Available free online at www.medjchem.com

Mediterranean Journal of Chemistry

Mediterranean Journal of Chemistry **2024**, 14(2), 105-111

Spatial structure of the heptapeptide analog of Nociceptin molecule

Larisa Ismail Ismailova*, and Namiq Abdulavval Akhmedov

Baku State University, Institute for Physical Problems, Z. Khalilov Str.23, Baku, AZ-1148, Azerbaijan

Abstract: It is known that nociceptins are a new type of regulatory peptide. Knowledge of these peptide molecules' structural and functional properties is of great practical importance for medicine and pharmacology. Their mechanisms of action are considered anti-opioid. This scientific work is devoted to studying the spatial structure of the heptapeptide H-Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7-OH. It examines the conformational capabilities of this heptapeptide molecule. This neuropeptide molecule is a stable analog of the nociceptin. The biologically active conformation of the peptide molecule, which is realized upon interaction with the receptor, is included in the set of low-energy structures. Therefore, studying the spatial structure of peptide molecules is of great interest. Theoretical conformational analysis about nonvalent, electrostatic, and torsional interactions, the energy of the hydrogen bonds, and a special computer program carried out the calculations. The 10 low-energy conformations of this molecule and the values of the dihedral angles of the main chain and side chains are found, and the energy of the intra- and inter-residue interactions is estimated. It is revealed that low energy conformations of this molecule have the half-folded and folded type of backbone. The side chains of the Phe1 and Phe4 amino acids in low-energy conformations carry out effective interactions and are conformationally labile amino acids; they bring together the regions of the main chain and the side chains of the amino acids included in the heptapeptide. These folded forms bring parts of the backbone and the amino acids' side chains together, resulting in important interactions.

Keywords: Structure; Nociceptin; Molecule, Heptapeptide; Conformation.

1. Introduction

The regulatory peptide molecules and their biological functions in living systems are related to their specific spatial organizations. Therefore, to understand the mechanism by which the peptides function, it is necessary to know their spatial structures. It is known that new families of the regulatory peptides are being discovered, and their properties are being studied. One of these families is nociceptins. For medicine and pharmacology, knowledge of the structure-functional properties of these peptide molecules is of great practical importance. Nociceptin is an opioid-related peptide with anti-analgetic solid properties. It is widely present in the central nervous system, affecting motor, anxiety, and pain sensitivity. It is important to note that the original synthetic analogs of the N-terminal fragment of nociceptin, the FGGF tetrapeptide, were studied. It causes the binding of natural nociceptin to a specific ORL1 receptor [1].

New nociceptin analogs FGGF-GP, FGGF-PGP, and FGGF-VGP have recently been synthesized [2]. It has been shown that the FGGF-VGP peptide, like natural nociceptin, significantly reduces locomotor activity in animals. The most pronounced effect of FGGF-GP was the anxiolytic effect. Our scientific work studies the spatial structure and conformational possibilities of the heptapeptide molecule H-Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7-OH. This neuropeptide molecule is a stable analog of the nociceptin. It was found that this molecule's N-terminal tripeptide and tetrapeptide are active [3,4].

Solutions' short linear regulatory peptides do not have a fixed spatial structure. Usually, the solvent's amino acid sequence and physicochemical properties determine the set of low-energy conformations of the peptide molecule. The biologically active conformation of this peptide molecule, which is realized upon interaction with the receptor molecule, is included in the set of low-energy structures. Therefore, studying peptide molecules' spatial structure and conformational capabilities is very interesting. The peptide molecules and their biological functions in living systems are related to their specific spatial structures. Therefore, they must know their three-dimensional structures to understand the mechanism by which the peptides function. It is important to know the full complement of low-energy conformational states.

