Medicinal Chemistry rescuing the empowerment of science to promote human health.

instituto de química
Universidade Federal do Rio de Janeiro

Sociedade Brasileira de Química

sbmed
Divisão de Química Medicinal
Sociedade Brasileira de Química

20-24th september
Atlântico Búzios Convention
Búzios, Rio de Janeiro - Brazil

II BrazMedChem 2025

Annals

Annals of XII BrazMedChem, 20-24th September, Búzios, RJ, Brazil
2025 - Instituto de Química - UFRJ (Federal University of Rio de Janeiro)

1st edition

Authors
Dr. Floriano Paes Silva Junior – Chair (FIOCRUZ, Rio de Janeiro-RJ)
Dra. Lídia Moreira Lima – Chair (UFRJ, Rio de Janeiro-RJ)

Illustrations, Editing and Layout

Cabeça de Papel Projetos e Design (www.cabecadepapel.com)

Photos

Freepik.com and Dreamstime

B827a Annals of XII BrazMedChem : 20-24th September, Búzios, RJ, Brazil / Floriano Paes Silva Junior; Lídia Moreira Lima. – 1. ed. – Rio de Janeiro: Instituto de Química - UFRJ, 2025.
282 p. : il.

Anais do 12º Simpósio Brasileiro de Química Medicinal. Ilustrações, Edição e Layout: Cabeça de Papel Projetos e Design. Fotos/Ilustrações: Freepik.com and Dreamstime.
ISBN: 978-85-61987-13-8

1. Química Medicinal – Congressos. 2. Química Farmacêutica – Congressos. I. Silva Junior, Floriano Paes. II. Lima, Lídia Moreira. III. Título.

CDU: 54:615(063)

Guanidine Derivatives as New *Plasmodium falciparum* Inhibitors

Giovana R. Mendes[1] (PG), Tales A. C. Goulart[2] (PQ), Roberto do C. Pinheiro[2] (PQ), Ronei M. S. Souza[2] (PG), Felipe F. F. C. Camargo[2] (IC), Talita A. Valdes[1] (PQ), Igor M. R. Moura[1] (PG), Sarah El Chamy Maluf[1] (PQ), Roberto G. S. Berlinck[3] (FM), Igor D. Jurberg[2] (FM) and Rafael V. C. Guido[1*] (FM)

***rvcguido@ifsc.usp.br**

1) São Carlos Institute of Physics, University of Sao Paulo, São Carlos, Brazil 2) Instituto de Química de São Carlos, Universidade de São Paulo, São Carlos, SP, Brazil 3) Institute of Chemistry, State University of Campinas, Campinas, Brazil

Key words: malaria, guanidine derivatives, P. falciparum.

Introduction

Malaria is a parasitic disease caused by the pathogenic protozoa *Plasmodium* spp., which has a significant global impact on human health.[1] The increasing resistance of *P. falciparum* strains to approved drugs highlights the urgent need for the discovery of new antimalarial candidates. Guanidine alkaloids emerged as promising natural products with antiparasitic activity, and a promising parasitological profile against malaria parasites.[2,3] Herein we report the results of investigating a series of synthetic guanidine derivatives with potent anti-plasmodial activity.

Results and Discussion

Based on our previous work with natural guanidine alkaloids batzelladines F and L,[3] we assessed the anti-plasmodial activity of 234 synthetic guanidine derivatives as new *P. falciparum* inhibitors (Figure1).

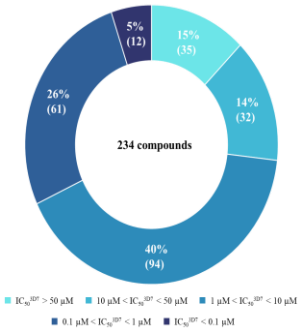

Figure 1: Percentage distribution of the activity of the 234 compounds evaluated against the 3D7 strain.

