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Antiplasmodial benzophenones from the trunk latex of *Moronobea coccinea* (Clusiaceae)

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ABSTRACT

In an effort to find antimalarial drugs, a systematic *in vitro* evaluation on a chloroquine-resistant strain of *Plasmodium falciparum* (FcB1) was undertaken on sixty plant extracts collected in French Guiana. The methanol extract obtained from the latex of *Moronobea coccinea* exhibited a strong antiplasmodial activity (95% at 10 μg/ml). The phytochemical investigation of this extract led to the isolation of eleven polycyclic polyprenylated acylphloroglucinols (PPAPs), from which eight showed potent antiplasmodial activity with IC50 ranged from 3.3 μM to 37.2 μM.

1. Introduction

With over 300 millions of new cases each year, resulting in more than one million deaths annually, malaria remains one of the most important infectious disease of the developing world. Fatal cases are generally caused by the most virulent human malaria parasite, *Plasmodium falciparum*. Symptoms occur during the asexual parasite development in human red blood cells. Current clinical treatment involves the use of inexpensive antimalarial drugs such as chloroquine and their derivatives. However, the emergence of resistant populations of *Plasmodium* sp. to this class of drugs has rendered most of them ineffective (Laufer and Plowe, 2004). Since few years, World Health Organization recommends the use of a combinatorial therapy to limit resistance phenomenon. The "Artemisinin Combination Therapy" is currently the most effective treatment. Although no clear clinical resistance was yet reported, there are accumulating evidences for increasing artemisinin resistance *in vitro* of *P. faciparum* isolates (Gay et al., 1994; Jambou et al., 2005). There is therefore an urgent need for the discovery of new efficient antimalarial drugs to cure this disease and to prevent the emergence of resistance.

In an effort to find new naturally antimalarial drugs, we screened a series of sixty plant extracts prepared from various species belonging to the French Guiana biodiversity. The results of this screening led us to investigate the latex of *Moronobea coccinea* Aubl. (Clusiaceae). Indeed, ethyl acetate extracts of trunk bark and fruits, having a rich latex secretion system, exhibited a strong antiplasmodial activity (75% and 83% of inhibitory growth at 10 μg/ml, respectively) whereas the leave and trunk root extracts did not show any significant activity (4% and 5% of inhibitory growth at 10 μg/ml, respectively). The latex was therefore collected separately by scraping the trunk bark. The methanol extract of the latex showed 95% of inhibitory growth at 10 μg/ml. In this report we described the isolation, structure elucidation and biological activities of eleven new polycyclic polyprenylated acylphloroglucinols (PPAPs) (**3–8, 10–14**) along with the known isogarcinol, cycloxanthochymol and garcinol (**1, 2, 9,** respectively).

The Clusiaceae family consists of 40 genera and 1200 species essentially mostly tropical. In French Guyana several species are well-known in the manufacture of hulls, for the quality of their wood *(Calophyllum brasiliense)* and for the healing properties of their latex (*Mahurea, Vismia, Symphonia* and *Moronobea* spp.) used traditionally for their effectiveness against dermatoses (Grenand et al., 2004). From a phytochemical point of view, this family is known to be a rich source of PPAPs with a large spectrum

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of biological activities (Cuesta-Rubio et al., 2005). However, to our knowledge only guttiferone A has been screened for its antiplasmodial activity (Ngouela et al., 2006). The genus *Moronobea* consists of some seven species strictly distributed in Amazonia. Only *Moronobea pulchra* has been investigated and the geranyl benzophenone marupone was isolated from the trunk wood (Dias et al., 1974).

2. Results and discussion

One hundred milligram of the latex methanolic extract was filtered on polyamide to remove tannins and 15 mg of the filtered extract was fractionated on a semipreparative C-18 column to give nine fractions according to a standardized method (see Section 4) (Bousserouel et al., 2005). Biological assay on *P. falciparum* allowed us to identify the active fraction (fraction 6, t_R from 42 to 50 min). A large amount of the extract (2.5 g) was then submitted to silica gel chromatography to give 18 fractions (F1–F18). Comparative study on analytical HPLC of these fractions with fraction 6 allowed us to target those containing the active compounds. Subsequent preparative HPLC purification resulted in the isolation of compounds **1**–**14** (Fig. 1).

Compounds **1**–**14** shared several common spectral characteristics. The UV spectra showed absorption bands at 230 and 280 nm consistent with aromatic rings and conjugated carbonyl groups. The IR spectra exhibited bands for hydroxyl (3350 cm^{-1}), α,β-unsaturated carbonyl groups (1650, 1668 cm^{-1}), ketone (1720 cm^{-1}) and aromatic rings (1600 cm^{-1}). The ^1H and ^{13}C NMR spectra recorded in CD_3OD appeared quite complex due to a keto-enol tautomeric balance within the molecules (Fuller et al., 1999; Gustafson et al., 1992; Williams et al., 2003). In contrast, only one set of signals was observed when pyridine-d_5 was used (Table 1). All the structures reported herein follow the IUPAC convention for numbering bicyclo[3.3.1]nonanes in which C(1)–C(9) and C(5)–C(9) bonds as bold or hashed wedges according to

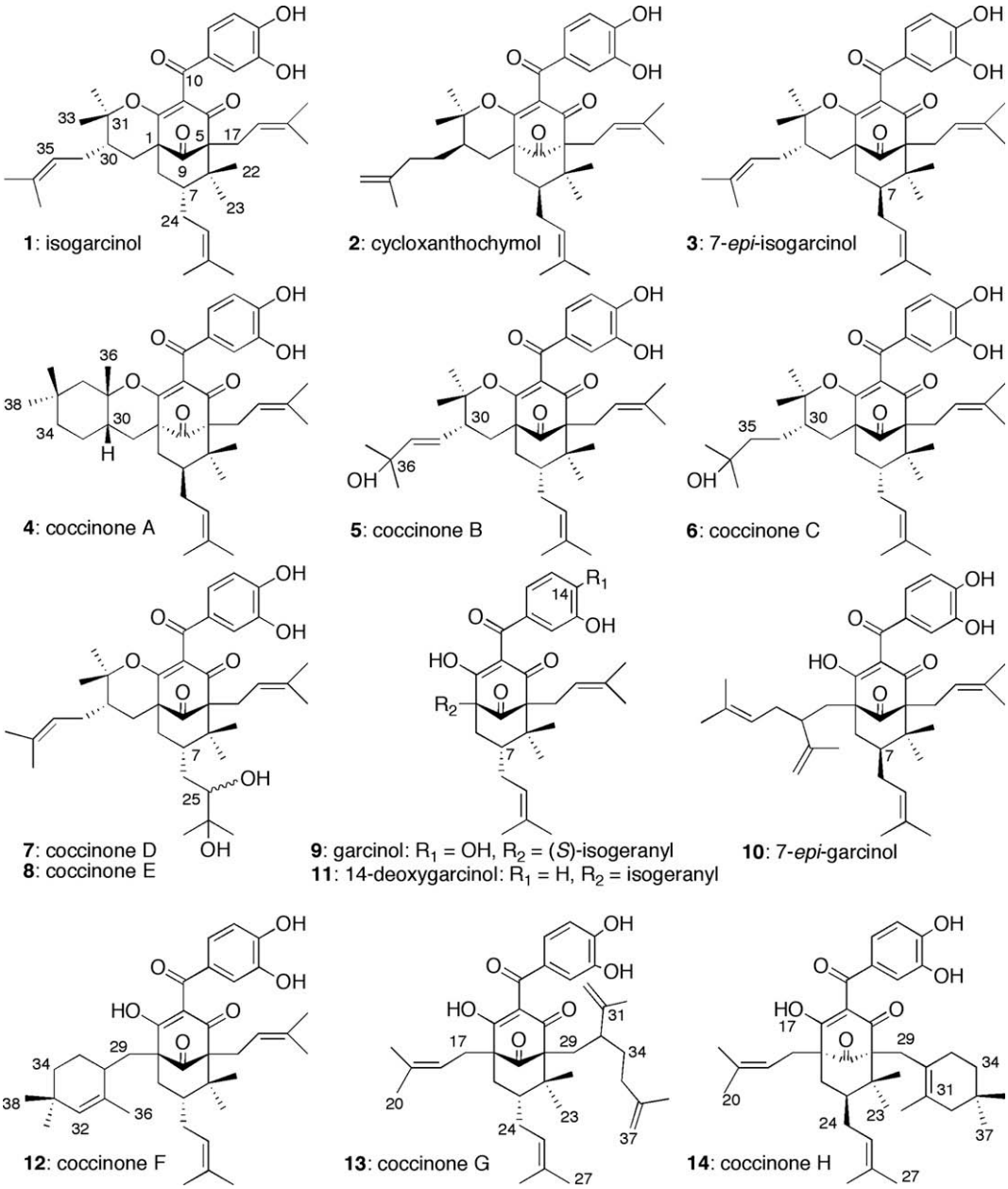

Fig. 1. Structures of compounds **1**–**14**.

