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Review Article

Mini review: Chalcone derivatives as Antimalarial agent

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Abstract

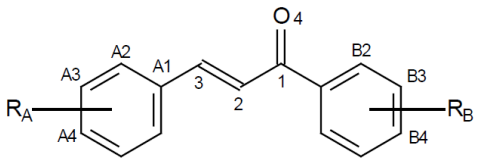
Malaria is a vector borne disease caused by plasmodium parasite. About 3.3 billion people, almost half of world's population is at risk of malaria. In every year, about 250 million cases and nearly one million deaths are attributed to malaria. Malaria is a serious problem in Africa, where it is responsible 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, and anti bacterial activities. Prenylated chalcones, chromanochalcones, chromenochalcones, anti-hyperglycemic, antimalarial 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, licochalconeA, morachalcones, microwave synthesis.

1. Introduction

Chalcone are group of compound with various substitution pattern on to aromatic rings of 1,3diphenyl 2 propan 1one. They constitute important class of natural product belonging to flavonoid family which have been reported to posses wide spectrum of biological activity including antibacterial, antiinflamatory, antimalarial and antidiabetic. Some chalcone derivatives have been found to inhibit several important enzymes in cellular system such as xanthin oxidase and tyrosinkinase [1]. Chalcone (1, 3 diphenyl 2propan 1one) and other biogenetically related compound belonging to flavonoid family are natural substance found in number of plant and prepared synthetically. And are precursor of cyclic flavonoid and isoflavonoids [2].

They consist of two aromatic ring joined between three carbon α and β unsaturated carbonyl system. They are abundantly present in eatable plant [3]. they are non chiral small molecule bearing relative molecular mass in the range of 300 to 600 g/mol. With relatively high lipophillicity (log ~ 5-7) [3]. Chalcone might subsist in both cis and trans isomeric form while the trans form is thermodynamically more stable [4]. Chalcone is conjugated double bond and entirely delocalised π electron system in both benzene rings. Such system has relatively low redox potential and has a greater probability of undergoing electron transfer reaction. There colour attributed to the presence of chromophore. (-CO-CH=CH) and other Auoxochrome [5]. In past few years it has been reported Morachalcone A.



IUPAC name: 1,3diphenyl- 2-propan- 1-one (21)

Methods of Synthesis:

1. Claisen - schmitidt condensation
2. Photo-fries rearrangement
3. Suzuki coupling reaction
4. Friedel craft acylation
5. Microwave radiation

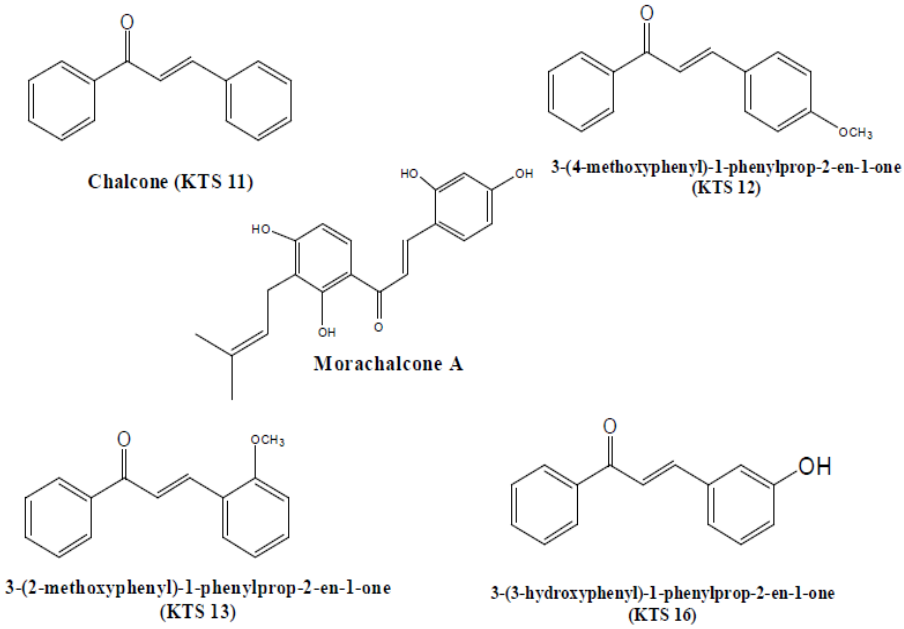


Fig. 1: Chalcone and Its Derivatives

Maleria annilating infective disease of nearly half of the world population; with over 275 million new cases annually, and mortality reaching 2 million. The majority in this case is paediatric date in developing countries. There are four species which cause malaria, *P. falciparum*, *P. vivax*, *P. ovale*, *P. malarie*. *P. falciparum* is for most killers and is found primarily in Africa there are currently no licence malaria vaccine and available drug including artimisinin combination therapy (ACT) [1-8].

