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DESIGN AND DOCKING STUDIES OF HIS-LEU ANALOGUES AS POTENTIOAL ACE INHIBITORS

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Abstract. Bioactive peptides are protein fragments that have a positive impact on body functions and may ultimately influence health. Angiotensin-converting enzyme plays an important role in the control of arterial blood pressure. The main action of Angiotensin II is to maintain blood pressure and fluid balance in the body. It is obtained from the precursor under catalytic action of angiotensin-converting enzyme (ACE). In order to control (inhibit) the action of the ACE different inhibitors were proposed and some of them are already in use in the clinic. In the present investigation we design and docking studies of fife new potential ACE inhibitors. Three of the proposed analogues have a potential to be ACE inhibitors, as they bind to the enzyme stronger than His-Leu. The studied peptides may form as a basis for the design of new compounds and will be synthesized and biologically tested.

Keywords: angiotensin-converting enzyme; docking study; short peptides; ACE inhibitors

Introduction

Bioactive peptides contain 2 – 20 amino acids with possible bioactivities including antihypertensive, antioxidant, antimicrobial, anticancer, and opioid activity (Shahidi & Zhong, 2008; Homayouni-Tabrizi et al., 2008; Suwanmanon & Hsieh, 2014). Among all the bioactive peptides, the antihypertensive peptides attract particular attention owing to the prevalence of high blood pressure, which plays an important role in cardiovascular diseases. These peptides have the ability to act as angiotensin I-converting enzyme (ACE) inhibitors (Arora & Chauhan, 2013). The antihypertensive peptides are effective mainly due to inhibiting the angiotensin-converting enzyme (ACE) (Shahidi & Zhong et al., 2008). Angiotensin-converting enzyme inhibitors (ACEIs) are a commonly used medication in the current management of various medical conditions, including heart failure, post-acute coronary syndrome, nephrotic syndrome and hypertension. ACE-inhibitors are widely used in the treatment of hypertension by inhibiting the angiotensin converting enzyme responsible for the conversion of angiotensin I to angiotensin II (responsible for vasoconstriction). Various structure activity relationship studies led to synthesis of different kinds ACE-inhibitors (Jao et al., 2012). ACE is crucial for cleaving the C-termini His-Leu dipeptide from angiotensin I to produce a potent vasopressor octapeptide, angiotensin II. ACE inhibitors are first line therapy for treatment of hypertension, heart failure, myocardial infarction (MI) and diabetic nephropathy (Natesh et al., 2003). Agents that block angiotensin-converting enzyme (ACE) and the formation of angiotensin II (Ang II) have become mainstays of cardiovascular and renal medicine.

The use of computational techniques in drug discovery and development process is rapidly gaining in popularity, implementation and appreciation. Computational methods are playing increasingly larger and more important role in drug discovery and development. They are expected to limit and focus chemical synthesis and biological testing and thereby greatly decrease traditional resource requirements (Kapetanovic, 2008). There is not enough literature data about application of computational methods especially including docking study of ACE-inhibitors (Khan et al., 2012; Shukla et al., 2014). In the present work we investigated a design and docking studies of five newly designed His-Leu analogues as potential ACE inhibitors.

Materials and methods

Dipeptides

In the present study, five dipeptides, analogues of His-Leu (Fig. 1) were used in order to check their ability to bind ACE and act as its inhibitors.

Peptide preparation is done with Avogadro (an open-source molecular builder and visualization tool – Version 1.0.3 (Hanwell et al., 2012).

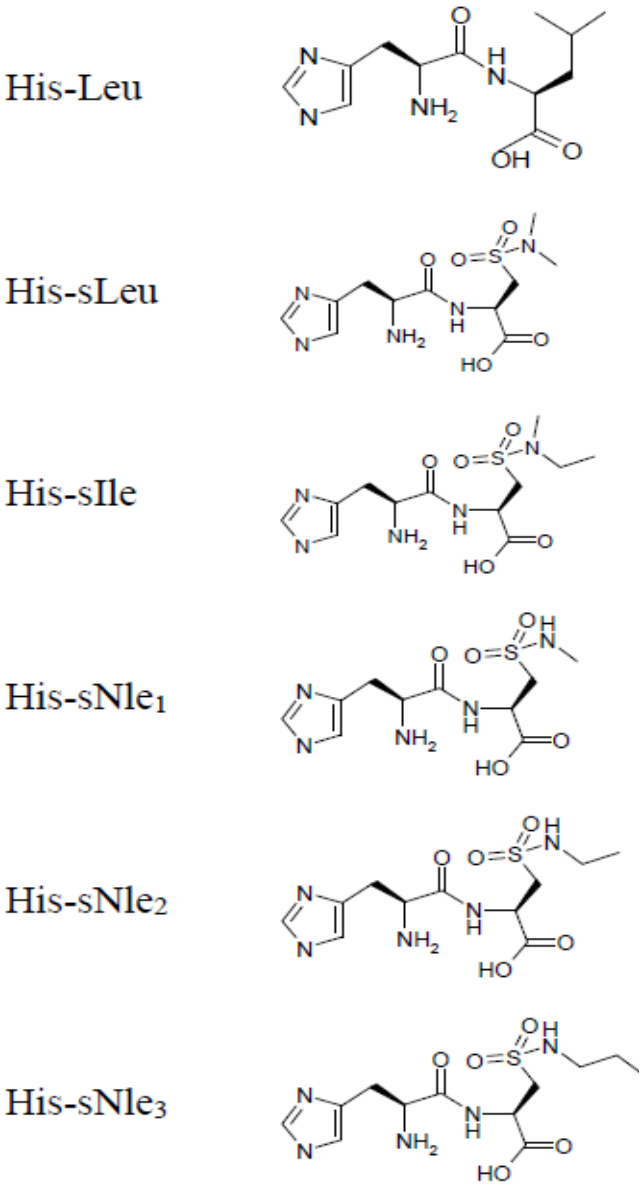

Figure 1. The structures of the used dipeptides.

