Original Article

Computational Design of Angiotensin Converting Enzyme Inhibitors

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Abstract

Hypertension is a primary risk factor for stroke, heart attack, heart failure, and aneurysm. High Blood Pressure is responsible for 7.6 million deaths per annum worldwide. Renin angiotensin system is responsible for controlling blood pressure, salt balance and fluid balance in mammals. Renin cleaves the angiotensinogen into angiotensin1, which is inactive in nature. Angiotensin converting enzyme (ACE) converts the inactive Ang1 to active Ang2 which leads to the vasoconstriction and the result is increased BP. ACE also inactivates the bradykinin which is responsible for vasodilation. The main way to control the hypertension is to inhibit the ACE. Fosinopril is one of the ACE inhibitors which have more binding affinity compared to the others. In this article, we report computational design methodology to improve the binding affinity of fosinopril, so as to improve specificity and to reduce side-effects. All the new derivatives of fosinopril showed better free energy of binding relative to fosinopril.

Introduction

Hypertension is a disease condition in which the force of the blood against the walls of the arteries is too high. Usually hypertension is defined as when the blood pressure (BP) is above 140/90 mmHg, and it is considered severe if the pressure is above 180/120. Hypertension can cause severe health complications and pose high risk for heart disease, stroke, and sometimes death. It mainly affects the organs such as brain, kidney, heart, eyes and arteries. Hypertension accounts for 7.6 million deaths per year worldwide (13.5% of the total), more than any other risk factors.[1] Hypertension and cardiovascular mortality are rising rapidly in low- and middle-income countries (LMIC).

Renin Angiotensin System is a circulating regulatory system, which controls the blood pressure (Fig.1), fluid and salt balances in mammals.[2] Renin is an aspartic protease; it cleaves angiotensinogen to generate angiotensin1 (Ang1). Angiotensin converting enzyme (ACE) cleaves the inactive Ang1 to angiotensin2 (Ang2). Ang2 has multiple actions; (i) acts on adrenal cortex to release aldosterone, (ii) stimulates the reabsorption of sodium ion and water and (iii) stimulates the production of vasopressin which enhances the fluid retention by the kidneys. All these contribute to increased blood pressure. ACE promotes vasoconstriction by increasing the production of Ang2 and inhibits vasodilation by deactivating Bradykinin, both of which lead to hypertension.

Fosinopril is a widely used ACE inhibitor which inhibits the conversion of inactive Ang1 to active Ang2.[3] It is also used in the treatment of some types of chronic heart diseases. It helps in relaxing the blood vessels and reduces hypertension which in turn prevents heart attack, stroke, and kidney problems. Studies show that the use of fosinopril leads to side effects such as light-headedness, ill felling, chill, throat pain, cough, troubled breathing, painful mouth sores, little or no urination, nausea, fatigue, slow or unusual heart rate.[3] Therefore, it is essential to decrease the dose of administrating drug by increasing the binding affinity. As the increase in binding affinity can allow the reduction in the dosage of drug needed, the current study is aimed to optimize the structure of the ligand with enhanced binding affinity. The ultimate aim is to achieve the maximum activity of the drug with minimized side effects.

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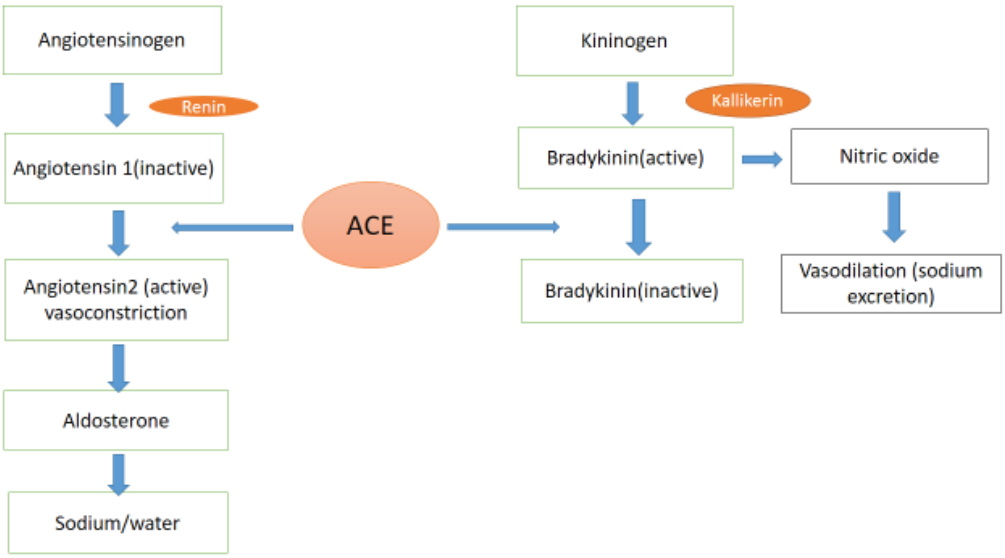

Figure 1: Renin-Angiotensin System pathway

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Methodology

Ligand construction and geometry optimization

Ligands were modeled using Avogadro program, an advanced tool used in modeling and visualizing three dimensional structures of molecules.[4] This is used in various fields like material science, computational chemistry, bioinformatics, molecular modeling, and other related areas. Modeled ligand structures were optimized using UFF force field calculations and then used for docking studies.

