Chalcones as an Emerging Lead Molecule for Antimalarial Therapy: A Review

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Abstract: Chalcones (1, 3, diaryl-2-propen-1-ones), are one of the plant secondary metabolite belonging to flavonoid family and has been widely explored in past decennium for its various pharmacological activities including antimalarial activity. *Plasmodium* aspartate proteases and cysteine proteases are the promising targets in malarial chemotherapy to overcome the drug resistance. Chalcones supposed to show antimalarial activity by inhibiting either *Plasmodium* aspartate proteases or cysteine proteases. This review covers the mechanism of action, previous reported studies showing antimalarial activity of natural and synthetic chalcones and its derivatives along with future prospects to fight against drug resistant malaria. These compounds provide an option of developing inexpensive, synthetic therapeutic antimalarial agents and may serve as lead compounds for development of drug in near future.

Keywords: Malaria, *Plasmodium*, activity, structure, cysteine protease.

INTRODUCTION

Malaria is a devastating infectious disease of almost half of the world's population which is caused by five species of parasites of the genus *Plasmodium* that affect humans (*P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi*). However, malaria due to *P. falciparum* is the most mortiferous, and it predominates in African region [1]. Every year about one million deaths and nearly 250 million cases are reported due to malaria. Among all geographical regions, sub-Sahara African have the highest risk of contracting malaria, with an estimation of 81% cases and 91% deaths in 2010 in the WHO African Region in which, children below the five years of age and pregnant women being most severely affected [2]. According to WHO, India has been accounted as the contributor of approximately 70% of the total cases of malaria evidenced in the South East Asian region [3] and annually around 1.5 million confirmed cases are reported by the National Vector Borne Disease Control Programme (NVBDCP), out of which 40–50% are due to *Plasmodium falciparum* [4].

For several decades, Chloroquine (CQ), a 4-aminoquinoline which was previously characterized by its efficacy, minimal host toxicity and affordability was the gold standard for the treatment of malaria [5]. Extensive worldwide use of CQ in the beginning of the late 1940s, led to the first reports of CQ-resistant strains of *P. falciparum* after a decade later [6]. Today, there is massive spread of CQ resistance in majority of malaria-endemic regions, rendering this drug to be ineffective. Currently, Artemisinin-based combination therapy (ACT) is the first line treatment in *P. falciparum* malaria (WHO, 2011). However, limited accessibility of ACT together with reduced susceptibility of *P. falciparum* to artemisinin derivatives [7, 8] has necessitated the development of novel antimalarial drugs [9, 10]. Another important scenario is the exploration of secondary plant metabolites for the antimalarial activity. Since, from past few decenniums the two most important drugs which are available today to treat severe *falciparum* malaria, quinine and derivatives of artemisinin are derived from plant sources. In the case of artemisinin, a moderate chemical modifications of the natural product parent nuclei have led to arrays of exceptionally potent antimalarial that are now widely used for the treatment of malaria [11]. However, Artimisnin-based antimalarial therapies are too expensive to be afforded by developing countries that needs most, as low yields from the origin plant, *Artemisia annua l*., and also due to the high cost of the specialized processing involved in the purification of these compounds. Since, malaria is strongly associated with poverty, it has been estimated that mortality rates from malaria are highest in countries with a lower GNI (Gross National Income) per capita [3]. So, to combat malaria, new drugs at reasonable cost are desperately needed. Chalcones constitute an important group of plant secondary metabolite with selective inhibition against *P. falciparum*, first reported for licochalcone A [12], with low cost of production, ease availability, thus making them promising antimalarial compounds. This review summarizes, proposed mechanism of action of

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chalcones on *Plasmodium* along with previously reported natural and synthetic chalcone derivatives showing potent antimalarial activity.

Chalcones

Chalcones (1,3-diaryl-2-propen-1-ones), are one of the plant secondary metabolite belonging to flavonoid family which are pigmented and are precursors of open chain flavonoids and isoflavonoids, that are abundantly present in edible plants. They are small, non-chiral molecules having molecular weight in the range of 300–600 g/mol with relatively high lipophilicity a (Log P ~5–7) [13]. Chalcone may exist in *cis* and *trans* isomeric forms, of which the *trans* form is thermodynamically more stable [14]. Chemically consists of open-chain flavonoids in which the three-carbon α,β-unsaturated carbonyl system is used as an adjunct between two aromatic rings A and B. Majority of naturally occurring chalcones is polyhydroxylated in the aryl rings. Most of the chalcones have radical quenching properties due to presence of phenolic groups that have raised interest in using the chalcone rich plant extracts as therapeutic compounds or food preservatives [15]. Primordial therapeutic applications of chalcones can be associated with the thousand-year old use of plants and herbs for the treatment of different medical disorders [16]. Chalcones, either natural or synthetic, are known to exhibit a broad spectrum of biological activities, including antimalarial [17], anti-inflammatory [18], cytotoxic [19, 20], anticancer properties [21, 22], modulation of P-glycoprotein-mediated multi-drug resistance [23] and antioxidant [24].

Biosynthesis and Chemical Synthesis of Chalcones

Kostanecki and Tomar [25], did pioneered work in the synthesis of natural coloring compounds and were first to coin the term 'chalcone'. Chalcone is found to be one of the major intermediate in the biosynthetic pathway of flavanoids and contribute significantly to the total amount of flavonoids [26] (Figure **1**).

Due to simple structure, ease availability, and various ways of cyclization, this class of compounds has emerged as paramount in the search for lead molecules with therapeutic potential. Briefly, the traditional methods for the synthesis of 1,3-diaryl-2-propenones involves the use of strong bases such as NaOH, KOH, Ba(OH)2, hydrotalcites, LiHMDS, calcites NaNO3/natural phosphate. An acid-catalyzed aldol condensation, e.g. AlCl3, BF3, dry HCl, ZrH2/NiCl2 and RuCl3 (for cyclic and acyclic ketones) has been also reported [27]. However, can be readily synthesized in laboratory by the Claisen-Schmidt reaction which is very easy and simple to conduct as well as inexpensive [28] (Figure **2**).