Table 1
NMR spectroscopic data for compound **1**, **3**–**8** and **10**–**14** (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR in pyridine-d_5.

Position	Compound **1**			Compound **3**			Compound **4**			Compound **5**		
	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)
1	52.2			52.2			48.4			51.7		
2	171.4			170.8			171.3			171.1		
3	127.2			129.1			128.5			127.0		
4	195.0			194.9			195.6			195.0		
5	69.2			71.4			69.4			69.3		
6	46.8			46.8			46.8			46.9		
7	47.0	1.59	*dt* (6.2, 6.1)	42.2	2.44	*m*	46.7	1.62	*m*	47.1	1.58	*m*
8	39.8	2.11	*dd* (14.1, 7.3)	43.1	1.77	*m*	42.1	2.05	*brd* (13.7)	40.0	2.10	*m*
–		2.43	*brd* (14.1)		2.43	*m*		2.78	*dd* (13.7, 5.8)		2.48	*m*
9	207.9			207.3			208.6			207.9		
10	193.0			193.2			192.5			193.0		
11	130.9			131.0			130.4			130.9		
12	116.6	8.05	*d* (2.0)	117.1	8.13	*brs*	117.1	8.04	*d* (2.2)	116.7	8.06	*d* (1.8)
13	147.8			147.9			147.5			147.8		
14	153.7			153.7			153.4			153.8		
15	116.5	7.28	*d* (8.1)	116.5	7.31	*brd* (7.6)	116.1	7.28	*d* (8.4)	116.6	7.29	*d* (8.0)
16	124.3	7.68	*dd* (8.1, 2)	124.4	7.72	*brd* (7.7)	124.5	7.60	*dd* (8.4, 2.2)	124.4	7.72	*dd* (8.0, 1.8)
17	26.7	2.76	*dd* (13.7, 5.6)	25.9	2.77	*dd* (13.6, 4.8)	26.4	2.81	*dd* (13.6, 6.8)	26.8	2.79	*dd* (13.3, 7.3)
–		2.95	*dd* (13.5, 7.6)		2.97	*dd* (13.6, 6.4)		2.93	*m*		2.85	*dd* (13.3, 7.3)
18	121.7	5.42	*brt* (6.5)	122.1	5.38	*brt* (6.2)	121.4	5.48	*brt* (7.0)	121.7	5.46	*brt* (5.7)
19	134.5			134.2			134.4			134.7		
20	26.6	1.57	*s*	26.2	1.55	*s*	26.5	1.76	*brs*	26.7	1.67	*s*
–												
21	18.8	1.71	*s*	18.8	1.73	*s*	18.7	1.76	*brs*	18.8	1.74	*s*
22	27.1	1.05	*s*	16.6	0.83	*s*	26.7	1.08	*s*	27.1	1.08	*s*
23	23.1	1.30	*s*	22.8	1.27	*s*	22.5	1.28	*s*	23.1	1.31	*s*
24	30.4	1.82	*ddd* (14.2, 9.5, 9.5)	28.5	1.82	*dd* (14.1, 8.5)	30.2	2.45	*m*	29.8	2.43	*m*[a]
–		3.21	*ddd* (14.4, 10.7, 9.5)		2.26	*dd* (14.1, 2.5)		3.03	*m*		3.19	*m*[a]
25	126.4	5.09	*brt* (6.5)	123.8	5.18	*brt* (6.2)	125.9	5.15	*brt* (7.0)	126.4	5.08	*brt* (5.7)
26	132.9			132.9			133.1			133.4		
27	26.5	1.74	*s*	26.2	1.62	*s*	26.1	1.71	*s*	26.5	1.73	*s*
28	19.0	1.91	*s*	18.4	1.62	*s*	18.5	1.86	*s*	19.1	1.86	*s*
29	29.1	1.14	*dd* (13.9, 13.7)	28.5	1.21	*dd* (13.9, 13.7)	29.8	1.40	*m*	30.4	1.41	*m*[a]
–		3.27	*dd* (13.9, 3.1)		3.28	*dd* (13.6, 3.2)		3.08	*dd* (14.5, 5.4)		3.18	*m*[a]
30	43.8	1.66	*dt* (9.9, 5.0)	43.8	1.65	*m*	37.1	1.49	*m*[a]	46.0	2.30	*m*
31	87.2			87.6			83.9			86.0		
32	21.7	1.23	*s*	21.7	1.14	*s*	48.8	1.04	*m*[a]	22.1	1.19	*s*
–								1.46	*m*[a]			
33	29.4	1.07	*s*	29.2	1.08	*s*	30.6			29.4	0.99	*s*
–												
34	30.4	1.96	*brd* (14.1)	30.4	1.79	*m*	37.9	1.03	*m*[a]	124.8	5.70	*d* (15.6)
–		2.42	*brd* (14.1)		1.96	*m*		1.35	*m*			
35	122.8	5.09	*brt* (6.5)	122.9	5.13	*brt* (6.6)	26.4	1.37	*m*	144.4	5.71	*d* (15.6)
–								1.89	*m*			
36	133.7			133.7			29.0	0.91	*s*	69.9		
37	26.2	1.68	*s*	26.2	1.71	*s*	32.1	0.72	*s*	31.0[b]	1.43	*s*
38	18.3	1.56	*s*	18.3	1.56	*s*	27.4	0.97	*s*	30.9[b]	1.45	*s*

(*continued on next page*)

Table 1 (*continued*)

