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The Theoretical Substantiation of the Targeted Search for New DPP4 Inhibitors. Computational Studies of Potential Candidates

Abstract
Growing evidence suggests that dipeptidyl peptidase 4 (DPP4) inhibitors, in addition to their role in improving glycemic control, help to reduce endothelial dysfunction and have hypolipidemic, anti-atherosclerotic, antitumor, antiviral, and neurotropic properties. This multi-target property may be one of the reasons for repurposing therapeutic treatment strategies with existing agents and the basis for finding new agents to inhibit this target. Based on the structural prerequisites and the evolutionary path of creating DPP4 inhibitors, an inhibitory (*R*)-β-aminoamide base was used as the basis for constructing potential candidates. It contained a substituted piperazine-2-one derivative and (*S*)-pyrrolidine-2-carbonitrile fragment, as well as phenyl and diphenyl rings, which were additionally saturated with substituents of various electronic structures, in position 4 of the β-aminoamide chain. The construction of the molecules was carried out taking into account the correspondence of chiral centers to combinations of chiral chains at the DPP4 binding site to possibly prevent a decrease in the inhibitory activity. *In silico* assessment of the "drug-likeness" and pharmacokinetic profile of the group of compounds studied showed that it had favorable characteristics and could be recommended for further molecular docking in order to predict the likely inhibition of the catalytic activity of DPP4. According to the results of docking, molecules with a moderate and high affinity were found. A detailed analysis of the resulting complexes showed that only nine compounds had a binding mode similar to classical inhibitors. According to the calculated array of values and analysis of the results of docking among the derivatives tested, a hit compound was found as a promising DPP4 inhibitor.
Keywords: gliptins; dipeptidyl peptidase-4 (DPP4); virtual screening; ADMET; molecular docking

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Теоретичне обґрунтування цілеспрямованого пошуку нових інгібіторів DPP4. Обчислювальні дослідження потенційних кандидатів

Анотація
Дедалі більша кількість доказів свідчить про те, що інгібітори дипептидилпептидази 4 (DPP4), окрім їхньої ролі в покращенні глікемічного контролю, допомагають полегшити ендотеліальну дисфункцію, володіють гіполіпідемічною, антиатеросклеротичною, протипухлинною, противірусною та нейротропною властивостями. Така мультитаргетна властивість може бути однією з підстав перепрофілювати терапевтичні стратегії лікування наявними засобами та приводом для пошуку нових агентів для інгібування цієї мішені. З огляду на структурні передумови та еволюційний шлях створення інгібіторів DPP4 для конструювання потенційних кандидатів було використано (*R*)-β-аміноамідну молекулярну платформу. Вона містила заміщене похідне піперазин-2-ону і (*S*)-піролідин-2-карбонітрильний фрагмент, а також фенільні й дифенільні кільця в положенні 4 β-аміноамідного ланцюга, які додатково було насичено замісниками різної електронної будови. Побудову молекул проведено з урахуванням відповідності хіральних центрів до комбінацій хіральних ланцюгів у сайті зв'язування DPP4 для можливого запобігання зниженню інгібіторної активності. *In silico* оцінювання «лікоподібності» і фармакокінетичного профілю досліджуваної групи сполук засвідчило, що вона має сприятливі характеристики і може бути рекомендована для подальшого молекулярного докінгу, за результатами якого виявлено молекули, які мали помірний і високий афінітет, проте лише дев'ять сполук мали тип зв'язування, подібний до класичних інгібіторів. За обчисленим масивом значень та аналізом результатів докінгу було визначено сполуку-хіт як перспективний інгібітор.
Ключові слова: гліптини; дипептидилпептидаза-4 (DPP4); віртуальний скринінг; ADMET; молекулярний докінг

