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TITLE

NOVEL PRAZIQUANTEL ANALOGS WITH TRPMPZQ MODULATORY ACTIVITY AND ANTIPARASITIC EFFECTS ON IMMATURE AND ADULT WORMS OF SCHISTOSOMA MANSONI

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ABSTRACT

Praziquantel (PZQ) is the standard treatment for schistosomiasis, but resistance may develop with its widespread use. The discovery of a transient receptor potential ion channel of the melastatin subfamily activated by PZQ (TRPMPZQ) has opened new opportunities for target-based drug discovery. In this study, we evaluated the schistosomicidal potential of a novel series of 1H-1,2,3-triazole derivatives of PZQ and their synthetic intermediates on immature and adult forms of Schistosoma mansoni and tested their ability to activate schistosome TRPMPZQ (Sm_TRPMPZQ). High content microscopy was used to determine the effect of the compounds on schistosomula and adult worms. Compounds' cytotoxicity was assessed in human kidney epithelial (WSS-1) cells by a viability assay. A Fluorescent Imaging Plate Reader (FLIPR) assay was conducted to test whether the compounds activate TRPMPZQ channels expressed transiently or stably in human embryonic kidney (HEK293) cells. The same method was carried out with a schistosome TRPM channel activated by meclonazepam (TRPMMCLZ) and TRPMPZQ from Fasciola hepatica (Fh_TRPMPZQ) to evaluate selectivity. Initial screening at 50 μM on schistosomula identified four compounds that altered the motility and morphology of the worms after 72 h of incubation: F23, F36, F38_12, and F41_17. F27 only affected parasites motility. F27, F36, and F38_12 significantly decreased the motility of adult worms after 24-72 h of incubation at 10/30 μM. None of them showed significant toxicity at 10 μM in WSS-1 cells after 48 h incubation. In the FLIPR assay, F27, F35_2, F36, and F38_12 activated Sm_TRPMPZQ channel at 0.3-100 μM, with F38_12 being the most potent, exhibiting a 50% effective concentration (EC50) of 0.81 and 0.52 μM for transient and stable expression of TRPMPZQ, respectively. All tested compounds showed only negligible effect on Sm_TRPMMCLZ and Fh_TRPMPZQ, suggesting they have a similar activity profile to PZQ. Apart from F27, the other compounds that modulated Sm_TRPMPZQ activity are intermediates in the synthesis of the triazoles, with small substituent groups (-N3, -NH2 or -NO2), at position 10 of the isoquinoline pyrazine nucleous. Inspection of a theoretical model of PZQ bound to Sm_TRPMPZQ suggests this result can be explained by the small volume available around position 10 of the isoquinoline pyrazine nucleus delineated by residues Tyr 1517, Arg1514, Asp1455 and Leu1454 from helices 1504-1512 and 1451-1467. F27 has a 4-propyl-1H-1,2,3-triazole group which, unlike other PZQ derivatives tested in this work with larger groups attached to the triazole ring, can still fit inside the subpocket within the PZQ binding site of the Sm_TRPMPZQ receptor. Interestingly, F41_17 was active on schistosomula and male worms after 72h of incubation, but showed no effect on Sm_TRPMPZQ, suggesting a different mechanism of action than PZQ. Other experiments are in progress, including the screening of the compounds on juvenile worms.

KEYWORDS

Praziquantel Analogs; Triazoles; TRPMPZQ; Schistosomiasis Drug Discovery

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