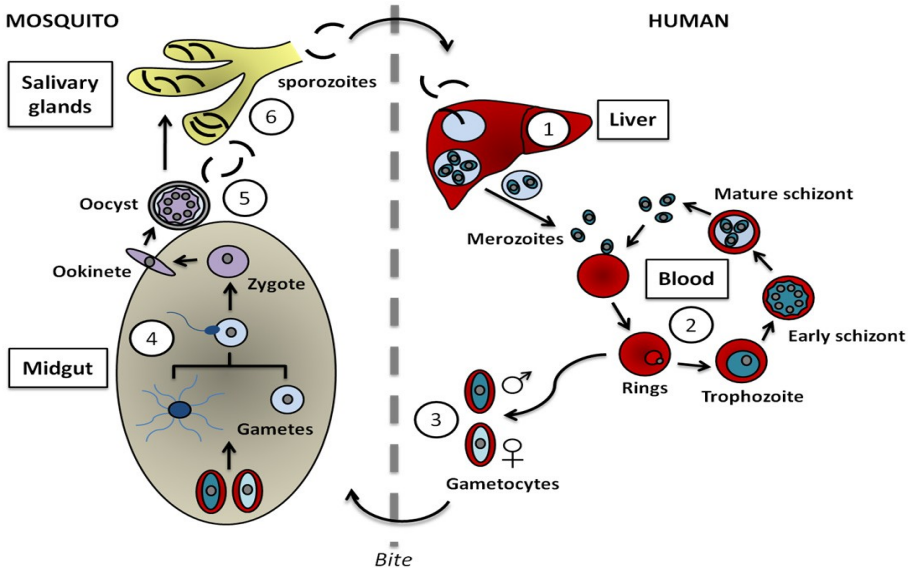


Figure 2: Life cycle of malaria (49)

2. Biosynthesis and chemical synthesis of chalcone

Kostanecki and Tomar [9] did pioneered work in the synthesis of natural colouring compounds and were first to coin the term 'chalcone'. Chalcone is found to be one of the major intermediate in the biosynthetic pathway of flavonoids and contribute significantly to the total amount of flavonoids [10] (Figure 3). 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 conventional method acting for the synthesis of 1, 3-diaryl-2-propenones necessitates the usage of firm bases such as NaOH, KOH, Ba $(OH)_2$, hydrotalcites, LiHMDS, calcites $NaNO_3$/natural phosphate. Anacid-atalyzedaldol condensation, e.g. AlC_{l3}, BF_3, dry HCl, $ZrH_2/NiC_{l2}$and RuC_{l3} (for cyclic and acyclic ketones) has been also reported [10] However, can be promptly synthesized in research laboratory by the Claisen-Schmidt reaction which is enormously easy going and uncomplicated to carry on as well as cheap [11] (Figure 4).

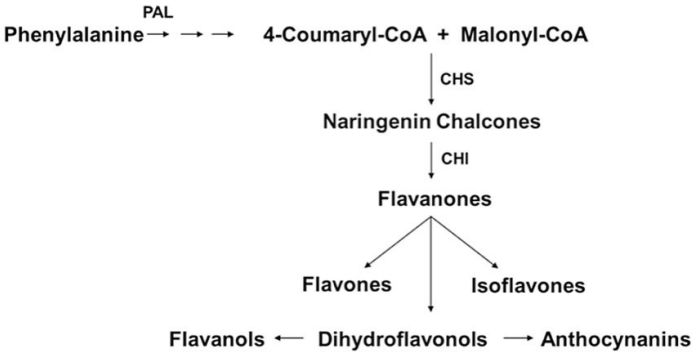


Figure 3: Schematic overview of the flavonoid biosynthesis pathway

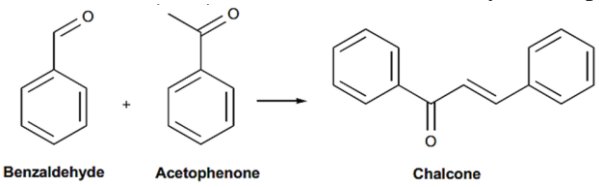


Figure 4: Chemical method for synthesis of chalcone

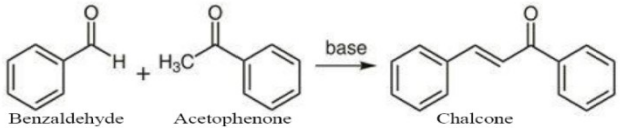
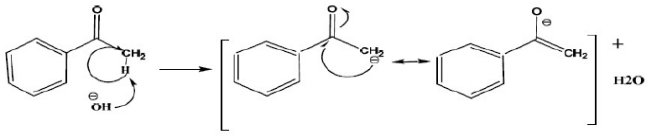


