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Short Communication

New syntheses and potential antimalarial activities of new 'retinoid-like chalcones'

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Abstract

A series of 'retinoid-like chalcones' and diverse derivatives relative to licochalcone A were synthesized from a new enaminone synthon. These syntheses occurred via a new aromatic annelation. These new derivatives have been tested in vitro as potential antimalarial agents. The 4-hydroxy-chalcone-like (compound **6a**, derived from β-ionone) exhibits a good and reproducible inhibitory effect on the in vitro culture of *Plasmodium falciparum*, with an IC 50 lower than 10 μM for inhibition of ^{3}H-hypoxanthine uptake by parasites (respectively, 4.93 and 8.47 μM for strains K1 and Thaï).

Keywords: Plasmodium falciparum; Anti-malaria compounds; Chalcones; Enaminones; Licochalcone A

1. Introduction

Malaria is the major growing parasitic disease in the world [1,2], at an alarming rate and concerns of the most important public health in tropical and sub-tropical regions. Moreover, the continuous evolution of drug resistance is a serious dilemma and thus, the research of new advances in antimalarial chemotherapy is a vital problem [3]. With the exception of artemisin and its derivatives for the treatment of malaria [4], the drugs actually utilized have significant toxicity and present adverse side effects [5].

Recently, a lot of chalcones and derivatives have been previously synthesized and identified as potential antimalarials, using both molecular modeling and in vitro testing against the intact parasite (for recent Refs. see [6–10]). Licochalcone A (Fig. 1), isolated from *Glycyrrhiza inflata*, was initially proposed as a new antimalarial agent in 1994 [11] and a lot of derivatives of this natural compound have been recently synthesized and recognized as potential antimalarials. Licochalcone A has been identified as a potent inhibitor of mitochondrial functions in *Leishmania*, such as fumarate reductase (FRD), succinate dehydrogenase (SDH), NADH dehydrogenase (NDH), and succinate and NADH-cytochrome *C* reductases [12–14], but also of protease activities of *Plasmodium* and Trypanosomes [7,15–18].

Starting from β-ionone (series **a**) or α-ionone (series **b**), we have synthesized a series of new compounds from new enaminone synthons **1a**, **b** (Fig. 2). The term enaminone was introduced by Greenhill [19] in 1977 to describe an enamine of a 1,3-diketone.

Some of these compounds could be considered as 'retinoid-like chalcones' and possess structural analogy with licochalcone A (Fig. 3). Hence, this fact prompt us to test them, in order to examine their potential antimalarial activity.

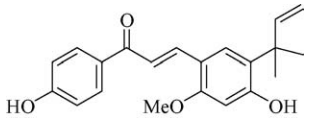

Fig. 1. Chemical structure of licochalcone A.

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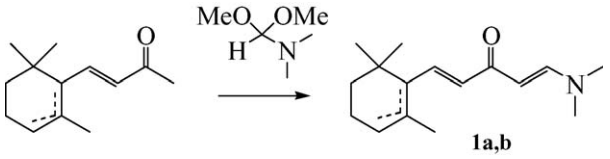

Fig. 2. Enaminones synthons.

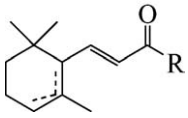

Fig. 3. Chalcones-like retinoids.

2. Chemistry

Condensations of **1a**, **b** with butyllithium [20] or the dianion derived from ethyl acetoacetate [21] led, in good yield, to compounds **2** and **3**. Similarly, 5-(1-pyrrolidinyl)-4*E*-penten-2-one reacted as reported above, leading to the correspondent salicylaldehyde **4**. Surprisingly, other selected dianions derivatives afforded the substituted α,β-unsaturated ketones **5-6**, 'retinoid analogs' of chalcones (Fig. 4).

3. Results and discussion

These new enaminones synthons **1a** or **1b** allow to obtain original retinoid compounds (**3**–**6**) substituted by an aromatic ring. These syntheses proceed via a novel annelation procedure with usually good yields (90–40%). Unexpectedly, compounds **4b** and **6b** were not isolated properly, and thus were not tested. In case of derivatives **5** and **6**, new retinoid-like chalcones were obtained. From enaminones synthons, this synthesis procedure was a new way to obtain aromatic substituted α,β-unsaturated ketones.

