UDK 547.854.856 doi: 10.33609/2708-129X.90.1.2024.15-25

PREDICTION OF BIOLOGICAL ACTIVITY OF AMINOQUINOLINE DERIVATIVES USING THE ADMET 2.0 WEB RESOURCE.

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The objective of this study was to predict the pharmacokinetic parameters of 5,6,7,8-tetrahydroquinoline-3-amine derivatives using the ADMET 2.0 web resource and compare them with 4-aminoquinoline and chloroquine. The tested substances exhibited favorable indicators of intestinal absorption, clearance, half-life, and liver damage, mutagenicity, and carcinogenicity. The derivatives of 5,6,7,8-tetrahydroquinolin-3-amine studied here have increased indicators of blood-brain barrier penetration. Therefore, they cannot be recommended for the production of drugs that act on the central nervous system. Based on the prediction results, the compounds with tert-butyl and tert-amyl substituents in the 7th position were found to be the most effective. The SuperPred 3.0 web resource was used to predict the molecular targets for binding of derivatives of 5,6,7,8-tetrahydroquinoline-3-amine. The aminoquinolines and chloroquine studied in this research have common binding targets, including tyrosyl-DNA-phosphodiesterase 1, DNA-(apurine or apyrimidine site) lyase, neuronal acetylcholine receptor alpha3/beta4, and cathepsin D. These predicted binding targets play important roles in regulating cell function. The derivatives of 5,6,7,8-tetrahydroquinoline-3-amines presented in this study are promising compounds for further pharmacological research due to their effective synthesis method and pharmacokinetic properties.

Keywords: 5,6,7,8-tetrahydroquinoline-3-amine derivatives, electrophilic rearrangement, spiroimidazolidones, in silico, ADMET 2.0, SuperPred 3.0

INTRODUCTION. Quinoline derivatives have a broad range of pharmacological activity, and the quinoline core is present in many drugs. Classical antimalarial drugs, such as 4-aminoquinoline [1], chloroquine [2], and hydroxychloroquine [3], are well-known examples. Although these compounds were tested for the treatment of COVID-19, they exhibited high toxicity and several side effects [4]. Dequalinium, the basis of a synthetic antibiotic, has antifungal and antiprotozoal effects and contains a quinoline core. Although hydroquinolines are not included in active drugs, there are examples of their pharmacological

activity. However, the lack of available methods for the synthesis of hydroquinoline derivatives has led scientists to focus on finding and developing effective synthesis methods. A previous method for synthesizing hydroquinolines with good yields was published, which resulted from the electrophilic rearrangement of spiroimidazolidones [12–13].

The aim of this article is to predict the biological activity of 5,6,7,8-tetrahydroquinoline-3-amine derivatives 1–8 (Figure 1) using in silico methods.

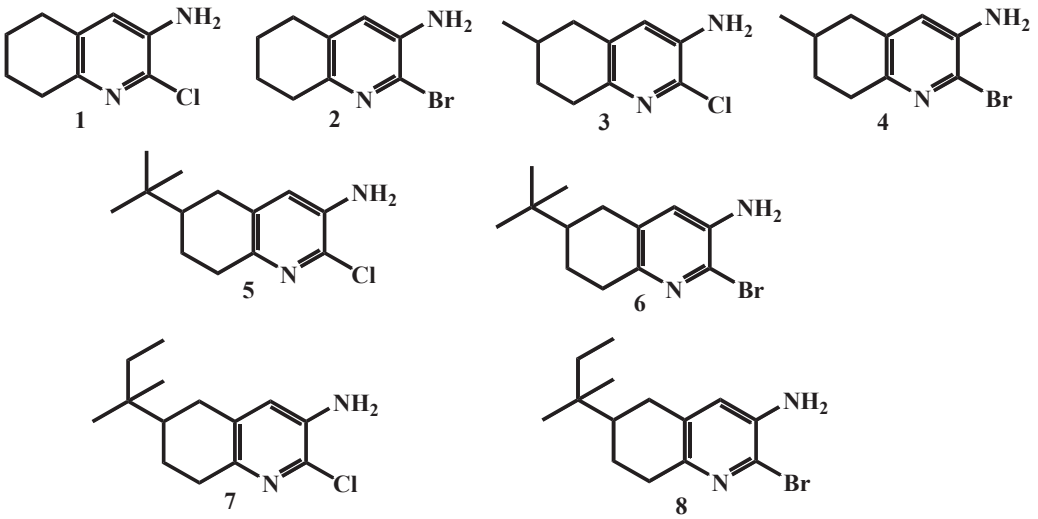


Figure 1. Synthesized derivatives of 5,6,7,8-tetrahydroquinoline-3-amine.

