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Is Discrete Incremental Meta Docking (DIMD) the Key to Success in Molecular Docking-based Drug Discovery? A comparison of the Results of the Novel Vinca Derivative VADRPA01

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Determining the crystal structure of vinca-site inhibitors in complex with the tubulin heterodimer is crucial for understanding binding modes and guiding the design of novel microtubule inhibitors targeting the vinca binding domain. However, the lack of a universally validated methodology for dataset preparation and protein-ligand validation complicates the comparison and reproduction of docking results. The present study addresses this issue by evaluating the molecular docking results using the Discrete Incremental Meta Docking (DIMD) technique. The DIMD method facilitated the identification of the best docking pose for a novel vinblastine derivative, VADRPA01, with a binding affinity of -15.416 kcal/mol (a 47.74% enhancement) and an inhibition constant of 0.0051 nM, compared to its best rigid docking pose (-10.8 kcal/mol) obtained through a general docking procedure. Crystallized water at the vinca binding site of the native vinblastine-5J2T (tubulin) complex was found to stabilize VADRPA01 within the binding domain. Molecular dynamics studies revealed that flexible amino acid residues in the receptor binding pocket contributed to the reduction of binding energy by forming hydrogen bonds with PHE351, LYS336, ALA333, and ASN329 on the alpha chain of the tubulin heterodimer. Additionally, the calculated protein-ligand binding affinities using MMPB(GB)SA indicated a total binding energy of -27.15 kcal/mol, confirming the stability of the 5J2T-VADRPA01 complex. The optimal docking pose of VADRPA01, derived from the hydrated flexible docking procedure, showed an RMSD of 1.5020 Å compared to the native vinblastine-5J2T complex. These advancements in the docking procedure have identified the most favorable docking pose for VADRPA01, supporting further drug discovery studies of vinca derivatives.

Keywords: *vinca alkaloids, molecular docking, tubulin, DIMD, drug discovery, gmxMMPBSA*