МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

МАТЕРІАЛИ
XXX МІЖНАРОДНОЇ НАУКОВО-ПРАКТИЧНОЇ
КОНФЕРЕНЦІЇ МОЛОДИХ ВЧЕНИХ ТА СТУДЕНТІВ

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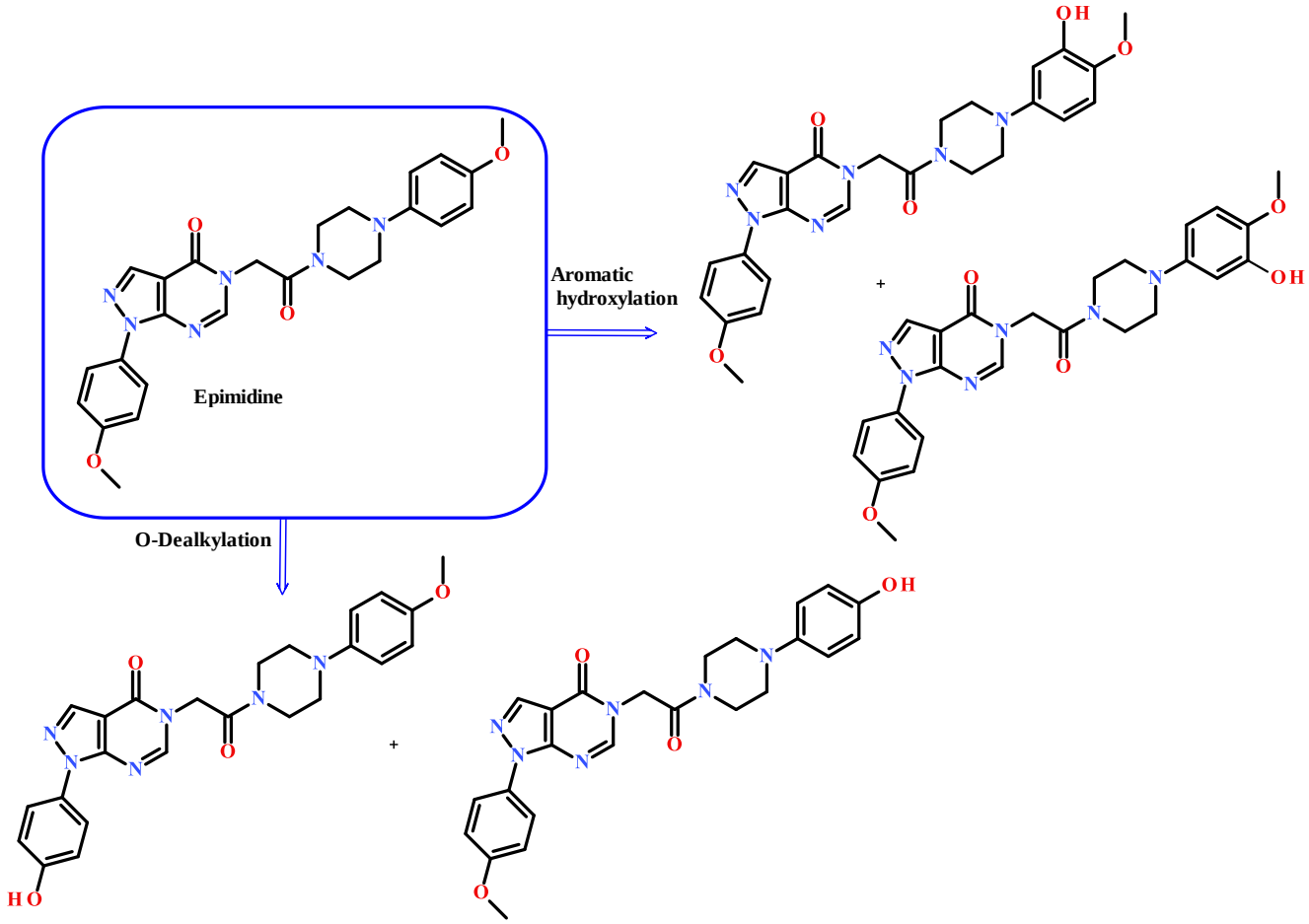
positions of the phenylpiperazine fragment with the formation of two products - 3-hydroxy- and 5-hydroxy-4-methoxy-phenylpiperazinyl derivatives. There is also a high probability of the O-dealkylation reaction with the cleavage of methyl groups and the formation of 4-hydroxyphenyl derivatives. The formation of glucuronide by N-glucuronidation at the tertiary nitrogen atom of the pyrazole cycle is predicted, but in our opinion, the probability of such a metabolic process is unlikely.



Conclusions. The probability of Epimidine metabolism by O-dealkylation and aromatic hydroxylation, as well as the absence of the possibility of toxic metabolites formation was determined. Epimidine is recommended for the next stage of *in vitro* study.