Mechanism of Action against *Plasmodium*

Phlorizidin, a naturally occurring dihydrochalcone glycoside extracted from *Micromelum tephrocarpum*

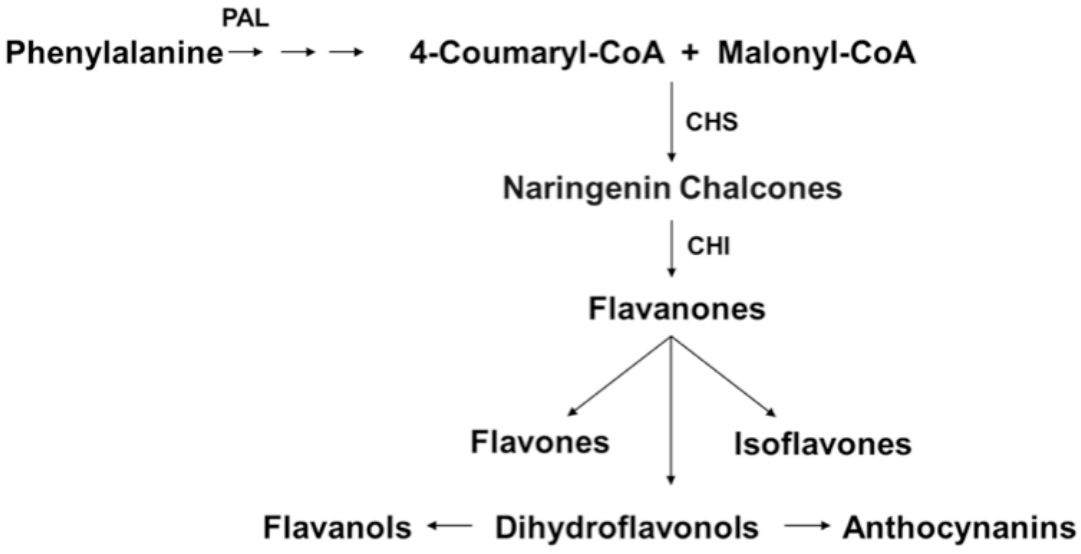


Figure 1: Schematic overview of the flavonoid biosynthesis pathway.

PAL: phenylalanine-ammonia, CHS: chalcone synthase, CHI: chalcone isomerase, F3H: flavanone-3-hydroxylase, IFS: isoflavone synthase, FNS: flavone synthase, FLS: flavonol synthase, DFR: dihydroflavonol reductase, ANS: anthocyanidin synthase.

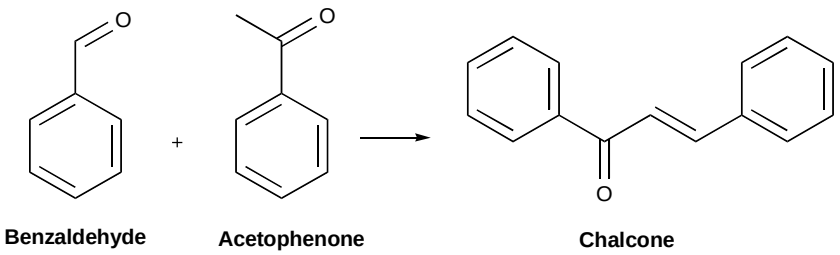


Figure 2: Chemical method for synthesis of chalcone.

(Rutaceae), was one of the first chalcones shown to possess antiparasitic activity [29]. In traditional medicine, it was used for the treatment of malaria, as it has bitter taste like quinine and other antimalarial drugs. Recent studies provide an experimental basis for its antiplasmodial activity. Phlorizidin hinders the permeability induced in *Plasmodium* infected erythrocytes to several substrates such as glucose. Out of this natural product Licochalcone A, isolated from Chinese licorice roots is the most promising compound [30]. The activity of Licochalcone A is well illustrated *in vitro* and *in vivo* against a panel of different parasites including *P. falciparum L. donovani* and *L. major*. Subsequently, with foundation of Licochalcone A as a lead structure, a large number of chalcones have been synthesized and structure-activity relationships determined with regard to their antiplasmodial, antileishmanial and trypanocidal activity [31]. Evidences from molecular modeling studies, reveals that chalcones have not only rigid confirmation but can also adopt an extended structure due to the nature of the conjugated linker. The resulting linear, nearly planar structure, fits perfectly into the active site of *Trypanosoma* and *Plasmodium* cysteine proteases [17] and responsible for its activity. Apart from this, exact mechanism for antiplasmodial activity of chalcones is still not clearly documented, although several mechanisms have been suggested for different chalcone derivatives including inhibition of a parasite-induced permeation pathway of erythrocyte membrane [32], glutathione (GSH)-dependent haemin degradation [33], components of mitochondrial respiratory chain, that is, bc1 complex and complex II, succinate ubiquinone reductase [34], cyclin-dependent protein kinases [35], and plasmepsin II [36]. Primarily during erythrocytic malarial life cycle, invasion of the host erythrocytes by free merozoites is responsible for most of the clinical manifestations of malaria. The intracellular parasite develops into a more metabolically active trophozoite from a ring stage then divides asexually and becomes a schizont, and ultimately cleaves the host erythrocyte, releasing daughter merozoites that breach other erythrocytes to commence another cycle. Malaria parasites have a limited capacity for synthesizing amino acids, and the quantity of free amino acids within host erythrocytes is not sufficient to the meet the protein requirement of the parasite [37]. To obtain free amino acids for protein synthesis, erythrocytic trophozoites degrade hemoglobin within an acid food vacuole. Various evidence supports that malarial cysteine and aspartyl proteases are mediator of hemoglobin degradation [38]. The cysteine protease inhibitor E-64 [L-trans-epoxysuccinylleucylamido (4-guanidino) butane] and the aspartyl protease inhibitor pepstatin known to block further growth and development of *P. falciparum* [39-43]. The chalcone derivatives are also believed to interact and inhibit the *P. falciparum* enzyme cysteine protease (falcipain), one of the key enzymes involved in the hemoglobin degradation within the acidic food vacuole of the intra-erythrocytic parasite [44]. The toxic heme (ferriprotoporphyrinIX) molecules released from hemoglobin catabolism is converted to non-toxic hemozoin (b-hematin) within the food vacuole [45] and inhibition of this process proves fatal for the parasite (shown below in Figure **3**). Structure-based drug design of antimalarial chalcone derivatives predicts trophozoite cysteine protease as the most likely target enzyme [46]. These compounds are stable in the presence of falcipain enzyme and adopt a unique folded conformation to fit into the long cleft of the active site of the cysteine protease enzyme [47]. Chloroquine evidently does not act by these mechanisms [48]. Thus, the malarial cysteine protease is a promising target for the development of treatments for chloroquine-resistant malaria.

Antimalarial Activity of Chalcone

Licochalcone A (1) present in the Chinese licorice root which, under the name of Gan Cao, is used in traditional Chinese medicine [49]. The structure of Licochalcone A was first reported in 1975, [50] in 1994, Chen *et al*. [12], first demonstrated significant inhibitory effect of Licochalcone A on *in vitro* growth of both chloroquine-susceptible (3D7) and chloroquine-

