Ars et Scientia, Humanitas et Virtus!

ISSN 2708-6615 (print)

ISSN 2708-6623 (online)

УКРАЇНСЬКИЙ ЖУРНАЛ ВІЙСЬКОВОЇ МЕДИЦИНИ

ЩОКВАРТАЛЬНИЙ НАУКОВО-ПРАКТИЧНИЙ ЖУРНАЛ
УКРАЇНСЬКОЇ ВІЙСЬКОВО-МЕДИЧНОЇ АКАДЕМІЇ

ТОМ 6
2.2025

UKRAINIAN JOURNAL OF MILITARY MEDICINE

QUARTERLY SCIENTIFIC AND PRACTICAL JOURNAL OF
UKRAINIAN MILITARY MEDICAL ACADEMY

UDC 615.277:615.015.21:615.31 DOI: 10.46847/ujmm.2025.2(6)-125

ANTIOXIDANT AGENTS IN WARTIME: PROSPECTS FOR THE DEVELOPMENT OF NEW BIOLOGICALLY ACTIVE COMPOUNDS BASED ON 1,2,4-TRIAZOLE DERIVATIVES

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Introduction. *This article presents an analysis of the antioxidant activity of 4-amino-5-(2-, 3-, 4-nitrophenyl)-1H-1,2,4-triazole-3-thiones and their synthetic analogues, 5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones and their synthetic analogues, and 5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R1-1,2,4-triazole-3-thiones. The main conclusions drawn from these studies are as follows:*

The purpose: *to evaluate the antioxidant activity of 1,2,4-triazole derivatives, specifically 4-amino-5-(2-, 3-, 4-nitrophenyl)-1H-1,2,4-triazole-3-thiones, 5-(4-methoxyphenyl-, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones, and 5-(quinolin-2-yl-, 2-hydroxyquinolin-4-yl)-4-R_1-1,2,4-triazole-3-thiones, in order to identify promising compounds with pronounced antioxidant activity for potential use in the correction of pathological conditions associated with oxidative stress, particularly among the military personnel of the Armed Forces of Ukraine.*

Materials and Methods: *The study involved the synthesis and structural analysis of 1,2,4-triazole derivatives. The antioxidant activity was assessed using spectrophotometric and electrochemical methods, determining the ability of the studied compounds to neutralize free radicals and inhibit oxidative processes. The influence of chemical structure, particularly the nature of substituents at positions 4 and 5 of the triazole ring, on antioxidant properties was analyzed through a comparative study of the obtained results.*

Results. *Derivatives of 5-R-3-thio-1,2,4-triazole show promise as potential matrices for the development of highly effective antioxidant agents. The antioxidant properties of these derivatives depend on the nature of the substituents at the 4 and 5 positions of the 1,2,4-triazole ring. The presence of a free SH group and its substituted products, such as thioacetic acids, their salts, and esters, also contribute to the antioxidant effect. Compounds with a greater number of electron-donating groups exhibit the highest antioxidant activity, highlighting the importance of these groups in providing effective protection against oxidative processes.*

Conclusions. *The results of the conducted study confirm the potential of 1,2,4-triazole derivatives as compounds with antioxidant activity and provide an important scientific basis for further structural optimization to enhance their effectiveness. The obtained data contribute to the development of novel highly active antioxidant agents for the correction of pathological conditions associated with oxidative stress, particularly among the military personnel of the Armed Forces of Ukraine.*

Key words: *heterocyclic molecules, 1,2,4-triazole, biological activity, antioxidant activity.*

АНТИОКСИДАНТНІ ЗАСОБИ У ВОЄННИЙ ЧАС: ПЕРСПЕКТИВИ РОЗРОБКИ НОВИХ БІОЛОГІЧНО АКТИВНИХ СПОЛУК НА ОСНОВІ ПОХІДНИХ 1,2,4-ТРІАЗОЛУ

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Вступ. *У цій статті представлено аналіз антиоксидантної активності 4-аміно-5-(2-, 3-, 4-нітрофеніл)-1H-1,2,4-тріазол-3-тіонів і їх синтетичних аналогів, 5-(4-метоксифеніл-, 3,4,5-триметоксифеніл)-1,2,4-тріазол-3-тіонів і їх синтетичних аналогів, а також 5-(хінолін-2-іл-, 2-гідроксихінолін-4-іл)-4-R_1-1,2,4-тріазол-3-тіонів. Основні висновки проведених досліджень:*

