Short Communication

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Naphthoquinone and Triazoles With Dual Action to Combat Infectious Disease with A Prominent Inflammatory Response

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ABSTRACT

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Chagas disease, also attributed to American trypanosomiasis, is an anthropozoonosis caused by the parasite Trypanosoma cruzi and transmitted by insect triatomine vectors [1]. This disease is considered endemic in 21 countries in Central and South America, consisting of a severe public health problem [2]. Regarding the clinical course, Chagas disease has two phases: an acute phase, characterized by high parasitemia, and a chronic phase that persists throughout the individual's life. In most cases, the acute phase is asymptomatic or oligosymptomatic with fever, inflammation at the inoculation site (inoculation chagoma), unilateral eyelid edema (Romaña sign), lymphadenopathy, and hepatosplenomegaly [3]. These manifestations spontaneously disappear in most infected individuals, even without drug intervention, and the disease progresses to the chronic phase. Approximately 60-70% of patients develop the chronic indeterminate form of the disease, characterized by the absence of clinical manifestations. The remaining 30-40% of patients who develop the disease have a chronic form 10-30 years after the initial infection.

This phase is characterized by neurological, cardiovascular, digestive system, or cardiodigestive impairment [3]. Currently, the treatment for Chagas disease is based only on two nitro-heterocyclic compounds, benznidazole (1) and nifurtimox (2) (Figure 1). However, both substances present several drawbacks: they are more effective in the initial stages of infection against trypomastigote and amastigote forms, require long treatment times, exhibit high toxicity in adults, and present different susceptibility profiles concerning the different strains of T. cruzi. In this sense, there is an immediate need to develop new trypanocidal drugs that are more effective and have an acceptable good safety profile [4]. In the development of Chagas disease, a high inflammatory response is present both in the acute and chronic phases. Particularly in patients with a determined chronic form, there is evidence that an uncontrolled inflammatory response contributes to the disease's pathogenesis. Among the different membrane receptors that modulate the inflammatory response, purinergic receptors can be promising molecular targets due to the evidence of receptors sensitive to extracellular ATP in the membrane of trypomastigote forms and the upregulation of ectonucleotidase activity in murine cells infected with T. cruzi [5-7].

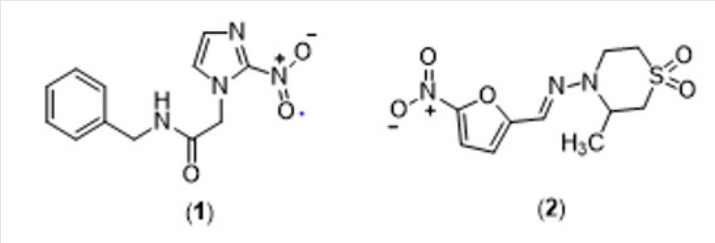

Figure 1: Structure of benzonidazole (1) and nifurtimox (2).

A vast number of natural substances have been continuously studied to search for a safer and more effective treatment for Chagas disease [8]. Naphthoquinones represent a promising class of natural products with trypanocidal activity [9]. Several natural and synthetic naphthoquinones have been evaluated against different developmental forms of T. cruzi [10-12]. In this context, naphthoquinones have served as useful synthetic platforms to obtain more selective and potent compounds. The addition of the nitrogen heterocycle 1,2,3-triazole has proven to be a promising chemical strategy to generate bioactive naphthoquinone derivatives [13-16]. Our research group has recently shown that different naphthoquinone derivatives have also exhibited potential inhibitory activity towards the P2X7 receptor, a subtype of purinergic receptors directly related to inflammatory responses [17]. Interestingly, we have also identified two triazoyl-naphthoquinone derivatives (Figure 2) with potent antagonist activity towards P2X7R [18]. Despite its fundamental role in inflammatory responses, to date, there are no studies that directly correlate P2X7R activity with the inflammatory dysregulation observed in patients with Chagas disease. Considering the pharmacological activities of naphthoquinone and triazole nuclei independently, we believe that this association can provide new compounds with immunomodulatory activity that may exert beneficial effects through P2X7R inhibition and direct trypanocidal action. However, we perceived that more studies are needed to identify the real relevance of P2X7R-mediated signaling pathways in Chagas disease pathogenesis, particularly in patients with chronic determinate infection.

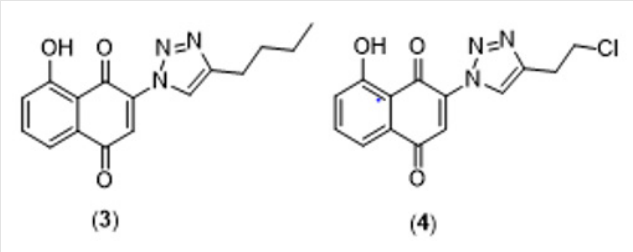

Figure 2: Structure of triazoyl-naphthoquinone derivatives with P2X7R inhibitory activity.

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