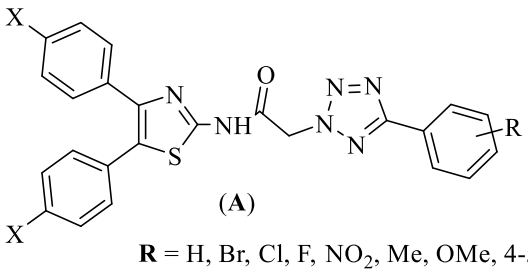
6. CONCLUSION

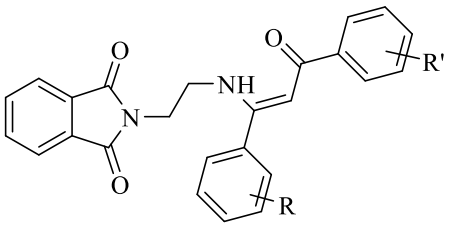
Malaria remains a significant global health challenge, primarily due to *Plasmodium falciparum*, which is responsible for the most severe forms of the disease. The emergence of resistance to current therapies such as chloroquine and artemisinin-based treatments underscores the urgent need for novel antimalarial agents with enhanced efficacy and better pharmacological profiles.

In the present reseasrch work, a series of vicinal diaryl based terazole derivatives (**A**) and phthalimide based derivatives (**B, C**) were strategically designed and synthesized to explore their potential as antimalarial agents. The synthesized compounds (**A-C**) were characterized using spectroscopic techniques, including IR, NMR and mass spectrometry, confirming their structur and purity.



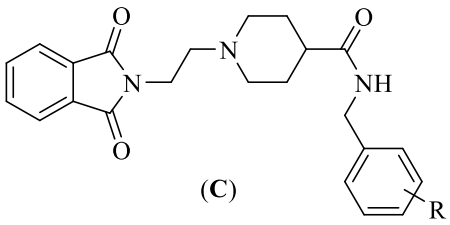
(**A**)

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,

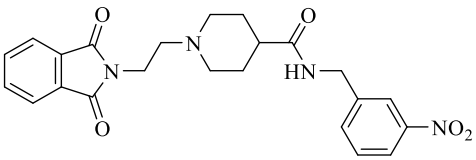


(**C**)

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

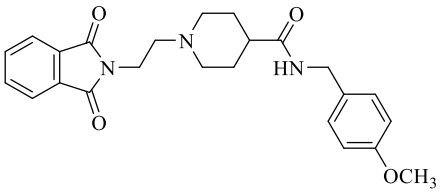
The *in vitro* biological evaluation of the synthesized compounds (**186–224, 263–275**, and **288–297)** against the *Plasmodium falciparum* 3D7 strain revealed a concentration-dependent antimalarial activity profile. Most compounds exhibited their highest percent inhibition at 10 µM, with a gradual decrease at lower concentrations (500 nM and 50 nM), reflecting a typical dose-response behavior. Notably, compounds (**189, 190, 198, 209, 273, 280** and **294)**, demonstrated measurable inhibition even at the lowest tested concentration of 50 nM, suggesting their potential as highly potent antimalarial candidates. Among the reported series, compounds (**289** and **293**) exhibited most potent activity across all tested concentrations, highlighting their

promise for further optimization and development.



(% Inhibition: 62.5)

(289)



(% Inhibition: 76.62)

(293)

To gain insights into the potential mechanism of action and target engagement, computational docking studies were conducted against key *P. falciparum* enzyme *Pf*DHFR,-TS. The molecular docking results revealed that the most potent compounds formed stable complexes with the active site amino acid residues asparagine and tryptophan, involved in strong hydrogen bonding, π-π stacking, and hydrophobic interactions. ADME predictions further supported the drug-likeness and pharmacokinetic favorability of the lead compounds. Additionally, toxicity prediction using the DEREK Nexus platform suggested a non-toxic profile for these compounds, further reinforcing their potential as safe and effective antimalarial agents..

Future perspectives: The findings from this study highlight the potential of vicinal diaryl based tetrazole derivatives and phthalimide based derivatives as promising candidates for antimalarial drug development. However, further research is required to refine these lead compounds by assessing it in animal models to evaluate their efficacy, toxicity, and metabolic stability. These compounds can be further processed to carry out pharmacokinetic and ADMET profiling ensuring drug-likeness, solubility, metabolic stability, and non-toxicity to facilitate further preclinical development.