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Relationship between lipophilicity and protein binding of some potential angiotensin-converting enzyme (ACE) inhibitors

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Absorption, distribution, metabolism and elimination (ADME) properties play an important role in application of the biologically active compounds as drugs. Protein binding is crucial for their effect but *in vivo* they should reach it. Different properties are essential in order to pass through gastrointestinal track and to reach target protein. Lipophilicity is one of the most important properties that significantly influence drugs absorption, distribution, binding to plasma proteins and elimination due to hydrophobic interactions of the drug with biological targets and its penetration across biological membranes during transport. The aim of the present study is to find a relationship between lipophilicity, solubility and protonated state of new analogues of His-Leu and their binding ability to angiotensin-converting enzyme (ACE). We found correlations between pKa acidic/ChemScore – r = 0.86 (p = 0.03) and pKa basic/ChemScore – r = 0.83 (0.04), proton acceptors and ChemScore function values (r = -0.86, p = 0.03), and logP and logS of the compounds and the total energies of their complexes with ACE (r = 0.83, p = 0.04). Combining docking and theoretical calculation of different properties of the molecules could help in a faster and accurate design of new potential drug candidates.

Keywords: ADME, ACE inhibitors, lipophilicity, log P, docking

INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors are a group of compounds with a variety of chemical properties that are effective in treatment of several medical conditions such as hypertension, congestive heart failure, post-myocardial infarction, and diabetic nephropathy [1, 2, 3, 4]. ACE inhibitors exhibit their effects by reacting with the enzyme and thus preventing the formation of angiotensin II. Most of the compounds are competitive inhibitors of ACE which is the rate-limiting enzyme in the formation of angiotensin II. The first developed ACE inhibitor is captopril, thiol-containing compound followed by enalapril, a compound without thiol group. The ACE inhibitors for medicinal use are currently classified into three classes. The first class are thiol-containing ACE inhibitors. To the second-largest class belong the dicarboxyl-containing compounds. And the third class contains phosphorus-containing inhibitors. It is known that ACE inhibitors only moderately differ in their pharmacodynamic efficacies [5]. All known ACE inhibitors used in practice are representatives of a wide variety of classes of organic compounds, so their chemical and biochemical properties are very different. Acidity, lipophilicity, solubility, absorption and polar surface differ among the ACE inhibitors and there are relationships between these properties and the biological action of the compound [6]. The computational modelling technique is a very suitable tool in the design of new compounds with desired biological effect.

The aim of the present study is to calculate some chemical and biochemical properties of new potential ACE inhibitors with peptide structure.

MATERIALS AND METHODS

Dipeptides

Five dipeptides, analogues of His-Leu (Table 1) were used in order to calculate their acidity, lipophilicity and solubility and to find relationships between these properties and their binding affinity to ACE. Results from docking of these compounds were published previously [7] and data are shown in Table 1.

Computational methods

The structure-based predictions for molecule structure and calculations that include hydrogen bond donors, hydrogen bond acceptors and pKa were performed using ChemAxon Ltd., 2019 (https://chemicalize.com/). For the prediction of log P and solubility, ALOGPS 2.1 was applied [8].

RESULTS AND DISCUSSION

The equilibrium of the protons of the drug at different conditions is very important for its receptor binding.

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Therefore, it would be useful to know whether the compound exists predominantly in its basic or protonated form. Most of the ACE inhibitors contain both proton acceptors and proton donors [6]. The results of our calculations are shown in Table 2.

Table 1. The structures of the used dipeptides and the values of total energy of the complexes with ACE and ChemScore function values

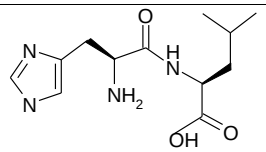
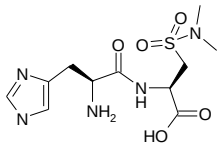
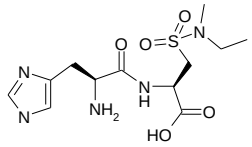
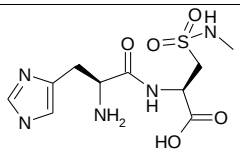
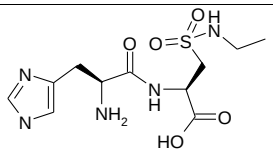
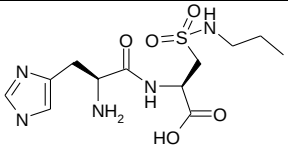
Compound	Structure	Total energy (MolDock Score)	ChemScore value
His-Leu		-89.46	18.95
His-sLeu		-82.48	15.13
His-sIle		-110.93	15.68
His-sNle$_1$		-108.15	17.03
His-sNle$_2$		-90.85	14.81
His-sNle$_3$		-102.29	14.72

Table 2. Theoretical calculations of the His-Leu analogues.