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■ Introduction

The search for new drugs among small molecules does not lose its relevance, and an effective tool for achieving this goal is certainly to identify a target that would be involved in a large number of biochemical and physiological processes. Based on this strategy, the therapeutic effectiveness of existing drugs used for other diseases can be repurposed for the treatment of seemingly unrelated pathologies. In our opinion, one of these targets is dipeptidyl peptidase-4 (DPP4), a widely expressed transmembrane glycoprotein with peptidase activity in the extracellular domain, which regulates numerous biological processes. DPP4 is a serine protease that can cleave substrates with proline or alanine fragments in the penultimate position [1]. Native substrates of the enzyme are glucagon-like peptide-1, neuropeptide Y, secretin, pituitary adenylate cyclase activating polypeptide, endorphins, endomorphins, brain natriuretic peptide, beta-melanocyte stimulating hormone, amyloid peptides. DPP4 degrades and regulates numerous chemokines and cytokines and acts as a cell surface receptor, binds to adenosine deaminase, interacts with the extracellular matrix, and controls cell migration and differentiation [2, 3]. Today, there is a group of substances (gliptins) that inhibit this protease [4, 5]. In addition to their role in improving glycemic control, they can relieve endothelial dysfunction in patients with Type 2 diabetes [6]. The anti-inflammatory effect of DPP4 inhibitors, which has been reported in clinical and preclinical studies of endothelial dysfunction and diabetic ulcers, indicates the additional usefulness of this class of drugs [7]. It is known that chronic vascular complications associated with diabetes are associated with atherosclerosis. DPP4 inhibitors are involved in controlling risk factors by regulating blood lipids and lowering blood pressure. The atherosclerotic effect is also associated with improved endothelial cell dysfunction by increasing the level of circulating endothelial progenitor cells, regulating mononuclear macrophages, and suppressing inflammation and oxidative stress [7, 8]. A large number of studies demonstrate that this protease also plays an important role in the immune system, and is especially expressed in immune cells, such as T cells, B cells, NK cells, dendritic cells, and macrophages [9]. In this regard, research is underway on known inhibitors for the treatment of immune-mediated diseases. Currently, there are studies on the possibility of using gliptins against COVID-19. Recent studies have shown that the binding domain of the spike protein receptor can interact with human DPP4 to facilitate viral entry, in addition to the usual pathway of binding to angiotensin-converting enzyme 2 (ACE2) [10, 11]. Interfering with such an interaction is a potential strategy for effectively preventing viral replication, but long-term clinical data have not yet been obtained. Growing evidence suggests that endogenous peptides, such as glucagon-like peptide-1 (GLP-1) and stromal cell-derived factor-1α (SDF-1α) provide neuroprotection in a number of experimental models of Alzheimer's disease. Thus, maintaining the functional activity of SDF-1α and GLP-1 by inhibiting DPP4 will enhance the involvement of resident and non-resident circulating brain stem cells, which is a non-invasive approach for stimulating neurogenesis [12, 14].

DPP4 inhibitors are considered viable agents for the treatment of neurodegenerative diseases, such as Parkinson's disease, which neuroprotective and therapeutic potential is provided by leveling dopaminergic degeneration, promoting neuronal regeneration [13, 14]. **Figure 1** shows the scheme of pharmacologically determined and potential therapeutic use of DPP4 inhibitors.

It should be noted that the use of existing DPP4 inhibitors for these pathologies has a softening effect. This effect is explained by the fact that the known inhibitors can affect peripheral DPP4 since they cannot pass through the intact blood-brain barrier [14]. In this regard, the search for the "ideal" DPP4 inhibitor is continuing so far.

■ Materials and methods

The design of potential inhibitors of dipeptidyl peptidase-4 for virtual screening was carried out using the Marvin Sketch 20.5 program.

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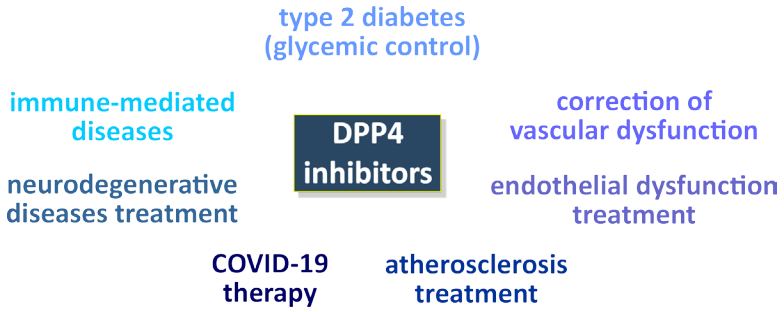

Figure 1. Pharmacologically determined and potential therapeutic use of DPP4 inhibitors

ADMET parameters were calculated using *in silico* tool – pkCSM [15]. Toxicity was assessed using the ProTox 3.0 online program [16]. For calculations, 2D structures of molecules were converted to the SMILES format using the SMILES Translator online tool. The Autodock 4.2 software package was used for the receptor-oriented flexible docking. Ligands were prepared using the MGL Tools 1.5.6 program. The Ligand optimization was performed using the Avogadro program. To perform calculations in the Autodock 4.2 program, the output formats of the receptor and ligand data were converted to a special PDBQT format. In our previous studies, a similar software package was used [17, 18]. The active macromolecule center of the dipeptidyl peptidase-4 (dpp4) (PDB ID: 5Y7J) from the Protein Data Bank (PDB) was used as a biological target for docking. The receptor maps were made in MGL Tools and AutoGrid programs. Water molecules, ions, and the ligand were removed from the PDB file. Visualization of the resulting complexes of the molecules studied in the active sites of the receptors was carried out using the Discovery Studio Visualizer program. The following docking parameters were set: the translational step was 2 Å; the torsional freedom coefficient was 0.2983; the cluster tolerance was 2 Å; the external lattice energy – 1000; the maximum initial energy – 0; the maximum number of attempts – 10,000; the number of structures in the population – 150; the maximum number of stages of energy estimation – 2,500,000; the maximum number of generations – 27,000; the number of structures passing to the next generation – 1; the level of gene mutation – 0.02; the level of the crossover – 0.8; the method of the crossover – arithmetic. The α-Gaussian distribution parameter was equal to 0, and the ß-parameter of the Gaussian distribution was 1.