Мета: *Оцінити антиоксидантну активність похідних 1,2,4-тріазолу, зокрема 4-аміно-5-(2-, 3-, 4-нітрофеніл)-1H-1,2,4-тріазол-3-тіонів, 5-(4-метоксифеніл-, 3,4,5-триметоксифеніл)-1,2,4-тріазол-3-тіонів та 5-(хінолін-2-іл-, 2-гідроксихінолін-4-іл)-4-R_1-1,2,4-тріазол-3-тіонів, з метою виявлення перспективних сполук із вираженою антиоксидантною активністю для потенційного застосування у корекції патологічних станів, зумовлених оксидативним стресом, зокрема серед військовослужбовців Збройних Сил України.*

Матеріали та методи. *Дослідження включало синтез та структурний аналіз похідних 1,2,4-тріазолу. Оцінку антиоксидантної активності здійснювали за допомогою спектрофотометричних та електрохімічних методів, визначаючи здатність досліджуваних сполук нейтралізувати вільні радикали*

та інгібувати окиснювальні процеси. Вплив хімічної будови, зокрема природи замісників у 4-му та 5-му положеннях тріазольного кільця, на антиоксидантні властивості аналізували шляхом порівняльного аналізу отриманих результатів.

Результати. *Похідні 5-R-3-тіо-1,2,4-тріазолу є перспективними матрицями для створення високоефективних антиоксидантних засобів. Антиоксидантні властивості цих сполук залежать від природи замісників у 4-му та 5-му положеннях тріазольного кільця. Наявність вільної SH-групи та її похідних, таких як тіоацетатні кислоти, їх солі та ефіри, також підсилює антиоксидантний ефект. Сполуки з більшою кількістю електронодонорних груп проявляють найвищу антиоксидантну активність, що підтверджує важливість цих груп у забезпеченні ефективного захисту від оксидативного стресу.*

Висновки. *Результати проведеного дослідження підтверджують потенціал похідних 1,2,4-тріазолу як сполук з антиоксидантною активністю та надають важливу наукову основу для подальшої структурної оптимізації з метою підвищення їхньої ефективності. Отримані дані сприяють розробці нових високоактивних антиоксидантних засобів для корекції патологічних станів, зумовлених оксидативним стресом, зокрема серед військовослужбовців Збройних Сил України.*

Ключові слова: *гетероциклічні молекули, 1,2,4-тріазол, біологічна активність, антиоксидантна активність.*

Introduction. Heterocyclic systems find extensive applications in modern medical and pharmaceutical fields. In particular, the scientific community is interested in heterocyclic molecules that are readily synthesized using accessible reagents, possess low molecular weight, exhibit low toxicity, and display high reactivity.

Among the wide array of different heterocyclic systems, special attention is given to 1,2,4-triazole. This heterocyclic system offers a straightforward synthesis route, low toxicity, and a broad spectrum of biological activity.

Literature sources contain data on its antimicrobial [1-6], antifungal, antitumor, and anticancer properties [7-20]. Research on the antioxidant effects of 1,2,4-triazole derivatives is also documented in the literature [21-25].

The antioxidant activity of compounds is of great interest in the development of biologically active substances.

The Importance of Antioxidant Therapy in Wartime and the Prospects of Using 1,2,4-Triazole Compounds. During wartime, the human body is subjected to significant stress factors, including hypoxia, intense physical exertion, psycho-emotional exhaustion, and toxic effects from a polluted environment. These factors lead to an imbalance in redox processes, resulting in increased free radical formation and the development of oxidative stress. Oxidative stress, in turn, contributes to the damage of cell membranes, proteins, and DNA, potentially leading to various pathological conditions, including cardiovascular, neurological, and immunodeficiency disorders.

Given these circumstances, the use of antioxidant drugs is a crucial aspect of pharmacological support in wartime. Antioxidants help neutralize free radicals, reducing oxidative stress levels, thereby preserving the functional activity of cells and physiological systems. Among the promising classes of compounds with antioxidant properties, 1,2,4-triazole derivatives have attracted significant attention.

1,2,4-Triazole-based compounds exhibit a broad spectrum of pharmacological activity, including antioxidant, anti-inflammatory, neuroprotective, and cardioprotective effects. Studies confirm their ability to inhibit lipid peroxidation, stimulate endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), and enhance cellular energy metabolism. These properties make 1,2,4-triazole derivatives promising candidates for the development of pharmaceutical agents capable of effectively counteracting the negative consequences of oxidative stress in wartime conditions.

