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EVALUATION OF THE ANTIOXIDANT POTENTIAL OF SOME 5-(2-BROMO-4-FLUOROPHENYL)-4-ETHYL-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

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The purpose of the study. The present research explored the molecular docking and antioxidant activity of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol derivatives. These compounds were assessed for their potential as antiradical agents to counter oxidative stress caused by free radicals.

Materials and methods. Molecular docking simulations were conducted to predict the interactions between the synthesized compounds and key amino acid residues of cytochrome c-peroxidase (PDB code: 2X08). The derivatives were prepared in docking-compatible formats to analyze binding energies. In vitro antiradical activity was evaluated using the DPPH assay, measuring the compounds' ability to neutralize free radicals through color changes when DPPH loses its radical properties upon antioxidant interaction. Absorption was measured at 516 nm to quantify radical scavenging activity.

Results and discussion. Molecular docking and in vitro testing showed most derivatives had antioxidant activity. The heptyl-containing compound displayed the highest antioxidant activity, marking it as a strong antiradical agent. Docking analysis confirmed strong interactions with the enzyme's active sites, with compound **2e** achieving the highest binding score, indicating its potential as an antioxidant.

While some discrepancies emerged between DPPH assay results and molecular docking, the findings highlight these derivatives' therapeutic potential against oxidative stress, linked to conditions like cardiovascular and neurodegenerative diseases, and cancer. Further research is recommended to optimize antioxidant efficacy and understand mechanisms of action, potentially leading to new antioxidant agents for medical and pharmaceutical applications against oxidative damage.

Key words: 1,2,4-triazole, antioxidant activity, molecular docking, DPPH.

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ДОСЛІДЖЕННЯ АНТИОКСИДАНТНОГО ПОТЕНЦІАЛУ ДЕЯКИХ ПОХІДНИХ 5-(2-БРОМ-4-ФЛУОРОФЕНІЛ)-4-ЕТИЛ-1,2,4-ТРИАЗОЛ-3-ТІОЛУ

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Досліджено антиоксидантну активність восьми алкільних похідних 5-(2-бром-4-флуорофеніл)-4-етил-1,2,4-триазол-3-тіолу з використанням методу молекулярного докінгу та взаємодії з 2,2-дифеніл-1-пікрилгідразилом (DPPH). За результатами дослідження молекулярний докінг показав, що сполука 3-(2-бром-4-флуорофеніл)-4-етил-5-(пентилтіо)-4H-1,2,4-триазол має більшу енергію взаємодії з ферментом цитохром *c*-пероксидазою (PDB код: 2X08) порівняно з іншими сполуками цього ряду. Водночас під час дослідження антиоксидантної активності методом DPPH встановлено, що сполука 3-(2-бром-4-флуорофеніл)-4-етил-5-(гептилтіо)-4H-1,2,4-триазол продемонструвала найвищий рівень активності. Результати свідчать про потенціал цих сполук як антиоксидантів і обґрунтовують перспективи подальших досліджень.

Ключові слова: 1,2,4-триазол, антиоксидантна активність, молекулярний докінг, DPPH.

Introduction. The study of free radicals and their impact on the human body has become one of the key topics in modern biology and medicine. Free radicals are molecules or fragments of molecules that have an unpaired electron and are therefore highly reactive. They can interact with other molecules in the body, causing chain reactions of oxidation, which can lead to damage to cellular structures, including DNA, proteins, and lipids. Studying the effects of free radicals on the body plays a key role in understanding the mechanisms of aging and the development of various diseases. For example, there is evidence that an excessive amount of free radicals is associated with

the development of cardiovascular disease, cancer, nervous system diseases, and other pathologies. In this regard, the concept of antioxidants has emerged – substances that have the ability to prevent or reduce oxidative stress caused by free radicals. Antioxidants work by neutralizing free radicals, preventing them from damaging the body's cells and tissues. They can be naturally occurring (e.g., vitamins C and E, carotenoids, flavonoids, polyphenols) or synthesized compounds. One of the groups of chemical compounds that attracts the attention of researchers is 1,2,4-triazole derivatives. These compounds have already shown significant biological activity and are promising as antiradical agents. Research in this area is ongoing to further understand their mechanism of action and possible use in medical and pharmaceutical practice [1–4].

