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Oxygenated Chalcones and Bischalcones as Potential Antimalarial Agents†

Vishnu J. Ram,[a,*] Abhishek S. Saxena,[a] Shalini Srivastava[b] and Subhash Chandra[b]

[a]*Medicinal Chemistry, Central Drug Research Institute, Lucknow 226001, India*
[b]*Parasitology Divisons, Central Drug Research Institute, Lucknow 226001, India*

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Abstract—Oxygenated chalcones (**3a**,**b**) and bischalcones (**4a**–**j**) have been synthesized and evaluated for antimalarial activity against chloroquine sensitive and resistant strains of *Plasmodium berghei* in mice. Some of the screened compounds, **3a**, **4c**, **4e**, **4f** and **4i**, have shown significant activity at 100 mg/kg dose against sensitive strain.

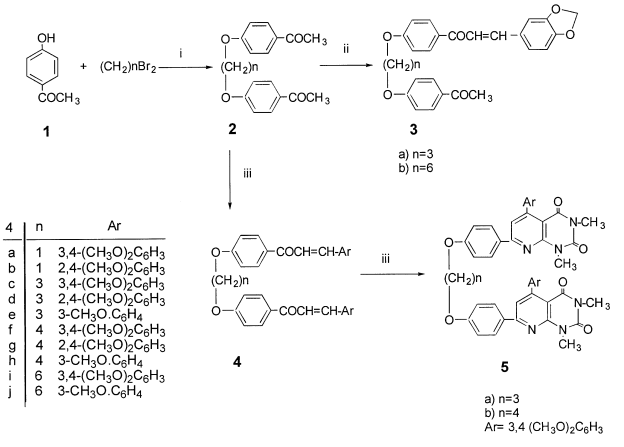
Introduction

The future of antimalarial chemotherapy appears bleak because of increasing cross-resistance to drugs, which are neither structurally similar nor pharmacologically related to those in clinical use. The main reason for this dangerous situation is the availability of a limited number of antimalarial drugs in clinical use. Thus the need for structurally different efficacious antimalarial drugs is self-evident. The problem of drug resistance can be circumvented either by identifying new targets which are critical to the disease process or essential for the survival of parasites. The other possible way could be to design and synthesize a new efficacious chemical entity with the least side effects. Natural products are known as the chief source of identification of lead structures. The structural modification of such compounds results in highly effective agents with reduced toxicity and side effects. Recently, licochalcone A, isolated from Chinese liquorice roots, has been reported[1,2] highly effective in an in vitro screen against chloroquine sensitive (3D7) and chloroquine resistant (Dd2) isolate of *Plasmodium falciparum*. The efficacy of this product is also confirmed against *Plasmodium yoelii* in mice. Thus, this provided a lead to design and synthesize chalcones and bischalcones as new antimalarials.

All the synthesized chalcones (**3a**,**b**) and bischalcones (**4a**–**j**) were evaluated for antimalarial activity against chloroquine sensitive and resistant strains of *Plasmodium berghei* in mice and some of the synthesized compounds indeed displayed significant activity for lead generation.

Synthesis

Chalcones (**3a**,**b**) and bischalcones (**4a**–**j**) were synthesized[3,4] by base catalyzed condensation of bisketones[5] (**1**) with aromatic aldehyde. To our surprise, a condensation of bisketones (**1**) with 3,4-methylenedioxybenzaldehyde always yielded chalcones (**3a**,**b**) under different reaction conditions. However, condensation of bisketones (**1**) with 3,4-dimethoxy-, 2,4-dimethoxy- and 3-methoxybenzaldehyde easily yielded bischalcones. Some of the bischalcone **4c** and **4f** on condensation–cyclization reactions[6] with 6-amino-1,3-dimethyluracil in sodium ethoxide solution led to bis-5-diazalumazines (**5a**,**b**) as shown in Scheme 1.



Scheme 1. Reagents and conditions: (i) K_2CO_3/acetone/reflux; (ii) piperonal/alc. KOH/rt; (iii) aryl aldehyde/alc. KOH/rt; (iv) NaOEt/6-amino-1,3-dimethyluracil/reflux.

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*Corresponding author.

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Biological Activity

Synthesized compounds were screened by suppressive method of Peters.[7] Male mice (Park strain) weighing (20 + 2) g were infected intraperitoneally with standard inoculum of one million parasitized RBC (1×10^6 PRBC). The animals were treated with 2–3 h of post inoculation. The inoculated animals were divided into two groups with five animals each for treatment. The first group of five animals received the same dose of a compound and the second group of five animals served as untreated control. The treatment was given for 4 consecutive days intraperitoneally.

In the case of screening against resistant strain, animals were divided into four groups of five animals each. During treatment the first group received a combined dose of test chemical and chloroquine (15 mg/kg), the second group received chloroquine (15 mg/kg) alone, the third group received test chemical alone and the fourth group received no drug and treated as control. Treatment was given for 4 consecutive days intraperitoneally. The screening results against sensitive and resistant strains in terms of % parasitaemia are presented in Table 1 and 2.

