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Área: MED

Design, Synthesis and *In Vitro* Evaluation of a Series of Arylmorpholine Derivative Compounds Against Chagas Disease

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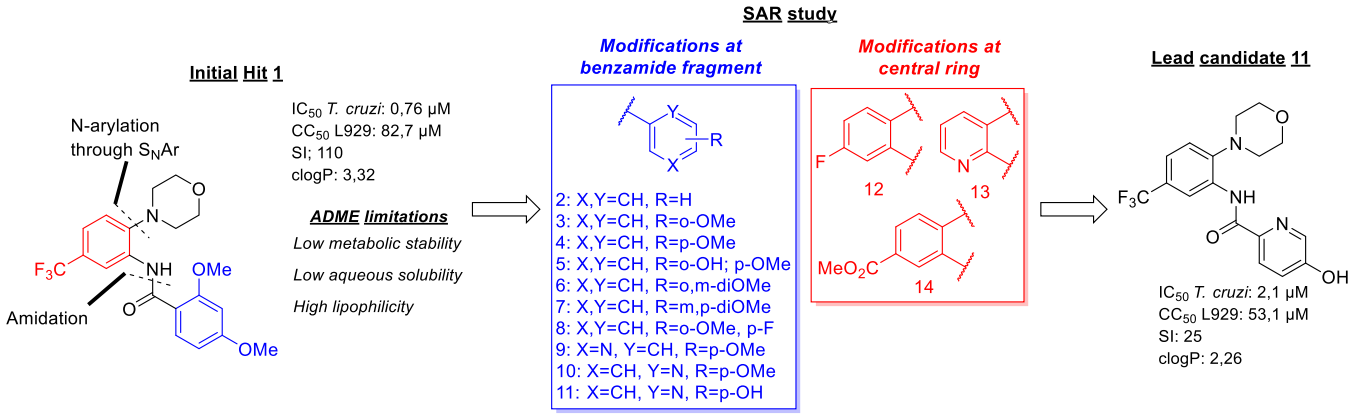
Palavras Chave: *Arylmorpholines, Chagas Disease, Medicinal Chemistry, ADME*.

Highlights

Investigating arylmorpholine derivatives for Chagas disease. Promising anti-*T. cruzi* activity, low cytotoxicity. Structural modifications to improve pharmacokinetics.

Resumo/Abstract

Chagas disease is a neglected tropical disease that affects approximately 7 million people worldwide, caused by the protozoan *T. cruzi* and transmitted to humans through the feces of infected triatomine bugs. The only two drugs available for treatment, nifurtimox and benznidazole, have significant limitations, including low efficacy, severe side effects, and high resistance levels (1). These challenges emphasize the urgent need for new efficient therapeutic drugs against this infection. In this work, we investigated the *in vitro* activity of a series of arylmorpholine derivatives inspired by the potent anti-*T. cruzi* activity of the **initial hit 1** (2). The **initial hit 1** and its analogs were synthesized via three main types of reactions: *N*-arylation through Nucleophilic Aromatic Substitution (S_NAr), nitro reduction and amidation. The biological results of the **initial hit 1** revealed a high anti-*T. cruzi* activity and a low cytotoxicity, but also low aqueous solubility and metabolic instability, along with high lipophilicity and low permeability. To overcome these limitations, structural modifications were performed on the benzamide and aryl fragments, and their activity against the amastigote form of *T. cruzi* was evaluated. The modifications focused on reducing the lipophilicity of **initial hit 1** (expressed by its clogP value). However, most modifications resulted in the loss of potency, except for compound **11**, with modifications on the benzamide fragment. Although compound **11** exhibited increased cytotoxicity, its selectivity was acceptable, and its reduced clogP made it the chosen lead candidate.



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