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SEARCHING FOR ANTIOXIDANTS AND ANTIHYPOXANTS AMONG 1,2,4-TRIAZOLE-3-THIONE DERIVATIVES AS PROMISING AGENTS FOR THE CORRECTION OF PATHOLOGICAL CONDITIONS INDUCED BY MILITARY HOSTILITIES

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Introduction. *A comprehensive study aimed at the search for promising antioxidants and antihypoxants among 1,2,4-triazole-3-thione derivatives for the pharmacological correction of pathological conditions arising as a result of combat actions. The objective was to combine modern methods of computer-based prediction of toxicity and ADME parameters with experimental evaluation of antihypoxic activity in order to determine the most effective and safe candidate compounds for further preclinical and clinical trials.*

Materials and Methods. *The objects of the study were 11 previously synthesized derivatives of 5-(2,4-, 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-thiones [19], for which at the in silico stage acute toxicity (LD_{50}, after oral administration to rats) was predicted using TEST 5.1.2.0 software [21], as well as indices of antioxidant activity were determined [14, 19]. For the discussed series of compounds, pharmacotechnological and pharmacokinetic characteristics (solubility, bioavailability, blood–brain barrier permeability, interaction with CYP isoenzymes) were assessed using SwissADME [22]. The experimental part included the study of antihypoxic action in the model of hypoxia with hypercapnia in a closed space on white Wistar rats [23]. Animals received the tested substances at a dose of 100 mg/kg (1/10 of the predicted LD_{50} value); armadin was used as the reference drug [24].*

Results. *Analysis of predictive data on acute toxicity indices showed that all studied compounds belong to toxicity classes III–IV according to the OECD classification [21], i.e., they are moderately toxic or low-toxic; thus, no highly toxic samples were identified among them. ADME analysis revealed the most optimal profile in compounds 4–7 (Table 2), which did not inhibit the main CYP450 isoenzymes and demonstrated acceptable solubility and polarity parameters. Experimental evaluation of antihypoxic activity showed that all studied substances (1–11, Table 3) prolonged the survival of animals under the experimental model, with three of them (compounds 3, 7, 8) exceeding the effectiveness of the comparison standard, the widely used drug armadin. Compound 3 prolonged life span by 51.6% relative to control, compound 7 – by 57.9%, derivative 8 – by 55.5%. At the same time, compound 3, namely 4-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)butanonitrile, combined high activity with low toxicity and balanced pharmacotechnological and pharmacokinetic properties, which makes it the most promising for further studies.*

Conclusions. *The synthesized derivatives of 1,2,4-triazole-3-thiones exhibit pronounced antioxidant and antihypoxic activity in combination with an acceptable safety profile. The most promising was defined as 4-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)butanonitrile, which demonstrated an optimal "efficacy/safety" ratio, while compounds 7 and 8, although exceeding the effectiveness of armadin, require additional toxicological and pharmacokinetic analysis. The obtained results confirm the relevance of further preclinical studies of 1,2,4-triazole-3-thione derivatives as potential agents for pharmacological correction of pathological conditions induced by combat actions.*

Keywords: *1,2,4-triazole-3-thione derivatives, antioxidant activity, antihypoxic effect, oxidative stress, hypoxia, military medicine.*

ПОШУК АНТИОКСИДАНТІВ ТА АНТИГІПОКСАНТІВ СЕРЕД ПОХІДНИХ 1,2,4-ТРІАЗОЛ-3-ТІОНІВ ЯК ПЕРСПЕКТИВНИХ ЗАСОБІВ КОРЕКЦІЇ ПАТОЛОГІЧНИХ СТАНІВ, ІНДУКОВАНИХ ВОЄННИМИ ДІЯМИ

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Мета. *Комплексне дослідження спрямоване на пошук перспективних антиоксидантів та антигіпоксантів серед похідних 1,2,4-тріазол-3-тіонів для фармакологічної корекції патологічних станів, що виникають унаслідок бойових дій. Мета - поєднання сучасних методів комп'ютерного прогнозування токсичності та ADME-параметрів з експериментальним оцінюванням антигіпоксичної активності для визначення найбільш ефективних та безпечних сполук-кандидатів для проведення подальших доклінічних і клінічних випробувань*

Матеріали і методи. *Об'єктами дослідження стали 11 синтезованих раніше похідних 5-(2,4-, 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-тіонів [19], для яких на etani in silico прогнозовано гостру токсичність (LD_{50}, при оральному введенні щурам) за допомогою програмного забезпечення TEST 5.1.2.0 [21], а також визначено показники антиоксидантної дії [14, 19]. Для обговорюваного ряду сполук, за допомогою SwissADME [22], проведено оцінку фармако-технологічних та фармакокінетичних характеристик (розчинність, біодоступність, проникність через ГЕБ, взаємодію з CYP-ізоферментами). Експериментальна частина містить вивчення антигіпоксичної дії на моделі гіпоксії з гіперкапнією у замкненому просторі на білих щурах лінії Вістар [23]. Тварини отримували досліджувані речовини у дозі 100 мг/кг (1/10 від прогностичного значення LD_{50}); як референтний препарат застосовували армадин [24].*