**Corresponding author: Larisa Ismail Ismailova*
Email address: lara.ismailova.52@mail.ru
DOI: http://dx.doi.org/10.13171/mjc02407111782ismailova

Received May 6, 2024
Accepted July 1, 2024
Published July 11, 2024

2. Materials and methods

The calculations were carried out using theoretical conformational analysis. The potential energy of this molecule was chosen as the sum of the nonvalent, electrostatic, and torsional interaction energies and the energy of hydrogen bonds. Nonvalent interactions were assessed using the Lennard-Jones potential. According to Coulomb's law, electrostatic interactions were calculated in the monopole approximation using partial charges on atoms. The conformational properties of the heptapeptide molecule were studied in an aqueous environment, and therefore, the dielectric constant was taken to be 10. The energy of hydrogen bonds was estimated using the Morse potential. We have compiled program [5] for linear peptide molecules and complexes based on the algorithm Hermans J. and Ferro D6 proposed. This program is published by [6]. The conjugate gradient method was used to search for the minimum potential energy of a peptide molecule, the algorithm of which was presented to us by V.G. Dashevsky [7]. Drawings of low-energy conformations of peptide molecules were performed using the Hyper Chem program [8].

The low-energy conformations of this molecule and the values of the dihedral angles of the main chain and side chains are found, and the energy of the intra- and inter-residue interactions is estimated. The present paper is an extension of our previous investigations of structural and functional organization of peptide molecules [9-20]. The spatial structure of peptide molecules has been studied in other works [21,22].

Neuropeptides play an important role in all nervous systems, and structure-functional studies of these peptides is one approach to understanding this role. The object of our scientific research is an analog of nociceptin molecule heptapeptide H-Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7-OH. This molecule has three amino acids Gly, which has no side chain; two amino acids Phe and one Val, which have large and labile side chains; and one amino acid, Pro, with a rigid side chain.

In presenting the results of the calculation of the spatial structure of the molecules, we used the classification suggested in work [23]. All structural versions are divided into shapes, including certain primary chain forms; a set of conformations represents each form. The conformations are determined by the number of rotational degrees of freedom of the side chains of the residues being included in the molecule. The conformational state of each amino residue is conveniently described by the backbone φ, ψ, ω and side chain χ_1, χ_2… dihedral angles. The term "conformation" used in the following analysis always implies exact quantitative residue or fragment geometry characteristics. The φ and ψ dihedral angles are located in low-energy regions R, B, L, and P of the conformational map for a stable conformation. We introduce the "form of a residue" notion to denote the region of its backbone dihedral angle. The conformation of the backbone forms of residue in a given amino acid sequence will specify the backbone form of a fragment. Forms belonging to a particular shape have an analogous peptide chain contour and a similar mutual arrangement of backbones and side chains. Designations indications of dihedral angles have been measured up to the generally accepted nomenclature [24].

3. Results and Discussion

The three-dimensional structure and conformational possibilities of the heptapeptide H-Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7-OH were studied in fragments. First, the conformational properties of the tripeptides Phe1-Gly2-Gly3 and Val5-Gly6-Pro7, tetrapeptide Phe1-Gly2-Gly3-Phe4 were determined based on the stable conformations of the monopeptides. And finally, adding the tetrapeptide Phe1-Gly2-Gly3-Phe4 and tripeptide Val5-Gly6-Pro7 allowed us to calculate the spatial structure of the heptapeptide molecule. It is known that the active site of the molecule that activates the receptor is the N-terminal tetrapeptide Phe1-Gly2-Gly3-Phe4 [3,4]. We carried out all of these structures by minimization over all the dihedral angles.

The conformational properties of the tripeptide Phe1-Gly2-Gly3 were studied based on the stable conformations of the monopeptides N-acetyl-L-phenylalanine and N-acetyl-L-glycine. For a given tripeptide containing 37 atoms and 10 variable dihedral angles, 4 shapes are possible (ee, ef, fe, and ff), represented by 16 main chain forms. About 100 conformations were calculated, all were minimized in energy, and their geometric and energy parameters were estimated. The calculation revealed the presence of a sharp energy differentiation in the forms of the main chain and shapes.

