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TITLE

DISCOVERY OF NEW ANTISCHISTOSOMAL THIOXANTONES AS POTENTIAL PARASITE EFFLUX PUMPS INHIBITORS

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ABSTRACT

Schistosomiasis affects approximately 250 million people globally and threatens over 700 million individuals, according to the World Health Organization. In Brazil, Schistosoma mansoni is the primary infecting species. The current treatment and prevention strategy relies solely on Praziquantel (PZQ), which although safe and effective against all Schistosoma species is less active on immature forms of the parasites. Moreover, its extensive use in endemic regions raises concerns about the emergence of drug-resistant strains. Efflux pumps, particularly ABC transporters, play a key role in resistance mechanisms. Recent studies have identified a connection between P-Glycoprotein (Pgp/ABCB1) and PZQ resistance in S. mansoni, highlighting the urgent need for alternative therapies to combat schistosomiasis. One promising avenue involves the use of thioxanthone, an S-heterocycle containing a dibenzo-g-thiopirone substructure. Thioxanthone derivatives have been explored for their role in developing Pgp inhibitors, particularly as antineoplastic agents. Historical drugs like Lucanthone and Hycanthone, previously used to treat schistosomiasis, are also thioxanthones, underscoring the potential of this substructure in the search for new therapeutic compounds. This study aimed to evaluate the antischistosomal activity of seven thioxanthone-derived compounds, along with their toxic effects on human cells. Adult S. mansoni parasites were assessed for motility using bright field microscopy and the ImageXpress Micro Confocal High-Content Imaging System. Adult worms were collected from Swiss mice infected with S. mansoni cercariae 42 days prior, via perfusion. The compounds were then tested on the worms, with a series of 100 time-lapse images of each well captured every 24 hours for a total of 72 hours. A convolutional neural network model processed these images and their binary masks, and motility metrics were calculated using the CellProfiler software. Cytotoxicity assays were performed on WSS-1 and HepG2 human cells using the resazurin reduction method. Results showed that compounds 1 and 2 inhibited the motility of adult S. mansoni worms to a degree comparable to PZQ at 50 μM. Interestingly, only compounds containing aliphatic tertiary amines as substituents exhibited activity against adult worms, suggesting this substructure may hold therapeutic potential. While compound 1 (50 μM) reduced the viability of WSS-1 cells by approximately 70%, compound 2 demonstrated safety across both human cell lines, even at higher concentrations (up to 300 μM). These findings indicate that the thioxanthone core structure is valuable in the ongoing search for effective antischistosomal compounds. Although these results are promising, further investigation is required to fully understand the mechanism of action. Docking, molecular dynamics simulations, and other in silico approaches will be conducted to elucidate the binding mode of these compounds to S. mansoni Pgp.

KEYWORDS

Medicinal Chemistry; High-Content Analysis; Ex Vivo Assays; Cytotoxicity.

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