Chemical Journal of Kazakhstan
Volume 2, Number 90(2025), 52-61 https://doi.org/10.51580/2025-2.2710-1185.22

УДК 547.823+547.861.3+615.2

In silico EVALUATION OF THE PHARMACOKINETICS AND TOXICITY OF NOVEL PIPERIDINE DERIVATIVES

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Abstract. *Introduction.* Modern computer modeling methods make it possible to predict the biological activity and pharmacokinetic properties of compounds at early stages of drug development, thereby accelerating the identification of promising candidates. Piperidine derivatives are of particular interest due to their high potential pharmacological value. *The aim of this study* is to evaluate the biological activity, pharmacokinetic parameters, and toxicity of novel piperidine derivatives using *in silico* methods. *Results and discussion.* Four new compounds were synthesized via aminomethylation of 1-(2-ethoxyethyl)-4-ethynylpiperidin-4-ol esters, isolated by column chromatography on Al_2O_3, and characterized using physicochemical analysis methods. Biological activity was assessed using the PASS program, pharmacokinetics via SwissADME, and toxicity via ProTox-III. The compounds demonstrated a high probability of antibacterial, anti-inflammatory, and analgesic activity, as well as potential effectiveness in the treatment of osteoporosis, diabetic neuropathy, and neurological disorders. Pharmacokinetic analysis indicated good absorption and the ability to cross the blood–brain barrier. According to ProTox-III, the compounds showed predominantly low toxicity (lowest for compound **5**, LD_{50} = 2935 mg/kg). *Conclusion.* Compounds **2**, **3**, **6**, and **7** are considered especially promising for further research due to their high bioavailability and low toxicity. The results support the feasibility of continued *in vitro* and *in vivo* screening of the synthesized compounds.

Keywords: piperidine derivatives, computer modeling, PASS, SwissADME, ProTox-III, pharmacokinetics, toxicity, drug-like compounds.

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Citation: Bissenbay D., Ten A.Yu., Yu V.K., Zhaxibayeva Zh.M., Dembitsky V. *In silico* evaluation of the pharmacokinetics and toxicity of novel piperidine derivatives. *Chem. J. Kaz.*, **2025**, 2*(90)*, 52-61. DOI: https://doi.org/10.51580/2025-2.2710-1185.22

1. Introduction

In the 21st century, there has been a shift from empirical drug discovery toward rational drug design based on theoretical prediction of biological activity. This approach considers the relationship between chemical structure and pharmacological effect, enabling the early exclusion of ineffective or toxic candidates and focusing efforts on promising molecules. One of the key strategies involves chemical modification through the introduction of functional groups capable of enhancing or altering biological activity.

Modern computational technologies play a crucial role in evaluating the biological activity, toxicity, lipophilicity, and pharmacokinetic properties of compounds, including gastrointestinal absorption and the ability to cross the blood–brain barrier. Computational methods, including ADME parameter prediction, are applied at all stages of drug development, facilitating the design of molecules with optimized pharmacodynamic and toxicological profiles. The use of machine learning algorithms enables the prediction of biological targets, protein interactions, and toxicity without the need for costly in vivo studies, thereby reducing expenses, development time, and reliance on animal testing.

The advancement of computational toxicology has become an integral part of preclinical safety assessment, relying on the progress in chemistry and molecular biology. Under these conditions, *in silico* methods provide an efficient means to evaluate the pharmacological and toxicological potential of compounds at the early stages of drug development [1].

The aim of the present *in silico* assessment is to determine the impact of chemical modification on the biological activity of the starting compounds. The study is focused on identifying enhancement, attenuation, or emergence of new types of activity, which contributes to predicting their pharmacological potential and optimizing synthetic strategies.

В настоящем исследовании в качестве предмета для ин силико оценки были выбраны проиводные пиперидина.

Piperidine derivatives are known for their high pharmacological activity and are considered “privileged structures,” serving as scaffolds for the development of drugs with various mechanisms of action. They are found in more than twenty drug classes [2], including anticancer agents [3], Alzheimer’s disease treatments [4], antibiotics [5], analgesics [6], antipsychotics [7], and antioxidants [8].

