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IN SILICO PREDICTION OF PASS AND ADME/TOX PROPERTIES OF NOVEL 1,3,5-TRIAZINE DERIVATIVES FOR DRUG DEVELOPMENT

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Abstract. *The relevance:* This study is driven by the need for preliminary screening in drug development, with a particular focus on a promising class of 1,3,5-triazine derivatives known for their diverse pharmacological potential. The high cost of experimental screening necessitates robust *in silico* methods to prioritize viable candidates. *Aim*: to conduct a comprehensive computer-aided screening of a series of novel 1,3,5-triazine derivatives. *Methods*: The research employed computational approaches to predict the biological activity, pharmacokinetics, and toxicity of six novel 1,3,5-triazine derivatives. The PASS algorithm predicted biological activities, while the ADMETlab-3.0 platform evaluated drug-like properties, including compliance with Lipinski's rule, intestinal permeability, blood-brain barrier penetration, metabolism by cytochrome P450 enzymes, and various toxicity endpoints. *Results*: Key findings

indicate promising predicted activities, particularly as inhibitors of testosterone-17β-dehydrogenase and anaphylatoxin receptors, suggesting applications in oncology and immunology. Pharmacokinetic analysis showed that all compounds have good predictable bioavailability when administered orally. Significant differences were identified: compound 4 showed high blood-brain barrier penetration, while compounds 1 and 2 were predicted to be safer with lower overall toxicity. However, critical toxicological risks were highlighted, such as potential cardiotoxicity for compounds 3 and 6, and neurotoxicity for compound 4. *Practical significance*: The results demonstrate the practical utility of integrated *in silico* profiling for rational lead selection. Study enables ranking of compounds by predicted activity and safety, helping to identify the lead candidates (1 and 2) for further development. This strategy can significantly accelerate early drug development by reducing the number of compounds requiring costly laboratory testing.

Key words: 1,3,5-Triazine; PASS; ADME/Tox; pharmacokinetics; toxicity; drug development

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IN SILICO PASS ЖӘНЕ ADME/TOX БАҒДАРЛАМАЛАРЫ АРҚЫЛЫ ДӘРІЛІК ЗАТТАР ӘЗІРЛЕУ ҮШІН 1,3,5-ТРИАЗИННІҢ ЖАҢА ТУЫНДЫЛАРЫНЫҢ ҚАСИЕТТЕРІН БОЛЖАУ

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Аннотация. *Өзектілігі:* Зерттеу жұмысы әртүрлі фармакологиялық әлеуетімен танымал 1,3,5-триазиннің жаңа 6 туындысының фармакологиялық қасиеттерін,

биологиялық белсенділігін және уыттылығын *in silico* әдісімен болжауға арналған. Эксперименттік скринингтің жоғары құндылығына байланысты перспективті үміткерлерге басымдылық беру үшін in silico әдістерін пайдалану қажеттілгі туындайды. *Мақсаты:* Жаңа 1,3,5-триазин туындыларының сериясын кешенді компьютерлік скринингтен өткізу. *Зерттеу әдістері*: Биологиялық белсенділік PASS алгоритмі арқылы болжанды, ал ADMETlab-3.0 платформасы негізгі фармакокинетикалық қасиеттерді, соның ішінде Липинский ережесін сақтау, ішек өткізгіштігі, гематоэнцефалдық бөгеттің енуі, P450 цитохром ферменттері арқылы метаболизм және әртүрлі уыттылықтары бағалау үшін қолданылды. *Нәтиже:* Алынған нәтижелер, атап айтқанда, тестостерон-17β-дегидрогеназа және анафилатоксин рецепторларының ингибиторлары ретінде онкология мен иммунологияда қолдануға мүмкіндік береді. Фармакокинетикалық талдау барлық қосылыстардың ішке қабылдағанда жақсы биожетімділігі болжанғанын көрсетті. Сонымен қатар келесідей айырмашылықтар да анықталды: 4-қосылыстың гематоэнцефалдық бөгет арқылы жоғары өткізгіштігі байқалды, ал 1 және 2-қосылыстардың жалпы уыттылығы төмен болды, дегенмен олар үшін белгілі бір қауіптер де байқалды. 3 және 6 қосылыстар үшін кардиоуыттылық және 4 қосылыс үшін нейроуыттылық сияқты маңызды токсикологиялық қауіптер анықталды. Нәтижелер *in silico* әдісінің қосылыстарды ұтымды іріктеудегі тәжірибелік құндылығын көрсетеді. *Практикалық маңызы:* Жұмысы қосылыстарды болжау мен қауіпсіздігі тұрғысынан саралауға мүмкінді береді. Бұл ары қарайғы әзірлеу үшін ең перспективті кандидаттарды (1 және 2) анықтауға көмектеседі. Бұл стратегия қымбат тұратын зертханалық сынақтарды қажет ететін қосылыстардың санын азайту арқылы дәрілік заттарды әзірлеуді айтарлықтай тездетуге мүмкіндік береді.