■ Results and discussions

Many DPP4 inhibitors have appeared in the pharmaceutical market. They are used as a relatively new class of hypoglycemic drugs called "gliptins" [19]. There are warnings that these compounds may have an increased risk of toxic effects on the pancreas, namely due to the occurrence of pancreatitis and pancreatic cancer during their long-term use. Large independent studies conducted by the Food and Drug Administration have not shown evidence of pancreatic toxicity and are not consistent with available scientific data [20]. Therefore, the search for new structural analogs of this group is undoubtedly relevant and justified. It should be noted that each of DPP4 inhibitors introduced into clinical practice has its own structural differences and binding mechanisms. At the first stage of the targeted search for new gliptins, empirical experience and logical-structural analysis were used to theoretically substantiate the choice of basic structures. **Figure 2** shows the Structure/Activity Relationships of the known DPP4 inhibitors.

Based on the structural prerequisites and the evolutionary path of creating gliptins, an inhibitory (*R*)-ß-aminoamide platform was taken as a basis for constructing potential inhibitors (**Table 1**). It contained either a substituted piperazine-2-one core or (*S*)-pyrrolidine-2-carbonitrile fragment, as well as phenyl rings in position 4 of the ß-aminoamide chain, which were additionally saturated with substituents of various electronic structures. The configuration of the molecule is crucial for ligand-enzyme interactions, so that the construction of the molecules was carried out taking into account the correspondence of the chiral centers to combinations of chiral chains at the DPP4 binding site to possibly prevent a decrease in the inhibitory activity.

For the constructed molecules, the parameters of "drug-likeness" were calculated for compliance with the Lipinsky's rule (**Table 1**). The Lipinski's rule of five requires that a compound has a molecular weight of no more than 500, should not form more than five hydrogen bonds, and should not accept more than ten hydrogen bonds, while the log*P* coefficient should be less than 5 [23].