Figure 4: Synthesis of chalcone by general procedure (23)

Mechanism



Acetophenone:

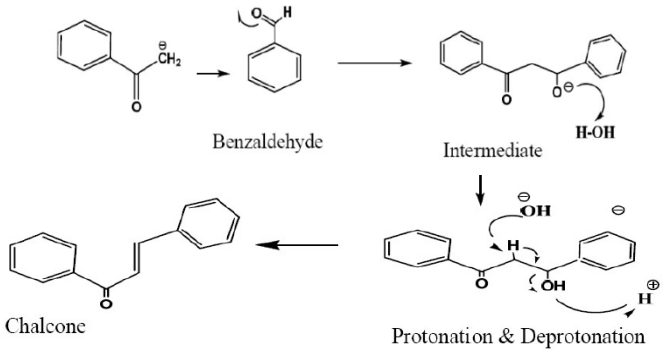


Figure 5: Mechanism for Claisen-Schmidt condensation of acetophenone and benzaldehyde [12]

1. Synthesis of the different chalcone derivatives

Chalcones (A-H) were prepared using the Claisen-Schmidt condensation procedure by condensing acetophenone [10 mmol/1.16 ml] or p-hydroxyacetophenone [10 mmol/1.36 gm] and benzaldehyde [10 mmol/1.01 ml] or one of the following substituted benzaldehydes (10 mmol): p-hydroxybenzaldehyde (1.22 gm), p-chlorobenzaldehyde (1.4 gm), p-fluorobenzaldehyde (1.07 ml), p-methoxybenzaldehyde (1.21 ml), p-nitrobenzaldehyde (1.51gm), m-nitrobenzaldehyde(1.51 gm) and p-dimethyl aminobenzaldehyde (1.49 gm) in dry absolute ethanol (5 ml) using thionyl chloride (8 mmol/ 0.5 ml) to prepare the corresponding chalcone derivatives Tables 1.[13]

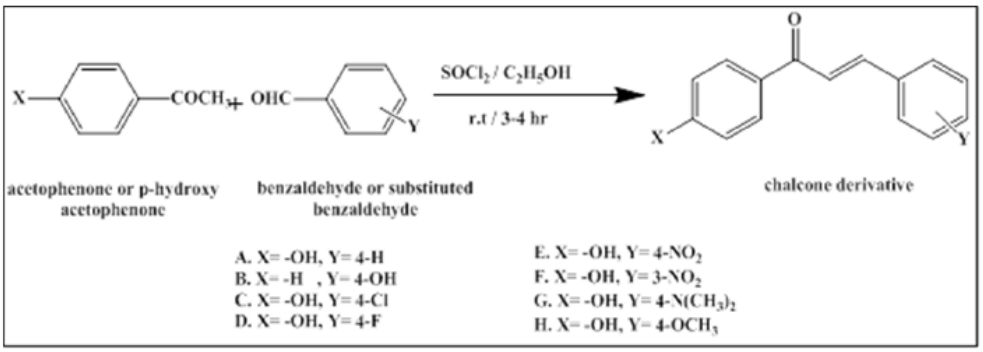


Figure 6: Synthetic diagram of the chalcone derivatives (A-H). [13]

2. 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*. 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 [14]. Isoquine is an analogue of amodiaquine, in which the 4I-hydroxy group on the aniline ring of amodiaquine is interchanged with a 3I-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 conjugate65. 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 [15]. 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 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 80-85oC overnight. The solid formed was filtered, washed with water, diethyl ether and recrystallized from ethanol to obtain [(7-chloroquinolin-4-yl) amino]-acetophenones [17,18]. 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-0]) [16]

