Binding Mode prediction of HMG-CoA Reductase Inhibitors Using Molecular Modelling Tools

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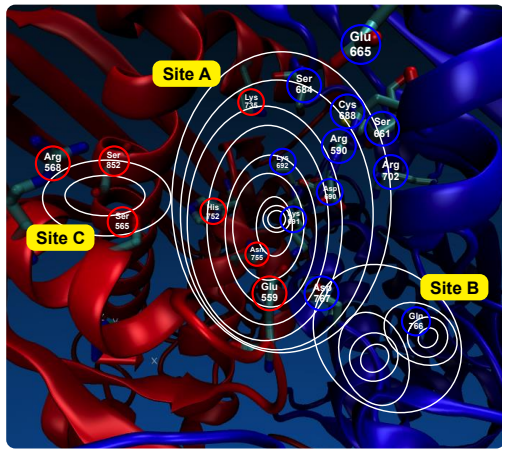
HMG-CoA reductase (HMG-CoA-R) is currently an important drug target to treat hypercholesterolemia and cardiovascular diseases [1]. In the present study, 320 compounds with HMG-CoA-R inhibitory activity were studied in order to unravel the source of their inhibitory activity. To this end, molecular dynamic simulations and molecular docking studies were conducted to predict the binding pose of the ligands in the active site of HMG-CoA-R. Further studies, such as solvent accessible surface area (SASA) and protein ligand interaction fingerprint (PLIF), were also conducted to understand which amino acid residues are important in the binding process and are important to control the specificity of the active site. The final results allowed us to divide the compounds in different classes based on their bonding pose and biological activities.



The retrived results have shown that the compounds with fused heterocyclic ring structures in the main scaffold of their structure and that mimics the mevalonic acid bind in the same position of the active site as the natural substrate and, interact very closely with the active site residues Ser565, Glu559, Asp609, Lys691, Lys692 and Arg568 [1,2] (Fig1- site A). These compounds are also the ones that show better biological activity. These results have also shown that the compounds that have bulkier and polar groups capable of interacting with the binding site that is normally occupied by the CoA cofactor tend to improve their inhibitory activity (Fig1 - site C). These studies have also revealed that some of the HMG-CoA-R inhibitors interact with some amino acid residues nearby the binding site that are important in the dimerization of HMG-CoA-R enzyme. These studies suggest therefore that some of the these inhibitors can also act as dimerization inhibitors [1].

[1] D.M. Black, *Am. J. Cardiol.*, **2003,** *91*, 40E-43E.

[2] E.S. Istvan, M. Palnitkar, S.K. Buchanan, J. Deisenhofer, *Embo J.*, **2000,** *19*, 819-830.