2. The experimental part

To identify the studied compounds as potential sources of biologically active agents, the following web-based tools were employed: PASS for predicting biological activity [9], SwissADME for evaluating pharmacokinetic properties (ADME) [10], and ProTox-III for toxicity prediction [11].

The synthesis methods for compounds **2** and **3** are described in reference [12].

*Synthesis of compounds **4–7**.* To a mixture of 0.0026 mol of paraformaldehyde and 0.0023 mol of 1-benzhydrylpiperazine or

pyrimidylpiperazine in acetonitrile, with continuous stirring at room temperature, 0.0019 mol of compound **2** or **3** was added dropwise. Then, 5 mol% of freshly prepared copper (I) chloride was introduced. The reaction was carried out at the boiling point of acetonitrile for 72–78 hours. Upon completion, the mixture was cooled, the acetonitrile was evaporated, and the residue was acidified with hydrochloric acid solution (1:1) to pH ~2 and washed with diethyl ether 3 times to remove paraformaldehyde residues. Next, the reaction mixture was then basified to pH ~10 using sodium hydroxide solution. The product is extracted with hexane. After, it was purified by column chromatography on Al_2O_3 using a chloroform:acetone system (10:1), followed by solvent evaporation. Yields ranged from 40% to 80%. The composition and structures of the synthesized compounds were confirmed by elemental analysis and spectral data.

*1-Benzhydryl-4-(3-(1-(2-ethoxyethyl)-4-(2-phenoxyethoxy)piperidin-4-yl)prop-2-yn-1-yl)piperazine **(4)***. $C_{37}H_{47}N_3O_3$; $n_{20}D$ = 1.546; Found, %: C 76.38, H 8.14, N 7.22. Calculated, %: C 76.25, H 8.09, N 7.35; IR spectra, ν, cm^{-1}: 1245.4 (-C-O-C(N)), 1110.7 ((-C-O-C(Ph)), 755.4, 1497.2, 1586.0 (Ph); ^{13}C NMR spectra (101 MHz, Chloroform-d) δ 152.07, 149.72, 130.64–121.26, 117.81 ($\underline{C}_{benz}$), 81.18, 86.17, 48.65 ($\underline{C}\equiv\underline{C}$-$\underline{C}H_2$), 76.83 ($\underline{C}$2Ph), 71.66, 50.62, 36.75 ($C_{piperidine}$), 52.65, 51.38 ($C_{piperazine}$), 69.38, 27.69 ($\underline{C}H_2\underline{C}H_2$OPh), 68.49, 66.69, 57.89, 15.64 (N$\underline{C}H_2\underline{C}H_2$O $\underline{C}H_2\underline{C}H_3$).

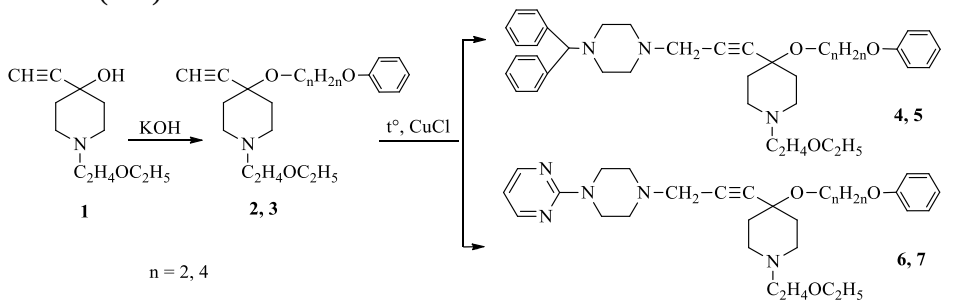
*1-Benzhydryl-4-(3-(1-(2-ethoxyethyl)-4-(2-phenoxybutoxy)piperidin-4-yl)prop-2-yn-1-yl)piperazine **(5)***. $C_{39}H_{51}N_3O_3$; n^{20}_D = 1.539; Found, %: C 76.81, H 8.43, N 6.89. Calculated, %: C 76.95, H 8.25, N 6.35; IR spectra, ν, cm^{-1}: 1245.8 (-C-O-C(N)), 1109.2 ((-C-O-C(Ph)), 756.4, 1497.1, 1586.0 (Ph); ^{13}C NMR spectra (101 MHz, Chloroform-d) δ 159.10, 142.79, 129.44–120.53, 114.50 (C_{benz}), 81.12, 86.11, 47.08 ($\underline{C}\equiv\underline{C}$-$\underline{C}H_2$), 75.94 ($\underline{C}$2Ph), 71.61, 50.58, 36.84 ($C_{piperidine}$), 52.27, 51.82 ($C_{piperazine}$), 67.62, 62.72, 26.78, 26.42 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2$OPh), 68.41, 66.54, 57.93, 15.28 (N$\underline{C}H_2\underline{C}H_2$O $\underline{C}H_2\underline{C}H_3$).

