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Synthesis of di(2-pyridyl)piperazine derivatives as potential antimalarial agents

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Palavras Chave: *Malaria, Plasmodium falciparum, di(2-pyridyl)piperazines, antimalarial agents, Structure-Activity Relationship.*

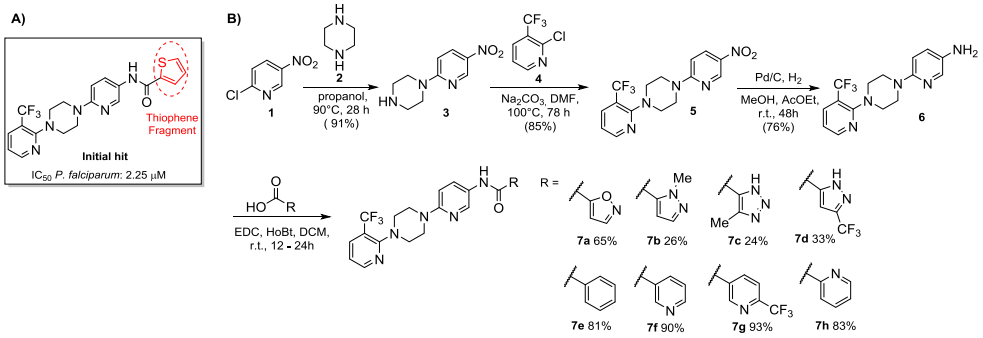
Highlights

A di(2-pyridyl)piperazine derivative was identified as a hit for antimalarial drug discovery, showcasing feasible synthesis and robust methods for diverse derivatives.

Resumo/Abstract

Malaria, caused by protozoan parasites of the genus *Plasmodium*, remains a major global health issue, with *Plasmodium falciparum* being the most lethal species. Despite significant progress, the emergence of resistance to current treatments, such as artemisinin-based combination therapies (ACTs), underscores the need for new antimalarial agents. Di(2-pyridyl)piperazines[1] have emerged as a promising chemical scaffold, with potential for structural modifications to enhance their activity. This work focuses on the synthesis of derivatives with modifications to the thiophene fragment, aiming to explore their feasibility as antimalarial candidates (scheme 1).

Scheme 1. A) Proposed initial hit from di(2-pyridyl)piperazines. B) Synthetic route developed.



The synthesis of di(2-pyridyl)piperazines bearing modifications on the thiophene fragment, exemplified by compound 7a-h, was achieved through a linear four-step synthetic route. This sequence involved two consecutive nucleophilic aromatic substitution reactions, followed by nitro group reduction and amidation (Scheme 1B). The thiophene fragment of the initial hit was replaced with 5- and 6-membered aromatic bioisosteres with the primary aim of conducting a SAR study. All compounds were characterized by ^{1}H and ^{13}C NMR and are being tested *in vitro* against *P. falciparum*. The biological results will be presented in the poster section. The synthesis of di(2-pyridyl)piperazines with modifications to the thiophene fragment demonstrates the potential of these scaffolds for further exploration as antimalarial agents. This work provides a detailed account of the synthetic strategies employed, serving as a foundation for future biological evaluations and SAR studies.

References

[1]ANTONOVA-KOCH, Y.; *et al*. **Open-source discovery of chemical leads for next-generation chemoprotective antimalarials**. *Science*, v. 362, eaat9446, 2018. DOI: 10.1126/science.aat9446.

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