Cumhuriyet Sci. J., 43(4) (2022) 739-745
DOI: https://doi.org/10.17776/csj.1146225

Cumhuriyet Science Journal

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Molecular Docking and ADME Analysis of L-Phe -L-Tyr Dipeptide

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Research Article

History
Received: 20/07/2022
Accepted: 01/11/2022

ABSTRACT

Hypertension is a serious risk factor for various diseases. Therefore, lowering and preventing high blood pressure is a significant issue. Blockage of the renin-angiotensin-aldosterone system (RAAS), which controls blood pressure, is important to reduce blood pressure and consequently reduce symptoms of heart failure. This blockage can be carried out by angiotensin-converting enzyme (ACE) and angiotensin II receptor blockers (ARBs). The phenylalanyltyrosine (H-Phe-Tyr-OH, Phe-Tyr, L-Phe-L-Tyr, L-phenylalanyl-L-tyrosine) dipeptide examined in this study is an important structure that shows blood pressure lowering properties. For this reason, the potential of the peptide to be an ACE inhibitor or ARB was investigated. The molecular activity of the Phe-Tyr dipeptide was compared with antihypertensive drugs using theoretical calculations. Molecular docking method, one of these theoretical methods, has a considerable process in illuminating biochemical processes by investigating the interactions of drugs (ligands) with targeted receptors. In this theoretical study, molecular docking analyses of H-Phe-Tyr-OH dipeptide with ACE and Angiotensin II type 1 receptor (AT1R) were implemented. The interaction types and interaction regions of the peptide were also determined in comparison with drug molecules (Captopril, Enalapril, Telmisartan and Eprosartan) that are ACE inhibitors and ARBs. Lastly, ADME (absorption, distribution, metabolism, and excretion) analysis of the H-Phe-Tyr-OH dipeptide was also performed to estimate its drug potential. In this study, the pharmacokinetic properties of Phe-Tyr dipeptide and its mechanism of action with ACE and AT1R were investigated for the first time by molecular docking and ADME calculations.

Keywords: Antihypertensive, Peptide, Docking, ADME.

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Introduction

Hypertension, which has been a subject of pharmacological research for many years, is a very serious and common risk factor for human health and stands out as an important risk group especially in cardiovascular diseases [1]. The renin-angiotensin-aldosterone system (RAAS) is important for regulating arterial blood pressure. The blockage of RAAS come forward in the treatment of several diseases including hypertension [2,3]. The blockage can be realized by renin inhibitors, ACE inhibitors and Angiotensin receptor blockers (ARBs) [4]. To better understand what type of hypertension a pharmacological class of antihypertensive is, its mechanism of action is being studied closely. Molecular receptor targets are of great importance in studies examining the mechanism of action. Various antihypertensive drugs can be used as angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) [5]. Angiotensin-converting enzyme (ACE) inhibitors, i.e. drugs, help relax the veins and arteries to reduce blood pressure. These drugs are used to treat and manage hypertension, which is a significant risk factor for coronary disease, and other cardiovascular conditions [6]. The treatment of patients who have difficulty in tolerating ACE inhibitors due to cough that occurs as a side effect is continued with angiotensin receptor blockers [2]. Angiotensin receptor blockers (ARBs) interact and inhibit with the angiotensin II type 1 receptor (AT1R). Therefore, ARBs can be used to treat hypertension and hypertension-related diseases [2].

Amino acid metabolism is an effective system for controlling blood pressure. In a L-phenylalanine (Phe) study, it was reported that L-phenylalanine reduces the high salt-induced hypertension in rats [7]. Additionally, in a tyrosine study, it was reported that tyrosine reduces blood pressure in spontaneously for hypertensive rats [8]. Phe-Tyr dipeptide has also antihypertensive effect, reduce blood pressure and can be used as a pharmaceutical drug for the treatment of hypertension and cardiovascular diseases [9,10]. Molecular docking method has an important perspective in elucidating biochemical processes by examining the interactions of drugs or drug candidates (ligands) with targeted receptors at the atomic level. This method provides an estimation of the ligand-receptor complex structure and enables the determination of the optimal pose of the ligand to obtain the lowest energy complex structure [11-13]. Determining the pharmacokinetic information of drug candidate molecules is of great importance for drug development studies in biological systems. Estimates of absorption, distribution, metabolism, and excretion can be determined by ADME analysis. In this study, to elucidate the ACE inhibitor activity and AT1R blockage mechanism of Phe-Tyr, its interactions with the ACE and AT1R were investigated by molecular docking method, and the binding mechanisms of the peptide were presented with ACE inhibitors and ARBs comparatively. Pharmacokinetic properties for the predictions of the drug potential of the Phe-Tyr dipeptide were also determined by the ADME study.