*2-(4-(3-(1-(2-Ethoxyethyl)-4-(4-phenoxyethoxy)piperidin-4-yl)prop-2-yn-1-yl)piperazin-1-yl)pyrimidine **(6)***. $C_{28}H_{39}N_5O_3$; n^{20}_D = 1.563; Found, %: C 68.13, H 7.96, N 14.19. Calculated, %: C 68.95, H 7.75, N 14.35; IR spectra, ν, cm^{-1}: 1245.2 (-C-O-C(N)), 1110.8 ((-C-O-C(Ph)), 753.3, 1496.2, 1599.7 (Ph), ^{13}C NMR spectra (101 MHz, Chloroform-d) δ 159.06, 129.41, 120.48, 114.48 (C_{benz}), 86.57, 80.57, 47.39 ($\underline{C}\equiv\underline{C}$-$\underline{C}H_2$), 51.71, 43.61 ($C_{piperazine}$), 161.68, 157.78, 110.12 ($C_{pyrimidine}$), 71.59, 50.53, 36.61 ($C_{piperidine}$), 67.57, 27.36 ($\underline{C}H_2\underline{C}H_2$OPh), 68.35, 66.49, 57.74, 15.24 (N$\underline{C}H_2\underline{C}H_2$O $\underline{C}H_2\underline{C}H_3$).

*2-(4-(3-(1-(2-Ethoxyethyl)-4-(4-phenoxybutoxy)piperidin-4-yl)prop-2-yn-1-yl)piperazin-1-yl)pyrimidine **(7)***. $C_{30}H_{43}N_5O_3$; n^{20}_D = 1.556; Found, %: C 69.07, H 8.31, N 13.42. Calculated, %: C 68.98, H 8.29, N 13.36; IR spectra, ν, cm^{-1}: 1245.6 (-C-O-C(N)), 1110.4 ((-C-O-C(Ph)), 756.3, 1496.0, 1597.7 (Ph), ^{13}C NMR spectra (101 MHz, Chloroform-d) δ, 159.16, 130.08, 120.51, 114.95 (C_{benz}), 86.68, 80.59, 47.45 ($\underline{C}\equiv\underline{C}$-$\underline{C}H_2$), 51.79, 43.69 ($C_{piperazine}$), 161.70, 157.77, 110.01 ($C_{pyrimidine}$), 71.65, 50.96, 36.78 ($C_{piperidine}$), 67.59, 62.36, 26.75, 26.41 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2$OPh), 68.42, 66.52, 57.81, 15.29 (N$\underline{C}H_2\underline{C}H_2$O $\underline{C}H_2\underline{C}H_3$).

3. Results and discussion

The compounds studied include the parent compound – 1-(2-ethoxyethyl)-4-ethynylpiperidin-4-ol (**1**), the intermediate ethers (**2** and **3**), and the final target products (**4–7**).



Compounds **2** and **3** were synthesized via the Williamson reaction by alkylation of the parent acetylenic alcohol 1 with the corresponding phenoxyalkyl bromides in the presence of powdered potassium hydroxide in acetonitrile at room temperature. Compounds **4–7** were obtained via aminomethylation of ethers **2** and **3** using a mixture of paraformaldehyde and a cyclic amine (pyrimidinylpiperazine or diphenylmethylpiperazine) in acetonitrile. The reaction was catalyzed by freshly prepared cuprous chloride. Upon completion, excess amine was removed based on differences in solubility between the product and the secondary amine in hexane. The structures of the synthesized compounds were confirmed using physicochemical analytical methods.

