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Synthesis and Antimalarial Activities of Chalcone Derivatives

Ugwu, David. I[1*]; Ezema, Benjamin, E[1]; Eze, Florence, U[1] Onoabedje Efeturi, A[1], Ezema, Chidimma G[2], Ekoh, Ogechi, C[1] and Ayogu, Jude. I[1]

[1]Synthetic Organic Chemistry Division, Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka.
[2]National Centre for Energy Research and Development, University of Nigeria, Nsukka

Abstract: Malaria is a vector borne disease caused by plasmodium parasite. About 3.3 billion people, almost half of world's population is at risk of malaria. In every year, about 250 million cases and nearly one million deaths are attributed to malaria. Malaria is a serious problem in Africa, where it is responsible for one in every five childhood deaths contributing to 20% of infant mortality. The arsenal of antimalarial drugs is limited and currently the most effective treatment against *P. falciparum* includes artemisinin combination therapies (ACT). The recent development of resistance against artemisinins poses a big threat to the current stride against malaria parasite. Chalcones are derivatives of 1, 3-diphenyl-2-propene-1-one, consisting of two aromatic rings linked by a three carbon α, β-unsaturated carbonyl system. Chalcones possess a wide range of pharmacological activities such as anti-oncogenic, anti-inflammatory, anti-ulcerative, analgesic, antiviral, anti-mutagenic, anti-hyperglycemic, antimalarial and anti bacterial activities. Prenylated chalcones, chromanochalcones, chromenochalcones, chromenodehydrochalcones, quinoxaline chalcones, quinolinyl chalcones, chalcone sulphonamides, licochalcones and morachalcones have been reported to possess good antimalarial property. Some chalcones have also been reported to show fascinating antimalarial activities against chloroquine resistant *P. falciparum* strain. The methods of chalcone synthesis have been improved from the usual conventional methods to microwave assisted protocols leading to drastic reduction in time required for the synthesis and as well improved yield. The ease of synthesis and fascinating biological activities of chalcones prompted this review.
Keywords: chalcones, antimalarial, licochalcone A, morachalcones, microwave synthesis.

Introduction:

Malaria constitutes the most important infectious disease problems of humans affecting third-world countries, with over 275 million new cases annually and mortality reaching 2 million[1]. The majority of these cases are pediatric deaths in developing countries which exemplify the tragedy of the disease caused by plasmodium. There are four species of the genus plasmodium viz *Plasmodium falciparum, P. vivax, P. ovale* and *P. malariae. Plasmodium falciparum* is the foremost killer and is found primarily in Africa. There is currently no licensed malaria vaccine and available drugs, including artemisinin combination therapies (ACTs), are becoming less effective due to parasite and clinical treatment failure[2-7]. Despite the severity of this problem, no new chemical class of antimalarial drug has been approved for use since 1996[8]. The spread of multidrug resistance is particularly troublesome with *P. falciparum* which causes cerebral malaria[9,10] and other very serious consequences and is responsible for nearly all of the annual 1-3 million deaths attributed to malaria[11,12].

Chalcones are a group of compounds with various substitution patterns on the two aromatic rings of 1,3-diphenyl-2-propen-1-one. They constitute an important class of natural products belonging to the flavonoid family, which have been reported to possess a wide spectrum of biological activities, including antibacterial, antifungal, anti-inflammatory, antitumour, insect anti-feedant and anti-mutagenic[13-15]. Some chalcone derivatives have been found to inhibit several important enzymes in cellular systems, such as xanthine oxidase[16] and protein tyrosine kinase[17,18]. There are chalcones with reported anti-hyperglycemic[19] and antimalarial effect[20]. They are α,β-unsaturated carbonyl system that assume linear or nearly planar structure[21,22]. They contain the ketoethylenic group (-COCH=CH) [23]. Chalcones possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings. The energy minimized 3D structure of chalcone is shown in figure 1.

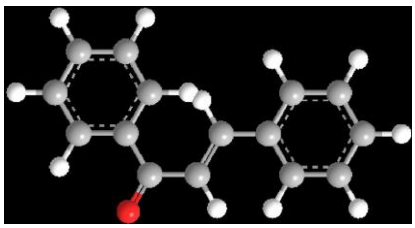
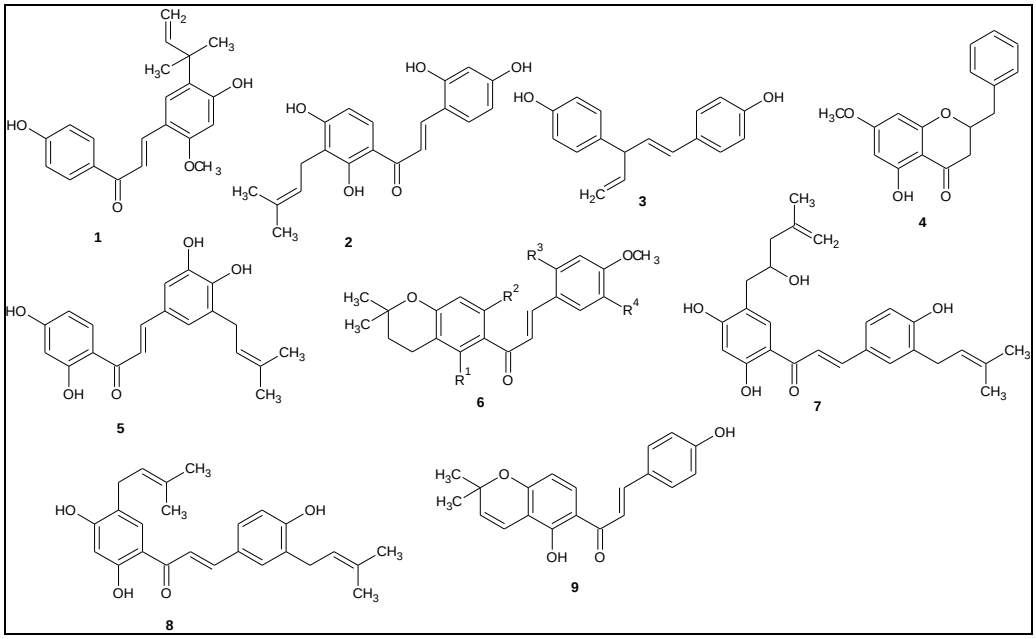


Fig. 1: 3D structure of chalcone

Chalcones extracted from *Cajanus cajan* has been shown to possess antimalarial property[24]. Licochalcone A (1), an oxygenated chalcone first isolated from roots of Chinese licorice, showed antimalarial activity in both *in vitro* and *in vivo* system[25]. A series of alkoxylated, hydroxylated, phenylated, oxygenated, quinolylated chalcones from natural sources and syntheses have been evaluated for antimalarial activity with encouraging results[26,27]. Morachalcone A (2), a naturally occurring substance from *Artocarpus champeden* spreng belonging to the family *Moraceae* has been shown to have significantly inhibited the in vitro growth of the human malaria parasite *Plasmodium falciparum*[28,29]. Licochalcone A (1), isolated from *Glycyrrhiza inflata* has been identified as potent inhibitor of protease activities of plasmodium[30]. (+)-Nyasol (3) isolated from *Asparagus africanus*[31] and pinostrobin (4) from *Cajanus cajan*[32], possess weak antimalarial activity. 5-Prenylbutein (5), from *Erythrina abyssinica*[33] and prenyl substituted dihydrochalcone (6), from *Piper hostmannianum*[34] exhibiting antimalarial activity has been reported. Bartericin A (7), stipulin (8), 4-hydroxyonchocarpin (9), isolated from *Dorstemia barbaric* var subtriangularis[35] showed in vitro activity against *P. falciparum* (scheme 1). The simple structure and effortless synthesis of chalcones clarify the substantial interest of chemist in this particular group of compounds. Various methods for the syntheses of chalcones have been discovered, including Claisen-Schmidt condensation[36,37], photo-Fries rearrangement[38], Suzuki coupling reaction[38,39], Friedel-Craft acylation[38], and also green chemistry methods via microwave irradiation[36,38].

The antimalarial activities of chalcones are associated with inhibiting either plasmodial aspartate proteases or cysteine proteases[40]. Plasmodial aspartate and cysteine proteases are attractive targets for antimalarial therapy due to their role in the degradation of haemoglobin during erythocytic parasite development[41]. Structure based activity studies expected antimalarial chalcone derivatives inhibition on trophozoite cysteine protease as most likely mode of action[42,43]. *In silico* simulations indicated that several antimalarial chalcones have an excellent fit onto falcipains active site[44]. Chalcones do interfere with critical processes that affect the growth of the intra erythrocytic plasmodia, namely enzymatic degradation of haemoglobin and binding to heme. It is unlikely that interference with these processes is solely responsible for the in vitro antimalarial activity of chalcones. It is possible that chalcones may interfere with targets outside the food vacuole. Ginburg *et al*[45] have proposed that monomeric heme exits the food vacuole and is subsequently degraded by reaction with glutathione in the parasite cytosol. Drugs like chloroquine[46] and clotrimazole[47] are reported to form complexes with heme, thus interfering with its degradation by glutathione. The resulting drug-heme complex is toxic and contributes to cell death. Chalcones may also interfere with transport pathways present in infected erythrocytes. Several flavonoids have been reported to inhibit the passage of essential solutes via parasite-induced pathways on the host erythrocytes[48,49]. Chalcones are biosynthetic precursor of flavonoids and as such may have similar effect.