Результати. *Аналіз прогностичних даних показників гострої токсичності показав, що всі досліджувані сполуки належать до III–IV класів токсичності за класифікацією OECD [21], тобто є помірнотоксичними або малотоксичними; отже серед них не виявлено високотоксичних зразків. ADME-аналіз виявив найоптимальніший профіль у сполук 4-7 (табл. 2), які не інгібували основні ізоферменти CYP450 та демонстрували прийнятні параметри розчинності й полярності. Експериментальна оцінка антигіпоксичної активності показала, що всі досліджувані речовини (1-11, табл. 3) подовжували виживання тварин за умов експериментальної моделі, причому три з них (сполуки 3, 7, 8) перевищили ефективність еталону порівняння, широковживаного препарату армадину. Сполука 3 подовжувала тривалість життя на 51,6% відносно контролю, речовина 7 - на 57,9%, похідна 8 - на 55,5%. При цьому сполука 3, а саме 4-((5-(3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)бутанонітрил поєднав високу активність із низькою токсичністю та збалансованими фармако-технологічними і фармакокінетичними властивостями, що робить її найбільш перспективною для подальших досліджень.*

Висновки. *Синтезовані похідні 1,2,4-тріазол-3-тіонів проявляють виражену антиоксидантну та антигіпоксичну активність у поєднанні з прийнятним профілем безпечності. Найбільш перспективною визначено 4-((5-(3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)бутанонітрил, який продемонстрував оптимальне співвідношення «ефективність/безпечність», тоді як сполуки 7 та 8 хоча і перевищили ефективність армадину, але потребують додаткового токсикологічного та фармакокінетичного аналізу. Отримані результати підтверджують актуальність подальших доклінічних випробувань похідних 1,2,4-тріазол-3-тіонів як потенційних засобів фармакологічної корекції патологічних станів, індукованих бойовими діями.*

Ключові слова: *похідні 1,2,4-тріазол-3-тіонів, антиоксидантна активність, антигіпоксична дія, оксидативний стрес, гіпоксія, військова медицина.*

Introduction. The military actions taking place on the territory of our state are accompanied by a significant increase in the number of severe injuries, explosive and mine-explosive traumas, burns, blood loss, and concussions, which are inextricably linked to the development of hypoxia and oxidative stress. It has been established that under conditions of combat injuries, the body undergoes massive formation of reactive oxygen species (ROS), which damage lipids, proteins, and nucleic acids, contributing to the development of systemic inflammatory response, endothelial dysfunction, and multiple organ failure [17]. Tissue damage induced by free radical processes plays a key role in the progression of post-traumatic conditions, exacerbates ischemia-reperfusion injuries, and largely determines the

mortality rate among severely wounded military personnel and civilians.

Under these conditions, the search for new drugs with combined antioxidant and antihypoxic activity, which could reduce the destructive consequences of combat injuries and normalize tissue respiration, becomes particularly relevant. Existing drugs with antioxidant activity (such as vitamin E, N-acetylcysteine, melatonin) or antihypoxic effects (mexidol, actovegin) have limited effectiveness and are characterized by a number of side effects that complicate their use in military field conditions. Therefore, an important direction of modern military medicine is the development of new domestic drugs based on synthetic molecules with a broad therapeutic profile, which combine antioxidant and antihypoxic properties while ensuring low toxicity and high bioavailability.

In this context, particular attention is drawn to 1,2,4-triazole derivatives, which represent a well-known platform for the creation of biologically active compounds. Due to their structural flexibility and ability for multi-target functionalization, these compounds demonstrate a wide spectrum of pharmacological effects, including antidiabetic [1], anti-inflammatory [2], antitumor [2–6], antimicrobial [7, 8], antioxidant [9–16], and antihypoxic [17, 18] activities. From the literature review published by Jinlian et al. [8], various methods of synthesizing 1,2,4-triazoles are known, providing opportunities for the development of derivatives with targeted properties. Studies by Yıldırım et al. [4] and Gu et al. [5] have demonstrated the promise of 1,2,4-triazole structures in the creation of antitumor agents, confirming their versatility as a chemical platform. At the same time, current research highlights the significance of the antioxidant potential of 1,2,4-triazole derivatives. In particular, Peng et al. [15] described the antioxidant properties of triazole hydrazones, which inhibited free radical reactions and tyrosinase activity, whereas Jawad et al. [6] obtained triazole metal complexes with pronounced antioxidant and antiproliferative activity. Hamoud and colleagues [2] showed that modified 1,2,4-triazole derivatives effectively inhibited cyclooxygenase-2 (COX-2) activity and exerted antioxidant effects in cellular models of inflammation. The summarized data of the mini-review by Pachuta-Stec [16] confirm that 1,2,4-triazole and its derivatives possess significant ability to bind reactive oxygen species, protect biomolecules from oxidative damage, and prevent the development of pathological conditions caused by oxidative stress. This makes them promising candidates for the pharmacological correction of hypoxic and oxidative injuries, including in military medical practice.