Furthermore, it is essential to emphasize that 1,2,4-triazole derivatives may be beneficial not only for military personnel but also for civilians experiencing constant stress, malnutrition, and exposure to environmental pollutants. The development and implementation of drugs in this category could enhance the body's resistance to adverse factors, improve cognitive functions, and reduce the risk of chronic diseases, which is particularly relevant during prolonged crises.

Thus, antioxidant drugs, particularly 1,2,4-triazole derivatives, may serve as essential pharmacological support in wartime, contributing to the preservation of health, work capacity, and resilience among both military personnel and the civilian population.

Review of Domestic Research on the Antioxidant Activity of 1,2,4-Triazole Derivatives. In particular, studies on the antioxidant activity of 1,2,4-triazole derivatives are being conducted at the Zaporizhzhia state

medical and pharmaceutical university. Fundamental research on the antioxidant effects of heterocyclic structures with a 1,2,4-triazole scaffold has been carried out in scientific works [22].

Taking into account the expertise of the scientific school on 1,2,4-triazoles at Zaporizhzhia state medical and pharmaceutical university., under the guidance of Professor A.G. Kaplaushenko, a comprehensive approach has been developed for studying the antioxidant activity of compounds.

The aim of our research is to investigate highly effective substances with antioxidant properties among derivatives of 1,2,4-triazole that were synthesized by the researchers from Zaporizhzhia state medical and pharmaceutical university.

Materials and Methods. In the article [26], an *in vitro* non-enzymatic method for initiating free radical oxidation (FRO) was discussed.

Authors [26] studying the antioxidant activity of the synthesized compounds will also help establish the relationship between the investigated biological activity and the chemical features of the compounds. This information can be valuable for further synthesis of antioxidant agents (BAR) and for selecting the most promising compounds for further in vivo studies.

The method of assessing antioxidant activity (AOA) during non-enzymatic initiation of FRO with ferrous salts (Fe(II)) is employed [26].

Egg lipoprotein suspension is used as a substrate. The suspension is prepared by homogenizing egg yolk with a phosphate buffer (pH 7.4). The investigated compounds are added to the suspension at a concentration of 10-3 mol/L. The free radical oxidation reaction is initiated by adding a solution of $FeSO_4 \times 7H_2O$. The mixture is incubated for 60 minutes at 37°C. The reaction is stopped with a 20% solution of trichloroacetic acid containing thrylon B. After centrifugation for 30 minutes, the supernatant is mixed with thiobarbituric acid (TBA) and boiled on a water bath for 60 minutes. The colored complex of TBA-reactive products (TBA-RP) is extracted by adding n-butanol. The concentration of TBA-RP is determined using spectrophotometry.

Antioxidant activity is calculated by the formula:

$$AOA = \frac{E_{control} - E_{exp}}{E_{control}} \times 100\%$$

where AOA – the antioxidant activity, %.

$E_{control}$ – optical density of the control solution; E_{exp} – optical density of the solution containing the test compound (ascorbic acid or thiotriazoline).

Here are the reagents and their preparations:

– Egg lipoprotein suspension: Add 1 egg yolk to 1 liter of phosphate buffer solution with a pH of 7.4 (determined using a pH meter).

– 20% solution of trichloroacetic acid: Dissolve 20 grams of trichloroacetic acid in 80 grams of purified water.

– 0.8% solution of thiobarbituric acid: Place 800 milligrams of thiobarbituric acid in a 100 ml measuring flask and fill it up to the mark with purified water.

– 10% solution of ferrous sulfate: Dissolve 10 grams of ferrous sulfate in 90 milliliters of purified water.

In total, the antioxidant activity of 67 compounds was investigated, evaluating their activity based on the concentration of TBA-reactants. The control sample was prepared in the same way as the tested compounds but without their addition. Vitamin E was used as a reference standard for comparison. Considering that the activity of the compounds is determined by their ability to form complexes with ferrous ions, inhibiting their oxidation processes, compounds containing free thio-, hydroxy-, carboxyl groups, and their structural analogs were selected for the study. Furthermore, attention was paid to the ability of nitrogen atoms of heterocyclic origin to form complexes.

Results and Discussion.