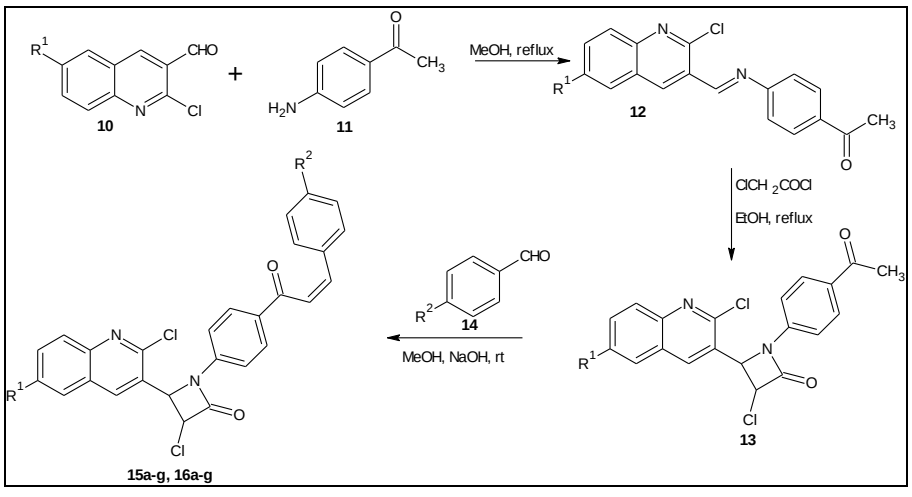


Scheme 1: examples of chalcones

One of the main challenges in the development of new antimalarial drugs is how to achieve a viable lead compound with good pharmacokinetic properties: absorption, distribution, metabolism, excretion, and toxicity[50]. It is well documented that artemisinin derivatives act only for a short time and by implication require frequent dosing to maintain efficacy[51]. Therefore the search for new antimalarial drugs with enhanced pharmaceutical properties motivated us to review the syntheses and structure activity relationship of chalcone derivatives with antimalarial potential.

2.0 Synthesis of functionalized chalcones

The reported biological activities of chalcone derivatives prompted Kunwarvir *et al*[52] to synthesize functionalized derivatives of chalcones and evaluated their in-vitro antimalarial property. They synthesized the compounds following a reported literature[53]. A mixture of 2-chloro-3-formyl-6-substituted quinolones (10a-b) (20 mmol) and 4-aminoacetophenone (11) (20 mmol) was refluxed for 12 h in dry methanol. The solution was cooled and poured into crushed ice and the precipitate was filtered and washed with water and dried to afford 1-{4-[(2-chloro-6-substituted-quinolin-3-yl methylene) amino]-phenyl}-ethanones (12a-b). Into a mixture of compound 12a-b (6.4 mmol) in 30 mL ethanol, triethylamine (0.8 mL) was added drop-wise at 0-5^{o}C temperature for 10 min and chloroacetyl chloride (6.4 mmol, 0.6 mL) was added. The solution was refluxed for 10 h and then poured into crushed ice and the precipitate filtered and washed with water. The product 1-[4-acetylphenyl-3-chloro-4-(2-chloro-6-substituted-quinolin-3-yl)-azetidin-2-ones (13a-b) were recrystallized from methanol. A solution of compound 13a-b (10 mmol) and substituted benzaldehydes (14) (10 mmol) in 15 mL dry methanol was stirred in the presence of one pellet of sodium hydroxide at room temperature for 24 h. The yellowish precipitate 4-(2-chloro-6-substituted-quinolin-3-yl)-3-chloro-1-{4-[3-(4-substituted phenyl)-acrylolyl] -phenyl}-azetidin-2-ones 15a-g and 16a-g was filtered, washed with methanol and recrystallized from ethanol (Scheme 2).



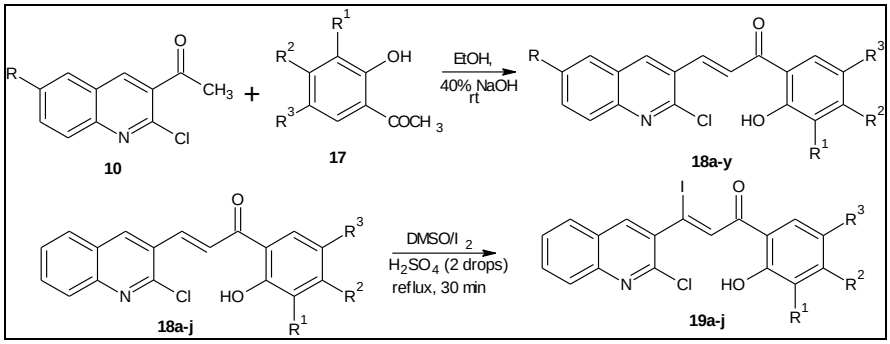
Scheme 2: synthesis of functionalized chalcones

They tested the antimalarial activities of the compounds in an in-vitro malaria assay against chloroquine sensitive strain of *Plasmodium falciparum* (NF-54) parasite. Out of the fourteen compounds, only five compounds viz 15f, 16b, 16e, 16f and 16g showed impressive antimalarial activity. Although none had comparable activity with chloroquine (IC_{50}= 0.03 µg/mL), compound 16b and 16g (IC_{50}= 5 µg/mL and 2 µg/mL respectively) could be developed further and may serve as an alternative to chloroquine in cases of allergy. The structure activity relationship revealed that replacement of hydrogen with chlorine generally improved the antimalarial activity except in compound 16c.

3.0 Synthesis of quinolinyl chalcones

Quinolones and their derivatives have been extensively explored for their biological[54-56], antifilarial[57], antibacterial[58,59] and antimalarial[60-61] activities and additionally for their cardiovascular, antineoplastic and receptor agonist activities. These wide biological activities of quinolines coupled with established pharmaceutical importance of chalcones prompted Shikha *et al*[62] to synthesize derivatives of chalcones containing quinoline groups.

They achieved the synthesis via Claisen-Schmidt condensations of 2-chloro-3-formyl-quinoline/2-chloro-6-ethoxy-3-formyl quinolone (10) (0.01 M) and ethanolic (15 mL) solution of substituted 2-hydroxyacetophenones (17) (0.01 M). To the reaction mixture, they added aqueous NaOH (0.03 M, 3 mL) drop wisely with constant stirring. The reaction mixture was kept overnight. The mixture was decomposed using cold 1:1 HCl, filtered, washed and dried to obtain (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones/substituted (E)-3-(2-chloro-6-ethoxy quinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones (18a-y). Further treatment of 18a-j with DMSO/I_2 gave the iodo derivatives (19a-j) (scheme 3).



10 17 18a-y 18a-j 19a-j

Scheme 3: synthesis of quinolinyl chalcones

They used molecular docking in establishing the antimalarial properties of the thirty five compounds synthesized. All the thirty five quinoline analogues showed binding in the *pf*LDH active site with binding scores between -7.1082 and -10.9698 Kcal/mole (table 1). Compounds 18c, 18k and 19b showed the highest binding score with *pf*LDH enzyme active site cavity with comparison to other chalcones, including some well-known antimalarial agent. Only atovaquone had better binding with *pf*LDH when compared to other lead antimalarial drugs. They further validated the computational evaluation using the in-vitro antimalarial activities of the respective compounds 18c, 18u and 19b. They observed that 18c and 18u completely inhibited the maturation of parasite at MIC 10 µg/mL and above whereas 19b inhibited 95% maturation of parasites at MIC 50 µg/mL.