Thus, the analysis of current literature data allows us to state that 1,2,4-triazole-3-thione derivatives have high potential as antioxidants and antihypoxants. Their investigation in the direction of developing new agents for the treatment and prevention of pathological conditions induced by combat actions is a relevant and justified task of military medicine.

Purpose. The aim of the study is one of the stages in the creation of an original drug with combined antioxidant and antihypoxic action, intended for pharmacological correction under combat conditions, based on the investigation of promising 1,2,4-triazole-3-thione derivatives for the correction of pathological states induced by military actions, through computer prediction of toxicity parameters, assessment of ADME characteristics, and experimental evaluation of antihypoxic activity using a model of hypoxia with hypercapnia in a closed space in white non-linear rats.

Materials and methods of research.

Ethical considerations. Pharmacological studies were carried out at the Educational and Scientific Medical-Laboratory Center with vivarium of Zaporizhzhia State Medical and Pharmaceutical University (ZSMPhU, head: DSc (Pharm.), Prof. Roman Shcherbyna) in accordance with Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes and the principles of the Helsinki Declaration. Animals were kept under standard vivarium conditions: temperature 20–22 °C, humidity 50–60%, 12-hour light cycle, free access to water and standard pelleted food for laboratory rodents. Wistar male rats, 10–12 weeks old, weighing 190–220 g, were used. The animals underwent a 14-day acclimatization period before the start of the experiment. The distribution of rats into groups (control and experimental) was carried out using randomization to ensure comparability in weight and age.

Modeling of hypoxia with hypercapnia was performed without the use of anesthetics or analgesics, since the model involved the evaluation of antihypoxic activity under conditions of acute stress, simulating pathological states induced by military actions. Euthanasia of animals was carried out by CO_2 inhalation in a special chamber (concentration 70–80%) for 5–7 minutes, followed by verification of the absence of

reflexes and heartbeat, in accordance with the recommendations of the American Veterinary Medical Association (AVMA Guidelines for the Euthanasia of Animals, 2020).

Methods and methodologies. The objects of the study were 11 synthesized derivatives of 5-(2,4-, 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thiones, previously synthesized by the authors during the performance of dissertation research [19]. Prediction of acute toxicity parameters was carried out using the computer service TEST version 5.1.2.0 [21]. The study of pharmacokinetic parameters of the synthesized compounds was implemented using the online service SwissADME (Swiss Institute of Bioinformatics, Switzerland) [22]. The antihypoxic effect of the studied compounds was investigated according to the methodological recommendations "Preclinical studies of medicinal products" [23] under the model of hypoxia with hypercapnia (in a closed space).

Computer prediction of acute toxicity. The acute toxicity of the compounds was evaluated using the TEST software, version 5.1.2.0, based on the model "Oral Rat LD_{50}" and the "Nearest Neighbor" method [21], in order to filter out potentially toxic substances as unsuitable candidates for experimental pharmacological screening, based on the SMILES structures of the studied 1,2,4-triazole-3-thione derivatives. QSAR algorithms were employed considering molecular structure descriptors: molecular weight, partition coefficient (logP), topological indices, and the number of hydrogen bonds. For each compound, the predicted LD_{50} value (mg/kg) and confidence interval were obtained, which allowed classification of the compounds according to their toxicity level.

Prediction of ADME parameters. The pharmacokinetic parameters of the studied compounds were assessed using the online service SwissADME (Swiss Institute of Bioinformatics, Switzerland) [22]. The following parameters were analyzed: water solubility (logS by the ESOL model), blood-brain barrier permeability (BBB permeant), bioavailability (Bioavailability Score according to Lipinski's and Veber's rules), potential interactions with cytochrome P450 isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), as well as absorption rate in the gastrointestinal tract (HIA). SMILES structures of the compounds served as input data. The obtained results were used to select compounds with optimal pharmacokinetic profiles for further experimental testing.

Experimental study of antihypoxic activity. The antihypoxic activity was investigated in accordance with the methodological guidelines "Preclinical Studies of Medicinal Products" [23]. Hypoxia with hypercapnia was modeled by placing rats (one per vessel) in standardized glass containers with a volume of 1300 ml, which were hermetically sealed, inverted, and immersed in a water bath to prevent oxygen entry. The time until the first signs of hypoxia (dyspnea, convulsions) and the total survival time (from sealing the vessel until respiratory arrest) were recorded.

The tested compounds and the reference drug (armadin) were administered at a dose of 100 mg/kg in the form of a finely dispersed aqueous suspension stabilized with 1% Tween-80 (Sigma-Aldrich, USA), prepared one hour prior to administration. The control group received isotonic sodium chloride solution (0.9% NaCl). Each compound was tested in a group of 6 rats (n=6), and the control group also consisted of 6 animals.