The purpose of the work is to study the antioxidant activity of some 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazol-3-thiol derivatives by molecular docking and interaction with 2,2-diphenyl-1-picrylhydrazyl (DPPH), followed by a comparison of the obtained results.

Materials and methods. The study and confirmation of the structures of the compounds were carried out in the scientific laboratories of the Department of Toxicological and Inorganic Chemistry of Zaporizhzhia State Medical and Pharmaceutical University [5] (Fig. 1).

Molecular docking. To perform docking analysis of 3D models of ligands and receptors, we used the AutoDock Tools software package. Information about the structure of the model enzyme cytochrome c-peroxidase (PDB code: 2X08) was taken from the Protein Data Bank (PDB) database. The molecular docking process consisted of three consecutive steps: 1) ligand preparation: creation of structural formulas of compounds in *.mol format (MarvinSketch 6.3. 0); construction of three-dimensional models of substances, which involves the use of the method of molecular mechanics MM+, as well as the semi-empirical quantum mechanical method PM3 in combination with the Polak-Ribiere algorithm, implemented in HyperChem 8 software; fixing molecules in *.pdb format and converting to *.pdbqt (AutoDock Tools-1.5. 6); 2) preparatory measures for active work with the enzyme: – exclusion of components, such as water molecules and ligand, from the model structure (Discovery Studio 4.0); saving the enzyme configuration in *. pdb format; – converting the enzyme structure file in the direction of *.pdb → *.pdbqt (AutoDockTools-1.5.6); 3) molecular docking: direct implementation of the process ("Vina"); visualization analysis and graphical interpretation of the result (Discovery Studio 4.0) [6–8].

Antioxidant activity. Study of an antioxidant activity. An exact weight of the substance (0.1 mM) is placed in a 25.00 ml volumetric flask, dissolved in dimethyl sulfoxide (USA, CAS Number: 67-68-5) and brought to the mark, stirred. 1.00 ml of the resulting solution was placed in a 10.00 ml volumetric flask (0.1 mM), brought to the mark, and stirred. 2.00 ml of the resulting solution is placed in a test tube, treated with 2.00 ml of 0.1 mM DPPH solution in methanol (Sigma-Aldrich, Germany), stirred, and tightly closed. The tubes were shaken vigorously and left for 30 min at room temperature in the dark. The absorbance was measured at 516 nm. The control was a solution of 2.00 ml of 0.1 mM DPPH solution in the presence of 2.00 ml of methanol, and the standard was ascorbic acid 10 μg/ml. The free radical scavenging activity was expressed as a percentage of inhibition and calculated by the formula:

$$AA = \frac{(A_0 - A_1)}{A_0} \cdot 100$$

where

AA – antioxidant activity,%;

A_0 – Absorption coefficient of the control sample;

A_1 – Absorption coefficient of the studied sample.

The absorbance of the studied solutions was measured in aqueous-organic solutions and the maximum absorbance was recorded at 516 nm using a Lambda 365 spectrophotometer [9–13].

Results of the study. The study of antioxidant activity was based on the interaction of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazol-3-thiol **(1e)** and its alkyl derivatives **(2a-2h)** with 2,2-diphenyl-1-picrylhydrazyl (DPPH, CAS Number: 1898-66-4) *in vitro*.

DPPH is a stable free radical. The color of its alcohol solutions is intense purple (λ_{max} = 517 nm). When DPPH interacts with compounds that can scavenge free radicals, colored products are formed: these substances are yellow in color and do not absorb light of the above wavelength.

Molecular docking. To predict the antioxidant activity of the study compounds, newly synthesized S-alkyl deriva-

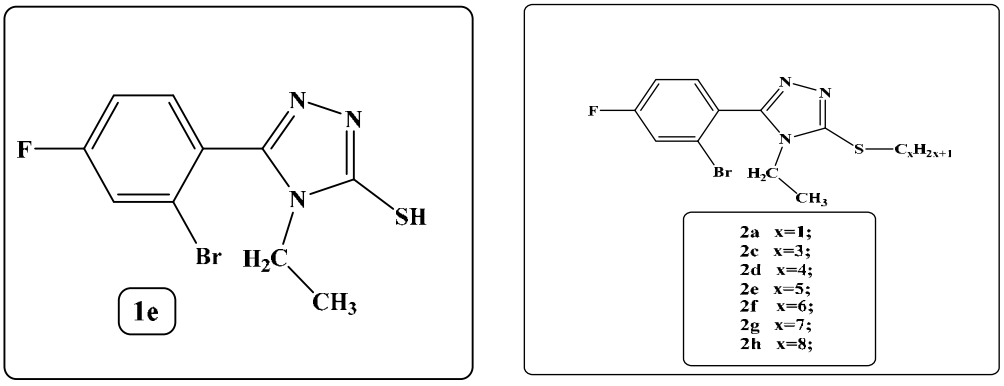

Fig. 1. General structures of the studied 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol (1e) and its alkyl derivatives (2a–2h).