Methods

The aim of molecular docking is to provide the prediction of a ligand and receptor complex [14]. To understand the reported antihypertensive activity of Phe-Tyr dipeptide, molecular docking studies were carried out using specific target receptor (ACE and AT1R). The binding mode of the Phe-Tyr dipeptide with the binding sites of ACE and AT1R were explored [15,16]. In this study, Phe-Tyr (antihypertensive dipeptide) was optimized at Gaussian09 with DFT method and B3LYP/6-31++G(d,p) basis set [17,18]. Phe-Tyr dipeptide was prepared as ligand by AutoDock Tools 1.5.6. Crystal structure of human angiotensin converting enzyme (PDB Code: 1O8A) and Angiotensin II type 1 receptor (PDB Code: 4ZUD) were downloaded from PDB DataBank (https://www.rcsb.org/). Receptors were prepared by deleting water, ions, and other ligands and adding polar hydrogens. After pdbqt files were obtained and grid box was adjusted, molecular docking study was run using AutoDock Vina [19]. After the binding affinities were obtained as a result of molecular docking analyses, the interaction region and interaction types of ligand-receptor complexes were determined with the help of Discovery Studio Visualizer 2019 [20]. Pharmacokinetic profile (ADME properties) of Phe-Tyr dipeptide were determined with the help of SwissADME online servers [21]. Docking studies and ADME analysis were carried out using Intel Core i7-6700HQ, up to 3.5 GHz workstation.

Result and Discussion

Molecular Docking Analysis

Molecular docking method investigates the behavior of small drug/drug candidate molecules in the binding site of a target receptor (protein, enzyme etc.). When the molecule is bound to a protein or enzyme receptor, this method presents an estimation about the ligand (small molecule) behavior using structure and electrostatic interactions [22]. Before molecular docking analyses, Phe-Tyr was optimized with DFT/B3LYP/6-31++G(d,p) basis set and the energy of optimized Phe-Tyr dipeptide was calculated as -695576.07609184 kcal/mol.

ACE receptor (PDB ID: 1O8A)

Phe-Tyr dipeptide was docked with ACE receptor using AutoDock Vina program. The best docking pose of Phe-Tyr dipeptide at the ACE active site was shown in Figure 1. The results of binding energies and close interactions of ligand-receptor complex were shown in Figure 2 and Table 1. As a result of molecular docking, the best binding energy was obtained as -7.8 kcal/mol (see Table 2). Gln-281, Asp-415 and Tyr-520 residues in the ACE formed hydrogen bonds having 2.99 Å, 2.30 Å and 3.08 Å bond lengths with Phe-Tyr dipeptide. Asp-453, Val-379, Val-380 and His383 residues formed pi interactions with Phe-Tyr. While Val-379 and Val-380 residues formed pi-alkyl interactions with Phe-Tyr, Asp-453 and His-383 formed pi-anion and pi-pi stacked interactions with dipeptide. In the literature, it was reported that ACE has three active site pockets. While Ala354, Glu384 and Tyr523 residues are included in S1 pocket, Gln281, His353, Lys511, His513 and Tyr520 residues are included in S2 pocket and Glu162 residue is included in S1' pocket [23,24]. When looking at close interactions in this study, Phe-Tyr formed hydrogen bonds (Gln-281 and Tyr-520) with S2 pocket of ACE. When the binding energy of the dipeptide with ACE in our study was compared with the docking studies performed with other peptides in the literature, it was observed that the binding energies with ACE were lower or close to that of our study [24,25]. In docking studies performed with various small peptide structures, it was observed that the binding energies with ACE ranged from -3.6 to -7.9 kcal/mol [24,25]. The binding energies of captopril and enalapril, which are antihypertensive drugs and defined as ACE inhibitors, with ACE were calculated as -5.99 kcal/mol and -6.38 kcal/mol in a literature study, respectively [26]. Accordingly, the peptide structure in our study was found to have a close binding energy or high binding energy profile with the peptides and drugs in the literature. In addition, when the binding sites were examined, it was determined that both the studied peptides and the antihypertensive drugs (captopril, enalapril) bind from the same region with ACE and interact with the same residues [24-27]. It was observed that there is interaction between ACE residues, especially Gln-281 and Tyr-520, and both captopril and peptides studied in the literature [24-27]. In this study, it was determined that Phe-Tyr dipeptide made H-bonds with these two important residues. According to these results, Phe-Tyr can have a good inhibition activity depending on its effective interaction with the active site of ACE.

