INHIBITION OF INTRACELLULAR PROTEOLYSIS IN MALARIA PARASITES

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The control of malaria is being challenged by the increasing resistance to available drugs. In this scenario, protease inhibitors emerge as promising therapeutic agents for malaria since they are able to block parasite intracellular development and erythrocyte invasion and egress, and, in some cases, kill the parasite *in vitro* through protease inhibition. For these reasons, the development of methodologies for screening and characterization of malarial protease inhibitors has strategic importance. We developed a drug screening assay using a rodent malaria model with *Plasmodium chabaudi* where it is possible to follow the intracellular parasite proteolysis as previously described (Farias SL. et al, Mol. Biochem Parasitol.2005). Herein we report our results on the evaluation of the effect of organotelluranes in intracellular proteolysis using Z-FR-AMC substrate using confocal microscopy and spectrofluorimetry. Initially a screening of a tellurane set was performed using a cellular suspension of *P. chabaudi* trophozoite, in both pH6.5 and 7.0. Thus, RF05 and RF19 compounds were found as the most potent in tested pH. Another tellurane, RF03, the most hydrophilic member of the set, was chosen for a preliminary evaluation of its chemotherapy potential. A group of mice were treated for 10 days with RF03. This non-optimized treatment increased mice survival significantly. Our data provided a new approach to study the protease activity in the cytosol of malaria parasites allowing to probe proteolysis under cell signaling changes (calcium homeostasis perturbation), and also for its inhibition, due to the promiscuous capacity of substrate internalization of *P. chabaudi* cells.

cysteine protease, protease inhibitor, calcium dependent proteolysis

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