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STUDY OF ANTIOXIDANT ACTIVITY OF 5-(THIOPHEN-3-YLMETHYL)-4R-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

Actuality. *Every day, the problem of overcoming the consequences of antioxidant suppression and the development of oxidative stress becomes more and more significant for the entire medical society. To overcome this problem, it is necessary to inhibit the release of reactive oxygen species and prevent damage to cellular structures. To this end, it is important to find and develop new compounds with antioxidant properties. Promising substances in this direction are derivatives of 1,2,4-triazole, which have repeatedly demonstrated efficacy and safety.*

Purpose of the work *– to study the antioxidant activity of new derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazlol-3-thiol using the in vitro method.*

Materials and methods. *The basis of the in vitro screening method is the determination of markers of oxidative degradation of proteins: aldehydphenylhydrazones (APH) and ketophenylhydrazones (KPH). The process of determining the oxidative modification of proteins consisted in passing the reaction of interaction of oxidized amino acid residues with 2,4-dinitrophenylhydrazone, followed by the formation of 2,4-dinitrophenylhydrazones, which had characteristic absorption spectra.*

Results. *As a result of the study, it was found that derivatives of 5-(thiophene-3-ylmet)-4R-1,2,4-triazole-3-thiol on the model of protein peroxidation inhibition in vitro have high antioxidant activity. At the same time, calcium salt 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate (compound 2.30), sodium salt 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio) ethanoate (compound 2.28) and ketoderivative 1-(3-fluorophenyl)-2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethane-1-on (compound 2.20). Comparison drug emoxipin was inferior to the leader compound 2.30 and exceeded the antioxidant effect enhancement of compound 2.28 and compound 2.20.*

Conclusions. *It was found that the level of APH and KPH was most significantly reduced under the influence of the calcium salt 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate, which was not inferior to emoxipin. The leader compound is promising for further research and study.*

Key words: *antioxidant activity, oxidative stress, 1,2,4-triazole.*

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ВИВЧЕННЯ АНТИОКСИДАНТНОЇ АКТИВНОСТІ ПОХІДНИХ 5-(ТІОФЕН-3-ІЛМЕТИЛ)-4R-1,2,4-ТРИАЗОЛ-3-ТІОЛУ

Актуальність. *З кожним днем проблема подолання наслідків пригнічення антиоксидантної системи та розвитку оксидативного стресу стає дедалі значущішою для всього медичного суспільства. Для подолання цієї проблеми необхідно інгібувати виділення активних форм кисню та запобігти пошкодженню клітинних структур. Із цією метою актуальним є пошук та розроблення нових сполук з антиоксидантними властивостями. Перспективними речовинами щодо цього є похідні 1,2,4-триазолу, які вже неодноразово демонстрували ефективність та безпечність.*

Мета роботи *– вивчити антиоксидантну активність нових похідних 5-(тіофен-3-ілметил)-4R-1,2,4-триазлол-3-тіолу з використанням методу in vitro.*

Матеріали та методи*. Основою скринінгового методу дослідження in vitro є визначення маркерів окиснювальної деструкції білків: альдегідфенілгідразонів (АФГ) та кетофенілгідразонів (КФГ). Процес визначення окиснювальної модифікації білків полягав у реакції взаємодії окиснених амінокислотних залишків з 2,4-динітрофенілгідразоном з подальшим утворенням 2,4-динітрофенілгідразонів, що мали характерні спектри поглинання.*

Результати дослідження. *У результаті дослідження виявлено, що похідні 5-(тіофен-3-ілмети)-4R-1,2,4-триазол-3-тіолу на моделі інгібування перекисного окиснення білків in vitro мають високу антиоксидантну активність. Водночас найзначущіший вплив на рівень АФГ та КФГ показали сіль кальцію 2-((5-(тіофен-3-ілметил)-4H-1,2,4-триазол-3-іл)тіо)етаноат (сполука 2.30), сіль натрію 2-((4-феніл-5-(тіофен-3-ілметил)-4H-1,2,4-триазол-3-іл)тіо)етаноат (сполука 2.28) та кетопохідне 1-(3-фторфеніл)-2-((5-(тіофен-3-ілметил)-4H-1,2,4-триазол-3-іл)тіо)етан-1-он (сполука 2.20). Препарат порівняння емоксипін поступався сполуці лідеру 2.30 та перевищував за силою антиоксидантного ефекту сполуки 2.28 та 2.20.*

