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Synthesis and Reactions of New 4-Methoxybenzyl- and 3-Chloro-4-methoxybenzyl-Substituted 1,2,4-Triazoles and 1,3,4-Thiadiazoles

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Abstract—Intermolecular cyclization of 1-phenyl(benzyl, allyl)-4-(4-methoxybenzyl- or 3-chloro-4-methoxybenzyl)thiosemicarbazides afforded the corresponding 3,4,5-substituted 4*H*-1,2,4-triazoles. Reactions of S-alkylation and aminomethylation of the latter were examined. Some 5-sulfanyl-substituted 1,3,4-thiadiazoles were also synthesized.

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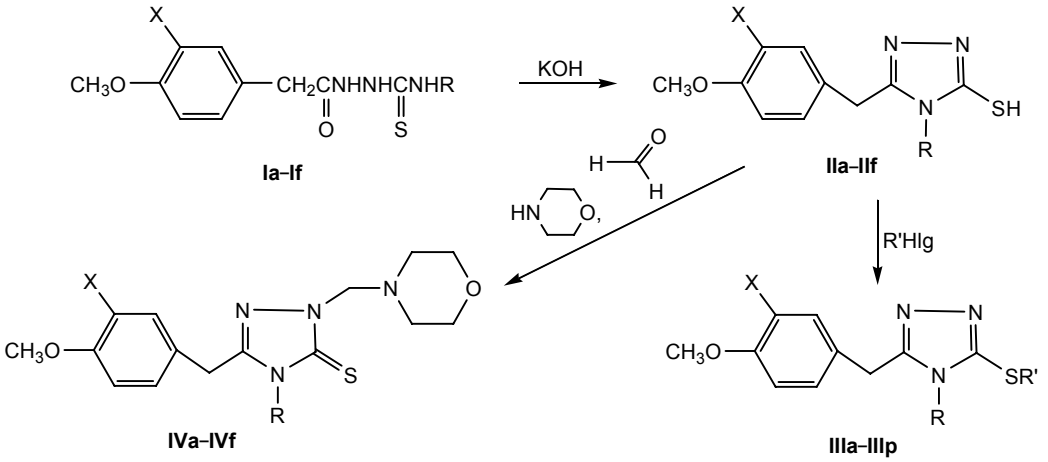
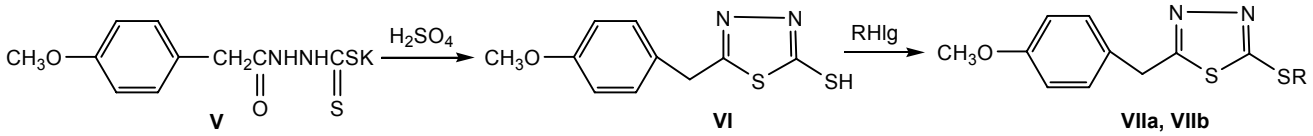
Many compounds containing the five-membered rings of 1,2,4-triazole and 1,3,4-thiadiazole are known to find versatile applications due to the wide range of their biological action, physicochemical and other properties [1–4]. Sulfanyl-substituted 1,2,4-triazoles and 1,3,4-thiadiazoles possess antibacterial [5], antitumor [4, 6], antiviral [7], and other actions. We formerly reported on the synthesis of a series of 1,2,4-triazole and 1,3,4-thiadiazole derivatives containing in their composition pharmacophoric fragments aiming at the search for new biologically active substances among them. In particular, compounds were found with moderate or pronounced hypoglycemic [8, 9], mutagenic [10], affecting DNA-methylation [11], and

Scheme 1.



I, **II**, **IV**, **X** = H, R = Ph (**a**), Bn (b), All (**c**); X = Cl, R = Ph (**d**), Bn (**e**), All (**f**); **III**, X = H: R = Ph, R' = Bn (**a**), CH_2CONH_2 (**b**), $CH(C_4H_9)COOH$ (**c**), CH_2COOH (**d**); R = Bn, R' = CH_2COOH (**e**), CH_2CH_2OH (**f**), $CH_2COOC_2H_5$ (**g**), CH_2CONH_2 (**h**); R = All, R' = CH_2CONH_2 (**i**), CH_2COOH (**j**); X = Cl: R = Ph, R' = $CH_2COOC_2H_5$ (**k**), CH_2CONH_2 (**l**), $CH_2CH_2C_6H_4$-2-Cl (**m**); R = Bn, R' = CH_2COOH (**n**), CH_2CONH_2 (**o**); R = All, R' = $CH_2COOC_2H_5$ (**p**).