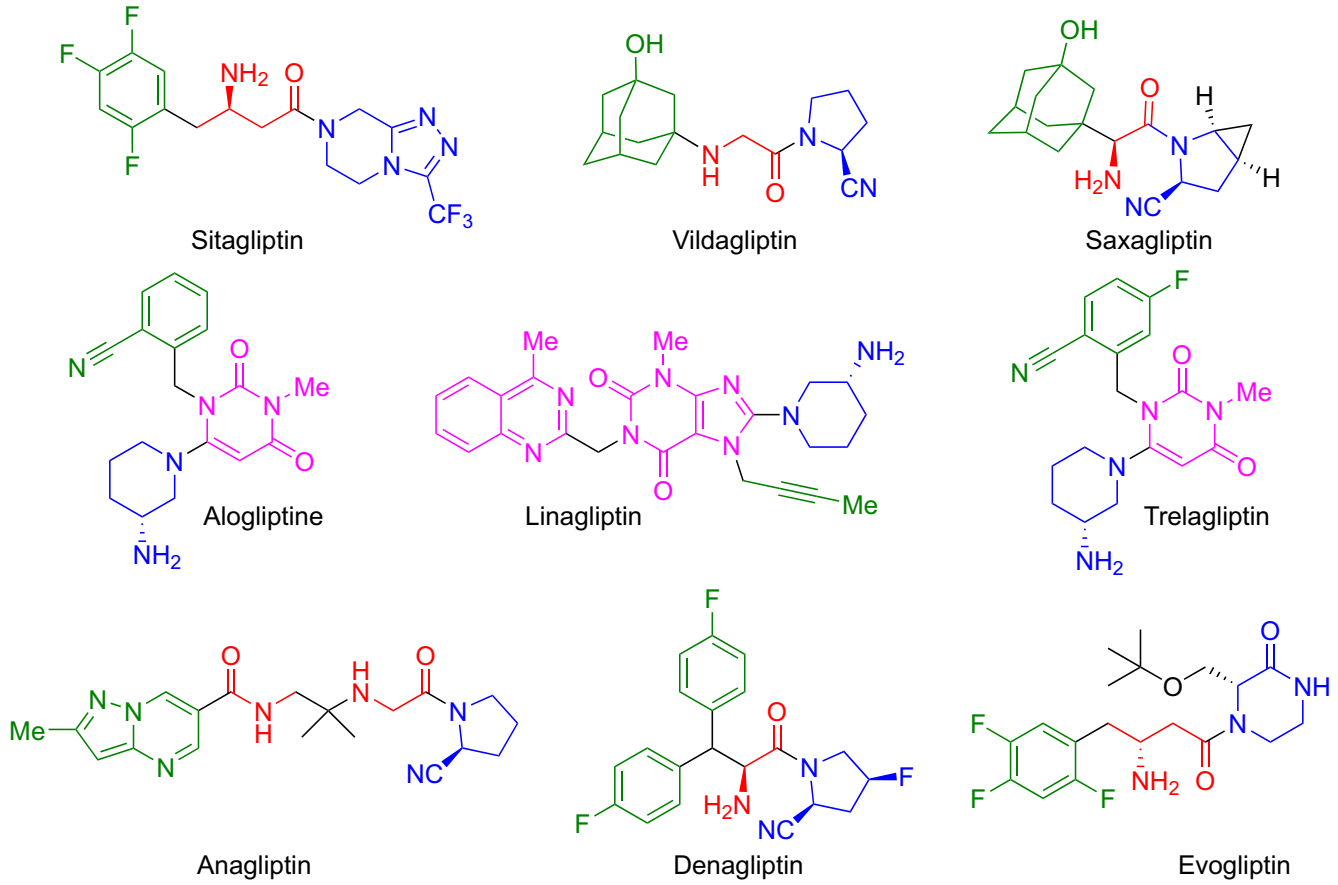

Figure 2. Structure/Activity Relationships within the group of known DPP4 inhibitors. Mandatory fragments responsible for the inhibitory activity of the enzyme are highlighted in red, blue, and green (occupy subsites S1, S2 and S2ext respectively); additional fragments highlighted in purple are located in subsites S1′ and S2′, which contribute to the increase of inhibitory activity [21, 22]

Based on the calculations, only compound **2** had a molecular weight not significantly higher than the established criteria, so we subjected all the compounds studied to the predictive ADMET analysis.

Absorption plays a significant role in the drug activity, i.e. poorly water-soluble drugs show a lower rate of absorption when taken orally, which may affect the revision of the dosage level. The calculated parameters for solubility and absorption determined that the molecules tested had moderate solubility and a high level of absorption in the intestine (**Table 2**).

P-glycoprotein is known to function as a biological barrier displacing toxins and xenobiotics from cells. According to the calculated data, compounds **1**, **2**, **10** and **11** are likely to have appropriate pharmacokinetic effects that can be used to obtain certain therapeutic benefits or lead to contraindications.

However, the calculated volumes of distribution of these compounds had optimal values comparable to other molecules studied. The level of the predicted fraction that will be unbound in plasma, the parameters of a possible penetration through the BBB and CNS indicate that all molecules have the moderate penetration and distribution indicators to a greater extent. Clinical trials have shown that the induction of isoenzymes, such as CYP2C9 and CYP3A4 is associated with diabetes; therefore, the interference with metabolism can lead to a decrease in the drug activity [23].

According to the values obtained, none of the compounds was a substrate for CYP2C9, and only compounds **1**, **2**, **10**, and **11** showed a possible inhibition of CYP3A4. As for the substrate activity to OCT2, only compound **1** might have a potential drug interaction, all other compounds did not show this possibility (**Table 2**).

In the next step, we assessed the toxic effects of the molecules tested using the pkCSM and ProTox tools and determined the class for each compound (**Table 3**). The lethal drug is classified as Class I, and the least toxic or beneficial compound as Class VI. Based on these properties, we have found that compounds **1**–**5** belong to Class V, and all others belong to Class IV [24]. The next step in computer assessment, which would allow selection of the most promising compounds for further experimental studies, is the computational molecular analysis method to describe the binding efficiency and affinity (molecular docking).

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Table 1. The calculated parameters of "drug-likeness" for potential DPP4 inhibitors

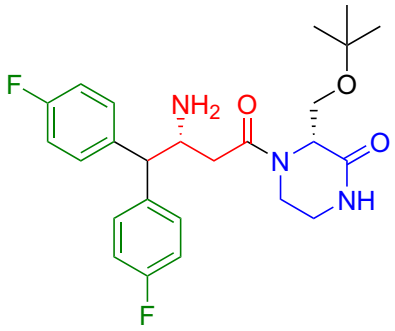
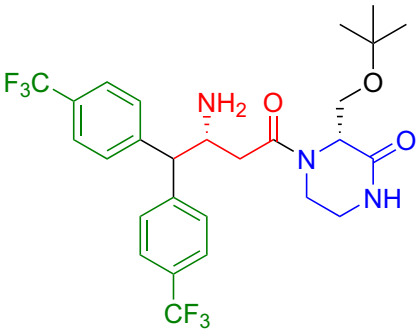
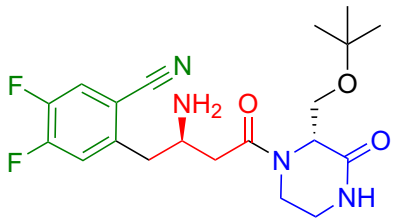
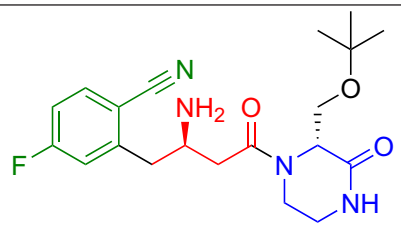
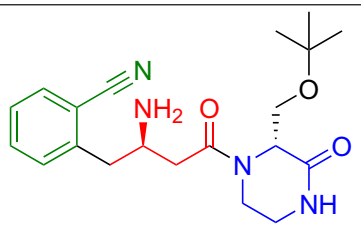
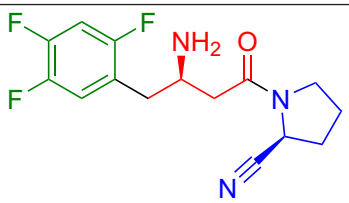
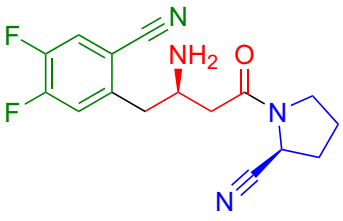
Compound	Structural formulas	Log*P*	Molecular Weight	H bond Donors	H bond Acceptors
1	2	*3*	4	5	6
1		2.9	459	2	4
2		4.7	559	2	4
3		1.2	408	2	5
4		1.1	390	2	5
5		0.9	372	2	5
6		1.8	311	1	3
7		1.6	318	1	4