The results given in Table 1 show that the 4-hydroxy 'retinoid-like' chalcone **6a** is the most active compound with low IC_{50} (a 0.93 and 8.47 μM for the two strains) and low standard deviations. Thus, the activity is well reproducible. According to Liu et al. [10] compounds with I_{50} values below 10 μM were considered as having a "very good" activity, even if these values are higher than those of chloroquine.

Table 1
In vitro assays of the given compounds performed using cultures with a 3–6% parasitemia. Data are IC_{50} (μM) and "S.D." standard deviations for the three experiments

	Strain K1		Strain Thaï	
Compound	Mean	S.D.	Mean	S.D.
2a	19.11	6.23	15.39	6.09
2b	15.46	6.32	18.87	5.34
3a	23.82	6.12	43.54	9.71
3b	29.82	8.25	52.48	9.71
4a	34.77	9.34	43.16	8.97
5a	44.58	11.82	60.29	6.91
5b	40.64	7.30	54.37	7.45
6a	4.93	1.65	8.47	1.99
Chloroquine	0.26	0.05	0.13	0.04

The sub-structural motif '4-hydroxy-phenyl', present in licochalcone A, has been recognized as an important factor of activity in a recent work [7] despite a previous report which shown (in other derivatives), that hydroxylated chalcones were less active than the corresponding methoxy analogs [8,9]. Series **3**–**5** which bear an *ortho* or *meta* phenolic group are considerably less active. Unexpectedly, compounds **2** which have no aromatic or phenolic subsistent possess some activity.

The targets of chalones on malaria parasites are not yet clearly identified during the in vitro erythrocytic stages. Chalcones are considered as inhibitors of *P. falciparum* cysteine protease falcipain [7,15]. It seems credible that the presently studied compounds have the same mode of action, but this is not demonstrated.

In contrast to the potent inhibitory effect of chalones on the mitochondrial functions of *Leishmania*, the action on *Plasmodium* is questionable since the mitochondria of the blood-stage malaria parasites was historically considered to be functionally

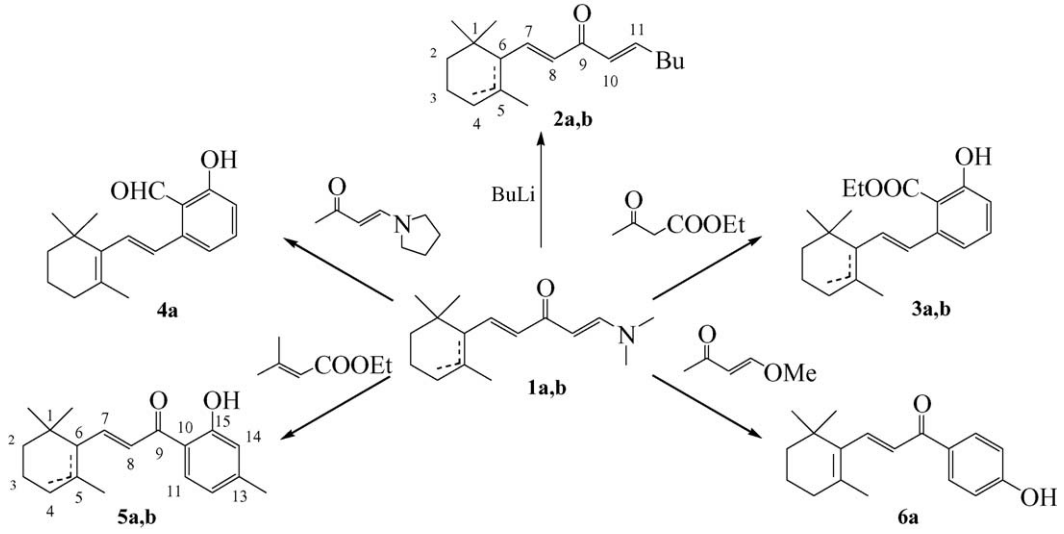

Fig. 4. Series **a:** double bond between C_5 and C_6; Series **b:** double bond between C_4 and C_5.

quiescent. However recent bioenergetic experiments [24,25] and data emerging from the genome project (http://plasmodb.org) suggest that mitochondria of *Plasmodium* blood stages are able to perform oxydative phosphorylation and they could harbor a full tricarboxylic acid cycle enzymes.