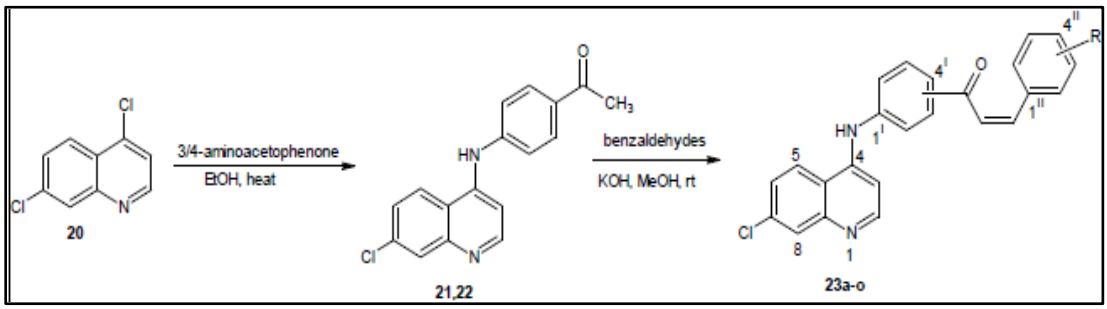


Figure 7: Synthesis of 4 amino quinolone chalcone derivatives

3. 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 molecules [43]. Daphnetin (7,8-dihydroxycoumarin) [20], a Chinese herbal product used for the treatment of coagulation disorders showed potency against malarial parasite both in-vivo and in-vitro [21,22]. In the light of these findings, Patel et alsynthesized a series chalcones with coumarinmoie Patel and his group accomplished the synthesis of the 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones by a two-step procedure.[44] The first step involved synthesis of the precursor 4-hydroxy-3-acetylcoumarin [41] 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.

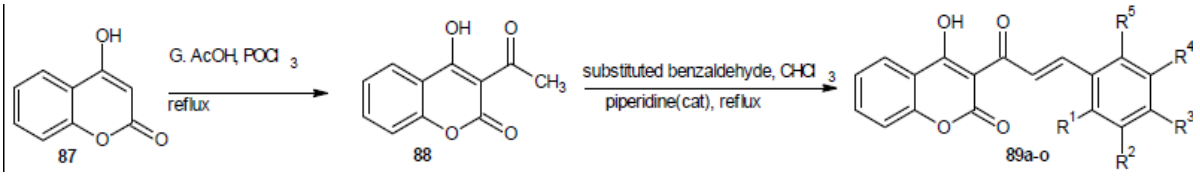


Figure 8: synthesis of 3-cinnamoyl-4-hydroxy-2H

4. Synthesis of Licochalcone A:

Licochalcones A-E is interesting retrochalcones that are distinguished from ordinary chalcones by the absence of oxygen functionality at the C-2I and C-6I position 101. They have been reported to have various biological activities such as antitumour [23], antiparasitic [24], and antileishmanial1, antioxidative, superoxide scavenging and antibacterial activities. Licochalcone A has been shown to have antimalarial activity. Given the reported biological activities of licochalcones, Jeon et al synthesized licochalcone A by modifying the existing routes of synthesis which either gave a low overall yield or have a very long step. [25] One of the routes for the synthesis of licochalcone A is by the methylation of 2-hydroxy-4-[(3- methylbut-2-en-1-yl) oxy] benzaldehyde [45] at the 2-position to form the protected aldehyde [46], followed by Claisen-Schmidt condensation with 4-hydroxyacetophenone [47] to afford chalconeprenyl ether [48]. Compound 77 underwent a [3,3]-sigmatropic rearrangement with acetic anhydride in N,N-diethylaniline to give the acetylated chalcone (48). Removal of the acetyl group under basic conditions gave thelicochalcone A [1].