EXPERIMENT AND RESULTS DISCUSSION. The ADMETlab 2.0 software resource [14] was used to assess the capabilities of compounds 1–8 to bind to biological targets and predict their metabolic profile, excretion, toxicity, and ADMET ligand properties. The predicted values for compounds 1–8 were compared to those of active drugs containing the quinoline core, 4-aminoquinoline 9, and chloroquine 10 (Figure 2).

During the comparative analysis, visualization of the results is presented in the form of "spider web" graphs in Figure 3.

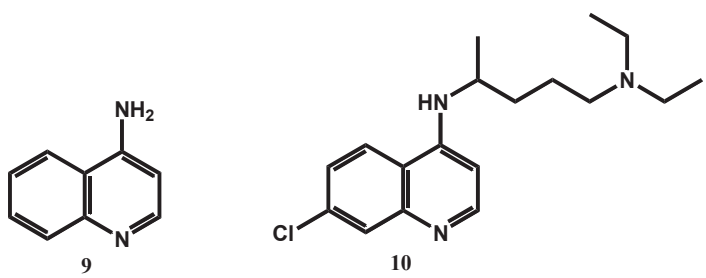
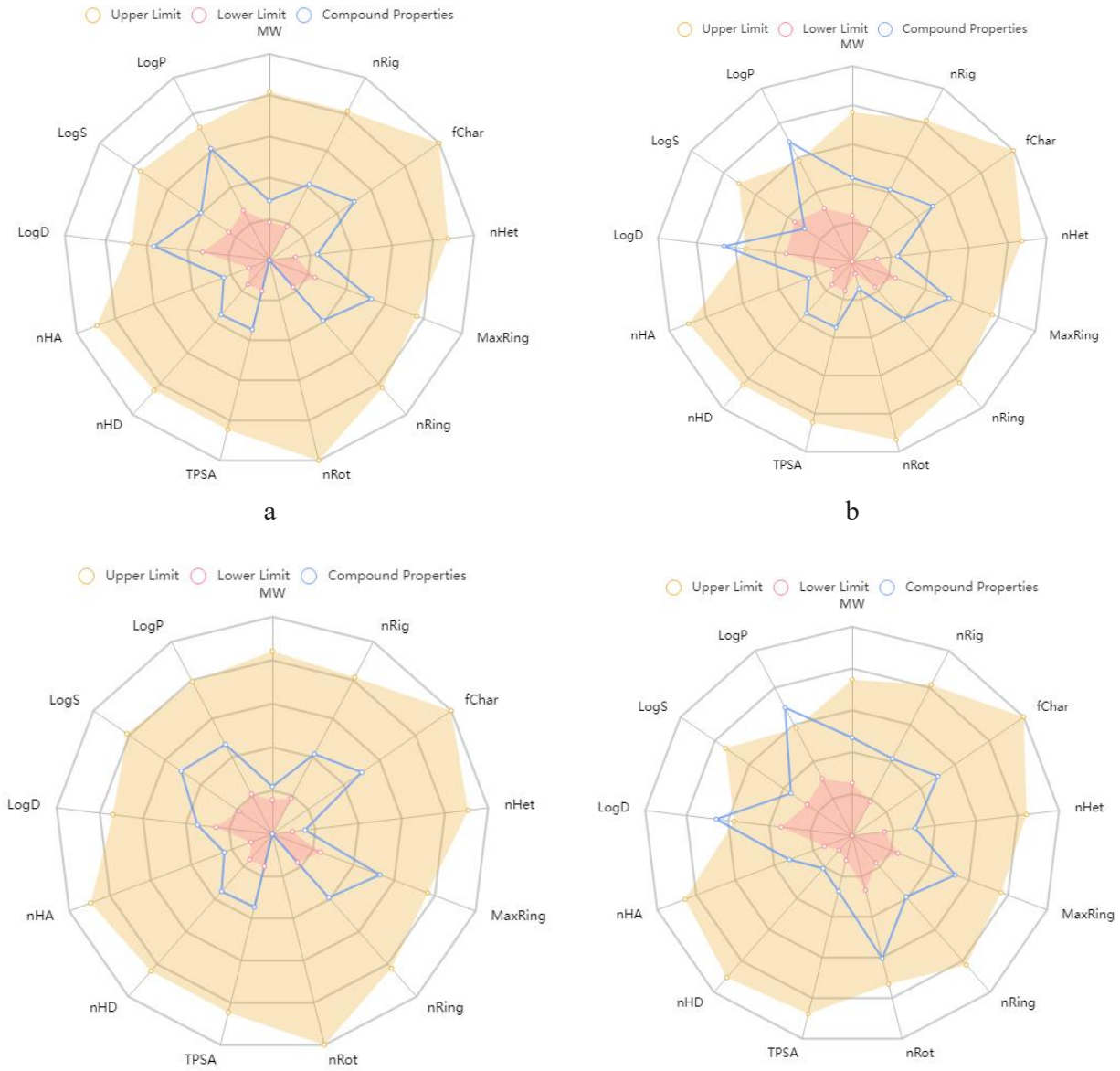


