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Research Article

Synthesis and antioxidant properties of some new 5-phenethyl-3-thio-1,2,4-triazoles

Tetiana Ihnatova[1], Andriy Kaplaushenko[1], Yuliia Frolova[1], Evheniy Pryhlo[1]

1 *Department of Physical and Colloidal Chemistry, Zaporizhzhia State Medical University, Maiakovskyi avenue 26, Zaporizhzhia, 69035, Ukraine*

Corresponding author: Yuliia Frolova (yuliia_hulina@ukr.net)

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Abstract

Novel derivatives of 4-R-5-phenethyl-4H-1,2,4-triazole-3-thiols were synthesized. The proposed approaches and developed synthetic protocols provided the possibility to design 4-R-5-phenethyl-4H-1,2,4-triazole-3-thiols and their derivatives have been shown. The antioxidant activity of the synthesized compounds was evaluated in vitro by the method of the non-enzymatic initiation of BOD with salts of iron (II). When compared with existing antioxidants, some of our compounds were found to be more potent.

Keywords

1,2,4-triazole, antioxidant activity, synthesis

Introduction

Antioxidants are chemical structures that prevent the oxidation of other chemicals. They protect key cell components by neutralizing the harmful effect of free radicals which are natural products of cell metabolism. Oxidative stress leads to serious cell damage which results in various human diseases such as Alzheimer's disease, Parkinson's disease, atherosclerosis, cancer, arthritis, neurodegenerative disorders, etc. The deficiency of antioxidants in food also leads to oxidative stress, which indicates a lack of antioxidant substances consumed by humans. Therefore, the search of substances that could not only prevent but also increase the resistance of the human body to active forms of oxygen or nitrogen and interfere with the processes of oxidative stress is an important task of medicine and pharmacy (Pruglo 2017).

Extensive research is going on around the world to discover novel molecules to fight various infections and diseases. The demand, therefore, is to synthesize new bioactive molecules that are more effective and have fewer or no side effects (Chand et al. 2018).

Global achievements of scientists are engaged in the 1,2,4-triazole system simulation, studying various properties of the heterocycle and the formation on its base prospective "structures" can create favorable conditions for further search of new molecules with unique properties (Bihdan et al. 2018).

The 1,2,4-triazole and its derivatives to exhibit various pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, antitumoural, cytotoxic, and antioxidant properties (Hulina and Kaplaushenko 2017, 2018; Dixit et al. 2019; İrfan et al. 2019).

Drugs such as itraconazole, loreclezole, voriconazole, letrozole, vorozole, fluconazole, and anastrozole are examples of triazole derivatives.

The analysis of scientific literature data indicates that the creation of new drugs of synthetic origin is based on the chemical substance hetero- and alkyl- cyclic characters.2 Therefore, the introduction into the structure of

5-phenethyl-3-thio-1,2,4-triazole these radicals as substitutes are relevant, have got practical significance and requires further study (Shcherbyna 2019).

Experimental part

Materials and methods

Physical-chemical properties of the synthesized compounds have been investigated according to the methods described in the State Pharmacopeia of Ukraine (The State Pharmacopoeia of Ukraine 2001).

The melting point has been determined by capillary method (2.2.14). The elemental composition of compounds has been set with the help of elemental analyzer Elementar Vario EL cube (CHNS) (standard – Sulfonamide). 1H NMR spectra of obtained compounds has been set with the help of Varian Mercury VX-200 (1H, 200 MHz), solvent – DMSO-d6, internal standard – Tetramethylsilane (TMS). Chromatography-mass spectrometry studies have been conducted on gas-liquid chromatograph Agilent 1260 Infinity HPLC equipped with a mass spectrometer Agilent 6120 (in electrospray ionization (ESI)) (Kazicyna 1979; Sajdov and Sverdlova 1980).

