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Short communication

Molecular docking study as approach for development of new targeted therapies targeting Aryl hydrocarbon receptor (AhR)

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Introduction

Molecular docking has emerged as a powerful computational strategy in modern drug discovery, enabling the prediction of interactions between small molecules and biological targets with increasing precision and efficiency (Sahoo et al., 2022). Among the diverse targets explored for therapeutic intervention, the aryl hydrocarbon receptor (AhR) has gained significant attention due to its critical role in regulating xenobiotic metabolism and toxicity, immune responses, and cellular proliferation. Dysregulation of AhR signaling has been implicated in various pathological conditions, including cancer, autoimmune disorders, and environmental toxicity, making it a promising target for the development of novel targeted therapies (Gutiérrez-Vázquez and Quintana, 2018; Safe et al., 2017).

In this context, molecular docking studies provide valuable insights into the binding affinities, structural conformations, and interaction mechanisms of potential ligands with the AhR protein. By simulating ligand–receptor interactions at the molecular level, researchers can efficiently screen and optimize compounds with high specificity and efficacy, thereby reducing the time and cost associated with experimental approaches. This study aims to utilize molecular docking techniques to identify and characterize potential AhR modulators, contributing to the rational design of innovative therapeutic agents targeting AhR-mediated pathways.

Materials and methods

A previously reported receptor model was obtained from the Protein Data Bank (PDB ID: 5NJ8) (https://www.rcsb.org/structure/5NJ8). Selected ligand structures were retrieved in MOL format from the MolView database (https://molview.org/). Both ligands and receptor structures were prepared and optimized for docking using AutoDock Tools (Morris et al., 2008). Docking simulations were carried out with the CB-Dock2 web server (https://cadd.labshare.cn/cb-dock2/index.php), which employs AutoDock Vina.

Results and discussion

In this work, molecular docking simulations were utilized to investigate the interactions between AhR and selected AhR antagonists (CH223191, BAY 2416964, and GNF-351) within the ligand-binding domain, with a particular focus on the canonical

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PAS-B region. The docking results highlighted the PAS-B cavity (pocket C1) as the most biologically relevant binding site for high-affinity ligands, in agreement with existing experimental findings (Bisson et al., 2009). Comparative analysis of established AhR antagonists demonstrated stable binding conformations, primarily driven by hydrophobic interactions, π–π stacking, and hydrogen-bonding networks, which collectively inhibit agonist binding and subsequently block receptor activation (Vuckovski and Gjorgieva Ackova, 2026).

Conclusion

These results reinforce the concept that competitive antagonism represents an effective strategy for mitigating xenobiotic-induced AhR signaling. Overall, this *in silico* investigation offers detailed molecular-level insight into the potential of AhR antagonists as a promising avenue for developing targeted treatments for AhR-associated diseases.

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