Preparation of macromolecule

Macromolecule (ACE) was obtained from the RCSB PDB (4BZS) as a complex with K26 inhibitor of ACE.[5] Chain A of ACE protein was isolated using VMD, a molecular visualization tool.[6] It is also used in analyzing results obtained from docking studies and molecular dynamics simulations.

Docking studies

For the docking studies, only the chain A of 4BZS was used. Autodock was used for all the docking studies reported here. Autodock tool is used to study the interaction between macromolecule and the ligand and to predict the three-dimensional complex structure formed by them.[7] For docking calculations polar hydrogens are added to the macromolecule and non-polar hydrogens are merged with the carbon atoms. In addition, the catalytically important Zn^{2+} ion was also included in the active site. The rotatable bonds of the ligand are then calculated and saved it as a PDBQT file. The grid box is then selected which determines the binding site, and is saved as GPF file. Autogrid helps in setting up affinity map for each ligand atom types in the 3-D space of the receptor, which speeds up the docking process. Finally, we analyzed the interaction of macromolecule and different variants of ligands.

Result and discussion

ACE inhibitors bind with ACE protein and inhibit the conversion of Ang1 to Ang2, thereby reducing blood pressure. Inhibitors with higher binding affinity have greater impact in the treatment of hypertension. Drug action is known to vary among the population in terms of efficacy and side effects. This may be attributed to the genetic variations among the subjects. This complexity makes the drug designing as a continuous process with enormous regulatory procedures. Thus, there is always a need for redesigning of drugs to improve the efficacy, mitigate the side effects and personalize the drugs. In the current work, we employed computational methods to optimize one of the ACE inhibitors to improve the binding affinity.

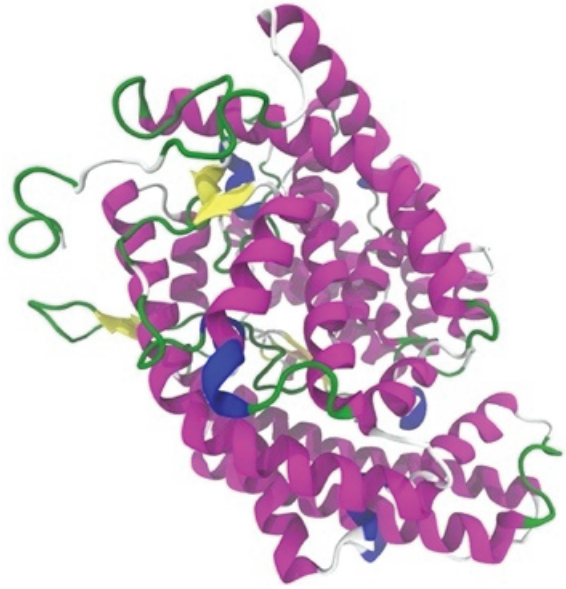

Figure 2: Structure of human ACE

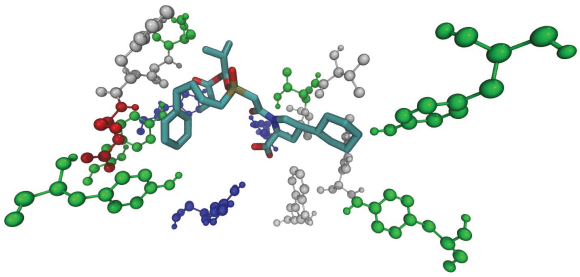

Figure 3: Binding pose of fosinopril with surrounding amino acids

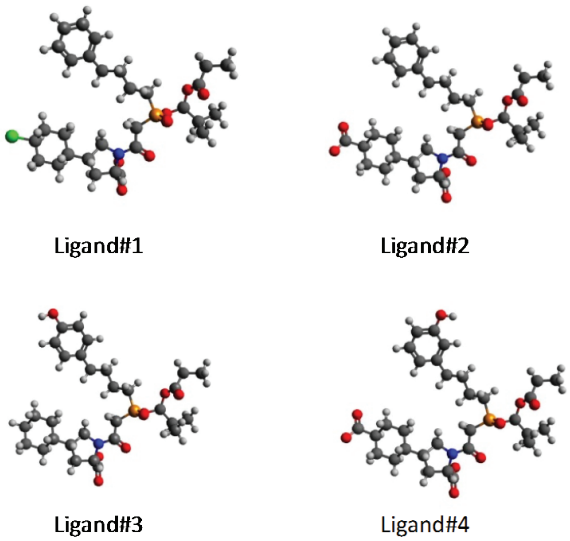

Figure 4: Chemical structure of optimized fosinopril derivatives

The macromolecule ACE was downloaded from RCSB PDB as a complex structure (4BZS). It is then isolated and obtained chain A of the protein by using VMD molecular visualizer (Fig.1). It is then docked with commercially available ACE inhibitor fosinopril by using Autodock4.

