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Research Article

Synthesis and antioxidant properties of new (2,4- and 3,4-dimethoxyphenyl)-1,2,4-triazoles

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Abstract

The purpose of the work is to develop preparative methods for the synthesis of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles, to investigate the reaction of acid hydrolysis, to receive the physical-chemical properties of the synthesized compounds, and to study antioxidant activity of new compounds. Preparative methods for the synthesis of (5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles have been developed for which studied the reaction of acid hydrolysis, resulting in the production of carboxylic acids. The structure of the obtained substances was confirmed by modern physical-chemical methods. 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).

Keywords

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

Introduction

In the 21st century, pharmacy is very popular and advanced science all over the world. There are many medicines with different pharmacological activities, but not even enough. Therefore, the search, synthesis, and implementation of new drugs with a wide range of biological activity and low toxicity is currently an urgent task of pharmacy.

Analysis of the current literature (Kaplaushenko 2008, 2013, 2015; Samelyuk and Kaplaushenko 2014, 2015; Kaplaushenko et al. 2016; Samelyuk 2016; Hulina and Kaplaushenko 2018; Sahu et al. 2018; Safonov 2020) indicates the prospect of finding biologically active substances among 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetonitriles. The works of ZSMU scientific school based on dissertations (Kaplaushenko 2008; Samelyuk 2016) and articles (Kaplaushenko 2013; Hulina and Kaplaushenko 2018) show that the discussed class of compounds serves as a basis for the creation of potential original drugs, with some already being actively used in medicine.

It is impossible to neglect the work of domestic authors (Samelyuk and Kaplaushenko 2014, 2015; Kaplaushenko et al. 2016; Sahu et al. 2018; Shcherbyna et al. 2019; Safonov 2020), which presents the results of the pharmacological activity of 5-R-1,2,4-triazole-3-ylthiol. But the pharmacological activity in a number of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles has not been sufficiently studied. Therefore, synthesis, study of physical-chemical and biological properties of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano- , benzo)nitriles are scientific novelty, theoretical and practical importance.

To obtain ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-,

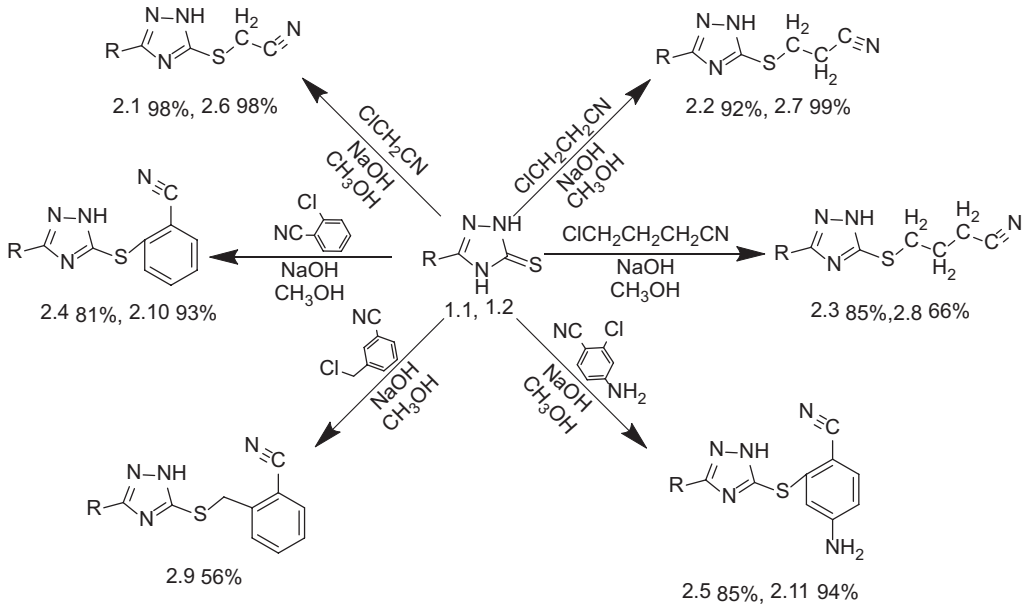

Figure 1. Scheme of the synthesis of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles (compounds 2.1–2.11).

benzo)nitriles (compounds 2.1–2.11, Fig. 1) the interaction between the corresponding halogennitriles (chloroacetonitrile, 3-chloropropanonitrile, 4-chlorobutanonitrile, 2-chlorobenzonitrile, 4-amino-2-chlorobenzonitrile, 3-(chloromethyl)benzonitrile) with 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione (compounds 1.1, 1.2, Fig. 1) in an alkaline alcohol medium were used.