The amino acid sequence of the tetrapeptide molecule included two amino acids, each phenylalanine and glycine. Tetrapeptide molecule Phe1-Gly2-Gly3-Phe4 contains 57 atoms and 15 variable dihedral angles. The specificity of the amino acid side chains of the Just as in the experimental work [3], these conformations can represent four structures. Our calculation of the spatial structure of the tripeptide molecule revealed low-energy conformations of four shapes. Several conformations represent each resulting structure. 12 low-energy conformations, including the global conformation B21BL, are possible for a semi-folded shape ef. A fully unfolded structure shape ee is represented by conformation B_{11}PL and a fully folded shape ff structure B_{21}PR. The semi-folded structure fe is defined by the conformation B_{21}BR. In all low-energy conformations of the tripeptide, the main energy contribution was made by dipeptide and tripeptide interactions. It should be noted that

dipeptide and tripeptide interactions mainly contribute to the energy of low-energy conformations. The main energy contribution comes from nonvalent interactions. All 24 low-energy conformations of the tripeptide molecule were considered when calculating the structure of the tetrapeptide Phe1-Gly2-Gly3-Phe4.

The tetrapeptide molecule determined the number of initial approximations. Over 150 conformations were calculated, belonging to 64 main chain forms and 8 possible shapes for this molecule. All of them were minimized in energy, and their geometric and energy parameters were estimated. There is energy differentiation regarding the conformations and forms of the main chain and shapes. Representatives of 22 main chain forms fall into the energy range 0 – 16.8 kJ/mol. The relative energy of the conformations of the tetrapeptide molecule varied within the range 0–33.6 kJ/mol.

The low energy conformations of tetrapeptide molecule are eff ($B_{11}RRR_{11}$, $B_{11}RRB_{11}$), efe ($B_{21}BLB_{11}$), fee ($B_{11}PLB_{11}$), fff ($B_{11}PRR_{11}$. $B_{11}LPR_{11}$), eee($B_{11}BBB_{11}$.) and fee ($B_{11}PLB_{11}$.). The global conformation of this molecule is $B_{11}RRR_{11}$. The main contributions of the inter-residual interactions in this conformation were dipeptide, tripeptide, and tetrapeptide contributions. In this conformation, amino acid residues Phe1-Gly2-Gly3-Phe4 form a folded structure. It is revealed that low energy conformations of this molecule have the folded and half-folded types of backbone. These folded forms bring parts of the backbone and the amino acids' side chains together, making convenient interactions. The results can be used to study the spatial structure of tetrapeptide molecules and the conformational capabilities of side chains of the Phe1 and Phe4 when interacting with receptor molecules. The side chains of these residues have conformational freedom in the low-energy structures of the tetrapeptide molecule. Thus, the theoretical conformational analysis of this peptide molecule led to such structural organizations of molecules that do not exclude the realization by the molecule of several various functions that require strictly specific interactions with various receptors.

The low-energy conformations of the tetrapeptide Phe1-Gly2-Gly3-Phe4 and the C-terminal tripeptide Val5-Gly6-Pro7 were taken into account when calculating the spatial structure of the entire heptapeptide molecule Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7. Molecule consists of phenylalanine, glycine, valin, and prolin amino acid residues. In order to study the spatial structure of the heptapeptide molecule, Phe1, and Phe4 were taken in the R and B form of the main chain, the χ1 angle was taken in the 60^0, $180^{0,}$ and -60^0 states, which was possible due to the torsion potential, and the χ2 angle was taken in the 90^0 state, which was possible due to the torsion potential.

The side chain of glycine amino acid consists of one atom H, so its φ and ψ angles have large rotational freedom. R, B, L, and P glycine amino acid backbone forms were all chosen as starting variants. For the valine amino acid residue, the R, B forms of the main chain, the 60^0, $180^{0,}$ and -60^0 states of χ1 angle, which are possible according to the torsion potential. For Pro7 amino acid residue R and B main chain forms were selected as starting conformation.