Chemistry

General procedure of synthesis of 4-R-5-phenethyl-4H-1,2,4-triazole-3-thiols (***1–2***). The carboxyl group of hydrocinnamic acid was esterified in butyl alcohol medium with presence of catalytic amount of sulphatic acid. Then butyl ester of hydrocinnamic acid was reacted with hydrazine hydrate to give hydrazide in the alcohol medium. During hydrazide interaction with ethyl or phenyl isothiocyanide in the 1,4-dioxane environment N-ethil-2-(3- phenylpropanoyl)hydrazine-1-carbotioamide or N-phenyl-2-(3-phenylpropanoyl)hydrazine-1-carbotioamide were received respectively. The cyclization of carbotiamids was performed in 2-mol water solution of sodium hydroxide, boiling them for two hours. The obtained compounds were recrystallised from acetic acid (Ignatova et al. 2018a).

4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-thiole (***1***). Yield 50%, m.p.= 143–144 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.31 (t, 3H, CH_3), 2.82–2.88 (t, 4H, $(CH_2)_2$), 4.12 (m, 2H, CH_2), 7.19–7.23 (m, 5H, C_6H_5), 13.05 (s, 1H, SH). Calcd for $C_{12}H_{15}N_3S$ %: C, 61.77; H, 6.48; N, 18.01; S, 13.74. Found %: C, 61.75; H, 6.45; N, 18.05; S, 13.75.

4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-thiole (***2***). Yield 98%, m.p.= 270 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.84–2.89 (t, 4H, $(CH_2)_2$), 7.19–7.23 (m, 5H, C_6H_5), 7.38–7.62 (m, 5H, C_6H_5), 13.15 (s, 1H, SH). Calcd for $C_{16}H_{15}N_3S$ %: C, 68.30; H, 5.37; N, 14.93; S, 11.39. Found %: C, 68.35; H, 5.32; N, 17.96; S, 11.37.

General procedure of synthesis of 2-((4-R-5-phenethyl-4H-1,2,4-triazole-3-yl)thio)nitriles (***3–4***). A mixture of 0.03 mol of 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-tioles (***1–2***) and 0.03 mol of sodium hydroxide in 50 ml of methanol (propanol), was heated to dissolve thiol. 0.03 mol of appropriate halogen nitriles (3-chloropropanenitrile, 2-chlorobenzonitrile), were added to the reaction mixture, and heated to the neutral environment. The primary precipitate of sodium chloride was filtered. After complete cooling the precipitate of 2-((4-R-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)nitriles (***3–4***) was filtered, washed and dried with diethyl ether. The obtained compounds were recrystallised from ethanol (Ignatova et al. 2018a).

3-((4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio) propanenitrile (***3***). Yield 20%, m.p.= 162–163 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.81 (m, 2H, CH_2-CN), 2.82–2.88 (t, 4H, $(CH_2)_2$), 3.30 (t, 2H, S-CH_2), 7.20–7.25 (m, 5H, C_6H_5), 7.40–7.65 (m, 5H, C_6H_5). Calcd for $C_{19}H_{18}N_4S$ %: C, 68.24; H, 5.43; N, 16.75; S, 9.59. Found %: C, 68.28; H, 5.39; N, 16.73; S, 9.60.

2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio) benzonitrile (***4***). Yield 98%, m.p.= 61 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.31 (t, 3H, CH_3), 2.80–2.85 (t, 4H, $(CH_2)_2$), 4.12 (m, 2H, CH_2-CH_3), 7.21–7.26 (m, 5H, C_6H_5), 7.44–7.89 (m, 4H, C_6H_4). Calcd for $C_{19}H_{18}N_4S$ %: C, 68.24; H, 5.43; N, 16.75; S, 9.59. Found %: C, 68.26; H, 5.45; N, 16.77; S, 9.52.

General procedure of synthesis of 2-((4-R-5-phenethyl-4H-1,2,4-triazole-3-yl)thio)acetic(benzoic) acids (***5–6***). To the round-bottom flask under reflux 1 mol of 2-(4-R-5-phenethyl-4*H*-1,2,4-triazole-3-ylthio)nitrile and 2 mol of 25% aqueous sodium hydroxide solution were added. This mixture was boiled until terminated the release of ammonia. After then under cooling, the aqueous solution was acidified with 20% sulfuric acid. The synthesized acids were filtered off, washed with water and recrystallized from ethanol (Ignatova et al. 2019a).