*Antioxidant Activity of 4-Amino-5-(2, 3, 4-Nitrophenyl)-1H-1,2,4-Triazole-3-Thiones and Their Synthetic Analogs***.** The obtained information about the compounds 4-amino-5-(2, 3, 4-nitrophenyl)-1H-1,2,4-triazole-3-thiones (Table 1) indicates their antioxidant properties, which significantly depend on the substituents in the 1,2,4-triazole ring [27].

Specifically, compounds 4-amino-5-(4-nitrophenyl)-1H-1,2,4-triazole-3-thione (2) and 2-(5-(4-nitrophenyl)-4-amino-1,2,4-triazol-3-ylthio)acetic acid (10) are the leaders in this series.

Therefore, it can be concluded that the substituents in the 1,2,4-triazole ring play a crucial role in determining the antioxidant properties of these compounds.

Alkylation of the thiones with halogenoalkanes (compounds 3-5) reduces the antioxidant activity. However, in addition to the previously observed regularities regarding the structure-activity relationship of antioxidants, it should be noted that shortening the carbon chain

of the alkyl radical leads to an increase in the activity of the compounds. Thus, the compound 5-(4-nitrophenyl)-3-propylthio-1,2,4-triazol-4-amine (5) exhibits the same effectiveness as the reference vitamin E. It is also worth mentioning that the oxidation of the compound 3-heptylthio-4-amino-5-(3-nitrophenyl)-1,2,4-triazole (3) to 3-heptylsulfinyl-4-amino-5-(3-nitrophenyl)-1,2,4-triazole (6) and 3-heptylsulfonyl-4-amino-5-(3-nitrophenyl)-1,2,4-triazole (7) results in a slight but increased antioxidant activity.

The authors of [27] investigated the 2-(5-(3-, 4-nitrophenyl)-4-amino-1,2,4-triazol-3-ylthio)acetic acids (9, 10), and the results of their antioxidant activity (AOA) are presented in Table 2. It is noted that the 2-(5-(4-nitrophenyl)-4-amino-1,2,4-triazol-3-ylthio)acetic acid (10) exhibits high AOA values and significantly surpasses the activity of the reference standard. Additionally, it was found that the salts of 2-(5-(3-, 4-nitrophenyl)-4-amino-1,2,4-triazol-3-ylthio)acetic acids (11, 12, 14-16) are quite active compounds. Sodium 2-(5-(3-nitrophenyl)-4-amino-1,2,4-triazol-3-ylthio)acetate (12) showed the highest activity.

Regarding the antioxidant activity of 1-R1-3-(3-thio-5-(2-, 3-nitrophenyl)-1,2,4-triazol-4-yl)thioureas [27] (17, 18), it should be noted that it is on par with the reference standard. The AOA of 5-(2-, 3-, 4-nitrophenyl)-4-benzylideneamino-1,2,4-triazole-3-thiones (19-21) exceeds the values of the reference standard.

Overall, based on the obtained results, it can be concluded that the antioxidant activity of the compounds depends on both the reactive centers that can form complexes with the oxidizing agent (in this case, iron (II) chloride) and the substituents in the 1,2,4-triazole cycle, as well as the radicals on the sulfur atom. The highest values are demonstrated by compounds containing free SH-groups (thiones) and compounds with a free or cation-bound carboxyl group (acids and salts).

*The antioxidant activity of 5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones and their synthetic analogs***.** The authors of the study [28] report high levels of antioxidant activity for new compounds – 5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones (22, 23). According to the research results, these compounds exhibited antioxidant activity at a level of 81.8%, surpassing the benchmark reference - alpha-tocopherol [28]. According to the authors, such high levels of antioxidant activity are attributed to the presence of an unsubstituted sulfhydryl group in the molecules of the investigated compounds, which facilitates the formation of complexes with divalent iron ions.

In the case of the investigated compound 2-(5-(3,4,5-trimethoxyphenyl)-1,2,4-triazol-3-yl)ethanethioic acid (27), the presence of an unsubstituted carboxylic group slightly increases the levels of antioxidant activity compared to vitamin E. However, compound 26, which contains a 4-methoxyphenyl substituent at the 5-position of the triazole ring, exhibits slightly lower levels of the investigated activity.