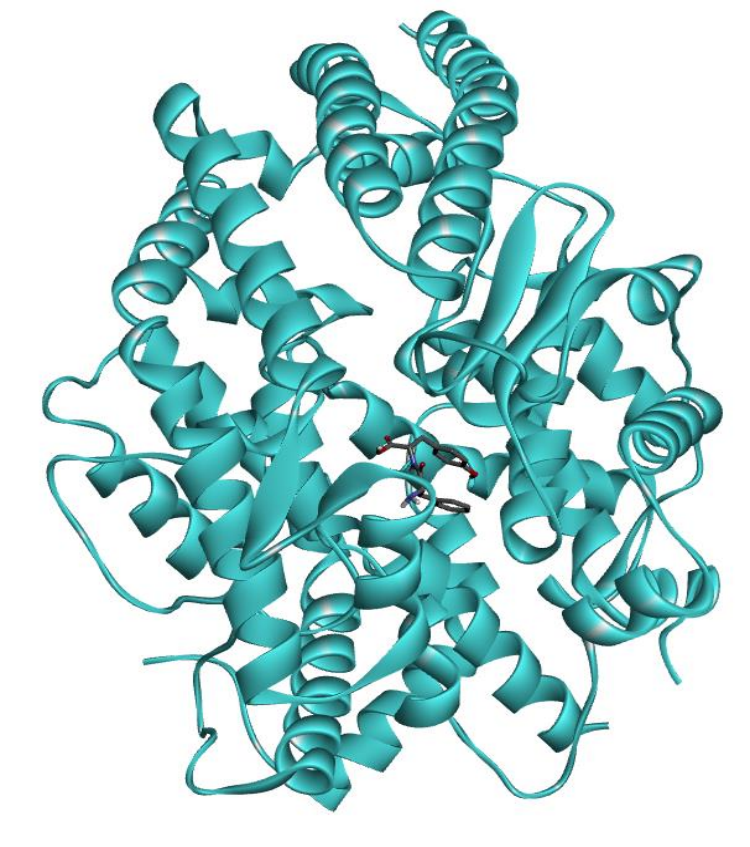

Figure 1. Phe-Tyr dipeptide at ACE active site.

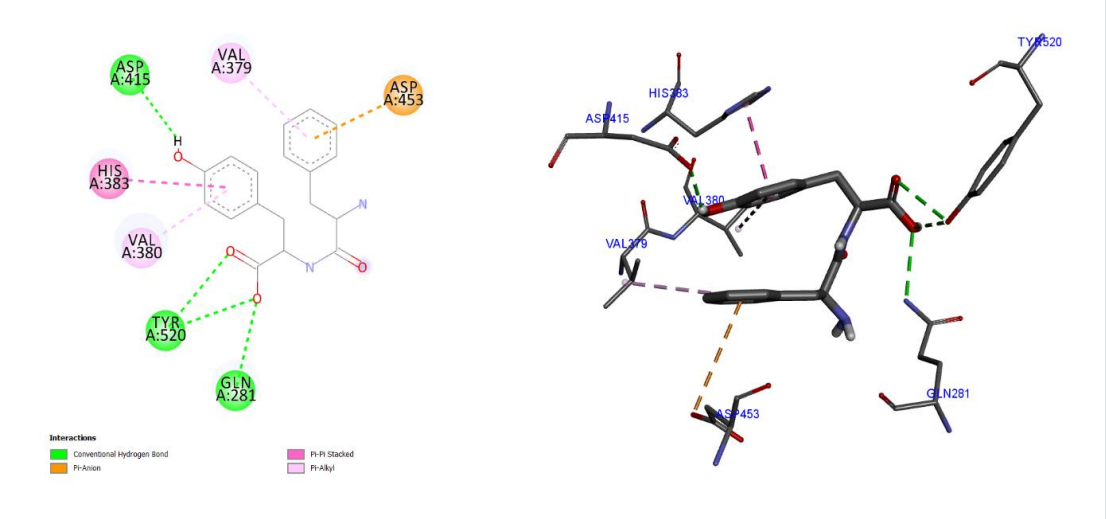

Figure 2. The close interactions of Phe-Tyr dipeptide with ACE.