Present efforts are dealing with synthesis of novel 'retinoid-like chalcone' with variations on the cyclocitral part of the molecule.

4. Experimental protocols

4.1. Chemistry

4.1.1. General procedures

All experiences were carried out under argon. All starting products were purchased from Sigma-Aldrich. Melting points were measured on a Leitz 350 heated stage microscope and were not corrected. IR spectra were recorded on a Bruker IFS 55 spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker Avance DPX 400 spectrophotometer (^{1}H, 400 MHz, ^{13}C, 100 MHz), using $CDCl_3$ as solvent. Chemicals shifts were expressed in ppm downfield from internal TMS and *J* values were reported in Hertz. Analyses indicated by the symbols of the elements were within 0.35 of the theoretical values. Analytical thin layer chromatography was performed on a plastic sheet (0.2 mm, silica gel 60 F254, Merck). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography. Microanalyses indicated by the symbols of the elements or functions were within ± 0.4% of the theoretical values.

4.1.2. General procedure for the preparation of compound **2**

Under argon, 15 mmol of enaminone in 10 ml of anhydrous DME was stirred at –20 °C and then, 15 mmol of the organometallic compound in hexane (MeLi or BuLi) was added dropwise. The mixture was stirred and warmed to r.t., then heated at reflux for 1 h. The crude mixture was cooled at 0 °C and hydrolyzed by a cold solution of 1 M HC1. After addition of 50 ml of ether, the organic layer was washed with brine and dried over $MgSO_4$. After distillation of the solvent under reduced pressure, the crude product was purified by column chromatography (SiO_2/CH_2Cl_2).

4.1.3. General procedure for the preparation of compound **3**

Fifteen millimol of ethyl acetoacetate in 10 ml of anhydrous DME were added at –20 °C in 3 min under argon, at 15 mmol. of LDA in 10 ml of anhydrous DME. The solution was stirred at –20 °C for 15 min and 15 mmol of enaminone in 20 ml of anhydrous DME was rapidly added. Product **3** was isolated after workup describe above.

4.1.4. Procedure for the preparation of compound **4a**

Fifteen millimol of 5-(1-pyrrolidinyl)-4*E*-penten-2-one in 10 ml of anhydrous DME were added at –20 °C in 3 min under argon, at 15 mmol of LDA in 10 ml of anhydrous DME. The solution was stirred at –20 °C for 15 min and 15 mmol of enaminone in 20 ml of anhydrous DME was rapidly added. Product **4a** was isolated after workup describe above. The compound **4b** was not obtained with sufficient yield and purity (degradation during chromatography) for analyses ant tests.

4.1.5. General procedure for the preparation of compounds **5a**, **b**

Fifteen millimol of ethyl dimethylacrylate in 10 ml of anhydrous DME were added at –20 °C in 3 min under argon, at 15 mmol of LDA in 10 ml of anhydrous DME. The solution was stirred at –20 °C for 15 min and 15 mmol of enaminone in 20 ml of anhydrous DME was rapidly. Product **5a**, **b** were isolated after workup describe above.

4.1.6. Procedure for the preparation of compound **6a**

Fifteen millimol of 3*E*-4-methoxy-3-buten-2-one in 10 ml of anhydrous DME were added at –20 °C in 3 min under argon, at 15 mmol of LDA in 10 ml of anhydrous DME. The solution was stirred at –20 °C for 15 min and 15 mmol of enaminone in 20 ml of anhydrous DME was rapidly added. Product **6a** was isolated after workup describe above. The compound **4b** was not obtained with sufficient yield and purity (degradation during chromatography) for analyses ant tests.