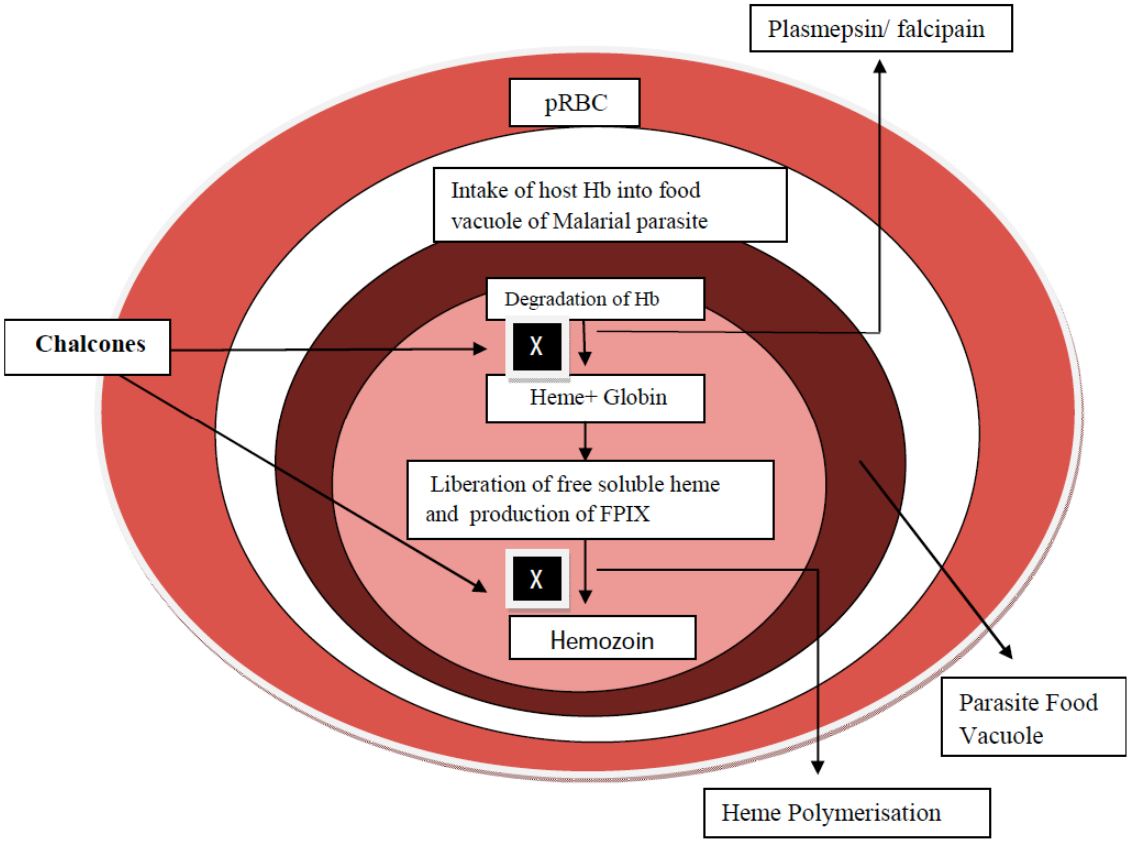
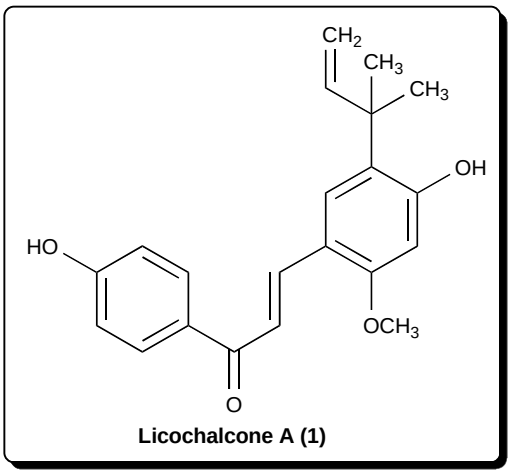


Figure 3: Illustration of Mechanism of action of chalcones on Malarial parasite.
Malarial parasite ingest hemoglobin and processed it in the digestive food vacuole to obtain essential amino acids for their growth and multiplication. Chalcones inhibit degradation of hemoglobin by binding to active site of cysteine protease (falcipain), enzyme involved in hemoglobin degradation. During this enzymatic beakdown of hemoglobin, a large amount of heme [ferrous proptoporphyrin IX, Fe(II)PPIX] which is the prosthetic group of hemoglobin, is released in the acidic digestive vacuole of *Plasmodium*. The ferrous ion in heme is oxidized in the presence of molecular oxygen to form ferriprotoporphyrin [Fe(III)PPIX], which is toxic to the parasite. To curb this, *Plasmodium* has evolved the unique ability to detoxify heme in the food vacuole by formatting it into a chemically inert, crystalline form called hemozoin. Chalcones also supposed to inhibit the polymerisation of heme into hemozoin. pRBC –parasitized Red blood cell, FPIX- ferriprotoporphyrin IX.

resistant (Dd2) *Plasmodium falciparum* strain. The growth inhibition of the chloroquine-resistant strain by Licochalcone A was found to be similar to chloroquine-susceptible strain. Following studies also reported



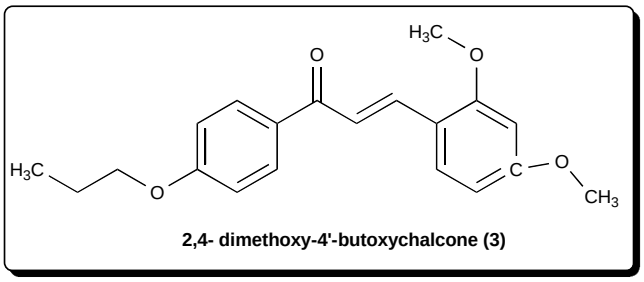
Licochalcone A (1)

antimalarial activity of Licochalcone A when administered either intraperitoneally or orally for 3-6 days to *Plasmodium yoelii* infected mice.

Afterwards, Li *et al.* [17], screened *in vitro* numbers of chalcones and their derivatives against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* and they were found to be active at nanomolar range of concentration. The most active chalcone derivative, 1-(2,5-dichlorophenyl)-3-(4-quinolinyl)-2-propen-1-one (2), had an IC50 value of 200 nmol/l against both a chloroquine-resistant strain (W2) and a chloroquine-sensitive strain (D6). The resistance indexes of all compounds were found to be substantially lower as compared to chloroquine, indicating that this series will be effective against chloroquine-resistant malaria.

Another synthetic analogue, 2,4-dimethoxy-4'-butoxychalcone (3), a novel derivative [51], also

possessed outstanding antimalarial activities both against a chloroquine-susceptible (3D7) and a chloroquine-resistant (Dd2) strain of *Plasmodium falciparum*as well as when this compound (4mbc), was administered either orally, intraperitoneally, or subcutaneously for 5 days in mice infected with *Plasmodium berghei* or *Plasmodium yoelii* and in rats infected with *Plasmodium berghei.* However, infected mice were protected from lethal infection of parasites and percentage parasetima was also found to be reduced in *P. berhei* infected rats with no observable signs of toxicity. In spite of this, the mechanism by which 2,4mbc inhibits the growth of the parasite was not clear and found to be related to Licochalcone A activity which alters the ultrastructure of the parasite mitochondria and inhibits their function [52].

