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SYNTHESIS AND PROPERTIES OF SOME 1,2,4-TRIAZOLE DERIVATIVES

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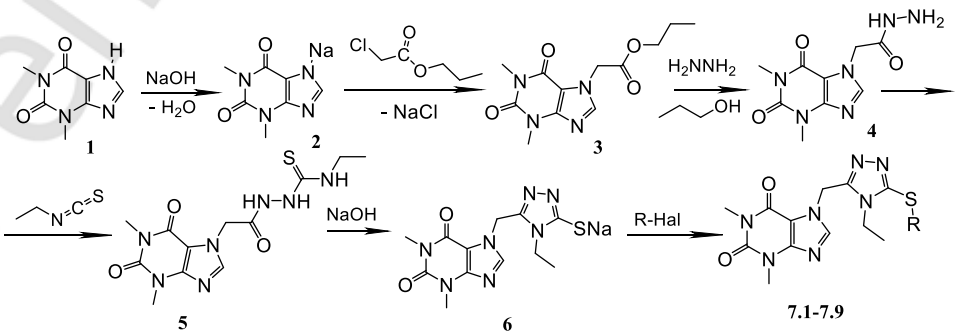
Key words: *1,2,4-triazole, theophylline, synthesis, antimicrobial activity*
Resume: *a series of the alkyl-, arylderivatives of 7'-((4-ethyl-5-thio-1,2,4-triazole-3-yl)methyl)theophylline was synthesized in order to determine their antimicrobial activity. The physical properties and chemical structures of the the target compounds were proved by infrared spectrophotometry, ^1H NMR spectroscopy, along with elemental analyses and gas chromatography mass spectrometry. Antibacterial activity of all the target compounds was investigated in vitro against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans.*

Actuality. One of the most important and difficult assignments of modern pharmaceutical science is the search for new biologically active substances, which have high effectiveness and low toxicity [3]. Derivatives of theophylline and 1,2,4-triazole are relevant and practically significant class of compounds for synthesis on their basis of biologically active substances, due to a wide range of biological activity of derivatives of these heterocycles [4].

The aim. A development of efficient methods for the synthesis of the alkyl-, arylderivatives of 7'-((4-ethyl-5-thio-1,2,4-triazole-3-yl)methyl)theophylline. To study antimicrobial and antifungal activity of synthesized substances on standard test cultures of bacteria and fungi: *S. aureus*, *E. coli*, *P. aeruginosa* and *C. albicans*.

The tasks: 1. Methods for the synthesis of heterocyclic compounds containing fragments of theophylline and 1,2,4-triazole to optimize; 2. Synthesized substances to study for antibacterial and antifungal activity.

Materials and methods. Theophylline was used as starting substance from which through a series successive stages of transformation (electrophilic substitution reaction, hydrazinolysis, etherification and intramolecular heterocyclization) starting thiol and *S*-alkyl derivatives were obtained (figure 1). Alkyl derivatives were synthesized in propan1-1-ol with heating. The product was crystallized from methanol.



R = C_3H_7; C_4H_9; C_5H_{11}; C_6H_{13}; C_7H_{15}; C_8H_{17}; C_9H_{19}; $C_{10}H_{21}$; $-CH_2-C_6H_5$; Hal = Br; Cl

Fig. 1 – The synthetic route of title compounds

The antimicrobial activities of the extracts and fractions were determined by the disk diffusion and minimum inhibitory concentration (MIC) methods at concentration 1 mg/ml (table 1).

Results and their discussion [1,2]: *7-((4-Ethyl-5-thio-1,2,4-triazole-3-yl)methyl)theophylline*: Yield: 79 %; m. p.: 250 °C; IR ν (cm^{-1}): 3235 (NH), 1609 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 7.98 (s, 1H, CH), 7.80 (s, 1H, SH), 5.31 (s, 2H, N_7-CH_2), 4.06-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.48 (s, 3H, N_3-CH_3), 3.36 (s, 3H, N_1-CH_3), 1.27 (t, *J* = 6.1 Hz, 3H, CH_2C$\underline{H}_3$). Anal. calcd. (%) for $C_{12}H_{15}N_7O_2S$: C, 44.32; H, 4.52; N, 25.84; S, 8.45. Found: C, 44.28; H, 4.54; N, 25.76; S, 8.42.