Table 1. The interaction types of ligand-receptor complex.

Residue	Interaction Type	Distance (Å)
GLN-281	H-Bond	2.99
TYR-520	H-Bond	3.03
		3.04
ASP-415	H-Bond	2.30
HIS-383	Pi-Pi Stacked	3.81
VAL-380	Pi-Alkyl	5.32
VAL-379	Pi-Alkyl	5.33
Asp-453	Pi-Anion	4.91

Table 2. The binding affinities and RMSD values as a result of molecular docking analysis.

		Dist from best mode	
Mode	**Affinity (kcal/mol)**	**rmsd l. b.**	**rmsd u. b.**
1	-7.8	0.000	0.000
2	-7.4	2.375	4.633
3	-7.3	1.856	2.988
4	-7.3	2.381	4.618
5	-7.2	1.729	4.489
6	-7.0	1.659	2.333
7	-7.0	2.819	5.000
8	-7.0	2.239	5.123
9	-6.9	1.693	4.492

AT1 receptor (PDB ID:4ZUD)

Phe-Tyr dipeptide was docked with AT1 receptor and the best docking pose of Phe-Tyr dipeptide at the AT1R active site was shown in Figure 3. The results of binding energies and close interactions of ligand-receptor complex were shown in Figure 4 and Table 3. As a result of molecular docking, the best binding energy was obtained as -8.6 kcal/mol (see Table 4). Tyr-35 and Thr-88 residues in the AT1R formed hydrogen bonds having 3.01 Å and 3.00 Å bond lengths with Phe-Tyr dipeptide. Ile-288 and Pro-285 residues in the AT1R formed pi-alkyl interactions with Phe-Tyr. Tyr-92, Val-108 and Tyr-292 residues formed pi-pi stacked, pi-sigma and pi-pi T-shaped interactions with Phe-Tyr dipeptide, respectively. When the literature was searched, it was seen that Phe-Tyr dipeptide binds with AT1R from the same region with angiotensin receptor blocking drugs and other drug candidate compounds in the literature, but each molecule interacts with different residue groups uniquely [28,29]. In the literature, it was emphasized that while most of the ARBs interact with residues Tyr-35, Trp-84 and Arg-167, the binding conformation and interact residues of each ARB differ [28]. It was also determined by Zhang et al that Telmisartan, an ARB, has pi-interaction with Tyr-92 [30]. In our study, it was determined that Phe-Tyr also has pi-pi stacked interaction with Tyr-92. It has been reported that eprosartan, which is an ARB, tends to have alkyl interactions with Tyr-292 and Ile-288 [30]. In our study, it was determined that Phe-Tyr has pi-alkyl interaction with Ile-288 and pi-pi t-shaped interaction with Tyr-292. In another literature study, docking studies of AT1R with quercetin and chlorogenic acid were performed and H-bond, Van der Waals and electrostatic interactions with Tyr-35, Trp-84, Thr-88, Ser-105, Val-108, Ser-109, Arg-167, Ile-288 residues were detected [29]. In our study, similar to the literature, it was determined that Phe-Tyr dipeptide form hydrogen bonds with Tyr-35 and Thr-88, and pi interactions with Val-108 and Ile-288.