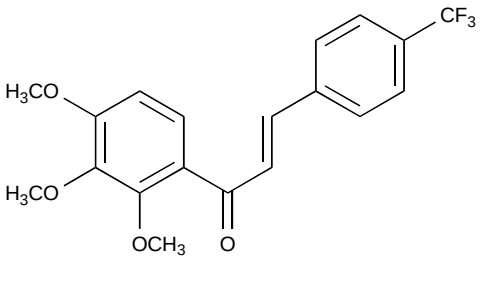


2,4- dimethoxy-4'-butoxychalcone (3)

In a detailed study, Liu *et al.* [53] and Go *et al*. [32] showed that *in vitro* antimalarial activity of chalcones against chloroquine-resistant, *Plasmodium falciparum* (K1) was mainly determined by the properties of ring B. The size and hydrophobicity of substituents were identified as critical parameters. Alkoxylated chalcones were more active than the corresponding hydroxylated analogues. A few of the alkoxylatedchalcones 4-10 had IC50 values below6.5 µmol/l.

Among the hydroxylated chalcones, the most active compound was 4-chloro-2',4'-dihydroxychalcone (11), with an IC50 of 12.3 µmol/l against a strain of chloroquine-resistant human malarial parasite, *P. falciparum* (K1) in a [3H]hypoxanthine uptake assay however, few other hydroxylated chalcones have IC50 values below 20 µmol/l.

The alkoxylated and hydroxylated chalcones were found to inhibit sorbitol-induced hemolysis of parasitized erythrocytes to a significant extent (≤40% of control values) at a concentration of 10 µmol/l [32]. Most of the good inhibitors of sorbitol-induced hemolysis appear also as active antiplasmodial agents, but not all active antiplasmodial chalcones inhibit sorbitol-induced hemolysis. There is a probability that the chalcone metabolites act synergistically with the core substance showing less potency than other inhibitors of the parasite-induced channels.



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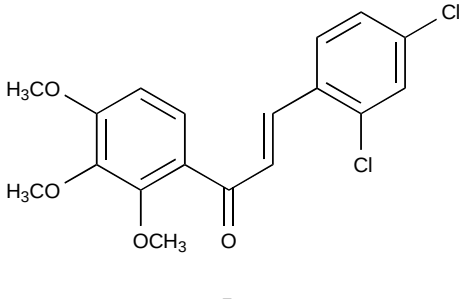

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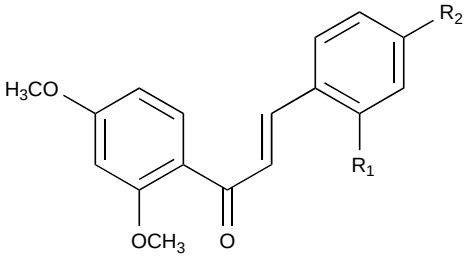


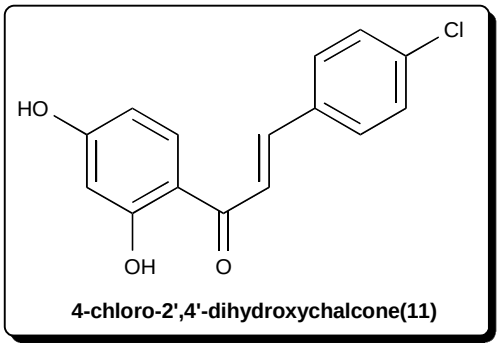
6

7 R^1R^2= OCH_3

8 R^1= H, R^2= C_2H_5

9 R^1= H, R^2= CF_3

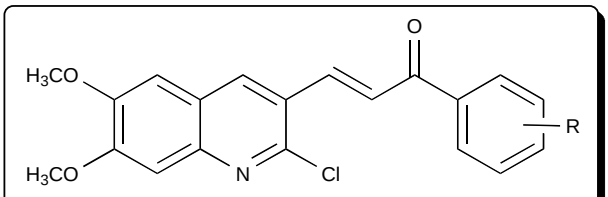
10 R^1R^2= F



4-chloro-2',4'-dihydroxychalcone(11)

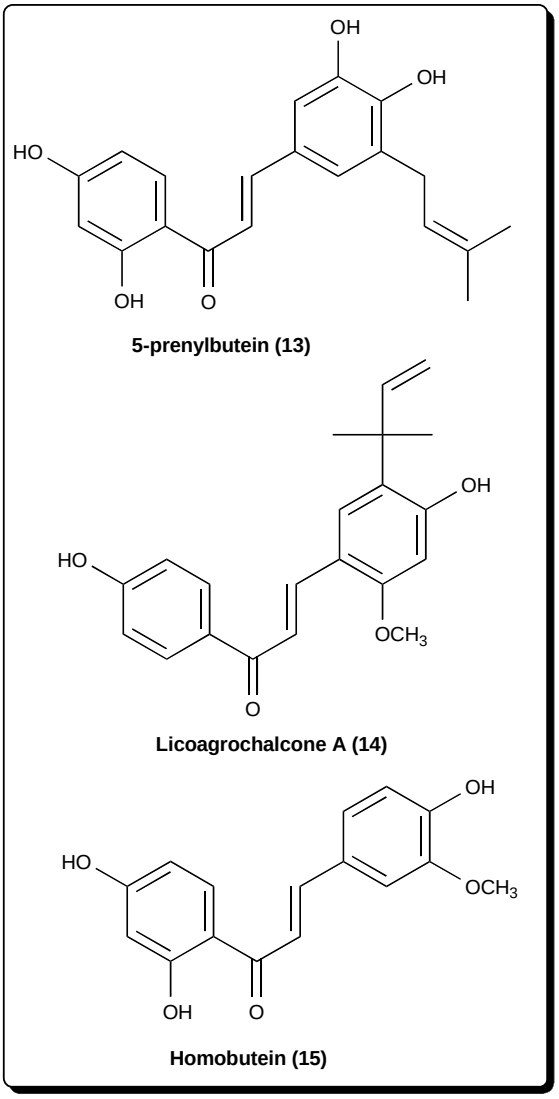
Subsequently, Zielger *et al.* [54], documented Licochalcone A as a potent membrane active agent that transforms normal erythrocytes to echinocytes concurrent with antiplasmodium activity in rapid and concentration dependent manner. The invasion and growth of *Plasmodium falciparum* in erythrocytes depend on the integrity and normal function of the erythrocyte membrane [55, 56]. Modification in composition of erythrocytic membrane can be expressed as echinocyte formation that develops conditions which are unfavorable for the *in vitro* proliferation of parasite. Licochalcone treated culture with 5.0 or 25.0 µg/ml showed only a few early trophozoites after 24 h, and those treated with 0.098 to 3.13 µg/mlcontained trophozoites and schizonts. After 48 h the culture treated with 25.0 µg/ml of Licochalcone A showed only a few early trophozoites and internal undeveloped merozoites. Transient modification of erythrocyte membrane was also observed *in vivo* in mice after intravenous administration.