7-((4-Ethyl-5-(propylthio)-1,2,4-triazole-3-yl)methyl)theophylline (7.1): Yield: 81 %; m. p.: 125 – 128 °C; IR ν (cm^{-1}): 3226 (NH), 1605 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.07 (s, 1H, CH), 5.32 (s, 2H, N_7-CH_2), 4.08-4.04 (m, 2H, C$\underline{H}_2$$CH_3$), 3.51 (s, 3H, N_3-CH_3), 3.44 (s, 3H, N_1-CH_3), 3.14 (t, *J* = 8.1 Hz, 2H, S-C$\underline{H}_2$-CH_2-CH_3), 1.73-1.76 (m, 2H, S-CH_2-C$\underline{H}_2$-CH_3), 1.33 (t, *J* = 6.4 Hz, 3H, CH_2C$\underline{H}_3$), 1.07 (t, *J* = 5.3 Hz,3H, S-$(CH_2)_2$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{15}H_{21}N_7O_2S$: C, 49.57; H, 5.82; N, 26.98; S, 8.82. Found: C, 49.45; H, 5.83; N, 26.94; S, 8.84.

7-((5-(Butylthio)-4-ethyl-1,2,4-triazole-3-yl)methyl)theophylline (7.2): Yield: 73 %; m. p.: 140 – 143 °C; IR ν (cm^{-1}): 3228 (NH), 1604 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.07 (s, 1H, CH), 5.29 (s, 2H, N_7-CH_2), 4.06-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.50 (s, 3H, N_3-CH_3), 3.44 (s, 3H, N_1-CH_3), 3.16 (t, *J* = 8.1 Hz, 2H, S-C$\underline{H}_2$-$(CH_2)_2$-CH_3), 1.72-1.67 (m, 2H, S-CH_2-C$\underline{H}_2$-CH_2-CH_3), 1.39-1.36 (m, 2H, S-$(CH_2)_2$-C$\underline{H}_2$-CH_3), 0.95-0.92 (t, *J* = 5.3 Hz, 3H, S-$(CH_2)_3$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{16}H_{23}N_7O_2S$: C, 50.91; H, 6.14; N, 25.98; S, 8.49. Found: C, 50.79; H, 6.15; N, 25.94; S, 8.51.

7-((4-Ethyl-5-(pentylthio)-1,2,4-triazole-3-yl)methyl)theophylline (7.3): Yield: 69 %; m. p.: 135 – 137 °C; IR ν (cm^{-1}): 3231 (NH), 1608 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.05 (s, 1H, CH), 5.27 (s, 2H, N_7-CH_2), 4.07-4.04 (m, 2H, C$\underline{H}_2$$CH_3$), 3.49 (s, 3H, N_3-CH_3), 3.43 (s, 3H, N_1-CH_3), 3.14 (t, *J* = 7.2 Hz, 2H, S-C$\underline{H}_2$-$(CH_2)_3$-CH_3), 1.69-1.65 (m, 2H, S-CH_2-C$\underline{H}_2$-$(CH_2)_2$-CH_3), 1.42-1.35 (m, 7H, CH_2C$\underline{H}_3$, S-$(CH_2)_2$-(C$\underline{H}_2$)$_2$-CH_3), 0.88-0.92 (t, *J* = 5.5 Hz,3H, S-$(CH_2)_4$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{17}H_{25}N_7O_2S$: C, 52.16; H, 6.44; N, 25.04; S, 8.19. Found: C, 52.02; H, 6.45; N, 25.01; S, 8.21.

7-((4-Ethyl-5-(hexylthio)-1,2,4-triazole-3-yl)methyl)theophylline (7.4): Yield: 76 %; m. p.: 100 – 103 °C; IR ν (cm^{-1}): 3225 (NH), 1606 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.05 (s, 1H, CH), 5.25 (s, 2H, N_7-CH_2), 4.07-4.04 (m, 2H, C$\underline{H}_2$$CH_3$), 3.49 (s, 3H, N_3-CH_3), 3.43 (s, 3H, N_1-CH_3), 3.17 (t, *J* = 7.9 Hz, 2H, S-C$\underline{H}_2$-$(CH_2)_4$-CH_3), 1.72-1.69 (m, 2H, S-CH_2-C$\underline{H}_2$-$(CH_2)_3$-CH_3), 1.41-1.34 (m, 9H, CH_2C$\underline{H}_3$, S-$(CH_2)_2$-(C$\underline{H}_2$)$_3$-CH_3), 0.89 (t, *J* = 5.5 Hz, 3H, S-$(CH_2)_5$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{18}H_{27}N_7O_2S$: C, 53.31; H, 6.71; N, 24.18; S, 7.91. Found: C, 53.18; H, 6.72; N, 24.14; S, 7.93.