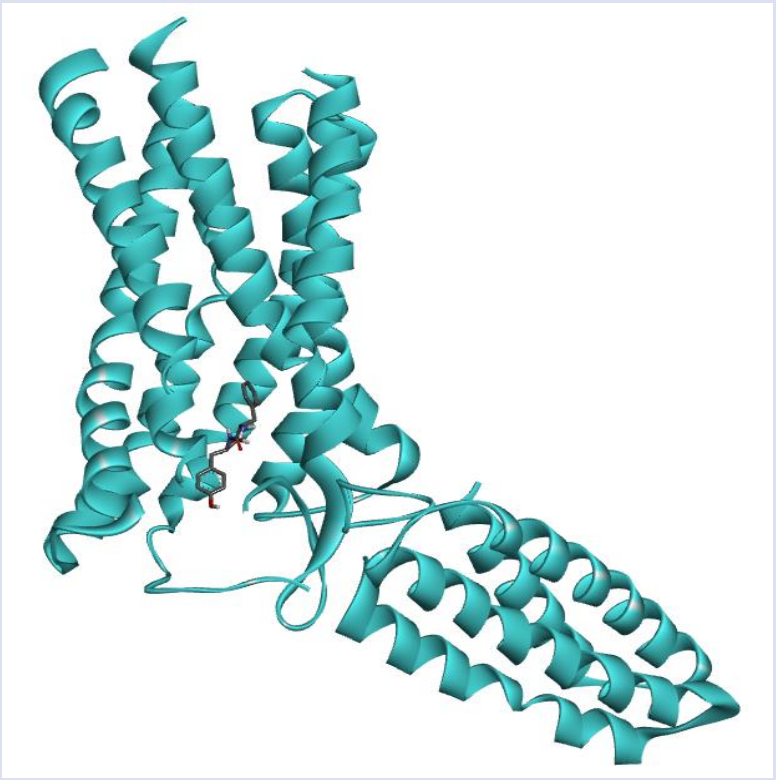

Figure 3. Phe-Tyr dipeptide at AT1R active site.

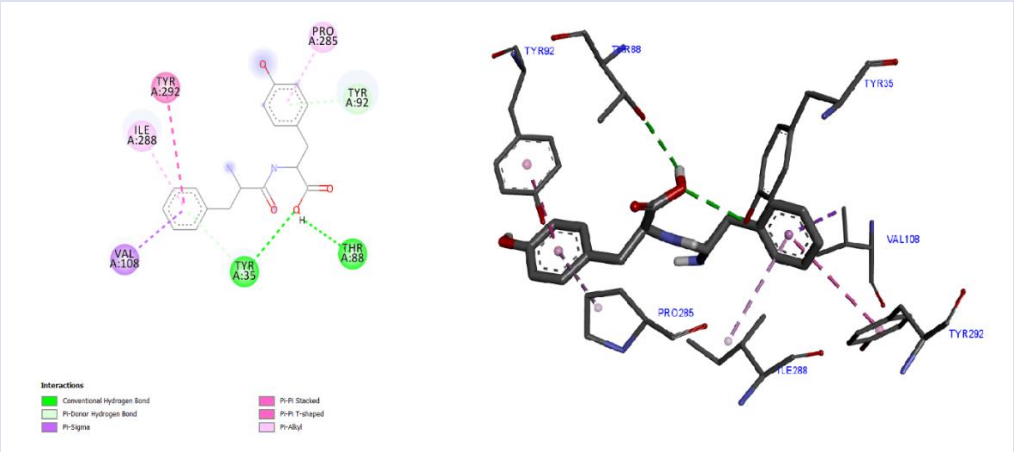

Figure 4. The close interactions of Phe-Tyr dipeptide with AT1R.

Table 3. The interaction types of ligand-receptor complex.

Residue	Interaction Type	Distance (Å)
TYR-35	H-Bond	3.01
THR-88	H-Bond	3.00
TYR-92	Pi-Pi Stacked	3.84
VAL-108	Pi-Sigma	3.90
TYR-292	Pi-Pi T-Shaped	5.21
ILE-288	Pi-Alkyl	5.11
PRO-285	Pi-Alkyl	5.28

Table 4. The binding affinities and RMSD values as a result of molecular docking analysis.

		Dist from best mode	
Mode	Affinity (kcal/mol)	rmsd l. b.	rmsd u. b.
1	-8.6	0.000	0.000
2	-8.4	2.158	4.289
3	-7.8	2.490	4.509
4	-7.6	2.421	7.767
5	-7.5	2.090	3.551
6	-7.5	2.263	8.316
7	-7.4	2.284	4.602
8	-7.3	1.982	7.935
9	-7.2	2.904	8.174

ADME Analysis

ADME (absorption, distribution, metabolism, excretion) analysis is used to obtain pharmacokinetic information for drug candidate molecules. ADME profile of Phe-Tyr dipeptide was determined by using SwissADME and was given in Table 5.

