Abstract

Introduction and Goal: The HSP90 molecular chaperone has emerged as one of the most exciting targets for cancer drug development. HSP90 is overexpressed in many malignancies, very likely as a result of the stress that is induced both by the hostile cancer microenvironment and also by the mutation and abberant expression of oncoproteins.

Materials and Methods: In this project, HSP90 inhibitors introduced into different phases of clinical trials and the reported compounds of HSP90 inhibitor were considered as the primary molecules of this study. Next, the chemical structure of the selected ligands was obtained by using the Zinc15 database and also based on literature review. Then, Genetic algorithm of AutoDock version 4.2 with incorporated MGL tools-1.5.6 was applied to elucidate the most probable binding interactions (to prioritized in terms of qualitative and quantitative analysis of the results in terms of receptor binding pattern) of the proposed ligands within active sites of selected HSP90 targets. In order to evaluate the stability of the observed interaction patterns, the superior molecules entered the molecular dynamics simulation stage by docking ensemble method and for this purpose 40 HSP90 files were considered using PDB database. In the next phase of this study, docked molecules were subjected to amino acid decomposition analysis via the DFT method by Gaussian 09 program to discover the structure binding relationship for proposing hypothetical pharmacophores with optimal binding modes/energies to HSP90.

Results: inertpreation of the molecular docking results elucidated that ligands with codes **15**, **19**, **20** and **30** had the ability to show high binding free energy with many induced forms of protein. Also, the results of intermolecular interaction analysis via quantum mechanical method at the ligand-amino acid level on selected complexes obtained from docking Ensemble showed that hydrogen bonding is very important in contrast to active site hydrophobic interactions, as well as Asn51, Gly97, Asp102 and Tyr139 are key residues in interaction with HSP90.

Discussion and conclusion: Due to the results of intermolecular interaction analysis at the ligand-amino acid level and finally based on the structure binding relationship, two hypothetical pharmacophores were presented according to the active site of **4NH8** receptor and the chemical structure of molecule **30**, in which the presence of hydrogen bond, ion bridge and π-π interaction between some of the ligand atoms and amino acids of the active site of the receptor were important to have a more stable complex and a stronger binding mode.

Key words: cancer, HSP90 inhibitors, molecular docking, induced fit, DFT calculation