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In vitro anti malarial evaluation of some thiazole containing chalcone derivatives

Mishra, Richa[1]; Jain, Surendra[2*]
[1] *Technocrats Institute of Technology-Pharmacy, Bhopal & R.A. at Mahatma Jyoti Rao Phoole Univeristy, Jaipur, India*
[2]*Sagar Institute of Research and Technology-Pharmacy, Bhopal, India*
*prof.surendrajain@gmail.com, rbmishra06@gmail.com

Abstract

Twenty thiazolyl chalcones were tested for their ability to inhibit the growth of *Plasmodium facliparum in vitro* by using the candle jar method for antimalarial assay. The percent inhibiton of parasitemia was calculated from blood smears stained with geimsa stain. The best compounds had chloro or methoxy group in the *para* position of the phenyl ring B of the molecule.

KEYWORDS: CHALCONE, PLASMODIUM FALCIPARUM, EC_{50}, CANDLE JAR, PARASITEMIA

Introduction

Despite several initiatives by the world health organization to curb malaria, the disease still remains one of the most serious health problems and a major cause of mortality and morbidity in the endemic regions. Resistance of *Plasmodium falciparum* to chloroquine and sulfadoxine-pyrimethamine result in millions of deaths every year. In the recent years, the treatment of malaria has been based on artemisinin and artemisinin resistance in *Plasmodium falciparum* has been reported in Cambodia. Newer antimalarial drugs have to be developed to overcome the deficiencies of the current therapies. Over the years chalcones have been the thrust molecule to be researched upon for their antimalarial and antileishmanial potentials. Several reports of antimalarial and antileishmanial activity of chalcones have been made. Structure activity relationship (SAR) studies of chalcones have been performed for chalcones to design newer chalcone derived potential molecules.

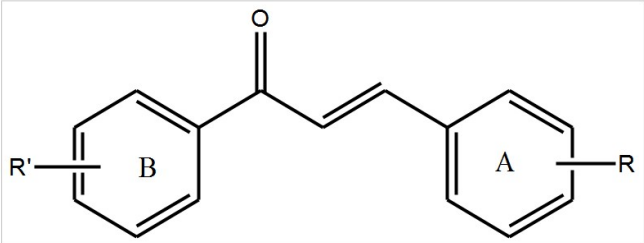

Fig. 1: Chalcone

The results reported by Liu Mei from structure activity relationship studies of chalcones as anti-malarial and antileishmanial compounds reveal the importance of ring A and ring B in the antiprotozoal activity of chalcone. The findings of the study for structural requirements of anti-malarial activity of chalcones analyzed by principal component analysis (PCA), projection to latent structures analysis (PCL), conventional multiple linear regression and CoMFA suggest the requirement of bulky substituent on ring B and a large sized ring A with low lipohilicity and presence of electron withdrawing and polar substituent on ring A.

Another SAR study initiated by Lim et al aimed to establish the structural requirements for novel chalcones revealed the importance of electron withdrawing substituent on ring A for tHe anti-malarial activity. A library of 88 chalcones were synthesized and evaluated for anti-malarial potency in order to establish the structure activity relationship of chalcones as anti-malarial compounds by Tadigoppula et al. The results obtained show that the presence of heteroatom in ring A (particulary 3-pyridine) was found to potentiate the anti-parasitic activity. Reduction of the α,β-olefinic bond reduced the anti-malarial potency of the compounds. The anti-parasitic potentiating effects of pyridine as ring A substituted with electron donating and electron withdrawing groups was also reported.

More than 200 derivatives of chalcones have been assayed for their antimalarial acitivity ever since the potential antimalarial activity of Licochalcone A was reported.

In the present study, the *in vitro* antimalarial potential of some novel thiazolyl chalcones has been reported against *Plasmodium falciparum*.

Methods

Twenty thiazolyl chalcones used in this study were synthesized using method described in our other report.