Висновок. *Установлено, що рівень АФГ та КФГ найбільше знижувався під впливом солі кальцію 2-((5-(тіофен-3-ілметил)-4H-1,2,4-триазол-3-іл)тіо)етаноату, яка не поступалася емоксипіну. Сполука лідер є перспективною для подальшого дослідження та вивчення.*

Ключові слова: *антиоксидантна активність, оксидативний стрес, 1,2,4-триазол.*

Actuality. In recent decades, doctors have begun to focus on changes in the development of traditional diseases. In the last century, the most common cause of death was infectious diseases, but thanks to the discovery of antibiotics, their number has significantly decreased. In the modern world, people are more likely to face and die from complications of cardiovascular and oncological diseases, as well as diseases associated with metabolic disorders. One of the significant causes of these conditions is an imbalance in the pro-oxidant-antioxidant system, a weakening of antioxidant protection, and, as a result, the development of oxidative stress (Москалюк,

Стравський, 2023). Intensification of lipid peroxidation leads to an increase in the concentration of reactive oxygen species (ROS), which in turn contributes to the accumulation of toxic products and, as a result, to a decrease in body resistance and inflammation (Violi F et al., 2017; Garramone A. et al., 2018; Черська та ін., 2021).

The fight against oxidative stress can be carried out in several directions, such as: inhibition of the formation of pro-oxidant substances, increasing the activity and level of endogenous antioxidant protection, and prescribing exogenous antioxidants. Under modern conditions of prolonged stress, it is quite difficult to influence the endogenous level of antioxidant protection, since stress is known to generate a large amount of reactive oxygen species in mitochondria, microsomes and other structures and cells. That is why exogenous antioxidants play a significant role today. In the context of the search for exogenous antioxidants, synthetic heterocyclic derivatives of 1,2,4-triazole are of interest, which have safety and the possibility of their long-term use without complications of pharmacotherapy (Карпун та ін., 2019; Karpenko et al., 2023). It is also a well-known fact that 1,2,4-triazole derivatives exhibit antioxidant, anti-ischemic and membrane-stabilizing effects (Shcherbyna et al., 2022, Fouad, 2023). A significant result is demonstrated by a successful "chemical symbiosis", namely the combination of thiophene and 1,2,4-triazole.

Purpose of the work. Study of the antioxidant activity of new 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiol derivatives using a modern in vitro method.

Materials and methods of research. In vitro methods are characterized by high specificity, do not require high expenditures on reagents and equipment, allow for the exclusion of extraneous factors from the model system that may influence the free radical process, provide the opportunity for quantitative assessment of the antioxidant activity (AOA) of the substances under investigation, and simultaneously enable screening of a large number of compounds (Chekman et al., 2016).

The basis of the screening method of the study is primarily the determination of markers of oxidative degradation of proteins: aldehydephenylhydrazones (APH) and ketonephenylhydrazones (KPH). The process of determining the oxidative modification of proteins consisted in passing the reaction of interaction of oxidized aminoxylate residues with 2,4-dinitrophenylhydrazine, followed by the formation of 2,4-dinitrophenylhydrazones, which had characteristic absorption spectra. According to the generally accepted method (Halliwell et al., 1999). 25% trichloroacetic acid was added to the biological material and centrifugal for 30 minutes. At 3000 rpm. Then 2.2% 2,4-dinitrophenylhydrazine was added to the resulting precipitate and incubated for 1 hour at a temperature of 37C. After that, it was re-centrifuged for 10 minutes at 3000 rpm. The resulting precipitate was washed with ethyl acetate and diluted with 3 ml of 50% urea solution. Then 1 drop of a 7% hydrochloric acid solution was added and diluted with distilled water 12 times. In the obtained solution, the content of APH (at a wavelength of 274 nm) and KPH (at a wavelength of 363 nm) was determined by spectrophotometric method. The antioxidant activity of the studied compounds was compared with the widely used classic antioxidant emoxipin.

Results. Antioxidant activity was investigated by primary in vitro pharmacological screening for twenty-three synthesized substances in a model of initiation of free radical protein oxidation (table 1).

It was found that the most significant level of APH was reduced by sodium salt 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate (compound 2.28) by 49.87%. At the same time, the compound 2.30 calcium 2-((5-(thiophene-3-ylnethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate and the compound 2.20 1-(3-fluorophenyl)-2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethane-1-on had significant antioxidant activity (reduced by 44.90% and 44.82%, respectively).