Түйін сөздер: 1,3,5-Триазин; PASS; ADME/Tox; фармакокинетикасы; уыттылық; дәрілік заттардың дамуы

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IN SILICO PASS И ADME/TOX ПРОГНОЗИРОВАНИЕ СВОЙСТВ НОВЫХ ПРОИЗВОДНЫХ 1,3,5-ТРИАЗИНА ДЛЯ РАЗРАБОТКИ ЛЕКАРСТВ

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Аннотация. *Актуальность:* Данное исследование обусловлено необходимостью предварительного скрининга в разработке лекарственных препаратов, уделяя особое внимание перспективному классу производных 1,3,5-триазина, известных своим разнообразным фармакологическим потенциалом. Высокая стоимость экспериментального скрининга обуславливает необходимость использования надежных методов *in silico* для определения приоритетности перспективных кандидатов. *Цель*: провести всесторонний компьютерный скрининг ряда новых производных 1,3,5-триазина. *Методы*: Биологическую активность прогнозировали с помощью алгоритма PASS, в то время как платформа ADMETlab-3.0 была использована для оценки ключевых фаркакокинетических свойств, включая соответствие правилу Липинского, кишечную проницаемость, проникновение через гематоэнцефалический барьер, метаболизм ферментами цитохрома P450 и оценки различных видов токсичности. *Результаты*: Основные выводы указывают на перспективные прогнозируемые активности, в частности, в качестве ингибиторов тестостерон-17β-дегидрогеназы и рецепторов анафилатоксина, что предполагает применение в онкологии и иммунологии. Фармакокинетический анализ показал, что все соединения обладают хорошей прогнозируемой биодоступностью при приеме внутрь. Были выявлены существенные различия: соединение 4 продемонстрировало высокую проницаемость через гематоэнцефалический барьер, в то время как соединения 1 и 2, обладали меньшей общей токсичностью, хотя и для них были отмечены определенные риски. Установлены критические токсикологические риски, такие как потенциальная кардиотоксичность для соединений 3 и 6 и нейротоксичность для соединения 4. Результаты демонстрируют практическую ценность интегрированного профилирования *in silico* для рационального выбора основных соединений. *Практическая значимость:* Исследование позволяет ранжировать соединения по перспективности и безопасности, выявляя наиболее подходящих кандидатов (1 и 2) для дальнейшей разработки. Эта стратегия может значительно ускорить раннюю разработку лекарственных препаратов за счет сокращения количества соединений, требующих дорогостоящих лабораторных испытаний.

Ключевые слова: 1,3,5-Триазин; PASS; ADME/Tox; фармакокинетика; токсичность; разработка лекарственных препаратов

Introduction. The relevance of searching for new highly effective compounds, both natural and synthetic, is confirmed by many research (Silva et al., 2025; Dyusebaeva, 2024; Duzbayeva et al., 2023; Ikhsanov et al., 2023; Kantureyeva et al., 2021; Zhonderbek et al., 2021). At the same time, the development of new drugs is a complex, multi-step, and resource-intensive process characterized by a high failure rate at late stages, often due to unexpected toxicity, unsatisfactory pharmacokinetics (ADME), or insufficient efficacy. In this context, computer prediction methods (*in silico*) have become an integral tool in modern medicinal chemistry, enabling virtual screening and prioritization of compounds at the earliest stages, significantly reducing time and costs.

The introduction of new pharmacologically active compounds based on nitrogen-containing heterocyclic systems is a strategic direction in the fight against socially significant diseases (Bayazit, 2025). Promising compounds in this regard include 1,3,5-triazines, which were chosen as the object of this study. 1,3,5-Triazines find wide application in chemistry, medicine and pharmacology due to their flexibility and diverse biological activity. These six-membered cyclic structures contain three nitrogen atoms, which allows them to be easily modified to obtain various derivatives with unique properties. Due to their versatility and ability to interact with various biological targets, they are actively studied for the creation of new therapeutic drugs.

However, the synthesis and experimental testing of all potentially interesting triazine derivatives is physically impossible. Therefore, the key task is to rationally select the most promising candidate structures for subsequent synthesis and in-depth study.

Here, modern *in silico* approaches come to the forefront, enabling:

1. Prediction of Activity Spectra for Substances (PASS). The PASS algorithm evaluates the likelihood of a compound exhibiting a broad spectrum of biological activity based on its molecular structure, helping to hypothesize primary and secondary pharmacological effects and identify potential new mechanisms of action (Sukhachev et al., 2025).

2. Evaluate ADME (Adsorption, Distribution, Metabolism, Excretion) properties and toxicological profile (ADME/Tox). The success of a molecule as a drug candidate is determined not only by its high activity *in vitro*, but also by its ability to reach the target in the body, have an adequate half-life, and an acceptable safety profile. Prediction of parameters such as solubility, permeability, metabolic stability, and cardiotoxicity (hERG) using modern computational platforms (such as ADMETlab) is an important step in the selection process (Dulsat et al., 2023; Xiong et al., 2021).

Thus, there is a clear scientific and practical need for comprehensive *in silico* analysis of new 1,3,5-triazine-based chemical structures prior to their synthesis. This allows for focusing experimental efforts on compounds that are highly likely to combine not only the target pharmacological effect but also favorable drug-like properties.

