Determination of the Inhibitory Capacity on HMG-CoA Reductase Enzyme by Statins Using Molecular Docking Method

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Statins are a class of lipid-lowering medications that reduce cardiovascular disease and mortality in pacients who are at high risk. The molecular docking technique has become an increasingly important tool for drug discovery which help us understand the most stable conformations resulting from ligand-active site of the biological receptor interaction. Partial atomic charges was determined for each molecule showing that the interaction of statins with the receptor is through areas of increased electronic density. The present molecular docking study using Autodock 4.2 was conducted in order to achieve accurate predictions of the best way for bonding and minimum bonding energy, method being applied for five statins drugs as potential inhibitors of HMG-CoA reductase enzyme. The results highlight that simvastatin represent the best inhibitory drug of HMG-CoA reductase enzyme, because the complex simvastatin-enzyme has the lowest binding energy value.

Keywords: molecular docking, statins, hmg co A reductase

Statins are very prescribed drugs worldwide, being cholesterol-lowering agents used to manage and prevent cardiovascular and coronary heart diseases [1]. The commonly known pharmacological activity of statins relies on a good inhibition of the endogenous mevalonate pathway, which goes directly to the biosynthesis of cholesterol and isoprenoids. Statins bind to HMG-CoA reductase at nanomolar concentrations, leading to an effective displacement of the natural substrate HMG-CoA, which binds instead at micromolar concentrations [12]. The interactions between statins and HMG-CoA reductase prevent the conversion of HMG-CoA to L-mevalonate resulting in the inhibition of the downstream cholesterol biosynthesis and various isoprenoid metabolites [3]. As of 2010, a number of statins are on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin [4]. By molecular docking was possible to predict the structural mechanism of station inhibition on HMG-CoA reductase [5]. The chemical structure of the statins has been modeled and it contain, the pharmacophore, which is a dihydroxyheptanoic acid segment, and its fragment composed of a ring system with different substituents. The structure of the ring can be a partially reduced naphthalene (lovastatin, simvastatin, pravastatin, mevastatin), a pyrrole (atorvastatin), an indole (fluvastatin), a pyrimidine (rosuvastatin), a pyridine (cerivastatin), or a quinoline (pitavastatin) [2].

Protein–ligand docking is the process of computationally predicting the placement and binding affinity of a small organic molecule in the binding pocket of a protein, usually for the purposes of drug discovery. Lot of techniques, starting from simple point-matching algorithms to explicit physical simulation methods have been developed to solve this problem[6].

Docking is widely used for the study of biomolecular interactions and mechanisms, and is applied to structure-based drug design [7] and as well as to elucidate fundamental biochemical processes [8].

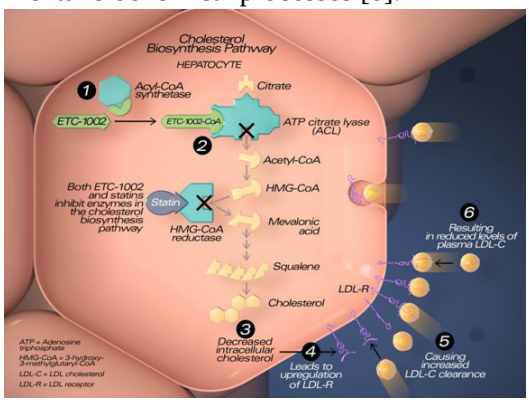

Fig. 1 Statins mechanism of action [9]

Experimental part

Materials and methods

Molecular docking technique was used for testing statins inhibitor capacity against HMG-CoA reductase, code 1DQ8 -Protein Data Bank [10].

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All statin molecules was geometrical optimized using Hyperchem 8 program (semiempirical method Parametrization Model 3 / SCF) [11]. Both enzyme and oxicams structures were prepared for the docking process using Autodock 4.2 software, the purpose being to achive accurate predictions on binding energy statin-enzyme [12]. All complexes drug- HMG-CoA reductase was visualized using Pymol software, in order to see polar contacts and their distances [13].

Results and discussions

It is well known that statins are 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitors, being prescribed extensively for cholesterol lowering in the primary and secondary prevention of cardiovascular disease. Recent studies suggests that statins have except cholesterol lowering effects, positive effects in restoring or improving endothelial function, attenuating vascular remodeling, inhibiting vascular inflammatory response and stabilizing atherosclerotic plaques [14, 15]. Atom charges distribution of statins describe nature and reactivity of atoms from molecules and relief the atoms that contribute to biological response formation for the studied ligands. 3D optimized structures of statins are presented in table 1, partial atomic charge for each molecule highlights the maximum electronic density centers that contribute to hydrogen bonds formation between the drug and enzyme. In this type of interaction ligand-receptor oxigen and nitrogen atoms might be involved for the inhibitory activity.