Position	Compound **6**			Compound **7**			Compound **8**			Compound **10**		
	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)	δ_C	δ_H	*J* (Hz)
1	52.3			52.3			52.7			61.5		
2	171.5			171.2			171.6			192.4		
3	127.4			127.2			127.5			120.6		
4	195.1			195.1			195.3			196.2		
5	69.4			69.5			69.6			70.2		
6	47.4			46.9			48.1			48.2		
7	46.9	1.54	*m*	43.2	2.29	*m*[a]	44.5	2.24	*m*	43.2	2.17	*m*
8	40.8	2.20	*brd* (14.6)	40.3	2.28	*m*[a]	45.5	2.47	*dd* (13.9-5.9)	45.4	1.63	*m*
–		2.51	*dd* (14.6, 7.1)		2.58	*brd* (13.3)		2.87	*brd* (13.9)		2.40	*m*
9	207.9			207.9			208.2			210.4		
10	193.4			193.7			193.7			195.8		
11	130.9			130.9			130.9			131.1		
12	116.6	8.08	*d* (1.7)	116.5	8.08	*d* (1.8)	116.5	8.1	*d* (1.8)	117.8	7.86	*brs*
13	147.8			147.8			147.8			147.4		
14	153.8			153.9			153.8			153.3		
15	117.0	7.27	*d* (8.2)	116.7	7.28	*d* (8.0)	116.7	7.30	*d* (8.0)	115.8	7.20	*d* (8.1)
16	124.2	7.70	*dd* (8.2, 1.7)	125.5	7.73	*dd* (8.0, 1.8)	121.8	7.71	*dd* (8.0, 1.8)	125.2	7.61	*brs*
17	26.6	2.75	*dd* (13.3, 5.0)	26.7	2.78	*m*[a]	26.4	2.74	*dd* (13.4, 5.0)	26.2	2.92	*m*
–		2.94	*dd* (13.3, 7.0)		2.95	*dd* (13.5, 7.4)		2.96	*dd* (13.4, 7.4)		3.04	*m*
18	121.9	5.42	*brt* (5.9)	121.8	5.43	*brt* (6.1)	121.8	5.45	*brt* (6.0)	122.8	5.55	*brt* (6.0)
19	134.4			134.3			134.3			133.3		
20	26.6	1.57	*s*	26.6	1.57	*s*	27.0	1.58	*s*	26.2	1.79	*s*
21	18.9	1.71	*s*	18.8	1.71	*s*	18.8	1.73	*s*	18.9	1.85	*s*
22	27.1	1.04	*s*	27.3	1.08	*s*	26.9	1.08	*s*	16.7	0.88	*s*
23	22.8	1.31	*s*	23.2	1.43	*s*	22.9	1.36	*s*	24.2	1.31	*s*
24	30.6	1.80	*m*	33.7	2.05	*dd* (13.9, 11.4)	36.9	2.25	*m*	29.2	1.78	*m*
–		1.97	*m*		2.80	*m*		2.63	*m*		2.15	*m*
25	122.9	5.08	*brt* (5.9)	78.5	3.80	*brd* (10.4)	83.1	3.69	*brd* (10.4)	124.5	5.08	*brt* (6.0)
26	133.7			73.4			73.5			133.9		
27	26.2	1.67	*s*	27.2[b]	1.74	*s*	26.6[b]	1.59	*s*	26.2	1.59	*s*
28	18.3	1.54	*s*	25.0[b]	1.66	*s*	25.2[b]	1.73	*s*	18.4	1.57	*s*
29	29.5	1.14	*dd* (14.3, 9.3)	29.2	1.14	*m*[a]	28.9	1.08	*m*[a]	36.8	2.23	*m*
–		3.29	*dd* (14.3, 3.5)		3.32	*dd* (14.3, 3.3)		3.37	*dd* (14.3, 3.3)		2.33	*m*
30	44.0	1.64	*m*	43.9	1.67	*m*	43.9	1.64	*m*[a]	44.9	3.16	*m*
31	87.2			87.2			87.3			149.5		
32	21.6	1.22	*s*	21.5	1.22	*s*	21.6	1.13	*s*	113.9	4.82	*brs*
–											4.93	*brs*
33	29.4	1.06	*s*	29.4	1.06	*s*	29.4	1.06	*s*	18.9	1.77	*s*
34	26.9	2.15	*m*	30.4	1.78	*m*	30.3	1.76	*m*[a]	33.6	2.28	*m*
–		2.43	*m*		1.98	*m*		1.94	*m*		2.37	*m*
35	46.6	1.89	*m*	122.8	5.09	*brd* (6.1)	122.8	5.07	*brd* (6.0)	124.9	5.31	*brt* (6.0)
–		1.64	*m*									
36	70.5			133.7			133.6			131.9		
37	30.5 [b]	1.56	*s*	26.2	1.67	*s*	26.2	1.66	*s*	26.3	1.64	*s*
38	30.2 [b]	1.56	*s*	18.3	1.54	*s*	18.3	1.52	*s*	18.6	1.68	*s*

Position	Compound **11**			Compound **12**			Compound **13**			Compound **14**		
1	60.4			62.2			62.6			62.8		
2	193.0			192.2			192.2			191.0		
3	119.5			119.3			119.6			118.0		
4	198.2			190.3			196.2			195.7		
5	68.6			66.1			66.2			66.3		
6	49.0			49.4			50.2			50.5		
7	47.8	1.56	*m*	47.9	1.58	*m*	47.0	1.51	*dt* (12.5, 5.1)	47.5	1.57	*m*
8	43.1	2.17	*dd* (13.9, 6.7)	40.4	2.22	*dd* (14.0, 7.0)	42.0	2.10	*o*	42.2	2.14	*dd* (14.0, 6.9)
–		2.48	*m*		2.40	*m*[a]		2.41	*m*		2.43	*dd* (14.0, 1.2)
9	206.4			211.3			210.9			210.1		
10	195.7			196.7			195.9			195.0		
11	142.7			131.4			130.1			129.9		
12	116.6	7.75	*brs*	117.9	7.95	*d* (2.0)	118.0	7.90	*s*	117.9	7.84	*d* (2.1)
13	159.3			147.3			147.4			147.4		
14	120.1	7.29	*brd*	153.2			153.4			153.7		
15	129.7	7.35	*m*	116.1	7.21	*d* (8.4)	116.0	7.19	*m*	115.9	7.20	*d* (8.2)
16	121.4	7.53	*brd*	124.4	7.70	*dd* (8.4, 2.0)	125.9	7.59	*m*	126.0	7.53	*dd* (8.2, 2.2)
17	27.0	2.91	*m*	32.2	2.87	*brs*	32.2	2.71	*dd* (13.6, 9.1)	32.2	2.78	*dd* (13.8, 5.6)
–		2.98	*m*		2.89	*brs*		2.91	*dd* (13.6, 5.7)		2.91	*dd* (13.8, 8.0)
18	122.8	5.60	*brt* (5.6)	122.2	5.81	*brt* (6.0)	122.5	5.67	*m*	121.7	5.69	*brt* (7.1)
19	133.6			133.8			133.8			134.7		
20	26.7	1.84	*s*	26.6	1.78	*m*[a]	26.7	1.88	*s*	26.7	1.86	*s*
21	18.9	1.83	*s*	18.7	1.78	*m*[a]	18.6	1.79	*s*	18.4	1.81	*s*
22	27.7	1.11	*s*	27.8	1.15	*s*	27.4	1.09	*s*	27.2	1.13	*s*
23	23.6	1.36	*s*	23.6	1.39	*s*	23.8	1.41	*s*	23.7	1.44	*s*
24	33.51	2.42	*m*	30.2	2.45	*m*	33.3	1.59	*m*	30.15	2.43	*dd* (15.0, 1.2)
–		2.67	*m*		2.78	*m*		1.65	*m*		2.50	*dd* (15.0, 9.5)
25	126.4	5.05	*brt* (5.6)	126.4	5.06	*brt* (6.0)	125.9	5.00	*m*	125.8	5.01	*brt* (7.0)
26	132.5			132.6			132.7			132.8		
27	26.3	1.62	*s*	26.4	1.62	*s*	26.2	1.61	*s*	26.3	1.63	*s*
28	18.5	1.60	*s*	18.6	1.63	*s*	18.4	1.56	*s*	18.4	1.58	*s*
29	37.6	2.28	*m*	29.5	2.30	*m*	32.2	2.09	*o*	30.2	3.10	*d* (15.0)
–					2.40	*m*		2.56	*m*		3.14	*d* (15.0)
30	44.8	3.14	*m*	35.9	2.66	*m*	45.4	2.52	*m*	128.8		
31	149.8			137.4			147.1			125.9		
32	112.7	4.81	*brs*	134.0	5.21	*brs*	113.5	4.81	*brs*	47.4	1.67	*d* (19.3)
–		4.92	*brs*					4.87	*brs*		1.74	*d* (19.3)
33	19.1	1.78	*s*	32.3			18.4	1.94	*s*	29.2		
34	27.7	2.32	*m*	34.5	1.62	*m*[a]	33.3	1.59	*m*	37.0	1.29	*m*
–		2.42	*m*		1.13	*m*[a]		1.65	*m*			
35	124.7	5.31	*brt* (5.6)	25.5	1.59	*m*[a]	36.6	1.87	*m*	29.3	1.96	*m*
–					1.78	*m*[a]		1.94	*m*		2.20	*m*
36	131.9			23.4	2.11	*s*	146.7			21.1	1.86	*s*
37	26.3	1.67	*s*	31.5	0.94	*s*	110.5	4.72	*brs*	28.3	0.69	*s*
–								4.76	*brs*			
38	18.7	1.71	*s*	29.9	0.84	*s*	22.5	1.65	*s*	28.9	0.84	*s*

[a] Overlap.
[b] Assignments are interchangeable, *brt*: broad triplet, *brs*: broad singulet.

