



## Antimalarial xanthenes from *Calophyllum caledonicum* and *Garcinia vieillardii*

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### Abstract

The antimalarial activity of 22 xanthenes against chloroquino-resistant strains of *Plasmodium falciparum* was evaluated. Natural caloxanthone C (**1**), demethylcalabaxanthone (**2**), calothwaitesixanthone (**3**), calozeyloxanthone (**4**), dombakinaxanthone (**5**), macluraxanthone (**6**), and 6-deoxy- $\gamma$ -mangostin (**7**) were isolated from *Calophyllum caledonicum*. 1,6-dihydroxyxanthone (**8**), pancixanthone A (**9**), isocudranixanthone B (**10**), isocudranixanthone A (**11**), 2-deprenylrheediaxanthone B (**12**) and 1,4,5-trihydroxyxanthone (**13**) were isolated from *Garcinia vieillardii*. Moreover, synthetic compounds (**14–22**) are analogues or intermediates of xanthenes purified from *Calophyllum caledonicum* (Oger J.M., Morel C., Hélesbeux J.J., Litaudon M., Séraphin D., Dartiguelongue C., Larcher G., Richomme P., Duval O. 2003. First 2-Hydroxy-3-Methylbut-3-Enyl substituted xanthenes isolated from Plants: structure elucidation, synthesis and antifungal activity. *Natural Product Research* 17(3), 195–199; Hélesbeux J.J., Duval O., Dartiguelongue C., Séraphin D., Oger J.M., Richomme P., 2004. Synthesis of 2-hydroxy-3-methylbut-3-enyl substituted coumarins and xanthenes as natural products. Application of the Schenck ene reaction of singlet oxygen with *ortho*-prenylphenol precursors. *Tetrahedron* 60(10), 2293–2300). The relationship between antimalarial activity and

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molecular structure of xanthenes has also been explored. The most potent xanthenes (2), (3) and (7) (IC<sub>50</sub> = c.a. 1.0 µg/mL) are 1,3,7 trioxxygenated and prenylated on the positions 2 and 8.

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*Keywords:* Xanthenes; Antimalarial activity; *Plasmodium falciparum*; Chloroquinoreistance; *Calophyllum caledonicum*; *Garcinia vieillardii*

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## Introduction

Malaria is a disease of enormous importance by any standard of measure and the recent emergence and rapid spread of chloroquino-resistant strains of *Plasmodium falciparum* threaten to increase the annual death toll. As a result, there is a great need for development of novel antimalarial drugs. Out of the four species of *Plasmodium* that affects humans, *Plasmodium falciparum* is the most prevalent and pathogenic. Terpens, alcaloids and oxygenated heterocycles are potentially active against malaria (Go, 2003). The *Calophyllum* and *Garcinia* species of the Clusiaceae family are a well-known source of phenolic secondary metabolites, especially xanthenes. In the last few years, a huge number of prenylated and non-prenylated xanthenes have been identified from those species (Sultanbawa, 1980; Bennett and Lee, 1988). In the present study, we focused our attention on two plants native to New-Caledonia: *Garcinia vieillardii*, from which we first isolated antioxidant xanthenes (Hay et al., 2004) and *Calophyllum caledonicum*, a tall tree locally known as “Tamanou des montagnes” whose latex is used as a diuretic. As part of our ongoing project on the isolation of natural compounds from Clusiaceae and the assessment of their biological activity, we recently characterized from *Calophyllum caledonicum* new antifungal xanthenes and chroman acids inhibiting pea seeds mitochondria (Morel et al., 2000; Morel et al., 2002; Hay et al., 2003). We now report the evaluation of the antiplasmodial activity of natural xanthenes isolated from both *Calophyllum caledonicum* and *Garcinia vieillardii* along with some synthetic derivatives prepared during the project dealing with the total synthesis of original natural xanthenes.