A moderate activity of Quinolinyl chalcones against *Plasmodium falciparum* cysteine protease falcipain as well as against cultured *Plasmodium falciparum* parasite was reported by Dominguez *et al*. [57]. From series of Quinolinyl chalcones 1-(2,4-Dichlorophenyl)-3-[3-(2-chloro-6,7-dimethoxiquinolinyl)]-2-propen-1-one (12) was most promising with reported IC50 value of 19.0µmol/l.



R= 2,4-chloride
1-(2,4-Dichlorophenyl)-3-[3-(2-chloro-6, 7-dimethoxiquinolinyl)]-2-propen-1-one(12)

In vitro antiplasmodial activity was shown by 5-Prenylbutein (13), licoagrochalcone A (14) andhomobutein (15) against thechloroquine-sensitive (D6) and the chloroquine-resistant (W2) strains of *Plasmodium falciparum* with IC50 values in the range10.3-16.1 µmol/l [58].



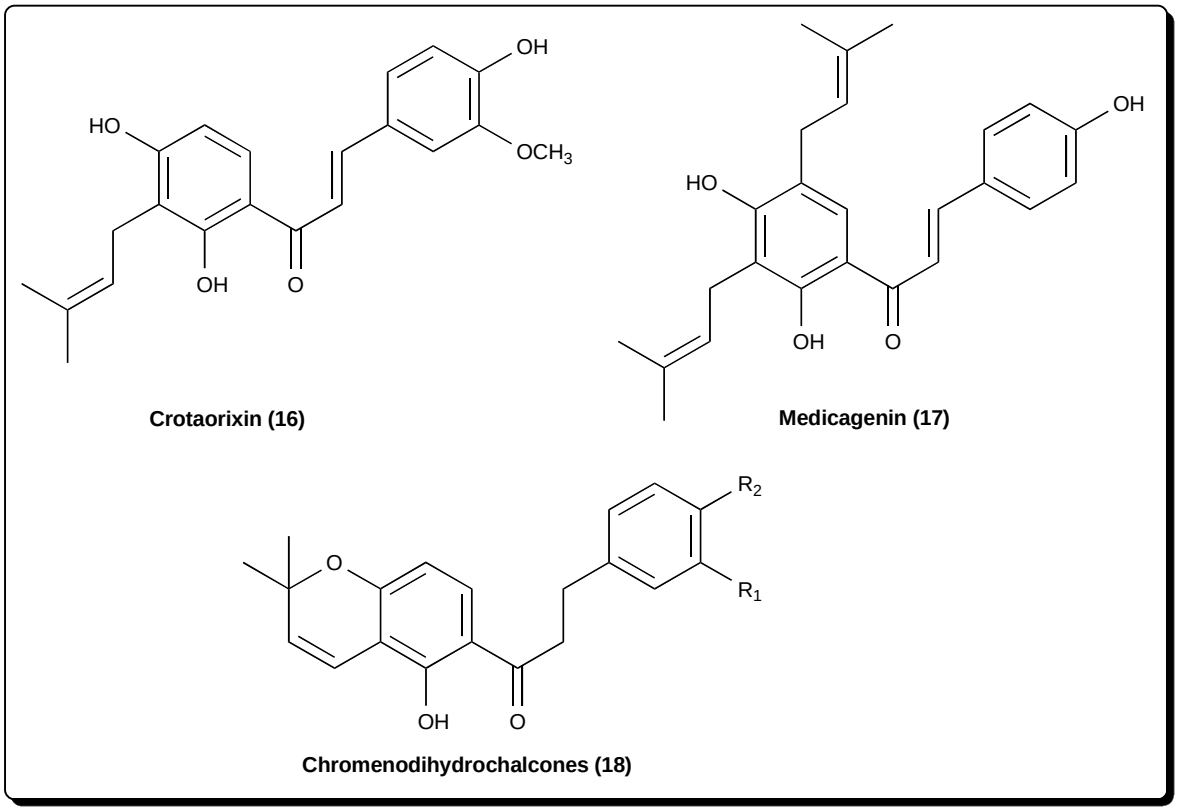
5-prenylbutein (13)

Licoagrochalcone A (14)

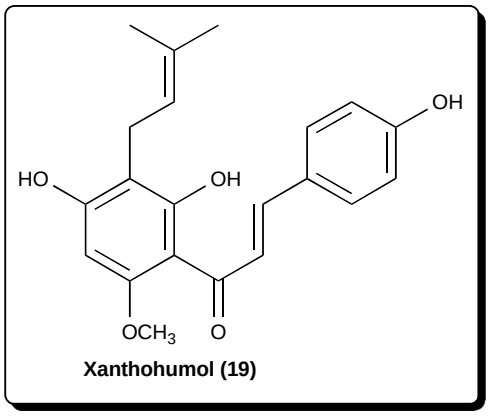
Homobutein (15)

Crotaorixin (16) isolated from the aerial parts of the *Crotalaria orixensis* [59], exhibited 100% inhibition of maturation of *P. falciparum* (strain NF-54) parasites from ring stage to schizont stage both at 50 and 10µg/ml concentrations. The diprenylated compound Medicagenin (17) which was isolated from the roots of *Crotalaria medicagenia* inhibited the parasites 100% at 2µg/ml concentration while the Chromenodihydro-chalcones (18) isolated from ariel parts of *Crotalaria ramosissima* showed lower level activity. The diprenylation with a free 4,4'-dihydroxy system led to improved activity.

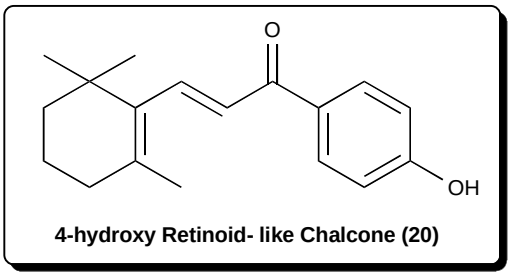
Frolich *et al*. [33], analyzed prenylated chalcone derivatives from hops (*Humulus lupulus*) for *in vitro*



antiplasmodial activity against the multiresistant clone Dd2 and chloroquine-sensitive strain poW using a [3H] hypoxanthine-incorporation assay. The main hop chalcone, Xanthohumol (19), was the most active with IC50 values of 8.2 ±0.3 (poW) and 24.0 ±0.8 mM (Dd2). The study demonstrated ability of chalcone derivatives to interfere with the haemin degradation process of *P. falciparum.*



A series of 'retinoid-like chalcones' and their contrary derivatives analogous to Licochalcone A were procured from a new enaminone synthon. These syntheses occurred through a new aromatic annelation. These novel derivatives have been tested as potential antimalarial agents *in vitro*. The 4-hydroxy Retinoid-like chalcone (20), obtained from β-ionone displays a good and remarkable inhibitory effect on the *in vitro* culture of *Plasmodium falciparum*, having IC50 less than 10 µmol/l for inhibiting 3H-hypoxanthine uptake by parasites [60].