Scheme 2.



R = CH_2COOCH_3 (**a**), CH_2COOH (**b**).

antitumor [12, 13] actions. In order to extend the range of new, more effective derivatives of this class compounds and for elucidating the dependence between the structure and biological activity we developed in this study simple reactions permitting the introduction of additional pharmacophoric groups and the preparation of sets of compounds with close structure (Schemes 1, 2).

Initial compounds were 1,4-substituted thiosemicarbazides **I** obtained in nearly quantitative yields by the reaction of 4-methoxy-phenyl- and 3-chloro-4-methoxyphenylacetic acids hydrazides with phenyl, benzyl, and allyl isothiocyanates in alcohol solution [8]. The variation of substituents X and R in the structure of compounds may provide a possibility to follow the changes in their biologic and physicochemical properties. In the synthesis of 4,5-substituted-1,2,4-triazole-3-thiols **IIa–IIf** we used the method we had developed [8–14] consisting in the intramolecular cyclization of an appropriate thiosemicarbazide **I** in 4.5% water solution of KOH followed by the acidification of the reaction mixture with glacial acetic acid. Triazoles **IIa–IIf** were isolated as stable colorless crystalline substances.

The alkylation of triazoles **IIa–IIf** occurs at the 3-thiol group characterized by a higher nucleophilicity as shows the presence of the characteristic singlets of the methylene protons belonging to the SCH_2 group in the region 3.2–4.3 ppm in the ^{1}H NMR spectra of sulfanyl-substituted 1,2,4-triazoles [12–15].

For the alkylation of 4*H*-1,2,4-triazolyl-3-thiols **IIa–IIf** we selected halides of special structure: chloro- or bromo-substituted aliphatic or unsaturated acids, or their esters and amides. In contrast to the alkylation of 1,2,4-triazole-3-thiols with benzyl chlorides at prolonged heating (10 h) in anhydrous acetone in the presence of potassium carbonate [16] we carried out the alkylation by boiling triazoles **IIa–IIf** and the corresponding halides (in particular, arylalkyl chlorides) in ethanol (2–3 h) or water (4–5 h) in the presence of a definite amount of KOH [13–15]. As a result 3-sulfanyl-substituted 4*H*-1,2,4-triazoles **IIa–IIf** were synthesized as stable crystalline substances.

Aminomethylation of triazoles **IIa–IIf** was performed in the conditions of Mannich reaction using morpholine as secondary amine in 20% excess. Crystalline Mannich bases **IVa–IVf** were isolated after keeping the reaction mixture at room temperature (20–25°C) for 10–12 h. The presence of a chlorine atom in the benzene ring favors the faster aminomethylation (5–6 h) and higher yields (91–96%) of compounds **IVd–IVf**.

Under similar conditions 2-sulfanyl-substituted 1,3,4-thiadiazoles **VIIa** and **VIIb** were synthesized along Scheme 2 proceeding from formerly described 1,3,4-thiadiazole-2-thiol (**VI**) [17]. The latter was easily obtained by cyclization of potassium dithiocarbazinate (**V**) in the presence of conc. H_2SO_4.

The purity, homogeneity, and the structure of compounds synthesized were confirmed by TLC, elemental analysis, and ^{1}H NMR spectra.

EXPERIMENTAL

TLC was carried out on Silufol UV-254 plates, development under UV irradiation. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury-300VX at operating frequency 300 MHz from solutions in DMSO-d_6, internal reference TMS. Melting points were measured on a heating microblock Boëtius 72/2064 (Germany). Initial thiosemicarbazides **I** were obtained by procedure [8].

4,5-Disubstituted 4*H*-1,2,4-triazole-3-thiols IIa–IIf. A solution of 10 mmol of an appropriate thiosemicarbazide **Ia–If** and 0.84 g (15 mmol) of KOH in 20 mL of water was boiled for 2 h, cooled, and acidified with glacial acetic acid. The separated precipitate was filtered off, washed with water, and recrystallized from ethanol.

5-(4-Methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (IIa), mp 162–163°C (161–163°C [8]).