## Methods

### *Plant material*

The root bark of *C. caledonicum* was collected from the “Rivière bleue” area, New-Caledonia, during September 1999. A herbarium specimen is deposited at the Laboratoire des Plantes Médicinales (CNRS) at Noumea in New-Caledonia, under reference LIT 733R. The stem bark of *G. vieillardii* was collected in January 2001 in the Froin Forest, on the Mandjélia’s massif located in the North of New Caledonia. A specimen (LIT 1298) is maintained at the laboratoire des Plantes Médicinales in Noumea.

### *Analytical material and methods*

UV spectra were recorded on a Helios α V1.08 UNICAM spectrophotometer. 1H, 13C and 2D NMR experiments (COSY, NOE, HMBC, HMQC) spectra were recorded on a Bruker Avance DRX 500 MHz.

Mass spectrometry analysis were performed on a JMS-700 (JEOL LTD, Akishima, Tokyo, Japan) double focussing mass spectrometer with reversed geometry, equipped with a pneumatically assisted electrospray ionization (ESI) source. Silica gel 60 (Macherey-Nagel, 0.04–0.063 mm) was used for column chromatography, precoated Silica gel (Macherey-Nagel, SIL G25 UV254, 0.25 mm) were used for analytical TLC.

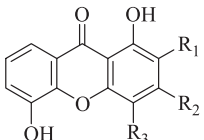
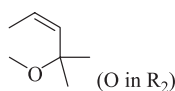


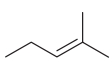
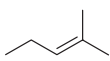
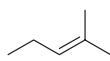
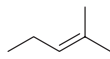
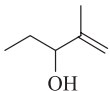
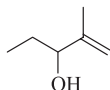
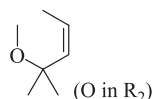
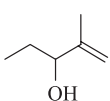
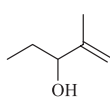
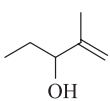
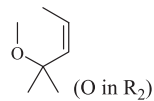
#### *Extraction, isolation and identification of xanthenes*

5.0 g of the hexane-soluble extract were subjected to a High-speed Counter-Current Chromatography (HSCCC) using hexane-methanol-water (6:5:1) as the solvent system. The lower aqueous phase was used as stationary phase and the upper hexane phase was pumped from the head of the column to the tail (flow rate: 1.5 mL/min, fraction collection time: 6 min, rotation: 450 rpm, column volume = 400 mL). The elutes were monitored by TLC with hexane-EtOAc (60:40) as the eluent. This separation afforded 8 fractions (1440 mL). The third (333 mL to 693 mL) fraction (1200 mg) was chromatographed over 30 g of silica gel eluting with cyclohexane-EtOAc (99:1 to 40:60), then CH<sub>2</sub>Cl<sub>2</sub>-EtOAc (50:50). This yielded caloxanthone C (**1**) (1.4 mg, 0.028%) (Iinuma et al., 1994a), demethylcalabaxanthone (**2**) (12.6 mg, 0.25%) (Ampofo and Waterman, 1986), calothwaitesixanthone (**3**) (27.6 mg, 0.55%) (Dharmaratne et al., 1986), and calozeyloxanthone (**4**) (9.4 mg, 0.19%) (Gunasekera et al., 1981). Further preparative TLC using toluene/ether (8/2) as the eluent yielded dombakinaxanthone (**5**) (4.0 mg, 0.08%, 0.46) (Dharmaratne and Wijesinghe, 1997). The seventh fraction (376 mg) was subjected to column chromatography over 15 g of silica gel eluting with cyclohexane-EtOAc (97:3 to 70:30), then CH<sub>2</sub>Cl<sub>2</sub>-EtOAc (85:15 to 75:25), and finally CH<sub>2</sub>Cl<sub>2</sub>-MeOH (98:2 to 80:20). After a preparative TLC using hexane/EtOAc (7/3) macluraxanthone (**6**) (26 mg, 0.52%, 0.53) (Iinuma et al., 1994b) and 6-deoxy- $\gamma$ -mangostin (**7**) (2.0 mg, 0.04%, 0.64) (Dharmaratne et al., 1986). The powdered stem bark (1.4 kg) of *G. vieillardii* was extracted successively with cyclohexane (6L), CH<sub>2</sub>Cl<sub>2</sub> (6L) and EtOAc (6L) in a Soxhlet apparatus. Concentration under reduced pressure gave 62 g (4.4%) of cyclohexane extract, 9.2 g (0.6%) of CH<sub>2</sub>Cl<sub>2</sub> extract, and 20 g (1.4%) of an EtOAc extract. CH<sub>2</sub>Cl<sub>2</sub> extract was subjected to MPLC over Silica gel using cyclohexane-EtOAc (100:0 to 20:80) and then MeOH-EtOAc (10:90 to 30:70) and afforded 56 fractions. Fractions 5 to 7 (200 mg) were combined and further chromatographed over Si gel (elution with Cyclohexane-EtOAc 100:0 to 0:100 and EtOAc-MeOH 80:20) and yielded 25 fractions. Further semi-preparative HPLC using an inverse phase column (Kromasil, 5  $\mu$ m 60 Å, 250\*10) with a water-CH<sub>3</sub>CN gradient yielded 1,6-dihydroxyxanthone (**8**) (10 mg, 0.11%, Rt 17.0 min) (Yang et al., 2001) and pancixanthone A (**9**) (1.3 mg, 0.014%, Rt 23.5 min) (Ito et al., 1996). Crystallization of the fourteenth fraction (70 mg) in CH<sub>3</sub>CN gave isocudranixanthone B (**10**) (50 mg, 0.54%) (Kobayashi et al., 1997). Fractions 17 (51 mg) was subjected to semi-preparative HPLC using a normal phase column (Kromasil, 5  $\mu$ m 60 Å, 250\*10) with a EtOAc-CHCl<sub>3</sub> gradient to yield isocudranixanthone A (**11**) (2.0 mg, 0.021%, Rt 54.0 min) (Kobayashi et al., 1997). The fractions 26 to 29 (220 mg) were combined and chromatographed over Si gel (Cyclohexane-EtOAc 100:0 to 0:100) to yield 2-deprenylrheediaxanthone B 12 (5.0 mg, 0.054%) (Rath et al., 1996) and 1,4,5-trihydroxyxanthone 13 (1.7 mg, 0.018%,  $[\alpha_D]^{25} = 0^\circ$ ) (Minami et al., 1995).

