Evaluation of new selective inhibitors of the Dynamin GTPase from Plasmodium falciparum

Thiago Albuquerque Souza Campos[1], Vanessa Bernadino Almeida [1], Beatriz Abreu Vasconcelos[1], Melina Mottin[2], Lucas Silva de Oliveira [1], Izabela Marques Dourado Bastos[1], Sébastien Olivier Charneau [1]

[1.] UnB , Universidade de Brasília , Universidade de Brasília, Brasília, Distrito Federal – 70910-900, Brasil.;
[2.] UFG, Universidade Federal de Goiás, Goiás, 74605-170, Brasil. ;

Evaluation of New Selective Inhibitors of the Dynamin GTPase from *Plasmodium falciparum*

Thiago Albuquerque Souza Campos[1], Vanessa Bernardino Almeida[1], Beatriz Abreu Vasconcelos[1], Melina Mota[2], Lucas Silva de Oliveira[1], Izabela Bastos[3], Sébastien Charneau[1].

[1]Biochemistry and Protein Chemistry Laboratory, Department of Cell Biology, Darcy Ribeiro University Campus, University of Brasília, Brasília, Federal District – 70910-900, Brazil.

[2]LabMol, Department of Pharmacy, University of Goiás, Goiânia – Goiás, 74605-170, Brazil.

[3]Pathogen-Host Interaction Laboratory, Department of Cell Biology, Darcy Ribeiro University Campus, University of Brasília, Brasília, Federal District – 70910-900, Brazil.

ABSTRACT

Malaria is the most lethal tropical disease worldwide, posing a global public health problem with unimaginable socioeconomic impacts. The disease is caused by protozoa of the genus *Plasmodium spp.*, transmitted through the blood meal of female mosquitoes of the genus *Anopheles*. Currently, treatment of the disease has faced difficulties due to the emergence of drug resistance by the parasite, making the search for new therapeutic targets a crucial strategy. In this context, dynamins emerge as a potential target; they are a superfamily of mechanochemical enzymes involved in various cellular processes. *Plasmodium spp.* can synthesize three dynamin-like proteins, of which only two have been previously characterized. PfDYN1 is produced throughout the erythrocytic cycle and may be involved in intracellular trafficking, while PfDYN2, synthesized during the schizont stage, may play a role in merozoite morphogenesis. Possible dynamin inhibitors were investigated using bioinformatics and in vitro assays. A molecule library was created through the ChemBridge website, selecting molecules with structural similarity to commercial dynamin inhibitors. These molecules were then evaluated through molecular docking, aiming for affinity with the active sites of PfDYN1 and PfDYN2. Molecules with higher affinity were selected for in vitro IC50 testing with antiplasmodial activity. Data were calculated using GraphPad Prism software. Among the molecules in the library, 12 showed high affinity. Molecules identified as 8676, 1707, and 7002 had an IC50 lower than the commercial dynamin inhibitor dynasore, making them candidates for additional cellular assays to be developed in the future. The IC50 values of the molecules suggest a potential inhibitory effect of the most promising compounds. However, their mechanism of action in *Plasmodium spp.* remains to be elucidated. To investigate this mechanism, further studies with purified dynamin should be conducted to explore the GTPase activity of these proteins. Additionally, cytotoxicity tests in human cells are important to assess the safety of the molecules. Successful identification of these inhibitors represents a significant advancement in understanding PfDYN proteins and discovering new targets for antimalarial treatments.

Keywords: Malaria; dynamins; *Plasmodium spp*; inhibitors

Agradecimentos: CAPES: (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPDF (Fundação de Amparo à Pesquisa do Distrito Federal) e FINEP (Financiadora de Estudos e Projetos).