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An integrative ligand-based pharmacophore modelling, virtual screening, and molecular docking simulation approaches identified potential lead compounds against pancreatic cancer by targeting FAK1

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Pancreatic cancer is a deadly disease with a 5-year survival rate, making it one of the leading causes of cancer-related deaths globally. Focal adhesion kinase 1 (FAK1) is a ubiquitously expressed protein in pancreatic cancer. FAK, a tyrosine kinase that is overexpressed in cancer cells, is crucial for the development of tumours into malignant phenotypes. FAK functions in response to extracellular signals by triggering transmembrane receptor signalling, which enhances focal adhesion turnover, cell adhesion, cell migration, and gene expression. Until now, no effective drug candidates have been developed that can block the progression of the cancer caused by the FAK1. Therefore, the study aimed to identify potential drug candidates from the purchasable and natural compounds library, which will be able to block the c progression of cancer by inhibiting the activity of the FAK1. Initially, ligand-based pharmacophore approaches were applied to create a top ten best models. The best one model was utilized for the pharmacophore modelling and validation, pharmacophore-based virtual screening, virtual hit profiling, molecular docking, MD simulation, MM/GBSA and lead identification. Following the retrieval of twenty hits, four compounds were selected for further evaluation based on a molecular docking approach. Four newly discovered compounds, including Pubchem CID24601203, CID1893370, CID16355541, and CID16467343 with binding scores of -10.4, -10.1, -9.7, and -9.5 kcal/mol, respectively, may serve as lead compounds for the treatment of pancreatic cancer associated with FAK1. The ADME (Absorption, distribution, metabolism, and excretion) and toxicity analyses demonstrated that the compounds were effective and nontoxic. However, further evaluation through a wet lab is needed to determine the compounds' effectiveness. Keywords: Pancreatic cancer; FAK1 protein; Ligand-based pharmacophore drug design; purchasable compounds; molecular docking; ADMET; MD simulation; MM/GBSA

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