The synthesized nitriles (2.1–2.11) (Table 1) are crystalline substances of yellow (2.1, 2.7, 2.11), white (2.2, 2.10), orange (2.3, 2.9), brown (2.4, 2.5, 2.8), black (2.6) colors, slightly soluble in water, soluble in alkaline solutions, as well as in organic solvents and mineral acids. For the analysis substances (2.1–2.11) were recrystallized from ethanol.

It is known that hydrolysis of nitriles can be performed by two methods: alkaline and acid hydrolysis. Considering the work of scientists (Kaplaushenko 2013; Samelyuk and Kaplaushenko 2015; Shcherbyna 2019), it can be concluded that in acid hydrolysis the target product is obtained with a higher percentage of yield. Therefore, we subsequently studied the reaction of acid hydrolysis for aceto(propano-, benzo)nitriles, resulting in acid.

The preparation of this class of compounds was carried out by the interaction of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, benzo) nitriles (compounds 2.1 , 2.7, 2.10, Fig. 2) with acid chloride, water was used as a solvent.

The obtained 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetate(propanoic, benzoic)acids (Table 1) are brown (2.12), orange (2.13), or white (2.14) crystalline substances, soluble in water (heated), in alkali metal, and in organic solvents. For the analysis acids (2.12–2.14) were recrystallized from propanol-water 2:1.

Table 1. Prediction of acute toxicity of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles using GUSAR-online prognosis.

Number compounds	Rat IP LD_{50} (mg/kg)	Rat IV LD_{50} (mg/kg)	Rat Oral LD_{50} (mg/kg)	Rat SC LD_{50} (mg/kg)
2.1	384,700 in AD	187,200 in AD	1420,000 out of AD	733,300 in AD
2.2	384,400 in AD	209,300 in AD	1650,000 out of AD	632,800 out of AD
2.3	409,900 out of AD	216,400 in AD	978,800 in AD	941,500 out of AD
2.4	446,300 in AD	164,800 in AD	1722,000 in AD	1742,000 out of AD
2.5	540,800 in AD	233,800 in AD	787,700 in AD	708,900 out of AD
2.6	259,800 in AD	166,200 in AD	348,100 in AD	636,400 in AD
2.7	391,000 out of AD	188,100 in AD	1348,000 out of AD	1377,000 in AD
2.8	398,000 out of AD	199,600 in AD	1701,000 out of AD	1544,000 out of AD
2.9	865,000 in AD	124,200 in AD	1195,000 in AD	2341,000 in AD
2.10	684,900 in AD	138,200 in AD	1268,000 in AD	1464,000 in AD
2.11	574,400 in AD	195,400 in AD	1000,000 in AD	1654,000 out of AD
2.12	840,300 in AD	335,800 in AD	1458,000 in AD	1929,000 in AD
2.13	273,000 in AD	398,800 in AD	1014,000 in AD	586,000 in AD
2.14	455,400 in AD	340,500 in AD	1235,000 in AD	1043,000 in AD

Toxicity

At the first stage of the study of biological activity of the derivatives of 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione the acute prediction of toxicity was performed with the program GUSAR-online. It was done to weed out potentially toxic substances as unpromising objects experimental pharmacological screening. Computer prediction of acute toxicity of the derivatives of 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione were carried out according to structural formulas compounds in the online version of GUSAR-online.

The on-line prognosis was performed for 14 compounds derived from 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione.