Pharmacological activity prediction using the PASS software evaluated the probabilities on a P_a scale: values of $P_a > 0.3$ indicate moderate likelihood, and $P_a > 0.7$ denote high probability and pharmacological relevance. According to these results, the compound **1** (acetylenic alcohol) showed antibacterial (0.304), anti-inflammatory (0.421), antiviral (0.352), and antioxidant (0.487) activities. These properties suggest potential in treating infections and inflammatory conditions, although the probability levels remain moderate.

Further modification of the molecule by synthesizing simple ethers **2** and **3** allowed for the assessment of the impact of phenoxyalkyl substituents on biological activity. Antibacterial activity slightly increased (to 0.321), potentially indicating enhanced cellular penetration. These compounds also exhibited predicted activity in bone disorders (0.536 and 0.498, respectively), implying potential utility in treating osteoporosis or related conditions. Compound **2** showed promising activity in the treatment of diabetic neuropathy (0.322) and cocaine dependence (0.372), suggesting potential in neurological therapy.

The incorporation of the bulky heterocyclic fragments (diphenylmethylpiperazine and pyrimidinylpiperazine) into the compounds **4–7** led to a marked increase in biological activity and the emergence of new pharmacological effects. Notably, analgesic activity was predicted with probabilities of 0.609 (compounds **4** and **5**) and 0.642 (compound **6**), positioning

these molecules as promising analgesic candidates. Spasmolytic activity reached 0.577 (**5**) and 0.551 (**7**), indicating potential for reducing smooth muscle tone. Additionally, an enhanced antisecretory effect was predicted for compound **7** (0.462), potentially relevant for treating peptic ulcer disease. Derivatives **4**–**7**, as their initials **2** and **3**, retained promising activity for bone disorders (0.528-0.363).

Thus, PASS predictions indicate a favorable biological activity profile for the studied compounds, warranting further experimental validation.

The SwissADME tool provides a cost-effective means to predict ADME (absorption, distribution, metabolism, excretion) pharmacokinetic properties and assess drug-likeness based on molecular structure and physicochemical parameters. Using the Boiled-Egg model which is calculated on the basis of lipophilicity (WLOGP) and polarity (TPSA), passive gastrointestinal absorption and blood-brain barrier (BBB) permeability were evaluated (Figure 1).

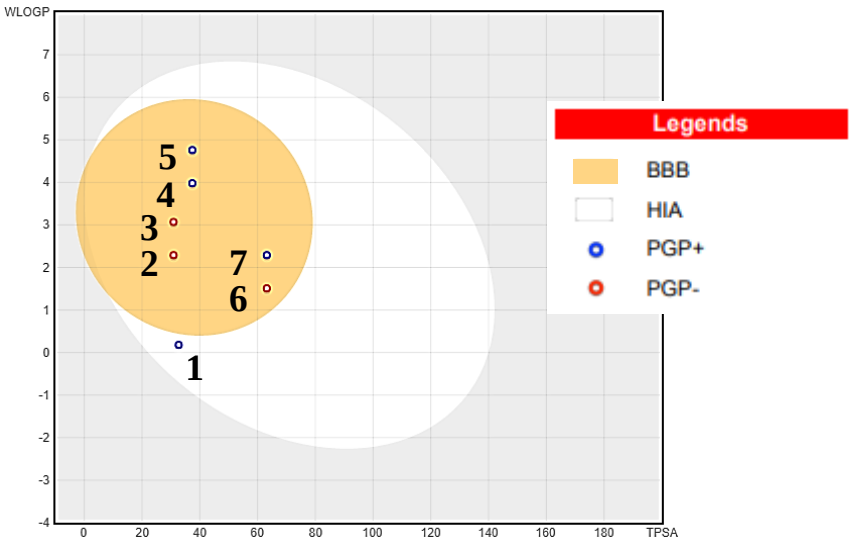


Figure 1 – The BOILED-Egg model for compounds **1**–**7**.

Compound **1**, located in the white ellipse, demonstrated high potential for passive gastrointestinal absorption. In contrast, compounds **2**–**7**, located in the yellow ellipse, showed high BBB permeability, indicating potential CNS availability. These categories are not mutually exclusive; molecules may exhibit both properties.