Figure 2. Comparison drugs, 4-aminoquinoline and chloroquine.



a – compound 1; b – compound 6; c – compound 9; d – compound 10

Figure 3. Graphic images of the analysis of physical and chemical authorities 1, 6, 9 and 10.

Table 1 presents prediction data for 13 physicochemical compounds 1–10. For clinical trial applicants, it is essential to comply with the Lipinski rule [15]. Additionally, topological polar surface area (TPSA), number of rotatable bonds (nRot), and lipid solubility parameter (Log P) at physiological pH = 7.4 Log D are also crucial in predicting the oral bioavailability of a substance.

Таблиця 1. **Фізико-хімічні показники сполук 1–10 за допомогою ADMETlab 2.0**
Table 1. **Physico-chemicalindicatorsofcompounds 1–10 using ADMETlab 2.0.**

Compound	MW	Log P	nHA	nHD	TPSA	nRot	Log D
Normativeindicators	<500	<5	<10	<5	<140	<11	<3
1	182	2.233	2	2	38.91	0	2.366
2	226	2.554	2	2	38.91	0	2.509
3	196	2.629	2	2	38.91	0	2.631
4	240	2.951	2	2	38.91	0	2.799
5	238	3.873	2	2	38.91	1	3.962
6	282	4.192	2	2	38.91	1	4.046
7	252	4.244	2	2	38.91	2	4.184
8	296	4.601	2	2	38.91	2	4.287
9	144	1.327	2	2	38.91	0	1.361
10	319	4.217	3	1	28.16	8	3.755

Upon analyzing the results, it is evident that 4-aminoquinoline and compounds 1–4 meet the required standards, while synthesized compounds 5, 6, 7, 8, and chloroquine 9 demonstrate a Log D parameter slightly outside the required range.

Subsequently, we conducted an analysis of the pharmacokinetic parameters, which are presented in Table 2.

Таблиця 2. **Фармакокінетичні показники сполук 1–10**
Table 2. **Pharmacokinetic parameters of compounds 1–10.**

Compound	HIA	BBB	CL	$T_{1/2}$
Normativeindicators	0–0.3 excellent 0.3–0.7 medium 0.7–1.0 poor	0–0.3 excellent 0.3–0.7 medium 0.7–1.0 poor	>5	0–0.3 excellent 0.3–0.7 medium 0.7–1.0 poor
1	0.003	0.99	8.248	0.337
2	0.004	0.995	4.336	0.289
3	0.004	0.986	9.976	0.286
4	0.007	0.992	5.437	0.251
5	0.007	0.966		0.177
6	0.031	0.977	4.966	0.145
7	0.07	0.967	8.242	0.154
8	0.029	0.981	4.475	0.12
9	0.006	0.402	6.122	0.32
10	0.002	0.679	6.818	0.134

The human intestinal absorption (HIA) parameter is considered an alternative indicator for oral bioavailability because good intestinal absorption is necessary for the effectiveness of an oral drug in humans. It is assumed that all compounds tested have good absorption.

