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Molecular Docking, PASS Prediction, Pharmacokinetic and Toxicity studies of Focal Adhesion Kinase Inhibitors

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

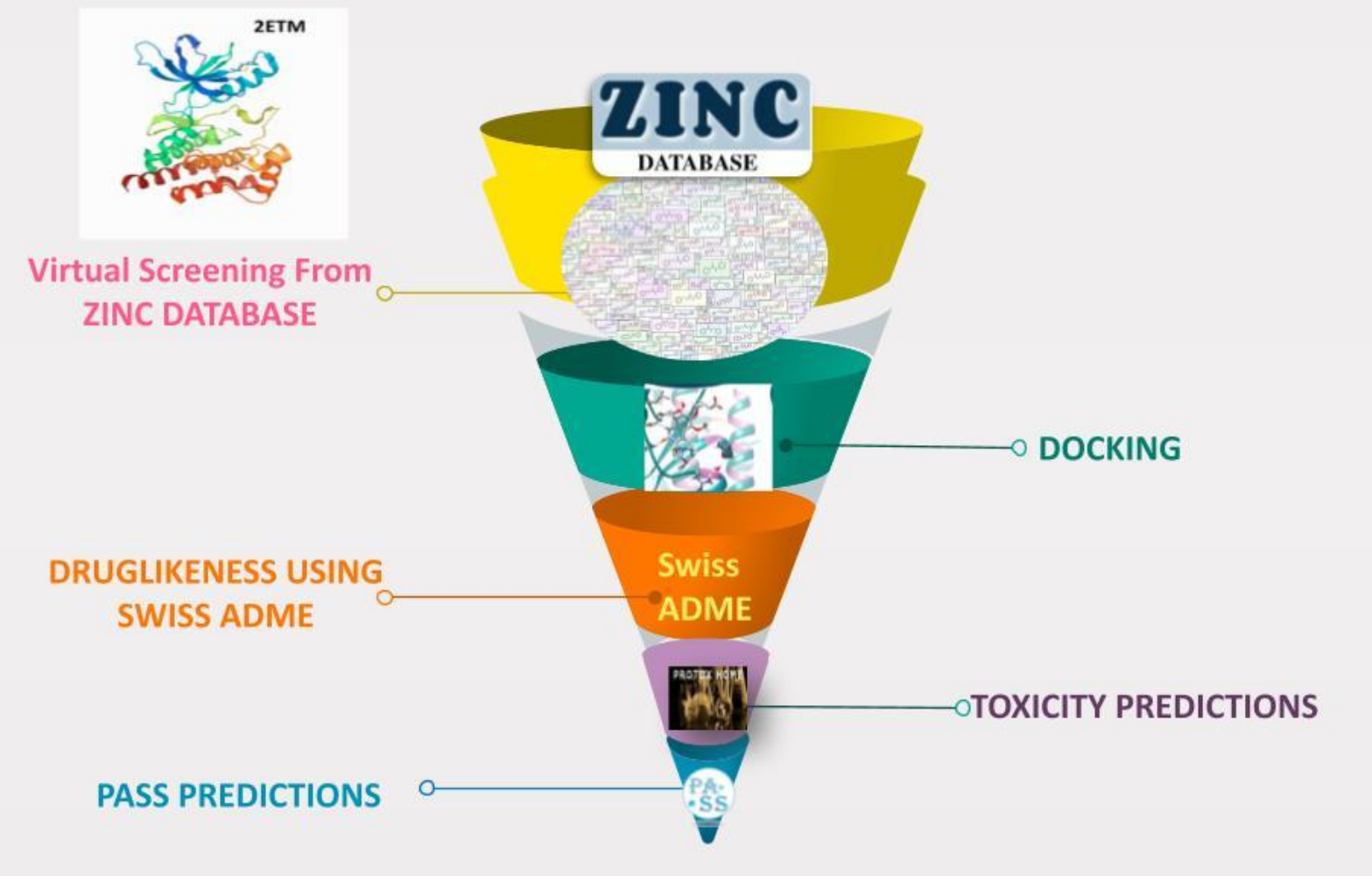
pharmaceuticals MDPI

Sahaya Nadar [1,*], Tabassum Khan [1]

[1] Dept of Pharmaceutical Chemistry, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle, Mumbai

* Corresponding author:sahaya1408@gmail.com

GRAPHICAL ABSTRACT



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Abstract:

Drug discovery relies on computational medicinal chemistry for designing and identifying new drug-like chemicals, predicting properties and pharmacological activities of molecules, and optimizing lead structures. Focal Adhesion Kinase (FAK) is an emerging target for cancer chemotherapy with mounting evidence that FAK activation or elevated expression is associated with cancer progression, invasion, and drug resistance. This work envisages identification and in silico screening of potential FAK inhibitors which could further be evaluated. A total of 862 compounds were screened from the ZINC database and docked on the refined FAK enzyme using Autodock Vina. The best spotted hits were filtered for their druglikeness using SwissADME. These potential hits were further evaluated for their in silico toxicity using ProTox II software. Promiscuous hits identified by the docking score and applying Lipinski's Rule of five were ZINC43200601, ZINC95593660 and ZINC95595125. These hits showed high binding scores and passed the colander of in silico pharmacokinetic and toxicity proving these ligands propitious to be further evaluated. For selecting the Activity Spectra for Substances PASS program was used to screen the anticancer potential of the compound. The hits displayed antitumor profile.