Compounds **1**, **4**, **6**, and **7** (blue dots), identified as P-glycoprotein substrates (PGP+), may be actively effluxed from the brain or intestinal lumen. Compounds **2**, **3**, and **5** (red dots), identified as non-substrates (PGP−), have a lower probability of active transport-based efflux.

Assessment of six key physicochemical parameters – lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX), and

saturation (SATU) – determines drug-likeness when values fall within the optimal range. These ranges are visualized in a radar plot (Figure 2) as a pink zone representing preferred values: lipophilicity (XLOGP3) from −0.7 to +5.0; molecular weight from 150 to 500 g/mol; topological polar surface area (TPSA) from 20 to 130 Å^2; solubility (log S) not greater than 6; saturation (fraction of sp^3 carbons) ≥ 0.25; and flexibility (number of rotatable bonds) ≤ 9. Full compliance indicates a high probability of drug-likeness

Radar plots revealed that compounds **2** and **3** fall within most optimal ranges (Figure 2), suggesting favorable drug-like properties. In contrast, compounds **4** and **5** containing diphenylmethylpiperazine moieties exceeded optimal flexibility limits, likely due to structural complexity. Compounds **6** and **7**, with pyrimidinylpiperazine fragments, displayed the most favorable physicochemical profiles within the optimal range, indicating the promise of this structural motif. These compounds showed the best alignment with drug-likeness criteria, making them strong candidates for further investigation and development.

Furthermore, all studied compounds meet Lipinski's rule of five, indicating favorable drug-likeness. However, compounds **4** and **6** do not fully comply with the more stringent Muegge rule, which considers additional structural parameters in early drug discovery (Table 1).

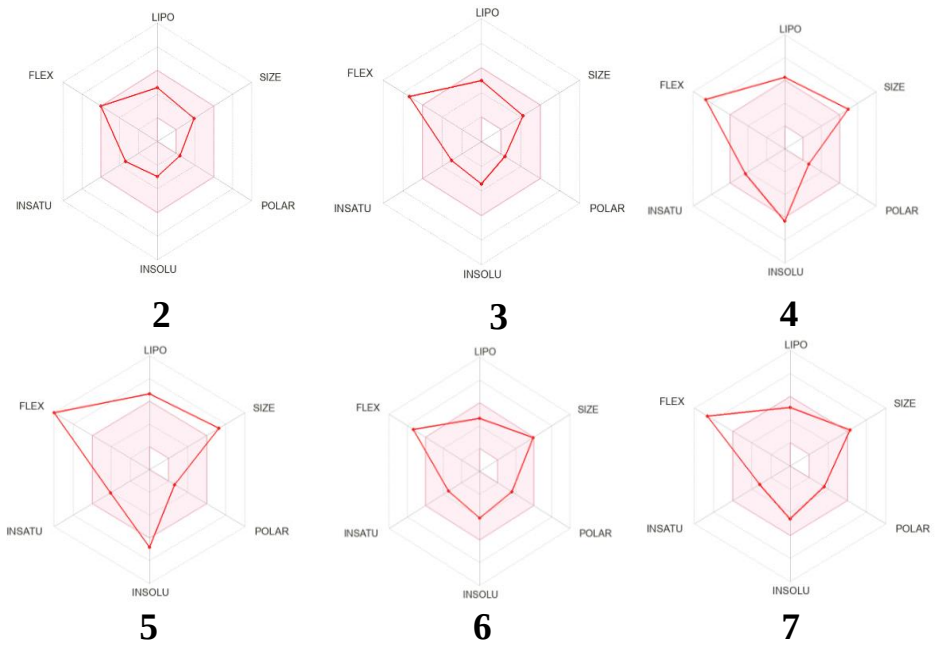


Figure 2 - Radar diagram of compounds **2–7**.