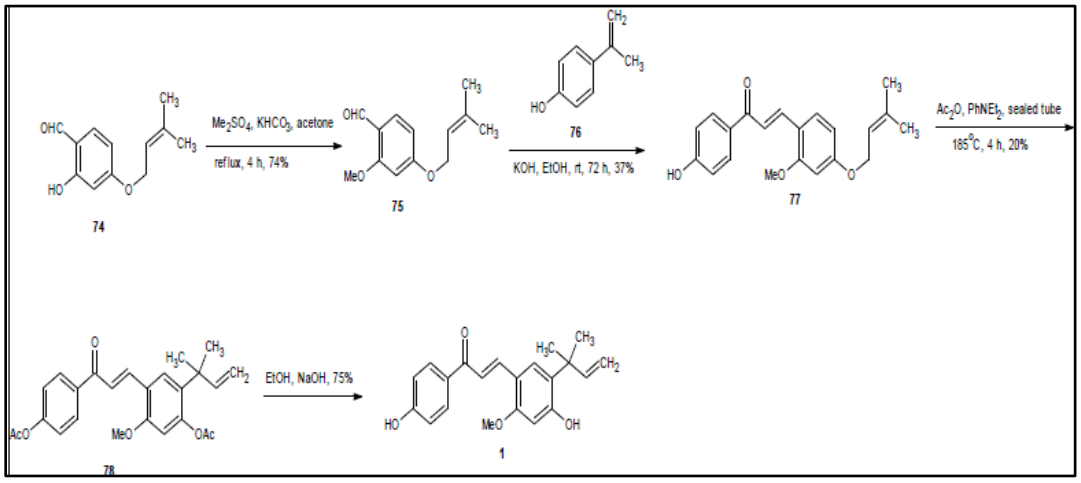


Figure 9: Synthesis of Lidocane A

5. Synthesis of quinolinyl chalcones:

Quinolones and their derivatives have been extensively explored for their biological [26,27] antifilarial28, antibacterial [29,30] 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 synthesize derivatives of chalcones containing quinoline groups. [31] They achieved the synthesis via Claisen-Schmidt condensations of 2-chloro-3-formyl-quinoline/2- chloro-6-ethoxy-3-formyl quinolone [32] (0.01 M) and ethanolic (15 mL) solution of substituted 2-hydroxyl acetophenones [33] (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/I2 gave the iodo derivatives (19a-j).[34]

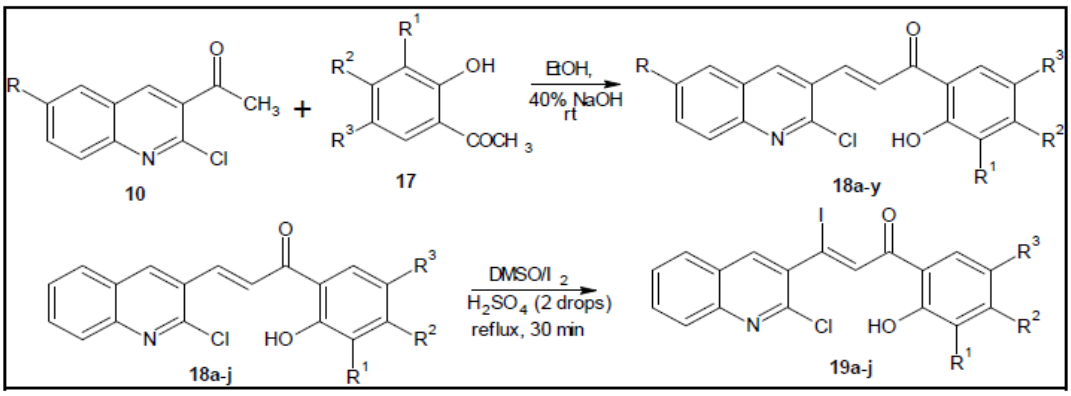
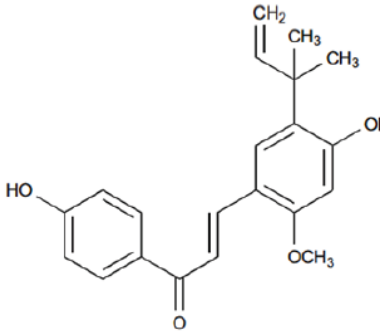