The determination of life span prolongation in experimental animals was performed six times for each experiment. Statistical processing of the obtained results was carried out according to Student's t-test [25] for each measurement (reference drug armadin, compounds 1–11). For each experiment, 6 values were used to calculate the mean "Average life span"; the "Deviation" from the mean value (Δ), the "Square of deviation" (Δ^2), and the "Sum of squares of deviations" ($\sum\Delta^2$) were also calculated, which made it possible to determine the "Standard deviation" (or variance).

Research results. Derivatives of 5-(2,4-, 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thiones were selected for the experimental study based on the results of previous investigations of their antioxidant activity [14, 19]. The comprehensive study of these compounds, including computer prediction of their acute toxicity (LD_{50}, oral, rats), assessment of pharmacokinetic parameters (ADME), and experimental modeling of hypoxia with hypercapnia in Wistar white rats, demonstrated the promise of the chosen approach. The obtained data include quantitative indicators of toxicity, pharmacokinetic properties, and the survival time of animals after administration of the 1,2,4-triazole derivatives. The results are illustrated in tables and figures reflecting the conducted experiments.

Prediction of acute toxicity of the synthesized compounds is a necessary stage for further studies of their biological activity, as it allows a preliminary assessment of the safety

profile and the exclusion of potentially toxic substances at the preclinical level. This approach aligns with the principles of rational search for pharmacologically active agents and enables the reduction of risks associated with the use of hazardous molecules in subsequent *in silico*, *in vitro*, and *in vivo* experiments.

In military medical practice, where agents for correcting pathological conditions induced by combat actions are of particular importance, the safety of drugs is critically important. Therefore, early toxicological modeling not only optimizes the selection of promising candidates among 1,2,4-triazole-3-thione derivatives but also contributes to the reduction of resource and time expenditures and minimizes the use of laboratory animals in further studies. The obtained results are presented in Table 1.

Table 1

Acute toxicity indicators of the studied compounds

Compound	Empirical formula	LD_{50} (oral), mg/kg	Toxicity class
1	$C_{12}H_{12}N_4O_2S$	348.1	3
2	$C_{13}H_{14}N_4O_2S$	1348.0	4
3	$C_{14}H_{16}N_4O_2S$	1701.0	4
4	$C_{12}H_{12}N_3NaO_4S$	1289.0	4
5	$C_{12}H_{12}KN_3O_4S$	1289.0	4
6	$C_{12}H_{16}N_4O_4S$	1289.0	4
7	$C_{14}H_{20}N_4O_4S$	340.4	3
8	$C_{19}H_{22}N_4O_4S$	402.5	3
9	$C_{21}H_{26}N_4O_4S$	430.5	3
10	$C_{15}H_{15}N_5O_2S$	983.2	4
11	$C_{22}H_{20}N_6O_2S_2$	1135.0	4

The obtained results showed that the median lethal dose (LD_{50}) values for the studied compounds ranged from 340.4 to 1701.0 mg/kg. This allowed them to be classified into III (moderately toxic) and IV (slightly toxic) toxicity classes according to OECD classification standards [21]. Specifically, compounds 1, 7, 8, and 9 demonstrated LD_{50} values in the range of 340.4–430.5 mg/kg, corresponding to toxicity class III. At the same time, these values are close to the upper limit of the class, indicating a relatively low level of hazard when dosing is controlled.

The remaining compounds, including 2, 3, 4–6, 10, and 11, had LD_{50} values between 983.2 and 1701.0 mg/kg, corresponding to toxicity class IV, which indicates their low toxicity.

Thus, most of the studied 1,2,4-triazole-3-thione derivatives belong to slightly toxic substances, making them promising candidates for further pharmacological screening. Importantly, none of the synthesized compounds belonged to toxicity classes I or II, i.e., extremely or highly toxic substances. This confirms the feasibility of continuing research on the antioxidant and antihypoxic activity of these compounds, as their safety profile is acceptable for further experimental studies.

Despite significant progress in studying the biological properties of 1,2,4-triazole derivatives, a key task remains the preliminary determination of their pharmacokinetic profile. ADME prediction (Absorption, Distribution, Metabolism, Excretion) [22] allows for the assessment of potential advantages and limitations of new molecules at the preclinical stage, determining their ability to enter systemic circulation, reach therapeutic concentrations in target tissues, and avoid rapid inactivation or accumulation with toxic consequences. Thus, studying antioxidant and antihypoxic activity without considering pharmacokinetic characteristics may have limited informativeness, as even high *in vitro* biological activity does not guarantee *in vivo* efficacy.

Recent literature emphasizes that the combination of pharmacodynamic and pharmacokinetic approaches ensures the most justified selection of promising compounds [7, 9, 11, 20]. For example, it is known that the ability of triazole derivatives to exhibit antioxidant properties often correlates with their lipophilicity, membrane permeability, and stability in metabolic systems [7, 9, 11, 20]. This indicates a direct interdependence between potential efficacy and the pharmacokinetic characteristics of the studied substances.