5-(4-Methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazole-3-thiol (IIb). Yield 91%, mp 167–168°C, R_f 0.71 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm:

3.75 s (3H, OCH_3), 3.75 s (2H, CH_2), 5.08 s (2H, NCH_2), 6.73–6.78 m ($2H_{arom}$), 6.95–7.00 m ($2H_{arom}$), 7.15–7.31 m ($5H_{arom}$), 13.51 br.s (1H, SH). Found, %: C 65.48; H 5.61; N 13.65; S 10.14. $C_{17}H_{17}N_3OS$. Calculated, %: C 65.57; H 5.50; N 13.50; S 10.30.

5-(4-Methoxybenzyl)-4-allyl-4*H*-1,2,4-triazole-3-thiol (IIc), mp 91–92°C (91–92°C [8]).

5-(3-Chloro-4-methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (IId). Yield 98%, mp 208–209°C, R_f 0.59 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.75 c (2H, CH_2), 3.83 s (3H, OCH_3), 6.82–6.83 m ($2H_{arom}$), 6.86–6.88 m ($1H_{arom}$), 7.16–7.22 m ($2H_{arom}$) and 7.46–7.52 m ($3H_{arom}$), 13.62 br.s (1H, SH). Found, %: C 57.80; H 4.31; N 12.40; S 9.37. $C_{16}H_{14}ClN_3OS$. Calculated, %: C 57.91; H 4.25; N 12.66; S 9.66.

5-(3-Chloro-4-methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazole-3-thiol (IIe). Yield 94%, mp 163–164°C, R_f 0.67 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.78 s (2H, CH_2), 3.83 s (3H, OCH_3), 5.17 s (2H, NCH_2), 6.83 d ($1H_{arom}$, *J* 8.5 Hz), 6.94 d.d ($1H_{arom}$, =CH, *J* 8.5, 2.2 Hz), 7.04 d ($1H_{arom}$, *J* 2.2 Hz), 7.16–7.30 m ($5H_{arom}$), 13.59 br.s (1H, SH). Found, %: C 59.24; H 4.60; N 12.41; S 9.11. $C_{17}H_{16}ClN_3OS$. Calculated, %: C 59.04; H 4.66; N 12.15; S 9.27.

5-(3-Chloro-4-methoxybenzyl)-4-allyl-4*H*-1,2,4-triazole-3-thiol (IIf). Yield 95%, mp 136–137°C, R_f 0.63 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.83 s (3H, OCH_3), 3.93 s (2H, CH_2), 4.54 d.t (2H, NCH_2, *J* 5.5, 1.5 Hz), 5.07 d.q (1H, $=CH_2$, *J* 17.1, 1.5 Hz), 5.16 d (1H, $=CH_2$, *J* 10.3, 1.5 Hz), 5.78 d.d.t (1H, =CH, *J* 17.1, 10.3, 5.5 Hz), 6.95 d ($1H_{arom}$, *J* 8.4 Hz), 7.11 d ($1H_{arom}$, *J* 8.4, 2.2 Hz), 7.26 d ($1H_{arom}$, *J* 2.2 Hz), 13.47 br.s (1H, SH). Found, %: C 52.70; H 4.81; N 14.10; S 10.57. $C_{13}H_{14}ClN_3OS$. Calculated, %: C 52.79; H 4.81; N 14.21; S 10.84.

Alkylation of 4,5-substituted 4*H*-1,2,4-triazole-3-thiols IIa–IIf. General procedure. A solution of 3 mmol of triazole **IIa–IIf** and 0.2 g (3.6 mmol) of KOH in 15 mL of C_2H_5OH was boiled for 20–30 min, then 3 mmol of an appropriate halide was added, and the reaction mixture was boiled for 2–3 h more. On cooling the reaction mixture was diluted with 30 mL of water, the separated precipitate was filtered off, dried in air, and recrystallized. The alkylation of haloacids was performed in 15 mL of water in the presence of a five-fold excess of KOH (15 mmol), the reaction mixture was boiled for 4–5 h. On cooling the reaction mixture was acidified with glacial acetic acid, the separated precipitate was filtered off, dried in air, and recrystallized.

5-(4-Methoxybenzyl)-4-phenyl-3-benzyl-sulfanyl-4*H*-1,2,4-triazole (IIIa) was obtained from compound **IIa** and benzyl chloride. Yield 78%, mp 74–75°C, R_f 0.44 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, OCH_3), 3.84 s (2H, CH_2), 4.31 s (2H, SCH_2), 6.64–6.69 m ($2H_{arom}$), 6.76–6.81 m ($2H_{arom}$), 6.86–6.93 m ($2H_{arom}$), 7.36–7.47 m ($3H_{arom}$), 7.19–7.27 m ($5H_{arom}$). Found, %: C 71.35; H 5.51; N 10.65; S 8.42. $C_{23}H_{21}N_3OS$. Calculated, %: C 71.29; H 5.46; N 10.84; S 8.27.