Keywords: Focal Adhesion kinase, PASS, docking, toxicity

Introduction

‘Cancer’ - 277 different types of cancer disease characterized by the abnormal growth of cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs. As per The Indian Council of Medical Research (ICMR), it was estimated to have about 13.9 lakhs cancer cases in 2020 which is likely to increase to 15.7 lakhs by 2025, based on current trends
Kinases are a vital group of enzymes that aid to maintain cell regulation by activating various signal transduction pathways. The most prominent group of kinases are protein kinases that phosphorylate serine threonine or tyrosine residues and play a key role in cell growth and protein regulation in various cancer pathways. Focal Adhesion kinase (FAK) is selected as potential target in this project .

Studies have suggested the importance of FAK in cancer cell adhesion, motility, proliferation, and survival and is over-expressed in cancer cells.
There are several patents on FAK inhibitors that could be utilized to map out FAK inhibitors as new chemical entities.

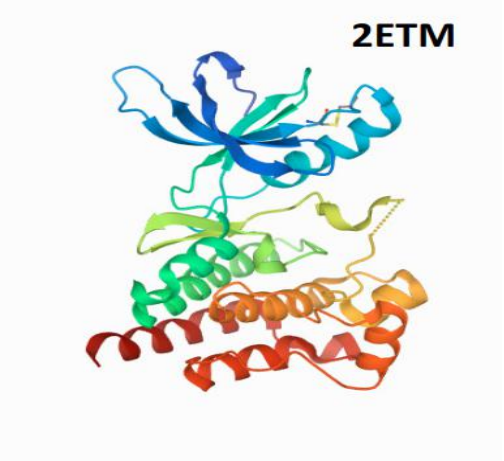
Results and discussion

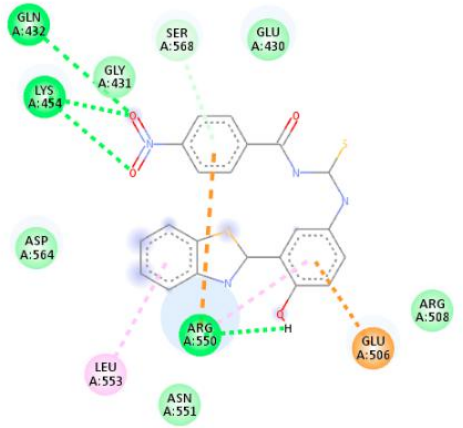
MGLTOOLS suite and Autodock tools were used subsequently to convert the receptor and ligands to PDBQT format.

Autodock Vina in PyRx 0.8 (Virtual Screening Tool) was used to dock all the selected ligand against the active site of 2ETM using a grid with dimensions of (24×24×24)

Parameters of the top ranked 50 compounds were then saved in a separate database.

Ligand- protein interaction





Results and discussion

ADME and Toxicity Prediction

To reduce the set of ligands Lipinski's Rule of five were set as a criteria to label the drug-like properties of the selected compounds.

Lipinski's rule of five states that a molecule having drug properties must have :

- molecular weight less than 500 kDa
- hydrogen bond acceptor atoms (HBA) less than 10
- hydrogen bond donor atoms (HBD) less than five and
- value of log P should be less than five

Lipinski's Rule of five was applied on the best hits identified through molecular docking studies to find their drug-likeness using **SwissADME.**

Results and discussion

Table 1: Binding affinities, Zinc compound IDs, Lipinski's Rule of five and the LD50 of the top ten ligands obtained from virtual screening are listed in the table below.

CompoundID	Binding Affinity(kcal/mol)	Lipinski's Rule of five					Predicted LD50
		MW (g/mol)	HBA	HBD	nRB	xLogP	
ZINC95595125	-9.6	385.39	6	3	5	4.81	200 mg/kg
ZINC43200601	-9.5	504.6	9	2	7	5	1000 mg/kg
ZINC73223145	-9.4	504.6	9	2	7	5	1000 mg/kg
ZINC73223148	-9.3	381.41	26	2	6	3.71	2000 mg/kg
ZINC73220041	-9.2	381.415	8	2	6	3.04	2000 mg/kg

Results and discussion

CompoundID	Binding Affinity(kcal/mol)	Lipinski's Rule of five					Predicted LD50
		MW (g/mol)	HBA	HBD	nRB	xLogP	
ZINC95593660	-9	494.474	8	2	7	3.4	135mg/kg
ZINC40395224	-9	399.376	6	3	6	3.74	1000mg/kg
ZINC36348818	-9	471.501	11	1	9	3.43	1000mg/kg
ZINC40896825	-8.9	385.353	7	3	6	3.08	1000mg/kg
ZINC40896425	-8.9	400.364	7	3	6	2.56	1000mg/kg

Results and discussion

In silico prediction using PASS

The biological activity spectra of ZINC95593660 and ZINC95595125 was determined by using an online version of PASS software.
Calculations using PASS software have been used extensively to confirm and correlate biological activities of chemicals
The calculation results suggest that ZINC95593660 (Pa,0.888) and ZINC95595125 (Pa, 0.585) are Focal adhesion kinase inhibitors.

Conclusions

Our analysis resulted in identifying four hits, compounds ZINC43200601 and ZINC95595125 which exhibited good binding score along with passing the ADMET evaluations making these ligands a primary choice to be tested experimentally.