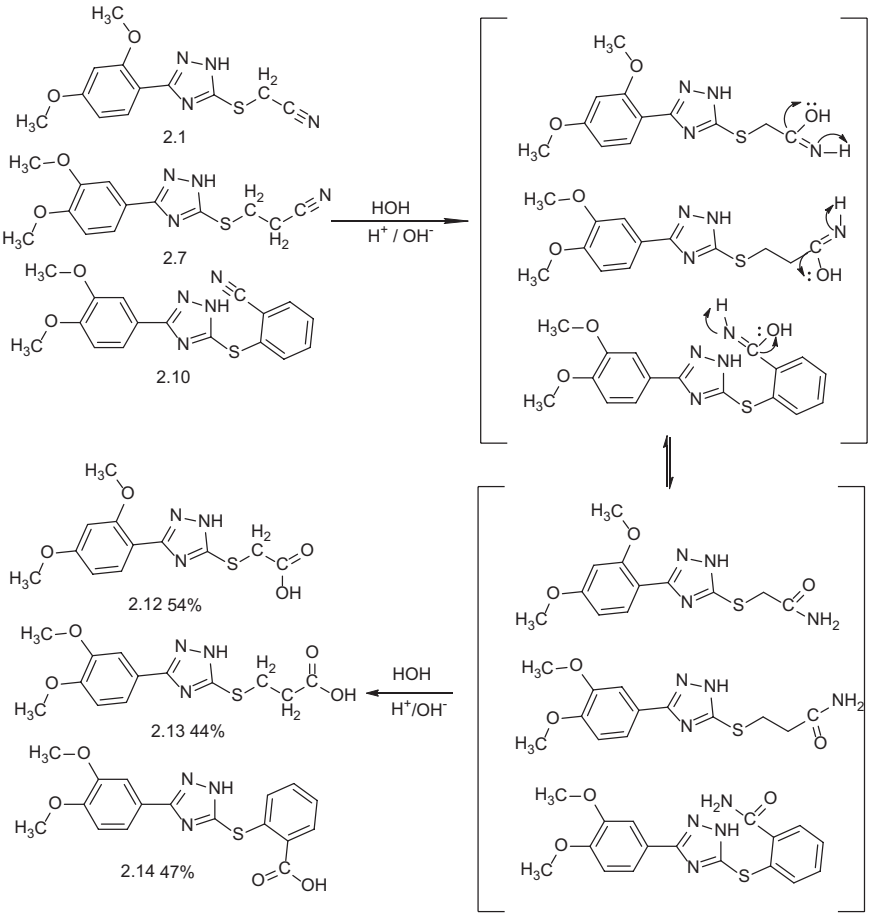

Figure 2. Scheme of the synthesis of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propanoic, benzoic) acids (compounds 2.12–2.14).

Antioxidant activity

The method of evaluation of AOA was used in the non-enzymatic initiation of BOD with salts of iron (II) (Pruglo 2017).

It has been chosen this method because it was the most accessible. With this method, antioxidant activity can be determined without animals. Also, the method of evaluation of AOA has made it possible to predict antihypoxic and antiischemic activity. For such drugs as Trifuzol, Avestim, Thiotriazolin, Thiometrizol, and many others, this research method was also used (Bushueva et al. 2017).

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:

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

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).

((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles (compounds 2.1–2.11)

A mixture of 0.03 mol of 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione (compounds 1.1–1.2) and 0.03 mol of sodium hydroxide solution in 50 ml of methanol, which was heated to complete dissolution of the corresponding thione (1.1, 1.2), 0.03 mol of the corresponding halogennitrile (chloroacetonitrile, 3-chloropropanitrile, 4-chlorobutanonitrile, 2-chlorobenzonitrile, 4-amino-2-chlorobenzonitrile, 3-chlorobenzonitrile) were added to the reaction mixture and were heated to a neutral medium.

The primary precipitate which had been formed of sodium chloride was filtered off. After complete cooling ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl) thio)aceto(propano-, butano-, benzo)nitriles (compounds 2.1–2.11) were filtered off, washed with diethyl ether and dried.

2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)acetonitrile (2.1). Yield 98%, m.p.= 153–155 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1573 cm^{-1}; $V_{C\equiv N}$ = 2247 cm^{-1}; $V_{O\text{-}CH_3}$ = 2817 cm^{-1}; $V_{CH_2}^{s/as}$ = 2843/2920 cm^{-1}; V_{Ar} = 1485 cm^{-1}; $V_{C\text{-}S}$ = 634 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 2.60–3.70 (2H, s, S-CH_2); 3.82–3.89 (6H, d, O-CH_3); 4.21(1H, s, CH); 6.67–7.83(3H, m, C_6H_3). Calcd for $C_{12}H_{12}N_4O_2S$ %: C, 52.16; H, 4.38; N, 20.28; S, 11.60. Found %: C, 52.17; H, 4.39; N, 20.27; S, 11.59. m \ z + (+1 amp) 276,31.

3-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)propanenitrile (2.2). Yield 92%, m.p.= 133–135 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1505 cm^{-1}; $V_{C\equiv N}$ = 2270 cm^{-1}; $V_{O\text{-}CH_3}$ = 2825 cm^{-1}; $V_{CH_2}^{s/as}$ = 2862/2935 cm^{-1}; V_{Ar} = 1497 cm^{-1}; $V_{C\text{-}S}$ = 622 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 2.78 (2H, m, CH_2-CH_2); 3.70 (2H, s, S-CH_2); 3.83–3.90 (6H, d, O-CH_3); 4.20(1H, s, CH); 6.67–7.49(3H, m, C_6H_3). Calcd for $C_{13}H_{14}N_4O_2S$ %: C, 53.78; H, 4.86; N, 19.30; S, 11.04. Found %: C, 53.79; H, 4.85; N, 19.29; S, 11.05. m \ z + (+1 amp) 290,34.

