Abstract

Introduction: Cancer is one of the most important diseases in the world that imposes a high cost on the health system. Despite the developing of new medicines, the progressive resistance of cancer cells to medicines is a major problem that reduces the therapeutic response. Among the medicines that are widely used in the treatment of cancer, Camptothecin analogues are highly useful. Their mechanism is to inhibit Topoisomerase I enzyme. This enzyme is responsible for relaxing super coiled DNA during replication and transcription. Therefore, the development of compounds that can inhibit mutant forms of topoisomerase I enzyme is noteworthy.

Method and Material: In this project, the 3D structure of Topoisomerase I was selected from PDB site with code of 1K4T. The clinical mutations reported in articles were generated by Missense 3D server using wild type form of Top I enzyme. The mutant forms were checked for stability by Dynamut server. The stable mutant forms of Top I were subjected to molecular docking study with topotecan and belotecan by Autodock 4.2 software. Mutant forms that had more positive binding energy than wildtype form of Top I were selected as mutations with the ability to produce drug resistance. In the next step ligands with the possibility of binding to the mutant forms were designed based on SAR of reported compounds in articles and protein data bank (PDB). Their drug-likeness were checked by SwissADME server. Designed compounds were subjected to molecular docking study on mutant and wildtype forms of Top I and the best ligand with higher binding ability to mutant forms was selected. In the final phase of study, the binding energy at level of ligand-residue was calculated using density functional theory (DFT) method by Gaussian 09 software.

Results: In bioinformatic analysis of clinical mutation, three mutant forms including D533G, E710G and E418K were estimated as stable mutations. A set of 40 belotecan and topotecan derivatives were designed based on the SAR of valid compounds. Compound P2a was recognized as the compound with the ability to achieve higher binding energy in all mutant forms. Based on the calculations, Gibbs free binding energies were obtained as -5.84, -5.94, -5.94 and -5.76 kcal/mol in the interaction with mutant forms D533G, E710G, E418K and wildtype of Top I, respectively. The interaction pattern of P2a, which was a derivative with 7-aryliminomethyl group, indicated the establishment of two stable π-cation interaction between Arg364 and quinoline rings. In addition, P2a established stable hydrogen interactions with Asn352, Asn722, Thr718 and Tyr426 residues.

Discussion and conclusion: incorporation of 10-flouro, 9-hydroxy and 7-aryliminomethy groups in CPT structure in P2a compound, resulted in overcoming drug resistance in mutant forms of Topoisomerase I. Based on interaction pattern observation, Arg364 residue has reduced its distance with P2a in binding site of Top I to establish a stable hydrogen bond with 9-hydroxy group. This conformational change has caused the distance between Arg364 and quinoline rings to be reduced to less than 5 Å and provides the situation for forming stable π-cation interaction. The results of this study show the high potential of P2a in binding to reported clinical mutant forms of Top I.

Key words: Topoisomerase I, Camptothecin, Molecular docking, Density functional theory, Mutation