7-((4-Ethyl-5-(heptylthio)-1,2,4-triazole-3-yl)methyl)theophylline (7.5): Yield: 86 %; m. p.: 104 – 106 °C; IR ν (cm^{-1}): 3228 (NH), 1607 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.04 (s, 1H, CH), 5.23 (s, 2H, N_7-CH_2), 4.07-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.49 (s, 3H, N_3-CH_3), 3.43 (s, 3H, N_1-CH_3), 3.13 (t, *J* = 7.9 Hz, 2H, S-C$\underline{H}_2$-$(CH_2)_5$-CH_3), 1.73-1.70 (m, 2H, S-CH_2-C$\underline{H}_2$-$(CH_2)_4$-CH_3), 1.41-1.29 (m, 11H, CH_2C$\underline{H}_3$, S-$(CH_2)_2$-(C$\underline{H}_2$)$_4$-CH_3), 0.86-0.83 (m, 3H,

S-(CH_2)$_6$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{19}H_{29}N_7O_2S$: C, 54.39; H, 6.97; N, 23.37; S, 7.64. Found: C, 54.26; H, 6.98; N, 23.34; S, 7.66.

7-((4-Ethyl-5-(octylthio)-1,2,4-triazole-3-yl)methyl)theophylline (7.6): Yield: 73 %; m. p.: 96 – 99 °C; IR ν (cm^{-1}): 3224 (NH), 1605 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.04 (s, 1H, CH), 5.22 (s, 2H, N_7-CH_2), 4.06-4.02 (m, 2H, C$\underline{H}_2$$CH_3$), 3.48 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 3.14 (t, *J* = 7.8 Hz, 2H, S-C$\underline{H}_2$-(CH_2)$_6$-CH_3), 1.67-1.71 (m, 2H, S-CH_2-C$\underline{H}_2$-(CH_2)$_5$-CH_3), 1.38-1.25 (m, 13H, CH_2C$\underline{H}_3$, S-(CH_2)$_2$-(C$\underline{H}_2$)$_5$-CH_3), 0.88-0.84 (m, 3H, S-(CH_2)$_7$-C$\underline{H}_3$). Anal. calcd. (%) for $C_{20}H_{31}N_7O_2S$: C, 55.40; H, 7.21; N, 22.61; S, 7.39. Found: C, 55.27; H, 7.22; N, 22.58; S, 7.42.

7-((5-(Nonylthio)-4-ethyl-1,2,4-triazole-3-yl)methyl)theophylline (7.7): Yield: 69 %; m. p.: 105 – 107 °C; IR ν (cm^{-1}): 3229 (NH), 1607 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.04 (s, 1H, CH), 5.20 (s, 2H, N_7-CH_2), 4.07-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.48 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 3.13 (t, *J* = 7.9 Hz, 2H, S-C$\underline{H}_2$-(CH_2)$_7$-CH_3), 1.71-1.67 (m, *J* = 8.2 Hz, 2H, S-CH_2-C$\underline{H}_2$-(CH_2)$_6$-CH_3), 1.38-1.24 (m, 15H, CH_2C$\underline{H}_3$, S-(CH_2)$_2$-(C$\underline{H}_2$)$_6$-CH_3), 0.85-0.82 (m, 3H, S-(CH_2)$_8$-C$\underline{H}_3$),. Anal. calcd. (%) for $C_{21}H_{33}N_7O_2S$: C, 56.35; H, 7.43; N, 21.91; S, 7.16. Found: C, 56.18; H, 7.44; N, 21.88; S, 7.18.

