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TITLE

SCREENING AND HIT VALIDATION OF MMV'S PANDEMIC RESPONSE AND GLOBAL HEALTH PRIORITY BOXES AGAINST SCHISTOSOMA MANSONI THIOREDOXIN GLUTATHIONE REDUCTASE (SMTGR)

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ABSTRACT

Schistosomiasis is a neglected tropical disease caused by parasites of the Schistosoma genus. In Brazil, this disease is caused by S. mansoni and affects approximately 1.5 million people annually, resulting in around 12,000 deaths. Transmission occurs through direct contact with contaminated water during recreational and occupational activities, with poor sanitation being a significant factor in the prevalence of the infection. The survival of S. mansoni depends on its ability to neutralize reactive oxygen species (ROS) produced by its metabolism and by the immune system of its host. In this context, the S. mansoni Thioredoxin Glutathione Reductase (SmTGR) enzyme plays a crucial role in neutralizing ROS, making it a validated target for the development of drugs against schistosomiasis.
This work aimed to screen 640 compounds from two sets provided by Medicines for Malaria Venture (MMV). The first set tested is the Pandemic Response Box (PRB), launched in 2019, containing 400 compounds aimed at infectious diseases. The second, launched in 2022, is the Global Health Priority Box (GHPB), with 240 compounds, including molecules active against infectious agents of neglected diseases. In the screening assay, the reductive activity of SmTGR on 5,5'-dithio-bis-[2-nitrobenzoic] acid (DTNB) was measured by spectrophotometry (412 nm, 5 minutes), recording the appearance of the product, thionitrobenzoic acid (TNB), in the presence of 10 µM of the compounds. So far, the results of inhibition assays on SmTGR using 120 of the 640 compounds from the PRB and GHPB sets allowed us to identify nine hits (GHPB: compounds 34 and 36; PRB: compounds 16, 23, 27, 42, 47, 49, and 53), capable of promoting more than 40% inhibition of enzymatic activity. Compounds 47 and 27 from the GHPB achieved 65.5% and 62.1% inhibition, respectively. All hit compounds will be selected for orthogonal validation by Thermal Shift Assay (TSA). Validated inhibitors will have their IC50 determined and will be subjected to phenotypic assays on distinct parasite life cycle stages. The most promising compounds will have their mechanism of inhibition studied by kinetic assays and biophysical techniques.

KEYWORDS

Thioredoxin Glutathione Reductase; Schistosomiasis; Enzymatic Assays; Thermal Shift Assays; Drug Discovery

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