tives, molecular docking with the enzyme cytochrome c-peroxidase (PDB code: 2X08) was performed in comparison with ascorbic acid as a reference ligand. The reference ligand forms four H-bonds with the amino acids His181, Gly41, Val45, and Arg184 for binding to the γ-heme edge of cytochrome c-peroxidase [14–16].

The studied compounds showed higher absolute values of the minimum energy of complexation (2e = -7.7, 2a = -6.9, 1e = -6.7, 2g = -6.5 kcal/mol) compared to the binding energy of ascorbic acid (-5.2 kcal/mol). These results lead to the conclusion that these compounds are stabilized within the binding pocket of cytochrome c-peroxidase (Table 1). In addition, ascorbic acid was stabilized inside the cytochrome c-peroxidase binding pocket by four H-bonds with Lys179, Leu177, Lys179 and Arg184, respectively. Compounds **2e, 2a, 1e,** and **2g** were stabilized in the binding pocket by forming contacts with the following key amino acids (Table 1): first, compound **2a** was bound by two bonds Alkyl, Pi-Alkyl with the amino acids PRO A:44 and ARG A:48. Secondly, by one Pi-Sulfur bond to the amino acid residue of PHE A:191, and also to ALA A:174 by a Carbon Hydrogen Bond. Thirdly, compound **1e** was bound to PHE A:191 by Pi-Sulfur bond, to ALA A:174 by Carbon Hydrogen Bond and to ARG A:48 by Alkyl, Pi-Alkyl bonds, and also by double bonds (Pi-Pi Stacked, Pi-Pi T-shaped) was bound to TRP A:51 and to HIS A:175. Compound **2g** demonstrated the formation of a single bond with ASP A:37, namely Halogen (Fluorine). Pi-Sulfur bonds were also formed with HIS A:175. In addition, Pi-Pi T-shaped interactions are formed with PHE A:191 and Pi-Sigma with amino acid residues of TRP A:51. It is necessary to note the participation of HIS A:181 residues in the Pi-Sigma interaction. The formation of Alkyl, Pi-Alkyl interactions with fragments VAL A:45, ARG A:48, ALA A:174 was also established. Finally, the most promising compound **2e**, formed bonds with TRP A:51 through one Pi-Pi-bond, and ARG A:48 – through one Pi-Alkyl bond. Additionally, Pi-Sulfur interactions were formed with PHE A:191, Pi-Pi Stacked and Pi-Pi T-shaped contacts with HIS A:175, Alkyl, Pi-Alkyl – with HIS A:181 and with PRO A:44, Carbon Hydrogen Bond – with ALA A:174. Receptor interactions in 2D and 3D formats of the prepared ligands with the largest pocket protein (2X08) are shown in Fig. 2.

Antioxidant activity. The antioxidant activity of eight new derivatives of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol was researched in the conducted study. The results showed that the majority of compounds demonstrated a certain level of antioxidant effect, indicating their potential usefulness in protecting cells from the impact of free radicals. This allows us to consider these derivatives as potential antioxidants that could be used in pharmaceutical or cosmetic products to protect the body

Table 1

The results of docking of the studied compounds to the active site of cytochrome c-peroxidase

