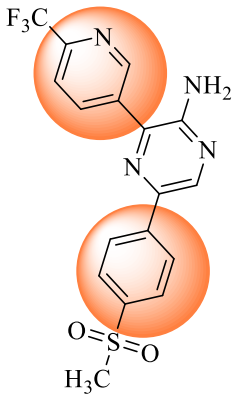
3. AIMS AND OBJECTIVES

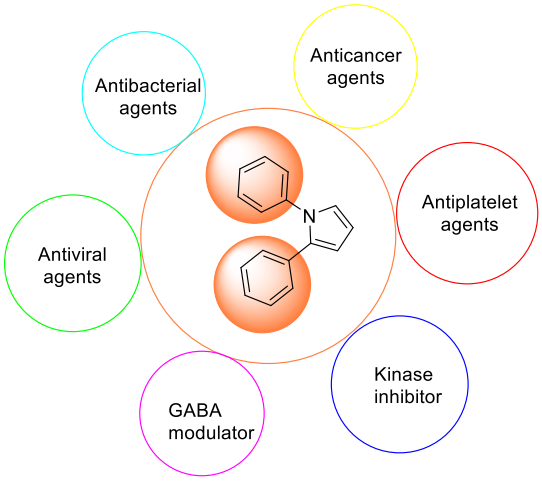
The malaria parasite possesses numerous potential targets as discussed in previous chapters such as haemoglobin digestion and heme polymerization[1], folate pathway[2], parasite transporter[3], nucleic acid metabolism etc. which are being utilized to develop antimalarial agents. Researchers have made significant progress in identifying and utilizing many of these druggable sites. However, advancements in drug discovery, non-target site resistance remains a persistent challenge, often emerging due to mechanisms that bypass the effects of existing treatments rather than direct alterations in the drug's target. To address this issue, it was envisaged to design novel hybrid molecules having two active pharmacophores within a single compound to act on multiple pathways simultaneously, thereby reducing the likelihood of resistance development. The rationale behind this approach is that if resistance affects one pharmacophore, the other remains active, ensuring sustained therapeutic efficacy. This dual-action strategy provides a promising avenue for overcoming resistance and enhancing the effectiveness of antimalarial treatments[4].

Diaryl derivatives have been identified as potent inhibitors of *Plasmodium falciparum* dihydrofolate reductase (DHFR), a critical enzyme in the parasite's folate biosynthesis pathway. Inhibition of DHFR disrupts DNA synthesis and cell proliferation, ultimately impairing parasite survival[5]. Compounds based on the diaryl scaffold **(I)** have exhibited impressive inhibitory activity, with IC_{50} values as low as 8.4 nM against both chloroquine-sensitive strain and resistant strain of *P. falciparum*, underscoring their potential as promising lead structures[5].



(IC_{50} 8.4 nM)

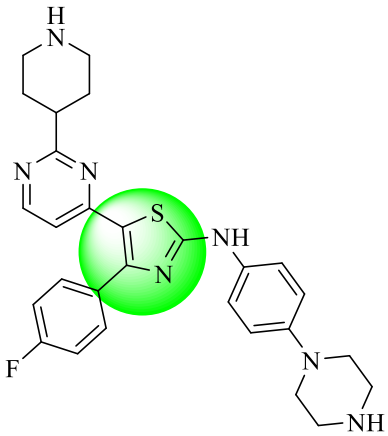
(I)



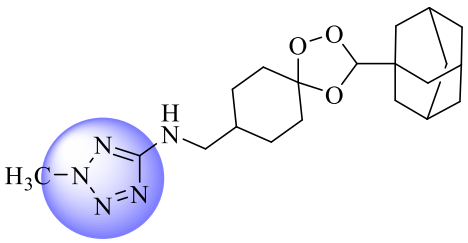
(II)

Vicinal diaryl **(II)** containing compounds have been explored having various therapeutic activities like antiviral agents, kinase inhibitor, antiplatelet agents, anticancer agents etc.[6,7]. While doing the literature survey it was observed that till date vicinal diaryl containing compounds have not been reported as antimalarial agents. Thus, taking inspiration from compound **(I),** the incorporation of vicinal diaryl motifs was considered a logical design strategy for development of novel antimalarial agents.