4-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)butanenitrile (2.3). Yield 85%, m.p.= 123–125 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1596 cm^{-1}; $V_{C\equiv N}$ = 2210 cm^{-1}; $V_{O\text{-}CH_3}$ = 2827 cm^{-1}; $V_{CH_2}^{s/as}$ = 2867/2922 cm^{-1}; V_{Ar} = 1512 cm^{-1}; $V_{C\text{–}S}$ = 583 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 1.85–2.76 (4H, m, CH_2-CH_2); 2.60–3.70 (2H, s, S-CH_2); 3.84–3.90 (6H, d, O-CH_3); 4.20(1H, s, CH); 6.67–7.81(3H, m, C_6H_3). Calcd for $C_{14}H_{16}N_4O_2S$ %: C, 55.25; H, 5.30; N, 18.41; S, 10.53. Found %: C, 55.27; H, 5.32; N, 18.39; S, 10.51. m \ z + (+1 amp) 304,37.

2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)benzonitrile (2.4). Yield 81%, m.p.= 95–97 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1530 cm^{-1}; $V_{C\equiv N}$ = 2249 cm^{-1}; $V_{O\text{-}CH_3}$ = 2825 cm^{-1}; $V_{CH_2}^{s/as}$ = 2848/2926 cm^{-1}; V_{Ar} = 1501 cm^{-1}; $V_{C\text{–}S}$ = 678 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.83–3.89 (6H, d, O-CH_3); 4.15(1H, s, CH); 6.67–7.81(3H, m, C_6H_3); 7.42–7.95(4H, m, C_6H_4). Calcd for $C_{17}H_{14}N_4O_2S$ %: C, 60.34; H, 4.17; N, 16.56; S, 9.47. Found %: C, 60.35; H, 4.16; N, 16.55; S, 9.48. m \ z + (+1 amp) 338,39.

4-amino-2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)benzonitrile (2.5). Yield 85%, m.p.= 115–117 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1579 cm^{-1}; $V_{C\equiv N}$ = 2263 cm^{-1}; $V_{O\text{-}CH_3}$ = 2821 cm^{-1}; $V_{CH_2}^{s/as}$ = 2856/2919 cm^{-1}; V_{Ar} = 1514 cm^{-1}; $V_{C\text{–}S}$ = 608 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.80–3.85 (6H, d, O-CH_3); 4.17(1H, s, CH); 5.29 (2H, s, NH_2); 6.68–7.81(3H, m, C_6H_3); 7.42–7.95(3H, m, C_6H_3). Calcd for $C_{17}H_{15}N_5O_2S$ %: C, 57.78; H, 4.28; N, 19.82; S, 9.07. Found %: C, 57.80; H, 4.30; N, 19.80; S, 9.05. m \ z + (+1 amp) 353,40.

2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)acetonitrile (2.6). Yield 98%, m.p.= 173–175 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1522 cm^{-1}; $V_{C\equiv N}$ = 2235 cm^{-1}; $V_{O\text{-}CH_3}$ = 2815 cm^{-1}; $V_{CH_2}^{s/as}$ = 2847/2923 cm^{-1}; V_{Ar} = 1482 cm^{-1}; $V_{C\text{–}S}$ = 665 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 2.60–3.56 (2H, s, S-CH_2); 3.82–3.84 (6H, d, O-CH_3); 4.18(1H, s, CH); 6.93–7.45(3H, m, C_6H_3). Calcd for $C_{12}H_{12}N_4O_2S$ %: C, 52.16; H, 4.38; N, 20.28; S, 11.60. Found %: C, 52.14; H, 4.36; N, 20.30; S, 11.62. m \ z + (+1 amp) 338,39. m \ z + (+1 amp) 276,31.

3-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)propanenitrile (2.7). Yield 99%, m.p.= 176–178 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1537 cm^{-1}; $V_{C\equiv N}$ = 2236 cm^{-1}; $V_{O\text{-}CH_3}$ = 2827 cm^{-1}; $V_{CH_2}^{s/as}$ = 2863/2930 cm^{-1}; V_{Ar} = 1587 cm^{-1}; $V_{C\text{–}S}$ = 679 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 2.78 (2H, m, CH_2-CH_2); 2.81 (2H, s, S-CH_2); 3.83–3.85 (6H, d, O-CH_3); 4.20(1H, s, CH); 6.98–7.49(3H, m, C_6H_3). Calcd for $C_{13}H_{14}N_4O_2S$ %: C, 53.78; H, 4.86; N, 19.30; S, 11.04. Found %: C, 53.80; H, 4.84; N, 19.29; S, 11.05. m \ z + (+1 amp) 290,34.