2-[5-(4-Methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetamide (IIIb) was obtained from compound **IIa** and 2-chloroacetamide. Yield 98%, mp 73–75°C, R_f 0.54 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.72 s (3H, OCH_3), 3.80 s (2H, CH_2), 3.87 s (2H, SCH_2), 6.64–6.69 m ($2H_{arom}$), 6.79–6.84 m ($2H_{arom}$), 6.93 br, 7.48 br (1H, NH_2), 7.15–7.21 m ($2H_{arom}$), 7.44–7.51 m ($3H_{arom}$). Found, %: C 61.11; H 5.22; N 15.67; S 9.31. $C_{18}H_{18}N_4O_2S$. Calculated, %: C 61.00; H 5.12; N 15.81; S 9.05.

2-[5-(4-Methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl]capronic acid (IIIc) was obtained from compound **IIa** and 2-bromocapronic acid. Yield 97%, mp 134–135°C, R_f 0.62 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 0.87–0.93 m (3H, CH_3), 1.25–1.83 m [4H, $(CH_2)_2$], 1.71–1.93 m (2H, CH_2), 3.73 s (3H, OCH_3), 3.87 s (2H, CH_2), 4.03 t (1H, CH, *J* 6.9 Hz), 6.64–6.69 m ($2H_{arom}$), 6.78–6.82 m ($2H_{arom}$),7.10–7.16 m ($2H_{arom}$), 7.43–7.50 m ($3H_{arom}$), 12.41 br.s (1H, COOH). Found, %: C 64.10; H 6.18; N 10.38; S 7.43. $C_{22}H_{25}N_3O_3S$. Calculated, %: C 64.21; H 6.12; N 10.21; S 7.79.

2-[5-(4-Methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetic acid (IIId) was obtained from compound **IIa** and chloroacetic acid. Yield 89%, mp 82–83°C, R_f 0.52 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.72 s (3H, OCH_3), 3.84 s (2H, CH_2), 3.86 s (2H, SCH_2), 6.64–6.69 m ($2H_{arom}$), 6.78–6.83 m ($2H_{arom}$), 7.15–7.20 m ($2H_{arom}$), 7.44–7.52 m ($3H_{arom}$), CO<u>OH</u> br. Found, %: C 60.79; H 4.77; N 11.55; S 9.27. $C_{18}H_{17}N_3O_3S$. Calculated, %: C 60.83; H 4.82; N 11.82; S 9.02.

2-[5-(4-Methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetic acid (IIIe) was obtained from compound **IIb** and chloroacetic acid. Yield 81%, mp

127–129°C, R_f 0.51 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.74 s (3H, OCH_3), 3.88 s (2H, CH_2), 3.94 s (2H, SCH_2), 5.02 s (2H, NCH_2), 6.71–6.76 m (2H$_{arom}$), 6.99–7.04 m (2H$_{arom}$), 6.92–6.97 m (2H$_{arom}$), 7.23–7.30 m (3H$_{arom}$), 12.62 br (1H, COOH). Found, %: C 61.69; H 5.23; N 11.21; S 8.36. $C_{19}H_{19}N_3O_3S$. Calculated, %: C 61.77; H 5.18; N 11.37; S 8.68.

2-[5-(4-Methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]ethanol (IIIf) was obtained from compound **IIb** and 2-chloroethanol. Yield 94%, mp 90–92°C, R_f 0.40 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 3.19 t (2H, SCH_2, *J* 6.4 Hz), 3.64–3.70 m (2H, CH_2OH), 3.74 s (3H, OCH_3), 3.93 s (2H, CH_2), 4.74 t (1H, OH, *J* 6.0 Hz), 4.98 s (2H, NCH_2), 6.71–6.76 m (2H$_{arom}$), 6.99–7.04 m (2H$_{arom}$), 6.89–6.94 m (2H$_{arom}$), 7.22–7.29 m (3H$_{arom}$). Found, %: C 64.34; H 5.80; N 11.67; S 9.34. $C_{19}H_{21}N_3O_2S$. Calculated, %: C 64.20; H 5.96; N 11.82; S 9.02.