In this series, *c.a.* 5% of the derivatives (12 compounds) showed potent antiparasitic activity against *P. falciparum*, with IC_{50} values < 0.1 μM. These results represent a notable improvement in antiplasmodial activity when compared to the activity of batzelladines F and L.[3] Additionally, guanidine derivatives with IC_{50}^{3D7} values < 10 μM were tested against human HepG2 cell lines to evaluate liver cytotoxic effects. In general, the most potent compounds exhibited good to excellent selectivity index (SI) values (SI > 10). In order to investigate the mechanism of action of these derivatives, compounds of each subseries (**FFC41**, **FFC53**, **RMS496**, **RMS502**, and **TAC20B4**) were selected for parasitological profile studies. The investigation included speed of action (as fast or non-fast acting inhibitor), combination profile with artesunate, resistant panel (3D7, Dd2, K1, Dd2R_DSM265, 3D7R_MMV692848, and TM90C6B strains) and stage specificity assays. Figure 2 summarizes the main findings.

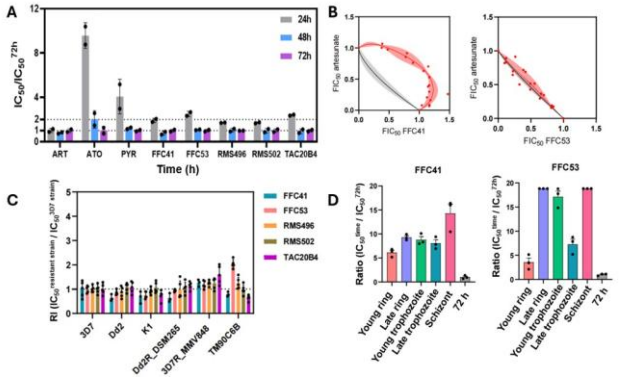

Figure 2. (**A**) Speed of action. (**B**) Representative combination profile with artesunate. (**C**) Resistant panel. (**D**) Representative stage specificity assay.

Guanidine-based compounds displayed unique parasitological profiles, indicating each subseries may act through a different mechanism (Figure 3).

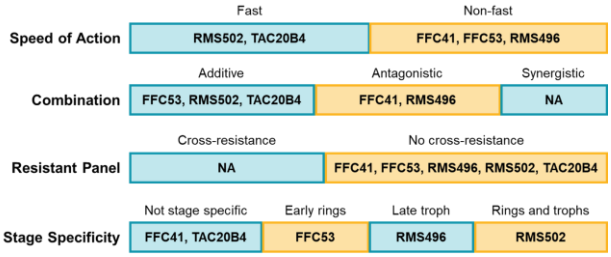

Figure 3: Schematic results for parasitological profile.

Conclusions

Among 234 synthetic guanidine derivatives assayed against *P. falciparum*, 5% showed inhibitory activity at low nanomolar concentrations. Five compounds of each subseries exhibited unique anti-plasmodial profiles, suggesting different mechanisms of action for these compounds. These results indicate that the guanidine derivatives are attractive candidates for drug development.

Disclaimer: The molecules described in this study are subject to a pending patent application.

Acknowledgements

FAPESP (2024/04949-0, 2022/01063-5, 2019/17721-9, 2020/12904-5; 2013/07600-3), CAPES (88887.646876/2021-00).

[1] Phillips, M. A.; *et al*. Malaria. *Nat. Rev. Dis. Prim.* **2017**, 3.
[2] Abd Rani, N. Z.; *et al*. Fused Tricyclic Guanidine Alkaloids: Insights into Their Structure, Synthesis and Bioactivity. *Mar. Drugs* **2022**, *20* (9)
[3] Mendes, G. R.; *et al*. Marine Guanidine Alkaloids Inhibit Malaria Parasites Development in In Vitro, In Vivo and Ex Vivo Assays. *ACS Infect. Dis.* **2025**. DOI : 10.1021/acsinfecdis.4c00714