4-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)butanenitrile (2.8). Yield 66%, m.p.= 97–99 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1512 cm^{-1}; $V_{C\equiv N}$ = 2243 cm^{-1}; $V_{O\text{-}CH_3}$ = 2824 cm^{-1}; $V_{CH_2}^{s/as}$ = 2845/2943 cm^{-1}; V_{Ar} = 1488 cm^{-1}; $V_{C\text{–}S}$ = 657 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 1.87–2.78 (4H, m, CH_2-CH_2); 2.83 (2H, s, S-CH_2); 3.84–3.86 (6H, d, O-CH_3); 4.22(1H, s, CH); 6.97–7.47(3H, m, C_6H_3). Calcd for $C_{14}H_{16}N_4O_2S$ %: C, 55.25; H, 5.30; N, 18.41; S, 10.53. Found %: C, 55.26; H, 5.31; N, 18.40; S, 10.52. m \ z + (+1 amp) 304,37.

2-(((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)methyl)benzonitrile (2.9). Yield 56%, m.p.= 112–114 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1555 cm^{-1}; $V_{C\equiv N}$ = 2231 cm^{-1}; $V_{O\text{-}CH_3}$ = 2811 cm^{-1}; $V_{CH_2}^{s/as}$ = 2840/2942 cm^{-1}; V_{Ar} = 1505 cm^{-1}; $V_{C\text{–}S}$ = 640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.70 (2H, s, S-CH_2); 3.83–3.85 (6H, d, O-CH_3); 4.20(1H, s, CH); 6.98–7.49(3H, m, C_6H_3); 7.34–7.55(4H, m, C_6H_4). Calcd for $C_{18}H_{16}N_4O_2S$ %: C, 61.35; H, 4.58; N, 15.90; S, 9.10. Found %: C, 61.37; H, 4.60; N, 15.88; S, 9.08. m \ z + (+1 amp) 338,39.

2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)benzonitrile (2.10). Yield 93%, m.p.= 93–95 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1538 cm^{-1}; $V_{C\equiv N}$ = 2247 cm^{-1}; $V_{O\text{-}CH_3}$ = 2816 cm^{-1}; $V_{CH_2}^{s/as}$ = 2863/2928 cm^{-1}; V_{Ar} = 1503 cm^{-1}; $V_{C\text{–}S}$ = 701 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.87–3.89 (6H, d, O-CH_3); 4.15(1H, s, CH); 6.67–7.95(4H, m, C_6H_4); 6.91–7.42(3H, m, C_6H_3). Calcd for $C_{17}H_{14}N_4O_2S$ %: C, 60.34; H, 4.17; N, 16.56; S, 9.47. Found %: C, 60.32; H, 4.15; N, 16.58; S, 9.49. m \ z + (+1 amp) 352,41.

4-amino-2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)benzonitrile (2.11). Yield 94%, m.p.= 121–123 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1509 cm^{-1}; $V_{C\equiv N}$ = 2252 cm^{-1}; $V_{O\text{-}CH_3}$ = 2828 cm^{-1}; $V_{CH_2}^{s/as}$ = 2861/2917 cm^{-1}; V_{Ar} = 1511 cm^{-1}; $V_{C\text{–}S}$ = 597 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.81–3.83 (6H, d, O-CH_3); 4.13(1H, s, CH); 5.28 (2H, s, NH_2); 6.37–7.54(3H, m, C_6H_3); 6.98–7.49(3H, m, C_6H_3). Calcd for $C_{17}H_{15}N_5O_2S$ %: C, 57.78; H, 4.28; N, 19.82; S, 9.07. Found %: C, 57.77; H, 4.29; N, 19.83; S, 9.06. m \ z + (+1 amp) 353,40.

((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)aceto(propanoic, benzoic)acid (compounds 2.12–2.14)

1 Mol of the corresponding nitrile (2.1, 2.7, 2.10), 65 ml of concentrated chloride acid were loaded into a glass of 250 ml and left at room temperature for 5 days for dissolved. Then 200 ml of water were added. The precipitates of the synthesized compounds were filtered off and air-dried.

2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)acetic acid (2.12). Yield 82%, m.p.= 143–145 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1600 cm^{-1}; V_{CH_3COOH} = 1698 cm^{-1}; $V_{O\text{-}CH_3}$ = 2821 cm^{-1}; $V_{CH_2}^{s/as}$ = 2843/2929 cm^{-1}; V_{Ar} = 1614 cm^{-1}; V_{C-S} = 637 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.38 (2H, s, S-CH_2); 3.83–3.90 (6H, d, O-CH_3); 4.22(1H, s, CH); 6.76–7.49(3H, m, C_6H_3); 12.34(1H, s, COOH). Calcd for $C_{12}H_{13}N_3O_4S$ %: C, 48.81; H, 4.44; N, 14.23; S, 10.86. Found %: C, 48.82; H, 4.45; N, 14.21; S, 10.86. m \ z + (+1 amp) 295,31.