Thus, integrating the results of ADME prediction into the strategy for searching for antioxidants and antihypoxants among 1,2,4-triazole-3-thione derivatives is a necessary condition for enhancing the scientific rationale and efficiency of pharmacological screening. This approach minimizes the risk of selecting ineffective or toxic molecules, optimizes resource use, and focuses subsequent *in vitro* and *in vivo* studies on the most promising candidates.

As a result of the pharmacokinetic parameter prediction, the obtained indicators are visualized below in Table 2 and Figures 1 and 2.

Table 2

Results of ADME prediction for the studied compounds

Compound	Molecular weight	Num. H-bond acceptors	Num. H-bond donors	TPSA	Log P	Log S	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
1	276.31	6	0	104.63	2.05	-3.70	-	+	+	-	-	-
2	290.34	6	0	104.63	2.30	-4.10	-	+	+	+	-	-
3	304.37	5	1	109.12	2.47	-5.03	-	+	+	+	-	-
4	317.30	7	0	120.97	-1.18	-2.98	+	-	-	-	-	-
5	333.40	7	0	120.97	-0.52	-2.98	+	-	-	-	-	-
6	312.34	7	1	120.97	-0.40	-2.98	-	-	-	-	-	-
7	340.40	7	1	137.58	0.17	-2.98	-	-	-	-	-	-
8	402.47	7	1	148.61	1.45	-5.06	-	+	-	-	-	+
9	430.52	7	1	137.58	1.94	-5.06	-	+	-	-	-	+
10	329.38	5	2	124.24	2.14	-5.51	+	+	+	+	+	+
11	465.56	7	1	156.92	4.07	-7.99	-	+	+	+	-	+

Radar diagrams of the ADME profile of the studied compounds

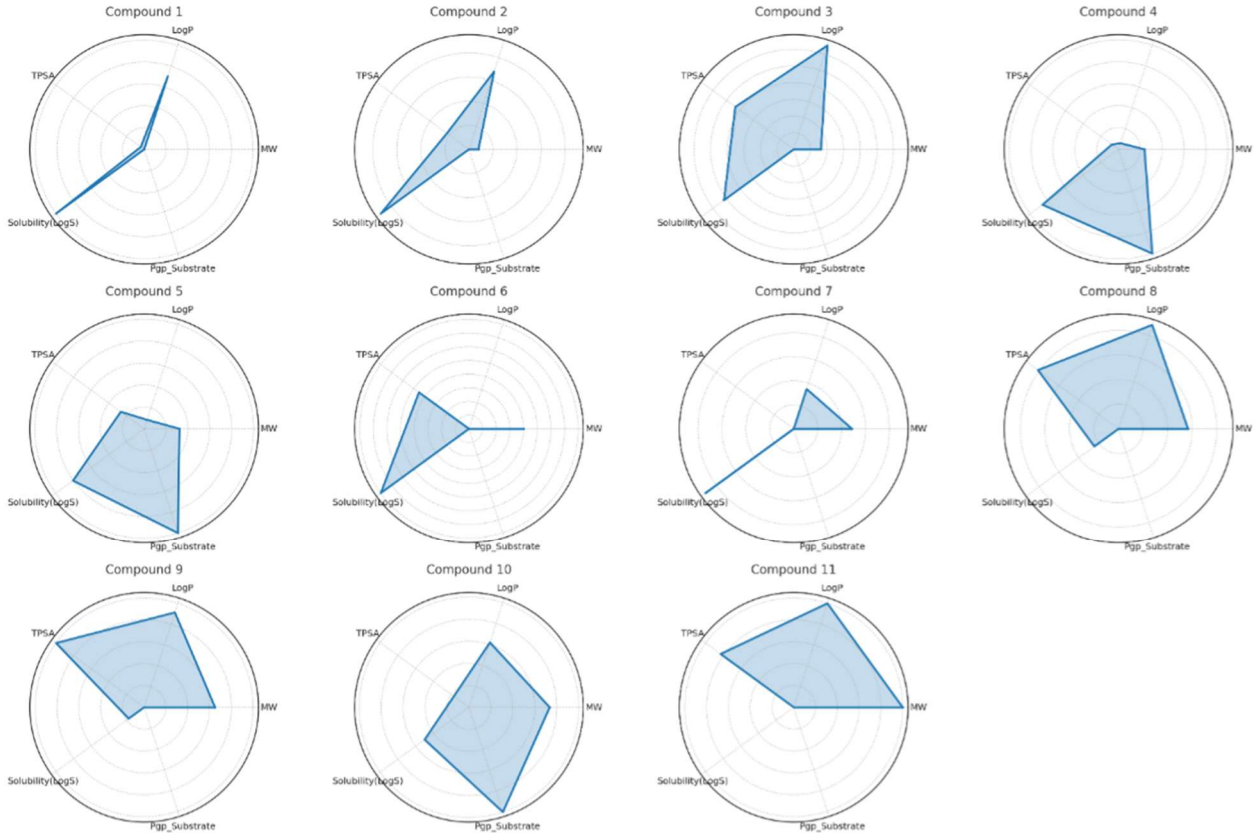

Figure 1. Radar plots of the ADME profile of the studied compounds

The diagram illustrates the comparative distribution of key pharmacokinetic parameters (Absorption, Distribution, Metabolism, Excretion) for each of the studied compounds. This approach allows for a visual assessment of the strengths and weaknesses of each compound under investigation.

