Abstract

Malaria continues to pose a significant global health burden, with *Plasmodium falciparum* being the primary cause of the most severe and life-threatening forms of the disease. The persistent emergence of drug resistance to conventional therapies, particularly chloroquine and artemisinin-based treatments, emphasizes the urgent need for novel antimalarial agents with improved pharmacological profiles. In this research, a series of structurally diverse vicinal diaryl-based tetrazole derivatives (A) and phthalimide-based derivatives (B, C) were rationally designed, synthesized, and characterized using spectroscopic techniques such as IR, NMR, and mass spectrometry, which confirmed their structural integrity and purity.

The in vitro biological evaluation of the synthesized derivatives (compounds 186–224, 263–275, and 288–297) against the *P. falciparum* 3D7 strain demonstrated concentration-dependent inhibitory activity. Most compounds displayed their highest inhibition at 10 μM, with reduced activity at lower concentrations (500 nM and 50 nM), exhibiting a typical dose–response relationship. Significantly, compounds 189, 190, 198, 209, 273, 280, and 294 retained inhibitory activity even at 50 nM, indicating high potency at nanomolar levels. Within the reported series, compounds 289 and 293 emerged as the most promising leads, showing consistent and superior inhibition across all tested concentrations, with percent inhibition values of 62.5% and 76.62%, respectively.

Molecular docking studies provided mechanistic insights into their mode of action, revealing stable binding of the most potent compounds to the active site of the key *P. falciparum* enzyme dihydrofolate reductase-thymidylate synthase (PfDHFR-TS). These interactions involved hydrogen bonding, π–π stacking, and hydrophobic contacts with crucial amino acid residues such as asparagine and tryptophan. ADME predictions supported favorable pharmacokinetic properties and drug-likeness, while toxicity profiling via the DEREK Nexus platform indicated a non-toxic profile for the lead compounds.

Collectively, these findings highlight the potential of vicinal diaryl tetrazole and phthalimide derivatives as promising scaffolds for antimalarial drug discovery. Compounds 289 and 293, in particular, stand out as potent and safe leads warranting further optimization. Future investigations should focus on in vivo validation in animal models to establish efficacy, metabolic stability, pharmacokinetics, and safety profiles, thereby facilitating their advancement into the preclinical pipeline.