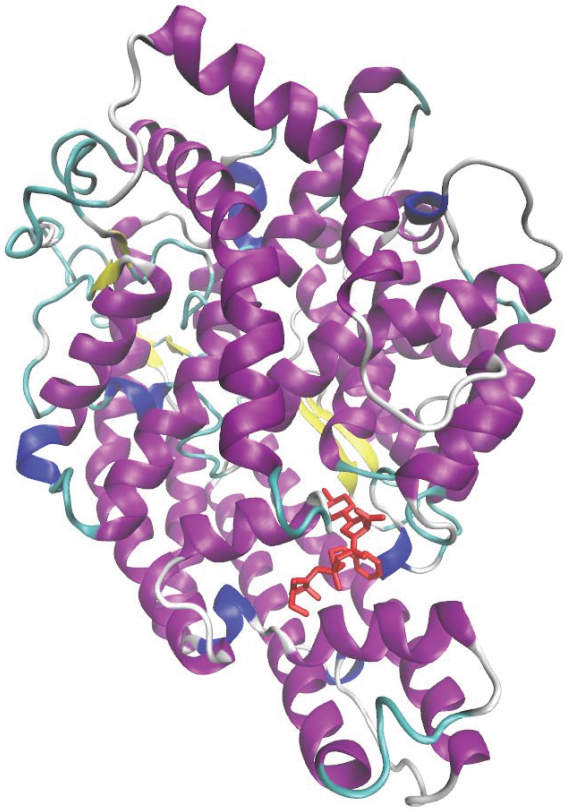

Figure 5: Binding pose of ACE inhibitors (red sticks) in the active site of ACE

Then the interaction between the macromolecule and the ligand is studied up to 4 Å. It is found that the ligand molecule is surrounded by amino acids such as SER333, TRP335, ASP336, TYR338, HIS365, TYR369, ARG500, TRP201, PRO497, TYR186, TYR111, VAL495, THR496, ARG381, TRP198. Next step is to modify the drug molecule in order to increase the binding affinity.

Ligand molecule was then modified by molecules according to the interaction of surrounding amino acids with the help of Avogadro molecular builder.

Ligand#1 was prepared by adding Cl atom to the cyclohexane ring of fosinopril. Ligand#2 was prepared by adding COO- to the cyclohexane ring. Ligand #3 was prepared by adding OH to the benzene ring of the ligand. Ligand#4 was prepared by adding OH to the benzene ring and COO- to the cyclohexane ring of the fosinopril molecule. The ligand structures are shown in Figure 4.

Then the binding pose for each ligand was studied by using autodock4 program. The binding position of Ligand#1 is shown in Figure 5.

The modified ligands were found to interact in a very similar manner, compared to the original fosinopril.

Then we compared docking score (free energy of binding) for each ligand variety (Table 1). Smaller the docking score, higher is the binding affinity. The binding poses of ACE with different ligand varieties were studied and it was found out that ligand#2 (i.e.,

LIGAND MOLECULES	DOCKING SCORE (kcal/mol)
Fosinopril	-6.81
Ligand#1	-8.61
Ligand#2	-8.72
Ligand#3	-7.22
Ligand#4	-7.49

Table 1: Docking score for different ACE inhibitors

fosinopril with COO- in the cyclohexane ring) has better binding affinity than the commercially available fosinopril molecule. It is found that the amino acids surrounding the ligand#2 is same as the amino acids surrounding the original drug molecule.

The binding pocket consists of amino acids such as SER333, TRP335, ASP336, TYR338, HIS365, TYR369, ARG500, TRP201, PRO497, TYR186, TYR111, VAL495, THR496, ARG381, and TRP198.

Our studies show that ligand#2 can be used as a better alternative for fosinopril. The table can also depict the functional group included to each ligand

Conclusion

The study was conducted with the objective of enhancing the binding affinity of fosinopril to ACE so as to reduce the dose requirement and to mitigate its adverse side effects. Towards this, Fosinopril was modified into 4 different ligands with certain groups using Avogadro molecular builder. These ligands were then docked with macromolecule ACE and collected the docking scores that reflect the binding affinity for each derivative. It is found out that fosinopril with functional group COO- attached to the cyclohexane ring has a better binding affinity compared to the commercially available ACE inhibitor.

Conflicts of interest

All the authors declare that they have no conflict of interest

Acknowledgement

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