International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1528-1532 www.ijprajournal.com ISSN: 2456-4494

Review of Chalcone Derivatives Possessing Potent Anti Malarial Activity

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Submitted: 10-12-2022 Accepted: 20-12-2022

ABSTRACT:
Malaria is still a major health problem prevailing in many south asaian countries. Malaria is basically caused by Plasmodium species like P. falciparum, P. ovle , P. vivax, P.malariae. Drugs like artemisnin is formally being used for treatment of malaria are difficult synthesize in laboratory and are very expensive . Chloroquine resistant strains of Plasmodium is a major set back control and treatment of malaria. So there is need to search for an alternative synthetic, cost- effective and potent anti malarial drugs which can be used as therapeutic agents in curing Malaria. Chalcones obtain from plant possess various medicinal value like antiviral,antibacterial, antileishmanial and antimicrobial activites.Lichochalcone obtain from roots of Chinese licorice is a potent anti malarial drug used againt P. falciparum. Thus this paper will try to propose importance chalcone moiety as potent anti malarial nuecleus .

I. INTRODUCTION

The malaria parasite is transmitted by a female Anopheles mosquito inoculating sporozoites into the human host. The sporozoites reach human liver cells, where they transform to next stage called the merozoite. The merozoite reaches the erythrocytes, through the bloodstream, and produce new merozoites. Some of the merozoites released after the brusting of the erythrocytes move to its next stage called gametocytes. Inside the midgut of mosquito sexual reproduction takes place, generating zygotes which develops into oocysts as they grow and transforms into sporozoites which invades the salivary glands of mosquito. A major difference in the life cycle of P. vivax is that it completes its development cycle in the mosquito at lower temperatures and faster than P. falciparum.

There is growing interest in natural products and its pharmacological importance. Chalcones constitute a vital group of natural products. Chemically, they consist of open chain of flavanoids in which the two aromatic rings are joined by a three chain carbonyl system consisting of α .β unsaturated carbon. The presence of active α .β unsaturated keto moiety in chalcone is responsible for their various biological activites. In recent years a variety of chalcones have been observed for their cytotoxic, chemoprevenive anticancer ,insecticidal , and anti viral activities. Chalcones containing hydroxyl, alkoxy groups at different positions in the ring have been found to possess various biological activites like anti-bacterial, antiulcer, antileshmanial , antifungal, antioxidant, vasodilatory, antimalarial tyrosinase inhibitor and aldose reductase inhibitor . Thus it provides a thrust and interest to propose that chalcone can be potent antimalarial agents too.

Mechanism action of antimalarial activity

Nutrients and drugs enter cells by crossing the membrane which is made of phospholipids, cholesterol and other bio-organic molecules arranged in a bilayer. The biological membranes are embedded with proteins that may function as receptors and solute transporters. Thus, biologically active molecules like nutrients and drugs may cross the film either by dissemination through the lipid bilayer or by utilization transporter protein. Antimalarials mainly act on few stages of the parasite's life cycle. One of them is to encroach upon the schizogonic blood sort out obligated for the signs of the contamination, that is, to kill the parasite during the formative cycle. The other is to hinder the progression of gametocytes, in other words, to rid of the parasite in the tissue for example of the species P. vivax and P. ovale, inhibiting the transmission of the parasite .

For example, chloroquine shows antimalarial property with various component of activity and which can be clarify by five diverse system of activity . Intestinal sickness parasites blend a huge assortment of proteins at various stages throughout their life cycle. The organic chemistry included is like that of other eukaryotic cells . In any case, it has as been accounted that high chloroquine focuses diminishes protein amalgamation in P. falciparum trophozoites around half and that ribosomes arranged from also

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treated cells are inadequate in blending proteins in vitro . It isn't known whether this outcome holds at fixations underneath 100 nM outside chloroquine. Surolia and Padmanaban also found that cell free protein combination in trophozoite removalinduces expansion of heme. They suggested that as chloroquine ties heme with high liking and parasite protein amalgamation is animated by heme, at that point chloroquine could decrease protein union in the parasite by restricting heme and causes lysis of
confined P. falciparum trophozoites.

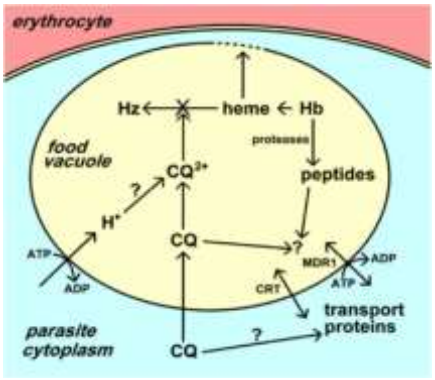
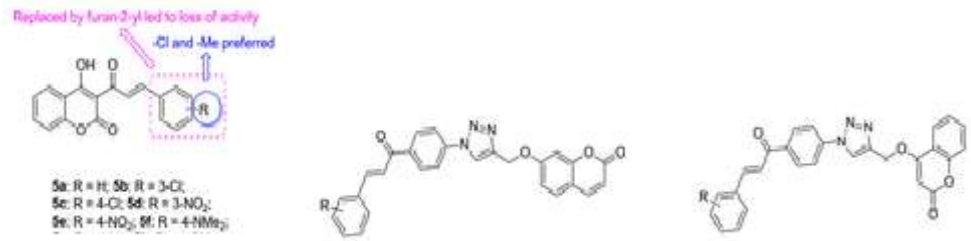