IN SILICO PREDICTION OF NOOTROPIC ACTIVITY OF NEW HALOGEN-SUBSTITUTED ANALOGS OF NEBRACETAM

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Introduction. Currently, there are many drugs with nootropic action of different chemical structures that act on relevant biological targets and, as a result, have a wide spectrum of pharmacological activity. Racetams are a common group of nootropics. Experimental and clinical

studies of racetams initially focused on their nootropic effects; later, information appears in the literature about their possible neuroprotective effect and use after stroke, as well as as antiepileptic agents. According to the literature data and the results of our own research, the sufficient manifestation of the effect of the introduction of substituents into the structure of the racetam nootropic Nebracetam indicates the perspective of modifying its framework with substituents, which can additionally affect the formation of stabilizing contacts with the manifested cognitive goals, given that there are sufficient results regarding its properties improve language learning and memory to help with dementia.

Aim. Prediction of nootropic activity of new halogen-substituted analogs of Nebracetam using molecular docking.

Materials and methods. Structures of new analogs of Nebracetam 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) muscarinic receptor (PDB ID: 5CXV), was used as biological targets for docking. The Autodock 4.2 software package was used for receptor-oriented flexible docking.

Results and discussion. At the stage of structure optimization, the corresponding enantiomer conformations were created (Fig. 1).

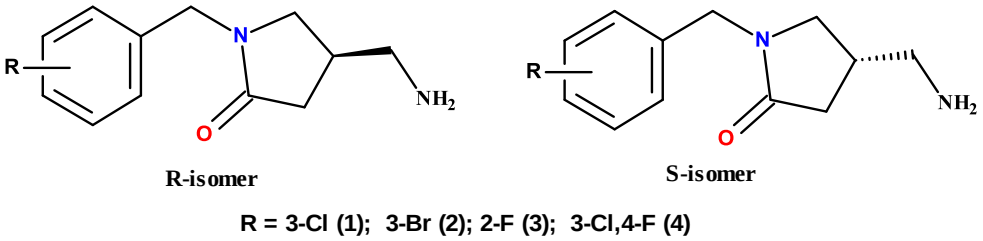

Fig. 1. Chemical structures of potential nootropic agents

The location of their energetically favorable positions depended on the conformations of the enantiomers. Table 1 shows the calculated scoring functions. The virtual screening revealed molecules with values equal to or higher than the absolute values for Nebracetam.

Table 1

Calculated scoring functions of generated molecules relative to muscarinic receptor

Molecule	Affinity DG, kcal/mol	Molecule	Affinity DG, kcal/mol
orthosteric site		allosteric site (extracellular vestibule)	
1-R	-7.9	-	-
1-S	-7.4	-	-
2-S	-7.9	2-R	-6.4
3-R	-8.1	3-S	-6.2
4-S	-7.7	4-R	-6.8
R-Nebracetam	-7.7	-	-
S- Nebracetam	-7.6	-	-

Depending on the enantiomeric configuration, the studied derivatives formed complexes with the target mainly through the orthosteric and allosteric site (extracellular vestibule), where they had extensive interactions with the corresponding amino acid residues (Tyr404, Tyr106, Tyr381, Trp378, Cys407, Thr192, Ala196 and Asn382). Visualization of the location of the investigated derivatives in

the orthosteric and allosteric sites of the muscarinic receptor in comparison with Nebracetam is shown in fig. 2.

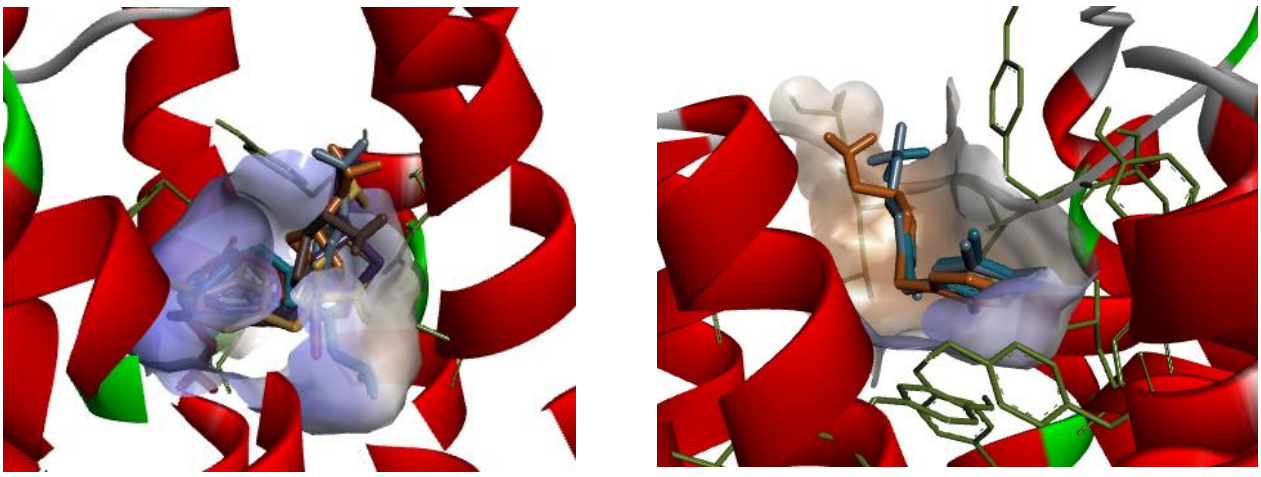

Fig. 2. Superpositions of the studied derivatives in the orthosteric (left panel) and allosteric (right panel) sites of the muscarinic receptor. *The (R) and (S) conformations of Nebracetam in the orthosteric site are shown in blue and orange, respectively.*

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.