Grossman's recommendations (Ciochina and Grossman, 2006). While several PPAPs have been isolated in both enantiomeric forms (Baggett et al., 2005; Gustafson et al., 1992; Iinuma et al., 1996; Krishnamurthy et al., 1981; Rao and Venkatswamy, 1980; Roux et al., 2000; Sahu et al., 1989) only few of them have their absolute configuration confirmed experimentally (Blount and Williams, 1976; Krishnamurthy et al., 1982). Therefore, it has been postulated that a positive or negative $[\alpha]_D$ value is due to the bicyclo[3.3.1]nonane system orientation. PPAPs presented here follow this rule.

Compound **1** has been isolated as a brown crystal, $[\alpha]_D$ −168° (*c* 1.0, $CHCl_3$). The HREIMS indicated a $[M+Na]^+$ ion peak at 625.3499, which suggested a molecular formula of $C_{38}H_{50}O_6Na$ (calc. 625.3505). Examination of the 1D and 2D NMR spectra associated with the value of optical rotation confirmed that **1** was isogarcinol (Iinuma et al., 1996; Krishnamurthy et al., 1981). However, no detailed NMR data were available in the literature. We reported in Table 1 the complete assignment of ^1H and ^{13}C NMR data of **1**. The X-ray diffraction analysis from crystals of the dibrosylate derivative of **1,** (**1′**) allowed us to confirm the absolute configuration of isogarcinol previously established by Krishnamurthy and coworkers (Krishnamurthy et al., 1982; Rogers et al., 1981). X-ray data are available on the Cambridge Crystallographic Data Centre (see supplementary material section).

The spectroscopic data of compound **2** were similar to those of cycloxanthochymol isolated from *Garcinia subelliptica* and *Garcinia pyrifera* (Iinuma et al., 1996; Roux et al., 2000).

Compound **3**, a brown powder, exhibited $[\alpha]_D$ −158° (*c* 1.0, $CHCl_3$). The HREIMS indicated an ion peak at *m*/*z* 625.3519, which suggested the same molecular formula as **1** and **2** ($C_{38}H_{50}O_6Na$). The ^1H and ^{13}C NMR spectral data were almost identical to those of **1**. In the ^{13}C NMR, only the signals of carbons C-7, C-8, C-22, C-23 and C-24 shifted slightly suggesting a β-orientation for the prenyl side chain located at position 7. According to Ciochina and Grossman, the orientation of the substituent on C-7 (axial or equatorial) can be deduced from the ^1H and ^{13}C NMR spectral data (Ciochina and Grossman, 2006; Hamed et al., 2006; Piccinelli et al., 2005). The C-22 and C-23 methyl resonate at δ 27.1 and 23.1 respectively for isogarcinol (**1**) having an axial prenyl side chain on position C-7, whereas the *gem*-dimethyl group showed chemicals shifts at δ 16.6 and δ 22.8, respectively in compound **3**. The upfield shift of the C-22_{ax} signal resulted from a γ-gauche interaction between this carbon and the CH_2-24 of the prenyl group. In the NOESY spectrum, nOe interactions between H-8_{eq}, H-7 and Me-23_{eq} (δ_H 1.77, 2.44 and 1.27, respectively) confirmed the absolute configuration (*S*) for C-7. Compound **3** was thus identified as 7-*epi*-isogarcinol.

Compound **4** was isolated as a brown oil. The HREIMS showed the same ion peak $[M+Na]^+$ *m*/*z* 625.3521 as compound **1** indicating the same formula $C_{38}H_{50}O_6Na$. The ^1H and ^{13}C NMR spectra confirmed the presence of a 1,2,4-trisubstituted benzene ring (Table 1) and displayed resonances for nine methyl groups [δ_H 1.08 (3 H, *s*, Me-22), 1.28 (3 H, *s*, Me-23), 0.91 (3 H, *s*, Me-36), 0.72 (3 H, *s*, Me-37), 0.97 (3 H, *s*, Me-38), 1.76 (6 H, *brs*, Me-20 and Me-21), 1.71 (3 H, *s*, Me-27), and 1.86 (3 H, *s*, Me-28)], and two vinylic protons [δ_H 5.48 (1H, *brt*, *J* = 7.0 Hz, H_1-18), and 5.15 (1H, *brt*, *J* = 7.0 Hz, H_1-25)]. The COSY and HMBC spectra revealed the presence of an additional 1,1-dimethylcyclohexane fused to the tetrahydropyrane ring on positions C-30 and C-31 instead of a prenyl side chain observed in **1** (Fig. 2). The relative configuration of the asymmetric carbons delineated in structure **4** has been determined by nOe experiment. Resonances for Me-36 with H-29_{ax} (δ_H 3.08), H-30 (δ_H 1.49) and H-32_{ax} (δ_H 1.46) allowed us to place these groups in the same face of the trimethylperhydrochromene moiety. On the other hand, resonances of Me-38 with H-35_{ax} (δ_H 1.89) allowed us to locate these groups on the opposite face. These correlations suggested a β-position of H-30 and the Me-36 group indicating a *cis*-junction between the tetrahydropyrane and the dimethylcyclohexane rings. From a biogenetic point of view, compound **4** could be derived from a double intramolecular cyclisation of the ω-isolavandulyl side chain at C-1 position of the known xanthochymol, although this last has not been isolated (Dreyer, 1974). The trimethylperhydrochromene system has already been described in a type A benzophenone derivative isolated from *Clusia obdeltifolia* (Teixeira and Cruz, 2005). Compound **4** was named coccinone A.

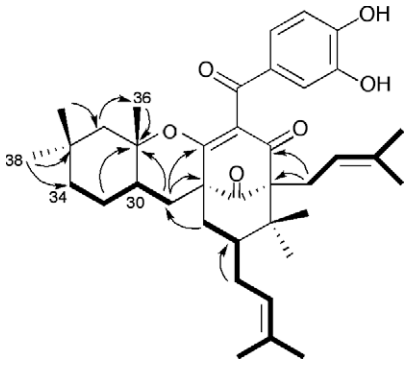

Fig. 2. Key HMBC (arrows) and COSY (bold) correlations for **4**.

Compound **5** was isolated as a brown oil. The HREIMS indicated a molecular formula $C_{38}H_{50}O_7$ deduced from the ion peak at *m*/*z* 641.3446 $M+Na^+$ (calc. 641.3454), which suggested the presence of an additional hydroxy group when compared with **1**. Examination of the 1D and 2D NMR spectral data of compound **5** confirmed that a benzoylphloglucinol skeleton is associated to a tetrahydropyrane ring. The presence of a 3-hydroxyl-3-methylbutenyl side chain in position C-30 was suggested by the following evidence. In the HMBC spectrum, correlations were observed from the quaternary carbon C-36 and the methine C-30 (δ_C 69.9 and 46.0, respectively) to the vinylic protons at δ_H 5.70 and 5.71 (each 1H, *d*, *J* = 15.6 Hz) H-34 and H-35, respectively, and from C-35 at δ_C 144.4 and C-36 to the methyl protons H_3-37 and H_3-38 (δ_H 1.43 and 1.45, respectively). The correlation between H-34 and H-30 (δ_H 2.30) in the COSY spectrum confirmed the location of the side chain at position C-30. These data, together with other results of 2D NMR analysis confirmed the structure of compound **5**, which was named coccinone B.

Compound **6** was isolated as a brown oil. The molecular formula $C_{38}H_{52}O_7$ has been deduced by HREIMS from the ion peak $[M+Na]^+$ *m*/*z* 643.3619 (calc. 643.3611) and suggested the presence of two additional protons when compared with **5**. The presence of a saturated side chain was confirmed in the ^1H and ^{13}C NMR spectra by signals for two additional methylene groups instead of two vinylic carbons. In the HMBC spectrum, correlations were observed from the quaternary carbon C-36 (δ_C 70.5) and the methylene C-35 (δ_C 46.6) to the methyl protons H_3-37 and H_3-38 (δ_H 1.56, 6 H, *s*). In the COSY spectrum, the correlations between H-35, H-34 and H-30 confirmed the location on position C-30 of the 3-hydroxy-3-methylbutyl side chain. This was further confirmed by NOESY interactions between Me-32 with H_α-34 (δ_H 2.43). Compound **6** was named coccinone C.

