In vitro phenotypic screening of novel aromatic amidines against Trypanosoma cruzi

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For the last four decades, Nifurtimox and Benznidazole (Bz) are the only drugs available for Chagas disease therapy. Both exhibit serious limitations such as (a) low efficiency during the late chronic phase, (b) extended periods of treatment (60 days) plus (c) several side effects often resulting in the abandonment of the treatment. Therefore, there is an urgent need to develop alternatives for the treatment of this silent and progressive neglected pathology. Heterocyclic molecules derived from pentamidine (including reversed amidines called arylimidamides) are potent anti-parasitic agents. In this context, our aim was to evaluate the biological effect of six novel amidines against Trypanosoma cruzi by in vitro and in vivo studies. The findings on bloodstream trypomastigotes (Y strain) showed that 5 out of 6 tested compounds were more active than Bz (EC₅₀ 3µM) after 24 h of drug exposure. Two of this series presented a fast trypanocidal level with EC₅₀ lower than 3 µM after only 2 h of incubation. Considering the toxicity profile towards mammalian host cells, unfortunately the most active agents were also the most toxic (exhibiting LC₅₀ ranging between 9 and 12 µM) and one compound (28SMB 032) displayed a considerable selectivity index (SI = 53). Regarding the activity against amastigotes (from different strains and DTUs as Tulahuen and Y), this aromatic amide also presented the highest SI, being about 60- and 200-fold more selective against intracellular parasite than mammalian cell, respectively. Due to the high SI against both parasite forms, this compound was moved to in vivo analysis of mouse acute T. cruzi infection that is underway.

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