Fig. 4. Chloroquine amasses in the food vacuole of the parasite. This gathering may include particle catching after protonation, explicit vehicle, as well as official to a receptor (model heme). The significant activity of chloroquine is to hinder the arrangement of hemozoin (Hz) from the heme discharged by the processing of hemoglobin (Hb).

CHALCONE–COUMARIN HYBRIDS

Coumarin is an important skeleton in the development of novel drugs and its derivatives are a large family of compounds associated with a broad range of biologically useful properties, including antiplasmodial and antimalarial activities. Thus, chalcone–coumarin hybrids are beneficial scaffolds for the development of novel antimalarial agents.

The chalcone–coumarin hybrids showed weak to moderate activity against CQS 3D7 and chloroquine-resistant strains, and all of them were far less potent than the reference chloroquine . The SAR suggested that replacement of the phenyl by furan-2-yl led to a significant loss of activity. The para-position of the phenyl ring was most suitable to introduce the substituents, and chloro as well as methyl were beneficial for the activity. The para-position tethered chalcone–coumarin were devoid of activity against multidrug-resistant K1 strain, while the majority of meta-position analogs showed certain activity. Further study implied that falcipain-2 may be a plausible target site of the hybrids given their antiplasmodial potency. The most active hybrid was still far less potent than the reference dihydroartemisinine ,so this kind of hybrids still needs to be further modified.



CHALCONE–QUINOLINE HYBRIDS

Quinoline-based antimalarials like chloroquine, amodiaquine, and mefloquine, which could block haemozoin formation, are mainstays of chemotherapy against malaria that have been used in clinics. Therefore, hybridization of chalcone with quinoline has the potential to provide agents for clinical deployment in the control and eradication of malaria.

The chalcone–quinoline hybrids showed considerable activity against P. falciparum strains. The SAR indicated that replacement of quinoline fragment by naphthalene led to loss of activity, while incorporation of substituents (especially halogen atoms and methoxy) into the C-3 and C-4 positions of the chalcone moiety could improve the activity. The mechanistic study showed that these hybrids could inhibit sorbitol-induced hemolysis of P. falciparum.

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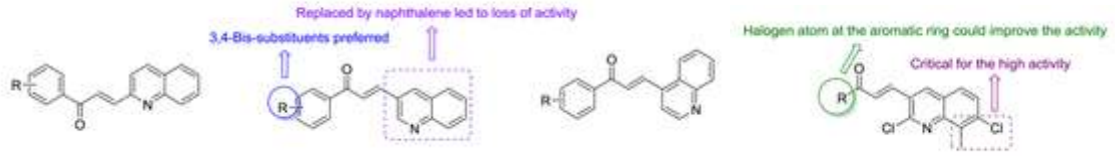
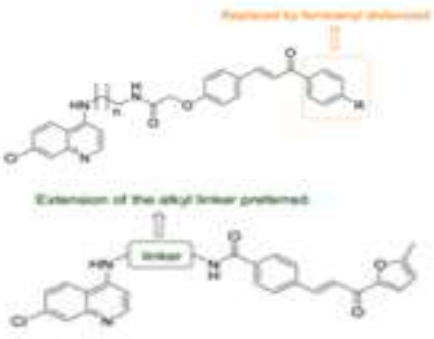


Incorporation of chloro into the C-2 position of quinoline moiety could enhance the activity to some extent and hybrids and showed potential activity against P.falciparum strains. The mode of action of these hybrids seems to be similar to that of chloroquine and involved the inhibition of hemozoin formation. Further study indicated that hybrids with 2,7-dichloro-8-methyl at quinoline moiety exhibited great potency against P. falciparum strains.The mechanistic study showed that these hybrids could block heme polymerization. For substituents at the R position, introduction of halogen atoms into the aromatic ring could boost up anti malarial activity.

The hybrids with carbonyl group next to quinoline skeleton also displayed promising activity against P. falciparum strain, suggesting that the position of the carbonyl group influenced the activity greatly. The docking study revealed that the binding orientations of these hybrids were at active-site amino acid residues of the falcipain-2 enzyme. Thus, these hybrids could act as cysteine protease inhibitors.

The amino tethered chalcone–quinoline hybrids showed weak to moderate activity against P. falciparum strain. The SAR proved that the linker between chalcone and quinoline moiety was crucial for the activity, and the piperazinyl-containing linkers were favorable to the activity. Biochemical studies strongly suggested that inhibition of hemozoin formation is the primary mechanism of action of these analogs.