Table 1: molecular docking and MIC of quinolinyl chalcone

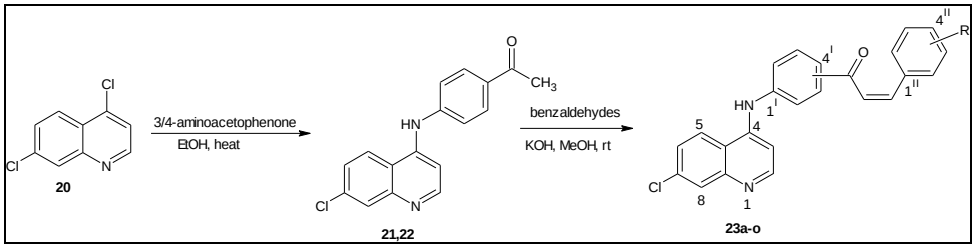
Compd. No.	R	R^1	R^2	R^3	Docking score (Kcal/mol)	MIC (µg/mL)
18a	H	Cl	H	H	-10.1523	-
18b	H	CH_3	H	H	-9.5259	-
18c	H	Cl	H	Br	-10.8542	10
18d	H	CH_3	H	Br	-9.6149	-
18e	H	Cl	H	I	-9.6231	-

18f	H	CH_3	H	I	-9.6562	-
18g	H	Cl	H	NO_2	-9.2419	-
18h	H	CH_3	H	NO_2	-9.2448	-
18i	H	Br	OCH_3	H	-9.7892	-
18q	OCH_3	H	H	NH_2	-8.2304	-
18r	OCH_3	Cl	H	H	-9.6745	-
18s	OCH_3	NO_2	H	Cl	-8.8018	-
18t	OCH_3	Br	H	Cl	-8.2911	-
18u	OCH_3	Cl	H	Br	-8.8395	10
18v	OCH_3	Cl	H	NO_2	-8.1910	-
18w	OCH_3	H	OCH_3	H	-8.2919	-
18y	OCH_3	H	OCH_3	Br	-9.3349	-
19a	H	Cl	H	H	-10.1965	-
19b	H	CH_3	H	H	-10.4993	50
19c	H	Cl	H	Br	-10.3002	-
19d	H	CH_3	H	Br	-10.2964	-
19e	H	Cl	H	I	-8.9384	-
19f	H	CH_3	H	I	-8.3574	-
19g	H	Cl	H	NO_2	-10.4113	-
19h	H	CH_3	H	NO_2	-9.0827	-
19i	H	Br	OCH_3	H	-10.3286	-
19j	H	I	OCH_3	H	-8.6395	-
Chloroquine	-	-	-	-	-7.72472	0.032
Atovaquone	-	-	-	-	-11.1610	-
Mefloquine	-	-	-	-	-8.08456	-
Pyrimethamine	-	-	-	-	-8.25773	-
Artemisinin	-	-	-	-	-8.62421	-

4.0 Synthesis of [(7-chloroquinolin-4-yl) amino] chalcones

Amodiaquine (AQ), a Mannich base of 4-aminoquinoline, is effective against chloroquine resistant strains of *P. falciparum*[63]. However, the clinical use of amodiaquine has been associated with its long term use: lysosomal accumulation and bioactivation of reactive quinoneimine metabolite, implicated to cause observed amodiaquine in-vivo toxicity[64]. Isoquine is an analogue of amodiaquine, in which the 4^{I}-hydroxy group on the aniline ring of amodiaquine is interchanged with a 3^{I}-Mannich base side chain. Isoquine was found to possess higher antimalarial activity against *P. yoelli* than amodiaquine. In contrast, isoquine was excreted primarily as a glucouronide, instead of a glutathione conjugate[65]. Tebuquine is a biaryl analogue of amodiaquine and it is significantly more active than amodiaquine and chloroquine in both in-vivo and in-vitro tests[66,67]. Similar to amodiaquine, tebuquine forms an active quinoneimine metabolite and consequently develops the same toxic side effects as amodiaquine in prolonged use. These reported antimalarial potentials of aminoquinolines prompted Ferrer *et al*[68] to synthesize the [(7-chloroquinolin-4-yl) amino] chalcones and screened them for antimalarial activity.

They synthesized the chalcones by treating a mixture of 4,7-dichloroquinoline (20) (0.5 g, 2.5 mmol) and 3- or 4-aminoacetophenone (0.37 g, 2.75 mmol) in ethanol (10 mL) and refluxed the mixture at 80-85^{o}C overnight. The solid formed was filtered, washed with water, diethyl ether and recrystallized from ethanol to obtain [(7-chloroquinolin-4-yl) amino]-acetophenones (21, 22). A mixture of [(7-chloroquinolin-4-yl) amino]-acetophenones 21 or 22 (100 mg, 0.36 mmol), the respective benzaldehydes (0.40 mmol) and potassium hydroxide (one pellet) in methanol (8 mL) was stirred at room temperature for 96 h. They added water and the resulting precipitate was collected after filtration and washed with water, diethyl ether and recrystallized from ethanol-water (1:0.5) to obtain the target compound [(7-chloroquinolin-4-yl) amino] chalcones (23a-o) (scheme 4).



Scheme 4: synthesis of 4-aminoquinoline chalcone derivatives

They evaluated the antimalarial potential of the compounds 23a-o by testing their in-vitro effects as inhibitors of β-hematin formation and inhibitors of haemoglobin proteolysis. Heme can crystallize spontaneously under acid and low oxygen conditions found in the vacuole of malaria parasite[69]. They found that compounds 23h, 23i, 23k, 23m and 23o had comparable % inhibition with chloroquine. The structure activity relationship revealed that the substitution of ketone α,β-unsaturated group on position 3 and the presence of a hydrogen, halogen or *N*-dimethyl groups as substituents in the aromatic ring appeared to be favourable for the potential antimalarial activity since most of the compounds possessing these groups showed measurable level of inhibition of β-hematin formation. Consequent upon these, the promising antimalarial chalcones were screened for inhibition of hemoglobin proteolysis. The result revealed that only compound 23f was partially effective as shown in table 2.

Table 2: hemoglobin proteolysis inhibition of [(7-chloroquinolin-4-yl) amino] chalcones

Compd. No.	**R**	**%IβHS**	**%IGP**
23h	4-N(CH_3)$_2$	94.55	<10
23i	4-Cl	94.34	12.22
23k	2-Cl	94.42	<10
23m	3-F	94.93	<10
23o	H	93.14	<10
Leupeptin	-	-	89.06
Pepstatin	-	-	92.94
Chloroquine	-	96.61	-

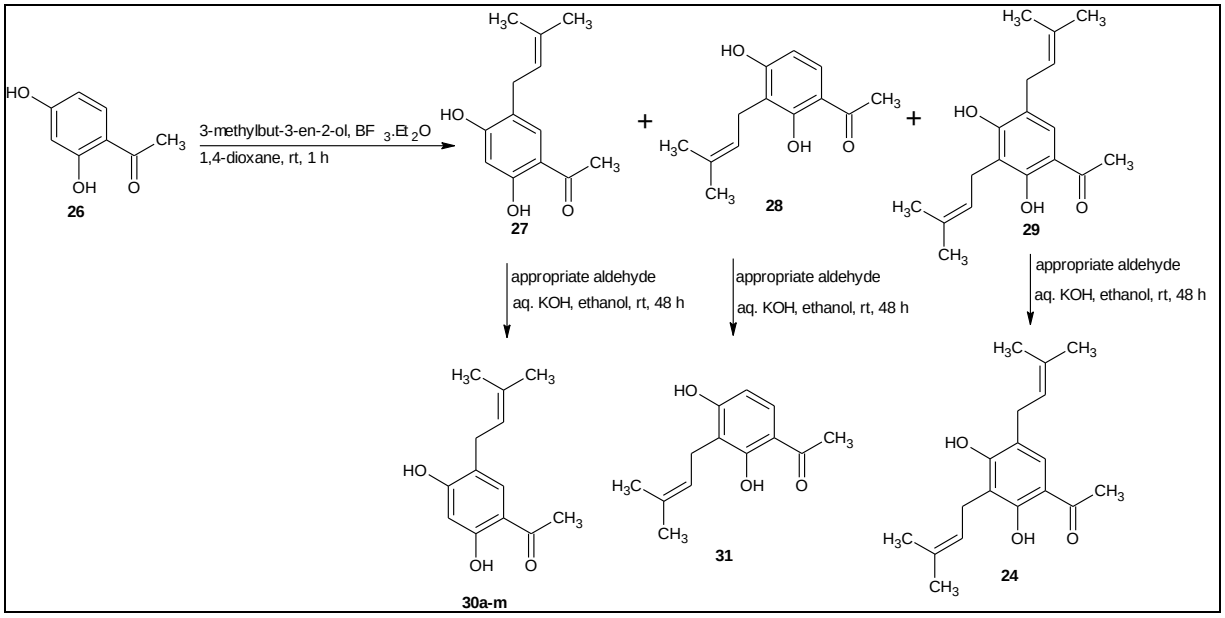
5.0 Synthesis of derivatives of natural chalcones

Medicagenin (24) is a diprenylated chalcone and munchiwarin (25) a triprenylated chalcone were both isolated from the root of *Crotalaria medicagenia*. These two chalcones where shown to exhibit in-vitro antimalarial activity (MIC=5.10 µM and 4.34 µM) respectively against *P. falciparum*[70-71]. This finding motivated Narender *et al*[72] to synthesize various analogues of these lead molecules as reported in scheme 5,6,7,8 and 9.

Synthesis of prenylated chalcones

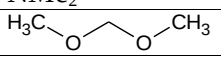
Prenylated chalcones 30a-j, 31 and 24 were prepared from 2,4-dihydroxyacetophenone (26). Prenylation of compound 26 with 2-methylbut-3-en-2-ol in the presence of $BF_3.OEt_2$ in dry 1,4-dioxane resulted into the mixture of three compounds: 2,4-dihydroxy-5-C-prenylacetophenone (27), 2,4-dihydroxy-3-C-prenylated acetophenone (28) and 2,4-dihydroxy-3,5-C-diprenylated acetophenone (29)[71,73]. The prenylated acetophenones (27-29) and various substituted benzaldehydes were subjected to Claisen-Schmidt condensation[74] using aqueous KOH in ethanol to afford the corresponding prenylated chalcones 30a-m, 31 and 24 as shown in scheme 5.

