New triazoles with action against *Trypanosoma cruzi* and as inhibitors of P2X7 receptor: a preliminary study

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Introduction: Chagas disease (CD) is a neglected disease caused by the protozoan *Trypanosoma cruzi* and affects millions of people, according to the World Health Organization (WHO). Currently, in Brazil, only benznidazole is available to treat this disease. However, this treatment causes features adverse effects that induce interruption of treatment. In CD, purinergic signalization (ATP and adenosine) actives an inflammatory response. Adenosine triphosphate (ATP) is found in millimolar levels extracellularly caused by rupture of infected cells by a parasite. These elevated levels stimulate the purinergic receptor-mediated pore formation, especially the P2X7 receptor involved with activation and release of inflammatory cytokines, cellular damage, and cell death. There are several selective antagonists to this receptor; however, they were not effective in clinical trials, which justify the search for new drugs. We aim to study new prototypes of triazoles with action against *T. cruzi* and antagonist activity upon receptor P2X7 with *in vitro* tests. Then, a series of triazoles (TD1-TD17) with selective action against P2X7 receptors and low toxicity towards mammalian have been tested against *T. cruzi in vitro.*

Methods: *In vitro* cell cytotoxicity was tested using peritoneal macrophages of Swiss Webster mice plated on transparent 96 wells plates and kept 24 hours at 37 ºC with a 5% CO_2 atmosphere. The cells were then incubated with 100 µM triazole derivatives, and cell-only wells were maintained as a control. After 24 hours, the resazurin colorimetric assay was performed, and the cytotoxicity was

expressed in percentage, with the aid of the program GraphPad Prism 5. The experiment was performed in triplicate on three different days.

Results: In the test evaluating the metabolic action we obtained: TD1 (55,7±4), TD2 (68,9±8), TD3 (81,6±2), TD4 (101,7±4), TD5 (95,8±7), TD6 (5,7±0,6), TD7 (78,9±9), TD8 (7±0,3), TD9 (10,2±3), TD10 (80,4±9), TD11 (90,2±5), TD12 (6,3±0,6), TD13 (54,6±3), TD14 (75,3±4), TD15 (80,8±3), TD16 (77±5), TD17 (81,7±16). The compounds TD6, TD8, TD9, and TD12 (p-value of 0.05) reduced, respectively, 5%, 7%, 10%, and 6% of the cellular metabolic activity. However, the other compounds did not interfere with the peritoneal macrophages' metabolism, even at their maximum concentration, indicating these compounds exhibited low toxicity.

Conclusion: Triazole prototypes exhibited low toxicity in mammalian cells. However, new tests about toxicity will be realized in mammalian cells and against *Trypanosoma cruzi*.

Keywords: Chagas Disease, Purinergic Receptors, *Trypanosoma cruzi*, Triazoles.

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