Under such circumstances, KPH levels were significantly reduced by compound 2.9 (alkyl derivative 3-(methylthio)-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole and compound 2.30 calcium 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate) by 39, 38% and 30.97%, respectively, which it indicated inhibition of the processes of oxidative modification of proteins. At the same time, as a trend, the level of KPH decreased under the action of compound 2.20 (ketoderivative 1-(3-fluorophenyl)-2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)ethane-1-on and compound 2.28 sodium 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate) by 14.53% and 14.34%, respectively.

Comparing the effect of the studied derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiol on models of inhibition of oxidative modification of proteins, we draw attention to a significant decrease in the level of APH and KPH in compound 2.30, which was the largest (the conditional effect index reached 75.87). The studied compound 2.28 was not inferior in activity to the reference drug emoxipin (a decrease in APH levels by 50.51%). At the same time, compound

Table 1

Study of new derivatives of 5-(thiophene-3-ylmethyl)-4-R1,2,4-triazole-3-thiol (10^{-6}M) on a model of inhibition of oxidative protein modification in vitro (n=9)

№ Compound, group	The wavelength is 270 nm		The wavelength is 363 nm	
	E_1	Antioxidant activity, %	E_2	Antioxidant activity, %
Control group	3,737±0,001		5,230±0,001	
Compound 2.5	5,082±0,001*	+35,99	8,890±0,001*	+69,98
Compound 2.9	4,006±0,001	+7,19	3,170±0,001*	39,38
Compound 2.11	3,976±0,001	+6,39	10,730±0,001*	+105,16
Compound 2.13	3,836±0,001	+2,64	6,027±0,001*	+15,23
Compound 2.16	4,015±0,001	+7,43	19,450±0,001*	+27,89
Compound 2.17	3,847±0,001	+2,94	6,910±0,001*	+32,12
Compound 2.20	2,062±0,001*	44,82	4,470±0,001	14,53
Compound 2.21	3,856±0,001	+3,18	8,320±0,001	+59,08
Compound 2.22	3,795±0,001	+1,55	6,130±0,001	+17,20
Compound 2.24	3,683±0,001	1,44	5,3700±0,001	+2,67
Compound 2.25	3,687±0,001	1,33	5,460±0,001	+4,39
Compound 2.26	3,734±0,001	0,08	6,130±0,001	+17,20
Compound 2,28	1,873±0,001*	49,87	4,480±0,001	14,34
Compound 2,29	3,835±0,001	+2,62	7,580±0,001	+44,93
Compound 2,30	2,059±0,001*	44,90	3,610±0,001*	30,97
Compound 2,31	3,985±0,001	6,63	13,640±0,001*	+160,80
Compound 2,33	5,659±0,001*	+51,43	7,430±0,001*	+42,06
Compound 2,34	3,803±0,001	+1,76	5,660±0,001	+8,22
Compound 2,35	3,971±0,001	+6,26	8,870±0,001*	+69,59
Compound 2,37	6,766±0,001*	+81,05	5,510±0,001	+5,35
Compound 2,38	3,807±0,001	+1,87	6,260±0,001*	+19,69
Compound 2,40	6,766±0,001*	+81,05	5,490±0,001	+4,97
Compound 2,41	3,702±0,001	0,93	5,600±0,001	+7,07
Control group	11,272±0,001		18,049±0,001	
Emoxipin	5,578± 0,667*	50,51	14,111± 0,220*	21,81

Note: * – reliability between the control and experimental groups ($p<0.05$)

2.20 and compound 2.30 were inferior to the comparison drug in terms of the strength of this indicator. Reference the drug emoxipin was also inferior in its effect on KPH levels to compound 2.9 and compound 2.30.

Based on the results of the study, it is also possible to draw certain conclusions about the structure-action relationship. An interesting fact is that the level of APH significantly decreased under the influence of compound 2.28, which is a sodium salt containing a phenyl radical in the fourth position of the 1,2,4-triazole ring. In turn, compounds 2.30 and 2.20, which have a hydrogen atom in the same position, also showed significant results, but still less than the results of compound 2.28. relative to the KPH level, the best indicators belong to compounds in which a hydrogen atom is present in this position, i.e. 2.9, 2.30 and 2.20. Conversely, the introduction of a phenyl radical into the fourth position of the triazole ring reduces the effect on KPH inhibition.