7-((5-(Decylthio)-4-ethyl-1,2,4-triazole-3-yl)methyl)theophylline (7.8): Yield: 94 %; m. p.: 108 – 110 °C; IR ν (cm^{-1}): 3229 (NH), 1607 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.04 (s, 1H, CH), 5.17 (s, 2H, N_7-CH_2), 4.07-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.46 (s, 3H, N_3-CH_3), 3.40 (s, 3H, N_1-CH_3), 3.10 (t, *J* = 7.7 Hz, 2H, S-C$\underline{H}_2$-(CH_2)$_8$-CH_3), 1.69-1.65 (m, 2H, S-CH_2-C$\underline{H}_2$-(CH_2)$_7$-CH_3), 1.36-1.22 (m, 17H, CH_2C$\underline{H}_3$, S-(CH_2)$_2$-(C$\underline{H}_2$)$_7$-CH_3), 0.83-0.80 (m, 3H, S-(CH_2)$_9$-C$\underline{H}_3$),. Anal. calcd. (%) for $C_{22}H_{35}N_7O_2S$: C, 57.24; H, 7.64; N, 21.24; S, 6.95. Found: C, 57.10; H, 7.65; N, 21.21; S, 6.97.

7-((5-(Benzylthio)-4-ethyl-1,2,4-triazole-3-yl)methyl)theophylline (7.9): Yield: 67 %; m. p.: 245 °C; IR ν (cm^{-1}): 3228 (NH), 1607 (C=N); ^{1}H NMR δ (ppm), *J (Hz)*: 8.01 (s, 1H, CH), 7.36 – 7.27 (м, 5H, C_6H_5), 5.19 (s, 2H, N_7-CH_2), 4.40 (d, *J* = 0.9 Hz, 2H, S-CH_2), 4.07-4.03 (m, 2H, C$\underline{H}_2$$CH_3$), 3.48 (s, 3H, N_3-CH_3), 3.41 (s, 3H, N_1-CH_3), 1.41 (t, *J* = 6.4 Hz, 3H, CH_2C$\underline{H}_3$). Anal. calcd. (%) for $C_{19}H_{21}N_7O_2S$: C, 55.46; H, 5.14; N, 23.83; S, 7.79. Found: C, 55.57; H, 5.13; N, 23.86; S, 7.94.

The results showed, that the greatest antimicrobial activity have 7-((5-(nonylthio)-4-ethyl-1,2,4-triazole-3-yl)methyl)theophylline (7.7) against *S. aureus* (tab. 1).

Tab. 1. Antimicrobial and antifungal activity of synthesized substances

Compou	The bacterial strains	Result		Compou	The bacterial strains	Result	
		MIC, μg/ml	MBC (MFC for *C. albscans*), μg/ml			MIC, μg/ml	MBC (MFC for *C. albscans*), μg/ml
6	*E. coli*	250	500	7.5	*E. coli*	62,5	125
	S. aureus	31,25	250		*S. aureus*	125	500
	P. aeruginosa	62,5	250		*P. aeruginosa*	62,5	125
	C. albicans	62,5	62,5		*C. albicans*	62,5	62,5
7.1	*E. coli*	125	250	7.6	*E. coli*	125	250
	S. aureus	125	250		*S. aureus*	7,8	31,25
	P. aeruginosa	62,5	250		*P. aeruginosa*	62,5	250
	C. albicans	31,25	31,25		*C. albicans*	31,25	31,25

7.2	*E. coli*	62,5	125	7.7	*E. coli*	62,5	125
	S. aureus	125	250		*S. aureus*	3,9	7,8
	P. aeruginosa	62,5	125		*P. aeruginosa*	62,5	125
	C. albicans	62,5	125		*C. albicans*	62,5	125
7.3	*E. coli*	62,5	125	7.8	*E. coli*,	62,5	125
	S. aureus	125	500		*S. aureus*,	31,25	500
	P. aeruginosa	62,5	250		*P. aeruginosa*,	62,5	250
	C. albicans	62,5	125		*C. albicans*	62,5	125
7.4	*E. coli*	62,5	125	7.9	*E. coli*	62,5	125
	S. aureus	125	250		*S. aureus*	125	250
	P. aeruginosa	125	250		*P. aeruginosa*	62,5	125
	C. albicans	62,5	125		*C. albicans*	62,5	125

Conclusion: 1. Obtained 10 new compounds and confirmed their structure. 2. Antimicrobial and antifungal activity screening title compounds were carried out.

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