3-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)propanoic acid (2.13). Yield 44%, m.p.= 183–185 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1588 cm^{-1}; V_{CH_3COOH} = 1760 cm^{-1}; $V_{O\text{-}CH_3}$ = 2827 cm^{-1}; $V_{CH_2}^{s/as}$ = 2848/2937 cm^{-1}; V_{Ar} = 1605 cm^{-1}; V_{C-S} = 659 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 2.60 (2H, m, CH_2-CH_2); 2.71 (2H, s, S-CH_2); 3.83–3.85 (6H, d, O-CH_3); 4.20(1H, s, CH); 6.98–7.49(3H, m, C_6H_3); 12.17(1H, s, COOH). Calcd for $C_{13}H_{15}N_3O_4S$ %: C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found %: C, 50.47; H, 4.88; N, 13.60; S, 10.36. m \ z + (+1 amp) 309,34.

2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl) thio)benzoic acid (2.14). Yield 47%, m.p.= 187–189 °C. Adsorption maxima in IR-spectra $V_{C=N\ cycle}$ = 1593 cm^{-1}; V_{CH_3COOH} = 1741 cm^{-1}; $V_{O\text{-}CH_3}$ = 2818 cm^{-1}; $V_{CH_2}^{s/as}$ = 2867/2922 cm^{-1}; V_{Ar} = 1608 cm^{-1}; V_{C-S} = 692 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6) d 3.85–3.87 (6H, d, O-CH_3); 4.15(1H, s, CH); 6.98–7.49(3H, m, C_6H_3); 7.69–8.30(4H, m, C_6H_4); 12.75(1H, s, COOH). Calcd for $C_{17}H_{15}N_3O_4S$ %: C, 57.13; H, 4.23; N, 11.76; S, 8.97. Found %: C, 57.15; H, 4.25; N, 11.74; S, 8.95. m \ z + (+1 amp) 357,38.

In the IR spectra of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles (compounds 2.1–2.11) there are absorption bands of vibrations of nitrile groups C=N at 2270–2210 cm^{-1}, scissor strips at 2870–2840 and at 2950–2915 cm^{-1}, methylene groups, as well as the bands inherent in aromatics and C = N-groups in the range of 1530–1505 and 1596–1550 cm^{-1} (Fig. 3).

Absorption bands in the IR spectra of all synthesized acids (2.12–2.14) can be caused by the presence of –C=N-groups at 1600–1588 cm^{-1}, absorption bands of the aromatic ring at 1614–1605 cm^{-1}, in the IR spectra of acids there are CH_2-COOH groups at 1760–1698 cm^{-1} (Kazitsyna 1979).

^{1}H NMR spectra of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles (compounds 2.1–2.11) were characterized by the presence of multiplet signals of aromatic