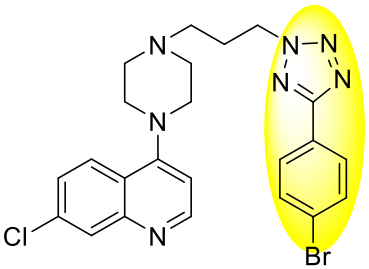
Thiazole-containing compounds have demonstrated notable antimalarial activity, in addition to exhibiting a broad spectrum of pharmacological effects across various therapeutic areas[8]. Compound **(III),** having a thiazole moiety, is known to inhibit *Plasmodium falciparum* DHFR (IC_{50} value 0.5 nM). Furthermore, it has also been implicated in disrupting heme detoxification, a crucial survival mechanism for the parasite[9], highlighting its strong inhibitory potential and supporting the continued exploration of thiazole scaffolds in antimalarial drug design[10].



IC_{50} 0.5nM
(III)



IC_{50} 1.9 nM
(IV)



IC_{50} < 10mM
(V)

Tetrazole containing compounds (**IV**) has emerged as a versatile scaffold in drug design due to its multifunctional properties. In the context of antimalarial therapy,

tetrazole not only contributes to the blockade of heme detoxification[11] akin to other azole-based structures but also acts as a bioisostere of carboxylic acids[12], enhancing pharmacokinetic attributes such as metabolic stability and membrane permeability. Notably, a tetrazole-containing compound (**IV**) has demonstrated potent antimalarial activity, with an impressive *in vitro* IC_{50} value of 1.9 nM[13]. From our own laboratory a quinoline–piperazinyl–aryltetrazole hybrid (**V**) was reported having antimalarial activity with an IC_{50} value of 2.25 µM, further supporting the incorporation of tetrazole into novel antimalarial framework[14].

Thus, by considering the importance of vicinal diaryl, thiazole and tetrazole moieties it was thought logical to design novel hybrid molecules incorporating three distinct pharmacophores: vicinal diaryl **(I),** thiazole **(III),** and tetrazole moieties **(IV),** in a single compound (**A, Fig 3.1).**

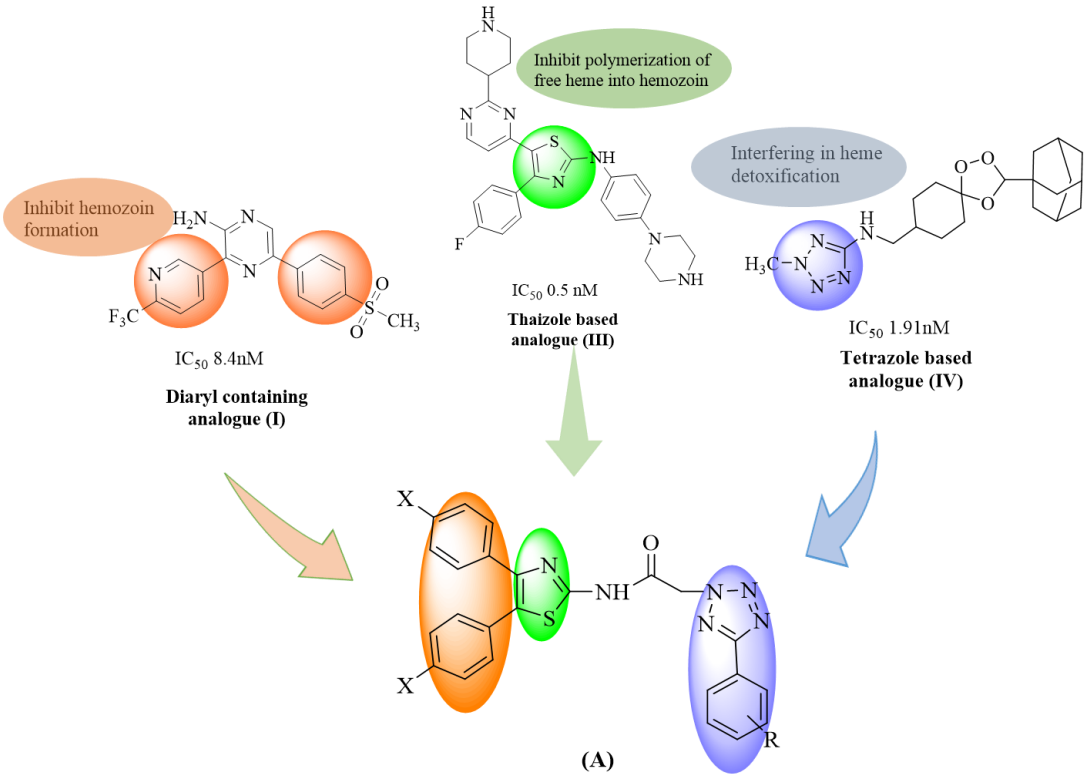
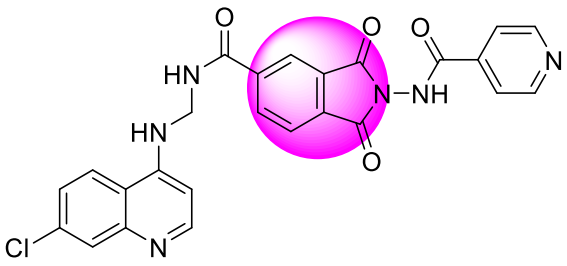