The antimalarial properties of these compounds were screened against *P. falciparum* chloroquine sensitive strain CQs. The minimum inhibitory concentration showed no improved activity when compared with compound 24 that was isolated from *C. medicagenia*.



Scheme 5: synthesis of prenylated chalcones

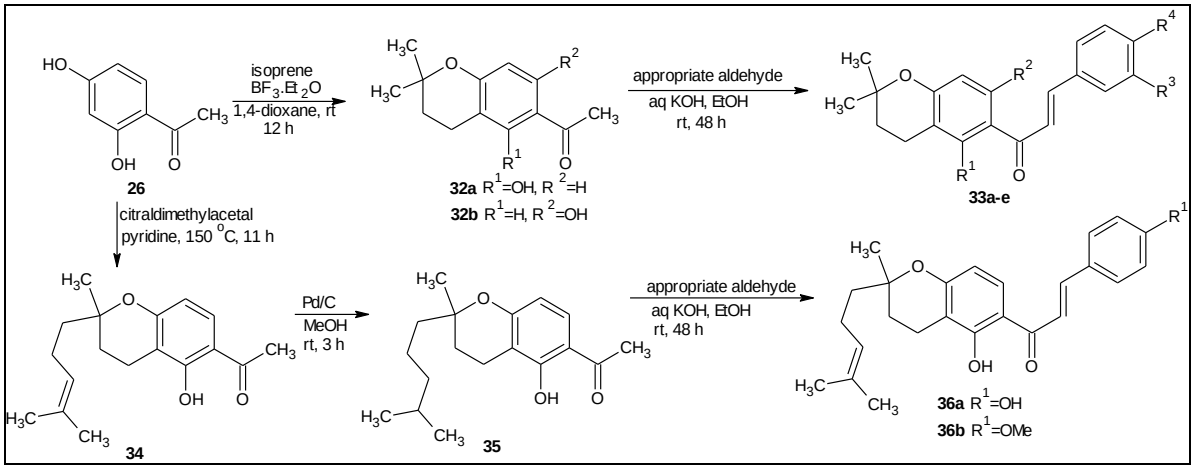
Table 3: MIC of prenylated chalcones

Compd. No.	R^1	R^2	R^3	R^4	MIC µM
30a	OMe	H	H	H	29.58
30b	H	H	OMe	H	29.58
30c	H	H	OEt	H	28.40
30d	H	H	NMe_2	H	142.45
30e	H	H		H	27.17
30f	H	OMe	OH	H	28.24
30g	H	OH	OMe	H	28.24
30h	H	OMe	OMe	H	27.17
30i	OMe	H	OMe	OMe	25.12
30j	H	H	Cl	H	146.16
31	-	-	-	-	28.24
24	-	-	-	-	5.10

One can therefore say from table 3 that diprenylated chalcone 24 has more antimalarial property when compared to the 2,4-dihydroxy-5-C-prenylated 30a-j and 31. Following this, the group went further to functionalize the isolated medicagen (24) and munchiwarin (25).

Synthesis of chromanochalcones

Chromanochalcones (33a-e) were prepared through a short and convenient route which involved one-pot synthesis of acetyl chalcones 32a-b by carrying out a reaction between 2,4-dihydroxyacetophenone (26) and isoprene using $BF_3.Et_2O$[75] and then Claisen-Schmidt condensation of resultant chromans (32a-b) with various substituted aromatic aldehydes. The chromanochalcones 36a-b was synthesized by pyridine catalyzed condensation between 26 and citraldimethylacetal to provide the acetylchromene (34)[76]. Compound 34 on reduction with Pd/C[77] gave acetylchroman (35) which was subsequently subjected to Claisen-Schmidt condensation with aromatic aldehydes to form the desired chromanochalcones 36a-b (scheme 6).



Scheme 6: Synthesis of chromanochalcones

The in-vitro antimalarial activity of the chalcones 33a-e and 36a-b is as presented in table 4

Table 4: MIC of chromanochalcones

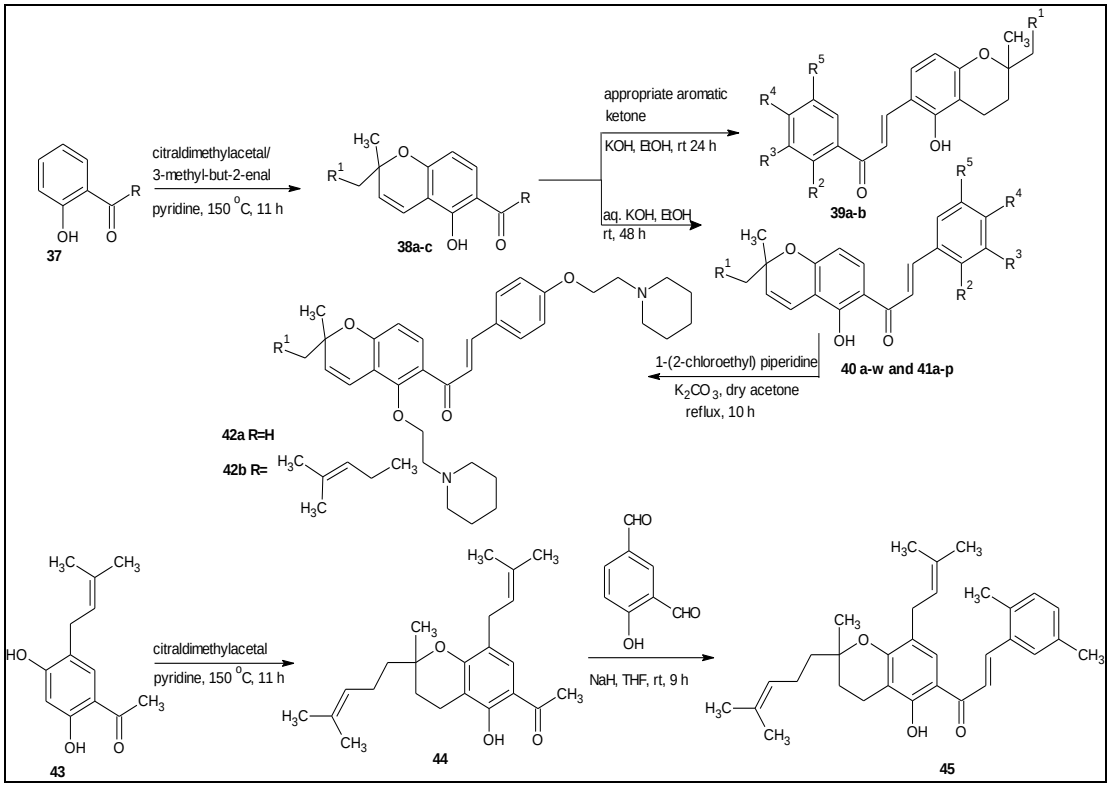
Compd. No.	R^1	R^2	R^3	R^4	MIC (µM)
33a	OH	H	H	NMe_2	>28.49
33b	H	OH	F	F	>29.06
33c	H	OH	Cl	Cl	>26.59
33d	H	OH	NO_2	H	>28.16
33e	H	OH	H	NO_2	>28.32
36a	OH	H	H	OH	126.90
36b	OH	H	H	OMe	122.54

Chalcones 33a-e has electron withdrawing groups, electron donating groups and halogen group substitution on ring A. They appear to be less potent when compared to chalcones 30a-m. In addition, chalcones 36a-b which contains an extra alkyl chain on benzopyran core also exhibited poor antimalarial activity. The diminished antimalarial activity of chromanochalcones when compared to *C*-prenylated chalcones is a pointer that cyclization of prenyl or geranyl group has negative impact on antimalarial activity.

Synthesis of chromenochalcones

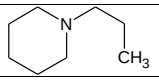
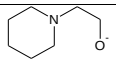
To study the role of olefinic bond in benzopyran moiety, a large number of chromenochalcones were synthesized. The chromenochalcones 39a-b, 40a-w, 41a-p, 42a-b and 45 were synthesized from acetyl/carboxaldehyde chromenes 38a-c using pyridine catalyzed condensation between 26 or 37 and 3-methyl-but-2-enal/citraldimethylacetal[76]. The resultant acetylchromenes 38a-c and substituted aromatic aldehydes of *p*-hydroxybenzene-1,3-dicarbaldehyde and chromene carboxaldehyde 38c and appropriate acetophenones were subjected to Claisen-Schmidt condensation using either aqueous KOH in ethanol or NaH in dry THF at room temperature to furnish the corresponding chromenochalcones (40a-w) and (41a-p)[77]. Introduction of aminoalkyl groups was done in 42a-b to improve the bioavailability. The synthesis of chalcones 42a-b was accomplished by the replacement of the hydrogen of the phenolic hydroxyl group of the chromenochalcones 41d and 41v with the alkyl part of the corresponding amines using K_2CO_3 in dry acetone[78]. They also synthesized prenylated chromenochalcone 45 which has an extra prenyl group on benzopyran moiety. The intermediate prenylated acetylchromene (44) was synthesized using pyridine catalyzed condensation between 43 and citraldimethylacetal. The intermediate 44 and *p*-hydroxybenzen-1,3-dicarbaldehyde were subjected to Claisen-Schmidt condensation using NaH in dry THF at room temperature to give the desired chalcone 45 (scheme 7).