Table 1 - Compliance of compounds 1-7 with bioavailability rules

Compound	Lipinski rule	Egan rule	Muegge rule
1	Yes	Yes	Yes
2	Yes	Yes	Yes
3	Yes	Yes	Yes
4	Yes	Yes	No
5	Yes	Yes	Yes
6	Yes	Yes	No
7	Yes	Yes	Yes

Finally, the ProTox-III web tool was employed to predict compound toxicity. Among all compounds, compound **3** showed the highest predicted toxicity (LD_{50} = 134 mg/kg), classifying it as class 3. Other compounds were categorized as class 4–5, indicating moderate to low toxicity. Compound **5** exhibited the lowest predicted toxicity (LD_{50} = 2935 mg/kg), placing it in class 5. Overall, the compounds varied in toxicity, but none fell into the most hazardous (classes 1–2) or least toxic (class 6) categories. Hepatotoxicity predictions were low across all compounds (0.04–0.25), with compounds **1-4** and **6** showing minimal values (≤0.07). Compounds **5** and **7** also remained within acceptable limits (0.25 and 0.23), indicating a generally safe liver toxicity profile. Cytotoxicity was similarly low for all compounds (0.18–0.3), supporting their favorable safety potential. The target compounds displayed the lowest toxicity, supporting their potential safety for therapeutic use.

Table 2 - Predicted toxicity of compounds **1–7**

Comp.	LD_{50} (mg/kg)	Hepatotoxicity, %	Cytotoxicity, %	Toxicity class	Average similarity (%)	Prediction accuracy (%)
1	1050	0.05	0.18	4	70.13	69.26
2	480	0.04	0.23	4	66.02	68.07
3	134	0.04	0.21	3	61.87	68.07
4	700	0.07	0.22	4	49.36	54.26
5	2935	0.25	0.3	5	45.23	54.26
6	1087	0.07	0.2	4	48.98	54.26
7	2000	0.23	0.3	4	45.24	54.26

4. Conclusion

The conducted *in silico* assessment demonstrated that the studied compounds possess a broad spectrum of predicted biological activities. According to PASS predictions, the parent compound and its derivatives exhibit antibacterial, anti-inflammatory, antiviral, and antioxidant properties, along with potential activity against osteoporosis, diabetic neuropathy, and neurological disorders. Compounds **4-7** showed pronounced analgesic and spasmolytic effects, making them promising candidates for the treatment of pain syndromes and related conditions.

Pharmacokinetic analysis using SwissADME confirmed that the compounds meet key drug-likeness criteria, including Lipinski's rule of five, indicating their potential oral bioavailability. According to the Boiled-Egg model, the compounds demonstrated good gastrointestinal absorption and the ability to penetrate the blood–brain barrier, which is particularly important for central nervous system (CNS) therapies. Compounds **2**, **3**, **6**, and **7** aligned well with bioavailability criteria, whereas compounds **4** and **5**, containing diphenylmethylpiperazine fragments, exceeded optimal flexibility parameters due to their structural complexity.

Toxicity evaluation using ProTox-III showed that most compounds exhibited moderate to low predicted toxicity. Compound **5** was the least toxic, while compound **3** showed higher toxicity, which could potentially be mitigated by immobilization strategies, such as encapsulation in dextrins. Importantly, compound **3** is considered an intermediate, and its derivatives demonstrated lower toxicity profiles.

Overall, the *in silico* analysis identified promising compounds for further pharmacological investigation and provided a rational basis for prioritizing candidates for experimental validation.

Funding: This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No AP23484420).

Conflict of interests: The authors declare that there are no conflicts of interests between the authors to disclose in this article.