№	Compound	Interaction energy with the protein active site, kcal/mol	Amino acid residues and the chemical bonds formed with them
1	**2**	**3**	**4**
1.	**1e**	-6.7	TRP A:51 π-π Stacked, π-π T-shaped ALA A:174 C-H Bond ARG A:48 Alkyl, π-Alkyl HIS A:175 π-π Stacked, π-π T-shaped PHE A:191 π-Sulfur
2.	2a	**-6.9**	PHE A:191 π-Sulfur HIS A:175 π-π Stacked, π-π T-shaped ARG A:48 Alkyl, π-Alkyl PRO A:44 Alkyl, π-Alkyl ALA A:174 C-H Bond TRP A:51 π-π Stacked, π-π T-shaped
3.	2c	**-2.6**	HIS A:181 C-H Bond ASP A:37 Halogen (Fluorine) VAL A:45 Alkyl, π-Alkyl PRO A:44 C-H Bond MET A:172 Alkyl, π-Alkyl LEU A:171 Alkyl, π-Alkyl ALA A:174 Alkyl, π-Alkyl HIS A:175 Alkyl, π-Alkyl TRP A:51 Alkyl, π-Alkyl ARG A:48 Alkyl, π-Alkyl
4.	2d	**-2.8**	HIS A:181 C-H Bond ASP A:37 Halogen (Fluorine) PRO A:44 C-H Bond LEU A:171 Alkyl, π-Alkyl PHE A:158 Alkyl, π-Alkyl ALA A:174 Alkyl, π-Alkyl MET A:172 Alkyl, π-Alkyl TRP A:51 Alkyl, π-Alkyl HIS A:175 Alkyl, π-Alkyl ARG A:48 Alkyl, π-Alkyl

Continuation of the table

1	2	3	4
5.	2e	**-7.7**	TRP A:51 π-π Stacked, π-π T-shaped ARG A:48 Alkyl, π-Alkyl PHE A:191 π-Sulfur HIS A:175 π-π Stacked, π-π T-shaped HIS A:181 Alkyl, π-Alkyl PRO A :44 Alkyl, π-Alkyl AALA A :174 C-H Bond
6.	2f	**-2.1**	PRO A:145 Alkyl, π-Alkyl PHE A:191 π-Sulfur HIS A:175 Alkyl, π-Alkyl ARG A:48 Alkyl, π-Alkyl ASP A:37 Halogen (Fluorine) VAL A:45 Alkyl, π-Alkyl HIS A:181 π-σ ARG A:184 π-Cation PRO A:44 Alkyl, π-Alkyl LYS A:179 C-H Bond
7.	2g	**-6.5**	ASP A:37 Halogen (Fluorine) VAL A:45 Alkyl, π-Alkyl HIS A:181 π-σ ARG A:48 Alkyl, π-Alkyl PHE A:191 π-π T-shaped HIS A:175 π-Sulfur PHE A:158 Alkyl, π-Alkyl TRP A:51 π-σ LEU A:171 Alkyl, π-Alkyl ALA A:174 Alkyl, π-Alkyl PRO A:44 C-H Bond
8.	2h	**- 2.7**	ASP A:37 Unfavorable Bump HIS A:181 Halogen (Fluorine) VAL A:45 Alkyl, π-Alkyl PRO A:44 Amide-πStacked PHE A:158 π-σ VAL A:168 Alkyl, π-Alkyl LEU A:171 Alkyl, π-Alkyl MET A:172 Alkyl, π-Alkyl TRP A:51 π-σ ALA A:174 Alkyl, π-Alkyl HIS A:175 Sulfur-x, π-Sulfur ARG A:48 Alkyl, π-Alkyl

from oxidative stress and prevent the development of various diseases. These results suggest further prospects for the study of this series of compounds (Table 2) [17–20].

As a result of the conducted studies on the antioxidant activity of the derivatives of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol, it was established that their effectiveness in this role depends on their structure (Table 2). The most active compound among them was 3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(heptylthio)-4H-1,2,4-triazole, which, at a concentration of 1×10^{-4} M, demonstrated an antioxidant effect of 68.39%.

The presence of the octyl **(2h)** fragment in the structure of the compounds leads to a significant decrease in their antioxidant activity. This highlights the importance of avoiding or limiting the presence of certain chemical groups in the molecule when developing antioxidant compounds. Molecular screening showed certain results for the compounds in the study, indicating their potential antioxidant activity. The most active compound, containing a pentyl fragment **2e** (3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(pentylthio)-4H-1,2,4-triazole) (-7.7 kcal/mol), exhibited the highest level of potential activity compared to ascorbic acid as the reference ligand. At the same time, the antioxidant activity study using the DPPH interaction method revealed that compound **2g** (3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(heptylthio)-4H-1,2,4-triazole), which contains a heptyl fragment, demonstrated the most pronounced antioxidant activity. Thus, some discrepancies can be noted between the results of antioxidant activity screening using molecular docking and the in vitro DPPH interaction study.