Discussion. It is known that under oxidative stress, a significant indicator of violation of the morphological and functional properties of macromolecules is a marker of oxidative modification of proteins. At the same time, studies in this aspect were only theoretical (Abed Elwahab & Al-Somaidai, 2023). At the present stage, methods for studying spontaneous and stimulated protein oxidation are used. They reproduce the oxidative balance and reserve-adaptive properties in the body. Such changes often lead to damage to genetic information, various mutations and cause disruption of cell functions, which leads to the emergence of many pathologies such as cardiovascular diseases, neurodegenerative and oncological diseases. Under this condition, the study of oxidative modification of proteins is important in assessing oxidative stress in individual cells and in the body as a whole (Austin et al., 2024).

Many studies have shown that protein peroxidation often causes inhibition of protein function in a number of electron carriers, interaction of transport proteins, and inhibition of ATP. Respiratory dysfunction occurs when the oxidative potential of the mitochondrial membrane

changes. All this indicates that oxidized proteins not only fix oxidative stress, but also actively participate in it (Li et al., 2024).

Therefore, protein peroxidation is important in the process of oxidative stress and plays an important role in the development of oxidative damage to DNA and lipids in cells. The next study of these processes may improve the methods of diagnosis and pharmacotherapy of neurodegenerative pathologies, since protein peroxidation is a specific and selective process and its metabolites are markers of early oxidative stress (Reddy, 2023). The emoxipin chosen by us as the reference drug is a highly effective inhibitor of protein oxidative modification. When emoxipin is used under conditions of cerebral and myocardial ischemia, there is an increase in SOD activity, a decrease in the formation of marker products of oxidative modification of proteins and phospholipids, and preservation of the physicochemical constants of the phospholipid bilayer of the membrane (Kamenshchyk et al, 2024).

In our study, we evaluated the processes of oxidative modification of proteins in vitro when studying the effect of new S-derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiol on models of protein peroxidation inhibition. Note that these compounds have a high antioxidant activity. At the same time, the most significant effect on the level of APH and KPH was shown by calcium salt 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate (compound 2.30), sodium 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate (compound 2.28) and ketoderivative 1-(3-fluorophenyl)-2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethane-1-on (compound 2.20), the conditional effect index of which was 75.87, 64.21 and 59.35, respectively. The comparison drug emoxipin had a conditional efficiency index of 72.32 and was inferior in this indicator to the compound sodium 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate and exceeded in this indicator compound 2.28 and compound 2.20. The similar action of 1,2,4-triazole derivatives regarding the inhibition of protein oxidative modification by the Fenton reagent can be explained by the peculiarities of their structure, which allow for both chelating divalent iron and reducing Fe-dependent initiation of free radical oxidation, as well as forming protective complexes with protein molecules (Belenichev et al., 2022). 1,2,4-Triazole derivatives are capable of "straightening out" oxidatively damaged protein molecules by increasing the expression of HSP70 (Belenichev et al., 2023) and directly neutralizing hydrophilic radicals (Popazova et al., 2023). These derivatives maintain the threshold sensitivity of membrane receptors, prevent the polarization of ion channels, normalize ion transport, preserve membrane fluidity, protect phospholipids from oxidation, and reduce the Stern-Volmer constant (the rate of quenching of free radicals) (Belenichev et al., 2019). The aforementioned findings provide experimental justification for further preclinical studies of the aforementioned 1,2,4-triazole derivatives.

Conclusions

1. New derivatives of 5-(thiophene-3-ylmethyl)-4R-1,2,4-triazole-3-thiol were studied on a model of inhibition of oxidative protein modification in vitro.

2. It was found that the level of APH was most significantly reduced by sodium 2-((4-phenyl-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio) ethanoate (compound 2.28), salt (compound 2.30) and ketoderivative 1-(3-fluorophenyl)-2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethane-1-on (compound 2.20).

3. It was found that KPH levels significantly decreased under the influence of alkyl derivatives 3-(methylthio)-5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole (compound 2.9) and calcium 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl)thio)ethanoate (compound 2.30)

4.The most active compound 2.30 calcium 2-((5-(thiophene-3-ylmethyl)-4H-1,2,4-triazole-3-yl) thio)ethanoate was not inferior in antioxidant activity to the reference drug emoxipin.

Prospects for further research. Synthetic derivatives of 1,2,4-triazole, which have antioxidant activity, are promising for further study as effective and safe drugs with the possibility of their long-term use without complications of pharmacotherapy.

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