Medicinal Chemistry

Title: Synthesis, Biological Evaluation and Molecular Docking of New Benzenesulfonylhydrazone as Potential anti-Trypanosoma cruzi Agents

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Author(s): Silvia Elizondo-Jimenez, Antonio Moreno-Herrera, Rogelio Reyes-Olivares, Edith Dorantes-Gonzalez, Benjamín Nogueda-Torres, Eduardo A. Gamosa de Oliveira, Nelilma C. Romeiro, Lidia M. Lima, Isidro Palos and Gildardo Rivera

Affiliation: Centro de Biotecnología Genómica, Instituto Politécnico Nacional, Boulevard del Maestro, s/n, Esq. Elias Pina, 88710, Reynosa

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Abstract: Background: Chagas disease is a public health problem caused by Trypanosoma cruzi. Cruzain is a pharmacological target for designing a new drug against this parasite. Hydrazone and Nacylhydrazone derivatives have been traditionally associated as potential Cruzain inhibitors. Additionally, benzenesulfonyl derivatives show trypanocidal activity. Therefore, in this study, the combination of both structures has been taken into account for drug design.

Methods: Seven benzenesulfonylhydrazone (BS-H) and seven N-propionyl benzenesulfonylhydrazone (BS-NAH) derivatives were synthetized and elucidated by infrared spectroscopy, nuclear magnetic resonance, and elemental analysis. All compounds were evaluated biologically in vitro against two strains of Trypanosoma cruzi (NINOA and INC-5), which are endemic in Mexico, and compared with the reference drugs nifurtimox and benznidazole. In order to gain insight into the putative molecular origin of the trypanocidal properties of these derivatives, docking studies were carried out with Cruzain.

Results: Compounds 4 and 6 (BS-H) and 10, 12-14 (BS-NAH) showed the best biological activity against NINOA and INC-5 strains, respectively. Compound 13 was the most potent trypanocidal compound showing a LC_{50} of 0.06 μM against INC-5 strain. However, compound 4 showed the best activity against both strains (LC_{50} <30 μM). Theoretical binding modes obtained suggested covalent binding that could explain their biological activity.

Conclusion: Benzenesulfonyl and N-propionyl benzenesulfonyl hydrazone derivatives are good options for developing new trypanocidal agents. Particularly, compound 4 could be considered a lead compound.

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