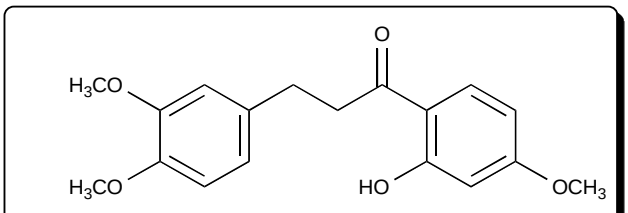


Motta *et al*. [61], explored the reasons that may be beneficial in the inhibitory effect of chalcone derivatives on *P*. *falciparum* cysteine protease enzyme and draw main conclusions out of this work. *(i)* The C2–C3 double bond is crucial for determining higher inhibitory activity. The conjugated linker between two aromatic rings A and B keeps extended molecular conformation, which is responsible for the drug molecule to bind more efficiently to the active site on the surface of enzyme cysteine protease. (*ii*) Substitutions of groups on the bridge portion of the chalcone derivatives cause a marked reduction in the inhibitory activity, apparently due to steric interactions. *(iii)* Substitution of chloro or

fluoro on the ring B and substitution of electron-donating groups on the ring A increases the antimalarial activity. (*iv*) Quinolinyl group present on ring B also resulted in increased antimalarial activity.

Two diprenylated chalcones Bartericin A and B, and four known natural products, stipulin, 4-hydroxylonchocarpin, I sobavachalcone and kanzonol B were isolated from the twigs of *Dorsteniabarteri var. subtriangularis* (Moraceae). These compounds were evaluated in culture against the W2 strain of *P. falciparum* and were found to be active *in vitro* against *P. falciparum*. Bartericin A, stipulin and 4-hydroxylonchocarpin display particular potencies with relatively low IC50 values in the range of 2.15, 5.13 and 3.36µmol/l respectively [62].

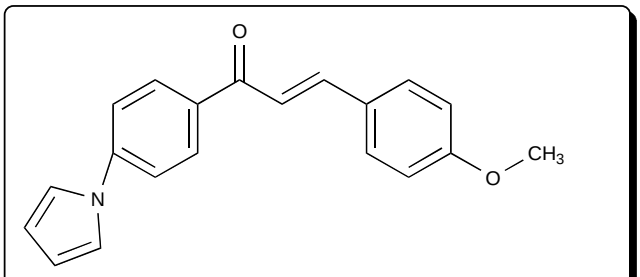
Lim *et al*. [63] prepared twenty derivatives of flavonoids and chalcones. In the chalcone series the compound 3-(3,4-Dimethoxyphenyl)-1-(2-hydroxy-4-methoxyphenyl) propan-1-one (21) was found to be the most active, EC50 = 1.0 µg/mL with 100% inhibition against *P. falciparum* and at the final concentration of 5.4 µg/ml. The compound also exhibited strong cytotoxicity toFM3A cells, with comparatively low EC50 values (>3.3 µg/ml) together with low selectivity index (>3.3) indicating non-selective antimalarial activity.



3-(3,4-Dimethoxyphenyl)-1-(2-hydroxy-4-methoxyphenyl) propan-1-one (21)

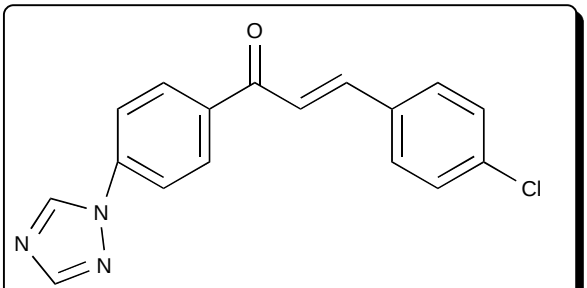
In vitro antiplasmodial results of 4-chloro, 4-methoxy and 3,4,5-trimethoxy series have antiplasmodial IC50 activity ranged between 1.5 to 12.3µg/ml suggesting that, small or medium sized but highly lipophilic groups containing multiple nitrogen or amine in acetophenone moiety impart antiplasmodial potential. Such compound may contribute in additional hydrogen bonding with the histidine residue located at the active site of the cysteine proteases. The chloro-series, 1,2,4-triazole substituted chalcones were found to be the highly effective in inhibiting the growth of *P. falciparum in vitro* while pyrrole and benzotriazole substituted chalcones showed relatively less inhibitory activity [47].

Awasthi *et al*. [64], synthesized several new chalcone analogues and evaluated as inhibitors of malaria parasite. Inhibitory activity was determined *in vitro* against a chloroquine-sensitive *P. falciparum* strain of parasites. The chalcone 3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl)prop-2-en-1-one(22) was found to be the most active with 50% inhibition concentration (IC50) of 1.61 µg/ml. This inhibitory concentration was comparable to a prototype phytochemical chalcone, Licochalcone, with an IC50 of 1.43 µg/ml. The study suggested that small lipophilic nitrogen heterocyclic at ring B together with small hydrophobic functionality at ring A can enhance antimalarial activity. The study revealed that chalcones are such a class of compounds that gives an opportunity to develop inexpensive, synthetic therapeutic antimalarial agents.



3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl)prop-2-en-1-one (22)

Bhattacharya *et al.* [65] reported *in vitro* antimalarial potential of chalcone derivatives in combination with artemisnin. The evaluated combination showed synergistic or additive interaction. 1-(4-(1H-1,2,4-triazole-1-lyl)-phenyl-3-(4-chlorophenyl)-prop-2-en-1-one (23) being most effective chalcone derivative evaluated in inhibiting the parasite growth showed additive interaction in combination with ART. The synergistic combination decreases hemozoin formation in parasitized erythrocytes, but do not affect new permeation pathways induced in the host cells.

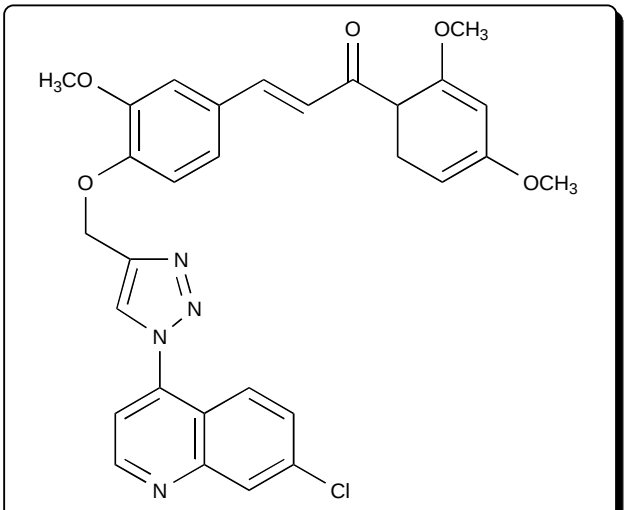


1-(4-(1H-1,2,4-triazole-1-lyl)-phenyl-3 -(4-chlorophenyl)-prop-2-en-1-one (23)

Several CDKs including Pfmrk and PfPK5 have been characterized from *Plasmodium falciparum* [66]. These cyclin dependent protein kinases, Pfmrk and PfPK5, play an essential role in cell cycle control and