A-	Mevastatin	D-	Simvastatin
B-	Pitavastatin	E-	Lovastatin
C-	Pravastatin		

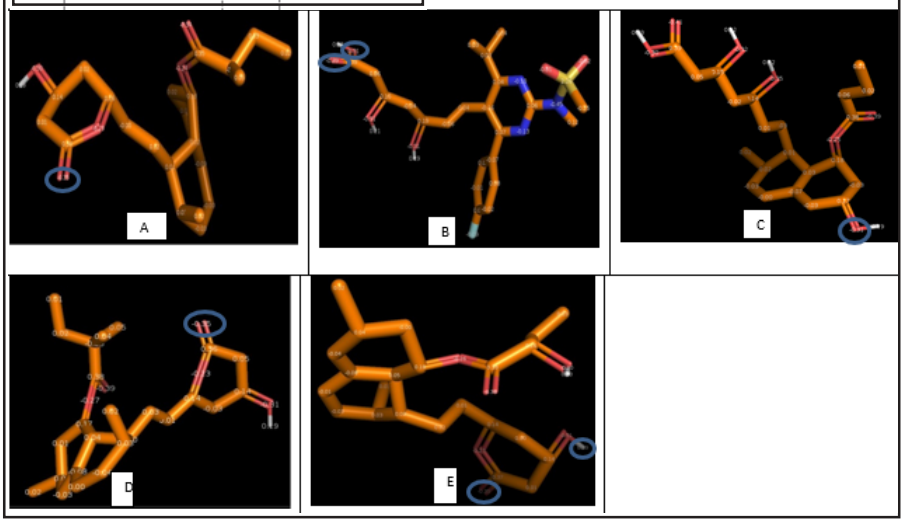


Table 1
OPTIMIZED STRUCTURES FOR STATINS AND VALUES OF THE PARTIAL ATOMIC CHARGES

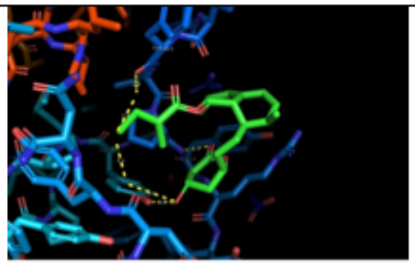
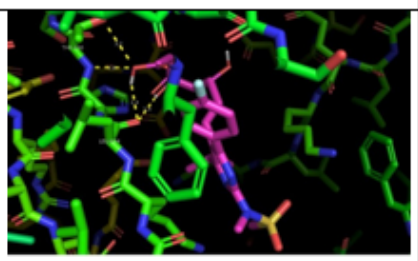
Statin	Value of the bonding energy (kcal/mol)	Interaction of statins and enzymes	The enzyme amino acids involved in the polar contacts formation
Mevastatin	-6.41		TYR 533, TYR 511, TYR 514
Pitavastatin	-1.91		THR 636, LEU 634

Table 2
BONDING ENERGIES (AFFINITIES) VALUES, MEASURED IN kcal/mol, FOR THE OXICAM - HMG COA REDUCTASE COMPLEXES AND AMINO ACIDS INVOLVED IN HYDROGEN BOND FORMATION

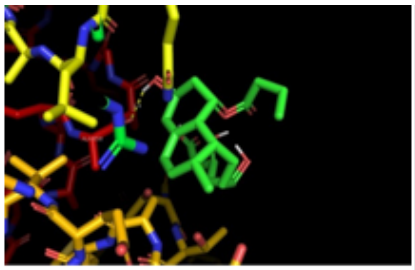
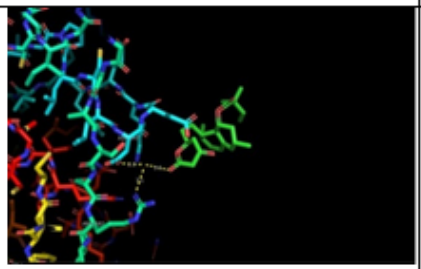
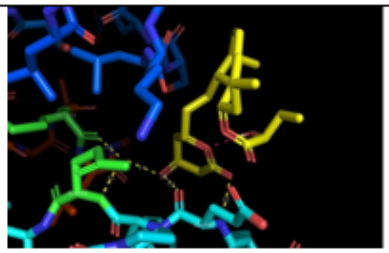
Pravastatin	-0.56		ALA 858
Simvastatin	-14.23		ASP 547, ARG 582
Lovastatin	-5.08		GLU 550, GLN 552, MET 820

Table 2
(continued)

We use computational docking to predict bound conformations and free energies of binding for statin molecule ligands to macromolecular targets. Data exposed in table 2 suggested that simvastatin-HMG coA reductase has the lowest enegy value (-14.23 kcal/mol), followed by mevastatin (-6.41 kcal/mol) and lovastatin (-5.08 kcal/mol).

Conclusions

Molecular docking is a good technique to understand and develop new therapeutic agents. Using Autodock can calculate and visualize the best conformation ligand-receptor and allows evaluation for minimum bonding energy. Computational chemistry and molecular docking relieves pharmaceutical researchers of time and money, helping them to focus only to the synthesis of drugs with the desired therapeutic effect.

The results obtained in the docking study show that simvastatin is the best HMG-Co A reductase inhibitory agent the complex simvastatin-enzyme havinh the lowest energy value.

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10.*** http://www.rcsb.org/structure/1DQ8
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