Drugs that act on the central nervous system must cross the blood-brain barrier (BBB) to reach their molecular target. For peripherally targeted drugs, little or no BBB penetration may be required to avoid CNS side effects. Compounds 1–8 cannot be recommended for manufacturing drugs that act on the central nervous system due to their increased BBB values. Control drugs 9 and 10 show average values.

When comparing clearance (CL), only compounds 2, 6, and 8 will be excreted less in urine.

The half-life of all tested compounds falls within normal limits.

Table 3 presents predicted toxicities for compounds 1–10, an important safety indicator.

Таблиця 3. **Показники токсичності, мутагенності і канцерогенності сполук 1–10**
Table 3. **Indicators of toxicity, mutagenicity and carcinogenicity of compounds 1–10.**

Compound Normative indicators	DILI	AMES 0–0.3 excellent 0.3–0.7 medium 0.7–1.0 poor	CARC
1	0.334	0.554	0.621
2	0.336	0.158	0.599
3	0.307	0.629	0.702
4	0.33	0.147	0.654
5	0.236	0.018	0.081
6	0.102	0.015	0.07
7	0.291	0.035	0.094
8	0.166	0.018	0.079
9	0.802	0.849	0.564
10	0.733	0.634	0.089

Drug-induced liver injury (DILI) is a major safety concern in drug withdrawal. The connections with the safest parameters are 5, 6, 7, and 8, while the control connections 9 and 10 have high readings.

The mutagenic effect (AMES) is closely related to carcinogenicity and is the most widely used method for testing the mutagenicity of compounds. The compounds with the best indications for predicting mutagenicity among those tested were compounds 2 and 4–8. For drugs 9 and 10, mutagenicity indicators are within normal limits, but may be overestimated.

Carcinogenicity (CARC) of chemical compounds is due to their ability to damage the genome and disrupt cellular metabolic processes. Compounds 5, 6, 7, 8, and 10 are expected to have the least carcinogenic effect. It is important

to note that toxicity of the compounds decreases with increasing branching of the alkyl substituent.

Based on the data analysis, compounds 5, 6, 7, and 8 show the most promise for further research.

The SuperPred 3.0 web resource (https://prediction.charite.de/index.php) was used to predict the binding of the tested compounds to molecular targets.

This web server compares the structural fingerprint of an incoming molecule with a database of drugs associated with their targets and pathways. The web server allows for predictions about the medical indication domain of new compounds to be made and new leads to be found for known targets, based on the highly predictable biological effect when the structural similarity is sufficient. This information can be useful for drug classification and target prediction [16, 17], as well as assisting in the drug development process by predicting ATC codes or small molecule targets and obtaining compound information. The web server's ATC forecast and target prediction are based on a machine learning model that uses logistic regression and Morgan fingerprints of length 2048. The ChEMBL version 29 database was used to identify the target.

Binding predictions were performed for compound 6 (Table 4) and chloroquine 10 (Table 5). The analysis considered results up to 80%.

Таблиця 4. **Прогнозовані цілі зв'язування з молекулою сполуки 6**
Table 4. **Predicted targets of binding to the compound 6.**

TargetName	ChEMBL-ID	PDB Visualization	Probability	Indications of predicted targets
Tyrosyl-DNA phosphodiesterase 1	CHEMBL1075138	6N0D	97.48%	
DNA-(apurinic or apyrimidinic site) lyase	CHEMBL5619	6BOW	93.29%	Glioma, Melanoma, Ocularcancer, Solid tumor/ cancer
Nuclear factor NF-kappa-B p105 subunit	CHEMBL3251	1SVC	92.74%	
Phosphodiesterase 3A	CHEMBL241	7LRC	92.51%	Bronchial asthma, Cardiacfailure, Cardiovascular disease, Cardiovasculardisease, Congestive heart failure, Intermittent claudication, Thrombocythemia
Neuronal acetylcholine receptor; alpha3/beta4	CHEMBL1907594	6PV7	90.11%	Alzheimerdisease, Tobaccodependence
LSD1/CoRESTcomplex	CHEMBL3137262	5L3D	89.15%	
G-proteincoupledreceptor 55	CHEMBL1075322	–	88.78%	Attentiondeficithyperactivity disorder

Таблиця 4.
Table 4.