The conducted studies allow for the identification of the 2-bromo-4-fluorophenyl and S-alkyl fragments as favorable for the creation of potential compounds with antioxidant activity. At the same time, the number of carbon atoms in the alkyl fragment structure should be 5 or 7, which ensures activity at the level of ascorbic acid.

It should also be noted that according to the DPPH study results, the compound containing the heptyl group **(2g)** demonstrated the highest antioxidant activity – 68.39% inhibition at a concentration of 1×10^{-4} M. This highlights the discrepancy between the docking results and the in vitro analysis, as it was expected that compound **2e** would show

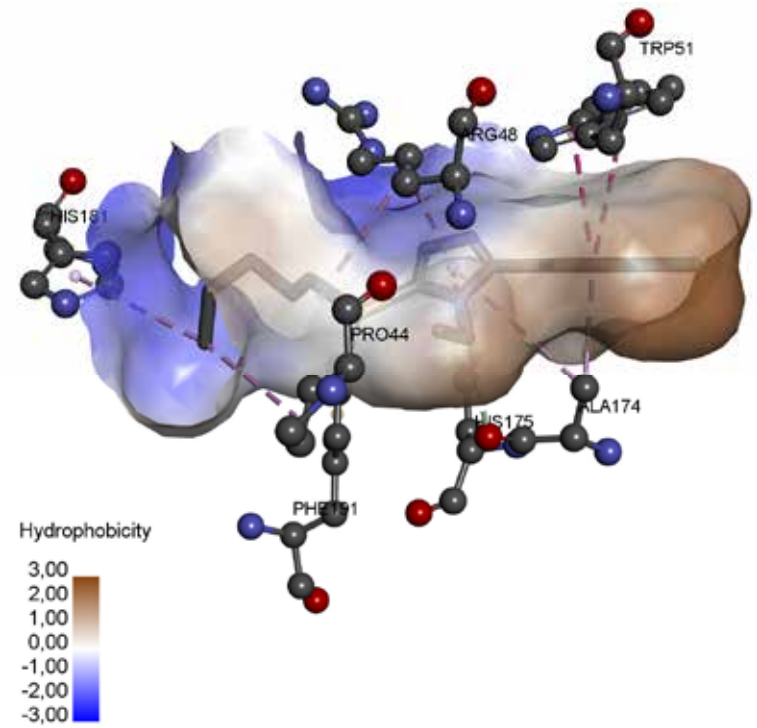

Fig. 2. Visualization of the interactions of the investigated ligand 2e with cytochrome c-peroxidase

Table 2

Results of antioxidant activity (AOA) of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol derivatives (1e–2h) in interaction with DPPH

Substance №	Name	AOA, %
	Ascorbic acid	51.28
1e	5-(2-bromo-4-fluorophenyl)-4-ethyl-4H-1,2,4-triazole-3-thiol	58.40
2a	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(methylthio)-4H-1,2,4-triazole	66.86
2c	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(propylthio)-4H-1,2,4-triazole	34.91
2d	3-(2-bromo-4-fluorophenyl)- 4-ethyl-5-(butylthio) -4H-1,2,4-triazole	59.02
2e	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(pentylthio)-4H-1,2,4-triazole	61.10
2f	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(hexylthio)-4H-1,2,4-triazole	64.67
2g	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(heptylthio)-4H-1,2,4-triazole	68.39
2h	3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(octylthio)-4H-1,2,4-triazole	31.03

better results based on the docking data. This conclusion emphasizes the importance of conducting comparative studies to verify the predicted results of calculations using experimental methods.

Conclusions. The study of certain S-derivatives of 1,2,4-triazole-3-thiol allowed to set the number of compounds with high antioxidant activity. Among the alkyl derivatives of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol, compounds **1e, 2a, 2d, 2e, 2f,** and **2g** should be highlighted, as they exhibit the highest activity at a concentration of 1×10^{-4} M. Among them, the compound **2g**, which contains a heptyl substituent, demonstrated the greatest potential for antioxidant activity. This suggests the potential advantage of such a structural configuration for further research, which may contribute to the development of a biologically active substance with antioxidant properties.

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