Trypanosoma cruzi, the agent of Chagas disease, comprises heterogeneous populations that may differ in biological, molecular, clinical and ecoepidemiological criteria. At present, the taxon T. cruzi is divided into six lineages, TcI-TcVI (Zingales et al., 2009), which can be genotyped by simple procedures manageable in laboratories of disease endemic areas. Compelling evidence indicate that TcI, TcII, TcV and TcVI are agents of human disease in different regions of Latin America (Zingales et al., 2012). New treatments for Chagas disease are urgently needed because the only drugs available, benznidazole (BZ) and nifurtimox (NFX), have low efficacy in the chronic phase of the disease. The reasons for treatment failures are unknown, but have been attributed mostly to diverse drug susceptibility among T. cruzi strains. No apparent lineage association with natural resistance to BZ and NFX has been observed. In collaboration with colleagues of the Faculty of Pharmaceutical Sciences (University of São Paulo), a set of fifteen compounds was designed and synthesized using Nifuroxazide (NF) as lead. The (5-nitrofuran-2-yl)methanamine moiety remained unchanged to preserve the similarity with the pharmacophoric group of NF and NFX. Bioactivity was evaluated against epimastigotes of three T. cruzi strains belonging to TcI, TcII, and TcV lineages. All the NF analogues, except one, showed enhanced trypanocidal activity against the three strains as compared to NF (IC_{50} \sim 300 \, \mu M) and BZ (IC_{50} \sim 33 \, \mu M). Three compounds had higher bioactivity than NFX (IC_{50} \sim 8.7 \, \mu M). 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 \, \mu M with 96 h exposure, while displaying minimal host cell cytotoxicity. The novel nitroderivatives are promising molecules for Chagas disease treatment.

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Key Words: Chagas disease; parasite lineages; novel nitroderivatives.