2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio) benzoic acid (***5***). Yield 86%, m.p.= 125–126 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.29 (m, 3H, CH_3); 2.80–4.20 (m, 6H, 3(CH_2)); 7.22–8.26 (m, 10H, 2(C_6H_5)); 12.75 (s, 1H, COOH). Calcd for $C_{19}H_{19}N_3O_2S$ %: C, 64.57; H, 5.42; N, 11.89; S, 9.07. Found %: C, 64.59; H, 5.40; N, 11.90; S, 13,09.

2-((4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio) acetic acid (***6***). Yield 82%, m.p.= 138–140 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.82–4.13 (m, 6H, 3(CH_2)); 7.20–7.75 (m, 10H, 2(C_6H_5)); 12.70 (s, 1H, COOH). Calcd for $C_{18}H_{17}N_3O_2S$ %: C, 63/70; H, 5.05; N, 12.38; S, 9.45. Found %: C, 63.72; H, 5.04; N, 12.39; S, 9.47.

General procedure of synthesis of salts of 2(4)-((4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio)ethanoic acids (***7–8***). 0.01 mol of 2(4)-(((4-phenyl-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)ethanoic acid, 0.01 mol of an alkaline aqueous solution was charged into a round bottom flask. For compound 8 to 0.01 mol of acid was added 50 ml of methyl alcohol and 0.01 mol of methylamine solution. The resulting mixtures were heated to complete dissolution. After cooling, the solvent was evaporated. For further analysis, the synthesized compounds were recrystallized from a 1: 1 mixture of ethanol-water (Ignatova et al. 2019a).

Sodium 2-((4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio)acetate (***7***). Yield 70%, m.p.= 126–128 °C. ^{1}H NMR

(400 MHz, DMSO-d6) d 2.80–4.02 (m, 6H, 3(CH_2)); 7.22–7.65 (m, 10H, (C_6H_5)). Calcd for $C_{18}H_{16}N_3NaO_2S$ %: C, 59.82; H, 4.46; N, 11,63; S, 8.87. Found % N, 11.66; S, 8.84.

Methylammonium 2-((4-phenyl-5-phenethyl-4H-1,2,4-triazol-3-yl)thio)acetate (***8***). Yield 42%, m.p.= 142–143 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.31 (s, 2H, CH_3); 2.84–4.10 (m, 8H, 4(CH_2)); 7.21–7.25 (m, 5H, C_6H_5). Calcd for $C_{19}H_{22}N_4O_2S$ %: C, 61.60; H, 5.99; N, 15.12; S, 8.65. Found %: C, 61.62; H, 6.01; N, 15.15; S, 8.68.

General procedure of synthesis of alkyl 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio)acet(benz)imidates (***9–10***). The mixture of 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio)aceto(benzo) nitrile (0,01 mol), chloroform (10 ml) and absolute alcohol (25 ml) was added into Bunsen flask. It was equipped with calcium chloride tube. The mixture was cooled to the temperature of -5 °C and was saturated with dry hydrogen chloride. The 2 moles excess of dry hydrogen chloride was used for the saturation of 1 mole of 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio) aceto(benzo) nitrile. Then, the mixture was left at 0 ^{0}C for 24 hours and the solvent was evaporated. Target compounds were recrystallized from ethanol for the analysis (Ignatova et al. 2019b).

Propyl 2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl) thio)acetimidate (***9***). Yield 55%, m.p.= 280 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.10–1.40 (m, 6H, CH_3); 1.80 (m, 2H, CH_2); 2.85–2.90 (m, 4H, $(CH_2)_2$); 3.64–4.15 (m, 6H, CH_2); 7.15–7.20 (m, 5H, C_6H_5); 9.30 (s, 1H, NH=C). Calcd for $C_{17}H_{24}N_4OS$ %: C, 61.42; H, 7.28; N, 16.85; S, 9.64. Found %: C, 61.44; H, 7.29; N, 16.85; S, 9.62.

Butyl 2-((4-ethyl-5-phenethyl-4H-1,2,4-triazole-3-yl) thio)benzimidate (***10***). Yield 59%, m.p.= 130–132 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.05–1.35 (m, 6H, CH_3); 1.45–4.20 (m, 10H, CH_2); 7.20–7.45 (m, 4H, C_6H_4); 7.25–7.30 (m, 5H, C_6H_5); 9.45 (s, 1H, NH=C). Calcd for $C_{23}H_{28}N_4OS$ %: C, 67.62; H, 6.91; N, 13.71; S, 7.85. Found %: C, 67.63; H, 6.92; N, 13.72; S, 7.86.

