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

Synthesis of new analogs of an anti-malarial agent in a hit-to-lead phase

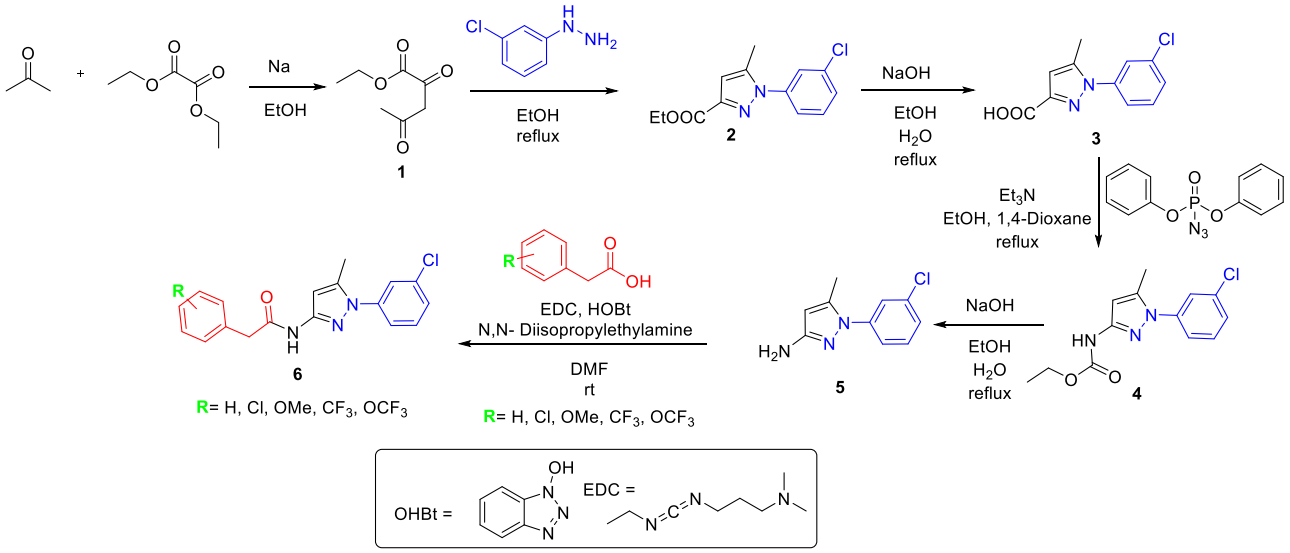
Natália Goedtel Medeiros[1*], Malkeet Kumar[1], Anees Ahmad[1], Mariana Ferrer-Casal[1], Celso Y. Okada Jr.[1], Anna C.C. Aguiar[2], Sarah Maluf[2], Guilherme de Souza[2], Rafael V. C. Guido[2], Thomas W. von Geldern[3], Dominique Soldati-Favre[4], Delphine Baud[3], Paul Willis[3], Barry Jones[3], Elodie Chenu[3], James Duffy[3], Luiz Carlos Dias[1]

1) Instituto de Química, Universidade Estadual de Campinas, Campinas, Brazil
2) Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, Brazil
3) Medicines for Malaria Venture, Geneva, Switzerland
4) Faculté de Médecine, Université de Genève, Geneva, Switzerland
****e-mail: dnatalia@unicamp.br***

Keywords: *Medicinal chemistry, hit-to-lead, anti-malarial agent.*

ABSTRACT

Malaria remains a significant global health challenge, necessitating the continuous development of new therapeutic agents[1,2]. In this study, we report the design, synthesis, and preliminary biological evaluation of novel analogs of anti-malarial agents during the hit-to-lead phase of a drug discovery program led by Medicines for Malaria Venture (MMV) in collaboration with UNICAMP and USP teams (MINDI Consortium). Our research focused on the structural modifications of compound **6**, generated as a Hit compound by an MMV screening for phenotypic blood stage. The most potent derivatives of the series were synthesized using a general protocol of 6-step synthetic route as shown in Scheme 1. *In vitro* anti-malarial activity was assessed against *Plasmodium falciparum* strain to build the SAR study. It was possible to improve the anti-malarial activity reaching IC_{50}=200 nM. However, the analogs exhibited metabolic instability, which was a restriction to move forward the series to lead optimization phase.



Scheme 1. Synthetic route used to obtain compound **6** and its derivatives.

ACKNOWLEDGEMENTS

The authors thank MMV for financial support. Financial support from FAPESP (The State of São Paulo Research Foundation) Project 2015/50655-9 and Process 2024/00815-9 are gratefully acknowledged. We also thank UNICAMP and USP for their support and infrastructure. We thank TCGLS for DMPK analysis.

REFERENCES

[1] World malaria report 2023. WHO, 2023, https://www.who.int/teams/global-malaria- programme/reports/world-malaria-report-2023, (accessed 2024-07-11).
[2] Wells, T.; van Huijsduijnen, R. & Van Voorhis, W. Malaria medicines: a glass half full?. *Nat Rev Drug Discov* **2015**, 14, 424–442. https://doi.org/10.1038/nrd4573.