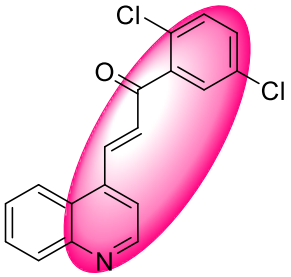
Fig. 3.1 Designing strategy adopted for vicinal-diaryl based novel antimalarial compounds **(A)**

Phthalimide derivatives **(VI)** have been previously reported[15] to inhibit DHFR, mirroring the mechanism of antifolate drugs. The imide moiety interacts with the catalytic residues in the enzyme's active site, blocking folate metabolism and DNA

synthesis, which are critical for parasite survival[16]. Chemical modifications to the phthalimide ring system have led to enhanced antiparasitic activity. Notably, the phthalimide-based test compound exhibited promising IC_{50} 11nM, suggesting its potential as an effective DHFR inhibitor[15]. By optimizing the ring system and functional groups, we aim to further improve the bioavailability and selectivity of these compounds against *Plasmodium*.



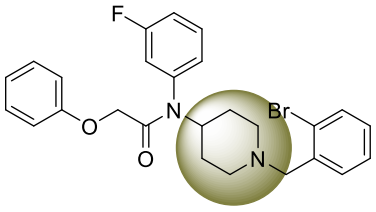
IC_{50} 11 nM
(VI)



IC_{50} 200 nM
(VII)

Chalcones have been reported potent antimalarial agents**,** characterized by their α,β-unsaturated carbonyl system, which allows them to form covalent bonds with nucleophilic residues in enzymes, disrupting critical enzymatic processes in the parasite[17]. This reactivity has been widely exploited in the design of antimalarial compounds. Compound **(VII)** synthesized using chalcone analog demonstrated an IC_{50} value of 200 nM, highlighting its potent antimalarial activity[18]. This scaffold offers the potential for further optimization through structural modifications to enhance antimalarial effects and explore additional mechanisms of action.

Piperidine derivatives **(VIII)** have been reported to target the heme detoxification process in *P. falciparum*. The piperidine moiety is known to destabilize the formation of inert hemozoin, leading to the accumulation of toxic heme, which results in parasite death[19]. The piperidine-based analog **(VIII)** in literature has exhibited



IC_{50} 4.19 nM
(VIII)

significant antimalarial activity with an IC_{50} value of 4.19nM, confirming its role in disrupting heme detoxification[20]. By fine-tuning the piperidine substitution patterns, the compound's potency and selectivity against the parasite can be improved. Thus, in addition to compound **A** we also thought it logical to exploit the structural diversity and synergistic potential of these pharmacophores: phthalimide (**VI**), chalcone (**VII**) and piperidine (**VIII**) and to incorporate it to design novel antimalarial compounds of type **B** and **C** **(Fig. 3.2).**