This research demonstrates that the modification of the carboxyl group in compounds of 2-(5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazol-3-ylthio)ethanoic acids (28-31) leads to a decrease in their antioxidant activity, regardless of the presence of 3,4,5-trimethoxyphenyl or 4-methoxyphenyl substituents at the C^5 position of the 1,2,4-triazole ring. However, when studying the salts of 2-(5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazol-3-ylthio)ethanoic acids (32, 33), higher antioxidant activity was observed compared to the esters of 2-(5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazol-3-ylthio)ethanoic acids (28-31). Furthermore, some of the synthesized compounds (33, 34, 36, 38) exhibited higher antioxidant activity than ascorbic acid. The most active among all investigated compounds were 2-(5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazol-3-ylthio)acetimidate hydrochlorides (24, 25 in Table 1), which, in our opinion, can be explained by the presence of the highest number of electron-donating groups in their structure.

During the analysis of the results, it was found that the antioxidant activity (AOA) depends on reactive centers that can facilitate complex formation with the oxidizing agent, which in our case is ferrous chloride, as well as on substituents on the 1,2,4-triazole ring and radicals at the sulfur atom. The highest activity values were observed for compounds with free SH- groups (22, 23), compounds with a carboxyl group that can be free or bound to a cation (26, 27; 32-39), as well as compounds with an imino group (24, 25). These results can be valuable for further research and development of new antioxidants with improved efficacy.

Antioxidant activity of 5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R1-1,2,4-triazole-3-thiones. The reporting of the research results [29] shows that the synthesized 5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-(H, C_6H_5)-1,2,4-triazole-3-thiones (40, 41) exhibited high levels of antioxidant activity, surpassing the activity of the

reference compound, alpha-tocopherol [29], at 81.8% and 81.2%, respectively, compared to the control. These values can be attributed to the presence of an unsubstituted sulfhydryl group in the molecules of the synthesized compounds, allowing them to form complexes with iron (II) ions. However, the situation is not as straightforward when studying structural analogs with different groups (H, C6H5). For example, the synthesized ester and hydrazide derivatives showed lower antioxidant activity compared to the control group.