Compound	Hydrogen bond donors	Hydrogen bond acceptors	pKa, acidic	pKa, basic	Log P	Log S
is-Leu	4	5	3.61	8.02	-1.52	-1.26
His-sIle	6	7	1.98	7.84	-2.31	-1.68
His-sLeu	6	7	1.97	7.84	-1.73	-1.54
His-sNle$_1$	7	7	1.97	7.84	-2.10	-1.59
His-sNle$_2$	7	7	1.97	7.84	-2.00	-1.68
His-sNle$_3$	7	7	1.98	7.84	-2.03	-1.85

All compounds bind to lysine and histidine residues in the active site of the enzyme. The pKa values for the terminal carboxy group vary only slightly within the range 1.97 – 1.98, indicating that their carboxyl group is more acidic than in His-Leu (pKa value is 3.61). At physiological pH = 7.4 the carboxyl groups of the analogues would be completely ionized as they behave as strong acids. All studied analogues have a terminal amino group which could be easily protonated at physiological conditions. Docking studies showed that positively charged α-amino group was bound to the anionic carboxyl group of the glutamate residue in the enzyme active site. The drug basicity (or acidity) can influence its bioavailability. It was found that oral availability of Brønsted acids is better than that of neutral molecules while that of Brønsted bases is lower [9].

We found a correlation between pKa values and values of the ChemScore function from docking studies. pKa acidic/ChemScore – r = 0.86 (p = 0.03) and pKa basic/ChemScore – r = 0.83 (0.04). These correlations showed once again the role of proton equilibrium for drug – receptor interaction.

Human bioavailability of a drug is influenced by additional physicochemical parameters such as lipophilicity, number of hydrogen bond acceptors and donors in the molecule.

There is a correlation between the number of proton acceptors and ChemScore function values (r = -0.86, p = 0.03). In His-Leu the proton acceptors are 5 while in its analogues they are 7. A larger number of proton acceptors decrease the value of the scoring function thus showing that the obtained pose does not fit well in the active site.

Before starting the synthetic work it is useful to determine another physicochemical property such as solubility. The log P and log S values are very informative for the solubility of the respective compound and could be easily calculated using different software. In our work ALOGPs and ALOGpS methods as a part of ALOGPS 2.1 program were used for prediction of these values. The log P value is a constant defined in the following manner:

log P = log (Partition Coefficient);
Partition Coefficient, P = [organic]/[aqueous],

where [ ] indicates the concentration of solute in the organic and aqueous phase. A negative value for log P means that the compound has higher affinity for the aqueous phase (it is more hydrophilic); when log P = 0 the compound is equally partitioned between the lipid and the aqueous phase; a positive value for log P denotes a higher concentration in the lipid phase (i.e., the compound is more lipophilic). Usually calculations are for the water – octan-1-ol system.

The log S is a common unit for measuring solubility. This unit is a 10-based logarithm of the solubility measured in mol/l unit, that is, log S = log (solubility measured in mol/l).

Poor solubility is among the causes for failure during drug development. Most of the ACE inhibitors currently used in practice are applied as prodrugs. All of them with exception of fosinopril are compounds with low lipophilicity. Pharmacokinetic investigations show that the low lipophilicity of ACE inhibitors is associated with poor absorption from the gastrointestinal tract. The investigated compounds are hydrophilic as their log P values are in the range -1.73 / -2.31 and it would be expected that their absorption will not be as good as we would like. Furthermore, there is a correlation between log P and ChemScore function value, which means that the less hydrophilic compound binds stronger to the enzyme. But there is a moderate correlation with log S and the more soluble compound has a higher value of ChemScore function (Figure 1).

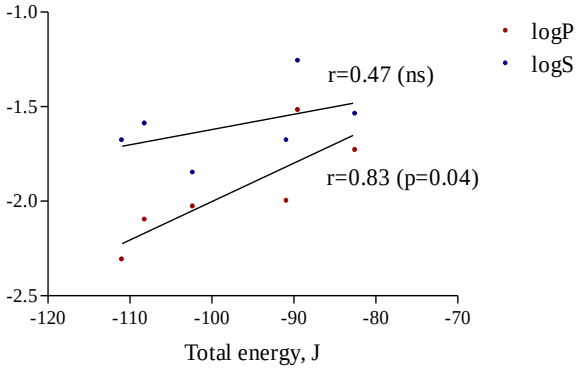


Fig. 1. Correlations between log P and log S and total energies of the complexes of analogues with ACE.

In order to design a compound with desired biological effect many different properties should be evaluated. It must strongly bind to the corresponding biomolecule (enzyme or receptor), and also have appropriate lipophilicity, solubility and right number of functional groups.

CONCLUSIONS

According to the performed analysis all investigated compounds would exhibit ACE inhibitory action, but because of their low lipophilicity, they will most probably encounter problems with the absorption from the gastrointestinal tract. The solution for this problem could be their coupling with different lipophilic

moieties in order to improve their partition in biological membranes. 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 the compound.

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