In silico ӘДІСІ АРҚЫЛЫ ЖАҢА ПИПЕРИДИН ТУЫНДЫЛАРЫНЫҢ ФАРМАКОКИНЕТИКАСЫ МЕН УЫТТЫЛЫҒЫН БАҒАЛАУ

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Түйіндеме. *Кіріспе.* Қазіргі заманғы компьютерлік модельдеу әдістері қосылыстардың биологиялық белсенділігі мен фармакокинетикалық қасиеттерін дәрілік заттарды әзірлеудің ерте кезеңдерінде болжауға мүмкіндік береді, бұл тиімді молекулаларды іріктеу үдерісін айтарлықтай жылдамдатады. Осы қосылыстардың ішінде пиперидин туындыларына олардың жоғары ықтимал фармакологиялық құндылығына байланысты ерекше назар аударылады. *Зерттеу мақсаты* - жаңа синтезделген пиперидин туындыларының биологиялық белсенділігін, фармакокинетикалық параметрлері мен уыттылығын компьютерлік модельдеу әдістерін қолдана отырып бағалау. *Нәтижелер және талқылау.* Сол үшін 1-(2-этоксиэтил)-4-этинилпиперидин-4-ол эфирлерін аминометилдеу нәтижесінде төрт жаңа қосылыс алынды. Бұл қосылыстар Al_2O_3 негізіндегі бағаналы хроматография әдісімен бөлініп, физика-химиялық талдау әдістері арқылы сипатталды. Қосылыстардың биологиялық белсенділігі PASS бағдарламасы арқылы, фармакокинетикалық қасиеттері SwissADME платформасында, ал уыттылығы ProTox-III көмегімен зерттелді. Зерттелген қосылыстардың бактерияға қарсы, қабынуға қарсы және анальгезиялық белсенділікке жоғары бейімділікке ие, сонымен қатар остеопороз, диабеттік нейропатия және жүйке жүйесі аурулары

сияқты патологиялық жағдайларға қарсы белсенділік көрсетуі мүмкін. Фармакокинетикалық сипаттамаларын талдау олардың жақсы абсорбцияланатын және гематоэнцефалдық бөгеттен өте алатынын көрсетті. ProTox-III көмегімен қосылыстардың уыттылығы төмен деңгейде екені анықталды (ең төмен уыттылық **5**-қосылыс, LD_{50} = 2935 мг/кг). *Қорытынды.* Әсіресе, **2**, **3**, **6** және **7**-қосылыстар биожетімділігі жоғары және уыттылығы төмен болуына байланысты әрі қарай зерттеуге аса перспективалы болып табылады. Алынған нәтижелер негізінде, синтезделген қосылыстарды әрі қарай *in vitro* және *in vivo* скринингтен өткізуі орынды деп айтуға болады.

Түйін сөздер: пиперидин туындылары, компьютерлік модельдеу, PASS, SwissADME, ProTox-III, фармакокинетика, уыттылық, дәрілік қосылыстар.

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In silico ОЦЕНКА ФАРМАКОКИНЕТИКИ И ТОКСИЧНОСТИ НОВЫХПИПЕРИДИНОВЫХ ПРОИЗВОДНЫХ

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Резюме. *Введение.* Современные методы компьютерного моделирования позволяют прогнозировать биологическую активность и фармакокинетические свойства соединений на ранних этапах разработки лекарств, ускоряя поиск перспективных кандидатов. Особый интерес представляют пиперидиновые производные благодаря их высокой потенциальной фармакологической ценности. *Целью настоящей работы* является оценка биологической активности, фармакокинетики и токсичности новых пиперидиновых производных методами *in silico*. *Результаты и обсуждение.* Путём аминометилирования эфиров 1-(2-этоксиэтил)-4-этинилпиперидин-4-ола синтезированы четыре соединения, выделенные колоночной хроматографией на Al_2O_3 и охарактеризованные физико-химическими методами. Биологическая активность оценивалась с использованием программы PASS, фармакокинетика – в SwissADME, токсичность – в ProTox-III. Установлено, что соединения обладают высокой вероятностью антибактериальной, противовоспалительной и анальгезирующей активности, а также потенциальной эффективностью при остеопорозе, диабетической нейропатии и заболеваниях нервной системы. Фармакокинетические характеристики свидетельствуют о хорошей абсорбции и способности проникать через гематоэнцефалический барьер. Согласно ProTox-III, соединения имеют преимущественно низкий уровень токсичности (наименьшая – у соединения 5, LD_{50} = 2935 мг/кг). *Заключение.* Особенно перспективными для дальнейших исследований являются соединения **2, 3, 6** и **7** благодаря высокой биодоступности и низкой токсичности. Полученные результаты подтверждают целесообразность дальнейшего *in vitro* и *in vivo* скрининга синтезированных соединений.

Ключевые слова: пиперидиновые производные, компьютерное моделирование, PASS, SwissADME, ProTox-III, фармакокинетика, токсичность, лекарственные соединения.

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