Figure 10: Synthesis of quinolone chalcone

6. Antimalarial activity of chalcone

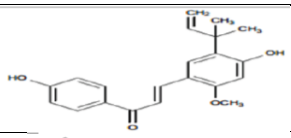
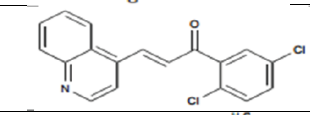
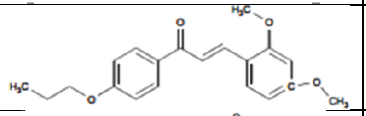
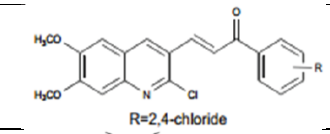
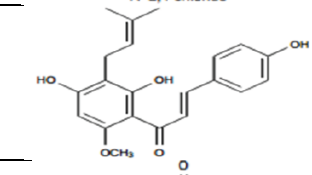
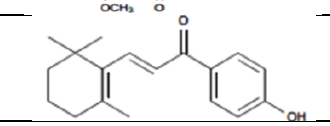
Licochalcone A [35] present in the Chinese licorice root which, under the name of Gan Cao, is utilized in conventional. Chinese medicinal drug (38). The structure of Licochalcone A was first described in 1975, [39] in 1994, Chen *et al.* for the first time manifested substantial inhibitory effect of Licochalcone A on *in vitro* development of both chloroquine-susceptible (3D7) and chloroquine-resistant (Dd_2) *Plasmodium falciparum* strain. Following reports also described antimalarial activity of Licochalcone A whenever administered either intraperitoneally or orally for 3-6 days. To *Plasmodium yoelii* infected mice subsequently, Li *et al. [*17], screened out *in vitro* numbers of chalcones and their derivatives against both chloroquine-sensitive and chloroquine-resistant. Strains of *Plasmodium falciparum* and they were observed 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 n mol/l versus both a chloroquine-resistant strain (W2) and a chloroquine sensitive strain (D6).Some other synthetic analogue, 2,4-dimethoxy-4'-butoxychalcone (3), a new derivative , as well owned prominent antimalarial actions both against a chloroquine-susceptible (3D7) and a chloroquine-resistant (Dd2) strain of *Plasmodium falciparum* as well as when this compound (4mbc),[37] 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. berghe* I infected rats with no more evident signs of toxicity. Despite of this, the mechanism by which 2,4mbcinhibits 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 [40]. In an elaborate study, depicted that in vitro antimalarial action of chalcones against chloroquine-resistant, *Plasmodium falciparum* (K1) was primarily influenced by the properties of ring B. A few of the alkoxylated chalcone 4-10 has value below 6.5 mole/ml [41].



Licochalcone A (1)

7. Chalcones derivatives as Antimalerial activity

Table 1: Chalcones derivatives as Antimalerial activity

Name	Source	Structure	Chloroquine sensitive strain (IC_{50})	Chloroquine resistance strain (IC_{50})
Licochalcone A	Glycyrrhizae uralensis, "Gan Cao		NA	4.22 mol/l
1-(2,5-dichlorophenyl)-3-(4-quinolinyl)-2-propen-1-one	synthetic		0.2 mol/l	0.2 mol/l
2-4 dimethoxy-4'-bytoxychalcone	synthetic		8.9 µmol/l	14.8 µmol/l
1-(2,4-Dichlorophenyl)-3-[3-(2-chloro-6,7-dimethoxiquinolinyl-2-propen-1-one	synthetic	 R=2,4-chloride	NA	19.0 µmol/l
Xanthohumol	*Humulus lupulus* L.		8.2 µmol/l	24.0 µmol/l
Retinoid-like Chalcones	synthetic		NA	>10 µmol/l

8. Conclusion

To synthesize different derivatives of chalcone use as antimalarial agent and find out their antimalarial activity. The present QSAR study investigated the factors that may be important in the inhibitory activity of chalcone derivatives on *P. falciparum* cysteine protease. The obtained models presented good capacity to explain the observed values of biological activity, high adjustment level, statistical significance and good predictive capacity. Hydrophobic and steric properties seem to play an important role in the explanation of the activity of the dataset. The results indicated that the activity on W2 and D6 strains is favored if ring A is a width–limited chemical substituent. The limited molecular width of these derivatives can be related with the activity against D6 strain. The molecular weight, which is related to molecular volume, appears to influence only the activity of D6 strain. The results also indicated that molar refractivity and molecular length have positive contribution to the activity against chloroquine–resistant (W2) Plasmodium falciparum strains, while molecular weight against mefloquine–resistant (D6) strains. The crystal structure of the parasitic cysteine protease remains undetermined. The availability of the enzyme structure would help researchers to go further in understanding the interactions that dominate chalcone–receptor binding.

Reference

[1]. Melanny Ika Sulistyowaty, Kholis Amalia No fianti, Suzana and Tutuk Budiati "Synthesis and brine shrimp bioassay of Chalcone and Its Two Methoxy Derivatives" *International Journal of Pharmaceutical and Chemical Sciences* 2013; 1(6): 110-115.

[2]. Ahmad, M. R. Sastry, V.G. Bano. "Synthesis and Cytotoxic, Antioxidant Activity of 1,3-diphenyl-2-propene- 1-one Derivatives" *Int. J. Chem.Tech. Res.* 2011; 3(3): 1462-1469.

