Anais da 48ª Reunião Anual da SBQ

48ª Reunião Anual da Sociedade Brasileira de Química

Campinas-SP
2025

Revisão textual e gramatical: Resposanbilidade dos respectivos autores.

Dados Internacionais de Catalogação na Publicação (CIP)
(Câmara Brasileira do Livro, SP, Brasil)

Reunião Anual da SBQ (48. : 2025 : Campinas, SP)
Anais da 48ª Reunião Anual da SBQ [livro eletrônico] / Sociedade Brasileira de Química. -- 1. ed. -- Campinas, SP : Aptor Software, 2025.
PDF

Vários autores.
Vários colaboradores.
Bibliografia.
ISBN 978-85-63273-70-3

1. Química I. Sociedade Brasileira de Química. II. Título.

25-282696 CDD-540

Índices para catálogo sistemático:

1. Química 540

Eliete Marques da Silva - Bibliotecária - CRB-8/9380

Área: MED

Hit-to-Lead optimization of pyridylpiperazine derivatives: promising antimalarial candidates with notable ADME profiles and metabolic stability

Douglas D. S. Oliveira (PG),[1] Arne Krüger,[2] Rafael C. Chelucci (PG),[3] Leonardo L. G. Ferreira (PQ),[3] Adriano D. Andricopulo (PQ),[3] Gerhard Wunderlich (PQ),[2] Neide Maria Silva (PQ),[4] Celso de O. Rezende Júnior (PQ)[1*]

douglas.davison@ufu.br; celso@ufu.br

[1]Instituto de Química, UFU; [2]Instituto de Ciências Biomédicas, USP; [3]Instituto de Física, USP São Carlos; [4]Instituto de Ciências Biomédicas, UFU.

Keywords: ADME properties, *In vivo* assay, *Plasmodium falciparum*, Malaria

Highlights

In vitro ADME: two derivatives showed >200 min half-life and clearance <14 µL/min/mg in mouse liver microsomes. *In vivo* assay: low mortality in mice infected with malaria parasite and treated with **2**.

Abstract

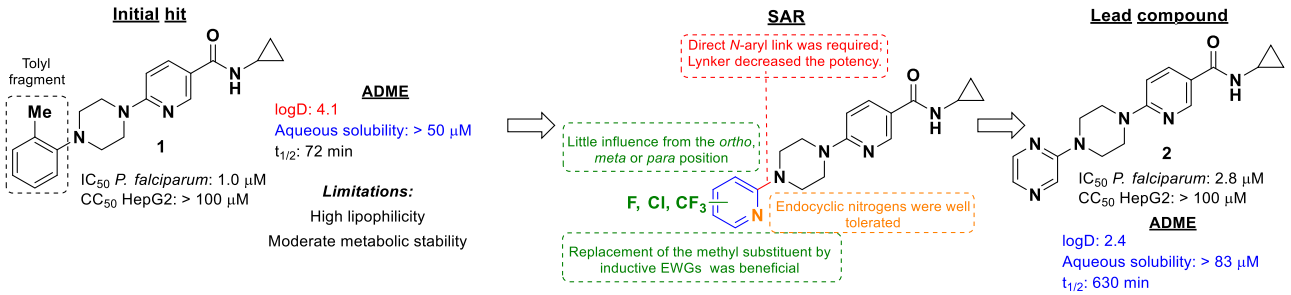

Figure 1. Graphical Abstract

This study represents a hit-to-lead optimization effort, where we explored the structure-activity relationship of pyridylpiperazine derivatives by synthesizing 22 compounds based on the initial hit (**1**), with modifications in the tolyl fragment (Figure 1). We identified ten pyridylpiperazine derivatives with IC_{50} values below 5 µM against *Plasmodium falciparum* chloroquine-resistant (Dd2) and sensitive (3D7) strains, along with four early-optimized analogs. Most of the compounds exhibited low level of cytotoxicity against HepG2 cell with CC_{50} >100. The *in vitro* ADME profile of these compounds revealed robust permeability (PAMPA values >3.28 x 10^{-6} cm/s), indicating strong passive diffusion potential essential for oral absorption. Most compounds demonstrated excellent kinetic solubility (>42 µM) at pH 2.0 and 7.4, except for two derivatives at pH 7.4 (26.02 µM and 8.32 µM). The eLogD values at pH 7.4 were generally favorable, indicating an appropriate lipophilic profile for most compounds, with emphasis on two derivatives with values of 2.3 and 2.5, which are significantly improved compared to initial hit with an eLogD of 4.1. The metabolic stability of the compounds was assessed in mouse and human liver microsomes, yielding notable results. In human liver microsomes, four derivatives exhibited half-life greater than 100 minutes and clearance between 25 and 27 µL/min/mg, a significant improvement compared to the initial hit. These results indicate low hepatic metabolic rates and, consequently, the potential for prolonged duration of action *in vivo*. The results in mouse liver microsomes were even more impressive. One of the derivatives demonstrated a half-life exceeding 200 minutes and a clearance of 13.6 µL/min/mg, while other exhibited a half-life greater than 600 minutes and a clearance below 12 µL/min/mg, making this derivative a highly promising candidate for *in vivo* evaluation. These compounds demonstrated robust ADME profiles, excellent metabolic stability, promising antimalarial activity, and low cytotoxicity. Based on these attributes, pyrazinylpiperazine derivatives (**2**) were selected for *in vivo* evaluation. Preliminary results revealed low mortality rates in mice infected with parasite and treated with **2**, compared to the untreated infected control group. These ongoing studies will provide additional critical data to support the potential of these compounds as promising candidates for the development of new antimalarial treatments.

Acknowledgments

FAPEMIG, CNPq, CAPES, LaSFar, LQMC, PPGQUI-UFU, IQUFU, ICBIM-UFU