TargetName	ChEMBL-ID	PDB Visualization	Probability	Indications of predicted targets
Endoplasmic reticulum-associated amyloid beta-peptide-binding protein	CHEMBL4159	2O23	85.82%	
Cannabinoid CB2 receptor	CHEMBL253	6KPF	84.56%	
Eglninehomolog 1	CHEMBL5697	4BQY	83.88%	
NT-3 growthfactorreceptor	CHEMBL5608	6KZD	83.38%	
Transcriptionintermediaryfactor 1-alpha	CHEMBL3108638	4YBM	83.06%	
Cathepsin D	CHEMBL2581	4OD9	82.5%	Hypertension, Multiplesclerosis
Kruppel-likefactor 5	CHEMBL1293249	–	82.02%	
Tyrosine-proteinkinase FYN	CHEMBL1841	2DQ7	81.88%	Chronic myelogenousleukaemia, Multiple myeloma, Solid tumour/cancer
LysosomalPro-X carboxypeptidase	CHEMBL2335	3N2Z	81.15%	
Proteinkinase N1	CHEMBL3384	4OTH	80.8%	
Sodium/hydrogenexchanger 1	CHEMBL2781	7DSX	80.44%	Angina pectoris, Cardiacarrhythmias, Heart arrhythmia, Myocardial infarction

Таблиця 5. **Прогнозовані цілі зв'язування сполуки 10**
Table 5. **Predicted targets of binding to the compound 10.**

TargetName	ChEMBL-ID	PDB Visualization	Probability	Indications of predicted targets
Sigma opioid receptor	CHEMBL287	5HK1	99%	
Sigmaintracellularreceptor 2	CHEMBL4105907	–	99%	
Tyrosyl-DNAphosphodiesterase 1	CHEMBL1075138	6N0D	99%	
HERG	CHEMBL240	5VA1	98.19%	Malaria, Angina pectoris,Cardiac failure, Heartarrhythmia, Pain, Ovariancancer
Pregnane X receptor	CHEMBL3401	6TFI	97.01%	Arteriosclerosis,

Таблиця 5.
Table 5.

TargetName	ChEMBL-ID	PDB Visualization	Probability	Indications of predicted targets
Cathepsin D	CHEMBL2581	4OD9	96.6%	Hypertension, Multiplesclerosis
Dual specificity protein kinase CLK4	CHEMBL4203	6FYV	93.63%	
Nuclear factor NF-kappa-B p105 subunit	CHEMBL3251	1SVC	93.32%	
DNA-(apurinic or apyrimidinic site) lyase	CHEMBL5619	6BOW	92.82%	Glioma, Melanoma, Ocular cancer
LysosomalPro-X carboxypeptidase	CHEMBL2335	3N2Z	91.57%	
Telomerasereversetranscriptase	CHEMBL2916	7BG9	90.86%	Acute myeloid leukaemia, Brain cancer, Breast cancer, Essentialthrombocythemia, Headand neck cancer
Dihydrofolatereductase	CHEMBL202	1KMV	90.57%	Acute bacterial skininfection, Bacterialinfection, Bladder cancer
Neuronal acetylcholine receptor; alpha3/beta4	CHEMBL1907594	6PV7	90.26%	Alzheimerdisease, Tobaccodependence
Adenosine A1 receptor	CHEMBL226	T92072	89.85%	Acute and chronic heart failure, Atrial fibrillation, Autoimmune diabetes
Serotonin 7 (5-HT7) receptor	CHEMBL3155	T79062	89.21%	Alzheimer disease, Attention deficit hyperactivity disorder, Major depressive disorder
Nuclear factor erythroid 2-related factor 2	CHEMBL1075094	–	88.99%	
Cyclooxygenase-1	CHEMBL221	–	88.27%	
Histonedeacetylase 7	CHEMBL2716	–	87.5%	
Glutathione S-transferasePi	CHEMBL3902	T21669	87.35%	
Sodium channel protein type III alpha subunit	CHEMBL5163	T76937	87.17%	
G-proteincoupledreceptor 55	CHEMBL1075322	T87670	86.82%	
Adenosine A2b receptor	CHEMBL255	T86679	85.96%	Acute and chronic heart-failure, Alzheimer disease, Asthma
Dipeptidylpeptidase II	CHEMBL3976	–	85.95%	

