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STUDY OF HEME ROLE IN MALARIA INFLUENCED RBC AND ANTI-MALARIAL CHALCONE DERIVATIVES

Chemistry

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ABSTRACT

Chalcone (1,3-diaryl propenone or 1,3-diphenyl-2-propen-1-one), constitutes an important natural product which possess a wide range of biological activities, such as antiviral, antioxidant, antibacterial, antifungal, antitumor, anti-inflamatory, antimutagenic and antimicrobial. Antimalarial activity is also shown by Licochalcone A and other oxygenated chalcones. Here we will listing antimalarial chalcone derivatives and discussed erythrocytic phase of malaria parasite and attractive target to develop antimalarial drugs.

KEYWORDS

Chalcone derivatives, Heme, Malaria, P. falciparum.

INTRODUCTION

Malaria occurs world-wide in over 90 countries. According to the World Health Organization, 36% of the global population live in areas where there is a risk of malaria transmission. Malaria transmission occurs primarily in tropical and subtropical regions in sub-Saharan Africa, Central and South America, The Indian subcontinent, South-East Asia, etc.

The word chalcone is derived from the Greek word "chalcos" meaning bronze. The chalcone compounds contain 1,3-diphenyl-2-propen-1-one. It exists in two forms, cis and trans as shown in Figure 1. Trans isomer of chalcone is thermodynamically favourable and more stable than cis isomer. They are the first isolable compounds during flavonoid biosynthesis in plants. It is formed abundantly in plant only if the enzyme chalcone isomerase, which catalyzes the cyclization of chalcone to flavonone is absent.[1] The numbering of the carbon atoms in aromatic rings A and B in chalcone is shown in Figure 1.

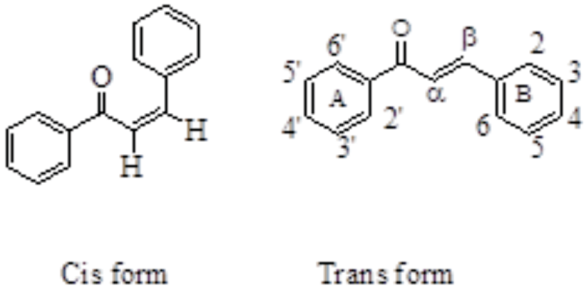

Figure 1: Geometrical isomers of Chalcone

Chalcones were first synthesized in the laboratory in the late 1800s but naturally occurring chalcones were not isolated until 1910. Natural chalcones occur mainly as petal pigments and have been found in the heartwood, bark, leaf, fruit & root of various species of trees and plants.

Heme Role In Malaria Influenced RBC

The symptomatology of malaria is due to erythrocytic phase. The synchronous maturation of parasites leads to the erythrocyte burst together with an attack of fever and deep anemia. As each red blood cell burst (every 48 hours for *P. falciparum*), parasites are released for further erythrocytic re-invasion. Thus, the parasite grows and reproduces asexually within the red blood cells by digesting hemoglobin of the host cell. The clinical manifestations are produced when the merozoites and other toxic materials are simultaneously released into the circulation with rupture of large number of infected erythrocytes. By degradation of hemoglobin, parasites release high quantities of free heme (which is the non-protein component of hemoglobin) and amino acid of globin protein. Amino acids are key food for parasites. Free heme is toxic to cells, so parasite converts it into an insoluble crystalline form called hemozoin or malaria pigment [2]. The formation of hemozoin is essential for the survival of these parasites; hence it is an attractive target for developing drugs.

There are two enzymes in parasite food vacuole which are responsible for cleavage of peptide bonds i) Cystein protease and ii) Plasmepsin. The mechanism of cleavage[3] of peptide bond by Cysteine protease is given in Figure 2.

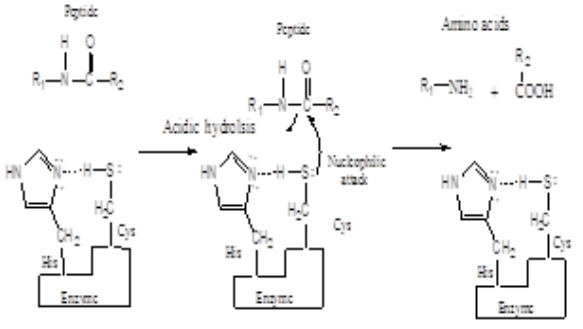

Figure 2: Mechanism of cleavage of peptide bond by cysteine protease

Free heme Fe(III) is very toxic because it can generate reactive oxygen species[4] and may induce oxidative stress leading to parasite death[5,6]. Since free heme Fe(III) is a lipophilic molecule, it can easily intercalate in the membrane and may cause changes in membrane permeability, lipid organization and induces lipid peroxidation of parasite membrane[7,8]. Oxidation of membrane components induced by free heme Fe(III) promotes cell lysis and ultimately death of the parasite[9].

Chalcone As Antimalarial Drugs

Plasmodium falciparum and *Plasmodium vivax* are the two major human malaria parasites. *P. falciparum* is responsible for most of the deaths, and it has developed resistance to nearly all available drugs. No wonder that the antimalarial activity of chalcones has generated great interest. Licochalcone A: An oxygenated chalcone isolated from the root of Chinese liquorice *Glycyrrhiza inflata* is found to inhibit fumarate reductase, a selective target present in parasite mitochondria. In this study, we found that Licochalcone A has multiple targets in *P. falciparum* mitochondria. Complex II and *bc*1 complex were inhibited by Licochalcone A at low concentrations**.** Thus, energy metabolism is one of the indispensable systems for the survival of the parasite, and the enzymes of the energy-transducing pathway are promising targets of antiparasitic drugs.