Ethyl 2-[5-(4-methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetate (IIIg) was obtained from compound **IIb** and ethyl chloroacetate. Yield 76%, mp 63–65°C, R_f 0.56 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, $OCH_2\underline{CH_3}$, *J* 7.1 Hz), 3.74 s (3H, OCH_3), 3.93 s (2H, CH_2), 3.95 s (2H, SCH_2), 4.13 q (2H, OCH_2, *J* 7.1 Hz), 5.02 s (2H, NCH_2), 6.71–6.76 m (2H$_{arom}$), 6.99–7.04 m (2H$_{arom}$), 6.91–6.96 m (2H$_{arom}$), 7.23–7.28 m (3H$_{arom}$). Found, %: C 63.53; H 5.75; N 10.28; S 8.41. $C_{21}H_{23}N_3O_3S$. Calculated, %: C 63.45; H 5.83; N 10.57; S 8.07.

2-[5-(4-Methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetamide (IIIh) was obtained from compound **IIb** and 2-chloroacetamide. Yield 74%, mp 148–149°C, R_f 0.39 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.74 s (3H, OCH_3), 3.78 s (2H, CH_2), 3.95 s (2H, SCH_2), 5.03 s (2H, NCH_2), 6.71–6.76 m (2H$_{arom}$), 6.99–7.04 m (2H$_{arom}$), 6.92 br (1H), 7.52 br (1H, NH_2), 6.91–6.96 m (2H$_{arom}$), 7.22–7.30 m (3H$_{arom}$). Found, %: C 61.80; H 5.57; N 15.47; S 8.92. $C_{19}H_{20}N_4O_2S$. Calculated, %: C 61.93; H 5.47; N 15.21; S 8.70.

2-[5-(4-Methoxybenzyl)-4-allyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetamide (IIIi) was obtained from compound **IIc** and 2-chloroacetamide. Yield 79%, mp 119–120°C, R_f 0.37 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.76 s (3H, OCH_3), 3.77 s (2H, CH_2), 4.02 s (2H, SCH_2), 4.44 d.t (2H, NCH_2, *J* 5.2, 1.6 Hz), 4.90 d.q (1H, =CH_2, *J* 17.1, 1.6 Hz), 5.12 d.q (1H, =CH_2, *J* 10.3, 1.6 Hz), 5.64 d.d.t (1H, =CH, *J* 17.1, 10.3, 5.2 Hz), 6.77–6.82 m (2H$_{arom}$), 7.07–7.12 m (2H$_{arom}$), 6.91 br (1H), 7.51 br (1H, NH_2). Found, %: C 56.50; H 5.78; N 17.81; S 10.32. $C_{15}H_{18}N_4O_2S$. Calculated, %: C 56.58; H 5.70; N 17.60; S 10.07.

2-[5-(4-Methoxybenzyl)-4-allyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetic acid (IIIj) was obtained from compound **IIc** and chloroacetic acid. Yield 88%, mp 154–156°C, R_f 0.41 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.76 s (3H, OCH_3), 3.87 s (2H, CH_2), 4.02 s (2H, SCH_2), 4.43 d.t (2H, NCH_2, *J* 5.2, 1.5 Hz), 4.90 d.q (1H, =CH_2, *J* 17.1, 1.5 Hz), 5.12 d.q (1H, =CH_2, *J* 10.4, 1.5 Hz), 5.63 d.d.q (1H, =CH, *J* 17.1, 10.4, 5.2 Hz), 6.77–6.82 m (2H$_{arom}$), 7.07–7.12 m (2H$_{arom}$), 12.58 br.s (1H, COOH). Found, %: C 56.52; H 5.41; N 13.41; S 10.29. $C_{15}H_{17}N_3O_3S$. Calculated, %: C 56.41; H 5.37; N 13.16; S 10.04.

Ethyl 2-[5-(3-chloro-4-methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetate (IIIk) was obtained from compound **IId** and ethyl chloroacetate. Yield 72%, mp 101–102°C, R_f 0.57 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3, *J* 7.1 Hz), 3.83 s (3H, OCH_3), 3.87 s (2H, SCH_2), 3.94 s (2H, CH_2), 4.15 q (2H, OCH_2, *J* 7.1 Hz), 6.82–6.83 m (2H$_{arom}$), 6.87–6.88 m (1H$_{arom}$), 7.18–7.22 m (2H$_{arom}$), 7.47–7.54 m (3H$_{arom}$). Found, %: C 57.60; H 4.72; N 10.27; S 8.39. $C_{20}H_{20}ClN_3O_3S$. Calculated, %: C 57.48; H 4.82; N 10.06; S 7.67.

