IDENTIFICATION OF POTENTIAL MOLECULAR TARGETS FOR NAPHTHOQUINONE-DERIVED COMPOUNDS IN COMBATING *TRYPANOSOMA CRUZI*

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Introduction

Chagas disease, caused by the parasite *Trypanosoma cruzi*, is primarily transmitted by triatomine insects and is prevalent in South America, leading to severe cardiac and gastrointestinal complications. Current treatments, nifurtimox and benznidazole, are effective in the acute phase, but their high toxicity and limited tolerance reduce their efficacy in the chronic phase, underscoring the need for new therapeutic options [1]. This project aims to identify novel molecular targets for naphthoquinone-derived compounds against *T. cruzi*, focusing specifically on four 1,4-naphthoquinone derivatives (C8, NSA15, NSA02, AN04) identified for their anti-inflammatory potential and possible toxic effects on the parasite [2]. Molecular modeling techniques were applied to optimize the structures of these compounds and evaluate their intermolecular interactions.

Material and Methods

The preparation and geometric optimization of the molecules using the Avogadro2 software, applying the MMFF94 force field and refinement with the PM7 method in the MOPAC2016 program. The Swiss Target Prediction server was employed to identify key classes of possible molecular targets. These proteins were cross-referenced in the UniProt database to select molecular targets specific to T. cruzi, which expanded the macromolecule library with 22 validated primary protein sequences. The Robetta server was employed for comparative modeling and 3D correction of the proteins. The comparative modeling results were verified with Ramachandran plots and QMEANDisCo scores [3], confirming that the 3D structures of the molecular targets are suitable for further analysis. Molecular docking was performed on all 22 protein models using the Molegro Virtual Docker program to evaluate the binding affinity between the naphthoquinone derivatives and the candidate targets.

Results and Discussion

Targets in *T. cruzi* were identified through target fishing technique, correlating them with homologous human proteins found in the parasite. Comparative modeling was applied to generate 22 protein models, which were validated using stereochemical criteria based on Ramachandran plots and QMEANDisCo score. All models were valid, with Ramachandran above 96%, indicating good quality. The trypanothione reductase (PDB ID: 1AOG), phosphoenolpyruvate carboxykinase (PEPCK) (PDB ID: 1II2), and arginine kinase (PDB ID: 2J1Q) were the targets with the highest affinities in molecular docking, with Ramachandran scores of 97.76%, 98.31%, and 98.97%, respectively. The ligands also showed highest affinities for targets in the transferase and protease classes, highlighting the relevance of exploring these molecular targets (Figure 1).

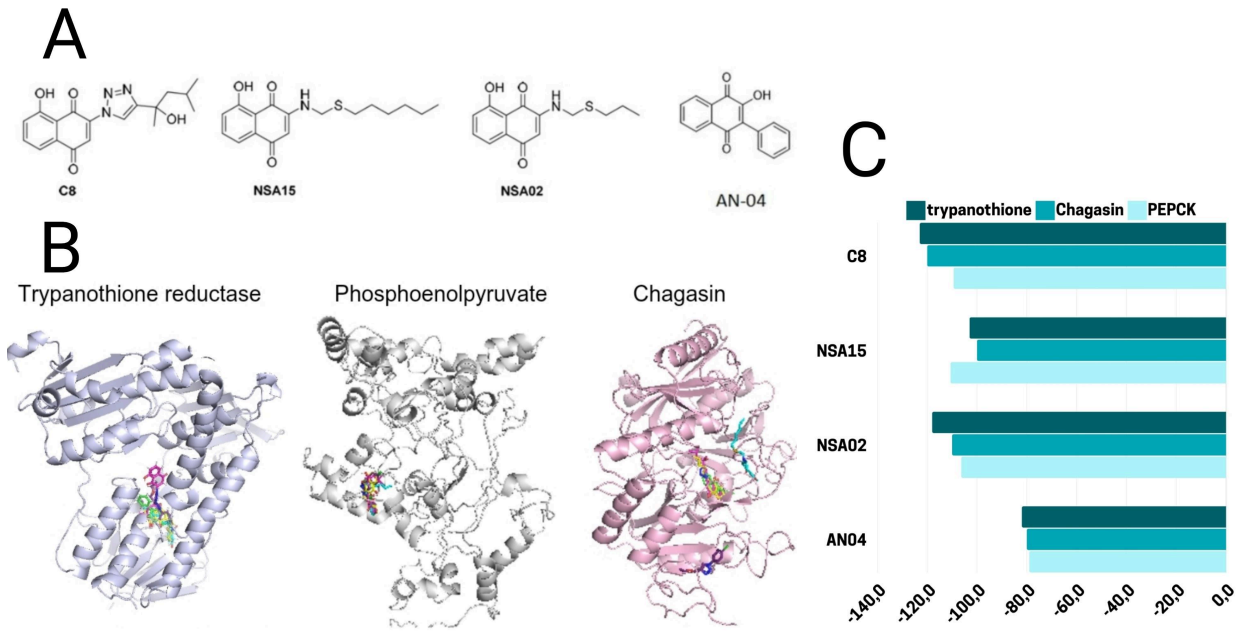

Figure 1. (**A)** Naphthoquinone-derived compounds. (**B)** Top 3 target complexes are represented in cartoon representation. (**C)** Rerank score of each complex (ligand and protein).

Conclusion

The results suggest that naphthoquinone-derived compounds, especially compound C8, have potential as promising inhibitors of *T. cruzi* targets, pointing to new therapeutic strategies for Chagas disease. The trypanothione reductase is the most promising target, with compound C8 identified as the best ligand. However, additional molecular dynamics studies are needed to confirm these interactions. The most promising targets will be investigated through in vitro assays, contributing to the development of new and effective drugs against the parasite that have low toxicity for the human.

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