When looking at druglikeness profile of Phe-Tyr, this dipeptide has the potential to be an oral drug. The most important proof of this is that the molecule obeys the Lipinski's rule of 5 [31]. 4 parameters (molecular weight <500 g/mol, have no more than 5 hydrogen bond donors and 10 hydrogen bond acceptors, and octanol/water partition coefficient <5) were determined by Lipinski using the common characteristics of most of the oral drug candidates that passed the phase II clinical stage. In this study, physicochemical and lipophilicity properties of Phe-Tyr were given in Table 5. In physicochemical and lipophilicity properties parts, it was seen that Phe-Tyr has a molecular weight of 328.36 g/mol, five H-bond acceptors, four H-bond donors and its octanol/water partition coefficient is less than five. In addition, it was determined that Phe-Tyr dipeptide is very soluble and has a high absorption property in the gastrointestinal system. It is important that drugs developed for CNS diseases pass through the BBB and other drugs do not affect the CNS [32]. The Phe-Tyr dipeptide is a drug candidate that does not affect the CNS, which has not BBB permeability. PSA is used to characterize the transport process of drug molecules and relates to various causes of drug absorption [33]. PSA value of Phe-Tyr was calculated as 112.65 $Å^2$. Some drugs can be inhibited or induced Cytochrome P450 enzymes. These conditions may cause drug-drug interactions and cause undesirable reactions [34]. Phe-Tyr didn't inhibit CYP450 enzymes in the result of SwissADME server. When the ADME profiles of the antihypertensive drugs losartan and captopril were compared [35], it was observed that the Phe-Tyr dipeptide also fully complied with the Lipinski's rule of 5. It has been determined to be high in gastrointestinal absorption like antihypertensive drugs. The profile of CYP3A4 inhibitor of Phe-Tyr dipeptide was similar to Captopril [35].

Table 5. ADME properties of Phe-Tyr dipeptide

Physicochemical Properties	Phe-Tyr
MW	328.36 g/mol
No. of heavy atoms	24
No. of arom. heavy atoms	12
No. rotatable bonds	8
No. of H-bond acceptors	5
No. of H-bond donors	4
Polar surface area	112.65 Å²
Lipophilicity	
$LogP_{O/W}$(iLOGP)	1.78
$LogP_{O/W}$(XLOGP3)	-1.68
$LogP_{O/W}$(WLOGP)	1.07
$LogP_{O/W}$(MLOGP)	1.35
$LogP_{O/W}$(SILICOS-IT)	1.75
Consensus LogPO/W	0.85
Water Solubility	
Log S (ESOL)	-0.66
Log S (Ali)	-0.17
Log S (SILICOS-IT)	-4.24
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_P (skin permeation)	-9.50 cm/s
Druglikeness	
Lipinski	Yes, 0 violation
Ghose	Yes
Veber	Yes
Muegge	Yes
Bioavailability Score	0.55

Conclusion

In conclusion, a novel study of Phe-Tyr dipeptide having antihypertensive were theoretically carried out using *in silico* methods. Molecular activity of Phe-Tyr dipeptide was compared with antihypertensive drugs by using theoretical calculations. Molecular docking method was used to obtain an estimate of the biological activity of the molecule. The interactions of the Phe-Tyr dipeptide with ACE and AT1 receptors were investigated by molecular docking method. It was determined that Phe-Tyr dipeptide interacts more with the S2 region (Gln-281 and Tyr-520), which is one of the active sites of ACE, where synthetic drugs like Captopril used in hypertension studies interact. In another molecular docking study, it was determined that the Phe-Tyr dipeptide interacted with AT1R and formed H-bond and pi interactions similar to ARBs like Telmisartan and Eprosartan synthetic drugs with Tyr-92 and Ile-288, Tyr-292 residues, respectively. In addition, the ADME profile was determined for Phe-Tyr, which has the potential to be an antihypertensive drug according to low molecular weight, appropriate H-bond acceptors and H-bond donor counts and favorable octanol/water partition coefficient. As a result of *in silico* ADME analysis, it was determined that the Phe-Tyr dipeptide is a drug candidate in accordance with Lipinski's rule of 5 and had an ADME profile similar to antihypertensive drugs. Finally, it can be said that this study will be helpful experimental studies.

Conflicts of interest

The authors stated that did not have conflict of interests.

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