Compound **7,** which was isolated as a brown oil, has an $[\alpha]_D$ value of −76° (*c* 0.4, $CHCl_3$). The HREIMS revealed an ion peak at $[M+Na]^+$ *m*/*z* 659.3563 (calc. 659.3560), giving the molecular formula $C_{38}H_{52}O_8$ suggesting the presence of an additional hydroxy group when compared with compound **6**. Examination of the 1D and 2D NMR spectra showed that compound **7** shared several characteristics with the previous compounds. The

^{1}H NMR spectrum showed only two vinylic protons at δ_H 5.09 and 5.43 (1H each, *brt*, J = 6.1 Hz, H_1-35 and H_1-18, respectively), which suggested the presence of two prenyl side chains. The location of the first prenyl side chain at C-5 was suggested by correlations from C-4, C-5, C-6 and C-18 to the methylene H_2-17 (δ_H 2.78) in the HMBC spectrum. In the COSY spectrum, correlations between protons at δ_H 1.14/3.32, 1.67, 1.78/1.98 and 5.09 (H_2-29, H-30, H_2-34 and H-35, respectively) confirmed the location of the second prenyl side chain at C-30. The presence of a 2,3-dihydroxy-3-methylbutyl side chain on position C-7 was suggested by the following evidence. In the HMBC spectrum, correlations were observed from the quaternary carbon C-26 (δ_C 73.4) and the methine carbon C-25 (δ_C 78.5) to the methyl protons H_3-27 and H_3-28 (3H, *s* each, δ_H 1.74 and 1.66, respectively). In addition, correlations between H-24, H-7 and H-25 in the COSY spectrum allowed to locate the side chain on position C-7. The chemical shifts of the carbons C-25 and C-26 observed in the ^{13}C NMR spectrum suggested the presence of two hydroxy groups. The chemical shifts of the *gem*-dimethyl group C-22 and C-23 (δ_C 27.3 and 23.2, respectively) suggested an axial position of the side chain. This was confirmed by the correlations between H-7$_{eq}$ (δ_H 2.29), H-8$_{eq}$ (δ_H 2.58) and Me-22 (δ_H 1.08) observed in the NOESY spectrum. On the other hand, despite the presence of correlations between H-25 (δ_H 3.80) with Me-27, Me-28, H-24$_\alpha$ (δ_H 2.80), H-7$_{eq}$ (δ_H 2.29) and H-8$_{eq}$ (δ_H 2.58), we cannot resolve the relative configuration at C-25. Compound **7** was named coccinone D.

Compound **8,** which was isolated as a brown oil, has an $[\alpha]_D$ value of −70° (*c* 0.3, $CHCl_3$). The HREIMS presented the same ion peak as compound **7** at *m*/*z* 659.3560 $[M+Na]^+$ (calc. 659.3560) indicating the same formula $C_{38}H_{52}O_8$. The ^{1}H and ^{13}C spectra of both compounds **7** and **8** were very similar except for the "south region" implying carbons C-6, C-7, C-8, C-24 and C-25. A close examination of the 1D and 2D NMR data allowed us to deduce that compound **8** possessed the same skeleton as compound **7** with an axial 2,3-dihydroxy-3-methylbutyl side chain at position C-7. In contrast with compound **7**, other correlations were observed between the protons H-25 and Me-27, Me28, H-24$_\beta$ (δ_H 2.25), H-7$_{eq}$ (δ_H 2.24) and Me-23$_{eq}$ (δ_H 1.36) in the NOESY spectrum. Compound **8** was named coccinone E.

The preparation of Mosher esters should confirm the absolute configuration at C-25. Unfortunately the amount of both compounds was not sufficient to obtain the desired products. To our knowledge, it is the first report of a 2,3-dihydroxy-3-methylbutyl side chain located at C-7 in the type B PPAPs.

Compound **9** was isolated as yellow crystals. The HREIMS $[M+Na]^+$ *m*/*z* 625.3494 indicated a molecular formula of $C_{38}H_{50}O_6$ (calc. 625.3505). The ^{1}H and ^{13}C NMR (Table 1) data and the value of $[\alpha]_D$ −135° (*c* 1.0, $CHCl_3$) were identical with those of garcinol isolated from *Garcinia xanthochymus* (Krishnamurthy et al., 1981; Rao and Venkatswamy, 1980). A complete set of data obtained from the X-ray crystallographic analysis is available on Cambridge Crystallographic Data Centre (see supplementary material section).

Compound **10**, a yellow oil, exhibited $[\alpha]_d$ −86° (c 0.8, $CHCl_3$). The HREIMS indicated an ion peak at *m*/*z* 625.3517, which suggested the same molecular formula as **9** ($C_{38}H_{50}O_6$). The ^{1}H and ^{13}C NMR spectral data were almost identical to those of **9**. In the ^{13}C NMR, only the signals of carbons C-7, C-8, C-22, C-23 and C-24 shifted slightly suggesting a β-orientation for the prenyl side chain located at position **7**. This was confirmed by nOe data (see discussion for compound **3**). Compound **10** was deduced to be the 7-*epi*-garcinol.

Compound **11** was purified as a yellow oil, the HREIMS indicated a molecular formula of $C_{38}H_{50}O_5$ $[M+Na]^+$ *m*/*z* = 609.3538 (calc. 609,3556). Examination of the 1D and 2D NMR data suggested the presence of a disubstituted benzene ring instead of the catechol previously observed for compounds **1–9**. All other data are fully similar to those of garcinol (**9**) indicating that compound **11** was 14-deoxygarcinol.

Compound **12**, a yellow oil, exhibited an $[\alpha]_D$ −32° (*c* 0.8, $CHCl_3$). The HREIMS indicated the same molecular formula as garcinol ($C_{38}H_{50}O_6$). The ^{1}H and ^{13}C NMR spectral data (Table 1) were very close to those of garcinol. The COSY and HMBC spectrum suggested that the ω-isolavandulyle side chain was replaced by a 1,3,3-trimethylcyclohex-1-enyl (Fig. 3). In the HMBC spectrum, a *gem*-dimethyl group is deduced from the correlations observed from the quaternary carbon C-33 (δ_C 32.3), the methylene carbon C-34 (δ_C 34.5) and the methine C-32 (δ_C 134.0) to the methyl protons H_3-37 and H_3-38. Correlations were also observed from the two methines C-32 and C-30 (δ_C 35.9) to the methyl protons H_3-36 (δ_H 2.11) and from the methylene carbon C-35 (δ_C 25.5) and the quaternary carbons C-1, C-2 and C-31 (δ_C 62.2, 192.2 and 137.4, respectively) to the methylene protons H_2-29, which confirmed the presence of the C10 moiety located at position C-1. In the NOESY spectrum, the correlation observed between H-30 (δ_H 2.66) and H-34$_{ax}$ (δ_H 1.62) suggested a β-orientation for H-30. This relative configuration was confirmed by correlations between H-34$_{ax}$ and H_3-38 from one side and H_3-37 with H-35$_{ax}$ (δ_H 1.59) on the other side. These data, together with other results of 2D NMR analysis confirmed the structure of compound **12**, which was named coccinone F.

Compound **13** was isolated as a yellow oil. The molecular formula of $C_{38}H_{50}O_6$ has been deduced from the ion peak at $[M+Na]^+$ *m*/*z* = 625.3524 (calc. 625.3505) obtained by HREIMS. The ^{1}H and ^{13}C NMR spectra suggested the presence of a 1,2,4-trisubstituted benzene ring (Table 1). In addition, resonances for eight methyl at δ_H 1.09 (3 H, *s*, Me-22), 1.41 (3 H, *s*, Me-23), 1.94 (3 H, *s*, Me-33), 1.65 (3 H, *s*, Me-38), 1.61 (3 H, *s*, Me-27), 1.56 (3 H, *s*, Me-28), 1.79 (3 H, *s*, Me-21) and 1.88 (3H, *s*, Me-20), two trisubstituted double bonds at δ_H 5.67 (1 H, *m*, H-18) and 5.00 (1 H, *m*, H-25), two olefinic exomethylenes at δ_H 4.81 and 4.87 (2 H,

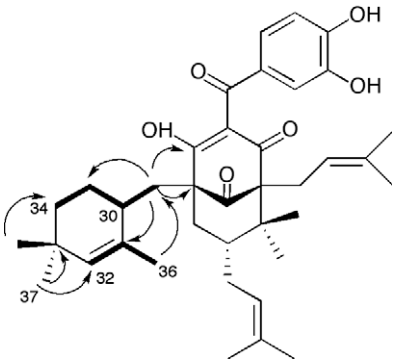

Fig. 3. Key HMBC (arrows) and COSY (bold) correlations for **12**.