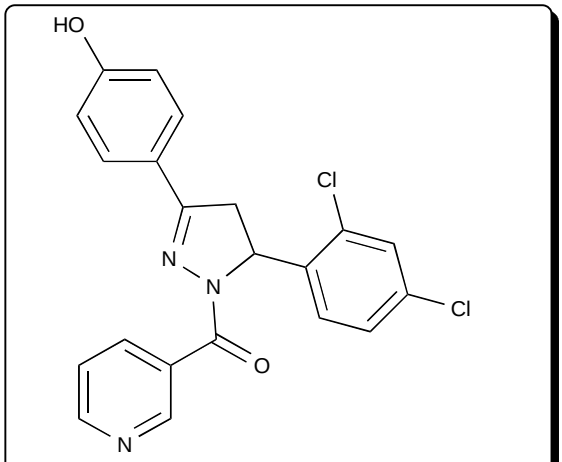
differentiation in *Plasmodium falciparum*. A diverse series of chalcone derivatives were tested for inhibition of Pfmrk over PfPK5 and are found that these derivatives are known to interfere with cell cycle progression. The inhibitions of Pfmrk selectivity over PfPK5 were in the low micro molar range. However the study reveals a weak correlation between Pfmrk inhibition and activity against the parasite *in vitro* and assumed that there might be some additional mechanism of antimalarial actions for inhibition of inhibition of Pfmrk [36].

A targeted series of chalcone and dienone hybrid compounds containing aminoquinoline and nucleoside templates were synthesized and evaluated for *in vitro* antimalarial activity. Several chalcone-chloroquinoline hybrid compounds were found to be notably active, with compound (24) the most active, exhibiting sub-micromolar IC50 values against the D10, Dd2 and W2 strains of *Plasmodium falciparum* [67].



3-{4-[1-(7-Chloro-quinolin-4-yl)-1H-[1,2,3]triazol-4-ylmethoxy] -3-methoxy-phenyl}-1-(2,4-dimethoxy-phenyl)-propenone (24)

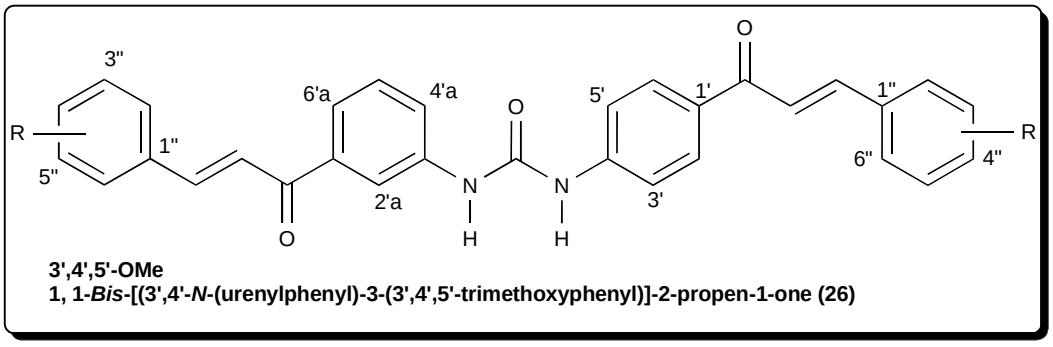
Acharya *et al*. [68] synthesized a series of 1, 3, 5-trisubstituted pyrazolines and evaluated for *in vitro* antimalarial efficacy against chloroquine sensitive (MRC-02) as well as chloroquine resistant (RKL9) strains of *Plasmodium falciparum*. The activity was at nanomolar concentration. *β*-hematin formation inhibition activity (BHIA50) of the pyrazolines were determined and correlated with antimalarial activity. A reasonably good correlation (r = 0.62) was observed between antimalarial activity (IC50) and BHIA50. This suggested that antimalarial mode of action of this class of compound appears to be similar to that of chloroquine and involves the inhibition of hemozoin formation. Some of the compounds showed better antimalarial activity than chloroquine against resistant strain of *P. falciparum* and were also found active in the *in vivo* experiment.



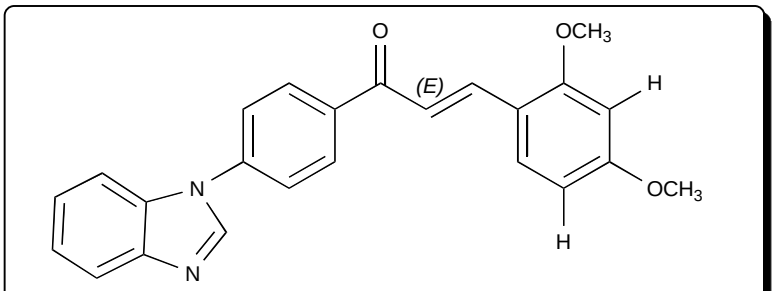
[5-(2,4-Dichloro-phenyl)-3-(4-hydroxy-phenyl) -4,5-dihydropyrazol-1-yl]-pyridin-3-yl-methanone (25)

J. N. Dominguez *et al.* [69] synthesized and characterized some novel derivatives of Bis-chalcone. All derivatives were screened for *in vitro* globin hydrolysis, β-hematin formation, and murine *Plasmodium berghei*, using chloroquine as the standard drug. Most of these compounds exhibit mild to moderate susceptibilities toward the parasite when compared with the standard. The most active antimalarial compound was 1,1-*Bis*-[(3′,4′-N-(urenylphenyl)-3-(3″,4″,5″-trimethoxyphenyl)]-2-propen-1-one (26), with a percentage of inhibition of heme polymerization of 87.05 ± 0.77, and this particular compound was tested in mice infected with *P. berghei* (ANKA), a chloroquine-susceptible strain of murine malaria and evaluated that the compound was able to reduce the parasitemia and delay the progression of malaria but did not eradicate the infection.

Yadav *et al.* [70] synthesized 27 chalcone derivatives, of which 1-(4-Benzimidazol-1-yl-phenyl)-3-(2,4-dimethoxy-phenyl)-propen-1-one (27) demonstrated to be the most potent antiplasmodial activity *in vitro* with IC50 of 1.1 µg/ml, as compared to Licochalcone (1.43 µg/ml). The study shows the presence of two methoxy groups at position 2 and 4 was found to be optimum for antimalarial activity followed by 3, 4 dimethoxy and 2, 5 dimethoxy with moderate activity, due to appropriate orientation on binding to the active site of the enzyme “cysteine protease”. Further, 3, 4, 5-trimethoxy group showed weaker activity, presumably due to the stearic hindrance in binding to the active site of the enzyme.