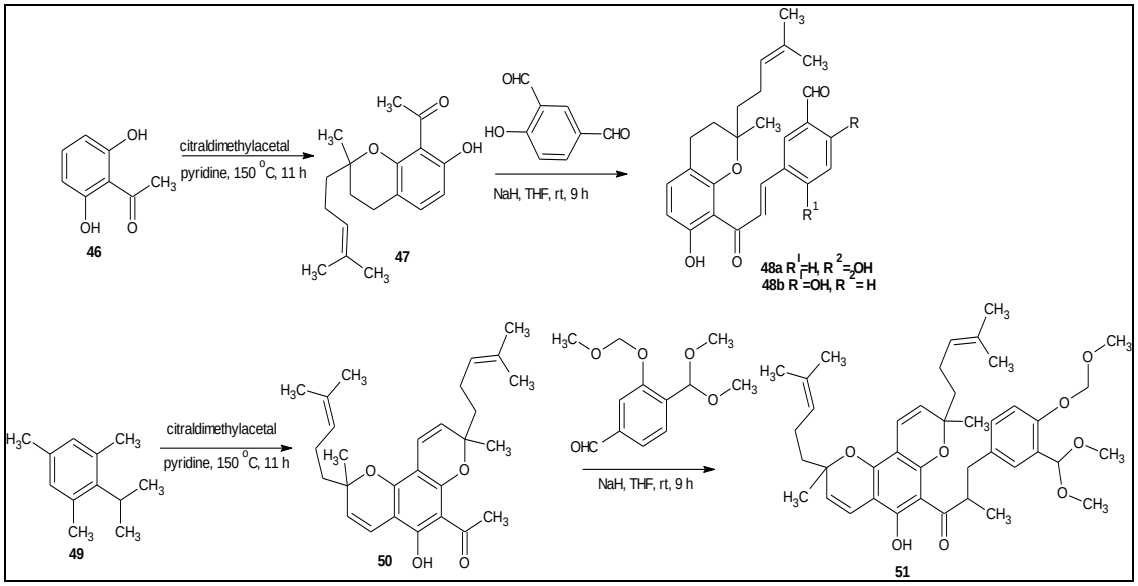
The in-vitro antimalarial activity of chromenochalcones showed that the presence of chromene moiety did not show improved activity when compared to chromanochalcones. Although some of the chromenochalcones had better activity than chromanochalcones, only compound 40m (MIC 5.34 µM) had a comparable antimalarial property on comparison with diprenylated chalcones medicagenin (24) (MIC 5.10 µM). It is interesting to note that the presence of aminoalkyl substituent as in 42a (MIC 3.67 µM) on the group of 40d (MIC 155.27 µM) significantly increased the activity profile as shown in table 5.



Scheme 7: Synthesis of chromenochalcones

Table 5: MIC of chromenochalcones

Compd. No.	R^1	R^2	R^3	R^4	R^5	MIC (µM)
40m	H	Cl	H	Cl	H	5.34
41i	H	H	H	CN	H	5.01
41k	H	H	NO_2	H	H	4.77
41l	H	OH	H	H	CHO	1.19
41m	H	H	CHO	OH	H	0.59
42b		H	H		H	3.26
45	-	-	-	-	-	0.25
48a	H	H	CHO	OH	H	0.39
48b	H	OH	H	H	CHO	0.31



Scheme 8: Synthesis of functionalized chromenochalcones

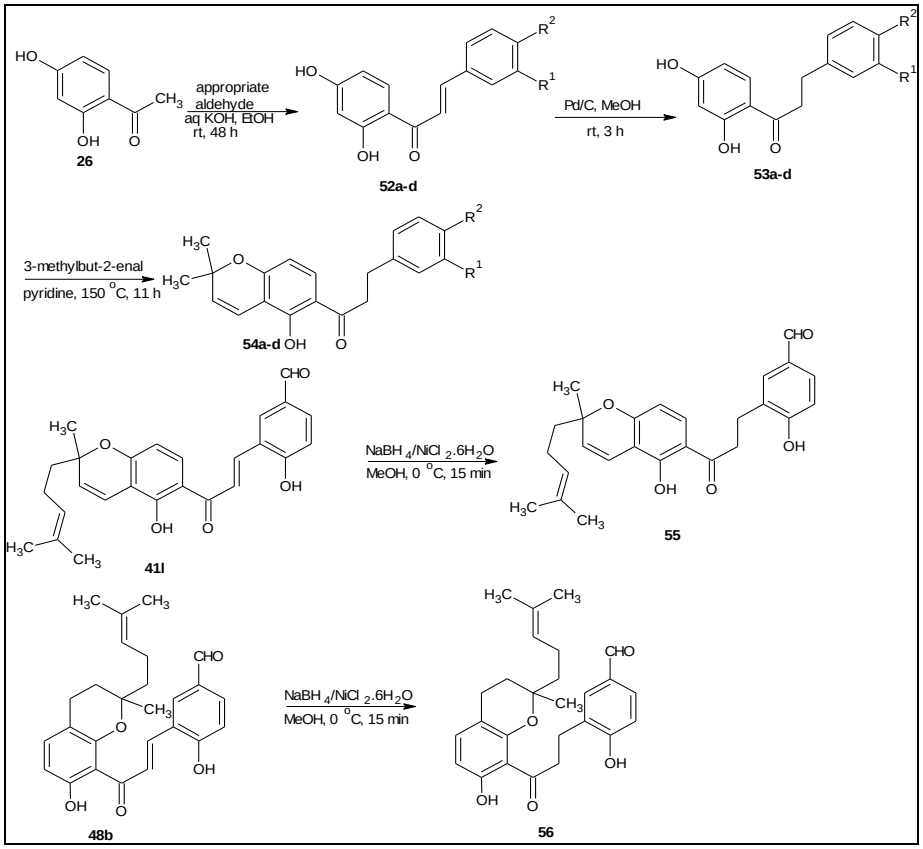
Chromenochalcones 48a-b which are isomers of 41l and 41m and dichromenochalcone 51 were also synthesized from 2,6-dihydroxyacetophenone (46), 2,4,6-trihydroxyacetophenone (49) and citraldimethylacetal via intermediates 47 and 50 respectively (scheme 8).

The chromenochalcones 41i, 41k, 41l, 41m, and 42b (MIC 5.01, 4.77, 1.19, 0.59 and 3.26 µM) respectively had improved antimalarial activity. The prenylated chalcone 45 (MIC= 0.25 µM) had the best antimalarial property which is comparable with the best chromenochalcones 48a (0.39 µM) and 48b (0.31 µM). The dichromenochalcone 51 had good antimalarial property but not comparable with other potential chromenochalcones or prenylated chalcones. It is important to note that the chalcones with electron donating groups on ring A (40q-w and 41a-b) showed no improved antimalarial activity: those with mono or di-halogen substituents in ring A were poorly active or inactive in some cases but those with electron withdrawing groups (4-cyano and 3-nitro) on ring A in exception of 41j (MIC= 119.33 µM) exhibited good antimalarial activity. Chalcones which have the combination of hydroxyl and aldehyde substituent on ring A showed good activity. Worthy to note is the fact that masking the hydroxyl group of 41m (MIC 0.59 µM) with methyl-oxy-methyl (MOM) substituent as in 41n dramatically reduced the activity 41n (MIC=21.64 µM)

A careful study of the in-vitro antimalarial activities of the chromenochalcones and their structural features suggests that both hydroxyl and aldehydes substituents on ring A, an extra alkenyl (prenyl or C-5 unit) substituent on benzopyran core, and an aminoalkyl substituent on hydroxyl groups are playing important role for good antimalarial activity. Since chromenochalcones 41l and 41m exhibited good activity (MIC=1.19 µM and 0.59 µM respectively), they prepared chalcones 45 with an additional prenyl substituent on ring B of 41l and the in-vitro antimalarial activity lead to improved activity (MIC= 0.25 µM). Isomeric chalcones 48a and 48b were prepared and they had good in-vitro antimalarial activity comparable to 41l and 41m (MIC= 0.39 and 0.31 µM respectively).