General procedure of synthesis of 3-(heptylthio)-5-phenethyl-4H-1,2,4-triazole (***11***). To a solution of 0.04 mol sodium hydroxide in 80 ml methanol 0.04 mol 5-phenethyl-4*H*-1,2,4-triazole-3-thiole and 0.04 mol of 1-bromoheptane was added, boiled to neutral medium, filtered, the filtrate evaporated to give compound ***11***. For the analysis of compound ***11*** was purified by crystallization from a mixture of ethanol-water 1: 1. Yield 57%, m.p.= 212 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 0.88 (t, 3H, CH_3), 1.26–2.83 (m, 12H, $(CH_2)_6$), 2.85–2.90 (m, 4H, $(CH_2)_2$); 7.18–7.23 (m, 5H, C_6H_5). Calcd for $C_{17}H_{25}N_3S$ %: C, 67.28; H, 8.30; N, 13.85; S, 10.56. Found %: C, 67.29; H, 8.28; N, 13.83; S, 10.60.

General procedure of synthesis of 6-((4-R-5-phenethyl-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines (***12–13***). To the solution of 0.02 mole of 6-(4-R-5-phenethyl-1,2,4-triazole-3-ylthio)pyridine-3-amine in 40 ml of acetic acid, it has been added 0.02 mole of aldehydes. The mixture has been left at room temperature for 6 hours. Then the compounds ***12–14*** have been filtered, washed with ether and dried. In addition, new compounds are soluble in organic solvents, but slightly soluble in water. Compounds ***12–14*** have been recrystallized from ethanol-water (1:1) medium (Ignatova et al. 2018b).

6-((4-phenyl-5-phenethyl-4H-1,2,4-triazole-3-yl)thio) pyridin-3-ylethanimine (***12***). Yield 79%, m.p.= 114–115 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 0.87 (d, 3H, CH_3), 2.85–2.90 (m, 4H, $(CH_2)_2$); 7.15–7.20 (m, 5H, C_6H_5); 7.38–7.62 (m, 5H, C_6H_5); 7.50–8.09 (m, 3H, pyridine). Calcd for $C_{23}H_{21}N_5S$ %: C, 69.15; H, 5.30; N, 17.53; S, 8.02. Found %: C, 69.14; H, 5.31; N, 17.52; S, 8.03.

6-((4-ethyl-5-phenethyl-4H-1,2,4-triazoel-3-yl)thio)pyridin-3-yl-1-(3-methoxyphenyl)methanimine (***13***). Yield 75%, m.p.= 128–129 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.31 (t, 3H, CH_2-CH_3), 2.83–2.88 (m, 4H, $(CH_2)_2$); 3.77 (s, 3H, O-CH_3), 7.18–7.26 (m, 5H, C_6H_5); 7.30–7.44 (m, 4H, C_6H_4), 7.48–8.05 (m, 3H, pyridine), 8.71 (s, 1H, N=CH). Calcd for $C_{25}H_{25}N_5OS$ %: C, 67.70; H, 5.68; N, 15.79; S, 7.23. Found %: C, 67.72; H, 5.69; N, 15.78; S, 7.24.

Antioxidant activity

The method of evaluation of AOA was used in the non-enzymatic initiation of BOD with salts of iron (II). The egg lipoprotein suspension (ELS) was used as the substrate. ELS was prepared by homogenizing egg yolk with phosphate buffer (pH = 7.4). To the suspension was added the test compounds at a concentration of 10–3 mol / l. The free radical oxidation reaction is initiated by the addition of $FeSO_4 \times 7H_2O$ solution. The mixture was incubated for 60 min at 37 °C. The reaction was stopped with a 20% solution of trichloroacetic acid with trilon B. After centrifugation for 30 min. a solution of thiobarbituric acid (TBA) was added to the supernatant and boiled in a water bath for 60 minutes. The colored complex of TBA-active products (TBA-AP) is extracted with the addition of n-butanol. Spectrophotometry determines the concentration of TBK-AP. Antioxidant activity (in percent) is determined by the formula:

