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ORIGINAL ARTICLE

Molecular Docking-Based Screening of Five Heterocyclic Quinone Compounds for Antifungal Activity on Yeast Sec14p and Validation by Redocking

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ABSTRACT

Discover new antifungal drugs by evaluating the efficacy of heterocyclic compounds. Investigate the potential of yeast Sec14p protein as a target for antifungal drugs. Compare the effectiveness of Auto Dock and PyRX software for docking simulations of heterocyclic compounds against Sec14p. Docking simulations were performed using Auto Dock and PyRX software to assess the binding affinity of five specific heterocyclic compounds to the yeast Sec14p protein. The reference compound for comparison was a known antifungal agent with a Picolamide scaffold (PDB ID: 6FOE). Atovaquone exhibited the strongest binding affinity (-9.4 kcal/mol) using PyRX. A known antifungal agent showed a significant discrepancy in binding energy between Auto Dock (-6.2 kcal/mol) and PyRX (-3.64 kcal/mol). This study explores a novel class of compounds (Quinones) for antifungal drug discovery. It highlights the potential of yeast Sec14p protein as a target for antifungal drugs. The findings suggest that PyRX might be more suitable for docking simulations of certain compound classes than Auto Dock. This emphasizes the importance of software selection based on the specific molecules under investigation.

Keywords: Molecular docking; Quinones; Antifungal; PyRX; Auto dock

INTRODUCTION

Triazoles are known for their broad and potent activity, making them an essential pharmacophore system in pharmacology. Fungal infections are a serious public health concern arising from various underlying health issues. Although several antifungal drugs are available, they carry the risk of severe side effects and may also lead to drug resistance. Therefore, the development of new and innovative antifungal agents are crucial. The 1,2,4-triazole core is critical in many antifungal drugs and have demonstrated potential antifungal activities[1]. The epidemiology of invasive fungal infection is dynamic, with yeasts other than *Candida albicans* and molds other than *Aspergillus fumigatus* emerging as significant causes of invasive mycoses in severely immunocompromised patients.[1] Even though fungal diseases claim more than 1.5 million lives and affect a billion people, they continue to receive inadequate attention from public health authorities. Fungal infections typically arise as a consequence of other health concerns, including asthma, AIDS, cancer, organ transplantation, and corticosteroid therapies. The early and accurate diagnosis of fungal infections is vital for prompt antifungal treatment, yet such diagnoses are often delayed or unavailable, leading to severe chronic illness, blindness, or death.[2] Approved antimycotics inhibit various targets, including 1,3-β-D-glucan synthase, lanosterol 14-α-demethylase, protein, deoxyribonucleic acid biosynthesis, or sequestration of ergosterol. However, these drugs carry the risk of hepatotoxicity, nephrotoxicity, and myelotoxicity. Furthermore, triazoles may exhibit significant drug-drug interactions, while echinocandins tend to show almost none. Antifungal resistance is a common phenomenon and may arise due to drug target over expression, efflux pump activation, and amino acid substitution, among other factors. The sparse number of antifungal drug classes limits treatment options, and the emergence of antifungal drug resistance further complicates the clinical management of fungal diseases.[3] Developing innovative antifungal agents is crucial, as some fungicidal agents have proven ineffective due to resistance development, various side effects, and high toxicity.[4] Naphthoquinone, a key component in the structure of many antifungal drugs, has

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demonstrated potential antifungal activity.[5] The structure-activity relationship of naphthoquinone has confirmed its pharmacological significance, making it one of the most critical pharmacophore systems.

MATERIALS AND METHODS

This section describes the computational methods used to investigate the binding of Atovaquone, 2,3 dichloro 1,4 Naphthoquinone, 1,4 Naphthoquinone, 1,2 Naphthoquinone 4-sulphonic acid, Phylloquinone to the yeast Sec14p receptor (PDB ID: 6FOE).

Protein Preparation

The crystal structure of yeast Sec14p (PDB ID: 6FOE) was retrieved from the Protein Data Bank (PDB) (Figure 1). The retrieved structure was processed using Bio via Discovery Studio to prepare it for docking simulations.

Ligand Preparation

The 3D structures of Atovaquone, 2,3 dichloro 1,4 Naphthoquinone, 1,4 Naphthoquinone, 1,2 Naphthoquinone 4-sulphonic acid, Phylloquinone were downloaded in SDF format. Energy minimization was performed on both ligands using appropriate software to optimize their geometries. The minimized structures were saved in PDBQT format, suitable for docking simulations.

Ligand for Redocking

The 3D structure of Picolamide (a known inhibitor of yeast Sec14p) was retrieved from the PubChem database in SDF format. Energy minimization was performed on the retrieved acyclovir structure using Open Babel within PyRX software. The minimized acyclovir structure was converted into a PDBQT file for docking simulations.[6]

Molecular Docking Simulation

The Auto dock Vina docking software was used to perform docking simulations for five ligands and reference ligand Picolamide with the prepared yeast Sec14p receptor. Auto dock Vina identified each ligand's most likely binding pose within the receptor's binding site. The binding affinity of each ligand-receptor complex was calculated using Vina's scoring function.