The aim of this study is to conduct a comprehensive computer-aided screening of a series of novel, previously undescribed 1,3,5-triazine derivatives using the PASS and ADMETlab prediction technologies to:

1. Predict potential biological activities.

2. Assess key pharmacokinetic and safety parameters.

3. Identify the most promising candidate structures that optimally combine predicted high activity and a favorable ADME/Tox profile for subsequent prioritized synthesis and biological validation.

The choice of the 1,3,5-triazine scaffold for this *in silico* study is justified by its exceptional versatility and proven potential across multiple therapeutic domains, as evidenced by recent research.

A brief review of the literature on 1,3,5-triazine derivatives. The relevance of searching for new nitrogen-containing heterocyclic compounds with targeted biological activity is confirmed by modern research aimed at overcoming drug resistance. For example, a recent study by Kazakhstan scientists presented a technology for the synthesis and preclinical evaluation of a new antimicrobial piperidine derivative, AIP-5, illustrating the current trend in medicinal chemistry toward the creation of such structures (Akhmetova et al., 2025).

Modern research also confirms that 1,3,5-triazines are a highly promising molecular scaffold for the development of broad-spectrum drugs due to the possibility of targeted synthesis and modification. Of particular interest is research into the creation of hybrid molecules and multitargeted ligands (MTDLs), a major trend in medicinal chemistry in recent years.

In oncology, the strategy of hybridizing the triazine core with other pharmacophores has yielded highly active and selective inhibitors of key targets. For example, quinazoline-1,3,5-triazine hybrids have proven to be potent inhibitors of the epidermal growth factor receptor (EGFR), demonstrating significant antitumor activity *in vivo* without toxicity to normal cells (Lim, 2024). Another successful strategy has been the development of new triazine and pyrimidine derivatives containing a dithiocarbamate moiety based on the well-known inhibitor ZSTK474. One such compound demonstrated high selectivity for the PI3Kα isoform and caused significant tumor regression in a U87-MG glioma xenograft model without signs of toxicity, indicating its potential as a targeted therapeutic agent (Sharma, 2024). Another successful strategy was the development of new derivatives containing a dithiocarbamate moiety based on the known inhibitor ZSTK474 (Tang et al., 2023). In this work, a rational structure-based modification was implemented to achieve high selectivity for the PI3Kα isoform. The lead compound demonstrated exceptional activity (IC_{50} = 1.2 nM against PI3Kα) and, in an experiment on mice bearing U87-MG glioma xenografts, caused significant tumor regression without signs of toxicity.

A promising avenue is the use of 1,3,5-triazines for the treatment of neurodegenerative diseases. A systematic review (Silva et al., 2025) highlights the potential of this scaffold in the treatment of Alzheimer's disease, analyzing the activity of derivatives within two main hypotheses: inhibition of acetylcholinesterase (AChE) and action on the amyloid cascade (inhibition of BACE-1 and β-amyloid aggregation). The authors conclude that triazines hold great promise for the development of multitargeted ligands capable of not only alleviating symptoms but also modifying the course of the disease.

Significant results have also been achieved in the fight against infectious diseases. The design of hybrid molecules combining a 1,3,5-triazine core with a 2,4-thiazolidinedione

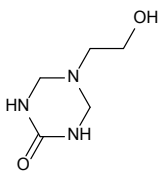
(TZD) moiety has led to the creation of compounds with activity against multiple pathogens simultaneously. The lead compound in this series demonstrated potent activity against HIV-1 (reverse transcriptase inhibition), demonstrated an inhibitory effect against SARS-CoV-2, and demonstrated strong antibacterial and antibiofilm activity, particularly against Gram-negative bacteria (Singh et al., 2025). This approach addresses the current challenge of coinfections and multidrug resistance.

Anti-inflammatory and metabolic research are also actively developing. For example, new 1,3,5-triazine derivatives, inspired by the structure of the drug imeglimine, were identified as selective and potent inhibitors of dipeptidyl peptidase-4 (DPP-4). In animal studies, the lead compound produced dose-dependent improvements in blood glucose and insulin levels, lipid profile, and antioxidant status, confirming the potential of this class for the treatment of type 2 diabetes (Gupta et al., 2023). Furthermore, new triazine-based histamine H4 receptor (H4R) antagonists have been synthesized, demonstrating pronounced analgesic and anti-inflammatory activity in vivo with low toxicity, opening up new possibilities for chronic pain treatment (Olejarz-Maciej et al., 2023).

Research in the field of antimicrobial therapy is also ongoing. A modern review (Rathod, 2024) summarizes trends in the development of antibacterial compounds containing a triazine moiety, emphasizing the key role of cyanuryl chloride as a versatile reagent for the preparation of biologically active derivatives.

Thus, a review of current publications convincingly demonstrates that 1,3,5-triazines remain an exceptionally flexible and productive platform for the design of innovative drugs. Current efforts are focused on the creation of hybrid molecules and multitargeted agents aimed at treating socially significant diseases: oncology, neurodegenerative, infectious, and metabolic. These data support the need for continued research and the search for new derivatives with targeted biological properties.

