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 patients 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

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].
All statin molecules were geometrically 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 achieve 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-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, being prescribed extensively for cholesterol lowering in the primary and secondary prevention of cardiovascular disease. Recent studies suggest 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 bond formation between the drug and enzyme. In this type of interaction ligand-receptor oxygen and nitrogen atoms might be involved for the inhibitory activity.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Value of the bonding energy (kcal/mol)</th>
<th>Interaction of statins and enzymes</th>
<th>The enzyme amino acids involved in the polar contacts formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mevastatin</td>
<td>-6.41</td>
<td></td>
<td>TTR 335, TTR 331, TTR 514</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>-1.91</td>
<td></td>
<td>THR 836, LEU 614</td>
</tr>
</tbody>
</table>

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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 energy 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-CoA reductase inhibitory agent the complex simvastatin-enzyme having the lowest energy value.

**References**

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**Table 2 (continued)**

| Pravastatin | -0.56 | ALA 858 |
| Simvastatin | -14.23 | ASP 347, ARG 382 |
| Lovastatin | -5.08 | GLU 550, GLN 552, MET 820 |