Table 1. The energy parameters: relative energy (U_{rel}) and energy contributions of nonvalent (U_{nv}), electrostatic (U_{el}), torsion (U_{tors}) interactions of optimal conformations of the heptapeptide Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7

№	Shapes	Conformation	U_{rel}	Energy range, kJ/mol		
				U_{nv}	U_{el}	U_{tors}
1	fffeff	B_{11} LP$B_{11}B_{222}$ PR	0.0	-105.4	9.7	9.7
2		$B_{11}PRB_{11}$ R_{222} RB	6.3	-105.8	10.9	15.1
3		B_{11} LP$B_{11}R_{222}$ RB	6.7	-101.2	8.4	12.6
4		R_{21} BP$B_{11}R_{222}$ RB	13.0	-100.0	9.7	17.2
5	fffeef	B_{11} LP$B_{21}B_{222}$ RR	9.7	-98.7	7.6	14.3
6		R_{31} BP$B_{21}B_{222}$ RR	7.6	-105.0	11.3	14.7
7	fffeee	R_{31} BPB_{21} B_{222} BR	17.6	-93.7	8.8	16.0
8		R_{11} BPB_{21} R_{222} LB	18.9	-93.2	10.9	14.7
9	fffefe	B_{11} LP$B_{11}B_{222}$ LR	19.3	-89.5	11.3	10.5
10		$B_{21}PRB_{11}R_{222}$ BB	23.1	-89.9	9.7	16.4

Over 400 initial approximations were complied, which were then minimized in energy. The calculation results are presented in Table 1. The heptapeptide molecule contains 94 atoms and 24 variable dihedral angles. The relative energy of the conformations of the heptapeptide molecule varied within the range of 0–30 kJ/mol. There is energy differentiation regarding the conformations and forms of the main chain and shapes. The number of possible shapes in a given molecule is 24.

For this reason, the conformations of 24 shapes were calculated. Since the starting conformations were chosen as mentioned above, the conformations of the main chain 168 forms were calculated. As can be seen from the molecule's sequence of amino acid residues, the molecule includes two amino acid residues, phenylalanine with aromatic side chains, three glycine, valine, and proline amino acid with rigid side chain.

The results of the calculations show that there is a sharp differentiation according to the energies of these forms of the main chain. The total energies of the calculated conformations of the 30 main chain forms vary in the range of (-86.5) – (-46.6) kJ/mol. The lowest energy conformation of each of the 10 forms of the main chain was selected, their shapes, nonvalent, electrostatic, torsional interaction energies, and relative energies are shown in Table 1. You can see that the contribution of nonvalent interaction energies to the low-energy conformations shown is in the range of (-105.8) – (-89.5) kJ/mol, electrostatic interaction energy is in the range of (7.6) – (11.3) kJ/mol, torsional interaction energy (9.7) – (17.2) kJ/mol and relative energies (0) – (2,3.1) kJ/mol. Various interaction energies that play a role in the stabilization of all the conformations shown in Table 2, monopeptide, dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, and heptapeptide interaction energies within an amino acid residue, between amino acid residues were calculated, their roles were determined, and their relative energies are shown in Table 2. Figures 1a, 1b, 1c, and 1d show the spatial arrangement of atoms in those conformations.

Table 2. Energy inside and between residual interactions in the conformations of the heptapeptide molecule: $B_{11}LPB_{11}B_{222}PR$ (U_{rel}=0 kJ/mol, first line), $B_{11}LPB_{21}B_{222}RR$ (U_{rel}=14.3 kJ/mol, second line), $R_{11}BPB_{21}R_{222}LB$ (U_{rel}=17.6 kJ/mol, third line), $B_{11}LPB_{11}B_{222}LR$ (U_{rel}=19.3 kJ/mol, fourth line).