Parasite culture

Blood culture of *Plasmodium falciparum* was continuously cultured according to the method described by Trager and Jensen. Briefly, parasites were maintained in continuous culture on human erythrocytes (O+ blood group), in RPMI 1640 medium supplemented with 10% of human AB+ serum, 25 mM HEPES, 19 mM sodium carbonate, and 45 µg/mL gentamicin sulfate, at pH 7.2 in an atmosphere of 91% nitrogen, 6% carbon dioxide and 3% oxygen. The medium was changed each day.

Antimalarial Assay

All the synthesized compounds were evaluated for antimalarial activity using the following procedures.

In a 96 well microtitre plates, 5 µl of erythrocytes with 0.3% parasitemia were maintained in 990 µl of RPMI-1640 medium to get a final concentration of 3% parasitemia. Various concentrations of test compounds were prepared in DMSO and 5 µl of each test solution was added to individual wells. The 1st well served as the control with only the medium, the 2nd well contained only the infected medium and served as the negative control whereas the 3rd well served as the positive control with pyrimethamine solution as the test compound. The plates were incubated in a candle jar at 37°C for 48 h. After incubation, blood smears from each well were stained with giemsa stain and the slides were microscopically observed for the presence of parasites. The percent parasitemia was calculated and the test concentration that inhibited 50% parasitemia relative to the negative control was recorded as the EC_{50} value of the test compounds. All the results reported represent a mean of three experiments.

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No. of parasites per µL of blood = No. of
parasites x (8000 / no. of WBCs counted)
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Results

The results of antiplasmodial assay are presented in table 1. The EC50 values represents the concentration of the test compound necessary to inhibit the increase in parasite density by 50% at 48 h.

See table 1.

Discussions

The results indicate that the position and the type of substitutions influence the antimalarial activity of the test compounds. The test compounds with substitution on the R_3 position exhibit a higher inhibition of parasitemia at a concentration range of 5- 50 µg/mL (compounds 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i). Compounds with substitutions at R_1, R_4 and R_5 (compounds **3j, 3k, 3l, 3m, 3o, 3q, 3s, 3t**)were the weakest antimalarial compounds and were unable to inhibit 50% parasitemia even at a concentration of 100 µg/mL. Compounds with substitution at R_2 exhibited and EC_{50} value in the range of 10-50 µg/mL concentration (compounds **3p, 3r**). The absence of substituent on any position of the ring B also led to inactivity of the molecule (**3a**).

The type of substitution on R_3 played important role in antimalarial activity with compounds with electron withdrawing groups being more active compared to others. The presence of nitro group on R_3 was found to be detrimental of inhibition of *Plasmodium falciparum*. The presence of an OCH_3 and Cl group at position R_3 exhbited the maximum potency at a concentration of 5 µg/mL (**3g, 3h**).

Conclusion

In summary, the study led to the conclusion that chalcones with a dichlorothiazolyl ring A and a phenyl ring B possess the potential to be a promising antimalarial compounds. The introduction of other electron withdrawing groups in the para position of phenyl ring B maybe useful for identifying other antimalarial compounds.

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Compd. No.	R_1	R_2	R_3	R_4	R_5	EC_{50} (µg/mL)
3a	H	H	H	H	H	>100
3b	H	H	OH	H	H	10
3c	H	H	NH_2	H	H	50
3d	H	H	NO_2	H	H	50
3e	H	H	Br	H	H	50
3f	H	H	CH_3	H	H	10
3g	H	H	OCH_3	H	H	5
3h	H	H	Cl	H	H	5
3i	H	H	F	H	H	50
3j	H	H	H	NO_2	H	>100
3k	NH_2	H	H	H	H	>100
3l	H	NH_2	H	H	H	>100
3m	H	Br	H	H	H	>100
3n	Cl	H	Cl	H	H	10
3o	Cl	H	H	H	H	>100
3p	H	OH	H	H	H	10
3q	CH_3	H	H	H	H	>100
3r	H	Cl	H	H	H	50
3s	OH	H	H	H	OH	>100
3t	OH	H	H	H	H	>100

Table 1: EC_{50} value of chalcones against *Plasmodium falciparum*