Synthesis of chromenodihydrochalcones

They carried out the synthesis of chromenodihydrochalcones (54a-d, 55 and 56) to determine the role of the α,β-olefinic bond which connects the ring A and carbonyl carbon. Initially, they prepared the chalcones 52a-d by Claisen-Schmidt condensation between 26 and substituted benzaldehydes. The resultant chalcones were hydrogenated using Pd/C to give dihydrochalcones 53a-d which subsequent chromenylation using 3-methylbut-2-enal in the presence of pyridine provided the chromenodihydrochalcones (scheme 8) [76]. Compounds 55 and 56 where synthesized by regioselective hydrogenation of 41l and 41m using $NaBH_4/NiCl_2.6H_2O$



Scheme 9: Synthesis of chromenodihydrochalcones

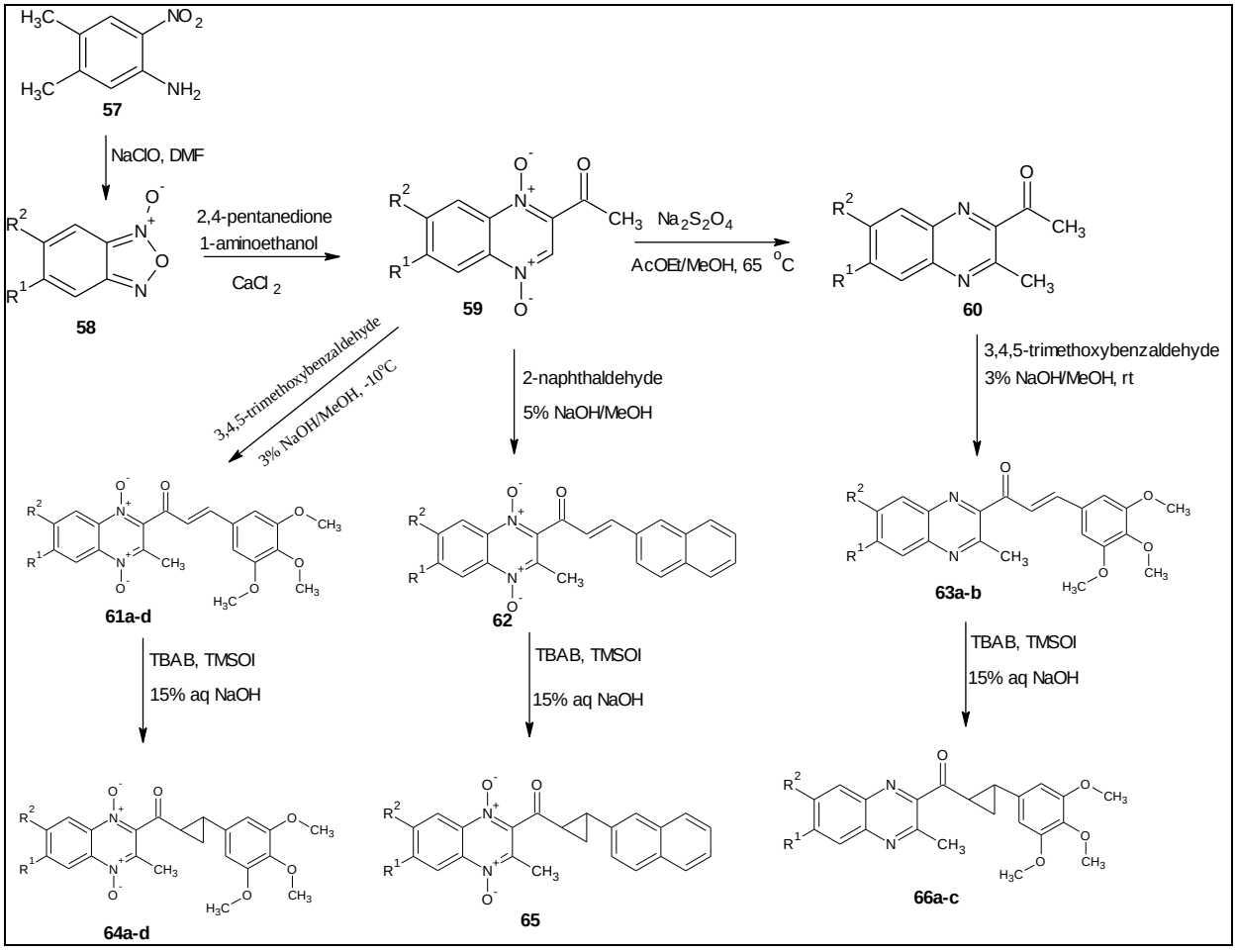
The in-vitro antimalarial activity of the chromenodihydrochalcones showed that the mono hydroxyl (54a, MIC 30.86 µM) or dihydroxyl (54c, MIC 29.41 µM) system on ring A exhibited moderate activity whereas their *O*-methyl derivatives (54b and 54d: MIC 147.92 and 135.86 µM respectively) were less active. Worthy of the mention is that compounds 55 and 56 which dihydro derivatives of 41l and 48b showed moderate activity (MIC 10.3 and 9.12 µM respectively) as against (1.19 and 0.31 µM respectively) for 41l and 48b. This findings underscore the importance of α,β-unsaturated ketone (Michael acceptor) moiety in the inhibition of parasitemia. Of all the eighty eight chalcones synthesized by this group, five compounds 41l, 41m, 45, 48a and 48b showed excellent antimalarial activity comparable with chloroquine and arterether. The antimalarial activities of the five compounds were screened in terms of IC_{50} against chloroquine sensitive strain (3D7) and chloroquine resistant strain (KI). The antimalarial activity profile is presented in table 6.

Table 6: MIC of chromenodihydrochalcones

Compd. No.	IC_{50} (nM) 3D7	IC_{50} (nM) KI	IC_{50} ration KI/3D7	Selectivity index 3D7	Selectivity index KI
45	73.25	366.25	5.0	1210	242
48a	94.73	84.21	0.9	334	376
Chloroquine	17.00	443.57	25.2	13393	530
Arteether	1.37	1.08	0.79	98720	124857

It is noteworthy that compound **48a** was almost equally effective against both 3D7 and KI strain. It also showed improved antimalarial activity against chloroquine resistant strain.

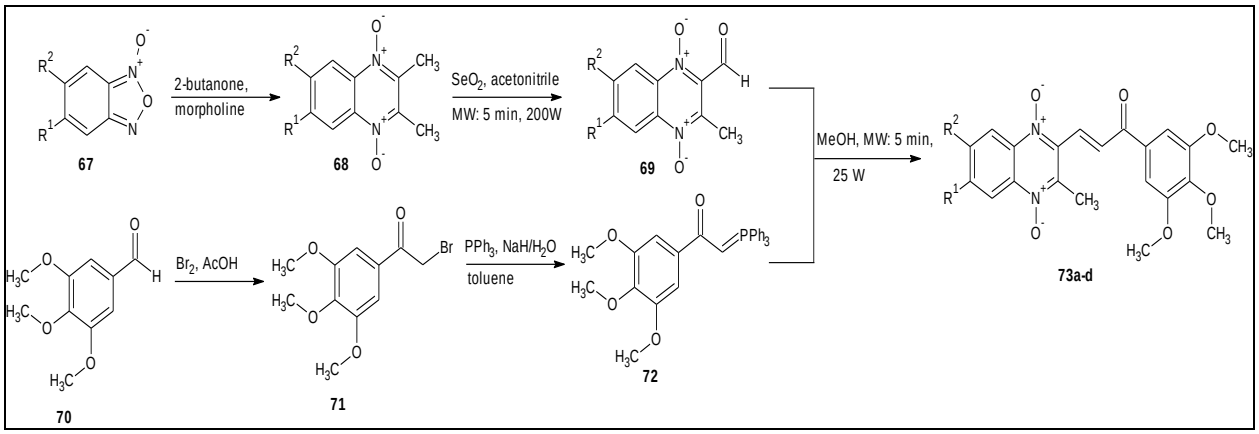
6.0 Synthesis of quinoxaline derivatives of chalcones



Scheme 10: Synthesis of quinoxaline derivatives of chalcones

The activities of quinoxaline-1,4-di-*N*-oxide derivatives against *Mycobacterium tuberculosis*[79-86], *Trypanosoma cruzi*[87,88], *Leishmania amazonensis*[89], *L. infantum*[90], *P. falciparum*[89-96], has been reported. These reported biological activities motivated Ana *et al*[97] to synthesize new quinoxaline derivatives and screened their antimalarial properties. The appropriate quinoxaline di-*N*-oxide 59 (2-acetyl-3-methylquinoxaline-1,4-di-*N*-oxide, 3 mmol) and 2-naphthaldehyde (3 mmol) were dissolved in methanol (30 mL). Sodium hydroxide (5%, 10 mL) was added drop-wise and the reaction mixture stirred at room temperature for 15 min, until a yellow precipitate appeared. The solid, 3-methyl-2-[3-(naphtha-2-yl-prop-2-enoyl)] quinoxaline-1,4-di-*N*-oxide derivatives 62 obtained was filtered off and washed with diethyl ether. The appropriate chalcones 61a-d, 62 and 63a-b (1 mmol), trimethylsulfoxonium iodide (TMSOI) (2 mmol) and tetrabutyl ammonium bromide (TBAB) (0.2 mmol) were dissolved in dichloromethane (40 mL) and stirred at room temperature for 15 min. Then a 15% aqueous solution of NaOH (10 mL) was added drop-wisely and the reaction mixture stirred at room temperature for 24 h. Excess dichloromethane and water were added to the reaction. The organic phase was extracted and dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate as the eluent. The desired compounds 64a-d, 65 and 66a-b were obtained after recrystallization from ethanol. The synthesis of compound 60 was achieved by reduction of compound 59 (scheme 10)

Compounds 73a-d were synthesized using microwave assisted Wittig reaction [97] between 2-formyl-3-methylquinoxaline-1,4-di-*N*-oxide derivatives 69 and a phosphonium ylide 72 both previously synthesized[98-100] (scheme 11).