Table 1 *(continued)*

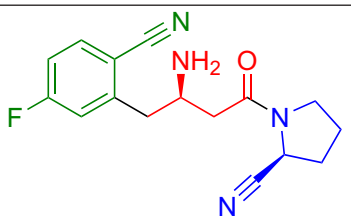
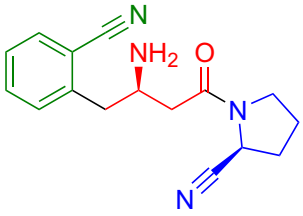
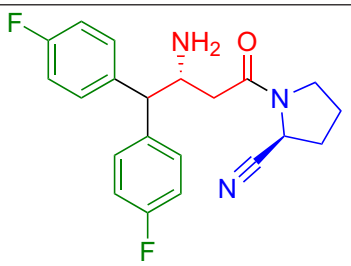
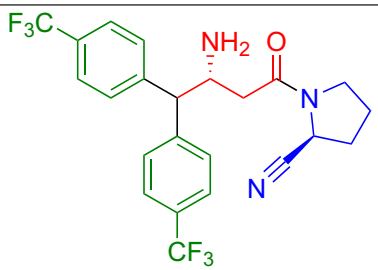
1	2	3	4	5	6
8		1.4	300	1	4
9		1.3	282	1	4
10		3.3	369	1	3
11		5.1	469	1	3

Table 2. The calculated ADME parameters for potential DPP4 inhibitors

Compound	Water solubility[1]	Caco-2 permeability[2]	Intestinal absorption (human)[3]	P-glycoprotein substrate / inhibitor I / II	VDss Human[4]	Fraction unbound[5]	BBB permeability[6]	CNS permeability[7]	CYP3A4 substrate / inhibitor	CYP2C9 inhibitor	Total clearance[8]	Renal OCT2 substrate
1	-4.759	1.017	96.476	Yes / Yes / Yes	0.79	0.102	-0.962	-2.615	Yes/ Yes	No	0.543	Yes
2	-4.766	0.99	90.996	Yes / Yes / Yes	0.671	0.061	-1.134	-2.175	Yes/ Yes	No	0.279	No
3	-3.297	0.209	73.656	Yes / No / No	0.104	0.312	-0.996	-2.974	No / No	No	0.726	No
4	-3.335	0.201	75.419	Yes / No / No	0.174	0.338	-0.793	-2.936	No / No	No	0.764	No
5	-3.301	0.186	72.034	Yes / No / No	0.275	0.389	-0.574	-2.876	No / No	No	0.831	No
6	-3.289	1.215	92.497	No / No / No	0.254	0.383	-0.622	-2.98	No / No	No	0.679	No
7	-3.269	0.146	80.607	No / No / No	0.227	0.357	-0.585	-3.002	No / No	No	0.708	No
8	-2.833	0.134	82.355	No / No / No	0.401	0.367	-0.38	-2.617	No / No	No	0.747	No
9	-2.211	0.12	78.938	No / No / No	0.588	0.379	-0.095	-2.561	Yes / No	No	0.831	No
10	-4.611	1.072	93.365	Yes / Yes / Yes	0.766	0.11	-0.187	-2.325	Yes / Yes	No	0.567	No
11	-5.741	0.55	87.878	Yes / Yes / Yes	0.997	0	-0.557	-1.874	Yes / Yes	No	0.309	No

Note: units of measurement [1](log*S* in mol L^{-1}), [2] (logP_{app} in 10^{-6} cm sec^{-1}), [3] (%absorbed), [4] (log in L kg^{-1}), [5] (Fu), [6] (log BB), [7] (log PS), [8] log in mL min^{-1} kg^{-1})

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Table 3. Basic toxicity parameters calculated using the pkCSM and ProTox tools

Compound	pkCSM tool		ProTox tool	
	Oral Rat Chronic Toxicity (LOAEL) log in mol kg^{-1}	Oral Rat Acute Toxicity (LD50) mol kg^{-1}	LD50 in mg kg^{-1}	toxicity class
1	1.193	3.338	2973	V[1]
2	0.909	3.251	2973	V
3	2.506	2.925	2973	V
4	1.428	2.745	2973	V
5	1.372	2.588	2973	V
6	2.070	2.600	1160	IV[2]
7	2.068	2.461	1160	IV
8	1.521	2.398	1160	IV
9	1.439	2.604	630	IV
10	1.412	2.606	1850	IV
11	0.932	3.016	326	IV

Note: [1]Class V: may be harmful if swallowed (2000 < LD50 ≤ 5000); [2]Class IV: harmful if swallowed (300 < LD50 ≤ 2000)

Molecular docking of compounds was performed relative to the selected crystallographic model (PDB ID: 5Y7J) at the well-controlled binding site of DPP4 inhibitors. Evogliptin was chosen as a reference drug since it was co-crystallized relative to the selected target, and the redocking results obtained (scoring function, free energy, and binding constant) were used as standard ones.

