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In Silico Discovery of Novel Compounds for FAK Activation Using Virtual Screening, AI-Based Prediction, and Molecular Dynamics

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Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase that plays a crucial role in cell proliferation, migration, and signal transduction. FAK is overexpressed in metastatic and advanced-stage cancers, where it is considered a key kinase in cancer growth and metastasis. However, recent research has revealed that FAK activity decreases in various diseases. we aimed to identify compounds that could enhance FAK activity using structure-based virtual screening and artificial intelligence models from a vast chemical database. We began with an extensive chemical database containing over 10 million compounds and used our newly developed pipeline to screen candidate molecules. To select compounds structurally similar to ZINC40099027 (ZN27), a known FAK activator, we calculated Tanimoto Similarity scores and chose compounds with a score of at least 0.8. Clustering was performed using K-means based on the molecular properties. This process reduced the number of compounds for physicochemical characterization to 70,244. Subsequently, we utilized docking simulation, deep learning and SAScorer to evaluate and predict the protein-ligand docking affinity and physicochemical properties of the candidate compounds. The deep learning models were selected as state-of-the-art models: GLAM predicts the blood-brain barrier permeability of FAK, and elEmBERT predicts the potential toxicity of compound. The combined results were used to create an evaluation matrix. we selected 10 promising candidate compounds from the initial dataset of 10 million. To evaluate the stability of these top 10 candidate compounds in interaction with the FAK protein, we conducted Molecular Dynamics (MD) simulations. We performed a molecular dynamics simulation for a total of 50 ns and identified the top three promising candidate compounds.