2-[5-(3-Chloro-4-methoxybenzyl)-4-phenyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetamide (IIIl) was obtained from compound **IId** and 2-chloroacetamide. Yield 77%, mp 152–154°C, R_f 0.77 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.81 s (2H, CH_2), 3.83 s (3H, OCH_3), 3.87 s (2H, SCH_2), 6.82–6.84 m (2H$_{arom}$), 6.88–6.90 m (1H$_{arom}$), 6.94 br.s (1H, NH_2), 7.19–7.26 m (2H$_{arom}$), 7.47–7.54 m (3H$_{arom}$ and 1H, NH_2). Found, %: C 55.71; H 4.53; N 14.57; S 8.41. $C_{18}H_{17}ClN_4O_2S$. Calculated, %: C 55.60; H 4.41; N 14.41; S 8.25.

2-[5-(3-Chloro-4-methoxybenzyl)-4-phenyl-3-2-(2-chlorophenethylsulfanyl)-4*H*-1,2,4-triazole (IIIm) was obtained from compound **IId** and 2-(2-chlorophenethyl) chloride. Yield 49%, mp 107–109°C, R_f 0.48 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.55 t (2H, SCH_2, *J* 6.4 Hz), 3.83 s (3H, OCH_3), 3.87 s (2H, CH_2), 4.39 t (2H, OCH_2, *J* 6.4 Hz), 6.82–6.83m (2H$_{arom}$), 6.85–6.91 m (2H$_{arom}$), 7.11–7.25 m (4H$_{arom}$), 7.30 d.d (1H$_{arom}$, *J* 7.8, 1.6 Hz), 7.46–7.53 m (3H$_{arom}$). Found, %: C 59.32; H 4.41; N 8.42; S 6.71. $C_{24}H_{21}ClN_3O_2S$. Calculated, %: C 59.26; H 4.35; N 8.64; S 6.59.

2-[5-(3-Chloro-4-methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetic acid (IIIn) was obtained from compound **IIe** and chloroacetic acid. Yield 70%, mp 162–163°C, R_f 0.61 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OCH_3), 3.90 s (2H, CH_2), 3.96 s (2H, SCH_2), 5.10 s (2H, NCH_2), 6.83 d (1H$_{arom}$, *J* 8.5 Hz), 6.93–6.98 m (2H$_{arom}$), 7.19–7.29 m (3H$_{arom}$), 6.98 d.d (1H$_{arom}$, *J* 8.5, 2.2 Hz), 7.09 d (1H$_{arom}$, *J* 2.2 Hz), 12.68 br.s (1H, COOH). Found, %: C 56.61; H 4.56; N 10.66; S 7.62. $C_{19}H_{18}ClN_3O_3S$. Calculated, %: C 56.50; H 4.49; N 10.40; S 7.94.

2-[5-(3-Chloro-4-methoxybenzyl)-4-benzyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetamide (IIIo) was obtained from compound **IIe** and 2-chloroacetamide. Yield 75%, mp 158–159°C, R_f 0.31 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.80 s (2H, CH_2), 3.82 s (3H, OCH_3), 3.97 s (2H, SCH_2), 5.11 s (2H, NCH_2), 6.84 d (1H$_{arom}$, *J* 8.5 Hz), 6.92–7.01 m (3H$_{arom}$ and 1H, NH_2), 7.10 d (1H$_{arom}$, *J* 2.2 Hz), 7.20–7.29 m (3H$_{arom}$), 7.53 br.s (1H, NH_2). Found, %: C 56.73; H 4.60; N 13.68; S 7.58. $C_{19}H_{19}ClN_4O_2S$. Calculated, %: C 56.64; H 4.75; N 13.91; S 7.96.