As a result of Evogliptin redocking, key interactions with DPP4, which were in good agreement with the results of crystallographic studies, were identified [25] (**Figure 3**).

According to the estimated values (**Table 4**), the molecules studied had the best energy positions with moderate values of the scoring function, except for molecules **2** and **11**, which had absolute affinity values higher than those of Evogliptin. In turn, compound **11** had a better result in terms of free energy and binding constant values compared to the reference indicators.

To assess the binding modes of new molecules relative to the DPP4 binding site, a detailed analysis of the geometric location of energy advantageous positions was performed, and all the resulting complexes with the target under study were analyzed.

As expected, almost all of the compounds tested (**3–9**) had the same binding mode to Evogliptin (**Figure 4**, *A*), namely the substituted phenyl rings occupied the hydrophobic pocket S1 and interacted with *Ser630*, *Val656*, *Tpr659*, *Tyr662*, *Tyr666*, *Val711,* and *Asn710* amino acid residues; piperazin-2-one and pyrrolidine parts were located against the *Phe357* side chain, thus occupying the extended S2 and S2ext subsites where the S2 pocket referred to the pocket formed by *Arg125*, *Arg669*, *Glu205*, *Glu206*, *Phe357*, and *Arg358*, and the S2ext subsite referred to the subsite formed by *Phe357*, *Arg358*, *Ser209*, and *Val207*. The (*R*)-ß-amino part of the butanoyl group formed hydrogen bonds with *Tyr662*, *Glu206*, and *Glu205* residues. In some complexes, hydrogen bonds with the *His740* amino acid residue – a part of the catalytic triad of the enzyme (*Ser630*, *His740*, *Asp708*) – were observed. It should be noted that molecules **10** and **11**, which substituted diphenyl rings in the (*R*)-ß-amino group, contributed to the immersion of molecules in both the hydrophobic pocket S1 and site S2 forming broad interactions with the corresponding amino acid chains (**Figure 4**, *B*).

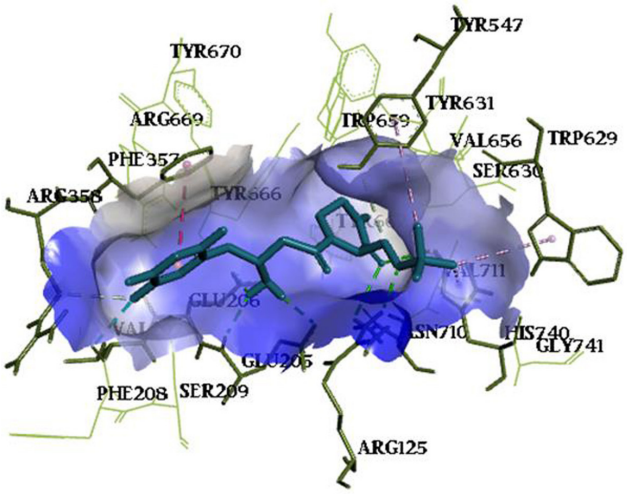

Figure 3. Visualization of Evogliptin redocking relative to DPP4

Table 4. The estimated values of docking of the compounds studied in the DPP4 site

Compound	Affinity DG[1], kcal mol^{-1}	EDoc[2], kcal mol^{-1}	Ki[3], μM
1	-8.5	-5.62	75.64
2	-9.0	-4.87	270.34
3	-8.4	-5.66	70.60
4	-8.0	-5.37	115.18
5	-8.0	-6.22	27.62
6	-7.6	-5.90	47.31
7	-7.7	-6.54	16.08
8	-8.1	-6.25	26.41
9	-8.1	-6.40	20.25
10	-8.4	-6.72	11.81
11	-9.7	-7.32	4.34
Evogliptin	-8.5	-5.53	88.17