[3]. Patil, C.B. Mahajan, S.K. Katti, S.A. "Chalcone: A Versatile Molecule". *Journal of Pharmaceutical Sciences and Research* 2009; 1(3): 11-22.

[4]. Rahman, M.A. "Chalcone: A Valuable Insight Into The Recent Advances and Potential Pharmacological Activities". *Chemical Sciences Journal* 2011, CSJ-29: 1-1

[5]. S.R. Sarda, W.N Jadhav, S.R Bhusare, S.K Wasmatkar, S.A Dake, R.P Pawar. "Solvent-free NaOH-Al2O3 Supported Synthesis of 1,3-diaryl-2-propene-1-ones" *International Journal of Chem Tech Research* 2009; 1(2): 265-269.

[6]. Edrarir, S., Cotelle, N., Bakkaour, Y., Rolando, C. "An Efficient Synthesis of Chalcones Based on the Suzuki Reaction" 2003; 44: 5359-5363.

[7]. T.S. Wahyuni, Wiwied Ekasari, Aty W., Yusuke Hirasawa, Hiroshi Morita, Noor C. Zaini. Artopeden A, "A New Antiplasmodial Isoprenylated Flavone from *Artocarpus Champeden*". 2009; 79: 1121-1126.

[8]. Melanny Ika Sulistyowaty, Kholis Amalia Nofianti, Suzana, Wiwied Ekasari, and Tutuk Budiati. "Synthesis and Antiplasmodium Activity of Monohidroxy Chalcone". Proceeding of The 3rd International Conference on Pharmacy and Advanced Pharmaceutical Sciences 2013; book I (Pharmaceutical Science & Technology): 236-239

[9]. Donnelly JA, Doran HA, Murphy JJ. "Chalcone dihalides—IV: Steric effects in the cyclization of 2-acetoxy-6-methoxyl Derivatives". *Tetrahedron* 1973; 29: 1037-42

[10]. Rahman MA, "Chalcone A valuable insight into the recent advances and potential pharmacological activities". *Chem Sci J* 2011; CSJ-29.

[11]. Siddiqui AA, Rahman MA, Shaharyar M, et al. "Synthesis and anticonvulsant activity of some substituted 3,5-diphenyl-2-pyrazoline-1-carboxamide derivatives". *Chem Sci J* 2010; CSJ-8.

[12]. Makarand Attarde, AmishaVora, Alice Varghese, Yusuf Kachwal *OCAIJ,* 10(5), 2014 [192-204] volume 10

[13]. Samir A. Hasan and Amer N. Elias "diclofenac – chalcone as possible mutable prodrugs."2013

[14]. Watkins, W., Sixsmith, D.; Spencer, H.; Boriga, D.; Karjuki, D.; Kipingor, T.; Koech, D. Lancet, 1984, 1, 357–359.

[15]. Ruscoe, J.;Tingle, M.; O'Neill, P.; Magg, J.; Ward, S.; Park, B. "*Antimicrob. Agents Chemother*". 1998, 42, 2410–2416.

[16]. O Neill, P.; Mukhtar, A.; Stocks, P.; Randle, L.; Hindley, S.; Ward, S.; Storr, R.; Bickley, J.; O'Neill, I.; Maggs, J.; Hughes, R.; Winstanley, P.; Bray, P.; Park, *B. J Med Chem.,* 2003, 46, 4933–4945.

[17]. Werbel, L.; Cook, P.; Elslager, E.; Hung, J.; Johnson, J.; Kesten, S.; Mc Namara, D.; Ortwine, D.; Worth, D. *J Med Chem*., 1986, 29, 924–939.

[18]. Awasthi, S. K.; Mishra, N.; Kumar, B.; Sharma, M.; Bhattacharya, A.; Mishra, L. C.; Bhasin, V. K. "*Medicinal Chemistry Research*", 2009, 18, 407-420.

[19]. Lim S , Kim H S and Lee D U, Bulletin of the Korean Chemical Society, 2007, 28, 2495-2497.

[20]. Torres E, Moreno E, Ancizu S, Barea C, Galiano S, Aldana I, Monge A and Pérez-Silanes S, Bioorg. *Med. Chem. Lett*. 2011, 21, 3699–3703

[21]. Yang Y Z, Ranz A, Pan H Z, Zhang Z N, Lin X B and Meshnick S R, Am. J. Trop. Med. Hyg., 1992, 46,15–20

[22]. Huang F, Tang L H, Yu L, Ni Y C, Wang Q M and Nan F J, *Biomed Environ Sci.,* 2006, 19, 367–370

[23]. Saitoh T, Shibata S and Sankawa U, *Tetrahedron Lett*., 1975, 50, 4461.