Phe1	**Gly2**	**Gly3**	**Phe4**	**Val5**	**Gly6**	**Pro7**	
-1.3 **1.7** **5.5** **-1.7**	-7.1 -5.9 1.7 -6.7	-1.3 -2.1 -5.0 -1.3	-17.6 -16.8 -17.2 -17.6	-9.2 -5.9 -21.0 -8.8	-2.9 -2.5 -2.1 -1.7	-10.9 -23.1 -8.8 -10.5	Phe1
	5.5 5.5 5.0 5.5	0.4 -1.3 -0.4 0.4	-7.1 -7.1 -8.0 -6.7	-0.8 -0.8 -0.8 -0.8	-0.4 -0.4 0.0 -0.4	0.4 0.4 0.4 0.4	Gly2
		5.5 5.5 5.5 5.5	-4.6 -4.2 -5.5 -5.0	-1.3 -2.1 -2.5 -1.3	0.0 0.0 -0.4 0.	-0.4 0.0 -2.1 -1.7	Gly3
			-2.1 -0.4 -0.4 -2.9	-7.6 -13.9 -12.2 -5.9	-8.4 -9.2 -9.7 -6.3	-18.1 -1.7 -1.7 -13.0	Phe4
				-2.5 -2.5 1.7 1.7	0.8 -1.7 -2.9 -1.3	-5.5 -2.9 -4.6 -1.7	Val5
					5.0 5.5 5.5 5.5	-10.9 -8.8 -8.4 -7.1	Gly6
						3.8 3.4 3.4 3.4	Pro7

The global conformation of the heptapeptide molecule (U_{rel}=0 kJ/mol) is $B_{11}LPB_{11}B_{222}PR$, belonging to the fffeff shape. This conformation is favorable due to both nonvalent and electrostatic

interaction energies. The contribution of the stabilizing nonvalent interactions to this conformation is (–105.4) kJ/mol, whereas electrostatic interactions account for 9.7 kJ/mol and torsion for 9.7 kJ/mol. This conformation is efficient in nonvalent interactions forming hydrogen bonds between main chain atoms, contributing (-8.4 kJ/mol) in total energy. The main contributions of the interresidual interactions in this conformation were dipeptide contributions (–29.0) kJ/mol, tripeptide (–23.6) kJ/mol, tetrapeptide (–36.5) kJ/mol, pentapeptide (–10.0) kJ/mol, hexapeptide (-2.5) kJ/mol and heptapeptide (-10.9) kJ/mol (Table 2). In this conformation, amino acid residues Phe1-Gly2-Gly3-Phe4-Pro5-Gly6-Pro7 form folded structure (fig. 1a). The geometric parameters of the four low-energy conformations B_{11}LP $B_{11}B_{222}$ PR, B_{11}LP$B_{21}B_{222}$RR, R_{31}BP$B_{21}R_{222}$LB and B_{11}LP $B_{11}B_{222}$ LR of the heptapeptide molecule are presented in Table 3. It is revealed that low energy conformations of this molecule have the folded and half-folded types of backbone. These folded forms bring parts of the backbone and the amino acids' side chains together, making convenient interactions.

Table 3. Geometric parameters (degree) of the optimal conformations of Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7 heptapeptide molecule.

Residues	Shape (conformation)			
	fffeff (B_{11}LP $B_{11}B_{222}$ PR)	fffeef (B_{11}LP$B_{21}B_{222}$RR)	fffeee (R_{31}BP$B_{21}R_{222}$LB)	fffefe (B_{11}LP $B_{11}B_{222}$ LR)
Phe 1	-178 161 183 65 88	-170 152 180 68 84	-43 -62 176 -63 99	-186 160 -177 65 89
Gly2	78 85 -176	82 79 -176	-102 56 -176	78 85 -177
Gly3	90 -57 180	80 -78 176	88 -61 174	91 -56 -178
Phe4	-140 149 -179 54 94	-92 145 180 -178 87	-87 140 -177 182 83	-139 148 180 53 92
Val5	-103 101 -175 180 180 180	-100 100 180 180 180 180	-100 -61 -178 180 180 180	-107 102 175 180 180 180
Gly6	106 -103 179	-90 -90 180	90 90 180	91 94 180
Pro7	-60 -50	-60 -50	-60 130	-60 -50
U_{rel} (kJ/mol)	0	14.3	17.6	19.3

Note: The values of dihedral angles are given in the sequence φ, ψ, ω, χ^1, χ^2.