Scheme 11: synthesis of quinoxaline derivatives of chalcones

The eighteen quinoxalines and quinoxaline-1,4-di-*N*-oxide derivatives were screened for in-vitro antimalarial activities against chloroquine resistant FCR-3 strain of *P. falciparum.* The antimalarial screening showed that almost all the compounds had antimalarial activity though none was comparable to chloroquine. Compounds 61a and 62 were the lead chalcones. Among inverted chalcones and cyclopropyl derivatives, 73b and 64b had the best activities with IC_{50} of 24.2 and 20.1 µM respectively.

Table 8: IC_{50} of quinoxaline derivatives of chalcones

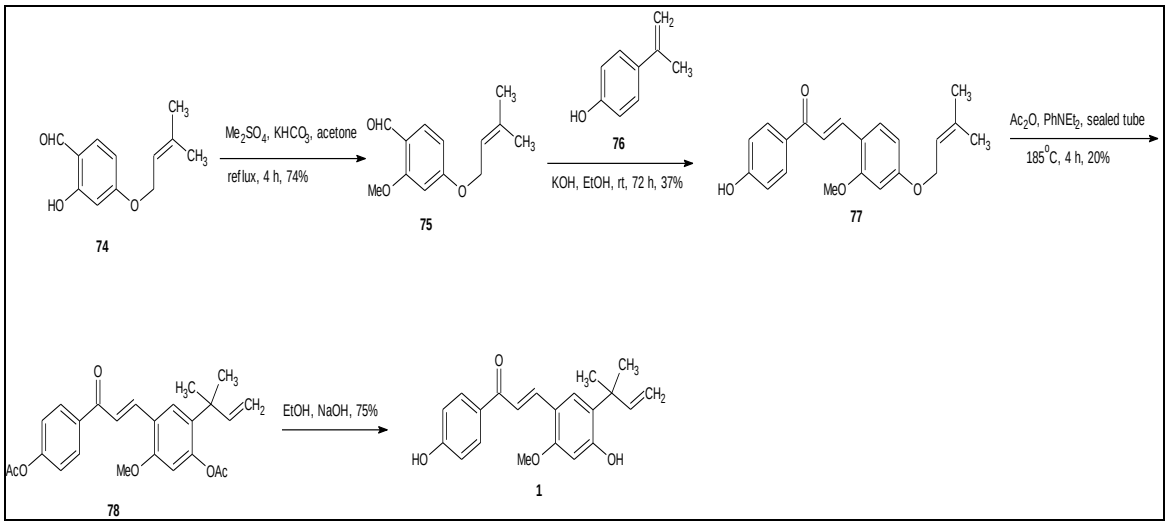
Compd. No.	R^1	R^2	IC_{50} (µM)
61a	H	H	6.2
62	H	H	5.8
64b	H	Cl	20.1
Chloroquine	-	-	0.173

Aside compound 64b (IC_{50} 20.1 µM), changing the double bond in chalcones (61a-d, 62 and 63a-b) for a cyclopropyl structure led to a dramatic drop in the antimalarial activity in each case (61a-d, 62 and 63a-b). The same trend was noted when comparing cyclopropyl derivatives 64a-d with their analogues in 73a-d. In exception of compound 61a (IC_{50} 6.2 µM), the inversion of the chalcones did not lead to significant change in the antimalarial activity in comparison with 61a-d (table 8).

7.0 Synthesis of licochalcone A

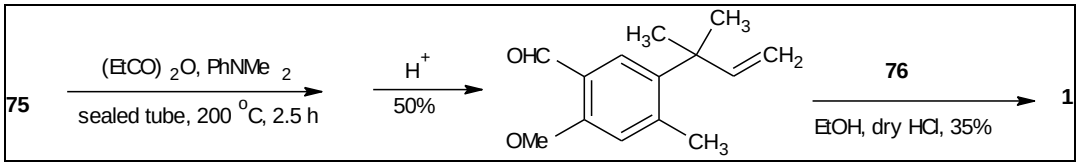
Licochalcones A-E are interesting retrochalcones that are distinguished from ordinary chalcones by the absence of an oxygen functionality at the C-2^I and C-6^I position[101]. They have been reported to have various biological activities such as antitumour[102], antiparasitic[103], antileishmanial[104], antioxidative[105], superoxide scavenging[106] and antibacterial[107] activities. Licochalcone A has been shown to have antimalarial activity[108]. Given the reported biological activities of licochalcones, Jeon *et al*[109] synthesized licochalcone A by modifying the existing routes of synthesis which either gave a low overall yield or have a very long steps.

One of the routes for the synthesis of licochalcoe A is by the methylation of 2-hydroxy-4-[(3-methylbut-2-en-1-yl) oxy] benzaldehyde (74) at the 2-position to form the protected aldehyde (75), followed by Claisen-Schmidt condensation[110] with 4-hydroxyacetophenone (76) to afford chalcone prenyl ether (77). Compound 77 underwent a [3,3]-sigmatropic rearrangement with acetic anhydride in *N*,*N*-diethylaniline to give the acetylated chalcone (78). Removal of the acetyl group under basic conditions gave the licochalcone A (1) in 4% yield[111] (scheme 12).



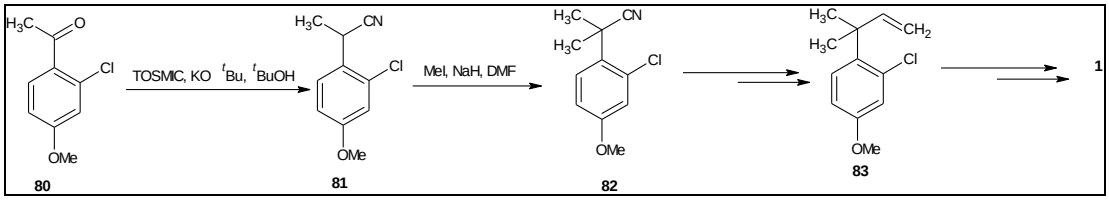
Scheme 12: synthesis of licochalcone A

The second route for the synthesis of licochalcone A was reported by Ren-Sheng *et al*[112] using a similar procedure involving a [3,3]-sigmatropic rearrangement. They dissolved aldehyde 75 in propionic anhydride and *N*,*N*-dimethylaniline and heated the mixture to 200°C for 2-5 h in a sealed tube. Acid hydrolysis and Claisen-Schmidt condensation with 4-hydroxy acetophenone (76) gave licochalcone A (scheme 13).



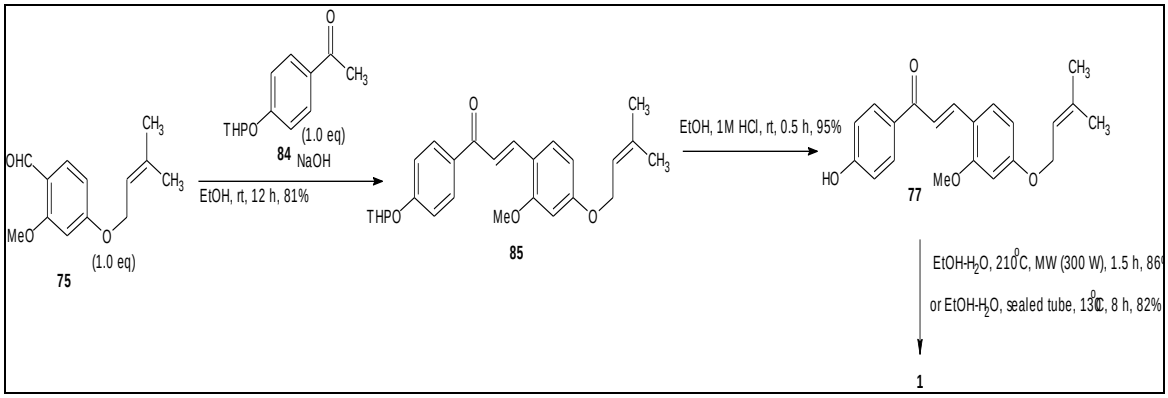
Scheme 13: synthesis of licochalcone A

In yet another route necessitated by low yield of the two routes discussed in scheme 12 and 13, treatment of 2-chloro-4-methoxyacetophenone (80) with tosyl methyl isocyanide (TOSMIC) gave a nitrile compound (81) which when methylated gave compound (82). Compound 82 when subjected to S_N2 reaction followed by a series of functional group transformations gave the required prenylated benzaldehyde (83) which was converted to licochalcone A (scheme 14).



