Molecular Modelling Studies on Farnesyltransferase Inhibitors

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Farnesyltransferase (FTase) is one of the targets in the development of potential anticancer drugs. Recently, it could be an effective target for drug development against Progeria and parasites diseases such as *P. falciparum* resistant malaria, trypanosomatid infections (African sleeping sickness), Chagas disease, Toxoplasmosis and Leishmaniasis and as antiviral agents [1,2]. In the present investigation, we have performed docking and molecular dynamic (MD) simulation on different FTase enzymes (with and without the farnesyl pyrophosphate (FPP) substrate). In addition, protein ligand interaction fingerprint (PLIF) analysis was performed on different docked conformations of a data set of natural products. The zinc ion in the FTase makes coordination bonding with residues such as Asp297, Cyp299 and His362 in B chain. The MD simulation performed on 10 ns showed that the drug complex is stable.

The docking analysis revealed that the positively charged groups on the active site of the enzyme or receptor (possibly the Arg202β amino acid residue and the Zn^{2+} ion), form hydrogen bonds with negatively charged groups (keto, hydroxyl, amino and heterocyclic rings) in their structures. The aromatic rings present in the natural product compounds have make pi-pi interaction with the aromatic amino acids (Tyr363, Tyr302 and Trp305 (without FPP) and Tyr361, Trp303 and Tyr300 (presence of FPP)).

These analyses highlighted that Chaetomellic acid A and B, Zaragonic acid, Arteminolide, etc have better inhibitory activities and bind significantly to the active site [1,3]. The PLIF analysis also confirms that the binding modes of the studied compounds are follows the same pattern as the compound in the PDB structure. Those compounds have fused ring system and more branched structures have better docking score. In order to confirm the binding behavior of the compounds molecular dynamic simulations is performed on the compounds. These studies provide some lead compounds for the development of novel bioactive molecules.

References

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