4.1.7. Structural data

1a: According to Hickmott [24] procedure. Yellow crystals F 70 °C (95% IR: 2962; 2925; 1653; 1621; 1568; 1441; 1362; 1092; 997; 981. ^{1}H RMN ($CDCl_3$): 7.70 (d, 1H, $J = 12.5$, H_{11}); 7.19 (d, 1H, $J = 16$, H_7); 6.15 (d, 1H, $J = 16$, H_8); 5.18 (d, 1H, $J = 12.5$, H_{10}); 3.10 and 2.90 (2s, 6H, $N(CH_3)_2$; 2.04 (m, 2H, 2-CH_2); 1.77 (s, 3H, 5-CH_3); 1.61 (m, 2H, 3-CH_2); 1.47 (m, 2H, 4-CH_2); 1.07 (s, 6H, 6-CH_3). ^{13}C RMN (CO): 186.8 (CH); 152.9; 138.1; 132.2; 96.2 (CH_2): 39.6; 33.2; 19.0 (CH_3): 28.8; 21.6. Anal. CHN $C_{16}H_{25}NO$.

1b Beige crystals F 64 °C (95%). IR: 2920; 2862; 1662; 1645; 1621; 1545; 1420; 1357; 1269; 1256; 1094; 980. ^{1}H RMN ($CDCl_3$): 7.60 (d, 1H, $J = 12.5$, H_{11}); 6.53 (dd, 1H, $J = 15.4$ and 9.8, H_7); 6.04 (d, 1H, $J = 15.4$, H_8); 5.40 (sa, 1H, H_3); 3.04 and 2.80 (2 broad s, 6H, $N(CH_3)_2$; 2.20 (d, 1H, $J = 9.5$, H_6); 1.98 (m, 2H, 2-CH_2); 1.52 (s, 3H, 5-CH_3); 1.46 and 1.13 (2m, 2H, 3-CH_2); 0.86 and 0.80 (2s, 6H, 6-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 186.5 (CH); 153.5; 143.4; 132.8; 122.1; 95.8 (CH_2): 31.6; 23.4 (CH_3): 28.2; 27.3; 23.3. Anal. CHN $C_{16}H_{25}NO$.

2a: Yellow oil (70%). IR: 2958; 2928; 2862; 1666; 1632; 1613; 1456; 1341 987. ^{1}H RMN ($CDCl_3$): 6.92 (m, 1H, H_{11}); 6.73 (dd, 2H, $J = 15{,}5$ and $9{,}7$, H_7); 6.35 and 6,29 (2d, 2H, $J = 15{,}5$ and $15{,}6$, $H_8 + H_{10}$); 5.48 (m, 1H, H_3); 2.27 (m, 2H, 12-CH_2); 2,05 (m, 2H, 2-CH_2); 1.58 (s, 3H, 5-CH_3); 1,47 and 1.20 (2m, 2H, 3-CH_2); 1.47 (m, 2H, 13-CH_2); 1.37 (m, 2H, 14-CH_2); 0.93 and 0.86 (2s, 6H, 6-CH_3); 0.92 (t, $J = 7.2$, 15-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 189.2 (CH): 148.8; 148.4; 130.4; 128.9; 122.9 (CH_2): 32.8; 31.6; 30.7; 23.4; 22.7 (CH_3): 28.3; 27.2; 23.3; 14.3. Anal. CHN $C_{18}H_{28}O$.

2b: Yellow oil (70%). IR: 2958; 2928; 2862; 1666; 1632; 1613; 1456; 1341 987. ^{1}H RMN ($CDCl_3$): 6.92 (m, 1H, H_{11}); 6.73 (dd, 2H, $J = 15.5$ and 9.7, H_7); 6.35 and 6.29 (2d, 2H,

J = 15.5 and 15.6, H_8 + H_{10}); 5.48 (m, 1H, H_3); 2.27 (m, 2H, 12-CH_2); 2.05 (m, 2H, 2-CH_2); 1.58 (s, 3H, 5-CH_3); 1.47 and 1.20 (2m, 2H, 3-CH_2); 1.47 (m, 2H, 13-CH_2); 1.37 (m, 2H, 14-CH_2); 0.93 and 0.86 (2s, 6H, 6-CH_3); 0.92 (t, J = 7.2, 15-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 189.2 (CH): 148.8; 148.4; 130.4; 128.9; 122.9 (CH_2): 32.8; 31.6; 30.7; 23.4; 22.7 (CH_3): 28.3; 27.2; 23.3; 14.3. Anal. CHN $C_{18}H_{28}O$.