The study of the spatial structure of the heptapeptide molecule shows that the molecule has such a set of spatial structures that it can perform various biological functions and interact with multiple receptor molecules. The results can be used to study the spatial structure of the heptapeptide molecule and the conformational capabilities of the Phe1 and Phe4 side chains when interacting with receptor molecules. Conformational possibilities of side chains of Phe1 and Phe4 in the best low-energy conformations of peptide molecules have been investigated by plotting conformational maps. The conformational maps show that the side chains of these residues have conformational freedom in the low-energy structures of the heptapeptide molecule.

Figures 1(a, b, c, d) represent schematically the backbone forms and positions of residues in low-energy conformations B_{11}LP $B_{11}B_{222}$ PR, B_{11}LP$B_{21}B_{222}$RR, R_{31}BP$B_{21}R_{222}$LB and B_{11}LP $B_{11}B_{222}$LR of the heptapeptide molecule. The figures show that this molecule has a folded N-terminal fragment.

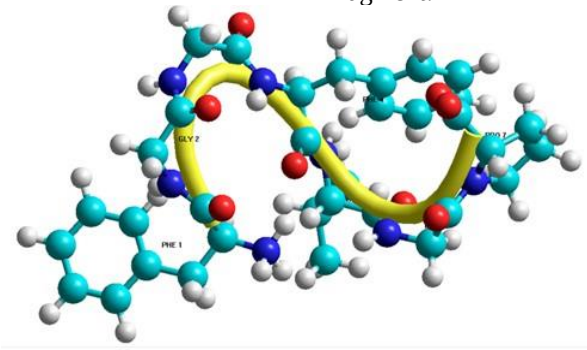

Figure 1a. Spatial structure of the low energy conformation B_{11}LP $B_{11}B_{222}$ PR of the heptapeptide molecule Phe1-Gly2-Gly3-Phe4-Val5-Gly6-Pro7

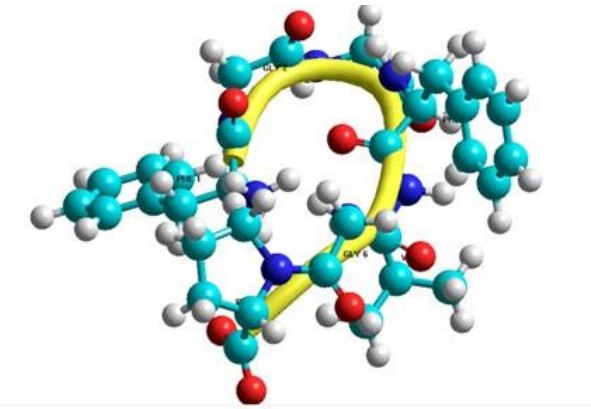

Figure 1b. Spatial structure of the low energy conformation $B_{11}LPB_{21}B_{222}RR$ of the heptapeptide molecule

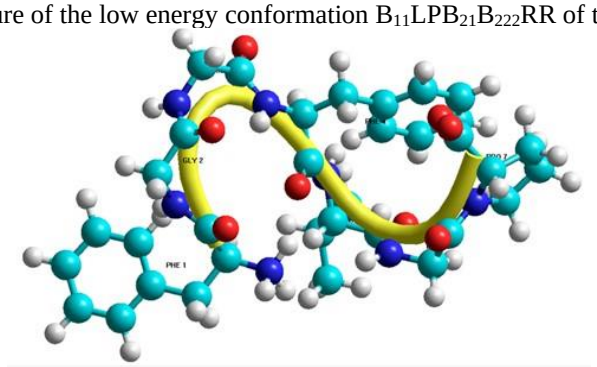

Figure 1c. Spatial structure of the low energy conformation $R_{31}BPB_{21}R_{222}LB$ of the heptapeptide molecule