The 1,2,3-triazole tethered chalcone–quinoline hybrids exhibited potential activity against P. falciparum. The demonstrating position of carbonyl group had a remarkable influence on the activity. The mechanistic study revealed that these hybrids could exert the antiplasmodial activity via inhibition of hemozoin formation. Moreover, this hybrid was nontoxic toward Chinese hamster ovarian cells .These results indicated that this hybrid could serve as a promising lead compound and deserve further investigation for prevention and treatment of malaria.

The amide-containing chalcone–quinoline showed considerable activity against strain of P. falciparum, and the SAR revealed that replacement of phenyl ring by ferrocenyl resulted in loss of activity and showed low cytotoxicity too.

The furan-containing chalcone–quinoline hybrids demonstrated great potency against P. falciparum strains. The SAR indicated that extension of the alkyl linker could boost up the activity, but replacement of alkyl linker by the ether and alkylamino linkers had little impact on the activity. Hybrid was found to be most active against P.falciparum strains, and the activity was not inferior to that of chloroquine . Moreover, this hybrid also showed low cytotoxicity . Thus, this hybrid could act as a promising therapeutic candidate for further investigation.

MISCELLANEOUS CHALCONE HYBRIDS

Artemisinin and its derivatives bind with parasite's heme, resulting in the formation of carbon-based free radicals which consequently

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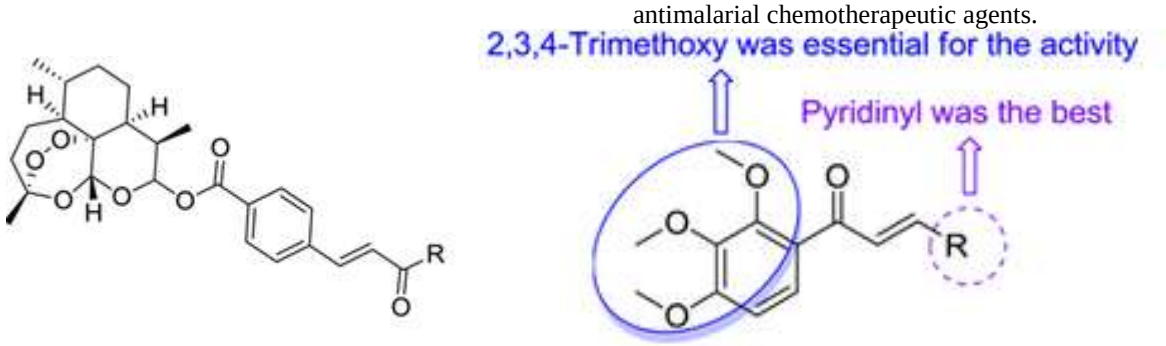
induce the death of the parasite. Artemisinin in combination with chalcone derivatives showed synergistic effect against P. falciparum, and decreased hemozoin formation in parasitized erythrocytes.

The chalcone–artemisinin hybrids showed great potency against P. falciparum strains, and all of them were more potent than chloroquine. Therefore, they can potentially serve as lead compounds for the development of novel antimalarial chemotherapeutic agents.



Pyridine is an important six-membered heterocycle, and its derivatives which could inhibit diverse enzymes like dihydrofolate reductase (DFHR) exhibited promising activity against both drug-sensitive and drug-resistant even multidrug-resistant P. falciparum strains. Chalcones are known to interfere with cell cycle progression, so hybridization of chalcone with pyridine has the potential to provide novel antimalarial candidates with multiple mechanisms of action.

The chalcone–pyridine hybrids demonstrated that pyridinyl at R position was more favorable than phenyl ring and naphthyl group. The 2,3,4-trimethoxy group on the phenyl ring was crucial for the activity, and replacement of it by nitro group or by monomethoxy group led to great loss of activity. The mechanistic study revealed that these hybrids could inhibit P. falciparum and plays an essential role in cell cycle control and differentiation in P. falciparum, Besides the chalcone hybrids mentioned above, chalcone–furan/thiophene, chalcone–indole, chalcone–pyrimidine, and chalcone–sulfamide hybrids also showed certain antiplasmodial activity.

II. CONCLUSION

Malaria remains a global public health concern due to its morbidity and mortality. The antimalarial agents are critical for the control and eradication of malaria, but the increasing emergence of drug-resistant malaria creates an urgent need to develop novel antimalarial agents.

The chalcone moiety represents a fruitful matrix for the development of novel antimalarials, and hybridization of chalcone with other antimalarial pharmacophores has the potential to provide valuable therapeutic intervention in the context of malaria control. Thousands of chalcone hybrids have been screened for their in vitro antiplasmodial and in vivo antimalarial activities in recent decades, and some of them showed promising potency against P. falciparum strains and exhibited great in vitro antiplasmodial and in vivo antimalarial potency. Based on the aforementioned findings, chalcone hybrids are useful templates for the development of novel antimalarial candidates.

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