Angiotensin converting enzyme

Crystal structure of the ACE is obtained from RCSB (Masuyer et al., 2012)

Docking study

In order to perform computational studies. different software ware used in the present work: docking studies were performed by using GOLD 5.2 (Genetic Optimization for Ligand Docking (Jones et al., 1997) run on Scientific LINUX 5.5 operating system, in the Center for Advanced Bioinformatics Research (CABR) at SWU "Neofit Rilski", Blagoevgrad; and for generation figures, Molegro Molecular Viewer (MVD) was used (Thomsen & Christensen, 2006).

Results and discussion

The prediction of active derivatives is a subject of molecular docking studies. The docking results provided pertinent information about the binding affinity, binding energy and orientation of ligand-receptor interactions (Shukla et al., 2014).

ACE catalyzes removal of His-Leu from the molecule of angiotensin I thus converting it to angiotensin II. After catalytic reaction, this dipeptide leaves enzymatic catalytic center and ACE is ready to convert another molecule of angiotensin I. If a molecule could stay longer in the catalytic center it would inhibit the action of the enzyme. Five different analogues were used in order to check if they could act as inhibitors for ACE.

Docking was performed using the crystal structure of ACE (PDB id: 4aph). This structure was prepared for the procedure, by removing the co-crystallized ligand and water molecules, by protonating at physiological pH (7.4) and optimizing. From the literature, it is known catalytic center of the enzyme [14,15]. We choose the residues within a radius of about 10 Å of Glu281. ChemScore function was used, which makes it possible to verify the ability the corresponding peptides to bind to the enzyme.

After ten independent runs of the program, the best pose for every peptide was chosen and the total energy of the formed complex with ACE was calculated using Molegro Molecular Viewer. The best docking poses with ACE were therefore selected based on docking energies and similarities in zinc binding and hydrogen bonding interactions. The docking results are summarized in Table 1.

Table 1. Total energies of the peptides

Dipeptide	Total energy
His-Leu	-89.462
His-sLeu	--110.931
His-sIle	-82.475

His-sNLe1	-108.153
His-sNle2	-90.848
His-sNLe3	-102.291

In the structure of the newly proposed dipeptide analogues there is and sulfo group. This group is capable to bind stronger to the receptors and enzymes, by interacting with different residues. Due to their analogy with His-Leu all peptides could enter and bind the catalytic center of ACE and their interactions are presented at Fig. 2.

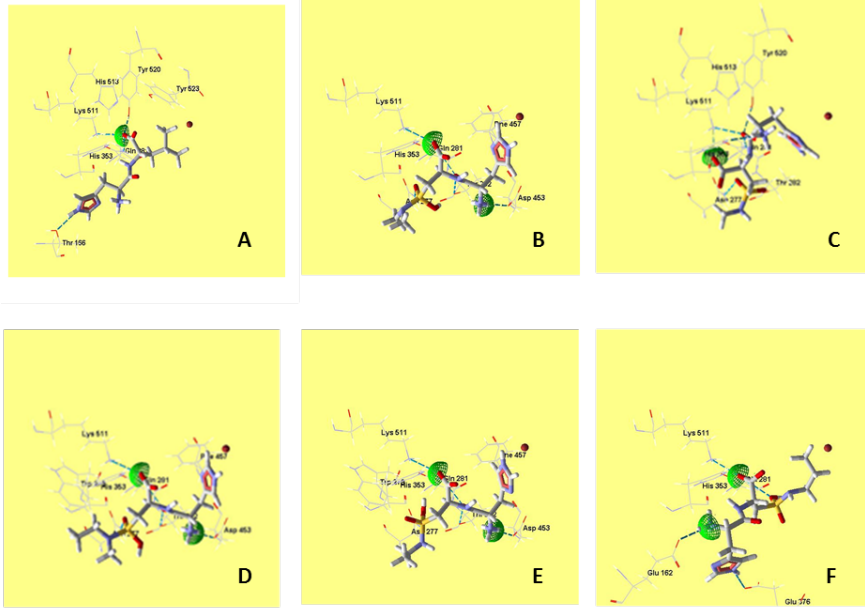

Figure 2. Interactions in the catalytic center of ACE of His-Leu (A), His-sLeu (B), His-sILe (C), His-sNLe$_1$ (D), His-sNLe$_2$ (F), and His-sNLe$_3$ (E).

His-Leu and His-sILe interact with ACE with higher energy than other compounds, -89.462 and -82.475 respectively. His-Leu interacts electrostatically with Lys511, His513, and His353. His-sIle interacts electrostatically with less residues, only Lys511 and His353 thus its energy of binding is higher than energy of ACE/His-Leu complex. Little lower is the energy of the complex ACE/His-sNLe$_2$, -90.848. Three of the tested dipeptide analogues bind stronger to the enzyme: His-sLeu, His-sNle1, and His-sNLe3 with energies of the obtained complexes -110.931, -108.153, and -102.291, respectively.

On the base of analyzed results from docking study we could conclude that three of the proposed His-Leu analogues could bind stronger to ACE thus inhibiting its action. Stronger binding means that the analogues will stay longer in the catalytic center of the enzyme and the molecule of angiotensin could not access catalytic center.

Conclusions

All proposed compounds could interact with the catalytic center of ACE and three of them bind stronger. They could play the role of the ACE-inhibitors so in the future they will be synthesized and biologically tested.

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