*Bulgarian Chemical Communications, Volume 54, Special Issue B1 (pp. 18-20) 2022 DOI: 10.34049/bcc.54.B1.0370*

# Combined action of His-Leu analogues on angiotensin converting enzyme (ACE) and angiotensin receptor (AR)

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Received: November 17, 2021; Accepted: May 20, 2022

Classically, the renin–angiotensin system (RAS) has been viewed solely as a hormonal circulating system involved in the regulation of blood pressure and salt and fluid homeostasis. According to this view, liver-derived circulating angiotensinogen (Aogen) is acting by renin released from the kidney forming the decapeptide angiotensin (Ang) I. Finally, angiotensin converting enzyme (ACE) present on the luminal surface of vascular endothelium converts Ang I to the biologically active end product Ang II by cleavage of the Phe$^{8}$–His$^{9}$-bond. This traditional concept has undergone several and important changes in recent years [1]. It has become clear that various fragments of the peptide can act on the receptor. Therefore, the purpose of the present study is to determine by docking whether His-Leu analogues, which act as ACE inhibitors, will have an effect on AR. The compounds were modelled with Avogadro software, the structure of the receptor was obtained from RCSB (PDB id: 4zud), and docking was performed with GOLD 5.2 software. The visualization of the obtained results was performed with a Molegro molecular view, where the energies of the ligand-receptor complexes were determined. The results of the docking indicate that all tested analogues bind to the receptor in an appropriate manner. Three of them – His-sLeu, His-sNle and His-sNle3, have the potential to act as its antagonists, as the formed ligand-receptor complexes have low enough energies to be stable over a long period of time. The test compounds can have a complex effect on RAS, on the one hand by inhibiting ACE and on the other hand by blocking AR.

**Key words:** renin–angiotensin system, angiotensin converting enzyme, angiotensin receptor, docking, GOLD 5.2

## INTRODUCTION

The relatively simple "classical" concept of "circulating RAS (Fig. 1) involves angiotensinogen (AGT) produced in the liver, renin formed in the kidneys, the major effector peptide angiotensin II (Ang II) formed in blood vessels under the action of ACE, and angiotensin receptors of type 1 and 2 (AR1 and AR2) [2].

The renin-angiotensin system (RAS) is a hormonal system that regulates blood pressure and fluid balance. Agents acting on RAS act by blocking various stages of the renin-angiotensin system by lowering blood pressure and their use in the treatment of hypertension and its complications (including acute myocardial infarction, congestive heart failure and chronic renal failure) is recommended in many of the current clinical guidelines. Agents acting on RAS include angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), as well as direct renin inhibitors.

