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Study of the Structure-Activity Relationship of Pyridylmorpholine Derivatives Against Malaria

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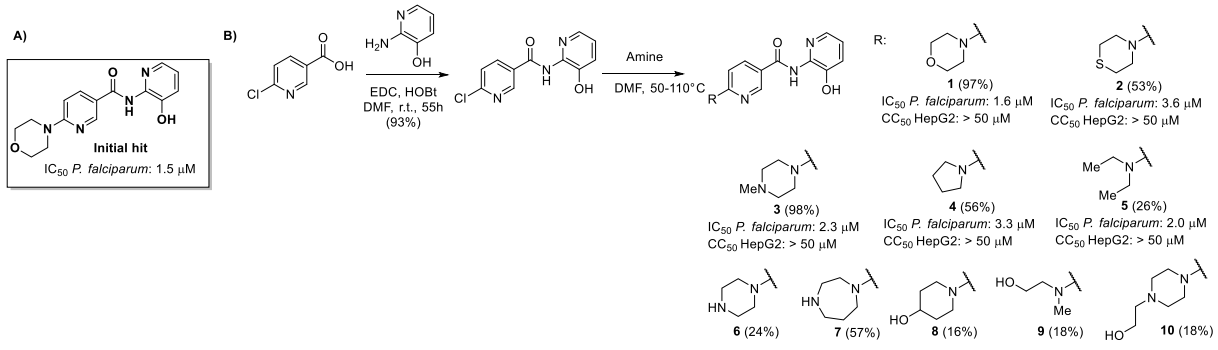
Highlights

The synthetic route used in this study proved to be efficient for obtaining pyridylmorpholine derivatives. Biological results of IC_{50} and CC_{50} demonstrated the potency and high selectivity of this chemical class against the parasite *P. falciparum.*

Abstract

Malaria is an infectious disease transmitted through the bite of infected Anopheles mosquitoes, caused by parasites of the genus *Plasmodium*, with the species *P. falciparum* and *P. vivax* being responsible for the most severe cases in humans. In 2023, approximately 263 million cases of the disease were reported, leading to an estimated 547,000 deaths worldwide[1]. The disease primarily affects poorer regions, where access to medicines and treatments is limited. However, the emergence of resistance to artemisinin, a drug currently used in the treatment of malaria, represents a significant threat to the fight against the disease[2]. Therefore, the development of new drugs that are more effective for the treatment of malaria is essential. This work aims to discover new drugs based on the design, synthesis, and structure-activity relationship (SAR) analysis of derivatives from the pyridylmorpholine class. For this study, modifications were made to the initial hit, a pyridylmorpholine derivative, previously selected for its potent antimalarial activity (Scheme 1A), based on the work developed by Yevgeniya, in which approximately 500,000 compounds were tested against the parasite *P. falciparum* using high-throughput screening[3]. The initial hit and a series of 9 novel analogs with structural modifications in the morpholine fragment were synthesized, through amidation and nucleophilic aromatic substitution reactions (Scheme 1B). The compounds were purified using techniques such as filtration, liquid-liquid extractions, and column chromatography. Subsequently, they were characterized by ^{1}H and ^{13}C NMR analyses and evaluated in *in vitro* assays for the determination of IC_{50} against *P. falciparum* and cytotoxicity (CC_{50}) against HepG2 cells. Notably, compounds **6–10** are currently undergoing *in vitro* potency assays against *P. falciparum*, and the results will be presented in this work's poster. Nevertheless, so far, the results of the *in vitro* assays obtained have shown the potential of this chemical class, with IC_{50} values between 1.6 and 3.6 µM and CC_{50} greater than 50 µM, highlighting the importance of the study of this class of pyridylmorpholines in the fight against malaria.

Scheme 1. A) Proposed initial hit of pyridylmorpholine. B) Synthetic route.



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