UDC 541.49

The Impact of Lipophilicity on Protein-Ligand Binding: Integrating In Silico Simulations and Atomic Force Microscopy for Drug Discovery

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Introduction

The optimization of drug discovery requires a deep understanding of the physicochemical properties that influence protein-ligand interactions [1]. One of the most critical parameters is the partition coefficient (logP), which determines a compound's lipophilicity and significantly affects its pharmacokinetic and pharmacodynamic properties. Lipophilicity plays a crucial role in drug absorption, membrane permeability, bioavailability, and, most importantly, binding affinity to target proteins [2].

By employing in silico approaches, such as molecular docking and molecular dynamics simulations, researchers can predict how lipophilicity influences ligand binding at the molecular level [3]. Complementary to this, AFM provides an experimental method for directly measuring the binding forces between proteins and ligands, offering insights into molecular interactions under physiological conditions [4].

The combination of computational and experimental techniques allows for a more precise evaluation of drug candidates, helping to identify promising compounds with optimal binding characteristics. This integrative approach not only enhances drug discovery efficiency but also provides a fundamental understanding of the relationship between partition coefficient and protein-ligand interactions, ultimately aiding in the development of more selective and potent therapeutics.

Methodology

The research began by obtaining two hydrophobic compounds from the PubChem database: fluorescein, with a low hydrophobic value, and rhodamine B, with a moderate hydrophobic value. Additionally, the bovine serum albumin (BSA) receptor (PDB ID: 4F5S) was obtained from the Protein Data Bank. These two compounds were docked to drug site I (IIA) of BSA, with the grid center coordinates set at x = -0.333 Å, y = 25.794 Å, and z = 108.281 Å, and the grid size set to 35, 35, and 23 for x, y, and z, respectively.

Before docking, polar hydrogen atoms and Kollman charges were assigned to the protein using the AutoDock4 algorithm. Molecular dynamics simulations provided insights into the protein-ligand interactions over 100 nanoseconds. Additionally, AFM was used to investigate the binding interactions.

The results show that fluorescein, with a lower logP value, exhibits low binding affinity with BSA, while rhodamine B, with higher lipophilicity, displays high binding affinity. This pattern was also observed using AFM.

Conclusions

This study highlights the implications of lipophilicity on the binding affinity of protein-ligand interactions. It is evident from the study that a low logP value correlates with low binding affinity, while a high logP value correlates with higher binding affinity. Thus, additional spectroscopic methods could be employed for further investigation.

References

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