$$AOA = \frac{E_0 - E_1}{E_0} * 100\%$$

where AOA – antioxidant activity, %

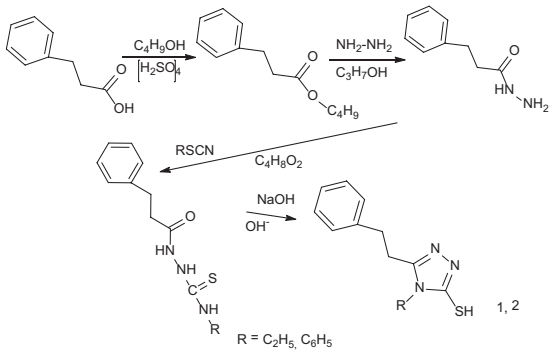
E_0 – the optical density of the control solution;

E_1 – the optical density of a solution containing the test compound (vitamin C)

Results and discussion

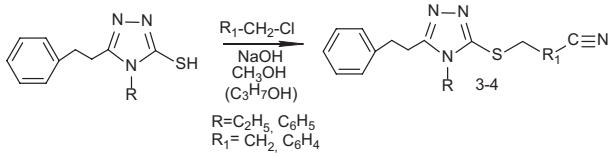
Chemistry

On the first stage the 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols (***1–2***) were received. For synthesized of 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols at first was esterified butyl ester of hydrocinnamic acid, then with hydrazine hydrate was given hydrazide 3-phenylpropanoate. Further was received carbothioamides and in the last step was gotten 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols (**Scheme 1**).



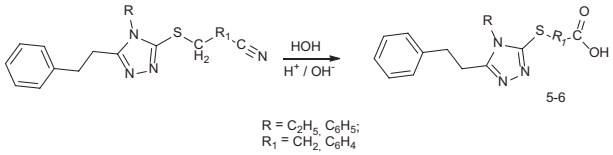
Scheme 1. Synthesis of 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols.

2-((4-R-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio) nitriles (***3–4***) were received by adding appropriate halogen nitriles (3-chloropropanenitrile, 2-chlorobenzonitrile) to 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols (***1–2***) in alkaline-alcohol environment (**Scheme 2**).



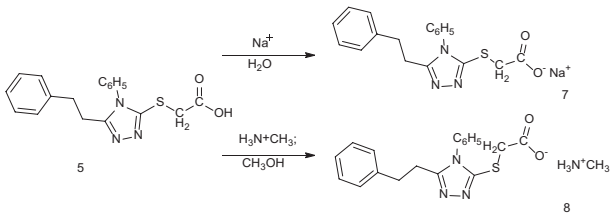
Scheme 2. Synthesis of 2-((4-R-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)nitriles.

On the next stage 2-((4-R-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)acetic(benzoic) acids (***5–6***) were received with 2-(4-R-5-phenethyl-4*H*-1,2,4-triazole-3-ylthio) nitriles and sulfuric acid (**Scheme 3**).



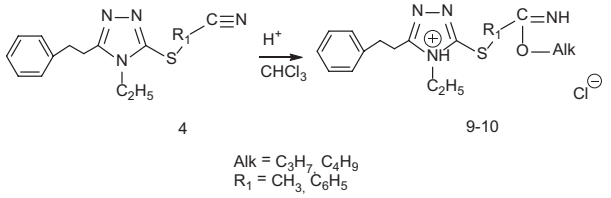
Scheme 3. Synthesis of 2-((4-R-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)acetic(benzoic) acids.

Salts of 2(4)-((4-phenyl-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)ethanoic acids (***7–8***) were obtained by the interaction of 2(4)-(((4-phenyl-5-phenethyl-4*H*-1,2,4-triazole-3-yl) thio)ethanoic acid (***5***) with salt of Na^+ in an alkaline medium or with methylamine in an alcohol medium (**Scheme 4**).



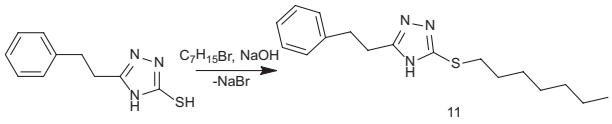
Scheme 4. Synthesis of salts of 2-(4-)((4-phenyl-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio)ethanoic acids.

