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Novel dimeric 2-nitroimidazole derivatives: design, synthesis and biological evaluation against amastigotes of *Trypanosoma cruzi*

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Introdução

Chagas disease (CD) is an illness caused by the hemoflagellate protozoan *Trypanosoma cruzi*. CD has vector transmission as the main route of transmission in endemic areas, which occurs through the insect popularly known as "kissing bug" (*Triatoma infestans*). According to WHO data, this parasitosis is part of a group of diseases called neglected tropical diseases, with CD being considered the most neglected among them. [1] Currently, the therapeutic arsenal available for the treatment of chagasic patients is very limited, with only two drugs, both nitroheterocyclic derivatives, nifurtimox and benznidazole. Which have limited therapeutic potential and low efficiency in the chronic phase of the disease, in addition to having serious side effects.

In order to meet the humanitarian demand for new antichagasic drugs, a series of simple *N*-alkylated 2-nitroimidazole derivatives molecules was planned herein. The nitroimidazole core is the main pharmacophore present in benznidazole, being one of the principal structural features for its antiparasitic activity. Notably, the 2-nitro-1H-imidazole (**1**) (known as: azomycin – natural antibiotic) has anti chagasic activity against the amastigotes of *T. cruzi* comparable to that of benznidazole. [2] Dimerization of an active compound is a strategy of molecular design that often results in enhanced binding and improved pharmacological properties. This improvement of potency is attributed to a higher concentration of pharmacophores in the proximity of molecular recognition sites in the biological environment.[3]

The main objective of this work was the synthesis of a series of *N*-alkylated 2-nitroimidazole derivatives, their characterization, and the biological evaluation of their cytotoxic and antiparasitic profile against intracellular replicative form of *T. cruzi* (Tulahuen C2C4-LacZ strain).[4]

Resultados e Discussão

The alkylation reactions were carried out by reacting the 2-nitroimidazole (**1**) with dibromoalkanes, with different chain sizes, The alkylation reactions were carried out under inert atmosphere (positive pressure of dry N_2), using anhydrous DMF as solvent. The derivatives obtained were analyzed by HPLC-MS, and had their structures confirmed by ^{13}C and ^{1}H NMR spectra data.

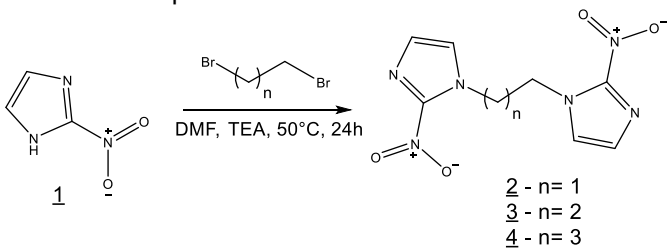

Figure 1. Synthetic strategy for the preparation of *bis*-2-nitroimidazole derivatives.

Table 1. Cytotoxicity and antiparasitic effects of dimeric 2-nitroimidazole derivatives on *T. cruzi* amastigotes and LLC-MK2 cells.

	Activity on *T. cruzi* amastigotes (Tulahuen C2C4 lacZ)	Cytotoxicity on LLC-MK2 (host cells)
	IC_{50} (**μM**)	
1	5,74 ± 1,89	>500
2	10,69 ± 1,04	>200
3	3,57 ± 1,07	>200
4	<0,64	>200
Benznidazole*	1,50 (±0,33)	

*Reference drug.

Conclusões

The results obtained herein pointed out the strategy of preparing simple-structured molecules having two 2-nitroimidazole pharmacophores as a very promising approach against amastigotes of *T. cruzi*. The new derivatives obtained in this work, in addition to being toxic against *T. cruzi*, also showed reduced cytotoxicity against the host cells, evidencing their high selectivities.

Agradecimentos

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