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АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ

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Conclusions. Using five different freely available online resources, a computer prediction of possible pathways of biotransformation of a promising compound, 3-[(2-aminoanilino)methyl]-2-methyl-1H-quinoline-4-one, was carried out. The general regularities of metabolic transformations of the test molecule completely coincide and fit into the current views of medicinal chemistry on the reactivity of xenobiotics under the influence of cytochrome P450 enzymes in the human body.

USING COMPUTER TECHNOLOGIES TO OPTIMIZE THE SEARCH FOR NEW "DRUG-LIKE" MOLECULES OF HYPOGLYCEMIC ACTION

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Introduction. It is known that dipeptidyl peptidase 4 (DPP4) inhibitors, in addition to their role in improving glycemic control, help alleviate endothelial dysfunction, have hypolipidemic and anti-atherosclerotic effects. Such a multiple effect will certainly contribute to the improvement of the quality of life of patients with type 2 diabetes. Currently, new molecules aimed at inhibiting DPP4 are being searched for in the treatment of neurodegenerative disorders, oncology, etc. Such a multi-target property can be one of the reasons for repurposing therapeutic strategies of treatment with existing agents and the basis for searching for new drug candidates for the inhibition of this peptidase. Therefore, the search for new DPP4 inhibitors is definitely a relevant area of research.

Aim. Prediction of toxicity and hypoglycemic activity of potential dpp4 inhibitors using *in silico* technologies.

Materials and methods. New dpp-4 inhibitors, which were generated using the Marvin Sketch 20.5 program, were chosen as objects of study. Toxicity was assessed using the ProTox 3.0 online program. 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 objects of the study were pharmacophore systems consisting of a derivative of piperazin-2-one or (S)-pyrrolidin-2-carbonitrile and substituted by a phenyl ring, connected by an inhibitory (R) β-aminoamide group (fig. 1).

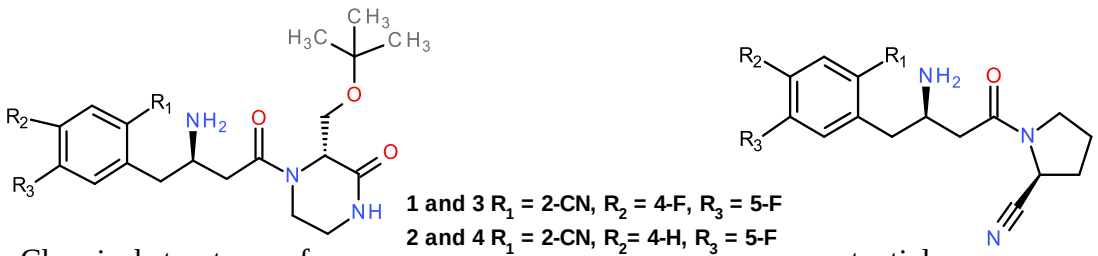

Fig. 1. Chemical structures of potential hypoglycemic agents as dpp-4 inhibitors

As part of the research, the toxic effects of the studied molecules were predicted using the ProTox tool, which was used to determine the toxicity class for each compound. The lethal drug is classified as Class I, and the least toxic or beneficial compound is Class VI. Based on these properties, we found that compounds 1 and 2 belong to class V, and 3 and 4 to class IV, that is, they are practically non-toxic.

The next step in computational evaluation that would allow activity to be predicted is a computational molecular analysis method to describe binding efficiency and affinity (molecular docking). According to the docking results, it was established that the compounds have a moderate affinity for dipeptidyl peptidase-4, as evidenced by the estimated values (table 1).

Table 1

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

Compound	Affinity DG	EDoc	Ki μM
1	-8.4	-5.66	70.60
2	-8.0	-5.37	115.18
3	-7.7	-6.54	16.08
4	-8.1	-6.25	26.41
Evogliptin	-8.5	-5.53	88.17

Visualization of the location of the studied derivatives in the dipeptyl petidase-4 site in comparison with Evogliptin is shown in fig. 2.

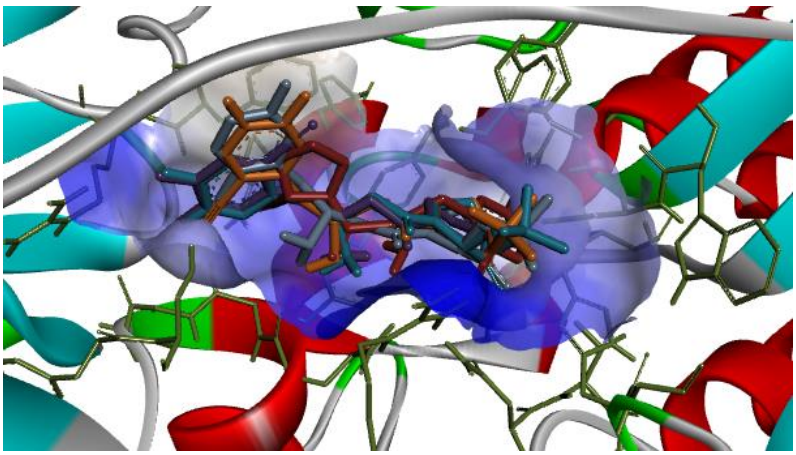

Fig. 2. Visualization of the molecular docking of the studied derivatives in the dipeptidyl peptidase-4 site in comparison with Evogliptin (blue)

Conclusions. According to the in silico assessment of toxicity and activity, the generated molecules are practically non-toxic and may have a moderate hypoglycemic effect due to the inhibition of dipeptidyl peptidase-4. A detailed analysis of the formed complexes revealed compounds that had a binding mode similar to classical inhibitors.

PREDICTION OF PROBABLE METABOLIC PATHWAYS OF THE POTENTIAL CANDIDATE FOR AN API WITH NEUROTROPIC PROPERTIES

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Introduction. Understanding metabolic processes at a molecular level is crucial for successful drug discovery and development. Knowledge of the metabolic properties of a molecule helps to