REPOSITIONING HDAC AND KINASE HYBRID INHIBITORS AGAINST MALARIA PARASITE *PLASMODIUM FALCIPARUM*

Bárbara K. M. Dias[1], Pedro Negrão Maiolini[1], Natacha Diesca[1], Karoline B. Waitman[2], Mônica F. Z. J. Toledo[2], Maurício T. Tavares[3], Roberto Parise-Filho[2], Célia R. S. Garcia[1]

1- Departamento de Análises Clínicas e Toxicológicas, Faculdade de Ciências Farmacêuticas da Universidade de São Paulo, São Paulo, Brazil
2- Departamento de Farmácia, Faculdade de Ciências Farmacêuticas da Universidade de São Paulo, São Paulo, Brazil
3- Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, United States.

Malaria disease is still one of the significant public health problems worldwide, resulting in thousands of deaths per year. The emergence of parasites resistant to classical antimalarials indicates the urgent need for repositioning drugs with different pharmacophores. Due to the complex life cycle of the malaria parasite, regulation of cellular processes is essential for parasite survival and infection progression. Epigenetic regulation such as histone modifications are associated with the regulation of key processes in the life cycle of the parasite. Moreover, post-translational modifications such as protein phosphorylation by kinases have been implicated in essential events for parasite development such as in invasion and egress from erythrocytes. This study tested a series of hybrid kinase and histone deacetylase (HDAC) inhibitors, bearing anticancer activity, in *Plasmodium falciparum in vitro*. To evaluate the effect of compounds in parasite development, infected red blood cells were incubated with varying concentrations of compounds for 72h, and final parasitemia was obtained by flow cytometry using double staining to check mitochondria viability with MitoTracker Deep Red and nucleus staining with SYBR Green. Our data show that these compounds impair the parasite development, with IC_{50} values in the nanomolar range against wild type 3D7 and parasites resistant to chloroquine, Dd2. Moreover, cytotoxicity data show that at least four compounds present high selectivity towards the malaria parasite, identifying them as potential hits for developing new antimalarials.

Supported by: This study was financed, in part, by the São Paulo Research Foundation (FAPESP), Brazil. Process Number 2022/15522-1 BKMD, 2024/09115-0 PNM, 2017/08684-7 CRSG.

Key words: Malaria, antimalarial, *Plasmodium*