CHARACTERIZATION OF THE ANTIPLASMODIAL ACTIVITY OF NOVEL INDOLE-BASED PEPTIDOMIMETIC COMPOUNDS

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Introduction: Malaria is an acute, febrile, and potentially severe infectious disease caused by protozoan parasites of the genus *Plasmodium*, representing a significant global health challenge. The continuous selection and spread of multi-resistant strains pose a serious threat to malaria treatment and control, underscoring the urgent need for the development of new drugs. In this context, indole-based peptidomimetics emerge as promising candidates, offering enhanced stability, bioavailability, and target specificity. These compounds can target both the hepatic and erythrocytic stages of the parasite, which is crucial for overcoming resistance and achieving broad-spectrum antimalarial activity. **Objective:** This study aimed to evaluate the antiplasmodial profile of novel indole-based peptidomimetics as potential therapeutic agents against malaria. **Methods:** The antiplasmodial activity of these compounds was investigated against the chloroquine-sensitive strain of *P. falciparum* (3D7), alongside their cytotoxicity and selectivity in HepG2 cells. For the most potent compounds in the series, the speed of action was measured, followed by interaction studies with artesunate and evaluation of activity against a panel of drug-resistant *Plasmodium* strains. **Results:** Compounds LSPN954 and LSPN959 exhibited antiplasmodial activity in the low micromolar range (IC_{50} values of 3 µM and 4 µM, respectively) against the 3D7 strain. These compounds demonstrated no cytotoxicity towards HepG2 cells, with selectivity indices greater than 33. Both compounds were identified as slow-acting inhibitors, making them promising candidates for combination therapy with fast-acting antimalarials. The inhibitory activity assessment revealed no cross-resistance in multidrug-resistant strains, suggesting a mechanism of action distinct from conventional antimalarials. **Conclusion:** The absence of cross-resistance with standard antimalarials, along with the potential for use in combination therapies, supports the investigation of indole-based peptidomimetics as promising candidates for new antimalarial drugs.

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