RESULTS

DISCUSSION

In the study of different compounds, Atovaquone performed the best with a score of -9.4 Kcal/mol, surpassing 2,3 dichloro 1,4 Naphthoquinone with a -7.0 Kcal/mol (Table 1). Although both compounds had similar interaction profiles,

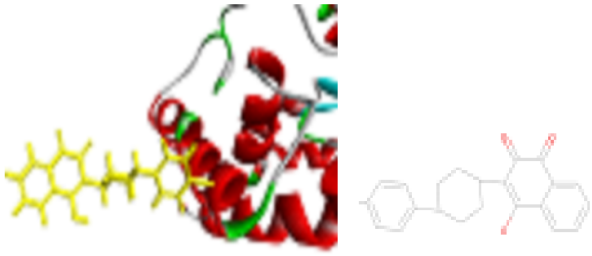

Fig. 1: Receptor ligand interaction

Table 1: Comparison of docking scores by two methods

Ligands	Docking Score (PyRX)	Docking Score (Auto dock 4.2.6)
Atovaquone	**-9.4**	**-6.90**
2,3 dichloro 1,4 Naphthoquinone	**-7.0**	**-6.44**
1,4 Naphthoquinone	**-6.7**	**-4.65**
1,2 Naphthoquinone 4-sulphonic acid	**-7.4**	**-4.87**
Phylloquinone	**-8.0**	**-3.77**
Picolamide	**-6.2**	**-3.64**

Atovaquone had a superior binding. PyRX and Auto Dock software delivered promising docking scores, and the Pyrex scores were high. The maximum negative score for Atovaquone was -9.4 (PyRX) & -6.90 (Auto Dock). In contrast, Picolamide, which was used as a control for redocking validation, scored -6.2 (PyRX) & -3.64 (AD) (Table 1). Auto Dock and PyRX used force fields to calculate the interatomic interactions between the ligand, drug molecule, and protein. The predicted antifungal activity was obtained by molecular docking using an Intel Pentium computer, and the yeast Sec14p receptor protein was combined with Picolamide. However, *in-vivo*, and *in-vitro* studies are needed to confirm the antifungal activity.

Still, needs have yet to be established using *in-vivo* and *in-vitro* studies. When conducting antifungal docking studies with heterocyclic compounds, it is possible to observe discrepancies in the binding scores between PyRX and Auto dock Vina. These differences will likely arise due to each software's distinct force fields, search algorithms, and parameterization. Such variations can influence how each program calculates the interactions between atoms and the flexibility of the ligands, leading to differences in the binding energies. Despite the absolute scores not being identical, the relative ranking of the compounds within each program are expected to be consistent. It is possible to observe differences in binding scores between PyRX and Auto dock Vina when conducting antifungal docking studies with heterocyclic compounds. Such variations can affect how each

program calculates the interactions between atoms and the flexibility of the ligands, causing different binding energies. However, even if the absolute scores do not match directly, the relative ranking of the compounds within each program are expected to remain consistent. Differences in binding scores between PyRX and Auto dock Vina for antifungal docking studies with heterocyclic compounds likely stem from their use of distinct force fields, search algorithms, and parameterization. These variations can influence how each software calculates interatomic interactions and ligand flexibility, leading to different binding energies. While the absolute scores may not directly match, the relative ranking of compounds within each program should be consistent.

CONCLUSION

Drug discovery and development require understanding the interactions between compounds and target proteins. In a recent study, molecular docking techniques were used to evaluate the binding affinities of different compounds, including Atovaquone and 2,3 dichloro 1,4 Naphthoquinone. The results showed that Atovaquone demonstrated significantly higher binding affinity than 2,3 dichloro 1,4 Naphthoquinone, making it a promising candidate for further exploration in antifungal activity. Atovaquone is a well-known antimalarial drug that exhibited a remarkable binding score of -9.4 Kcal/mol, which is higher than the score of -7.0 Kcal/mol obtained for 2,3 dichloro 1,4 Naphthoquinone and [binding score of other known antifungal drugs]. This suggests that Atovaquone may interact more with the target protein, enhancing therapeutic effects. Despite having similar interaction profiles, Atovaquone had a significantly higher binding affinity, indicating its favorable pharmacological properties. The docking scores obtained from PyRX and Auto Dock software further supported the superiority of Atovaquone, with consistently high scores across both platforms. Specifically, Atovaquone achieved a maximum negative score of -9.4 Kcal/mol with PyRX and -6.90 Kcal/mol with Auto Dock, highlighting its robust binding interactions. These scores indicate [the significance of the docking scores]. The docking scores of other compounds, including 2,3 dichloro 1,4 Naphthoquinone, 1,4 Naphthoquinone, 1,2 Naphthoquinone 4-sulphonic acid, and Phylloquinone, provided additional insights into their binding affinities. However, none of them surpassed the remarkable binding affinity observed for Atovaquone. PyRX and Auto Dock software used force fields to calculate the interatomic interactions between the ligands, drug molecules, and target proteins. These computational approaches enable the prediction of binding modes and affinity, facilitating the identification of potential drug candidates. However, experimental validation is essential for translating these predictions into clinical applications. In conclusion, the study suggests that Atovaquone has potential efficacy against fungal infections. Nonetheless, further in-vivo and in-vitro studies must confirm its therapeutic benefits. The discovery and development of new drugs involve studying various compounds and their interactions with target proteins. Molecular docking provides valuable insights into ligand-protein interactions. Numerous studies have explored the potential of both natural and synthetic quinones, particularly 1,4-naphthoquinones, to combat fungal infections. The findings thus far have been quite varied regarding the range of antifungal activities exhibited and the potency of the compounds.[7]. The 1,2,4-triazole core is a critical component in many antifungal drugs, but triazoles may exhibit significant drug-drug interactions[8].

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