#### *Synthesis of xanthenes*

The methodology of the xanthone synthesis has been described previously (Oger et al., 2003; Hélesbeux et al., 2004).

Table 1  
1,3,5-trioxygenated xanthone derivatives (1, 9, 14–22)

			
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
Caloxanthone C (1)	 (O in R <sub>2</sub> )		
Pancixanthone A (9)	H	OH	
(14)	H	OH	H
(15)		OH	H
(16)		OH	
(17)	H	OH	
(18)		OH	H
(19)	H	OH	
(20)	H	 (O in R <sub>2</sub> )	
(21)		OH	
(22)		 (O in R <sub>2</sub> )	

*In vitro P. falciparum* culture and drug assays

*P. falciparum* strain FcB1/colombia was maintained continuously in culture on human erythrocytes as described by Trager and Jensen (Trager and Jensen, 1976). In vitro antiplasmodial activity was determined using a modification of the semi-automated microdilution technique of Desjardins et al. (Desjardins et al., 1979). Stock solutions of chloroquine diphosphate and test compounds were prepared in sterile, distilled water and DMSO, respectively. Drug solutions were serially diluted with culture medium and added to asynchronous parasite cultures (1% parasitemia and 1% final hematocrite) in 96-well plates for 24 h, at 37 °C, prior to the addition of 0.5 μCi of [3H]hypoxanthine (1 to 5 Ci/mmol; Amersham, Les Ulis, France) per well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50% inhibition (IC<sub>50</sub>) was obtained from the drug concentration-response curve and the results were expressed as the mean of the standard deviations determined from several independent experiments. The DMSO concentration never exceeded 0.1% and did not inhibit the parasite growth.

