Antischistosomal activity of pyrido[1,2-a]benzimidazole derivatives and correlation with inhibition of beta-hematin formation

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The extensive use of praziquantel against schistosomiasis raises concerns about drug resistance. New therapeutic alternatives targeting critical pathways within the parasite are therefore urgently needed. Hemozoin formation in Schistosoma presents one such target. We assessed the in vitro antischistosomal activity of pyrido[1,2-a]benzimidazoles (PBIs) and investigated correlations with their ability to inhibit β-hematin formation. We further evaluated the in vivo efficacy of representative compounds in experimental mice and conducted pharmacokinetic analysis on the most potent. At 10 μM, 48/57 compounds resulted in >70% mortality of newly transformed schistosomula, whereas 37 of these maintained >60% mortality of adult S. mansoni. No correlations were observed between β-hematin inhibitory and antischistosomal activities against both larval and adult parasites, suggesting possible presence of other target(s) or a mode of inhibition of crystal formation that is not adequately modeled by the assay. The most active compound in vivo showed 58.7 and 61.3% total and female worm burden reduction, respectively. Pharmacokinetic analysis suggested solubility-limited absorption and high hepatic clearance as possible contributors to the modest efficacy despite good in vitro activity. The PBIs evaluated in this report thus merit further optimization to improve their efficacy and to elucidate their possible mode of action.
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