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НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

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XXX МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
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the orthosteric and allosteric sites of the muscarinic receptor in comparison with Nebracetam is shown in fig. 2.

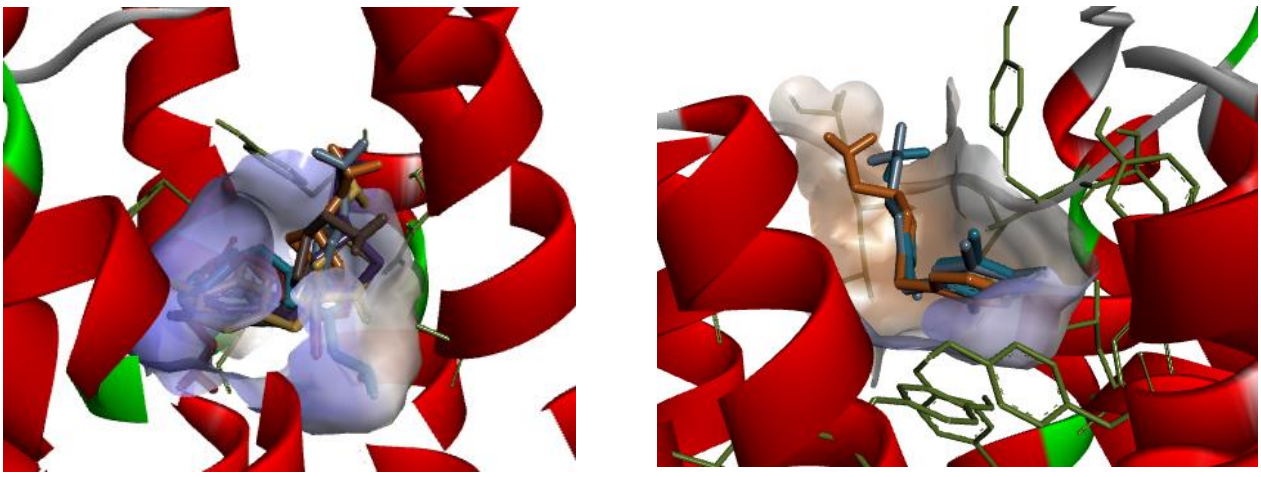

Fig. 2. Superpositions of the studied derivatives in the orthosteric (left panel) and allosteric (right panel) sites of the muscarinic receptor. *The (R) and (S) conformations of Nebracetam in the orthosteric site are shown in blue and orange, respectively.*

Conclusions. According to the estimated values and detailed analysis of the locations of the studied derivatives, the possibility of nootropic activity through the muscarinic receptor was established. It was also established that, depending on the enantiomeric configuration, the molecules formed stable complexes with the target and had characteristic binding modes both in the orthosteric site and in the site of positive allosteric modulation of mAChR.

USING MOLECULAR DOCKING TO OPTIMIZE THE SEARCH FOR NEW DIPEPTIDYLPEPTIDASE-4 (DPP4) INHIBITORS

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Introduction. About 500 million people worldwide have diabetes, and about 1.5 million deaths each year are directly related to the disease. Both the incidence and prevalence of diabetes have been steadily increasing over the past few decades. Diabetes in Ukraine ranks 3rd in prevalence after cardiovascular diseases and oncology. Protocols for the control of type 2 diabetes include most oral hypoglycemic agents that enhance insulin secretion. Constant use of such drugs can lead to the depletion of β-cells, which can later lead to a severe form of diabetes. Dipeptidyl peptidase-4 (dpp-4) inhibitors are an important class of antidiabetic drugs recognized for their systemic biological effects. The main factor of such activity is that they inhibit the glucose-dependent secretion of glucagon against the background of increased blood glucose levels. Therefore, the search for new hypoglycemic agents aimed at this target is definitely relevant and meets all the challenges of today.

Aim. Optimizing the search for new dpp-4 inhibitors by modifying existing frameworks and further using the molecular docking methodology for the generated derivatives.

Materials and methods. New dpp-4 inhibitors, which were generated using the Marvin Sketch 20.5 program, were chosen as objects of study. Active center of macromolecule from the Protein Data Bank (PDB) dipeptidylpeptidase-4 (PDB ID: 5Y7J), was used as biological targets for docking. The Autodock 4.2 software package was used for receptor-oriented flexible docking.

Results and discussion. The design of potential inhibitors was based on the inhibitory (R) β-aminoamide base, which contained a substituted piperazin-2-one derivative or (S)-pyrrolidine-2-carbonitrile fragment and substituted diphenyl rings in the 4th position of the β-aminoamide chain (fig. 1).

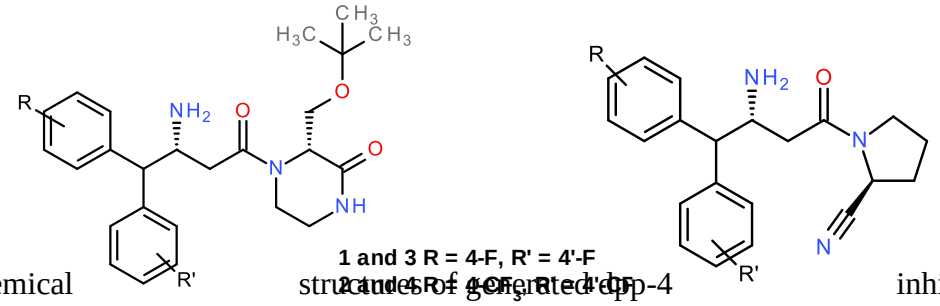

Fig. 1. Chemical structures of generated dpp-4 inhibitors

The calculated molecular docking values indicate that the generated molecules have an affinity for the selected target (Tab. 1).

Table 1

Estimated molecular docking values of generated molecules relative to dpp-4

Compound	Affinity DG	EDoc	Ki μM
1	-8.5	-5.62	75.64
2	-9.0	-4.87	270.34
3	-8.4	-6.72	11.81
4	-9.7	-7.32	4.34
Evogliptin	-8.5	-5.53	88.17

The inhibition activity of the studied molecules in relation to the selected target can be realized due to the formation of complexes between them, the stability of which is ensured due to the energetically advantageous geometric arrangement of the tested molecules in the active site of the enzyme, the formation of intermolecular interactions between them, namely: hydrogen bonds, electrostatic and hydrophobic interactions. Visualization of the location (Affinity DG = -9.7 kcal/mol, EDoc = -7.32 kcal/mol, Ki μM = 5.34 μmol) of the leader compound (4) in the dipeptyl petidase-4 site in comparison with Evogliptin is shown in fig. 2.

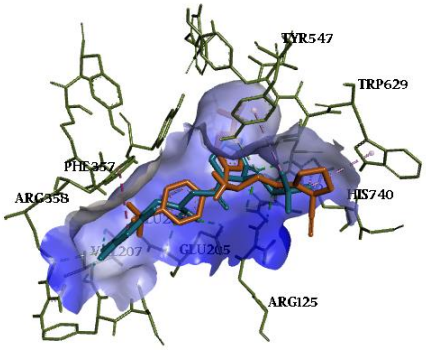

Fig. 2. Visualization of the molecular docking of the lead compound 4 (orange) in the dipeptidyl peptidase-4 site in comparison with Evogliptin (blue)

Conclusions. According to the docking results, the studied molecules had moderate and high affinity to dipeptidyl peptidase-4. A detailed analysis of the formed complexes revealed compounds that had a binding mode similar to classical inhibitors. According to the calculated array of values and the analysis of docking results, compound 4 was found as a promising inhibitor.