Table 1

The indicators of antioxidant activity of 4-R, 5-R_1-1,2,4-triazole-3-thiones

The compound	The empirical formula	The optical density (control)			The optical density (experimental group)			Percentage of activity
		C_1	C_2	C_{cp}	C_1	C_2	C_{cp}	
The indicators of antioxidant activity of 4-amino-5-(2-, 3-, 4-nitrophenyl)-1*H*-1,2,4-triazole-3-thiones and their synthetic analogues.								
Vitamin E		0,11	0,11	0,11	0,020	0,025	0,023	79,0
1	$C_8H_7N_5O_2S$	0,12	0,11	0,13	0,017	0,015	0,016	86,7
2	$C_8H_7N_5O_2S$	0,12	0,11	0,13	0,014	0,012	0,013	89,1
3	$C_{15}H_{21}N_5O_2S$	0,11	0,11	0,11	0,029	0,030	0,031	72,8
4	$C_{17}H_{25}N_5O_2S$	0,11	0,11	0,11	0,034	0,032	0,034	70,3
5	$C_{11}H_{13}N_5O_2S$	0,11	0,11	0,11	0,022	0,023	0,020	80,3
6	$C_{15}H_{21}N_5O_3S$	0,13	0,15	0,14	0,037	0,039	0,037	73,1
7	$C_{15}H_{21}N_5O_4S$	0,13	0,15	0,14	0,037	0,37	0,036	73,8
8	$C_{17}H_{25}N_5O_4S$	0,13	0,15	0,14	0,026	0,27	0,028	80,7
Vitamin E		0,11	0,11	0,11	0,045	0,050	0,048	56,4
9	$C_{10}H_9N_5O_4S$	0,11	0,11	0,11	0,017	0,018	0,016	84,5
10	$C_{10}H_9N_5O_4S$	0,11	0,11	0,11	0,006	0,006	0,004	95,1
11	$C_{10}H_8KN_5O_4S$	0,11	0,11	0,11	0,020	0,021	0,022	80,9
12	$C_{10}H_8N_5NaO_4S$	0,11	0,11	0,11	0,021	0,019	0,018	82,4
13	$C_{20}H_{16}FeN_{10}O_8S_2$	0,11	0,11	0,11	0,024	0,023	0,023	78,8
14	$C_{11}H_{14}N_6O_4S$	0,11	0,11	0,11	0,024	0,024	0,025	77,8
15	$C_{12}H_{16}N_6O_4S$	0,11	0,11	0,11	0,021	0,024	0,023	79,4
16	$C_{14}H_{18}N_6O_5S$	0,11	0,11	0,11	0,022	0,019	0,021	81,2
Vitamin E		0,055	0,055	0,055	0,065	0,050	0,058	58,6
17	$C_{10}H_{10}N_2O_6S_2$	0,11	0,11	0,11	0,024	0,023	0,023	78,8
18	$C_{11}H_{12}N_2O_6S_2$	0,11	0,11	0,11	0,023	0,022	0,022	79,7
19	$C_{15}H_{11}N_5O_3S$	0,055	0,055	0,055	0,010	0,011	0,011	80,6
20	$C_{15}H_{10}N_6O_4S$	0,055	0,055	0,055	0,010	0,010	0,011	81,2
21	$C_{15}H_{12}FN_5O_2S$	0,055	0,055	0,055	0,012	0,010	0,011	80,0
The indicators of antioxidant activity of 5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones and their synthetic analogues.								
22	$C_9H_9N_3OS$	0,11	0,11	0,11	0,020	0,020	0,020	81,8
23	$C_{11}H_{13}N_3O_3S$	0,11	0,11	0,11	0,025	0,015	0,020	81,8
24	$C_{19}H_{28}N_4O_2S$	0,11	0,11	0,11	0,020	0,020	0,020	81,8
25	$C_{16}H_{22}N_4O_4S$	0,11	0,11	0,11	0,020	0,015	0,018	83,6
Vitamin E		0,11	0,11	0,11	0,020	0,025	0,023	79,0
26	$C_{11}H_{11}N_3O_3S$	0,12	0,11	0,115	0,040	0,050	0,045	60,7
27	$C_{13}H_{15}N_3O_5S$	0,12	0,11	0,115	0,015	0,025	0,020	82,6
28	$C_{12}H_{13}N_3O_3S$	0,12	0,11	0,115	0,035	0,030	0,033	71,3
29	$C_{13}H_{15}N_3O_3S$	0,12	0,11	0,115	0,035	0,045	0,040	65,2
30	$C_{14}H_{17}N_3O_5S$	0,12	0,11	0,115	0,075	0,070	0,073	36,5
31	$C_{15}H_{19}N_3O_5S$	0,12	0,11	0,115	0,030	0,035	0,033	71,3
Vitamin E		0,12	0,11	0,115	0,020	0,020	0,020	82,6
32	$C_{11}H_{10}N_3NaO_3S$	0,15	0,13	0,14	0,065	0,050	0,058	58,6
33	$C_{11}H_{10}KN_3O_3S$	0,11	0,11	0,11	0,03	0,03	0,03	72,7
34	$C_{11}H_{14}N_4O_3S$	0,11	0,11	0,11	0,030	0,030	0,030	72,7
35	$C_{13}H_{18}N_4O_4S$	0,11	0,11	0,11	0,030	0,035	0,033	70,0
36	$C_{15}H_{22}N_4O_5S$	0,11	0,11	0,11	0,025	0,035	0,030	72,7
37	$C_{15}H_{20}N_4O_4S$	0,11	0,11	0,11	0,04	0,025	0,033	70,0
38	$C_{13}H_{14}N_3NaO_5S$	0,11	0,11	0,11	0,03	0,025	0,028	74,5
39	$C_{13}H_{14}KN_3O_5S$	0,11	0,11	0,11	0,030	0,035	0,033	70,0