Ethyl 2-[5-(3-Chloro-4-methoxybenzyl)-4-allyl-4*H*-1,2,4-triazol-3-ylsulfanyl]acetate (IIIp) was obtained from compound **IIf** and ethyl chloroacetate. Yield 74%, mp 65–67°C, R_f 0.51 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3, *J* 7.1 Hz), 3.86 s (3H, OCH_3), 3.94 s (2H, CH_2), 4.03 s (2H, SCH_2), 4.13 q (2H, OCH_2, *J* 7.1 Hz), 4.49 d.t (2H, NCH_2, *J* 5.1, 1.6 Hz), 4.89 d.q (1H, =CH_2, *J* 17.1, 1.6 Hz), 5.13 d.q (1H, =CH_2, *J* 10.3, 1.6 Hz), 5.69 d.d.t (1H, =CH, *J* 17.1, 10.3, 5.1 Hz), 6.94 d (1H$_{arom}$, *J* 8.1 Hz), 7.10 d.d (1H$_{arom}$, *J* 8.1, 2.2 Hz), 7.24 d (1H$_{arom}$, *J* 2.2 Hz). Found, %: C 53.40; H 5.31; N 11.31; S 8.59. $C_{17}H_{20}ClN_3O_3S$. Calculated, %: C 53.47; H 5.28; N 11.00; S 8.40.

Aminomethylation of 4,5-substituted 4*H*-1,2,4-triazole-3-thiols IIa–IIf. General procedure. In 5–10 mL of methanol was dissolved 5 mmol of an appropriate triazole **IIa–IIf**, 6 mmol of morpholine was added, and after that 8 mmol of formaldehyde water solution was added dropwise at shaking. The reaction proceeded with heat liberation. The reaction mixture was left standing for 8–10 h (5–6 h in case of compounds **IId–IIf**), diluted with 15–20 mL of water, the separated precipitate was filtered off and recrystallized from ethanol.

3-(4-Methoxybenzyl)-4-phenyl-1-morpholinomethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVa). Yield 77%, mp 138–139°C, R_f 0.70 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.77–2.82 m [4H, N(CH_2)$_2$], 3.60–3.64 m [4H, O(CH_2)$_2$], 3.73 s (3H, OCH_3), 3.79 s (2H, CH_2), 5.05 s (2H, NCH_2N), 6.66–6.71 m (2H$_{arom}$), 6.76–6.81 m (2H$_{arom}$), 7.11–7.16 m (2H$_{arom}$), 7.43–7.49 m (3H$_{arom}$). Found, %: C 63.44; H 6.22; N 14.39; S 8.47. $C_{21}H_{24}N_4O_2S$. Calculated, %: C 63.61; H 6.10; N 14.13; S 8.09.

3-(4-Methoxybenzyl)-4-benzyl-1-morpholinomethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVb). Yield 73%, mp 104–106°C, R_f 0.71 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 2.72–2.77 m [4H, N(CH_2)$_2$], 3.57–3.63 m [4H, O(CH_2)$_2$], 3.75 s (3H, OCH_3), 3.80 s (2H, CH_2), 5.06 s (2H, NCH_2), 5.13 s (2H, NCH_2N), 6.74–6.79 m (2H$_{arom}$), 6.96–7.01 m (2H$_{arom}$), 7.14–7.19 m (2H$_{arom}$), 7.22–7.33 m (3H$_{arom}$). Found, %: C 64.43; H 6.20; N 13.45; S 7.58. $C_{22}H_{26}N_4O_2S$. Calculated, %: C 64.36; H 6.38; N 13.65; S 7.81.

3-(4-Methoxybenzyl)-4-allyl-1-morpholinomethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVc). Yield 69%, mp 83–85°C, R_f 0.70 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 2.69–2.74 m [4H, N(CH_2)$_2$], 3.57–3.61 m [4H, O(CH_2)$_2$], 3.77 s (3H, OCH_3), 3.97 s (2H, CH_2), 4.52 d.t (2H, NCH_2, *J* 5.5, 1.5 Hz), 5.01 s (2H, NCH_2N), 5.04 d.q (1H, =CH_2, *J* 17.1, 1.5 Hz), 5.15 d.q (1H, =CH_2, *J* 10.3, 1.5 Hz), 5.74 d.d.t (1H, =CH, *J* 17.1, 10.3, 5.5 Hz), 6.81–6.86 m (2H$_{arom}$), 7.09–7.14 m (2H$_{arom}$). Found, %: C 59.80; H 6.69; N 15.42; S 8.64. $C_{18}H_{24}N_4O_2S$. Calculated, %: C 59.97; H 6.71; N 15.54; S 8.90.