Materials and methods. This study utilized a sequential computational (in silico) approach that precedes labor-intensive and costly chemical synthesis and biological screening. The primary goal of the methodology was to predict the properties of six new 1,3,5-triazine derivatives, given on the scheme. This approach enables the early identification of the most promising candidate compounds possessing both the desired biological activity and favorable pharmacokinetic and toxicological profiles, significantly increasing the efficiency of subsequent experimental stages of drug development.



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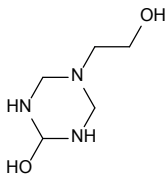

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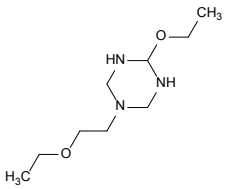

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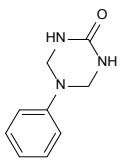

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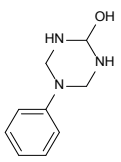

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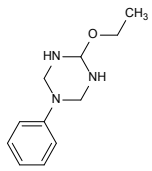

6

Two-dimensional (2D) chemical structures of all derivatives were constructed and optimized using the Avogadro software package (v.1.2.0) using the Universal Force Field (UFF) for energy minimization. The resulting three-dimensional (3D) molecular models were saved in .mol and .sdf formats for subsequent computer analysis.

The PASS (Prediction of Activity Spectra for Substances, online version) algorithm was used to predict the potential biological activities of the derivatives. This algorithm, based on the analysis of over 300,000 known biologically active compounds and their structural descriptors, estimates the likelihood that a given molecule will exhibit a particular pharmacological effect. Standardized SMILES (Simplified Molecular Input Line Entry System) notations for all six derivatives were uploaded to the PASS web server. The analysis was performed in prediction-only mode. Standard values of 0.5 were used as thresholds for the probabilities of activity (P_a) and inactivity (P_i). The results were analyzed, and the most probable biological activities with the highest P_a values (>0.7) were selected for each compound.

An assessment of the ADMET properties (absorption, distribution, metabolism, excretion, and toxicity) of new 1,3,5-triazine derivatives was performed using the ADMETlab 3.0 web platform. Using standardized SMILES notations, key physicochemical descriptors were calculated for each compound, including molecular weight, LogP, number of hydrogen bond donors and acceptors, and topological polar surface area. These descriptors were used to assess compliance with drug similarity rules (Lipinski, Hahn, and Wieber). Absorption and distribution parameters were modeled by predicting permeability through Caco-2 and MDCK cell monolayers, blood-brain barrier penetration, and plasma protein binding. To assess the metabolic profile, the compounds' potential to act as inhibitors or substrates of the major cytochrome P450 isoforms was analyzed. The toxicological assessment included determination of the risk of hERG channel inhibition (cardiotoxicity), hepatotoxicity potential, mutagenicity, carcinogenicity, and calculation of the integral toxicity index (Tox-score) in the range from 0 to 1, where values approaching 1 indicate a high overall risk.

These *in silico* approach efficiently prioritized candidates for further testing. The criteria for identifying promising candidates were defined as follows:

1. At least one predicted therapeutically relevant activity with a Pa > 0.7 based on PASS data.

2. Full compliance with Lipinsky's rules.

3. Favorable absorption parameters: Caco-2 permeability > -5.15 log cm/s (high), predicted BBB penetration consistent with the target site of action.

4. Low toxicity risk: no high risk (Tox score < 0.5) for key parameters (hERG, hepatotoxicity, mutagenicity).

Results. ***PASS prediction of compounds 1–6.*** The results of computer prediction of the spectrum of biological activity for 1,3,5-triazine derivatives **1–6** revealed a number of potentially significant pharmacological effects, which confirms the promise of the selected molecular framework. Computed PASS profiles **1–6** are given in Table 1, highlighting predicted "property of being active" ($P_a > 0.7$) and "property of being inactive" (P_i).

Table 1 – PASS predicted activities of compounds **1–6**

Compound	P_a	P_i	Activity
1	0.84	0.01	Anaphylatoxin receptor antagonist
	0.82	0.02	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.80	0.01	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
	0.79	0.00	Growth hormone agonist
	0.78	0.00	(R)-Pantolactone dehydrogenase (flavin) inhibitor
	0.76	0.05	Phobic disorders treatment
	0.75	0.01	2-Dehydropantoate 2-reductase inhibitor
	0.74	0.01	Pterin deaminase inhibitor
	0.74	0.01	Trimethylamine-oxide aldolase inhibitor
	0.73	0.02	NADPH peroxidase inhibitor
	0.73	0.01	Leukopoiesis stimulant
	0.72	0.00	CYP2C19 inducer
	0.70	0.02	Fucosterol-epoxide lyase inhibitor
2	0.84	0.01	Anaphylatoxin receptor antagonist
	0.75	0.02	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
	0.74	0.02	NADPH peroxidase inhibitor
	0.73	0.06	Phobic disorders treatment
	0.71	0.00	Growth hormone agonist
3	0.87	0.01	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
	0.72	0.07	Phobic disorders treatment
	0.70	0.00	Growth hormone agonist
4	0.85	0.01	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.80	0.00	Pterin deaminase inhibitor
	0.78	0.00	CYP2C19 inducer
	0.76	0.02	Nicotinic alpha2beta2 receptor antagonist
5	0.76	0.04	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0.74	0.01	Thioredoxin inhibitor
	0.74	0.02	NADPH peroxidase inhibitor
	0.74	0.05	Aspulvinone dimethylallyltransferase inhibitor
6	0.79	0.04	CYP2C12 substrate
	0.76	0.01	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
	0.75	0.02	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor

