Computational Identification of Novel Endocan Inhibitors for Targeted Glioblastoma Therapy Through Molecular Docking and ADMET Analysis

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Glioblastoma multiforme (GBM) is a highly aggressive and vascularized brain tumor with poor prognosis and limited therapeutic options. Endocan (ESM1), a tumor-associated endothelial proteoglycan overexpressed in glioblastoma vasculature, promotes angiogenesis and tumor progression, making it a promising therapeutic target. This study aimed to identify novel small-molecule inhibitors of endocan using an integrated computational docking and fragment-based drug design approach. The amino acid sequence of endocan was retrieved from UniProt and used to generate a three-dimensional protein structure with AlphaFold 3, followed by structural preparation in AutoDock Tools. Candidate compounds were obtained from the ZINC20 database and subjected to virtual screening using AutoDock Vina through automated workflows. Docked complexes were analyzed using PyMOL, LigPlot, and PLIP to characterize hydrogen bonds, hydrophobic contacts, and p-based interactions, while binding energies and complex stability were estimated using PRODIGY. Among the screened ligands, compound 1249 demonstrated one of the strongest and most stable interaction profiles and was selected as the core scaffold for fragment-based drug design. Optimization of this scaffold led to the development of FBDD1, FBDD2, and FBDD3, which exhibited binding energies of -5.89, -4.93, and -5.48 kcal/mol, respectively, and showed enhanced interaction networks within the predicted binding pocket. ADMET properties were evaluated using SwissADME, indicating favorable drug-likeness and predicted blood-brain barrier permeability for top candidates. These findings identify optimized endocan inhibitors and provide a computational foundation for future molecular dynamics simulations and experimental validation in glioblastoma models.

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