
- Matsumoto K., Akao Y., Kobayashi E., Ito T., Ohguchi K., Tanaka T., Iinuma M., and Nozawa Y. (2003a), Cytotoxic benzophenone derivatives from *Garcinia* species display a strong apoptosis-inducing effect against human leukemia cell lines. *Biol. Pharm. Bull.* **26**, 569–571.
- Matsumoto K., Akao Y., Kobayashi E., Ohguchi K., Ito T., Tanaka T., Iinuma M., and Nozawa Y. (2003b), Induction of apoptosis by xanthonoids from mangosteen in human leukemia cell lines. *J. Nat. Prod.* **66**, 1124–1127.
- Nakatani K., Nakahata N., Arakawa T., Yasuda H., and Ohizumi Y. (2002), Inhibition of cyclooxygenase and

- prostaglandin E2 synthesis by α -mangostin, a xanthone derivative in mangosteen, in C6 rat glioma cells. *Biochem. Pharmacol.* **63**, 73–79.
- Notarbartolo M., Poma P., Perri D., Dusonchet L., Cervello M., and D'Alessandro N. (2005), Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF- κ B activation levels and in IAP gene expression. *Cancer Lett.* **224**, 53–65.
- Peres V., Nagem T. J., and de Oliveira F. F. (2000), Tetraoxygenated naturally occurring xanthenes. *Phytochemistry* **55**, 683–710.
- Permana D., Lajis N. H., Mackeen M. M., Ali A. M., Aimi N., Kitajima M., and Takayama H. (2001), Isolation and bioactivities of constituents of the roots of *Garcinia atroviridis*. *J. Nat. Prod.* **64**, 976–979.
- Queiroga C. L., Silva G. F., Dias P. C., Possenti A., and de Carvalho J. E. (2000), Evaluation of the antiulcerogenic activity of friedelan-3[β]-ol and friedelin isolated from *Maytenus ilicifolia* (Celastraceae). *J. Ethnopharmacol.* **72**, 465–468.
- Rukachaisirikul V., Kamkaew M., Sukavisit D., Phongpaichit S., Sawangchote P., and Taylor W. C. (2003), Antibacterial xanthenes from the leaves of *Garcinia nigrolineata*. *J. Nat. Prod.* **66**, 1531–1535.
- Sen S., Sharma H., and Singh N. (2005), Curcumin enhances vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. *Biochem. Biophys. Res. Commun.* **331**, 1245–1252.
- Stanslas J., Hagan D. J., Ellis M. J., Turner C., Carmichael J., Ward W., Hammonds T. R., and Stevens M. F. G. (2000), Antitumor polycyclic acridines. 7. Synthesis and biological properties of DNA affinic tetra- and pentacyclic acridines. *J. Med. Chem.* **43**, 1563–1572.
- Thoison O., Fahy J., Dumontet V., Chiaroni A., Riche C., Van Tri M., and Sevenet T. (2000), Cytotoxic prenylxanthenes from *Garcinia bracteata*. *J. Nat. Prod.* **63**, 441–446.
- Tona L., Ngimbi N. P., Tsakala M., Mesia K., Cimanga K., Apers S., De Bruyne T., Pieters L., Totte J., and Vlietinck A. J. (1999), Antimalarial activity of 20 crude extracts from nine African medicinal plants used in Kinshasa, Congo. *J. Ethnopharmacol.* **68**, 193–203.
- Waterman P. G. and Hussain R. A. (1983), Systematic significance of xanthenes, benzophenones and biflavonoids in *Garcinia*. *Biochem. Syst. Ecol.* **11**, 21–28.
- Zou Y.-S., Hou A.-J., Zhu G.-F., Chen Y.-F., Sun H.-D., and Zhao Q.-S. (2004), Cytotoxic isoprenylated xanthenes from *Cudrania tricuspidata*. *Bioorg. Med. Chem.* **12**, 1947–1953.