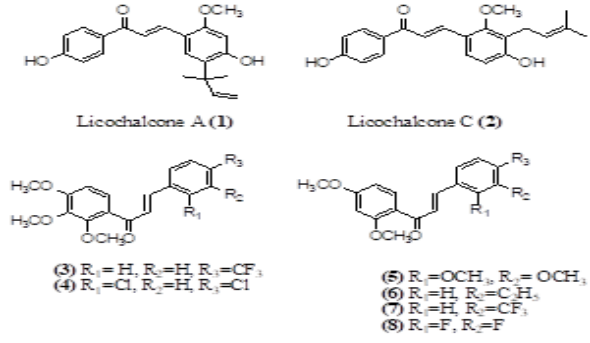

Figure 3: Chalcone derivatives (1-8)

Antimalarial properties of some chalcones derivatives are derived from their ability to inhibit the parasitic enzyme cysteine protease. Enzymes catabolise globin into small peptides within the acidic food vacuole of the intra-erythrocytic malaria parasite. Many chalcones have been described for their high antimalarial activity, probably as the result of a Michael addition of nucleophilic species to the double bond of the enone[10-12].

Licochalcone A **(1)** has been reported [13,14] as highly effective in an *in vitro* screen against chloroquine-susceptible (3D7) and chloroquine-resistant (Dd_2) *P. falciparum* strains in a [3H] hypoxanthine uptake assay. Licochalcone A administered either intraperitoneally or orally for 3-6 days protected the mice from the otherwise lethal *P. yoelii* infection.

In a detailed study Liu et al.[15] and Go et al.[16] showed that *in vitro* antimalarial activity of chalcones against a chloroquine-resistant strain of human malarial parasite, *P. falciparum* (K1) was mainly determined by the properties of ring B. The size and hydrophobicity of substituents were identified as critical parameters. Hydroxylated chalcones were less active than the corresponding alkoxylated analogues. A few of the alkoxylated chalcones **(3-8)** had IC_{50} values below 6.5μM.

5-Prenylbutein **(9)**, Licoagrochalcone A **(10)** and Homobutein **(11)** [17] showed *in vitro* antiplasmodial activity against the chloroquine-sensitive (D6) and the chloroquine-resistant (W2) strains of *P.falciparum* with IC_{50} values in the range of 10.3 -16.1μM.

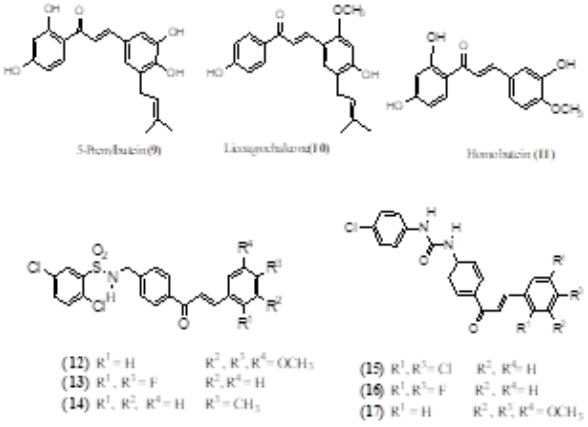

Figure 4: Structure of chalcone derivatives (9-17)

Most of the sulphonamide chalcones[18] possessing di- and trimethoxy substituted groups in the aromatic ring A showed measurable levels of inhibition of β-hematin formation with IC_{50} 0.48μM for compound **12** and 0.67μM for compound **13**. The most active compound **14** was also effective as anti-malarial by the inhibition of cultured *P.falciparum* (1μM). Having only one Cl, F, CH_3 or OCH_3 substituent in the aromatic ring did not improve the activity of the sulphonamide chalcones compared with that of the corresponding disubstituted or trisubstituted analogues. The compounds which are not strongly basic, a property required for accumulation in the malaria parasite acidic food vacuole in which hemozoin formation takes place, have poor antimalarial activities.

Dominguez et al.[19] reported a series of phenylurenyl chalcone derivatives with substitution in ring A. Their data suggests that the activity in most cases was governed to a large extent by groups attached to the substituted aromatic ring A (difluoro, dichloro, trimethoxy). The phenyl urenyl chalcone derivatives **(15-17)** were excellent inhibitors against cultured *P. falciparum* parasites (IC_{50} 1.76 - 10μM), with a good correlation.

Yadav et al.[20] synthesized a series of twenty-seven novel chalcone derivatives and their antimalarial activity was determined against asexual blood stages of *P. falciparum*. In that series the chalcone derivative 1-(4-Benzimidazole-1-yl-phenyl)-3-(2,4-dimethoxy-phenyl)-propen-1-one demonstrated the most potent antiplasmodial activity in vitro with IC_{50} of 1.1 μg/ml, as compared to natural phytochemical licochalcone A (IC_{50} of 1.43 μg/ml).

CONCLUSION

This study will open new window for researchers to develop new libraries of chalcone derivatives and find more potent drugs to cure malaria that would be cost effective, especially considering rising drug resistance.

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