SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Synthesis and optimization of MMV1788223 as new anti-Malarial agent

Thaís H. M. Fernandes[1], Anees Ahmad[1], Malkeet Kumar[1], Mariana Ferrer-Casal[1], Anna C.C. Aguiar[2], Sarah E. C. Maluf[2], Guilherme E. de Souza[2], Rafael V. C. Guido[2], Thomas W. von Geldern[3], Barry Jones[3], Dominique Soldati-Favre[4], Delphine Baud[3], Paul Willis[3], Elodie Chenu[3], James Duffy[3] Luiz Carlos Dias[1]

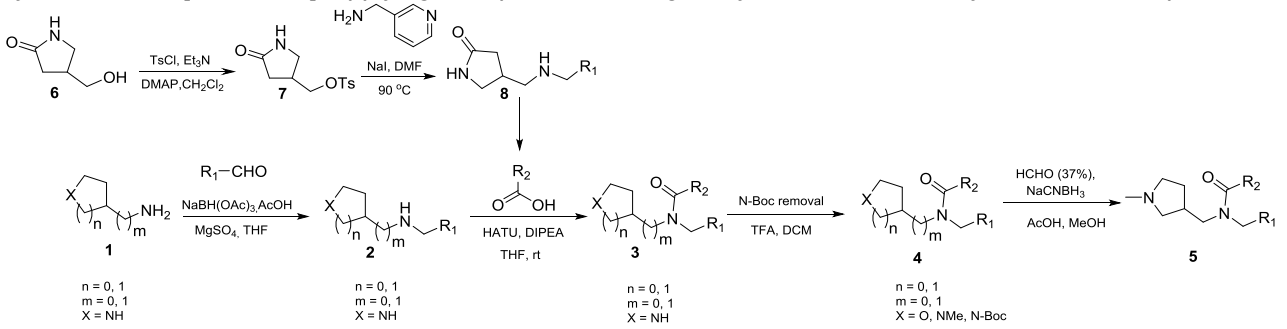
1) Universidade Estadual de Campinas, São Paulo, Brazil.
2) Universidade de São Paulo, São Paulo, Brazil.
3) Medicines for Malaria Venture, Geneva, Switzerland.
4) Université de Genève, Geneva, Switzerland

****e-mail: thaishmf@unicamp.br***

Keywords: *Medicinal Chemistry, Malaria, Drug Discovery.*

ABSTRACT

Medicines for Malaria Venture (MMV) has been committed to reduce the burden of malaria in endemic countries since 1999, by promoting and supporting drug discovery projects focused on the discovery of clinical candidates for malaria treatment and prophylaxis[1]. In line with this goal, UNICAMP team, USP team, and MMV work in collaboration to discover novel clinical candidates to treat Malaria. Malaria is a disease with prevalence in low-income countries, disproportionately affecting children and pregnant women[2]. The ideal candidate for treatment must have low predicted dose, long duration and low resistance risk, combined with acceptable DMPK properties. An efficient and low-cost synthesis is desirable, to guarantee an accessible treatment for every patient[3]. **MMV1788223** was identified in an MMV screen as a Hit Compound, with interesting activity (Pf IC_{50} = 1.39 µM) and a good ADME profile, as an attractive candidate to be optimized for potency and to minimize hERG risk. To prepare the **MMV1788223** and a series of derivatives, we developed an 8-step synthetic route [Scheme 1], applying 3-steps in a convergent synthesis to efficiently obtain the compounds.



Scheme 1. Synthetic approach to obtain compound **MMV1788223** and its derivatives.

30 compounds were obtained to elucidate SAR in this series. The most promising compound of the series showed low hERG risk and an improved potency to 0.22 µM. Despite the promising activity of the series, screening of representative analogs against the Swiss Tropical and Public Health Institute (STPH) resistant panel, highlighted the presence of cross resistance (XR) against *Pf*k1 and *Pf*Dd2 strains**.** Unfortunately, XR is an eliminatory parameter for further investigation of the series by MMV. The work done on this series reinforces the importance of screening confirmed active compounds against resistant strains of *P. falciparum* at an early stage of the drug discovery process.

ACKNOWLEDGEMENTS

The authors thank MMV for financial support of this research. Financial support from FAPESP (The State of São Paulo Research Foundation, project #2015/50655-9 and scholarship #2023/12973-5 are gratefully acknowledged. Thanks UNICAMP and USP for support and infrastructure and TCGLS for DMPK studies.

REFERENCES

1 MMV Product development partnership model https://acesse.dev/yRHZ3 (Accessed 07-08-24).
2 World malaria report 2023. Geneva: World Health Organization; 2023.
3 O. Pelkonen, A. Baumann, A. Reichel. *Pharmacokinetic Challenges in Drug Discovery.* 1st ed., 2002.