As starting materials for synthesis of alkyl 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio)acet(benz)imidates (***9–10***), the corresponding 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio)aceto(benzo)nitriles have been used. Synthesis has been set in the absolute alcohol medium (propanol or butanol alcohol) with chloroform, using the saturation with dry hydrogen chloride (**Scheme 5**).



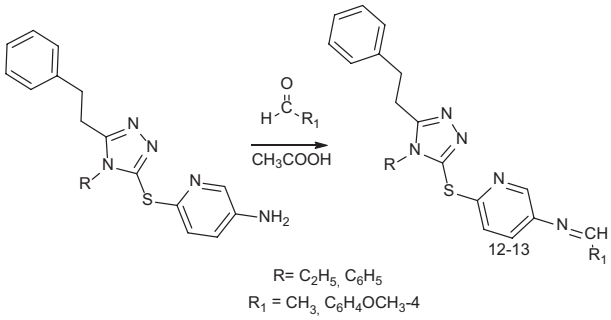
Scheme 5. Synthesis of alkyl 2-((4-ethyl-5-phenethyl-1,2,4-triazole-3-yl)thio)acet(benz)imidates.

3-(heptylthio)-5-phenethyl-4*H*-1,2,4-triazole (***11***) was gotten from 5-phenethyl-4*H*-1,2,4-triazole-3-thiole and 1-bromoheptane in the sodium hydroxide medium (**Scheme 6**).



Scheme 6. Synthesis of 3-(heptylthio)-5-phenethyl-4*H*-1,2,4-triazole.

6-((4-R-5-phenethyl-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines (***12–13***) have been obtained by mixture from 6-(4-R-5-phenethyl-1,2,4-triazole-3-ylthio)pyridine-3-amine and aldehydes. Synthesis has been carried out in the acetic acid medium. The mixture has been left at room temperature for 6 hours (**Scheme 7**).



Scheme 7. Synthesis of 6-((4-R-5-phenethyl-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines.

Antioxidant activity

The results of the determination of AOA obtained in the experiment 1,2,4-triazole derivatives in model experiments under conditions Fe^{2+}-induced POL are presented in Table 1, from which can be seen: of the 13 compounds

Table 1. Antioxidant activity of 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols on their derivatives *in vitro* at non-enzymatic initiation of VRO.

Compound	Optical density (λ = 232 нм) M ± m (n = 7)	AOA, %
Control	0.6731±0.004	0
Vitamin C	0.4485±0.0018	33,41
1	0.4515±0.0139	33,06
2	0.6464±0.0108	-2,48
3	0.584±0.0141	5,02
4	0.6405±0.011	2,49
5	0.5209±0.0134	32,53
8	0.4806±0.0174	38,79
13	0.5005±0.015	26,5
Control	0.6891±0.0058	0
Vitamin C	0.4447±0.0015	34,77
6	0.523±0.013	19,56
7	0.5248±0.0111	22,43
9	0.581±0.008	20,41
10	0.4405±0.016	32,4
11	0.5115±0.0117	27,04
12	0.5105±0.0095	22,63

tested 4 in varying degrees of expression capable of inhibiting the generation of free radicals.

Moderate antioxidant activity among the studied of 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols possessed in compounds 3, 4, 13, 6, 7, 9, 11, 12 which reduced the level TBC – AP by 2.49–27.04% ($p < 0.001$).

Compounds 1, 5, 10 had high AOA, which reduced the TBC-AP content by 32.40 -33.06 % ($p < 0.001$).

The most pronounced AOA had methylammonium 2-((4-phenyl-5-phenethyl-4*H*-1,2,4-triazole-3-yl)thio) acetate (8), which reduced the TBC-AP content by 38.79% ($p < 0.001$) and which exceeds the ascorbic reference drug by this ability acid by 5.38%.

Conclusions

A series of novel 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols derivatives, possessing antioxidant activity, was prepared. We have shown that the proposed approaches and developed synthetic protocols provided the possibility to design 4-R-5-phenethyl-4*H*-1,2,4-triazole-3-thiols and their derivatives. The pharmacological screening allowed the identification of only one lead compound whose antioxidant activity exceeded that for ascorbic acid. Further optimization of the structure to improve their activities is currently in progress.

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