Antiplasmodial Activity Evaluation of Novel Indole Peptidomimetics as Lead Candidates for Malaria

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Introduction: Malaria, caused by protozoan parasites of the *Plasmodium* genus, remains a major global health challenge, with ~282 million cases and 610,000 deaths estimated in 2024.[1] The increasing resistance to antimalarial drugs and the difficulty in controlling *Anopheles* spp. vectors highlight the urgent need for new antimalarial agents. In this context, the indole scaffold is a privileged structure in medicinal chemistry, as many indole derivatives display diverse biological activities.[2, 3] Recently, we reported new indole-derived compounds with low micromolar antiplasmodial activity, no cross-resistance against drug-resistant *P. falciparum* strains, and a slow-acting profile with additive effects when combined with artesunate. Based on these findings, new derivatives were designed, synthesized and had their antiplasmodial activity evaluated

Objective: To further investigate the antimalarial potential of the indole peptidomimetics series as new leads for drug discovery.

Methods: Antiplasmodial activity was evaluated against chloroquine-sensitive *P. falciparum* 3D7 and chloroquine-resistant *P. falciparum* Dd2 strains using the SYBR Green I assay. Cytotoxicity in HepG2 cells was assessed by the resazurin assay to determine the selectivity index (SI).

Results: All compounds displayed relevant antiplasmodial activity, with IC_{50} values ≤ 10 μM. The derivatives maintained activity against the chloroquine-resistant Dd2 strain and showed low cytotoxicity toward HepG2 cells, resulting in favorable selectivity indices (SI > 25). These results indicate that structural modifications can retain potency against sensitive and resistant parasite strains and showing a moderate safety profile.

Conclusion: These findings suggest that indole peptidomimetics are promising starting point for the discovery of new antimalarial drug candidates.

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