Thus, the predicted activity spectra of these compounds demonstrate their potential as modulators of hormonal regulation, including inhibition of testosterone-17β-dehydrogenase (**1**, $P_a = 0.82$; **4**, $P_a = 0.85$; **5**, $P_a = 0.76$) and activation of growth hormone (**1**, $P_a = 0.79$; **2**, $P_a = 0.71$; **3**, $P_a = 0.70$). These properties indicate the potential

of these derivatives for the development of therapeutic agents for hormone-dependent oncological diseases (Li et al., 2024) or the correction of metabolic disorders.

Anti-inflammatory and immunomodulatory potential: a pronounced tendency to suppress inflammatory processes is observed. Thus, compounds **1** and **2** are highly likely (P_a = 0.84) to act as antagonists of the anaphylatoxin receptor, a key mediator of inflammation [Buelli et al., 2024]. Additionally, compounds **2** and **5** are predicted to be inhibitors of NADPH peroxidase (P_a = 0.74), and compound **5** is predicted to be an inhibitor of thioredoxin (P_a = 0.74), indicating a possible mechanism for modulating oxidative stress. The activity of compounds **3** and **6** as inhibitors of mannotetraose-2-alpha-N-acetylglucosaminyltransferase (P_a = 0.87 and 0.75) may be associated with the effect on carbohydrate metabolism in the context of inflammatory processes, which opens up prospects for the treatment of autoimmune diseases.

Neurotropic activity: the prediction indicates possible effects on the central nervous system. Compounds **1–3** showed probable activity as agents for the treatment of phobic disorders (P_a = 0.72–0.76), and compound **4** showed probable activity as a pterine deaminase inhibitor (P_a = 0.80) and nicotinic α2β2 receptor antagonist (P_a = 0.76) (El Nebrisi et al., 2025). However, the relatively high probabilities of inactivity (P_i) for some of these effects (*e.g.*, 0.07 for compound **3**) require cautious interpretation and the need for experimental confirmation.

Pharmacokinetics of compounds 1–6. Analysis of the physicochemical properties of compounds **1–6** predicted by ADMETlab-.0 shows that all compounds meet the Lipinski rule (MW < 500, logP < 5, TPSA < 140 Å²), indicating a high probability of their oral bioavailability (Table 2). However, compound **3** has the highest logP (1.027) and the lowest TPSA value (45.76 Å²), which may lead to high lipophilicity, potentially reducing water solubility. At the same time, compounds **1** and **2** have higher hydrophilicity (logP < 0), which may limit their membrane permeability.

Table 2 – Pharmacokinetic parameters of compounds **1–6**

Property	Compound					
	1	**2**	**3**	**4**	**5**	**6**
Molecular Weight (MW)	145.09	147.1	203.16	177.09	179.11	207.14
TPSA. Å²	64.6	67.76	45.76	44.37	47.53	36.53
logP	-1.024	-1.463	1.027	1.091	0.48	1.395
logD7.4	-0.316	-0.591	1.472	1.308	0.899	1.67
Caco-2 permeability. log cm/s	-5.777	-5.263	-5.33	-5.092	-5.095	-5.027
MDCK permeability. log cm/s	-5.101	-5.12	-4.856	-4.679	-4.826	-4.749
BBB Penetration	+	--	-	+++	++	++
PPB (%)	3.9	10.6	20.6	56.2	37.0	37.5
Fu (%)	95.7	84.2	66.3	40.1	54.1	55.0
CLplasma. ml/min/kg	8.455	8.404	9.499	6.202	9.806	9.266

Drug absorption and transport are studied in intestinal permeability cell models such as Caco-2 and Madin−Darby Canine Kidney cells (MDCK). A compound is considered to be Caco-2 permeable if the value is > -5.15 log cm/s. MDCK Permeability >20×10^{-6}

cm/s is assessed as high permeability; 2×10^{-6} cm/s $\leq 20\times10^{-6}$ cm/s – average permeability: 2×10^{-6} cm/s; $\leq 2\times10^{-6}$ cm/s – low permeability (Xiong (2021)). Intestinal permeability is important for drug development, as it ensures efficient absorption and achievement of therapeutic concentrations in the blood. Predicted permeability indicates average absorption for most compounds (Table 2). Compounds **4**, **5** and **6** have higher Caco-2 permeability values, indicating more favorable pharmacokinetic properties.

The ability of compounds **1**–**6** to penetrate the blood-brain barrier (BBB) varies. Compound **4** shows the highest penetration (+++), making it a promising candidate for central nervous system (CNS) activity. Compounds **6** and **5** also have good values (++), indicating a probable neurotropic effect.