3-(3-Chloro-4-methoxybenzyl)-4-phenyl-1-morpholinomethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVd). Yield 96%, mp 143–145°C, R_f 0.78 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.77–2.81 m [4H, N(CH_2)$_2$], 3.60–3.65 m [4H, O(CH_2)$_2$], 3.79 s (2H, CH_2), 3.84 s (3H, OCH_3), 5.05 s (2H, NCH_2N), 6.78–6.87 m (3H$_{arom}$), 7.17–7.21 m (2H$_{arom}$), 7.47–7.52 m (3H$_{arom}$). Found, %: C 58.63; H 5.43; N 13.27; S 7.12. $C_{21}H_{23}ClN_4O_2S$. Calculated, %: C 58.53; H 5.38; N 13.00; S 7.44.

3-(3-Chloro-4-methoxybenzyl)-4-benzyl-1-morpholino-methyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVe). Yield 92%, mp 93–95°C, R_f 0.72 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.72–2.77 m [4H, N(CH_2)$_2$], 3.57–3.63 m [4H, O(CH_2)$_2$], 3.84 s (3H, OCH_3), 3.84 s (2H, CH_2), 5.06 s (2H, NCH_2), 5.22 s (2H, NCH_2N), 6.84 d (1H$_{arom}$, *J* 8.4 Hz), 6.93 d.d (1H$_{arom}$, *J* 8.4, 2.2 Hz), 7.08 d (1H$_{arom}$, *J* 2.2 Hz), 7.13–7.30 m (5H$_{arom}$). Found, %: C 59.46; H 5.58; N 12.31;

S 7.48. $C_{22}H_{25}ClN_4O_2S$. Calculated, %: C 59.38; H 5.66; N 12.59; S 7.21.

3-(3-Chloro-4-methoxybenzyl)-4-allyl-1-morpholinomethyl-1*H*-1,2,4-triazole-5(4*H*)-thione (IVf). Yield 91%, mp 87–88°C, R_f 0.70 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 2.69–2.73 m [4H, $N(CH_2)_2$], 3.55–3.61 m [4H, $O(CH_2)_2$], 3.87 s (3H, OCH_3), 3.98 s (2H, CH_2), 4.58 d.t (2H, NCH_2, *J* 5.5, 1.5 Hz), 5.00 s (2H, NCH_2N), 5.06 d.q (1H, $=CH_2$, *J* 17.1, 1.5 Hz), 5.15 d.q (1H, $=CH_2$, *J* 10.3, 1.5 Hz), 5.77 d.d.t (1H, =CH, *J* 17.1, 10.3, 5.5 Hz), 6.97 d ($1H_{arom}$, *J* 8.5 Hz), 7.11 d.d ($1H_{arom}$, *J* 8.5, 2.2 Hz), 7.29 d ($1H_{arom}$, *J* 2.2 Hz). Found, %: C 54.68; H 5.79; N 14.41; S 7.87. $C_{18}H_{23}ClN_4O_2S$. Calculated, %: C 54.74; H 5.87; N 14.19; S 8.12.

5-(4-Methoxybenzyl)-1,3,4-thiadiazole-2-thiol (VI) was obtained from compound **V** and H_2SO_4, mp 129–131°C (124–125°C [12]).

Methyl 2-[5-(4-methoxybenzyl)-1,3,4-thiadiazol-2-ylsulfanyl]acetate (VIIa) was obtained from compound **VI** and methyl chloroacetate. Yield 74%, mp 46–47°C, R_f 0.53 (dioxane–benzene, 1 : 2). ^{1}H NMR spectrum, δ, ppm: 3.73 s (3H, OCH_3), 3.77 s (2H, CH_2), 4.28 s (2H, SCH_2), 6.80–6.85 m ($2H_{arom}$), 7.17–7.22 m ($2H_{arom}$). Found, %: C 50.41; H 4.44; N 9.03; S 20.66. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 50.30; H 4.55; N 9.16; S 20.53.

2-[5-(4-Methoxybenzyl)-1,3,4-thiadiazole-2-ylsulfanyl]acetic acid (VIIb) was obtained from compound **VI** and chloroacetic acid. Yield 67%, mp >260°C, R_f 0.40 (dioxane–benzene, 1 : 1). ^{1}H NMR spectrum, δ, ppm: 3.78 s (3H, OCH_3), 4.03 s (2H, CH_2), 4.27 s (2H, SCH_2), 6.78–6.84 m ($2H_{arom}$), 7.12–7.23 m ($2H_{arom}$), 12.52 br.s (1H, COOH). Found, %: C 48.71; H 4.28; N 9.45; S 21.64. $C_{12}H_{12}N_2O_3S_2$. Calculated, %: C 48.63; H 4.08; N 9.35; S 21.78.

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