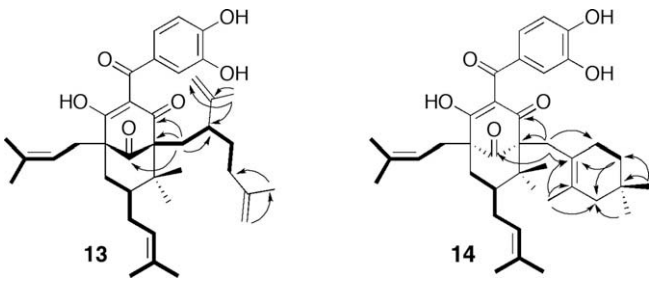

Fig. 4. Key HMBC (arrows) and COSY (bold) correlations for **13** and **14**.

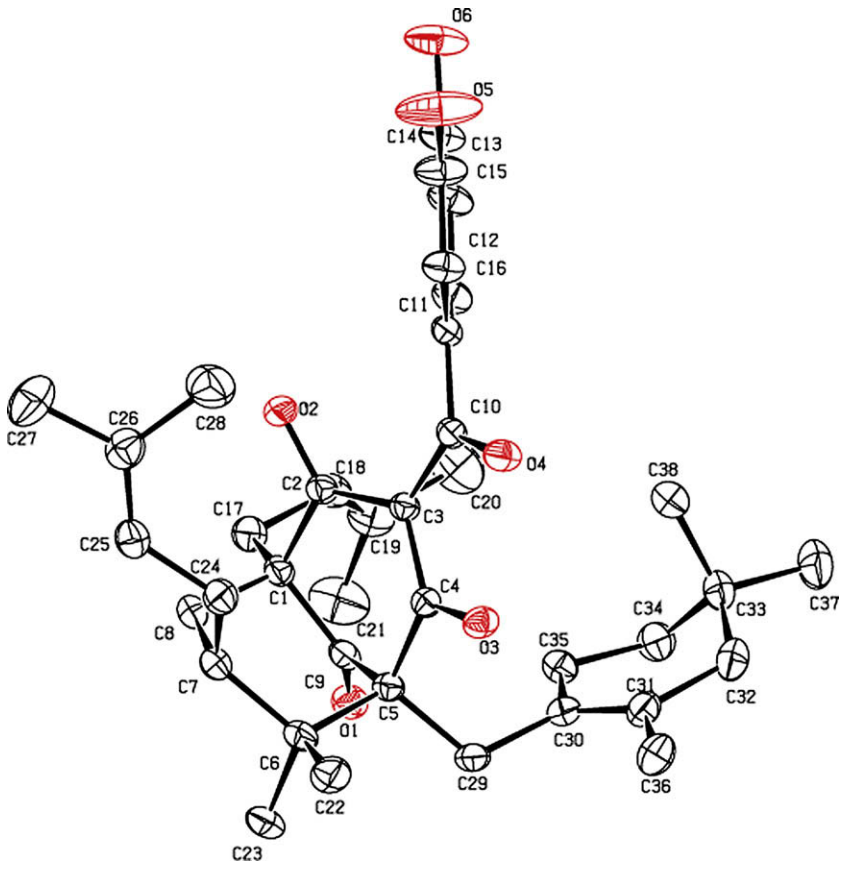

Fig. 5. X-ray crystal structure for compound **14**.

brs, H-32) and δ_H 4.72 (1 H, *m*, H-37), 4.76 (1 H, *m*, H-37), and seven allylic protons at δ_H 2.1-2.9 (10 H, *m*) were observed (Table 1). These data associated with the correlations observed in the COSY and the HMBC spectra, suggested the presence of a ω-isolavandulyl and two prenyl side chains (Fig. 4). The location of the prenyl side chain, α-oriented, at position C-7 was deduced from the chemical shifts of the *gem*-dimethyl at δ_C 27.4 and 23.8 (H_3-22 and H_3-23, respectively) observed in the ^{13}C NMR spectra. The location of the ω-isolavandulyl side chain at position C-5 was deduced from the correlations from the carbons C-4, C-5, C-9 and C-30 to the methylene protons H_2-29 observed in the HMBC spectrum (Fig. 4). The relative configuration of the methine C-30 remains unknown. Compound **13** was named coccinone G.

Compound **14** was purified as a yellow crystal. The ion peak in HREIMS $[M+Na]^+$ *m*/*z* 625.3499 indicated the same molecular formula as compound **13**, $C_{38}H_{50}O_6Na$ (calc. 625.3505). The ^1H and ^{13}C NMR spectra showed the same benzoylphloroglucinol skeleton as the previous one (Table 1). The 2D NMR data were very similar with those of compound **11**, except for the ω-isolavandulyl side chain, which is replaced by a 2,4,4-trimethylcyclohex-1-enyl moiety in the case of compound **14**. In the HMBC spectrum, an additional *gem*-dimethyl group is deduced from the correlations observed from the quaternary carbon C-33 (δ_C 29.2) and the methylenes C-32 and C-34 (δ_C 47.4 and 37.0, respectively) to the methyl protons H_3-37 and H_3-38. In addition, correlations from the carbons C-30 (δ_C 128.8), C-31 (δ_C 125.9) and C-32 (δ_C 47.4) to the methyl protons H_3-36, and from the carbons C-32 and C-35 (δ_C 29.3) to the methylene protons H_2-34 confirmed the presence of a 2,4,4-trimethylcyclohex-1-enyl moiety. Finally, correlations from the carbons C-4, C-5, C-9, C-30 and C-35 to the methylene protons H_2-29 indicated that the C10 moiety is attached at position C-5 (Fig. 4). The relative configuration of compound **14** was confirmed by the X-ray crystallographic analysis (Fig. 5, see supplementary material section). Compound **14** was named coccinone H. To our knowledge, coccinones G and H are the first example of PPAPs having a C10 side chain attached at C-5.

2.1. Biological activity

The antiplasmodial activity of compounds **1**–**14** was evaluated by their ability to inhibit the growth of *P. falciparum* following

Table 2
IC50 value of compounds **1**–**14** tested against FcB1 strain of *P. falciparum* and MRC5 cells.

Compound	IC50 *P.f.* FcB1 (μM) ± SD (*n* = 3)	IC50 MRC 5 (μM) (*n* = 3)
Isogarcinol (**1**)	3.5 ± 1.1	3.5 ± 0.4
Cycloxanthochymol (**2**)	2.1 ± 0.5	3.6 ± 0.6
7-*epi*-isogarcinol (**3**)	5.1 ± 1.3	2.3 ± 0.5
Coccinone A (**4**)	4.3 ± 0.5	3.3 ± 0.8
Coccinone B (**5**)	5.5 ± 0.4	11.7 ± 0.6
Coccinone C (**6**)	9.0 ± 1.2	9.3 ± 1.1
Coccinone D (**7**)	7.0 ± 0.9	10.9 ± 0.3
Coccinone E (**8**)	4.9 ± 0.7	9.1 ± 1.3
Garcinol (**9**)	12.6 ± 4.8	11.0 ± 0.2
7-*epi*-garcinol (**10**)	10.1 ± 4.6	11.3 ± 0.6
14-deoxygarcinol (**11**)	37.2 ± 9.7	19.1 ± 0.2
Coccinone F (**12**)	17.0 ± 9.4	21.3 ± 2.8
Coccinone G (**13**)	19.2 ± 5.9	11.5 ± 0.4
Coccinone H (**14**)	16.6 ± 6.1	10.5 ± 0.6
Chloroquine	0.078 ± 0.006	25 ± 3.8
Taxotere	0.010 ± 0.005	31.5 ± 4.5

the method of Desjardins et al. (1979). The anti-plasmodial activity against the chloroquine-resistant strain of *P. falciparum* FcB1 and the cytotoxicity on the human MRC-5 cell line are summarized in Table 2. The results demonstrated that compounds **1**–**14** exhibited potent antiplasmodial activity. Compounds **1**–**8** have shown the best IC50s between 3.3 and 9.0 μM, indicating that the benzophenones having a tetrahydropyrane ring are the most potent compounds. In contrast, compounds **9**–**14** showed moderate antiplasmodial activities with IC50s over 10 μM. Moreover, hydroxyl position on the benzoyl groups seems to play an important role for the antiplasmodial activity regarding the IC50 values for garcinol and dehydroxygarcinol. The analysis of the IC50s obtained on the MRC-5 cell line indicated that compounds having a hydroxylated side chain (**5**–**8**) exhibited a lowest cytotoxicity. Further mechanistic and structure-activity relationship studies have to be done in order to better understand the structural features needed for developing new anti-malarial drugs based on PPAPs.