**Results and discussion**

Twenty two xanthenes isolated from *Calophyllum caledonicum* or *Garcinia vieillardii* (Tables 1–3 and Fig. 1) have been tested on a chloroquino-resistant strain of *Plasmodium falciparum*. The results of these tests are presented in Table 4. The antimalarial activity of compounds (1) to (22) may be related to some of their structural features. The 1,3,5-trihydroxyxanthone (14) showed the lowest activity (IC<sub>50</sub> = 24.7 μg/mL) in the 1,3,5-trioxygenated xanthone series (Table 1). The addition of an isopentenyl chain

Table 2  
1,3,5,6-tetraoxygenated xanthone derivatives (6, 10–12)

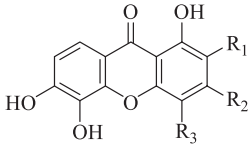
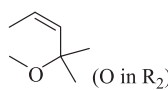



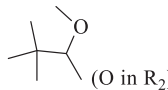
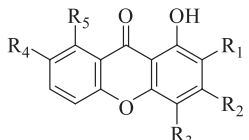

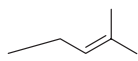
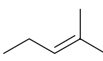

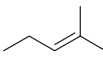
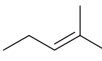
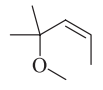
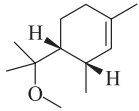
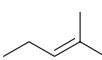
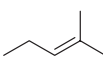
			
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
Macluraxanthone (6)	 (O in R <sub>2</sub> )		
Isocudraniaxanthone B (10)	H	OMe	
Isocudraniaxanthone A (11)	H	OH	
2-deprenylrheediaxanthone B (12)	H	 (O in R <sub>2</sub> )	

Table 3  
1,3,7-trioxygenated xanthone derivatives (2–5, 7)

					
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
Dombakinoxanthone (2)		(O in R <sub>2</sub> )		OH	
Demethylcalabaxanthone (3)		(O in R <sub>2</sub> )	H	OH	
Calothwaitesixanthone (4)		OH	H		(O in R <sub>4</sub> )
Calozeyloxanthone (5)	H	OH	H		(O in R <sub>4</sub> )
6-Deoxy-γ-mangostin (7)		OH	H	OH	

in position 2 and/or 4 (**15–17**) increased the activity with the best result when both positions were substituted (**16**),  $IC_{50} = 1.8 \mu\text{g/mL}$ ). The exchange of the 3-methylbut-2-enyl chain with a 1,1-dimethylallyl chain in position 4 (**9**),  $IC_{50} = 1.6 \mu\text{g/mL}$  resulted in a slight increase of activity in comparison with the regioisomer **17** ( $IC_{50} = 4.1 \mu\text{g/mL}$ ). When the 3-methylbut-2-enyl chain is oxidized into 2-hydroxy-3-methylbut-3-enyl, no significant variation of activity was observed for a chain in position 2 (**18**),  $IC_{50} = 3.7 \mu\text{g/mL}$  or 4 (**19**),  $IC_{50} = 6.6 \mu\text{g/mL}$ ) whereas the transformation in both positions, 2 and 4 (**21**),  $IC_{50} = 14.8 \mu\text{g/mL}$  were disfavoured. Finally, in that series, similar results were obtained for compound (**9**) ( $IC_{50} = 1.6 \mu\text{g/mL}$ ) with a 1,1-dimethylallyl group in the position 4 and compound (**16**) ( $IC_{50} = 1.8 \mu\text{g/mL}$ ) with a 3-methylbut-2-enyl in the positions 2 and 4. The cyclisation into a pyranic ring (**20**) seemed to be important to increase the potency of the molecule ( $IC_{50} = 1.4 \mu\text{g/}$

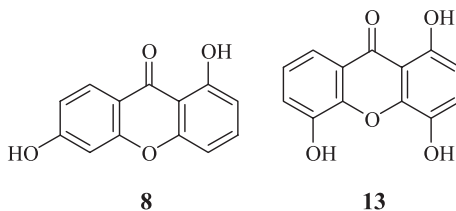


Fig. 1. 1,6-dihydroxyxanthone (**8**) and 1,4,5-trihydroxyxanthone (**13**).