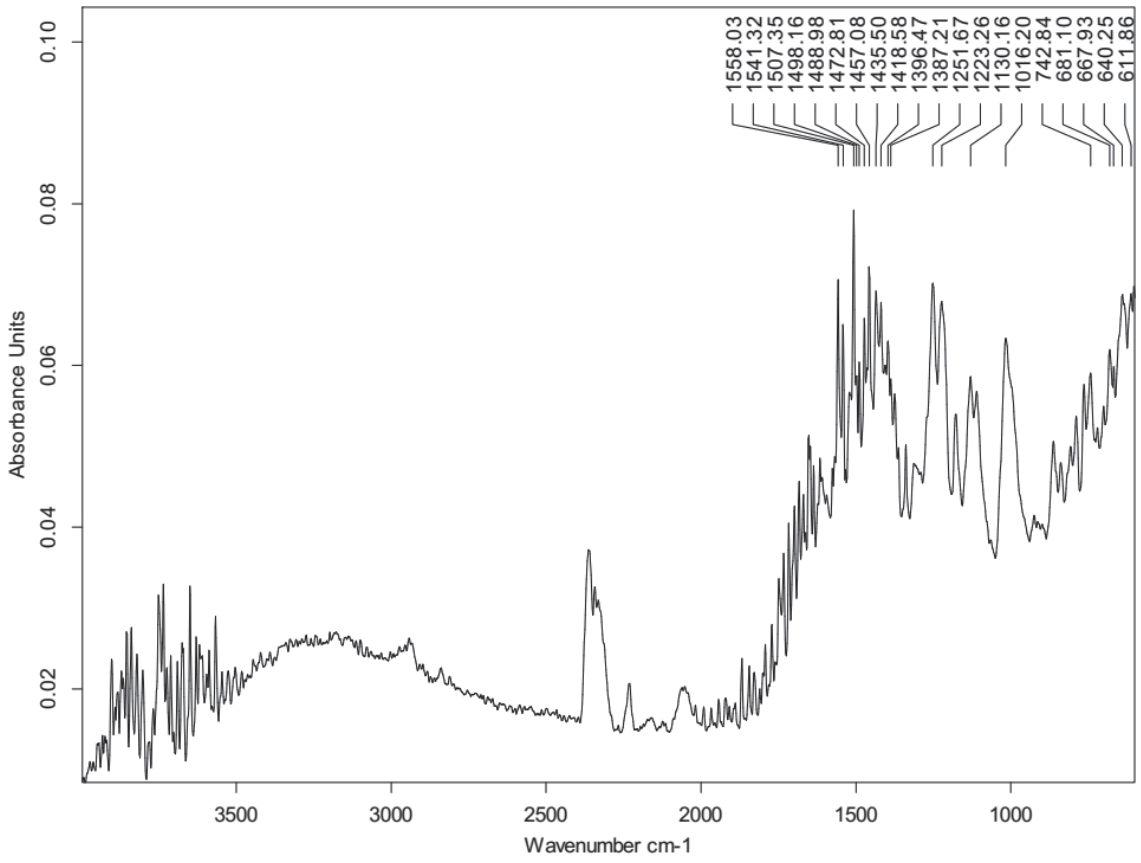

Figure 3. IR spectra of 2-(((5-(3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)methyl)benzonitrile (2.9).

protons at 6.67–7.95 ppm, duplicate signals of protons of methoxy groups at 3.80–3.90 ppm. Singlet signals of the thiomethylene group at 2.60–3.70 ppm were also supported, which was confirming the passage of the alkylation reaction on the Sulfur atom (Samelyuk and Kaplaushenko 2014).

^{1}H NMR spectra of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propanoic-, benzoic)acids (compounds 2.12–2.14) were characterized by extended singlets of protons of the carboxyl groups at 12.17–12.75 ppm, singlet signals of protons of the S-CH_2 groups at 2.71–3.38 ppm, which was confirmed the passage of the alkylation reaction, as well as characteristic singlet signals of protons of the methoxy groups at 3.83–3.90 ppm (Kazitsyna 1979).

The identity of the synthesized compounds was proved by chromatographic mass spectrometry. However, only one peak corresponding to the molecular weight of the product of the interaction m \ z + (+1 amp) was detected (Figs 4, 5).

Toxicity

According to the results of the GUSAR-online, for derivatives of 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione average lethal dose LD_{50} was when administered: intraperitoneally – from 273.0 to 865.0 mg / kg, intravenously – from 124.2 to 398.8 mg / kg, orally – from 348.1 to 1722.0 mg / kg and subcutaneously – from 586.0 to 2341.0 mg / kg (Table 1).

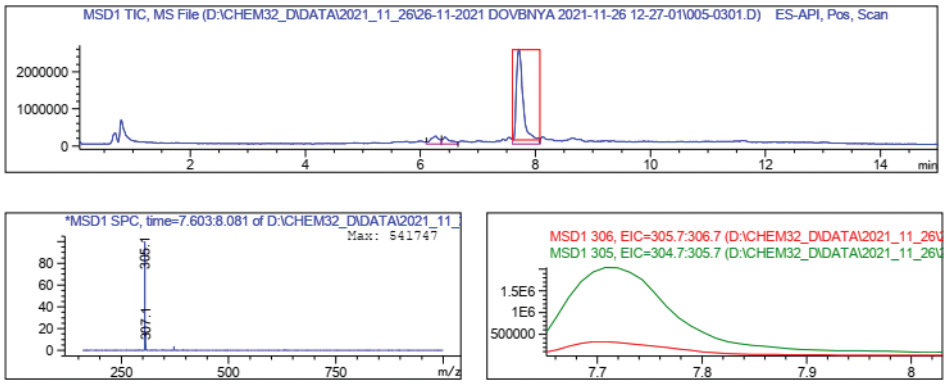

Figure 4. Mass spectra of 4-((5-(2,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)butanenitrile (2.3).