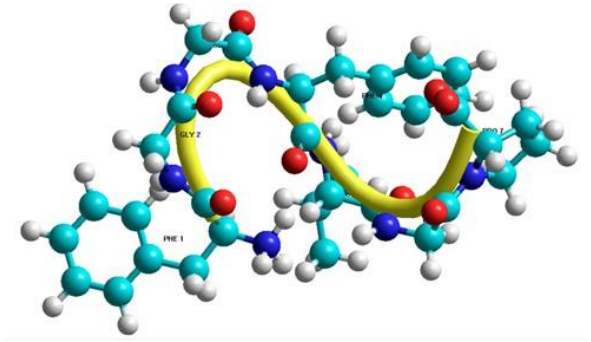

Figure 1d. Spatial structure of the low energy conformation $B_{11}LP\ B_{11}B_{222}\ LR$ of the heptapeptide molecule

4. Conclusion

In detail, we have studied the spatial structure and conformational properties of heptapeptide molecule H-Phe1-Gly2-Gly3-Phe4-Pro5-Gly6-Pro7-OH. The conformational possibilities of these molecules were analyzed using theoretical conformational analysis. The potential function of the system is chosen as the sum of non-valence, electrostatic, and torsion interactions and the energy of hydrogen bonds. The low-energy conformations of this molecule, the values of the dihedral angles of the main and side chains of amino acid residues were found, and the energy of intra- and inter-residual interactions was estimated. The study of the spatial structure of heptapeptide molecules has almost 10 low-energy conformations. It is revealed that low energy conformations of this molecule have the half-folded and folded type of backbone. It can be assumed that the low-energy folded form of the main chain of the molecule provides intramolecular interactions. Amino acids Phe1 and Phe4 cannot interact with the receptor. Conformational maps were constructed around the dihedral angles of the Phe1 and Phe4 side chains. The conformational maps show that almost complete conformational freedom is possible around the dihedral angles χ1 of the Phe1 and Phe4 residues. Therefore, the lack of activity of the heptapeptide molecule can be associated with the folded form of the molecule and the lack of conformational freedom of amino acid residues

References

1. J.M. Witkin, M.A. Statnick, L.M. Rorick-Khin, J.E. Pintar? The biology of Nociceptin/Orphanin FQ(N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence, Pharmacol. Ther., **2014**, 141, 283-299.
2. E.A. Ivanova, N.Yu. Sarycheva, V.A. Dubynin, A.V. Malyshev, Behavioral effects of original tetrapeptide an analog of N-terminal nociceptin fragment, Bulletin of Experimental Biology and Medicine, **2012**, 13, 851-857.