3a: Yellow oil (70%). IR: 2926; 2863; 1661; 1599; 1573; 1449; 1372; 1336; 1258; 1214; 1170; 1114. ^{1}H RMN ($CDCl_3$): 7.38 (dd, 1H, $J = J'$ = 8.2, H_{11}); 7.04 (d, 1H, J = 8.2, H_{12}); 6.94 (d, 1H, J = 16, H_7); 6.92 (dd, 1H, J = 16.0 and 1.0, H_{10}); 6.43 (dd, 1H, J = 16.0 and 1.0, H_8); 4.46 (q, 2H, J = 7.1, 14-$COOCH_2$); 2.06 (m, 2H, 2-CH_2); 1.79 (s, 3H, 5-CH_3); 1.65 (m, 2H, 3-CH_2); 1.51 (m, 2H, 4-CH_2); 1.39 (t, 3H, J = 7.1, 14-$COOCH_2CH_3$); 1.09 (s, 6H, 6-CH_3). ^{13}C RMN (CO): 171.0; 162.1 (CH): 134.0; 133.5; 130.0; 119.6; 116.2 (CH2): 61.7; 39.4; 32.7; 19.2 (CH_3): 28.8; 21.4; 14.3. Anal. CHN $C_{20}H_{26}O_3$.

3b: Yellow oil (80%). IR: 2960; 2917; 2854; 1660; 1601; 1572; 1449; 1372; 1335; 1278; 1254; 1215; 1115. ^{1}H RMN ($CDCl_3$): 7.38 (m, 1H, H_{12}); 6.99 (d, 1H, J = 15.4, H_8); 6.93 and 6.89 (m, 2H, H_{13} + H_{14}); 5.80 (dd, 1H, $J = J'$ = 9.5, H_7); 5.43 (m, 1H, H_3); 4.46 (q, 2H, J = 7.1, 14-$COOCH_2$); 2.31 (d, 1H, H_1); 2.06 (m, 2H, 5-CH_2); 1.69 (s, 3H, 2-CH_3); 1.54 and 1.25 (2m, 2H, 4-CH_2); 1.23 (t, 3H, J = 7.1, 14-$COOCH_2CH_3$); 0.98 and 0.94 (2s, 6H, 6-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 171.3; 162.2 (CH): 134.5; 134.4; 132.6; 121.6; 120.4; 116.8 (CH2): 62.1; 32.2; 32.7; 27.5 (CH_3): 27.3; 23.5; 15.7; 14.8. Anal. CHN $C_{20}H_{26}O_3$.

4a: Yellow oil (40%). IR: 2927; 2864; 1643; 1605; 1568; 1449; 1327; 1311; 1236; 1192; 1162; 762; 717. ^{1}H RMN ($CDCl_3$): 10.34 (s, 1H, CHO); 7.46 (dd, 1H, $J = J'$ = 8.0, H_{11}); 6.99 (d, 1H, J = 8.0, H_{12}); 6.86 (d, 1H, J = 8.0, H_{10}); 6.85 (d, 1H, J = 16, H_7); 6.55 (dd, 1H, J = 16, J' = 1, H_8); 2.06 (m, 2H, 2-CH_2); 1.79 (s, 3H, 5-CH_3); 1.65 (m, 2H, 3-CH_2); 1.51 (m, 2H, 4-CH_2); 1.08 (s, 6H, 6-CH_3). ^{13}C RMN (CO): 195.9 (CH): 137.5; 135.8; 127.8; 119.0; 116.7 (CH_2): 39.8; 33.3; 19.6 (CH_3): 29.3; 22.2; 15.7. Anal. CHN $C_{18}H_{22}O_2$.

5a: Yellow crystals, mp: 90 °C (70%). IR: 2931; 2866; 1638; 1575; 1504; 1364; 1351; 1297; 1258; 1234; 1208; 795. ^{1}H RMN ($CDCl_3$): 7.71 (d, 1H, J = 15.6, H_7); 7.70 (d, 1H, J = 8.2, H_{15}); 7.06 (d, 1H, J = 15.6, H_8); 6.83 (s, 1H, H_{12}); 6.73 (d, 1H, J = 8.2, H_{14}); 2.37 (s, 3H 13-CH_3); 2.14 (m, 2H, 2-CH_2); 1.89 (s, 3H, 5-CH_3); 1.67 (m, 2H, 3-CH_2); 1.53 (m, 2H, 4-CH_2); 1.16 (s, 6H, 6-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 193.3; 163.6 (CH): 145.1; 129.9; 124.4; 120.5; 119.0 (CH_2): 40.3; 34.3; 19.3 (CH_3): 53.3; 29.3; 22.4.

