Molecular Docking of Thiophene-Acridine Derivatives

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ABSTRACT

Background: In the therapy of neglected diseases, computational methods serve as predictive tools, analyzing multiple compounds against specific target proteins. These methods allow the selection of compounds based on their interaction potential, selectivity, and cellular activity. Consequently, molecular docking emerges as a predictive technique that simulates the interaction between drugs and receptor sites on macromolecules. **Objective:** This study aimed to investigate acridinic thiophene derivatives from the MAL series, with structural variations in the thiophene ring size (5CN, 6CN, and 7CN), evaluating their interactions with receptors of the pathogen Leishmania amazonensis. The study focused on two biological targets: trypanothione reductase (TR; PDB ID: 2JK6) and 14-dismethylase (CYP51; PDB ID: 3L4D). Methods: MAL series compounds were evaluated using predictive computational tools. Molecular docking was performed against the targets TR (PDB ID: 2JK6) and CYP51 (PDB ID: 3L4D), using AutoDock Tools 1.5.6. The results were validated through a redocking process. **Results and Discussion**: Redocking yielded a reference RMSD of 1.10 Å, indicating reliable results. Acridinic thiophene derivatives from the MAL series demonstrated negative binding energies when docked against TR, suggesting strong affinity and stability in complex formation with the protein. The binding energies for these compounds ranged from -9.77 to -12.04 kcal/mol, all showing superior interaction profiles compared to the co-crystallized ligand (flavin adenine dinucleotide, FAD). MAL1 had the lowest binding energy at -12.04 kcal/mol, indicating its potential as the most stable complex with TR. Regarding CYP51, the binding energies ranged from -10.88 to -9.61 kcal/mol, surpassing the interaction profile of fluconazole, the co-crystallized ligand, which had a binding energy of -7.2 kcal/mol. MAL1 also displayed the most stable binding within the active site of CYP51, with a binding energy of -11.39 kcal/mol. Overall, each compound in the MAL series showed improved interaction profiles compared to fluconazole, supporting MAL1 as a multitarget agent with stable interactions against both TR and CYP51. **Conclusion:** Among the tested compounds, MAL1 demonstrated a multitarget profile, showing efficacy against trypanothione reductase, a critical enzyme of Leishmania spp., which plays a role in oxidative stress management by eliminating peroxides and maintaining intracellular thiol levels. This strengthens the hypothesis of its direct action on the pathogen. For MAL3, its lack of activation or inhibition at the target sites is consistent with its known immunomodulatory role in macrophages, rather than a direct effect on the pathogen, as observed in previous studies.