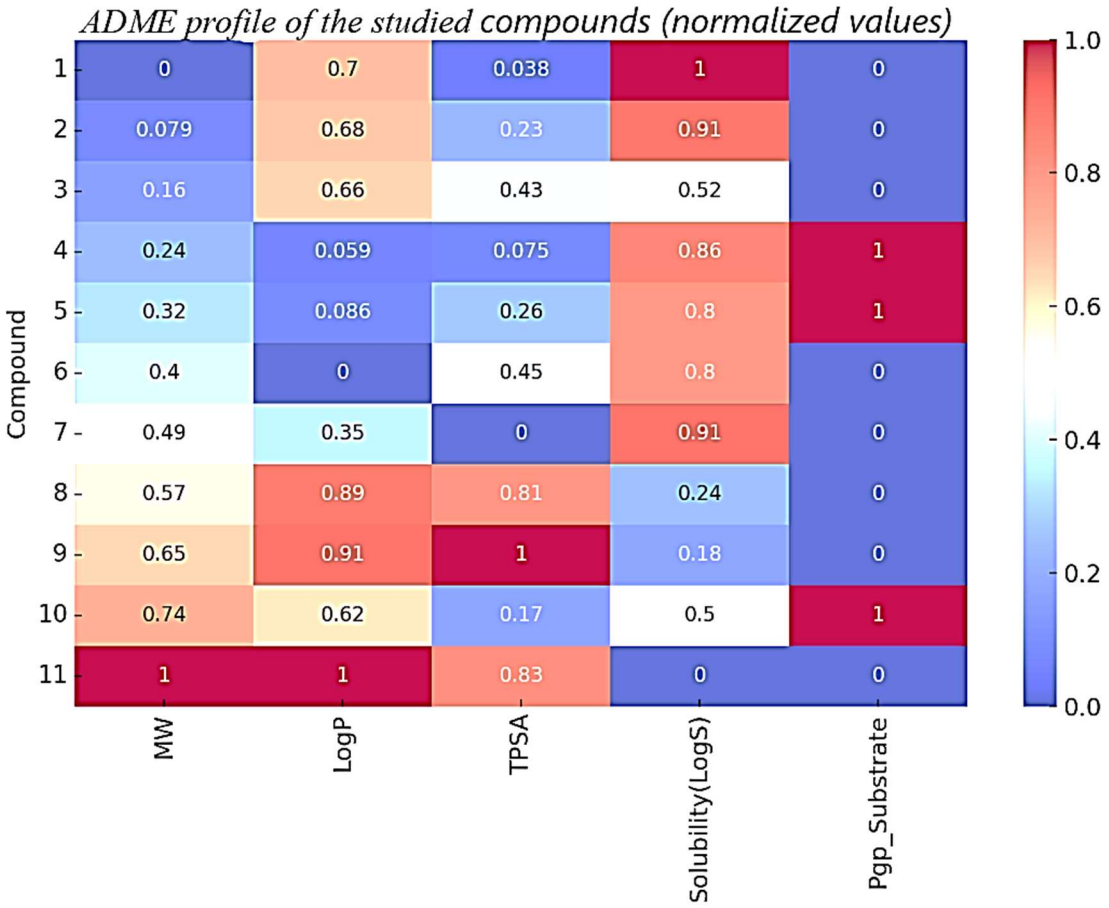

Figure 2. Heatmap of ADME parameters for the studied compounds

Color coding demonstrates the level of predicted pharmacokinetic characteristics. Green shades correspond to more favorable values, while red shades indicate less optimal ones. This facilitates rapid comparison of the compounds potential for further biological screening.

The obtained ADME prediction results indicate that the synthesized 1,2,4-triazole-3-thione derivatives exhibit varying degrees of promise as potential antioxidant and antihypoxic agents.

Compounds 1–3 are characterized by optimal molecular weight and polar surface area, with moderate lipophilicity (LogP ~2.3–2.5), which supports bioavailability. At the same time, they act as multi-CYP450 inhibitors, which may limit their use due to a high risk of drug–drug interactions.

Compounds 4–7 have the most balanced profile: they do not inhibit CYP450 and demonstrate satisfactory solubility and polarity parameters. A limitation is their low LogP values (<1), which may reduce cellular permeability. This group is considered the primary basis for further optimization through the introduction of moderately lipophilic substituents.