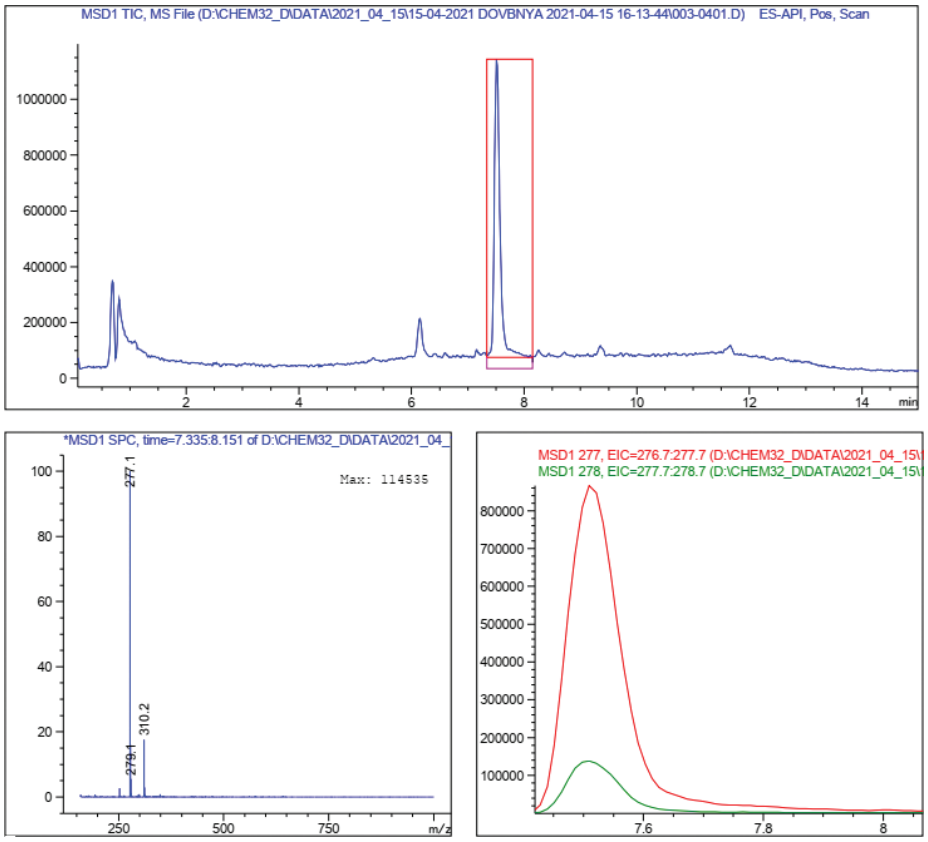

Figure 5. Mass spectra of 2-((5-(2,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetonitrile (2.1).

Antioxidant activity

For the study of antioxidant activity, ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles (2.1–2.11) were chosen, because acids did not give high values of this activity. This fact was confirmed by the scientists of our scientific school of ZSMU (Kaplaushenko 2008; Samelyuk 2016). ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propanoic, benzoic)acids (2.12–2.14) did not show high indicators of antioxidant activity, but their derivatives: salts, nitriles, ethers were quite active.

The results of the determination of AOA in model experiments under conditions Fe^{2+} -induced POL are presented in table 1. It can be seen: 3 compounds in varying degrees of expression can inhibit the generation of free radicals.

Moderate antioxidant activity among the studied of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl) thio)aceto(propano-, butano-, benzo)nitriles possessed in compounds 2.2, 2.10 which reduced the level TBC – AP by 12.07–13.55% ($p < 0.001$).

Compounds 2.1, 2.8 had high AOA, which reduced the TBC-AP content by 16.55–16.71% ($p < 0.001$).

The most pronounced AOA had methylammonium 3-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio) propanenitrile (2.7), which reduced the TBC-AP content by 29.03% ($p < 0.001$), but did not reach the level of the ascorbic reference drug by this ability acid by 7.94% (Table 2).

In future research, we plan to carry out the synthesis of the derivatives of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propanoic, benzoic)acids, such as salts and esters. As the analysis of the previous works of our scientific school of ZSMU (Kaplaushenko 2008; Samelyuk 2016) was shown that salts and esters were exhibited the highest indicators of antioxidant activity. Salts were showed high performance, but short-term activity. Esters had a longer-lasting effect but had not high enough.

Table 2. Antioxidant activity of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)aceto(propano-, butano-, benzo)nitriles on their derivatives *in vitro* at non-enzymatic initiation of VRO.

Compound	Optical density (λ = 232 нм) M ± m (n = 7)	AOA, %
Control	0.69±0.01	0
Vitamin C	0.43±0.0	36.97
2.1	0.57±0.01	16.55
2.2	0.6±0.01	12.07
2.3	0.69±0.01	-0.6
2.4	0.7±0.01	-5.55
2.5	0.78±0.01	-13.49
2.6	0.68±0.01	0.65
2.7	0.49±0.01	29.03
2.8	0.57±0.01	16.71
2.9	0.73±0.0	-5.55
2.10	0.59±0.01	13.55
2.11	0.68±0.01	0.44

Conclusions

1. New ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)nitriles were synthesized.
2. Preparative methods for the synthesis of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl) thio)aceto(propanoic, benzoic) acids have been developed.
3. The structure of the obtained compounds was confirmed by elemental analysis by IR spectroscopy, clear bands of oscillations of nitrile groups of CN at 2270–2210 cm^{-1} were revealed, which confirms the production of the target product and ^1H NMR spectra, and their individuality by chromato-mass spectrometry.
4. Pharmacological screening did not make it possible to identify compounds whose antioxidant activity exceeded that of ascorbic acid. Further optimization of the structure to improve their activities is currently in progress.

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