3',4',5'-OMe
1, 1-*Bis*-[(3',4'-*N*-(urenylphenyl)-3-(3',4',5'-trimethoxyphenyl)]-2-propen-1-one (26)



1-(4-Benzimidazol-1-yl-phenyl)-3-(2,4-dimethoxy-phenyl)-propen-1-one (27)

Recently, based on natural product lead molecule a library of 88 chalcones with various structural features such as prenylatedchalcones, chromanochalcones, chromenochalcones, and chromenodihydrochalcones were synthesizd and evaluated for their *in vitro* antimalarial activity. Among these, few exhibited good *in vitro* antimalarial activity against *P. falciparum* strains 3D7 and K1 with low cytotoxicity. These chalcones also showed reduction in parasitemia and increased survival time of Swiss mice infected with *Plasmodium yoelii*.

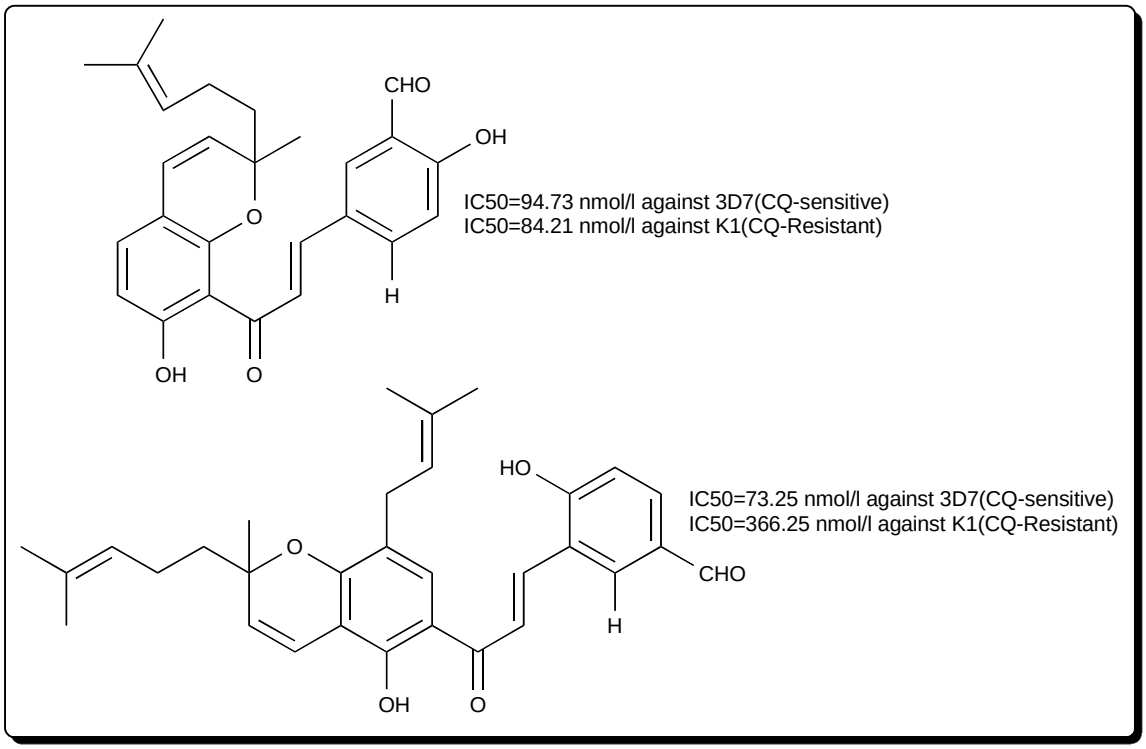
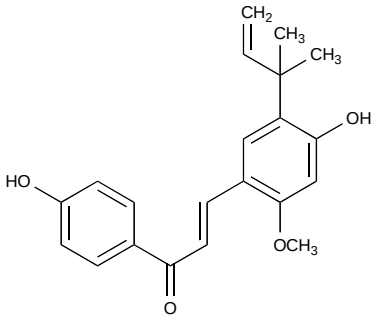
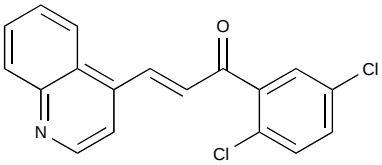
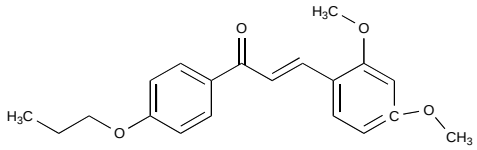
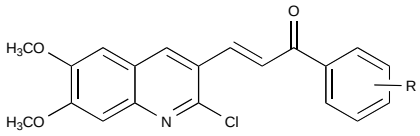
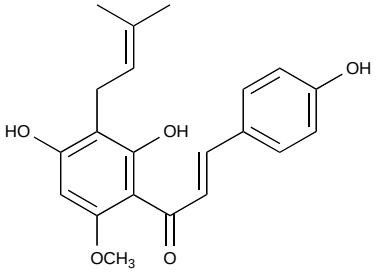
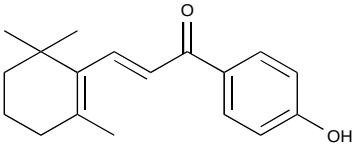


Table 1: Antimalarial Activity of Chalcones and its Derivatives

Name	Source	Structure	Chloroquine sensitive strain(IC50)	Chloroquine resistance strain(IC50)	Refs.
Licochalcone A	*Glycyrrhizae uralensis*, "Gan Cao"		NA	4.22µmol/l	[12]
1-(2,5-dichlorophenyl)-3-(4-quinolinyl)-2-propen-1-one	synthetic		0.2µmol/l	0.2µmol/l	[17]
2,4- dimethoxy-4'-butoxychalcone	synthetic		8.9µmol/l	14.8µmol/l	[51]
1-(2,4-Dichlorophenyl)-3-[3-(2-chloro-6,7-dimethoxiquinolinyl)]-2-propen-1-one	synthetic	 R=2,4-chloride	NA	19.0µmol/l	[57]
Xanthohumol	*Humulus lupulus L.*		8.2µmol/l	24.0µmol/l	[33]
Retinoid-like Chalcones	synthetic		NA	>10µmol/l	[60]

However, some compounds showed modest inhibitory activity against the major hemoglobin degrading cysteine protease FP-2 [71].

A brief illustration of antimalarial effect of chalcones and its synthetic derivatives is mentioned in the Table **1**.

FUTURE PROSPECTS

To combat malaria, one of the most deadly infectious disease of the developing world, drug after drug has fallen by the wayside as the malaria parasite has become resistant to it. Only artemisinin, and presently ACTs are considered as drug of choice to

treat any malaria, including chloroquine-resistant infections. However, sooner it is likely to expect the emergence of resistance to this combination. Accordingly, there is an immediate need to search for alternate combinations which could decrease dependence on artemisinin without compromising on the potency to cure malaria. The simple structure, low-cost synthesis of chalcones, minimal host toxicity and ease availability have attracted the attention of chemists and Research organisation to develop different analogs of this compound for numerous infectious diseases including malaria. The reported antimalarial activity of the various chalcone derivatives provides the incentive to synthesize novel chalcone derivatives with improved antiplasmodial activity on the basis of structure activity relationships.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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