EZ-CDD: Computational Drug Discovery and Design of EZH2 Inhibitors for Glioblastoma Multiforme Large-Scale Virtual Screening, Rational Optimization, Fragment-Based Design

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Glioblastoma Multiforme is the most common aggressive brain tumor and is difficult to treat due to its invasive growth, tumor heterogeneity, and blood-brain barrier. EZH2, an epigenetic regulator enzyme, plays a key role in regulating gene expression and is located mainly in the cell nucleus where it functions as part of a larger protein complex PRC2. Studies show that the catalyst subunit of PRC2 contributes to gene slicing through H3k27 methylation and is linked to GBM stem cell maintenance and therapy resistance. This makes EZH2 a promising target. My study aimed to identify small molecules that inhibit EZH2 activity using computational modelling. Obtained the EZH2 sequence from UniProt and predicted the protein structure using AlphaFold. The protein was prepared for docking by adding polar hydrogens and Kollam charges and saved as PDBQT for AutoDock Vina virtual screening. My library consists of 5229 small molecule compounds from Zinc20 and was organized into folders and screened using AutoDock Vina workflows. Selected 5 small molecules (M275, M179, M295, M400, M332) with most electro negativity (<= -8.5 kcal/mol) and filtered these molecules for drug properties GI absorption and BBB permeability using SwissADME. Protein-ligand interactions were determined with PLIP and binding affinity was estimated using PRODIGY-LIG. Lead optimization was done by chemical alterations using CReM and fragment-based replacement using FragRep and then redocking. Analyzed MD simulations using RMSD to check the complex stability and RMSF for residue-level flexibility. By combing docking with extra validations, pharmacokinetic filters, interaction/affinity profiling, optimization, and MD checks, the workflow produced stable, CNS-relevant EZH2 candidates for GBM therapeutic research.

Awards Won:

Zydus Pharmaceuticals USA Inc.: First Place Computational Biology and Bioinformatics