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Design and syntheses of 4-aminoquinoline-thiazolidinone hybrids as anti-protozoal agents

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Introduction: Molecular hybridization is an effective approach employed to synthesize molecules that possess the ability to function as dual inhibitors, thereby addressing the issue of growing resistance. Resistance by the malaria parasite is one such example. Therefore, the study aims to develop hybrid compounds consisting of 4-aminoquinoline and 4-thiazolidinone, utilizing molecular docking for sorting, followed by synthesis and evaluation of their anti-malarial potential.

Methods: The molecules were selected on the basis of affinity from the computational study. To strengthen the *in silico* docking, a 200ns molecular dynamics simulation study was also performed. The title compounds, 7-18, were synthesized in a three-step reaction, involving non-polar solvent addition reaction resulting in heterocyclization. The synthesis was followed by characterization of all the synthesized compounds, and they were further subjected to biological screening through *in-vitro*, and the selected actives to *in-vivo* evaluation. An acute toxicity study was also conducted.

Results: The compounds exhibited promising action, with five compounds, 8, 9, 14, 15, and 18, demonstrating efficacy comparable to the reference drug in the *Pf*-DHFR enzyme inhibition assay. Four of the active compounds selected for the *Plasmodium berghei* murine model displayed excellent activity, with percentage parasitaemia inhibition to the extent of 84%, and mean survival time up to 27 days. The MD simulation study showed the stability of the ligand-protein complex up to 200 ns. The *in silico* ADMET prediction, along with acute toxicity testing of the most active compound, showed no major toxicity.

Discussion: The study concludes the hybrid compounds to be promising antimalarial agents, and the scaffold may be a good lead for the development of next-generation antimalarials.

KEYWORDS
4-aminoquinoline, 4-thiazolidinone, *in-vitro*, *in-vivo*, molecular docking, molecular hybridization

1 Introduction

The life cycle of the parasite in the human host begins when the sporozoites are introduced into the bloodstream during a blood meal by infected female Anopheles mosquitoes (Bousema et al., 2014; Rosado-Quiñones et al., 2024). These are subsequently transported to the liver, reach the pre-erythrocytic schizont phase, mature to disseminate merozoites, followed by invasion and proliferation (Farrow et al., 2011). However, due to restricted capacity for *de novo* amino acid synthesis, the plasmodium depends on the hemoglobin of the host's erythrocytes (Renar et al., 2016). In this process, the