5-NITRO-2-FURFURILIDEN DERIVATIVES ARE ACTIVE AGAINST TRYpanosoma CRUZI LINEAGES PREVALENT IN HUMAN PATIENTS


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The search for new compounds for Chagas disease treatment is of high priority, because the only available drugs Benznidazole (BZ) and Nifurtimox (NFX) have low efficacy in the chronic phase of the disease. Our group has reported that some nifuroxazide (NF) derivatives have trypanocidal activity against T. cruzi. The goal of this study was to design and synthesize an additional set of fifteen NF analogues and to screen their activity against three T. cruzi strains, which represent the genetic lineages more prevalent in Latin American patients (Zingales et al., 2012). The 5-nitro-2-furan present in NF and NFX and considered as the pharmacophore was maintained in the skeleton of the NF analogues. The Lipinski’s rule of 5’ was taken into account, mainly regarding the hydrophobic property (ClogP). Bioactivity was evaluated against epimastigotes of Silvio X10 cl1 (TcI), Y (TcII), and Bug 2149 cl10 (TcV). Similar IC50 values for the three strains were verified for most of the NF analogues, which showed better anti-T. cruzi activity than BZ (IC50 33 μM). Three compounds had higher trypanocidal activity than NFX (IC50 8.7 μM). Cytotoxicity of the most active compounds was evaluated against LLC-MK2 cells. Only two compounds had IC50 values lower than 160 μM, which was the maximum drug concentration used. A time-kill assay, by high-content screening image analysis (Moraes et al., 2014), was conducted to estimate how long intracellular amastigotes of the Y strain should be exposed to compound concentrations to reduce cellular infection to undetectable levels. NF analogues abolished intracellular infection at 3–10 μM with at least 96 h of exposure, while displaying minimal host cell cytotoxicity. These results suggest that the novel nitroderivatives have trypanocidal activity in vitro against both insect and mammalian replicative stages of divergent T. cruzi strains.

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