3. D. Reha, H. Valdes, J. Vondrasek, P. Hobza, Structure and IR spectrum of phenylalanyl-glycyl-glycine tripeptide in the gas-phase: IR/UV experiments ab initio quantum chemical calculations, and molecular dynamic simulations, Chemistry, A European Journal, **2005**, 11, 6803-6817.
4. K.R. Wilson, M.J. Cruz, Ch. Nicolas, L. Belau, Thermal vaporization of biological nanoparticles: fragment-free vacuum ultraviolet photoionization mass spectra of tryptophan, phenylalanine-glycine-glycine, and beta-carotene, J. Phys. Chem., **2006**, 110, 2106-2113.
5. I.S. Maksumov, L.I. Ismailova, N.M. Godjaev, A computer program for calculation of conformations of molecular systems, J. Struc. Chem., **1983**, 24, 147-148.
6. J. Hermans, D. Ferro, Representation of a protein molecule as a tree and application to modular computer programs which calculate and modify atomic coordinates, Biopolymers, **1971**, 10, 1121-1138.
7. V.G. Dashevskiy, Conformations of the organic molecules, Moskow, Chemistry, **1974**, 432.
8. http//www.Hyper Chem.com
9. L.I. Ismailova, G.A. Akverdieva, S.D. Demukhamedova, N.A. Akhmedov, Molecular modelling of Pro-Gly gliproline and its complexes, Moscow University Physics Bulletin, **2023**, 78, 668-680.
10. N.A. Akhmedov, Sh.N. Gadjiyeva, R.M. Abbasli, Structural organization of Asp-Pro-Lys-Gln-Asp-Phe-Met-Arg-Phe-NH_2 molecule, Cur.Top. in Pept. & Prot.Res., **2009**, 10, 57-62.
11. N.A. Akhmedov, L.I. Ismailova, L.N. Agayeva, N.M. Gocayev, The spatial structure of the cardio active peptides, Cur.Top. in Pept. & Prot. Res., **2010**, 11, 87-93.
12. N.A. Akhmedov, L.I. Ismailova, R.M. Abbasli, L.N. Agayeva, S.R. Akhmedova, Spatial structure of Octarphin molecule, IOSR JAP., **2016**, 8, 66-70.
13. N. Akhmedov, L. Agayeva, G. Akverdieva, R. Abbasli, L. Ismailova, Spatial structure of the ACTH-(6-9)-PGP molecule, J. Chem. Soc. Pak., **2021**, 43, 500-504.
14. N. Akhmedov, L. Agayeva, S. Akhmedova, R. Abbasli, L. Ismailova, Spatial structure of the β-Casomorphin-7 Molecule, IOSR Journal of Applied Physics, **2021**, 5, 62-67.
15. L.I. Ismailova, R.M. Abbasli, N.A. Akhmedov, Computer modeling of the spatial atructure of nonapeptide molecule, Control and Optimization with Industrial Applications, Proceedings of the 7-th International Conference, **2020**, 218-220.
16. N.A. Akhmedov, L.N. Agayeva, R.M. Abbasli, L.I. Ismailova, Computer modeling of law-energy spatial structures of casoxin G molecule. Proceedings of the 8th International Conference on Control and Optimization with Industrial Applications (COIA-22), Azerbaijan, **2022**, 1, 63-65.
17. L.I. Ismailova, R.M. Abbasli, N.A. Akhmedov, Structural organization of the Gly-Pro-Arg-Pro molecule, Actual questions of the biological physics and chemistry **2021**, 6, 53-56.
18. L.N. Agaeva, A.A. Abdinova, S.R. Akhmedova, N.F. Akhmedov, N.A. Akhmedov, Spatial Structure of Soymorphin-6 molecule, Biophysics, **2023**, 68, 929–933.
19. N.A. Akhmedov, L.N. Agaeva, R.M. Abbasli, L.I. Ismailova, Spatial Structure of the Casoxin C molecule, Biophysics, **2024**, 69, 43–50.
20. L.N. Agayeva, N.A. Akhmedov, G.T. Imanova, Spatial Structure of the Casoxin D Molecule, Materials Research Innovations, **2024**.
21. S. Tahirli, F. Aliyeva, H. Şenol, S. Demukhamedova, G. Akverdieva, I. Aliyeva, S. Veysova, N. Sadeghian, S. Günay, Y. Erden, P. Taslimi, A. Sujayev,F.Chiragov, Novel complex compounds of nickel with 3-(1-phenyl-2,3-dimethyl-pyrazolone-5) azopentadione-2,4: synthesis, NBO analysis, reactivity descriptors and in silico and in vitro anti-cancer and bioactivity studies, Journal of Biomolecular Structure and Dynamics, **2024**, 1-25.
22. S. Wang, Y. Li, H. Xu, Y. Sun, S. Xu, Design, structure of Amphiphiphilic peptide and its application from single molecule to nanoparticle, Results in Ingineering, **2022**, 16, 100747-10055.
23. E.M. Popov, An Approach to calculations of the problem of structure functional organization of natural peptides, Mol. Biol., **1985**, 19, 1107-1138.
24. A. Kotyk, Quantities, Units and Symbols in Physical Chemistry, Blackwell Scientific Publications, Oxford, **1999**.