Table 1. In-vivo activity of chalcones (**3a**,**b**) and bischalcone (**4a**–**j**) against chloroquine sensitive strain of *P. berghei* infection in mice in terms of percent parasitaemia at 100 mg/kg dose ×4 days (ip)

	% Parasitaemia on days						
Sample no.	D5	D7	D9	D11	D13	D15	D17
3a	0	0.35	1.7	2.75	3.0	3.85	D[a]
3b	1.0	2.1	4.0	6.3	D		
4a	2.8	5.6	7.25	D			
4b	3.4	5.0	2.0	D			
4c	0.01	0.05	0.6	0.9	1.5	3.0	
4d	3.2	4.7	8.0	D			
4e	0	0.52	1.0	1.8	1.81	1.7	
4f	0	0	0.7	1.0	1.5	2.0	
4g	1.5	2.0	2.4	5.2	6.6	9.5	D
4h	1.5	2.0	3.9	6.4	19	D	
4i	0	0.16	1.3	2.1	3.1	4.25	D
4j	2.1	3.4	6.8	11	D		

[a]D, death of animal.

Among all the screened chalcones (**3**) and bischalcones (**4**) against chloroquine sensitive strain, only compounds **3a**, **4c**, **4e**, **4f** and **4i** exhibited significant activity at 100 mg/kg dose on day 5. It is evident from the screening data (Table 1) that the level of parasitaemia usually increased with advancement of days. Only compound **4f** showed zero percent parasitaemia even on day 7, increasing slowly to 2% on day 15. In the case of **4e**, percent parasitaemia also increased at the rate of 1.7% on day 15. The compound **4c** was also active but inferior to **4f**.

The antimalarial activity of these compounds revealed that the sites of oxygenated substituents in the phenyl ring greatly influence the activity profile. In general, chalcones with 3,4-methoxy substituents in the phenyl ring displayed significant activity compared to 2,4-dimethoxy substituents. The importance of methylene chain length in **3** and **4** cannot be ignored. As is evident, the activity data of **4e**, **4h** and **4j**, the three-methylene-groups chain contributes significantly more to the activity than the four- and six-methylene-groups chain. This observation was also found true in the case of **3a** and **3b**.

The antimalarial activity of these compounds in the resistant strain was quite surprising, as inactive compounds in the sensitive strain were found significantly active in the resistant strain. As it is evident from the screening results (Table 2), only compounds **4a** and **4j** displayed zero percent parasitaemia on day 7, slowly increasing on subsequent days. Two other compounds **3a**

Table 2. Effect of chloroquine (CQ, 15 mg/kg/day), test compounds (TC, 50 mg/kg/day) for 4 days and their combination thereof on parasitaemia in resistant strain

		% Parasitaemia on days							
Sample no.		D5	D7	D9	D11	D13	D15	D17	D19
Control		3.2	5.4	8.1	14.6	22	D[a]		
3a	TC	0.7	1.8	2.2	6.7	7.8	11.5	D	
	TC + CQ	0	0.04	1.96	3.0	5.1	7.0	13	D
3b	TC	2.2	3.2	4.8	6.5	9	10	D	
	TC + CQ	0.02	2.0	3.2	3.2	5.5	8	D	
4a	TC	1.5	2.3	5.8	10.2	14.3	D		
	TC + CQ	0	0	0.3	0.8	1.4	4.4	11.6	22.6
4c	TC	0.74	2.4	2.0	5.0	10.4	D		
	TC + CQ	0	1.3	1.9	7.6	12.2	18	24	D
4d	TC	1.3	2.2	4.8	8.4	10.0	12.5	16	D
	TC + CQ	1.2	2.3	3.76	7.7	9.5	13.7	18	D
4e	TC	1.75	1.9	4.2	4.2	5.4	13	19	D
	TC + CQ	0.08	1.1	3.0	3.0	4.6	7.0	9.5	13
4f	TC	1.2	2.5	2.5	5.0	6.9	13.2	D	
	TC + CQ	0.002	0.3	1.8	2.7	7.5	D		
4g	TC	2.6	3.5	3.4	8.0	7.2	8.3	D	
	TC + CQ	0.2	0.6	4.0	4.9	7.5	13	18	D
4h	TC	1.9	2.1	5.7	6.6	10.8	13.3	D	
	TC + CQ	0.8	3.2	2.9	5.0	7.5	10	16	D
4i	TC	0.8	1.6	2.0	4.3	7.3	15	D	
	TC + CQ	0	0.06	1.8	2.3	6.0	7.5	11.0	D
4j	TC	1.8	3.2	7.9	9.5	13	D		
	TC + CQ	0	0	0.14	2.0	3.6	6.6	11.5	

[a]D, Death of animal.

and **4i**, also showed antimalarial activity but were inferior to **4a**. The order of activity of these compounds was **4j** >**4a** >**3a** >**4i**. Activity in the case of resistant strain was also influenced by site-oxygenated substituents. Compounds with 3-methoxy and 3,4-dimethoxy groups were found significantly active, compared to 3,4-methylenedioxy and 2,4-dimethoxy substituted derivatives.

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