Abstract:

Background: Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.(Brown et al., 2023) Cancer interrupts normal bodily functions and causes pain, organ failure, and syndromes such as cachexia. It also spreads quickly and uses resources and produces metabolites, disrupts tissue, and coopts normal noncancerous cells.

Objective: investigate the reduction of anti-her2 resistance in breast cancer by eliminating the steric clashes at the orthostatic site in mutant her2^{t798i}

Methods: Computational methodologies and modeling software was used to generate data and guide decisions in designing different flexible lapatinib analogs to avoid the steric clashes generated at the binding site by using maestro software to prepare and dock for ligand and protein. The next step is to assign pose ligand by Molecular Dynamics (MD) Simulations, and monitoring pharmacokinetics by Swiss ADME.

Results and conclusion: It was concluded that among the screened compounds, ten compounds showed better docking scores compared to the reference drug. Compound **856174** (Docking Score -9.921 kcal/mol). H-bonds with the receptor residues of THR 862 and methionine 801(98%), LEU 753 and SER 783(50%) by water bridge and hydrophobic bonds. In addition to hydrophobic bonds with LEU 726, ALA 751, LEU 785 along with favorable physicochemical properties, such as moderate solubility, molecular weight of less than 500 Da, and TPSA of 99.37. Furthermore, this candidate compound exhibited lower hepato- toxicity (inactive), had an average number of rotatable bonds 8, LD50 10000 mg/kg, lead likeness 3, PAINS 0 and high GI absorption, with no BBB penetration, H bound accept 7 with 1 donor, clog p 3.29 and stable in protein.