[24]. Kim J-K, Shin E K, Park J H, Kim Y H, Yoon Park J H, *J. Mol. Med.,* 2010, 88, 829.

[25]. Jeon J H, Mi R K and Jun J G, *Synthesis,* 2011, 3, 370–376.

[26]. Gupta, R.; Gupta, A. K.; Paul, S. *Indian J. Chem*., 1998, 37B, 1211.

[27]. Dube, D.; Blowin, M.; Brideau, C. Bioorg. *Med. Chem. Lett*., 1998, 8, 1255.

[28]. Gupta, R.; Gupta, A. K.; Paul, S. *Indian J. Chem*., 2000, 39B, 847.

[29]. Tiwari, S.; Chauhan, P. M. S.; Bhaduri, D. P. *Bioorg. Med. Chem. Lett*., 2000, 10, 1409.

[30]. Kidwai, M.; Bhushan, K. R.; Sapra. Bioorg. *Med. Chem*., 2000, 8, 69.

[31]. Fujita, M.; Ciba, K.; Tominaga, Y. *Chem. Pharm. Bull.,* 1998, 46, 787.

[32]. Ziegler, J.; Linck, R.; Wright, D. W. *Curr. Med. Chem*., 2001, 8, 171.

[33]. Chauhan, P. M. S.; Srivastava, S. K. *Curr. Med. Chem*., 2001, 8, 1535.

[34]. Dave, S. S.; Ghatole, A. M.; Rahatgaonkar, A. M.; Chorghade, M. S.; Chauhan, P. M. S.; Srivasta, K. *Indian J. Chem*., 2009, 48B, 1780-1793.

[35]. http://www.who.int/malaria/publications/world_malaria_report_2014/wmr-2014-no-profiles.pdf

[36]. Dondorp, A. M.; Yeung, S.; White, L.; Nguon, C.; Day, N. P. J.; Socheat, D von Seidlein, L. *Nat. Rev. Microbiol*., 2010, 8, 272.

[37]. Dondorp, A. M.; Nosten, F.; Yi, P.; Das, D.; Phyo, A. P.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; Ana, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P. J.; Lindegardh, N.; Socheat, D.; White, N. *J. N. Engl. J. Med*., 2009, 361, 455.

[38]. Silfen, J.; Yanai, P.; Cabantchik, Z. I. *Biochem. Pharmacol*., 1988, 37, 4269-4276.

[39]. Lipinski, C. A. J. *Pharmacol. Toxicol. Method*, 2000, 44, 235–249.

[40]. Singh, K.; Manisha.; Likhawat, M.; Singh, L. *Journal of Chemical, Biological And Physical Sciences*, 2011,

[41]. Kidwai, M.; Bhushan, K. R.; Sapra. *Bioorg. Med. Chem*., 2000, 8, 69.

[42]. Benitez D, Cabrera M, Hernández P, Boiani L, Lavaggi M L, di Maio R, Yaluff G, Serna E, Torres S and Ferreira M E, *J. Med. Chem.* 2011, 54:3624–3636

[43]. Sun Y-F and Cui Y-P, *Dyes Pigments*, 2008, 78: 65–76

[44]. Patel K, Karthikeyan C, Hari N S, Moorthy N, Deora G S, Solomon V R, Lee H and Trivedi P, *Med Chem Res,* 2011, DOI 10.1007/s00044-011-9694

[45]. Narender, T.; Reddy, K. P.; Shweta, G. *Syn. Commun*. 2009, 39, 384−394.

[46]. Bandaranayke, W. M.; Crumbier, L.; Whiting, D. A. J. Chem. Soc. 1971, C, 804−810.

[47]. Narender, T.; Khaliq, T.; Shweta, G.; Nishi, Goyal, N.; Gupta, S. *Bioorg. Med. Chem.* 2005, 13, 6543–6550.

[48]. Kumar, A.; Tripathi, V. D.; Kumar, P.; Gupta, L. P. Akanksha, Trivedi, R.; Bid, H.; Nayak, V. L.; Siddiqui, J. A.; Chakravarti, B.; Saxena, R.; Dwivedi, A.; Siddiquee, M. I.; Siddiqui, U.; Konwar, R.; Chattopadhyay, N. *Bioorg. Med. Chem*. 2011, 19, 5409–5419.

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