Plasma protein binding (PPB) also influences the distribution of compounds in the body. The high binding (PPB > 50%) of compound **4** (56.2%) may slow its elimination and prolong its duration of action. In contrast, compounds **1** and **2** have low PPB values (3.9% and 10.6%), which may contribute to their faster elimination and lower effect on the body.

Fu (%) is the free fraction of the substance in the blood plasma, showing the percentage of the compound not bound to proteins (e.g. albumin). Only the unbound fraction is able to penetrate membranes, interact with targets and be metabolized. High Fu (>20% High Fu; 5-20% medium Fu; <5% low Fu) increases the availability of the substance, but can accelerate its elimination. CLplasma is the plasma clearance (ml/min/kg), reflecting the rate of elimination of the substance from the body through metabolism and excretion (>15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; <5 ml/min/kg: low clearance).

Compounds **1**–**3** have high Fu (>20%), indicating high availability for target interaction and metabolism. However, this also increases the risk of rapid elimination. For all three compounds, CLplasma is in the moderate range (8.4–9.5 mL/min/kg), consistent with the high Fu.

Compounds **4**–**6** have a moderate Fu (5–20%), indicating moderate availability. The CLplasma values for these compounds are also in the moderate range (6.2–9.8 mL/min/kg), providing a balance between availability and stability in the body. Compound **4** has the lowest clearance (6.202), indicating its long-term presence in the body and potentially longer-lasting therapeutic effect.

The metabolism of the studied compounds is associated with CYP450 isoenzymes. The most important CYP enzymes for the metabolism of the compounds are CYP3A4, CYP2C19 and CYP1A2. These enzymes are actively involved in the metabolism of many drugs, so high activity with them increases the risk of drug interactions, requiring caution in combination therapy (Sakamuru et al., 2025).

Table 3 – Metabolism and excretion of compounds **1**–**6**

Property	Compound					
	1	**2**	**3**	**4**	**5**	**6**
CYP2C19 Substrate	+++	---	+++	---	---	+
CYP2D6 Substrate	-	---	---	---	--	++

CYP1A2 Substrate	++	--	-	+	-	+++
CYP2C9 Substrate	-	+	++	---	+	-
CYP3A4 Substrate	+++	++	+	---	-	++
HLM Stability	---	---	-	+++	---	+++

Compounds **1**, **3** and **6** demonstrate high activity with CYP enzymes: **1** with CYP2C19 and CYP3A4, **3** with CYP2C19, and **6** with CYP1A2 (Table 3). This makes them more susceptible to metabolic interactions with other drugs, which requires caution when used together (Sakamuru et al., 2025).

Compounds **2, 3** and **6** also exhibit moderate activity with CYP enzymes. Their moderate metabolism reduces the risks, but still requires attention in combination therapy.

Compounds **4** and **5** are practically not metabolized by the main CYP enzymes, which makes them the most stable and safe in terms of metabolic interactions.

Compounds **4** and **6** show high stability in the liver (HLM Stability +++), which may indicate a longer duration of action in the body. In contrast, 3 and 5 are rapidly metabolized, which may require more frequent dosing.

Prediction of toxicity parameters of compounds 1–6. The types of toxicity predicted by the ADMETlab-3.0 tool (Table 4) represent *in silico* assessments of potential toxicological risks of compounds. According to the toxicophore theory used in this type of prediction, fragments that correlate with a certain type of toxicity can be identified in the structures of molecules. Information on the presence of toxicophores allows preliminary selection of potentially hazardous compounds (Sukhachev (2025)).

Table 4 – Toxicophores of structures **1–6**

Property	Compound					
	1	**2**	**3**	**4**	**5**	**6**
Aquatic Toxicity Rule	0	0	0	0	0	0
Genotoxic Carcinogenicity Mutagenicity Rule	0	0	0	1	1	1
NonGenotoxic Carcinogenicity Rule	0	0	0	0	0	0
Skin Sensitization Rule	2	2	2	2	2	2
Acute Toxicity Rule	0	0	0	0	0	0
NonBiodegradable	0	0	1	0	0	1
SureChEMBL Rule	0	0	0	0	0	0
FAF-Drugs4 Rule	0	0	0	1	1	1

As a result of prediction, the structure of compounds **4**, **5** and **6** was found to contain toxicophores that lead to the risk of genotoxicity, carcinogenicity and mutagenicity.

The presence of two skin sensitizing toxicophores in the structures of compounds **1–6** indicates a high probability of skin irritation.

It was also found that compounds **3** and **6** are non-biodegradable, which indicates their possible persistence in the environment and potential accumulation in living organisms.

SureChEMBL and FAF-Drugs4 are filters that identify medically unfriendly

compounds. According to SureChEMBL, no structural features of high toxicity were found in the structure of compounds **1**–**6**. Compounds **4**, **5** and **6** do not meet the requirements of the FAF-Drugs4 rule.