5b: Yellow oil (90%). IR: 2957; 2918; 2865; 1643; 1585; 1504; 1365; 1301; 1246; 1149; 793. ^{1}H RMN ($CDCl_3$): 7.72 (d, 1H, J = 8.2, H_{15}); 7.04 (dd, 1H, J = 15.0 and 7.0, H_7); 6.98 (d, 1H, J = 15.0, H_8); 6.82 (s, 1H, H_{12}); 6.74 (d, 1H, J = 8.2, H_{14}); 2.37 (s, 3H 13-CH_3); 1.90 (m, 2H, 2-CH_2); 1.63 (s, 3H, 5-CH_3); 1.55 and 1.24 (2 m, 2H, 3-CH_2); 0.98 and 0.90 (2s, 6H, 6-CH_3). ^{13}C RMN ($CDCl_3$) (CO): 193.1 (CH): 151.3; 130.1; 125.9; 123.3; 120.5; 119.0 (CH2): 31.5; 23.5 (CH_3): 28.3; 27.3; 23.3; 22.4. Anal. CHN $C_{19}H_{24}O_2$.

6a: Yellow oil (50%). IR: 3262; 2957; 2930; 1644; 1603; 1320; 1281; 1263; 1222; 1167; 839. ^{1}H RMN ($CDCl_3$): 8.35 (s, 1H, OH); 7.94 (d, 2H, J = 8.5, H_{11}+H_{15}); 7.62 (d, 1H, J = 15.8, H_7); 6.98 (d, 1H, J = 15.8, H_8); 6.99 (d, 2H, J = 8.5, H_{12}+H_{14}); 2.12 (m, 2H, 4-CH_2); 1.86 (s, 3H, 5-CH_3); 1.64 (m, 2H, 3-CH_2); 1.50 (m, 2H, 2-CH_2); 1.13 (s, 6H, 6-CH_3). ^{13}C RMN (CO): 190.1; 163.6 (CH): 144.9; 131.7; 130.0; 126.0; 116.1; 115.8 (CH_2): 40.3; 34.2; 19.3 (CH_3): 29.3; 22.3. Anal. CHN $C_{18}H_{22}O_2$

4.2. Biology

4.2.1. Parasite cultures

The *P. falciparum* Thailand strain Thai and strain K1 were used throughout this work. They gave similar results. Cultures were grown in complete medium consisting of RPMI 1640 (Life technologies, Inc.) supplemented with 11 mM glucose, 27.5 mM sodium hydrogen carbonate ($NaHCO_3$), 100 UI/ml penicillin, 100 μg/ml streptomycin and 8% heat-inactivated human serum albumin, following the procedure of Trager and Jensen [22]. Parasites were grown, at 37 °C, in human A^+ red blood cells (RBCs) at a 2% hematocrit, under a 3% CO_2, 6% O_2 and 91% N_2 atmosphere. The in vitro assays were performed using cultures with a 3–6% parasitemia as determined by counting parasites on Giemsa-stained smears.

4.2.2. Inhibition tests

Increasing concentrations of the different retinoid-like chalcones, dissolved in methyl sulfoxide (DMSO), were tested for their inhibitory effect toward the *P. falciparum* intraerythrocytic development. Parasites were allowed to grow at 37 °C for 24 h in a candle jar, then 0.5 μCi ^{3}H-hypoxanthine was added per well. After an additional 24 h incubation period, plates were freeze–thawed and harvested on filters. Dried filters were moistened in scintillation liquid mixture (OptiScint, Hisafe) and counted in a 1450 Microbeta counter (Wallac, Perkin Elmer).

Growth inhibition in percent was calculated from the parasite-associated radioactivity. Hundred percent ^{3}H-hypoxanthine incorporation was determined from control grown in the absence of the retinoid-like chalcones. Values for the IC_{50} were determined according to DesJardins et al. [23]. Each mean concentration was estimated from three different experiment sets.

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