Note: [1]scoring function; [2]binding free energy; [3]binding constant

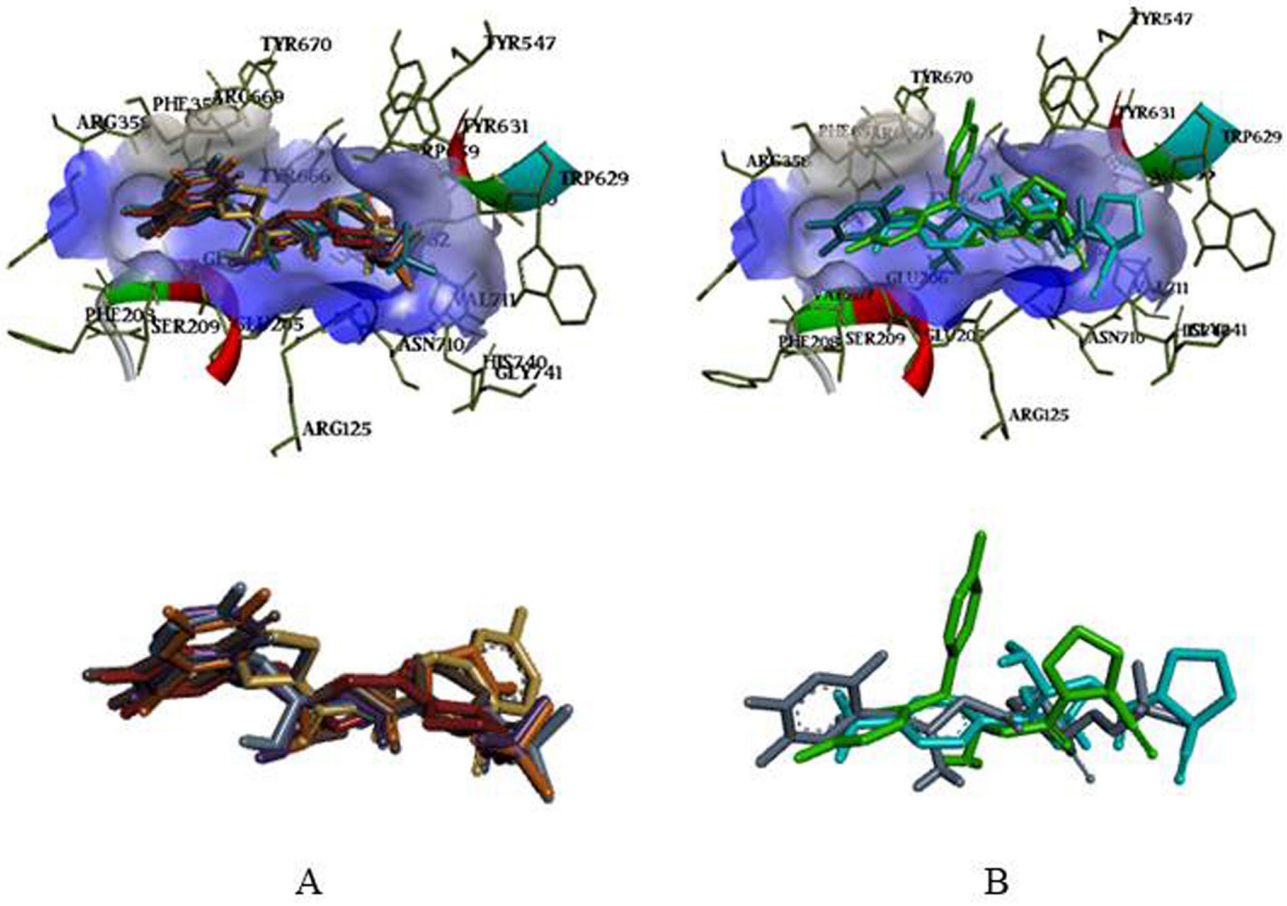

Figure 4. Superpositions of molecules **3**–**9** (A), and **10**–**11** (B) at the DPP4 binding site compared to Evogliptin (compound **3** – orange, compound **4** – gray, compound **5** – purple, compound **6** – red, compound **7** – brown, compound **8** – yellow, compound **9** – lilac, compound **10** – green, compound **11** – blue, Evogliptin – blue)

