Investigating the Binding Interactions of Small-Molecule Inhibitors to PLKs Using Molecular Dynamics Simulations

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Protein kinases are important anticancer drug targets due to their crucial role in regulating key biochemical and cellular processes. Polo-like kinase 1 (PLK-1) is a key regulatory marker for the cell cycle and is overexpressed in various types of human cancer. PLK-1 inhibition has been shown to induce cancerous cells in mitotic arrest and induce apoptosis in cancerous cells. Therefore, PLK-1 inhibition is of critical importance particularly for metastatic cancer and for tumors with acquired resistance to earlier targeted therapies and/or endocrine therapies. The researcher's overarching goal is to study the binding of top-identified small-molecule inhibitors of the polo-box domain (PBD) of PLK-1. The researcher set up a molecular dynamics simulation protocol that involves an initial normal-mode-based sampling and calculation of PMF for certain ligand-protein parameters. The researcher selected four small molecules with known binding profiles (IC50 and Kd values). Protein-ligand interactions between PLK-1 and each of these molecules were studied with molecular docking (using CBDock) and molecular dynamics simulations (using VMD and NAMD). The resulting trajectories were analyzed to reveal RMSD, RMSF, total interaction energies, hydrogen binding profiles, SASA changes over time, as well as their binding profiles. These analyses will yield insight into the stability of these protein-ligand complexes. Preliminary results suggest that all 4 small molecules tested are good inhibitors of PLK-1. These results suggest all compounds should be explored for further development. Further analysis of more molecules and longer simulation run times are required to determine the most potent inhibitors of PLK-1.

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