ISSN 2708-129X. Укр. хім. журн., 2024

Common binding targets for compound 6 and chloroquine 10 include Tyrosyl-DNA phosphodiesterase 1, DNA-(apurinic or apyrimidinic site) lyase, Neuronal acetylcholine receptor alpha3/beta4, and Cathepsin D. These predicted targets play important roles in regulating cell activity. For example, DNA-(apurinic or apyrimidinic site) lyase is a multifunctional protein that plays a central role in the cellular response to oxidative stress during oxidative stress, melanoma, and cancer of the eye [18].

CONCLUSIONS. A prediction of the pharmacological activity of previously synthesized 5,6,7,8-tetrahydroquinoline-3-amine derivatives was conducted in silico. The results of the prediction were compared to those of the active drugs, 4-aminoquinoline and chloroquine. All synthesized compounds comply with Lipinski's rule and exhibit good intestinal absorption, clearance, and half-life. The synthesized compounds exhibit lower predicted toxicity, mutagenicity, and carcinogenicity compared to the comparison drugs. Additionally, the study predicts future molecular targets for the synthesized substances in living cells. The derivatives of 5,6,7,8-tetrahydroquinoline-3-amines presented in this study are promising compounds for further pharmacological studies due to their effective synthesis method and pharmacokinetic properties.

ACKNOWLEDGMENTS.
Authors are thankful to the Ministry of education and science of Ukraine (project № 0123U101168) and scholarship of the Cabinet of Ministers of Ukraine for the financial support.

ПРОГНОЗУВАННЯ БІОЛОГІЧНОЇ АКТИВНОСТІ ПОХІДНИХ АМІНОХІНОЛІНУ ЗА ДОПОМОГОЮ ВЕБ-РЕСУРСУ ADMET 2.0

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Метою цього дослідження було прогнозування фармакокінетичних параметрів похідних 5,6,7,8-тетрагідрохінолін-3-аміну за допомогою веб-ресурсу ADMET 2.0 та порівняння їх із 4-амінохіноліном і хлорохіном. Досліджувані речовини продемонстрували сприятливі показники кишкової абсорбції, кліренсу, періоду напіввиведення та пошкодження печінки, мутагенності та канцерогенності. Досліджені похідні 5,6,7,8-тетрагідрохінолін-3-аміну мають підвищені показники проникнення через гематоенцефалічний бар'єр. Тому їх не можна рекомендувати для розроблення препаратів, що діють на центральну нервову систему. За результатами прогнозу найефективнішими виявилися сполуки з трет-бутильним і трет-амільним замісниками в 7-му положенні. Веб-ресурс SuperPred 3.0 використовували для прогнозування молекулярних мішеней зв'язування похідних 5,6,7,8-тетрагідрохінолін-3-аміну.

Амінохіноліни та хлорохін, досліджені в цій роботі, мають загальні мішені зв'язування, включаючи тирозил-ДНК-фосфодіестеразу 1, ДНК-(апуриновий або апіримідиновий сайт) ліазу, нейрональний ацетилхоліновий рецептор альфа3/бета4

та катепсин D. Ці передбачені мішені зв'язування відіграють важливу роль у регуляції роботи клітин. Представлені в цьому дослідженні похідні 5,6,7,8-тетрагідрохінолін-3-амінів є перспективними сполуками для подальших фармакологічних досліджень завдяки їхньому ефективному методу синтезу та фармакокінетичним властивостям.

Ключові слова: Похідні 5,6,7,8-тетрагідрохінолін-3-аміну, електрофільне перегрупування, спіроімідазолідони, insilico, ADMET 2.0, SuperPred 3.0.

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Стаття надійшла 24.09.2023.