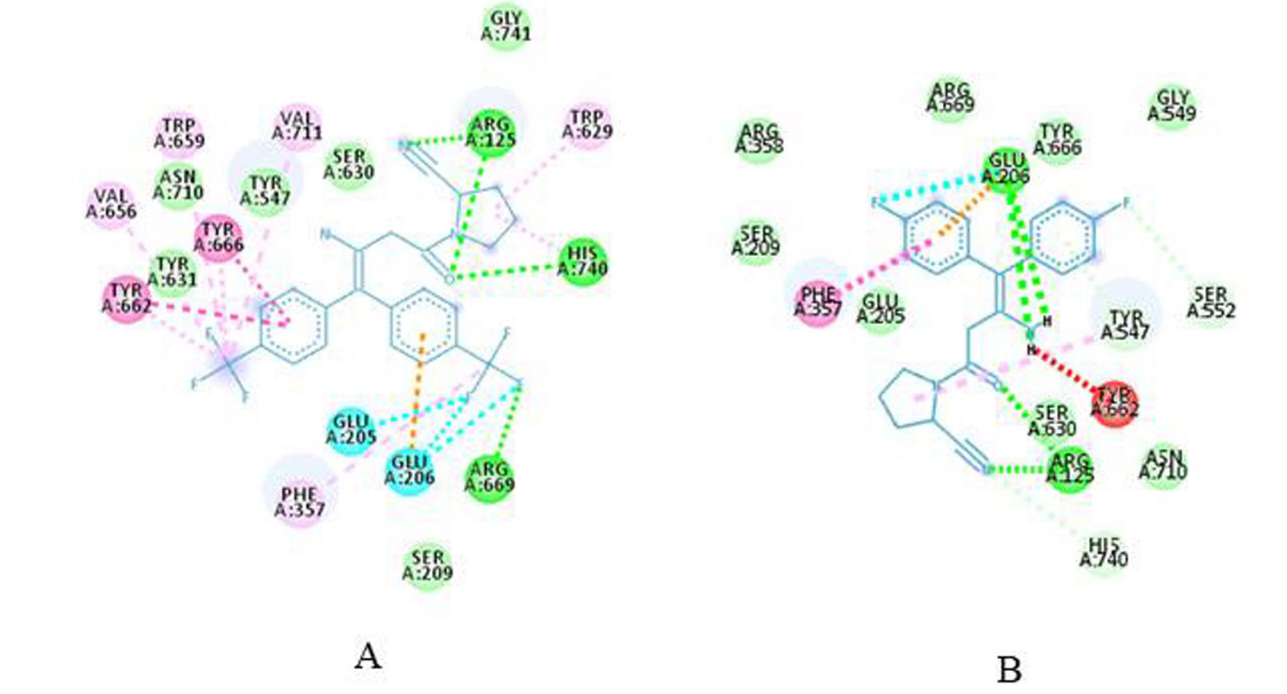

Figure 5. Diagrams of intermolecular interactions of hit compound **11** (A) and compound **10** (B). Visualization of bonds is shown by dashed lines of the corresponding color: Vander Waals forces – light green, hydrogen bonds – green, light gray; halogen – blue; π-anion interaction – orange; donor–donor bond – red; π-π interaction – purple, π-Alk and Alk interaction – pink

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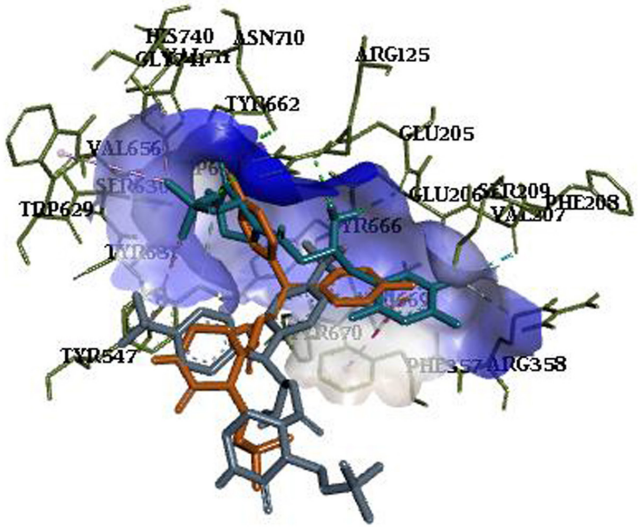

Figure 6. Superpositions of compound **1** (orange) and compound **2** (gray) relative to DPP4 compared to Evogliptin (blue)

Among the molecules studied, a hit compound **11** (affinity DG = -9.7 kcal mol^{-1}, EDoc = -7.32 kcal mol^{-1}, Ki = 4.34 μm) was found. It formed a number of favorable interactions with the amino acid chains of the DPP4 site (**Figure 5**, *A*). However, among the compounds that had an inherent binding mode for enzyme inhibitors, compound **10** was found with moderate calculated docking values (affinity DG = -8.4 kcal mol^{-1}, EDoc = -6.72 kcal mol^{-1}, Ki = 11.81 μm). It formed an unfavorable donor–donor interaction with the *Tyr662* residue with the participation of the (*R*)-ß-amino part of the butanoyl group (**Figure 5**, *B*). This type of interaction can lead to nonbinding efficacy. Therefore, compound **10** is not recommended for further research.

Among the compounds studied, molecules **1** and **2** had a binding mode that was not characteristic for DPP4 inhibitors. According to a detailed analysis of the location of these molecules, it has been found that the interaction with the site occurs due to the substituted diphenyl rings that interact with the corresponding amino acid chains of sites S1 and S2, and the inhibitory (*R*)-ß-amino group and the substituted piperazine-2-one part do not have a characteristic binding to amino acids in well-documented sites. This indicates that these compounds probably will not be able to inhibit the catalytic activity of DPP4, despite the fairly good calculated docking values (**Table 3**). Therefore, they are not recommended for further research. **Figure 6** shows superpositions of compounds **1** and **2** relative to the target under study compared to Evogliptin.

■ Conclusions

In silico assessment of the "drug-likeness" and pharmacokinetic profile of the group of compounds studied has shown that it has favorable characteristics and can be recommended for further molecular docking in order to predict the likely inhibition of the catalytic activity of DPP4. According to the results of docking, molecules with a moderate and high affinity have been found. A detailed analysis of the resulting complexes has demonstrated that only 9 compounds have a binding mode similar to classical inhibitors. According to the calculated array of values and analysis of the results of docking hit compound **11** has been found as a promising inhibitor.

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