# Optimization of SmTGR inhibitors using a Fragment-Based Drug Design (FBDD) approach.

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**Abstract**

Schistosomiasis is a neglected tropical parasitic disease caused by trematodes of the genus Schistosoma and specifically S. mansoni in Brazil. Schistosomiasis is the most important human helminth infection in terms of morbidity and mortality. The disease occurs in areas with poor sanitation and approximately 1.6 millions individuals were infected with S. mansoni in Brazil. Praziquantel is the unique drug employed for the treatment of the disease. Although the success of the treatment, the concern about resistance is growing and the development of new drugs is urgent. Thioredoxin glutathione reductase of Schistosoma mansoni (SmTGR) is a validated drug target that plays a crucial role in the redox homeostasis of the parasite. A crystallographic screening was held to detect the ligation of small fragments to SmTGR. 32 fragments were found to be ligated around 8 sites of the protein. After the search of analogues molecules and the study of the site of activity of the fragments, six fragments was found presenting an inhibitory activity against SmTGR acting in an allosteric site of the protein, located in the NADPH site. In this work an in silico fragment-based drug design (FBDD) will be carry out to optimize the compounds with highest inhibitory activity in order to propose new drug candidates against S. mansoni. Cavity analisis will be held to study the binding properties of the binding site. Linking and growing approach will be apply to the optimization of the hits. Evaluation of synthetic accessibility and ADMET properties prediction will be performed. Finally, the selected compounds will be object of docking and molecular dynamic studies.

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