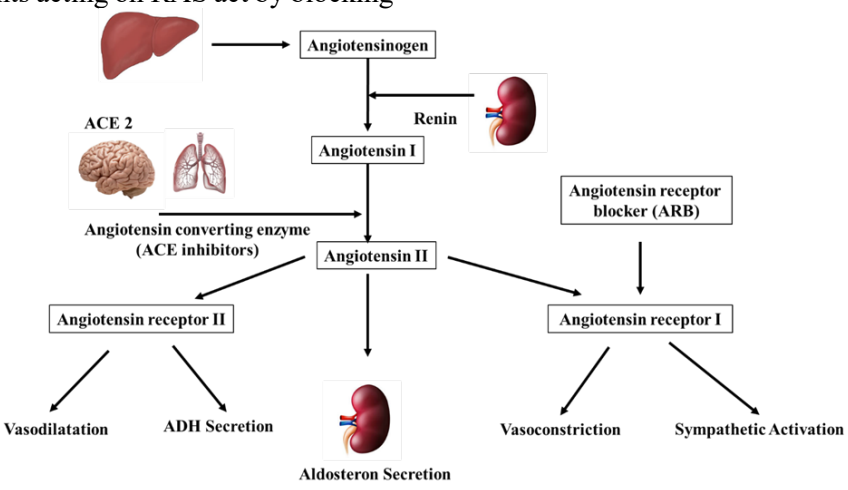


**Fig. 1**. A simplified model of the "classical" circulating renin-angiotensin system.

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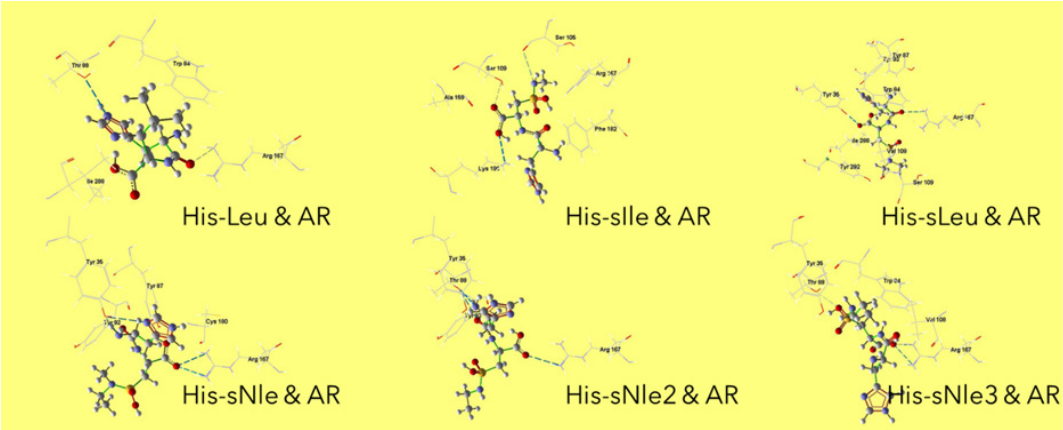


**Fig. 2.** Binding of the ligand with AR.

## MATERIALS AND METHODS

### *Ligands*

Ligands used in this work were previously used [6]: His-sLeu, His-sNle and His-sNle3.

### *Computational tools*

In order to perform computational studies, different software was used in the present work. Ligand preparation was done with Avogadro [7]. Docking studies were performed by using GOLD 5.2 (Genetic Optimization for Ligand Docking) [8], run on Scientific LINUX 5.5 operating system. Molegro Molecular Viewer [9] was used for generating figures.

### *Docking of ligands*

Six ligands, investigated for their binding to AR, were selected for docking studies. 3D structures of the ligands were modeled in Avogadro. Ligands were protonated at the physiological pH 7.4. Docking was carried out with GOLD 5.2 software. It uses a generic algorithm and considers full ligand conformational flexibility and partial protein flexibility. The binding site for AR (PDB id: 4zud), we assumed that like in all G-protein couple receptors, it was on the third transmembrane helix (TM). For the docking we used Arg167 residue from the TM and the space within 10 Å radius of them. GoldScore scoring function of GOLD was used. The conformations of the ligands with best scoring functions were selected and the total energies of the complexes with AR were used for analysis.

## RESULTS AND DISCUSSION

The residues from TM helix 3 are important residues for ligand recognition. The binding site was defined as residues within 10 Å radius of Arg167 on TM3. Docking was performed with AR (PDB id: 4zud) and 6 ligands.

The results from docking were analyzed in Molegro Molecular Viewer, where total energies of the obtained ligand-receptor complexes were calculated (Table 1).

**Table 1.** Total energies of the complexes between ligands and the model of AR

| Ligand | Total energies of complexes with AR |
|---|---|
| His-Leu | -34.27 |
| His-sIle | -25.08 |
| His-sLeu | -49.05 |
| His-sNle | -82.91 |
| His-sNle2 | -55.45 |
| His-sNle3 | -85.72 |

Total energies show how strong the ligand binds the receptor. We could assume that they represent the affinity of the compound to the respective receptor type. The table shows that all analogues bind strongly to AR, but three of them – His-sLeu, His-sNle and His-sNle3, have the potential to act as its antagonists, as the formed ligand-receptor complexes have low enough energies to be stable over a long period of time. The same can be seen in the way they bind to the receptors (Fig. 2). The ligand His-sNle3 forms a larger number of hydrogen bonds, and interactions (electrostatic, hydrophobic) with the AR than the other.

All of the peptides interacted with the crucial amino acid residue of the receptor sequence Arg167. The most potent ligands had an additional interaction with Tyr35 which stabilizes the complex. Our previous study showed that the same ligands His-sLeu, His-sNle and His-sNle3 bound strongly ACE [6]. So, these three compounds have the potential to block RAS by inhibiting both ACE and AR.

## CONCLUSION

The test compounds can have a complex effect on RAS, on the one hand by inhibiting ACE and on the other hand by blocking AR. Compounds His-sLeu, His-sNle and His-sNle3 bind strongly not only with the AR, but also with ACE as we reported previously. This study shows once again the possibilities of docking studies for prediction of the biological effect in a faster way. Computer-aided drug design is a useful approach in the modern design of new compounds with a desired biological effect. It could shorten the process by calculating different constants thus helping in improving structure and properties of a compound.

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