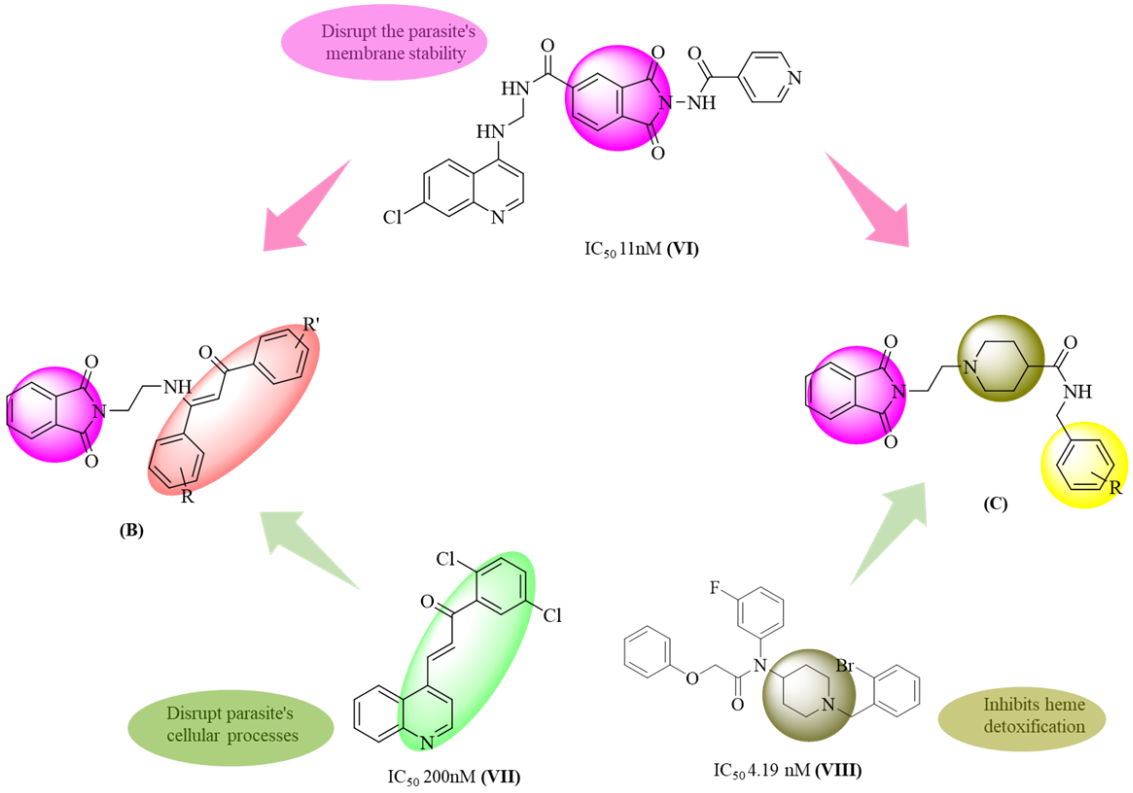
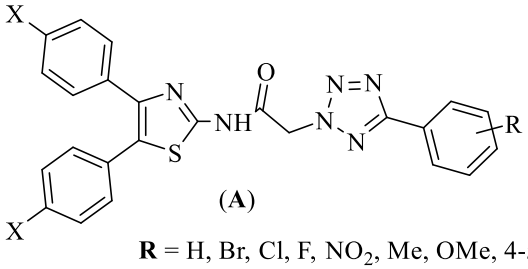


Fig. 3.2 Designing strategies adopted for phthalimide based novel antimalarial agents **(B** and **C)**

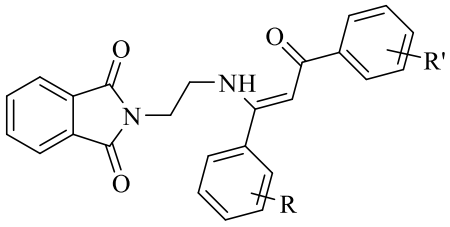
Thus, the main aims and objectives of the present research work is:

1. To design and synthesize novel hybrid antimalarial compounds of type **(A-C)**
2. To carry out spectral characterization of the designed compounds.
3. To evaluate antimalarial potential of the synthesized compounds along with computational studies.



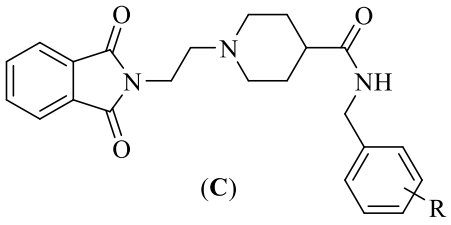
(**A**)

R = H, Br, Cl, F, NO_2, Me, OMe, 4-*iP*r, 3,4-Di-OMe
X = H, Cl, OMe



(**B**)

R = H, Br, Cl, F, NO_2, Me, OMe,
R'= H, Br, Cl, Me, OMe,



(**C**)

R = H, Br, Cl, F, NO_2, Me, OMe, 4-DiCF_3,

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