The above results of toxicophore detection do not provide information on the numerical values of toxicity, for example, they do not allow calculating the contributions of the identified groups to the toxicological properties. Table 5 shows the results of predicting the quantitative values of various types of toxicity calculated by ADMETlab-3.0. The results are presented on a scale from 0 to 1, where 0 is no toxicity.

Table 5 - Toxicological parameters of compounds **1–6**

Property	Compound					
	1	**2**	**3**	**4**	**5**	**6**
hERG Blockers	0.077	0.148	0.264	0.065	0.202	0.299
hERG Blockers (10um)	0.307	0.501	0.675	0.421	0.64	0.687
DILI	0.188	0.152	0.210	0.333	0.243	0.296
AMES Toxicity	0.506	0.485	0.582	0.593	0.381	0.401
Rat Oral Acute Toxicity	0.203	0.506	0.491	0.162	0.681	0.646
FDAMDD	0.071	0.155	0.112	0.142	0.217	0.175
Skin Sensitization	0.911	0.576	0.357	0.784	0.091	0.25
Carcinogenicity	0.545	0.282	0.465	0.636	0.189	0.255
Eye Corrosion	0.336	0.724	0.795	0.107	0.144	0.262
Eye Irritation	0.989	0.926	0.773	0.987	0.847	0.840
Respiratory	0.661	0.899	0.786	0.415	0.821	0.810
Human Hepatotoxicity	0.493	0.540	0.337	0.389	0.559	0.562
Drug-induced Nephrotoxicity	0.354	0.720	0.456	0.133	0.694	0.471
Drug-induced Neurotoxicity	0.799	0.703	0.580	0.915	0.829	0.778
Ototoxicity	0.361	0.733	0.351	0.206	0.732	0.433
Hematotoxicity	0.262	0.285	0.166	0.302	0.342	0.326
Genotoxicity	0.834	0.357	0.042	0.996	0.926	0.779
RPMI-8226 Immunotoxicity	0.028	0.037	0.059	0.016	0.021	0.023
A549 Cytotoxicity	0.012	0.013	0.011	0.027	0.015	0.027
Hek293 Cytotoxicity	0.111	0.074	0.125	0.149	0.059	0.084
BCF (log10(L/kg)	0.067	0.254	0.330	0.102	0.262	0.500
IGC_{50} (−log□□[(mg/L)/(1000×MW)])	1.438	1.461	2.216	2.698	2.506	2.696
LC_{50}DM (−log□□[(mg/L)/(1000×MW)])	2.160	2.183	3.332	4.055	3.876	4.115
LC_{50}FM (−log□□[(mg/L)/(1000×MW)])	1.333	1.332	2.462	3.148	2.972	3.159

Interpretation of the data presented in the table **5** allows us to identify the following key toxicological risks for each of the compounds. The mechanisms of cardiotoxicity are associated with the possibility of inhibiting hERG (human ether-a-go-go related gene) channels and may cause a risk of cardiac arrhythmia (Liao et al., 2024). The highest risk of cardiotoxicity was found for compound **6** (hERG Blockers (10um) 0.687). High values were also found for **3** (0.675) and **5** (0.64).

Hepatotoxicity and drug-induced liver injury (DILI) are among the most common reasons for drug recalls. The highest DILI is found in compound **4** (0.333), hepatotoxicity is most pronounced in **5** (0.559) and **6** (0.562).

High values of the genotoxicity assessment of compounds **4** (0.996) and **5** (0.926) indicate a significant risk of DNA damage. The greatest neurotoxicity is predicted for **4** (0.915) and **5** (0.829).

Carcinogenicity reflects the ability of compounds to cause malignant neoplasms. Among the studied substances, the highest risk of cancer development was noted for compound **4** (0.636), which may indicate its potential danger with long-term exposure.

Strong irritant effect was noted for all compounds: **1**-**6**, indicating a high risk if the substance gets into the eyes. In addition, **2** (0.724) and **3** (0.795) have the potential to cause damage to eye tissue, which can lead to irreversible damage.

Immunotoxicity is a property that shows the ability of substances to suppress or damage the immune system. All compounds show a low level of influence on immune cells. As for cytotoxicity, all values are also low.

Thus, the analysis revealed significant toxicological risks for most compounds, in particular high cardio-, hepato-, and neurotoxicity, as well as potential carcinogenicity, especially for compounds **4** and **5**. To reduce risks during further development, modification of the chemical structure of the problematic compounds and careful monitoring of relevant parameters in the preclinical stages of research are necessary.

The ecotoxicity assessment demonstrates a clear trend of increasing hazard from compounds **1** and **2** to compounds **4** and **6**. Compounds **4** and **6** pose the greatest hazard to aquatic organisms, demonstrating maximum toxicity values for daphnia (4.055 and 4.115) and fish (3.148 and 3.159). However, compound **6** has the greatest potential for bioaccumulation (BCF 0.500), which increases the long-term environmental risks of its potential spread.

Discussion. The results of an *in silico* screening of six new 1,3,5-triazine derivatives provide a comprehensive view of their therapeutic potential and associated risks, which is fully consistent with the well-known high structural flexibility of this heterocyclic scaffold. Our data not only confirm its role as a versatile platform for the design of agents with diverse targets but also reveal subtle relationships between structure, activity, and safety profile, which is key to rational drug design.