Compounds 8 and 9 have higher molecular weights, large polar surface areas (>150 Å^2), and low solubility, which may negatively affect oral bioavailability and blood–brain barrier penetration. At the same time, their CYP inhibitory activity is limited to CYP1A2/3A4, making them less risky in terms of drug–drug interactions.

Compound 10 has the poorest profile: it is a P-gp substrate and a multi-CYP inhibitor, combined with high polarity. This suggests potentially low bioavailability and a high risk of metabolic complications.

Compound 11 stands out with the largest molecular weight and TPSA among the studied compounds, low solubility, and inhibition of several CYP isoforms. This makes it less promising for further development.

Overall, compounds 4-7 are of the greatest interest for further studies, as they offer the best balance between pharmacokinetic safety and potential pharmacological activity. In contrast, compounds 1-3, 10, and 11 require extensive structural optimization to reduce CYP450 inhibitory activity and improve solubility. Therefore, the obtained results confirm the feasibility of continuing work on this series of compounds, focusing on optimizing lipophilicity and polarity to develop new low-toxicity drugs with antioxidant and antihypoxic activity.

The antioxidant and antihypoxic activities of the synthesized compounds are closely interconnected due to the shared key pathogenetic mechanisms underlying tissue damage during hypoxia. Under oxygen-deficient conditions, excessive formation of reactive oxygen species (ROS) plays a leading role in the development of cellular damage, initiating lipid peroxidation, disrupting the structural and functional integrity of membranes, and disturbing ion homeostasis. Therefore, the antioxidant action of pharmacological agents forms a fundamental basis for their antihypoxic effect.

It has been demonstrated that compounds capable of suppressing the intensity of free radical reactions and activating endogenous antioxidant systems simultaneously exhibit pronounced cytoprotective potential under hypoxic conditions [13-15]. The stronger a compound inhibits lipid peroxidation processes, the greater its protective effect on cellular membranes and mitochondria during oxygen deficiency. This manifests in the preservation of mitochondrial enzyme activity, maintenance of ATP synthesis, and increased overall tolerance of the organism to hypoxic stress.

At the molecular level, antioxidant activity contributes to the stabilization of intracellular processes, particularly by preventing the opening of the mitochondrial permeability transition pore, a key step in apoptosis initiation. In addition, activation of the Nrf2-dependent pathway by antioxidant compounds enhances the expression of endogenous protective enzymes, providing a prolonged protective effect against oxidative stress. Thus, antioxidant activity not only reduces oxidative damage but also forms the basis for realizing the antihypoxic effect.

Experimental studies of 1,2,4-triazole-3-thione derivatives demonstrate a clear correlation between antioxidant and antihypoxic activity indicators [17-19]. Compounds exhibiting low IC_{50} values in lipid peroxidation inhibition assays simultaneously show the highest efficacy in hypoxia models, allowing antioxidant properties to be considered a predictor of antihypoxic potential. This has significant practical importance, as initial assessment of antioxidant activity can be used as a screening approach in the search for new agents to correct pathological conditions, including those arising from combat injuries, blood loss, or ischemic damage under military field conditions.

The results of the pharmacological activity study showed that all 11 compounds exhibited antihypoxic effects to varying degrees. Eight of them reached a level of activity close to that of the reference drug Armadin, while three compounds exceeded its efficacy, namely: 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile (compound 3) by 2.7%, dimethylammonium 2-((5-(2,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)acetate (compound 7) by 9%, and ethylamine 2-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)benzoate (compound 8) by 6.7%. These compounds are recommended for further detailed pharmacological studies. Detailed study results are presented in Table 3.

Table 3

Indicators of the antihypoxic activity of the studied compounds

Compound	Mean survival time, M±m	Activity relative to control, %
Control	25.4±3.07	100
Armadin	37.8±3.56	148.81
1	30.5±3.26	120.07
2	36.3±2.18	142.91
3	38.5±4.29	151.57
4	33.4±3.55	131.49
5	36.4±2.56	143.30
6	33.5±1.58	131.88
7	40.1±4.25	157.87
8	39.5±1.47	155.51
9	30.5±1.17	120.07
10	37.1±3.25	146.06
11	33,2±3,47	130,70

Discussion. The results of the comprehensive study of the synthesized 1,2,4-triazole-3-thione derivatives demonstrate consistency between *in silico* predictions of acute toxicity, pharmacokinetic parameters, and experimental evaluation of anti-hypoxic activity *in vivo*. According to the hypoxia with hypercapnia model in a confined space using Wistar rats, several compounds significantly increased the survival time of the animals compared to the control and either matched or exceeded the effect of the reference drug, Armadin. In particular, compounds 7 and 8 showed the highest activity (approximately 158% and 156% relative to control, respectively), while compound 3 reached about 152%. This indicates that at least three synthesized molecules (3, 7, 8) outperform the clinically used anti-hypoxic agent in this model, confirming the relevance of the selected chemical platform for the further development of agents for correcting hypoxic conditions relevant to military medical practice.