3. Conclusions

Phytochemical investigation of *M. coccinea* led to the isolation of eleven new PPAPs derivatives. This is the first report on the isolation of PPAPs with a C_{10} side chain attached at C5. Furthermore, *in vitro* antiplasmodial assays reveal that PPAPs having a furan ring fused to the phloroglucinol moiety exhibited potent biological activity. Biological and phytochemical investigations of other tropical Clusiaceae species are underway in order to confirm this hypothesis.

4. Experimental

4.1. General

The NMR spectra were recorded with a Bruker 500 MHz (advance 500) spectrometer with pyridine-d_5 as solvent. ESIMS were obtained on a Navigator mass Thermoquest. HRESIMS were run on a MALDI-TOF spectrometer (Voyager-De STR; Perspective Biosystems). Kromasil analytic, semi-preparative and preparative C-18 columns (250 × 4.5 mm; 250 × 10 mm and 250 × 21.2 mm I.D, 5 μm Thermo®) were used for preparative HPLC separations using a Waters autopurification system equipped with a binary pump (Waters 2525), a UV–vis diode array detector (190–600 nm, Waters 2996) and a PL-ELS 1000 ELSD detector Polymer Laboratory. IR spectra were obtained on a Nicolet FTIR 205 spectrophotometer. The UV spectra were recorded on a Perkin–Elmer Lambda 5 spectrophotometer. Specific rotation was obtained in $CHCL_3$ with a JASCO P-1010 polarimeter. Melting point for isolated crystals was done on a Büchi B-540. Silica gel 60 (35–70 μm) and analytical TLC plates (Si gel 60 F 254) were purchased from SDS (France). Polyamide DC 6 and polyamide cartridge was purchased from Macherey–Nagel (Chromabond PA®, 1 g). All other chemicals and solvents were of analytical grade and purchased from SDS (France).

4.2. Plant material

Trunk barks, roots barks, fruits, leaves and latex of *M. coccinea* were collected in the dense rain forest of French Guyana by one of us (G.M). Latex was collected by scoring trunk tissue and then scraping the latex as it oozed from the wound. This yellow resin was transferred to Teflon-stoppered glass vials. A herbarium sample (GM-008) was deposited in the Guyane Herbarium of Cayenne, and identified by M-F. Prevost (Institut de Recherche pour le Développement).

4.3. Extraction and isolation procedures

Trunk bark, roots bark, fruits, and leaves (20 g each) were extracted three times using the automatic extractor Dionex® ASE 300 with EtOAc (3 × 100 ml) followed by MeOH (3 × 100 ml) at 40 °C and 100 bar. Each extract were concentrated *in vacuo* at 40 °C to yield 2.69 g (trunk bark, EtOAc), 1.48 g (trunk bark, MeOH), 5.14 g (roots bark, EtOAc) 0.96 g (trunk bark, MeOH), 2.57 g (fruits, EtOAc), 5.23 g (fruits, MeOH), 1.71 g (leaves, EtOAc) and 1.13 g (leaves, MeOH). Aliquot of 100 mg of each extract and yellow resin were dissolved in MeOH and then were filtered on polyamide cartridge before being tested at 10 μg/ml on *P. falciparum* FcB1 strain. The resin-filtered extract was then fractionated on a semi-preparative C-18 column according to a standardized method previously detailed (Bousserouel et al., 2005). Fraction 6 was shown to possess antiplasmodial activity.

A larger amount of latex (3.51 g) was dissolved in MeOH and filtered on polyamide DC 6 to remove bark residue and tannins. The filtered extract was dried under vacuum at 40 °C to give a yellow gummy residue (2.35 g), which was subjected to silica gel chromatography using cyclohexane, mixtures of cyclohexane–ethyl acetate (9:1–1:9) and ethyl acetate as eluents. According to their TLC profiles, 18 fractions (F1–F18) were obtained. Analytical HPLC was used to compare these fractions with the active fraction 6 previously identified and allowed us to identify those containing the active compounds. Fraction 12 (740 mg) was submitted to a preparative C-18 column using an isocratic mobile phase consisting of MeCN–H_2O 90:10 + 0.1% formic acid, leading to the isolation of 7-*epi*-isogarcinol **3** (109 mg; w/w 4.6%), isogarcinol **1** (332 mg; w/w 14.1%), cycloxanthochymol **2** (11 mg; w/w 0.5%), coccinone A **4** (18 mg; w/w 0.76%), 14-dehydroxygarcinol **11** (4 mg; w/w 0.17%) garcinol **9** (134 mg; w/w 5.7%), 7-*epi*-garcinol **10** (20 mg; w/w 0.85%) coccinone F **12** (16 mg; w/w 0.68%), coccinone G **13** (61 mg; w/w 2.6%) and coccinone H **14** (30 mg; w/w 1.4%), with retention times of 4.7, 5.2, 5.5, 6.0, 9.3, 9.4, 16.5, 13.5 and 12.6 min, respectively. Fraction 13 (100 mg) using an isocratic system consisting of MeCN–H_2O 70:30 + 0.1% formic acid on the same column, afforded coccinone B **5** (4 mg; 0.17%), coccinone C **6** (3 mg; 0.12%), coccinone D **7** (3 mg; 0.12%) and coccinone E **8** (4 mg, 0.17%) with retention times of 6.5, 7.2, 10.6 and 11.4 min, respectively.

4.3.1. Isogarcinol ***1***

Brown crystal, HR-EIMS $[M+Na]^+$ *m/z* 625.3499, $C_{38}H_{50}O_6Na$ requires 625.3505; $[\alpha]_D$ −158° (*c* 1, $CHCl_3$); mp 251 °C; UV λ_{max} ($\log\varepsilon$): 317 (3.82), 277 (4.14), 233 (4.07); IR ν_{max} (ns) 3290, 2920, 2850, 1730, 1670, 1590, 1520, 1440, 1370, 1290, 1170 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1). CCDC (Deposit No: 689070) contains the supplementary crystallographic data (Krishnamurthy et al., 1982).

4.3.2. 13-*O*,14-*O*-Bis(4-bromobenzoylsulfonyl)-isogarcinol ***1′***

At a pyridine solution of isogarcinol (32 mg in 350 μl, 0.053 mmol) were added DMAP (3 mg, 0.024 mmol) and 4-bromobenzenesulfonyl chloride (44 mg, 0.17 mmol). After stirring for 4 h at 0 °C, the solution was extracted with diisopropyl ether and washed with HCl 1 N. Four products were separated using preparative TLC plates (cyclohexane/EtOAc 7:3): starting materials (17 mg); 13-*O*-(4-bromobenzoylsulfonyl)-isogarcinol (5 mg); 14-*O*-(4-bromobenzoylsulfonyl)-isogarcinol (9 mg); and the desired product 13-*O*,14-*O*-bis(4-bromobenzoylsulfonyl)-isogarcinol (7 mg). The last was crystallized under MeOH/$H_2$0 95:5. mp 138 °C; CCDC (Deposit No: 688119) contains the supplementary crystallographic data.

