Abstract

Cancer represents a multifaceted challenge on a global scale, encompassing clinical, financial, and social realms. Among cancers, breast cancer (BC) stands out as the most prevalent worldwide, posing a significant threat to women's health. Alarmingly, nearly 500,000 patients worldwide die from metastatic BC annually. The HER2 kinase is a pivotal target in combating resistant BC. Despite the approval of Lapatinib in 2007, the rapid development of drug resistance ensued, primarily attributed to a mutation occurring at the gatekeeper HER2T798I residue. Herein, we attempted to identify novel rational approaches to design new therapy to overcome the resistance in HER2T798I kinase domine using *in sillico* approaches. Herein, we endeavor to propose rational approaches for designing therapeutic interventions aimed at overcoming resistance mediated through the HER2T798I kinase mutation, employing advanced in silico techniques.

We identified four potential allosteric sites located on the surface and within cavities of the HER2 kinase. Subsequently, we screened a database comprising 26,000 potential kinase allosteric modulators using High Throughput virtual Screening (HTVS), followed by docking standard precision against the newly identified allosteric sites. The best compound at each allosteric site underwent molecular dynamic simulations (MDS) to observe the results of the RMSD analysis at 1000ns. For the stable ligands in sites B and D, we had increased the simulation time to 5000 ns in the presence of TAK-285 in the orthosteric site, mentoring behaviors TAK-285 in the orthosteric site, and we found TAK-285 more stable with allosteric site D. Unlike in case allosteric site B with ortho steric site. The impact of the best-docked hits “allosteric modulators” within the potential allosteric site(s) on the conformation of the orthosteric (ATP binding) site was investigated. These findings hold promise for the discovery of a novel therapy for aggressive, resistant BC, featuring a novel mechanism of action with potentially fewer off-target side effects. These outcomes are promising in finding a new treatment for BC with a novel mechanism of action.

Key words: Breast Cancer, Lapatinib, HER2 kinase, docking, MDS