Comparative analysis of the pharmacodynamic profile. The identified spectrum of biological activity naturally reflects trends described in the current literature. Thus, the predicted endocrine modulation (AKR1C3 inhibition) for compounds **1**, **4**, and **5** correlates with the known role of 1,3,5-triazine derivatives in the treatment of hormone-dependent tumors, where inhibition of this enzyme is a promising strategy (Sharma et al., 2024). However, the uniqueness of our study lies in the combination of this activity with other activities. For example, compound **1** potentially combines an antiandrogenic effect with potent anti-inflammatory activity (anaphylatoxin receptor antagonism, Pa=0.84), which may open new avenues for the treatment of inflammatory forms of prostate cancer. Similarly, the neurotropic potential of compounds **1**–**4** (anxiolytic, effects on nicotinic receptors), combined with their overall pharmacokinetic profile, suggests the possibility of CNS action, which is less commonly described for this class of compounds.

Pharmacokinetics and metabolism assessment. Compounds **1** and **2**, with negative

LogP, exhibit excellent aqueous solubility, which is a major advantage for dosage form development, but their relatively low predicted permeability through intestinal barrier models (Caco-2 ~ -5.8 and -5.3 log cm/s) may limit bioavailability. In contrast, more lipophilic compounds **4–6** exhibit better permeability, but their solubility will likely require specialized pharmaceutical management. The metabolic prediction deserves special attention. The fact that compounds **4** and **5** are not predicted to be substrates of major CYP isoenzymes is a significant strategic advantage, as it minimizes the risk of serious drug interactions – a common problem in oncology and anti-inflammatory therapeutic regimens (Sakamuru et al., 2025).

Analysis of toxicological risks and their structural origins. The high cardiotoxicity (hERG) values for compounds **3**, **5**, and **6** (>0.64) and genotoxicity values for **4** and **5** (>0.92) require detailed attention. It is important to emphasize that these risks are likely related not to the 1,3,5-triazine core *per se*, but to specific substituents and side chains introduced into the structure. For example, the identified toxicophores, which pose a risk of skin sensitization for all compounds, require careful analysis of specific fragments. This points to a clear direction for optimization: future medicinal chemical synthesis should focus on isosteric substitution or minimal modification of problematic fragments while preserving the key pharmacophores responsible for the target activity. Comparison with data on known triazine-based drugs (*e.g.*, gedatolisib) would reveal whether the identified risks are typical for the class or specific to our new structures (Rossetti et al., 2024).

Limitations of the method and the way forward. It should be noted that all conclusions are predictive in nature. Although the PASS and ADMETlab 3.0 algorithms are based on extensive experimental data, false positive and false negative results are possible. For example, the high predicted neurotoxicity of compound 4 (0.915) requires priority testing in specialized in vitro assays on neuronal cell lines. Thus, this study does not replace, but rather strategically guides subsequent experimental work, indicating what exactly and in what order to test, which ultimately leads to significant resource savings.

Conclusion. In conclusion, a comprehensive computer-aided screening of six new 1,3,5-triazine derivatives using the PASS and ADMETlab 3.0 platforms enabled not only the filtering of compounds but also their multi-level stratification and the formulation of specific research hypotheses for the next stage of development.

1. Identification of lead candidates. Based on integrated analysis, compound **2** was identified as the most balanced candidate for immediate synthesis and primary biological testing. It combines predicted antiandrogenic (P_a=0.75, mannotetraose-2-alpha-N-acetylglucosaminyltransferase inhibitor) and anti-inflammatory activity (P_a=0.84, anaphylatoxin receptor antagonist) with the most favorable toxicological profile in the series: low risk of cardiotoxicity (hERG=0.148), genotoxicity (0.357), and hepatotoxicity (0.152). Its high free fraction in plasma (Fu=84.2%) predicts good tissue target availability.

2. Identification of candidates for targeted optimization. Compound **4**, which exhibits exceptional BBB permeability (+++) and a unique combination of activity (AKR1C3 inhibition, P_a=0.85), is recognized as highly potent but requires modification. The

primary objective is to reduce the unacceptably high predicted risks of genotoxicity (0.996) and neurotoxicity (0.915) by redesigning specific structural fragments identified as toxicophores, followed by repeated *in silico* validation.

3. Practical recommendations for the preclinical program.

Priority is given for compounds **1** and **2** to *in vitro* tests for AKR1C3 inhibition and in inflammatory models (e.g., inhibition of complement activation), as well as to assess membrane permeability using the PAMPA system to refine the bioavailability prediction. For compounds **4–6** prior to efficacy studies, *in vitro* assessments for toxicity are mandatory to experimentally confirm or refute key risks.

Thus, this study serves as a clear demonstration of the "screening-stratification-optimization" paradigm in modern medicinal chemistry. Computational methods have demonstrated their power as a decision support system that allows for focusing real laboratory efforts and resources on the most promising and rational directions, accelerating the discovery of new drugs based on the high-potential 1,3,5-triazine scaffold.

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