Acute toxicity prediction (oral rat LD_{50} model, TEST v5.1.2.0) revealed that most of the studied derivatives belong to toxicity classes III and IV. When compared with *in vivo* activity, this creates a favorable "safety window" for the leading compounds. Notably, compound 3, 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile, combines high anti-hypoxic efficacy and antioxidant activity (confirmed by *in silico* and *in vitro* studies) with low acute toxicity (class IV). In contrast, compounds 7 and 8, although demonstrating maximal anti-hypoxic effects, require careful dose selection and safety monitoring due to their class III toxicity. Therefore, the best balance of "efficacy/safety" appears to be achieved for 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile.

The ADME analysis, presented as radar plots and heatmaps, provided key pharmacokinetic guidance for interpreting the biological results. These visualizations allowed the identification of compounds with more balanced absorption, distribution, metabolism, and excretion profiles, which are potentially capable of reaching therapeutically relevant concentrations in target tissues without excessive inactivation or accumulation. Notably, the leading compounds in terms of anti-hypoxic activity were found among these molecules, indicating a causal relationship between the ability to realize pharmacodynamic potential *in vivo* and the pharmacokinetic "delivery" of the active substance. In this context, 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile demonstrates the best compromise between activity, acute toxicity, and a balanced ADME profile, whereas the profiles of compounds 7 and 8 suggest strong absorption and distribution with somewhat more aggressive metabolism, consistent with their higher acute toxicity and indicating the need for careful ongoing monitoring.

From a clinical-pathophysiological perspective, the data align well with current understanding of the multifactorial nature of the anti-hypoxic effect of triazole derivatives, where the antioxidant component is complemented by metabolic support of tissues under oxygen-deficient conditions. The superiority of the leading compounds over Armadin in this model may indicate additional mechanisms combining direct radical scavenging with modulation of enzymatic oxidative stress pathways. Cross-validation of the in silico data (ADME and acute toxicity predictions) with *in vivo* results strengthens confidence in 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile as a "balanced" lead and highlights compounds 7 and 8 as candidates for further structural optimization or dose adjustment.

Overall, the integration of acute toxicity predictions, ADME parameters, and antioxidant and anti-hypoxic activities enabled a rational prioritization of safer, pharmacokinetically favorable lead compounds with pronounced pharmacological efficacy. Practically, for military medicine, this allows focusing subsequent resource-intensive preclinical studies on compounds with the best benefit/risk profile-specifically, 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio) butanonitrile as the most promising candidate. The next steps should include confirmation of antioxidant mechanisms in cellular models of oxidative stress, detailed *in vivo* pharmacokinetics (including bioavailability, distribution to critically important organs, and metabolic stability), and expanded toxicological profiling to validate the *in silico* findings and prepare for the drug formulation development stage.

Conclusion

1. The studied 1,2,4-triazol-3-thione derivatives, based on predictions of acute toxicity, ADME analysis, and experimental evaluation of antioxidant and anti-hypoxic activities, are promising candidates for further investigation as potential agents for pharmacological correction of

pathological conditions induced by combat-related injuries.

2. Acute toxicity prediction indicated that the studied compounds belong to toxicity classes III–IV, demonstrating the absence of highly toxic samples and providing a basis for the safe conduct of further studies.

3. ADME analysis confirmed a favorable pharmacokinetic profile for certain compounds, suggesting the likelihood of achieving therapeutic concentrations in target tissues and realizing pharmacological effects *in vivo*.

4. Evaluation of anti-hypoxic activity using a hypoxia-hypercapnia model in Wistar rats showed that compounds 3, 7, and 8 increased the animals survival time and exceeded the efficacy of the reference drug, Armadin.

5. The most promising compound was identified as 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile, which combines high anti-hypoxic and antioxidant activity, low toxicity (class IV), and optimal pharmacokinetic characteristics. Compounds 7 and 8, which demonstrated the highest anti-hypoxic effect, require further safety assessment and correlation with therapeutic doses.

6. The results support the feasibility of further preclinical studies of 1,2,4-triazol-3-thione derivatives, aimed at detailed investigation of their antioxidant mechanisms, pharmacokinetic and toxicological profiles, which is crucial for the development of new drugs for military medicine.

Future research prospects. Further studies will involve an in-depth preclinical investigation of the most promising 1,2,4-triazol-3-thione derivatives, particularly 4-((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazol-3-yl)thio)butanonitrile, which demonstrated pronounced antioxidant and anti-hypoxic activity. The next stage will focus on evaluating their efficacy in models of combat trauma, ischemic injuries, and multimodal pathological conditions associated with hypoxia and oxidative stress. The results obtained may serve as a basis for the development of novel dual-action drugs-antioxidants and anti-hypoxants-capable of enhancing endurance, reducing the risk of complications, and improving recovery of military personnel under combat conditions.

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