4.3.3. Cycloxanthochymol ***2***

Yellow oil, $[\alpha]_D$ +112° (*c* 1, $CHCl_3$), HR-EIMS $[M+Na]^+$ *m/z* 625.3512, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 315 (3.87), 277 (4.18), 229 (4.16); IR ν_{max} 3330, 2920, 1730, 1650, 1590, 1520, 1440, 1370, 1290, 1190, 1120 cm^{-1}.

4.3.4. 7-Epi-isogarcinol ***3***

Brown powder, $[\alpha]_D$ −158° (*c* 1.0, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 625.3519, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 319 (3.85), 276 (4.15), 233 (4.12); IR ν_{max} 3320, 2970, 2930, 1730, 1650, 1590, 1520, 1440, 1370, 1290, 1170 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.5. Coccinone A ***4***

Brown oil, $[\alpha]_D$ +28° (*c* 1.0, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 625.3521, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 276 (3.23), 232 (3.19); IR ν_{max} 3280, 2920, 2850, 1730, 1650, 1550, 1440, 1370, 1290, 1170 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.6. Coccinone B ***5***

Brown oil, $[\alpha]_D$ −55° (*c* 0.3, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 641.3446, $C_{38}H_{50}O_7Na$ requires calc. 641.3454; UV λ_{max} ($\log\varepsilon$): 316 (3.71), 278 (4.03), 233 (3.99); IR ν_{max} 3330, 2930, 1730, 1650, 1590, 1440, 1350, 1290, 1120 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.7. Coccinone C ***6***

Brown oil, $[\alpha]_D$ −60° (*c* 0.2, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 643.3619, $C_{38}H_{52}O_7$ (calc. 643.3611); UV λ_{max} ($\log\varepsilon$): 316 (3.83), 277 (4.15), 233 (4.11); IR ν_{max} 3350, 2930, 1730, 1640, 1590, 1440, 1350, 1290, 1120 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.8. Coccinone D ***7***

Brown oil, $[\alpha]_d$ −76° (*c* 0.4, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 659.3563, $C_{38}H_{52}O_8$ (calc. 659.3560); UV λ_{max} ($\log\varepsilon$): 313 (3.83), 278 (4.14), 233 (4.08); IR ν_{max} 3410, 2930, 1730, 1590, 1440, 1350, 1290, 1120 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.9. Coccinone E ***8***

Brown oil, $[\alpha]_D$ −70° (*c* 0.3, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 659.3560, $C_{38}H_{52}O_8$ (calc. 659.3560); UV λ_{max} ($\log\varepsilon$): 313 (3.82), 278 (4.14), 233 (4.08); IR ν_{max} 3430, 2930, 1730, 1590, 1440, 1350, 1290, 1120 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.10. Garcinol ***9***

Yellow crystal, $[\alpha]_D$ −135° (*c* 1.0, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 625.3494, $C_{38}H_{50}O_6Na$ requires 625.3505; mp 132 °C; UV λ_{max} ($\log\varepsilon$): 279 (4.18), 232 (4.04); IR ν_{max} 3300, 2920, 1720, 1640, 1590, 1440, 1370, 1290, 1190 cm^{-1}; ^1H NMR and ^{13}C NMR are consistent with published data (Krishnamurthy et al., 1981; Rao and Venkatswamy, 1980; Sahu et al., 1989). CCDC (Deposit No: 688120) contains the supplementary crystallographic data (see supplementary material section).

4.3.11. 7-epi-garcinol ***10***

Yellow oil, $[\alpha]_D$ −86° (*c* 0.8, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 625.3517, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 280 (4.32), 230 (4.17); IR ν_{max} 3300, 2920, 1720, 1640, 1520, 1440, 1375, 1290, 1200 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.12. 14-deoxygarcinol ***11***

Yellow oil, $[\alpha]_D$ −42° (*c* 0.3, $CHCl_3$); HR-EIMS $[M+Na]^+$ *m/z* 609.3538, $C_{38}H_{50}O_5$ (calc. 609.3556); UV λ_{max} ($\log\varepsilon$): 283 (4.05), 258 (4.03); IR ν_{max} 3290, 2920, 1720, 1640, 1560, 1440, 1370, 1290, 1190 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.13. Coccinone F ***12***

Yellow oil, $[\alpha]_D$ −32° (*c* 0.7, $CHCl_3$), HR-EIMS $[M+Na]^+$ *m/z* 625.3490, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 280 (4.09), 229 (4.03); IR ν_{max} 3300, 2920, 1720, 1660, 1590, 1440, 1375, 1290, 1200 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.14. Coccinone G ***13***

Yellow oil, $[\alpha]_D$ −16° (*c* 1.0, $CHCl_3$); HR-EIMS $(M+Na^+)$ *m/z* 625.3524, $C_{38}H_{50}O_6Na$ requires 625.3505; UV λ_{max} ($\log\varepsilon$): 279 (4.18), 233 (4.10); IR ν_{max} 3280, 2920, 2850, 1730, 1640, 1600, 1440, 1380, 1290, 1180 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.15. Coccinone H ***14***

Yellow crystal, $[\alpha]_D$ +2° (*c* 1.0, $CHCl_3$); HR-EIMS $(M+Na^+)$ *m/z* 625.3499, $C_{38}H_{50}O_6Na$ requires 625.3505; mp 169 °C; UV λ_{max} ($\log\varepsilon$): 282 (3.96), 232 (3.88); IR ν_{max} 3310, 2940, 2870, 1720, 1590, 1440, 1380, 1290, 1190 cm^{-1}; ^1H NMR and ^{13}C NMR (Table 1).

4.3.16. The crystal data of ***14***

$C_{38}H_{50}O_6$, $M = 602.78$, monoclinic, space group C2, $a = 31.987(5)$, $b = 12.928(2)$, $c = 8.847(2)$ Å, $\beta = 98.54(2)°$, $V = 3617.9(11)$ $Å^3$, $Z = 4$, $D_c = 1.107$ g cm^{-3}, μ(Mo–Ka) = 0.073 mm^{-1}, $F(000) = 1304$, prismatic crystal, colorless, size = 0.20 × 0.15 × 0.08 mm, 21043 reflections measured [$R_{int} = 0.022$], 3376 unique, $wR_2 = 0.115$ for all data, conventional $R = 0.044$ [$(D/s)_{max} = 0.001$] on *F*-values of 2587 reflections with $I > 2\ s(I)$, GooF = 1.039 for all data and 407 parameters. Unit cell determination and intensity data collection ($q = 25.1°$) were performed on an Enraf–Nonius KAPPA CCD diffractometer at 293(2) K. Structure solution by direct methods and refinement by full-matrix least-squares on F^2. Programs: COLLECT, (Nonius, 1997–2000) HKL2000 (Otwinowski and Minor, 1997), SHELX97 (Sheldrick, 2008). CCDC [Deposit No: 688118] contains the supplementary crystallographic data for this paper (see supplementary material section).

4.4. Biological activities

Extracts were tested against the chloroquine-resistant FcB1/Colombia strain of *P. falciparum* (Frappier et al., 1996). *P. falciparum* was maintained continuously *in vitro* in human erythrocytes according to Trager and Jensen (2005). The antiplasmodial activity was determined according to Desjardins et al. (1979). The extracts were dissolved in dimethylsulfoxide (DMSO) and tested at a concentration of 10 μg/ml. Compounds showing significant inhibition rates were submitted to serial dilutions with culture medium before being added to asynchronous parasite cultures (1% parasitemia and 1% final hematocrite) in 96-well microplates for 24 h at 37 °C. A concentration of 0.5 μCi of [^{3}H] hypoxanthine was then added to each well, and parasites were maintained for an additional 24 h. The growth inhibition for each compound concentration was determined by comparing the radioactivity incorporated in the treated culture with that in the control culture maintained on the same plate. The concentrations causing 50% inhibition of parasite growth (IC50) were calculated from the drug concentration-response curves.

The human diploid embryonic lung cells MRC-5 were seeded into 96-well microplates at 2000 cells per well. The cytotoxicity assays were performed according to a published procedure (Tempete et al., 1995). Taxotere® was used as a control compound.

Supplementary material

CCDC 689070 (**1**), CCDC 688119 (**1′**), CCDC 688120 (**9**) and CCDC 688118 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://

www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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