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IN VITRO TRYPANOCIDAL ACTIVITY OF A NEW COMPOUND NITROIMIDAZOLE-BASED

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ABSTRACT

Chagas disease (CD) is the second most important cause of infectious cardiomyopathy in the world, behind only COVID-19. Chagas cardiomyopathy is the most disabling and deadly manifestation of *Trypanosoma cruzi* infection, and this scenario is aggravated limited treatment efficacy, which currently consist only of benznidazole (BZ) and nitroheterocyclic nifurtimox (NFx). There is a growing interest in new nitroimidazole (ME)-based compounds with anti-*T. cruzi* efficacy. Thus, this study investigated the antiparasitic activity *in vitro* of a novel nitroimidazole derivative (ME) obtained by chemical synthesis. Initially, antiparasitic activity against extracellular forms of *T. cruzi in vitro* was evaluated. Blood trypomastigotes (Y strain) were isolated from *Swiss* mice and resuspended in DMEM (10% FBS). Isolated trypomastigotes (500000/mL) were incubated (24h at 37 ºC) in RPMI in the absence and presence of different ME concentrations (1.72, 3.43, 6.86, 13.73, 27.46 µM) and BZ (2.40, 4.80, 9.60, 19.21, 38.43 µM) dissolved in culture medium. After 24h, the number of live trypomastigotes was microscopically quantified using a Neubauer chamber. In a second step, antiparasitic activity against intracellular forms of *T. cruzi in vitro* was analyzed. C2C12 skeletal myocytes (10000 cells/well) were incubated (DMEM; 1% penicillin-streptomycin and 5% FBS) for 24h at 37 °C and 5% CO_2. Cell incubation was conducted in 24-wells plates coated with glass coverslips. Cells were co-cultured with trypomastigotes (Y strain) in a 10:1 (parasite:C2C12) cell ratio. Non internalized parasites were removed 2h after trypomastigotes challenge by washing the cells with fresh DMEM, and more 48h incubation was used to establish infection. Then, ME and BZ were added at the same concentrations, and untreated cells were used as control. After 48h incubation with both drugs, the coverslips were fixed with 4% paraformaldehyde and stained with Giemsa. Cell infection rate and parasite load were determined by counting the number of infected cells and the number of intracellular parasites in 100 cells randomly sampled at ×400 magnification using a light microscope. In the assay to investigate the extracellular antiparasitic activity, the results showed that both treatments (BZ and ME) significantly reduced the parasite viability at all concentrations tested ($P<0.05$) compared to the control. It was possible to observe that the new nitroimidazole derivative (ME) reduced the parasite viability at lower concentrations than BZ (e.g.: 2.4 µM of BZ reduced the extracellular parasite viability by 20%, while 1.72 µM of ME reduced the same 20%). Similar reductions in the parasite viability extracellular were observed for the other ME concentrations. This evidence suggests that when it comes to extracellular antiparasitic activity, ME at lower concentrations can achieve the same efficacy as BZ. Now, the results of antiparasitic activity against intracellular forms of T. cruzi in vitro showed that all tested concentrations of BZ and ME significantly reduced ($P<0.05$) the host cell infection rate. However, a higher concentration of ME is required to achieve the same percentage reduction as BZ (e.g.: 2.4 µM of BZ reduces 70% of intracellular antiparasitic activity, while 6.86 µM of ME is required to achieve the same reduction). Similar results were observed for skeletal cell parasitism (trypomastigotes/C2C12). Where, although both treatments (BZ and ME) significantly reduced the parasitism rate ($P<0.05$) compared to the control, a higher concentration of ME was required to achieve the same parasitism rate as BZ (e.g.: 2.4 µM BZ resulted in 9 trypomastigotes/1 C2C12, while 27.46 µM ME was required to achieve a similar rate). Taken together, it was possible to conclude that the new nitroimidazole-based derivative (ME) presents effective extracellular trypanocidal activity in vitro, and promising antiparasitic activity in vitro.