The compound	The empirical formula	The optical density (control)			The optical density (experimental group)			Percentage of activity
		C_1	C_2	C_{cp}	C_1	C_2	C_{cp}	
The indicators of antioxidant activity of 5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R1-1,2,4-triazole-3-thiones..								
Vitamin E		0,11	0,11	0,11	0,020	0,025	0,023	79,0
40	$C_{11}H_8N_4S$	0,11	0,11	0,11	0,022	0,019	0,021	81,2
41	$C_{17}H_{12}N_4OS$	0,11	0,11	0,11	0,020	0,020	0,020	81,8
42	$C_{13}H_{10}N_4O_2S$	0,11	0,11	0,11	0,024	0,024	0,025	77,8
43	$C_{13}H_{10}N_4O_3S$	0,12	0,11	0,13	0,017	0,015	0,016	86,7
44	$C_{19}H_{14}N_4O_3S$	0,11	0,11	0,11	0,017	0,018	0,016	84,5
45	$C_{13}H_9KN_4O_2S$	0,11	0,11	0,11	0,021	0,019	0,018	82,4
46	$C_{13}H_9N_4NaO_2S$	0,11	0,11	0,11	0,025	0,015	0,020	81,8
47	$C_{13}H_{13}N_5O_2S$	0,11	0,11	0,11	0,020	0,020	0,020	81,8
48	$C_{15}H_{17}N_5O_3S$	0,11	0,11	0,11	0,020	0,021	0,022	80,9
49	$C_{25}H_{37}N_5O_2S$	0,11	0,11	0,11	0,021	0,024	0,023	79,4
50	$C_{18}H_{21}N_5O_2S$	0,11	0,11	0,11	0,020	0,015	0,018	83,6
51	$C_{17}H_{19}N_5O_3S$	0,11	0,11	0,11	0,034	0,032	0,034	70,3
Vitamin E		0,12	0,11	0,115	0,020	0,020	0,020	82,6
52	$C_{14}H_{12}N_4O_2S$	0,11	0,11	0,11	0,045	0,065	0,055	50,0
53	$C_{15}H_{14}N_4O_2S$	0,15	0,13	0,14	0,065	0,050	0,058	58,6
54	$C_{16}H_{16}N_4O_2S$	0,11	0,11	0,11	0,045	0,045	0,045	56,4
55	$C_{17}H_{18}N_4O_2S$	0,11	0,11	0,11	0,060	0,055	0,058	47,3
56	$C_{14}H_{12}N_4O_3S$	0,11	0,11	0,11	0,065	0,060	0,063	42,7
57	$C_{15}H_{14}N_4O_3S$	0,11	0,11	0,11	0,065	0,060	0,063	42,9
Vitamin E		0,12	0,11	0,115	0,030	0,035	0,033	71,0
58	$C_{14}H_{14}N_4O_2S$	0,11	0,11	0,11	0,080	0,085	0,083	24,6
59	$C_{13}H_{12}N_4O_3S$	0,12	0,11	0,115	0,075	0,070	0,073	36,5
60	$C_{16}H_{18}N_4O_3S$	0,11	0,11	0,11	0,075	0,080	0,078	29,1
61	$C_{24}H_{18}N_4O_3S$	0,055	0,055	0,055	0,065	0,050	0,058	58,7
62	$C_{13}H_{10}N_4O_4S$	0,11	0,11	0,11	0,029	0,030	0,031	72,8
63	$C_{14}H_{12}N_4O_4S$	0,12	0,11	0,115	0,030	0,035	0,033	71,3
64	$C_{15}H_{14}N_4O_4S$	0,055	0,055	0,055	0,055	0,055	0,055	60,7
65	$C_{16}H_{16}N_4O_4S$	0,11	0,11	0,11	0,024	0,023	0,023	78,8
66	$C_{21}H_{15}KN_6O_3S$	0,11	0,11	0,11	0,006	0,006	0,004	95,1
67	$C_{21}H_{15}N_6NaO_3S$	0,12	0,11	0,13	0,014	0,012	0,013	89,1

In the molecules of the investigated 2-(5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-(H, C_6H_5)-1,2,4-triazol-3-ylthio)acetate acids (42-44), the presence of a carboxyl group substituent enhances the antioxidant activity, similar to vitamin E. However, compound 2.38, which contains a quinoline substituent at the 5 position of the triazole ring, exhibits lower AOA values compared to other compounds.

The investigation of the antioxidant activity (AOA) of esters of 2-(5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-(H, C_6H_5)-1,2,4-triazole-3-thio)acetic acids (52-57) indicates that the synthesis through the carboxyl group leads to a decrease in AOA in compounds with a quinoline or 2-hydroxyquinoline substituent at the C5 position of the 1,2,4-triazole ring.

During the study of salts of 2-(5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-(H, C_6H_5)-1,2,4-triazole-3-thio)acetic acids (45-51), it was observed that compared to the esters of 2-(5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-(H, C_6H_5)-1,2,4-triazole-3-thio)acetic acids (52-57), the synthesized compounds exhibited higher AOA. Specifically, compounds 45 and 50 showed greater activity than ascorbic acid.

The results of the experimental research revealed that potassium and sodium 4-((2-((5-(quinolin-2-yl)-1H-1,2,4-triazol-3-yl)thio)acetyl)hydrazono)methyl)benzoates (66, 67 in Table 1) were the most active among all investigated compounds. This can be attributed to the presence of the highest number of electron-donating groups in their structure.

