Structural planning, synthesis and evaluation of properties trypanocidal aryl-1,3-thiazoles

Miria O. Barbosa[1]; Gevanio B. O. Filho[1]; Lucianna R. P. Siqueira[1]; Arsênio R. Oliveira[1]; Carlos A. L. M. Filho[1]; Ulisses J. F. T. Oliveira[1]; Diogo R. M. Moreira[2]; Cássio S. Meira[2]; Milena B. P. Soares[2]; Ana Cristina L. Leite[1]

[1]Laboratório de Planejamento em Química Medicinal – LpQM; UFPE; Recife – PE, Brasil. Email: miria211@gmail.com
[2]Fundação Oswaldo Cruz, Centro de Pesquisas Gonçalo Moniz - BA. LETI - Laboratório de Engenharia Tecidual e Imunofarmacologia; Salvador – BA, Brasil.

Chagas disease is a parasitic infection caused by protozoan *T. cruzi*, which affects around 7 million people worldwide. Benznidazole (BZD) is the sole drug approved for treatment during the acute and asymptomatic chronic phases, however it has not efficacy during the chronic phase. Therefore, the development of new medicines is needed. To identify new trypanocidal compounds, we performed a structural planning and synthesis of new aryl-1,3-thiazoles (LpQM-7-28). Aryl-4-thiazoles were designed with the aim to identify less cytotoxic and more potent trypanocidal agents than the thiosemicarbazones (Int1-3). We also looked for understand most the structure-anti-*T. cruzi* activity relationships for this class of thiazoles, thus several substituents were attached to the N3 and C4 position of the heterocyclic ring. The trypanocidal activity was determined for Y strain trypomastigotes and the toxicity was measured for J774 macrophages. After the screening for compounds, it was possible to identify the compounds (LpQM-12, 15, 16, 21, 23 and LpQM-26) as trypanocidal agents equipotent to BZD but with the advantage of these displayed low toxicity for macrophages. These compounds have as common structural feature a 4-metoxi-phenyl, or 4-methyl-pheny, or phenyl or pyridyl group attached at C4, suggesting theses groups are important for warrant anti-T. cruzi activity. The inserting alkyl substituents at the 5-position of the heterocycle increased pharmacological activity, and should be explored by our research group. Five of most active compounds for tripomastigote form (LpQM-7, 9, 12, 16 and LpQM-23) present more of 70% of inhibitory activity of cruzain, suggesting a possible mechanism of action these compounds. Overall, we have shown here that thiazoles are endowed with trypanocidal activity greater than thiosemicarbazones (Int1-3), besides of being more selective in regard to toxicity in macrophages, therefore suggesting these thiazoles are potential anti-*T. cruzi* drug prototypes.

Palavras-chave: Chagas disease, *Trypanosoma cruzi*, 1,3-thiazoles.

Apoio: FACEPE, CAPES, CNPq.