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TITLE

REPURPOSING HUMAN CATHEPSIN D INHIBITORS FOR FIGHTING SCHISTOSOMIASIS

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ABSTRACT

Schistosomiasis is a disease caused by trematodes of the genus Schistosoma. Endemic in several countries, more than 264 million people required preventive chemotherapy in 20221. The disease is treated almost exclusively with praziquantel (PZQ), the drug of choice for more than 40 years2. Given this limited treatment , a few molecular targets have already been identified and validated for the development of new drugs to treat schistosomiasis3. One validated targets is S. mansoni's cathepsin D (SmCD1)4, an aspartyl protease that stands out for its role in the digestion of hemoglobin. Obtained from ingested host erythrocytes, hemoglobin is the parasite's main source of aminoacids, therefore, interfering with its digestion has a fundamental impact in the nutrition and normal development of S. mansoni. In our group, the production of recombinant SmCD1 (rSmCD1) and the identification of hit compounds have been carried out in the last years5,6. In this work, we present new SmCD1 inhibitors, identified using a drug repositioning strategy, an alternative to traditional drug development with reduced time spent in the approval of a molecule. In partnership with Merck's GHI we had access to a series of 78 acylguanidines, previously investigated as human cathepsin D (hCD) inhibitors. All compounds are being screened in ex vivo experiments, with adult S. mansoni. Compounds' effect on parasite are evaluated by automated high-content microscopy (HCS)7, and the images obtained are analyzed using the Cellprofiler software version 4.2.18, to segment the parasite as an object and extract features related to motility and morphology. In parallel, enzymatic assay are also being carried out, to evaluate the potency of the compounds as rSmCD1 inhibitors. In this assay, a FRET peptide (Abz-AIAFFSRQ-EDDnp) is used as a substrate, and the fluorescence produced by the product is used to analyze rSmCD1 activity. In both screenings, compounds are evaluated at 10 μM. To date, 68 compounds were tested in the ex-vivo assay and 21 of them have reduced S. mansoni motility by up to 78%. These compounds were also active against rSmCD1, decreasing its activity by up to 99%. Taken together, these results may indicate a decrease in parasite motility caused by inhibition of rSmCD1 activity. One of these compounds, M8214, is more selective for rSmCD1 (IC50 = 0.09 μM) than for hCD (IC50 = 1.1 μM). Using Deep-PK platform9, M8214 was predicted to have high gastrointestinal absorption, and interesting pharmacokinetic properties. Both characteristics are desirable in a candidate drug molecule. Currently, ex vivo screening, cytotoxicity of the active compounds and molecular modeling studies with rSmCD1 are ongoing. 1ISBN: 978-92-4-009153-5. 2DOI: 10.1016/j.pt.2019.11.002. 3DOI: 10.3389/fimmu.2021.642383. 4DOI: 10.1016/j.molbiopara.2007.10.009. 5DOI: 10.1016/j.pep.2019.105532. 6DOI: 10.1590/0074-02760230031.7DOI: 10.1021/acs.jmedchem.5b02038.8DOI: 10.2144/000112257. 9DOI: 10.1093/nar/gkae254.

KEYWORDS

Schistosoma mansoni; Aspartyl Protease

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