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SYNTHESIS, PHARMACOLOGICAL AND SOLUBILITY EVALUATION OF ANTIPLASMODIAL PYRIDO [1, 2A] BENZIMIDAZOLES WITH CYCLIC AND FUNCTIONALIZED AMINE SIDE CHAIN SUBSTITUENTS

Malaria continues to be a leading cause of morbidity and mortality, especially in sub-Saharan Africa. The burden of malaria is worsened by antimicrobial resistance (AMR), a phenomenon that could render currently useful antimalarial medicines obsolete. Chloroquine, once the gold standard in malaria treatment, now offers minimal to zero clinical benefit due to widespread resistance. Use of Sulfadoxine/Pyrimethamine and Atovaquone is currently limited to a few geographical zones as a consequence of resistance by P. falciparum to these agents. A serious concern is emergence of resistance to ACTs, the WHO-recommended first-line therapy for P. falciparum malaria. Consequently, research targeting antimalarial drug discovery and development is a vital intervention to reverse the effects of AMR in malaria therapy. This study focused on synthesis of pyrido [1, 2a] benzimidazoles analogs and their evaluation for in vitro antimalarial activity as well as physicochemical. These were characterized using spectroscopic and chromatographic methods. They were then assessed for in vitro antiplasmodial activity against P. falciparum isolates and physicochemical properties determined. Aminopiperidine-based compounds were found to be the most potent, while those bearing pyrrolidine and piperazine substituents displayed only moderate activity. Azetidine and cyclohexylamine substitution produced compounds with moderate to poor in vitro activity and solubility. Cyclic amine groups were detrimental to both activity and solubility, and a number of active compounds also displayed significant cytotoxicity. Cyloalkylamine-functionalized benzimidazoles analogs possess potent antimalarial activity and are promising leads for development of preclinical candidates for treatment of malaria. Further work is required to investigate antimalarial activity of benzimidazoles and optimize these compounds to achieve an acceptable balance between activity and physicochemical properties.

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