Scheme 14: synthesis of licochalcone A

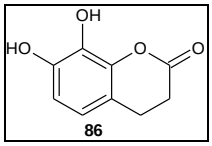
The synthetic routes presented in scheme 12 and 13 were very useful in constructing licochalcone A backbone but the reported yields were generally poor. The route in scheme 14 was interesting but involves seven steps. Following the short steps but poor yield of scheme 12 and 13 Jeon *et al*[109] worked on improving the yield of the Claisen rearrangement step (scheme 12 and 13). Their work involved: the aryl ether 75 underwent Claisen-Schmidt condensation with 4-[(tetrahydropyran-2-yl) oxy] acetophenone (84) to give the protected chalcone 85 in 81% yields. They removed the tetrahydropyranyl group under mildly acidic conditions to obtain the chalcone ether 77 in 95 % yield. They carried out [3,3]-sigmatropic rearrangement reactions of chalcone ether 77 in ethanol-water (4:1) under microwave irradiation at 300 W for 1.5 h to obtain licochalcone A in 86% yield without deprenylated and abnormal Claisen rearrangement products. Similarly, they performed the reaction with the same solvent system in a sealed tube in a furnace for 8 h at 130^{o}C and licochalcone A was obtained at 82 % yield (scheme 15).



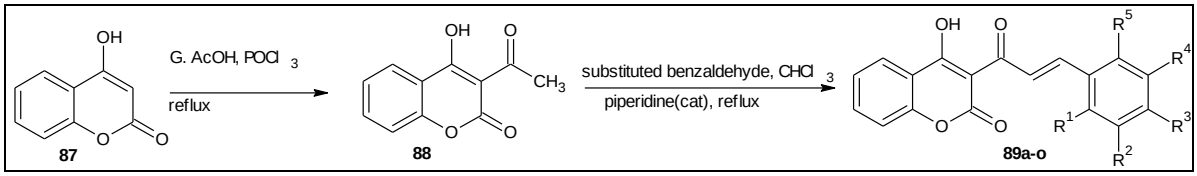
Scheme 15: microwave assisted synthesis of licochalcone A

8.0 Synthesis of 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones

Coumarin, an organic heterocyclic scaffold, constitutes an important class of compound with versatile biological activities and can be found in many natural or synthetic drug molecule[113]. Daphnetin (7,8-dihydroxycoumarin) (86), a Chinese herbal product used for the treatment of coagulation disorders showed potency against malarial parasite both in-vivo and in-vitro[114,115]. In the light of these findings, Patel *et al*[116] synthesized a series chalcones with coumarin moiety.



Patel and his group accomplished the synthesis of the 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones by a two-step procedure. The first step involved synthesis of the precursor 4-hydroxy-3-acetylcoumarin (88) by reacting 4-hydroxy coumarin (87) with phosphorus oxychloride and glacial acetic acid and the step involved Knoevenagel condensation between compound 88 and substituted benzaldehydes in chloroform in the presence of catalytic amount of piperidine gave the 3-cinnamoyl -4-hydroxy-2H-chromen-2-ones 89a-o (scheme 16).



Scheme 16: synthesis of 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones

They ascertained the antiplasmodial efficacy of 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones using chloroquine sensitive (3D7) and chloroquine resistant strain (W2) of *P. falciparum.*

Table 9: MIC of 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones

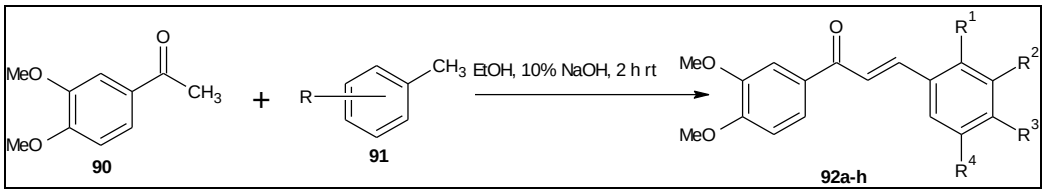
Compd. No.	R^1	R^2	R^3	R^4	R^5	IC50 3D7 (µg/mL)	IC80 3D7(µg/mL)	IC50 W2(µg/mL)
89c	H	Cl	H	H	H	4.2	9.0	6.2
89d	H	H	Cl	H	H	5.1	14.2	6.5
89g	H	H	NO_2	H	H	3.1	7	4
CQ	-	-	-	-	-	0.0223	0.0401	0.2301

They explored the effect of structural variation in the antimalarial activity of 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones. It is evident from table 9, that *meta* and *para* substitution in the phenyl ring are mostly favoured by low IC_{50} values (IC_{50} < 10 µg/mL). Amongst the para substituted compounds, nitro substitutions on the phenyl rings compound 89g showed highest antimalarial potency (IC_{50} < 5µg/mL) against 3D7 and W2. The potency decreases in the order NO_2>Cl>CH_3>N(CH_3). In case of meta substitution in the phenyl ring, chloro group seems to be a substituent of choice as indicated by low IC_{50} values (< 5 µg/mL).

9.0 Microwave-Assisted Synthesis of Aryl and Heteroaryl Chalcones.

Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with higher chemical yields due to which this method becomes superior to the conventional method. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards[117].

The synthesis of 1,3-diaryl-2-propen-1-ones (aryl chalcones) (92a-h) was achieved by both conventional and microwave irradiation (MW) methods by adding different aldehydes (91) (0.005 mol) to a mixture of 3,4-dimethoxyacetophenone (90) (0.99 g, 0.005 mol), sodium hydroxide solution (10 mL, 10 % w/v) and ethanol (10 mL). For the synthesis of these compounds by conventional method, the reaction mixture was stirred for 2 h at room temperature and kept aside for 1 h to get the solid crude product. In the microwave irradiation method, the reaction mixture was placed in a microwave oven and was stirred at 140 W. For all the compounds synthesized by both methods, completion of the reaction was monitored by TLC on silica gel coated plates using hexane: ethyl acetate (2:1) as the mobile phase. Solid crude products obtained by both methods were filtered and washed with cold ethanol. All the compounds were recrystallized using a mixture of ethanol and water (80:20[118] (scheme 17).



Scheme 17: microwave assisted synthesis of 1,3-diaryl-2-propen-1-ones (aryl chalcones)

Vaidya1 and Mahajan[118] evaluated all the synthesized chalcones for their antimalarial activity using Rane's test[119]. The antimalarial activity was expressed as the mean survival time of mice at the end of the observation period of 40 days.

Table 10: antimalarial activities of 1,3-diaryl-2-propen-1-ones

Compd. No.	R^1	R^2	R^3	R^4	Mean survival time	remark
92a	H	H	H	H	22.00 ±1.060*	Active*
92c	H	OCH_3	OCH_3	OCH_3	20.33 ± 7.120*	Active*
92d	H	OCH_3	H	OCH_3	21.66 ± 0.220*	Active
92e	Cl	H	H	H	23.33 ± 2.560*	active
92g	H	H	F	H	23.00 ± 0.050*	Active*
92h	H	H	OH	H	26.66 ± 0.667*	Active*
chloroquine	-	-	-	-	>40 days	
-ve control	-	-	-	-	10.33 ± 0.421	

*** The values of the treated group (compounds 92a-h and 95a-b) significantly different from the control group at p < 0.01. [a] = Curative compounds**

Out of the ten chalcones synthesized, compounds 92a, 92c, 92d, 92e, 92g and 92h were found to be *"Active"*, i.e. the mean survival time (MST) of mice treated with these compounds was double the mean survival time (MSTC) of mice in the negative control group. Out of the six active compounds, 92a, 92c, 92g and 92h were found to be *"Curative"*, since out of six mice in a group, treated with these compounds, at least one mouse was alive even after 40 days of the observation period. In the *positive control group* (chloroquine, 10 mg/kg body weight), all the mice were found to be alive after 40 days. The compounds possessing a methoxy group at 3″, 4″ or 5″ positions (compounds 92c and 92d), a chloro group at 2″ position (compound 92e), a fluoro group at 4″ position (compound 92g) and a hydroxyl group at 4″ position (compound 92h) of 1,3-diaryl-2-propen-1-ones, showed good antimalarial activity. The compounds having a benzotriazole moiety at position 1 (compounds 95a and 95b) of 1, 3-diaryl-2-propen-1-ones did not show good antimalarial activity. Thus, activating groups or electron releasing groups are found to contribute towards antimalarial activity of 1, 3-diaryl-2-propen-1-ones (table 10).

Conclusion

This work has reviewed the synthesis and antimalarial activities of about two hundred chalcone derivatives. In most of the synthesis reported, there was almost always a comparison between the antimalarial activities of the novel compounds with chloroquine and in some cases arteether. The following compounds 16g, 18a, 18c, 18k, 19a, 19b, 19d, 19g, 19i, 23i, 23k, 23m, 23o, 24, 40m, 41l, 41m, 45, 48a, 48b, 62, 89g, 92a, 92c, 92g and 92h has been revealed as having comparable antimalarial activities with chloroquine. Although none of the chalcones reviewed had better antimalarial activity against chloroquine sensitive strain of *P. falciparum*, compounds 45 and 48a (IC_{50} 366.25 nM and 84.21 nM respectively) had better antimalarial activity against chloroquine resistant strain of *P. falciparum* than chloroquine (IC_{50} 443.57 nM). The most active of the compounds is 45 (MIC 0.25 μM).

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