During the analysis of the research results on the antioxidant effect, several factors that influence this effect for all investigated compounds need to be taken into account. Firstly, it is important to consider the presence of reactive centers that interact with the oxidizing agent (in this case, ferrous chloride) and induce complex formation. Additionally, the effectiveness of

antioxidant protection also depends on the substituents on the 1,2,4-triazole ring and the radicals near the sulfur atom. These factors can affect the efficiency of antioxidant protection in all investigated compounds.

Compounds containing free SH- groups (40, 41) as well as those containing a carboxyl group bound to a cation (45-51) exhibited the highest levels of antioxidant activity. This can be explained by the presence of free SH- groups and carboxyl groups that facilitate complex formation with the oxidizing agent, leading to high effectiveness in protecting against oxidative processes. It is important to note that the indicators of antioxidant activity depend not only on the presence of these groups but also on other factors such as substituents on the 1,2,4-triazole ring and radicals at the sulfur atom.

*Prospects for Further Research on the Antioxidant Activity of 1,2,4-Triazole Derivatives***.** Currently, scientists at Zaporizhzhia State Medical and Pharmaceutical University are studying the antioxidant activity using an alternative methodology based on DPPH (2,2-diphenyl-1-picrylhydrazyl). This method offers several advantages, including:

– Simplicity and speed – the method does not require complex equipment and provides rapid results.

– Sensitivity – allows the detection of even low concentrations of antioxidants.

– Reproducibility – the stability of the DPPH radical ensures high accuracy and repeatability of measurements.

– Colorimetric analysis – the color change (from purple to yellow) can be easily measured spectrophotometrically at 517 nm.

– Applicability to various samples – suitable for evaluating the antioxidant activity of both pure compounds and complex biological systems (extracts, food products, pharmaceutical preparations).

– Low cost – the reagents are affordable and inexpensive.

The results of antioxidant activity studies using the DPPH method, conducted by researchers [30], confirm the advantages of this approach.

The use of 1,2,4-triazole derivatives as a matrix for the search for highly effective antioxidants remains a promising direction in modern research. According to the findings of various authors [30–33], triazole-based biologically active compounds not only demonstrate superior antioxidant properties but also hold potential for further investigation as antihypoxants.

Conclusions. Analyzing the research on the antioxidant activity of 4-amino-5-(2-, 3-, 4-nitrophenyl)-1H-1,2,4-triazole-3-thiones and their synthetic analogues [27], 5-(4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thiones and their synthetic analogues [28], and 5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R1-1,2,4-triazole-3-thiones [29], the following conclusions can be drawn:

1. 5-R-3-Thio-1,2,4-triazole derivatives represent a promising matrix for the search for highly effective antioxidant agents that can mitigate the negative consequences of oxidative stress under wartime conditions, particularly in response to hypoxia, physical exhaustion, and toxic environmental factors.
2. The antioxidant properties of 5-R-3-thio-1,2,4-triazole derivatives depend on the nature of the substituents at positions 4 and 5 of the 1,2,4-triazole core. The presence of a free SH group and its substitution products, such as thioacetic acids, their salts, and esters, significantly influence the antioxidant effect. Structural optimization of these compounds may contribute to the development of effective agents for protecting the body in extreme wartime conditions.
3. The highest antioxidant activity is expected from compounds with the greatest number of electron-donating groups, which can effectively neutralize free radicals. This opens up prospects for developing new pharmacological agents capable of supporting physiological functions in both military personnel and civilians exposed to chronic stress, oxygen deficiency, and other challenges associated with wartime conditions.

Prospects for Further Research. Further research will focus on optimizing the structure of 1,2,4-triazole derivatives to enhance their antioxidant activity. Special attention will be given to pharmacokinetic and toxicological studies to assess their safety and efficacy.

As part of scientific collaboration, preclinical and clinical trials are planned in partnership with medical institutions providing care to the military personnel of the Armed Forces of Ukraine. This will contribute to the development of highly effective antioxidant agents for the correction of oxidative stress-related conditions in military settings.

Acknowledgments. The authors express their sincere gratitude to the Armed Forces of Ukraine for the opportunity to work under martial law and work on joint scientific projects.

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Конфлікт інтересів: відсутній.
Conflicts of Interest: authors have no conflict of interest to declare.

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