Table 4  
Antimalarial activity of synthetic or natural xanthenes from *C. caledonicum*, *G. vieillardii*<sup>a</sup>

	IC <sub>50</sub> ± SD (µg/mL)		IC <sub>50</sub> ± SD (µg/mL)
(1)	1.3 ± 0.5	(13)	3.5 ± 0.3
(2)	0.9 ± 0.2	(14)	24.7 ± 2.1
(3)	1.0 ± 0.1	(15)	4.9 ± 1.5
(4)	2.7 ± 0.8	(16)	1.8 ± 0.7
(5)	4.4 ± 0.2	(17)	4.1 ± 0.5
(6)	1.9 ± 0.3	(18)	3.7 ± 0.4
(7)	0.8 ± 0.1	(19)	6.6 ± 0.8
(8)	4.2 ± 2.0	(20)	1.4 ± 0.4
(9)	1.6 ± 0.4	(21)	14.8 ± 1.5
(10)	3.2 ± 0.6	(22)	5.4 ± 1.8
(11)	2.3 ± 0.6	chloroquine <sup>b</sup>	0.03
(12)	3.5 ± 0.3		

SD is the standard error.

<sup>a</sup> IC<sub>50</sub> values were obtained from triplicate experiments.

<sup>b</sup> Reference compound.

mL). This result was confirmed when the pyranic ring was introduced with a secondary alcohol chain in position 2 ((22), IC<sub>50</sub> = 5.4 µg/mL versus (21), IC<sub>50</sub> = 14.8 µg/mL).

For 1,3,5,6 tetraoxygenated xanthenes (6, 10, 11, 12) (Table 2), the best potency is obtained with a pyranic ring and a 1,1-dimethylallyl chain in position 4 ((6), IC<sub>50</sub> = 1.9 µg/mL). In our xanthenes series, the antiplasmodic best result was obtained among the five other xanthenes, oxygenated in positions 1, 3 and 7 (5, 2, 3, 4, 7) (Table 3). They combined one pyranic ring and one isopentenyl group, or two isopentenyl groups in positions 2 and 8 (with the best result for 7, IC<sub>50</sub> = 0.8 µg/mL). Finally, the 1,4,5-trihydroxyxanthone (13) (IC<sub>50</sub> = 3.5 µg/mL) and 1,6-dihydroxyxanthone (8) (IC<sub>50</sub> = 4.2 µg/mL) showed better activities compared to the 1,3,5-trihydroxylated structure (14) (IC<sub>50</sub> = 24.7 µg/mL) (Fig. 1).

## Conclusion

As a conclusion, twenty-two tested xanthenes showed moderate activity on a chloroquino-resistant strain of *Plasmodium falciparum*. The natural and synthetic approaches developed here to isolate new xanthone structures, in association with the biological evaluation, is providing interesting clues in the step-by-step improvement of the antiplasmodial activity. Firstly, the position of the hydroxyl groups appears to be important as indicated by the differences of activity observed in the present report. Indeed, oxygenation on the three positions 1, 3 and 7 seems to improve the antimalarial activity. Secondly, the substitution by a 1,1-dimethylallyl chain, or the presence of an additional pyranic ring appear to be factors for good activity (1, 6, 9, 20) as well as the substitution with two isopentenyl chains (7, 16), or the combination of one isopentenyl chain and a pyranic ring (5, 3). Lastly, hydroxylation of the prenyl side chain is not required for higher activity.

So far, the antimalarial potency of 2,3,4,5,6-pentahydroxyxanthone correlated well with its ability to inhibit in vitro heme polymerization, suggesting that this compound exerts its antimalarial action by preventing hemozoin formation (Ignatuschenko et al., 1997). Moreover, the in vivo antimalarial activity of some hydroxyxanthenes has been recently demonstrated for the first time (Fotie et al., 2003). Earlier

this year, Portela et al. concluded that electronic features rather than steric factors control primarily the inhibitory activity of xanthenes against hematin aggregation, and thus their potential antimalarial activity (Portela et al., 2004).

In addition to the study of Ignatuschenko et al. regarding the mode of action of xanthenes culminating in their antimalarial activity (Ignatuschenko et al., 1997), the present work may help to design new structures for the discovery of efficient xanthonic antimalarial drugs.

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