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Research Article

Synthesis and Antimicrobial Action of 1,2,4-Triazole Derivatives Containing Theophylline and 1,3,4-Thiadiazole Fragments In their Structure.

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ABSTRACT

1,2,4-triazole derivatives display a wide range of biological properties, such as antimicrobial, antimycotic, antiviral and other ones. Synthesis of new 1,2,4-triazole derivatives is a very relevant approach as this heterocyclic system is low toxic and pharmacologically active. This prompted us to synthesize in one structure a heterocycle with theophylline and 1,3,4-thiadiazole fragments and to study their biological properties further. This work presents our studies of the antimicrobial activity of the synthesized compounds Piperazin-1-ium 2-((5-((theophylline-7-yl)methyl)-4-ethyl-1,2,4-triazol-3-yl)thio)acetate (GKP-F-67) and Piperazin-1-ium 2-(((4-phenyl-5-(((5-(phenylamino)-1,3,4-thiadiazol-2-yl)thio)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate (GKP-245). Estimation of the minimum inhibitory concentration of the synthesized compounds was carried out with the method of serial dilution in the Mueller-Hinton Broth inoculated with 1 ml of the microorganism under study. The presence or absence of visible growth was evaluated after incubation. 6-hour broth cultures of the microorganisms under study were used for the preparation of the inoculum. The concentration of the microbial suspension was equivalent to the 0.5 McFarland turbidity standard. As test cultures we used 18-hour agar or broth cultures of museum strains of S. aureus ATCC 25923, E. coli ATCC 25922, E. faecalis ATCC 29212, *C. albicans* CCM 885 and clinical strains of P. haemolytica, Enterobacter spp., Proteus spp., Staph. spp., S. pyogenes. Microorganisms were considered sensitive to the test compounds if the inhibition zone was larger than 10 mm. The minimum inhibitory concentration of GKP-F-67 and GKP-245 solutions was 750 mkg/ml for most microorganisms tested. The best antimicrobial activity of GKP-F-67 and GKP-245 solutions was exhibited at concentrations of 1% and 3%.

Keywords: *1,2,4-triazole, theophylline, 1,3,4-thiadiazole, microorganisms, antimicrobial action*

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INTRODUCTION

The primary task for the modern pharmaceutical industry is to search for potentially biologically active compounds and to create new drugs based on them. Present in a large number of pharmacotherapeutic agents heterocyclic systems attract particular attention in this aspect. 1,2,4-triazole, 1,3,4-thiadiazole and theophylline derivatives are among the interesting objects of study. Different combinations of these heterocyclic structures within a single molecule with subsequent chemical modification create favorable conditions for the search for biologically active substances. Moreover, derivatives of such heterocycles are characterized by low toxicity and simple chemical modification methods. The 1,2,4-triazole nucleus is a structural fragment of many synthetic drugs with antifungal (fluconazole, intraconazole) (Collin *et al*., 2003, Ezabadi *et al*., 2008, Gupta *et al*., 2007), antidepressant (trazodone, alprazolam), hepatoprotective (Shcherbyna *et al*., 2017), wound healing and antiviral (thiotriazoline) activity (Rawal *et al*., 2005; Jiao *et al*., 2012; Lieberman-Blum *et al*., 2008). Many 1,3,4-thiadiazole derivatives show a wide range of biological activities such as antimicrobial, antibacterial, antimycobacterial, antitrypanosomal, analgesic, anti-inflammatory, antifungal, antituberculosis, antitumor, antihypertensive, anesthetic, and anticonvulsant (Rawal *et al*., 2007; Shobha *et al*., 2013, Bektaş

et al., 2010, Gupta *et al*., 2007). Thus, the biological activity of these compounds prompted us to synthesize the above-mentioned synthons in one structure and to proceed with screening of their microbiological properties.

The purpose of the work is to synthesize substances that combine fragments of 1,2,4-triazole, 1,3,4-thiadiazole and theophylline in their structure and to study their antimicrobial activity.

MATERIALS AND METHODS

Chemistry: As the starting compound, 4-phenylthiosemicarbazide was used, which in the DMF medium, when mixed with carbon disulfide, formed 5-phenylamino-1,3,4-thiadiazole-2-thione. The resulting reaction product and theophylline were subjected to alkylation with prop-2-yl ester of 2-chloroethanoic acid followed by hydrazinolysis, nucleophilic addition of phenylisothiocyanate and intramolecular alkaline heterocyclization. The reaction of the corresponding thiol with sodium monochloroacetate in aqueous medium and subsequent acidification with ethanoic acid gave the target acid. Piperazine salts of 2-((4-phenyl5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid and 2-((5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)methyl)-4-phenyl-1,2,4-triazole-3-yl)thio)acetic acid were obtained by the interaction of the corresponding acid with piperazine in propan-2-ol followed by evaporation of the solvent. For analysis, the synthesized substances were purified by crystallization from a mixture of water – propan-2-ol (1:1).

General procedure: Melting points were determined in open capillary tubes in a "Stanford Research Systems Melting Point Apparatus 100" (SRS, USA). The elemental analysis (C, H, N) was performed using the "Elementar vario EL cube" analyzer (Elementar Analysensysteme, Germany). IR spectra (4000 - 400 cm^{-1}) were taken off the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). ^1H NMR spectra (400 MHz) were recorded at a "Varian-Mercury 400" spectrometer with $SiMe_4$ as an internal standard in the DMSO-d_6 solution. Chromatography-mass spectral studies were conducted on the Agilent 1260 Infinity HPLC instrument equipped with an Agilent 6120 mass spectrometer (electrospray ionization method (ESI)) (Breitmaier, 2002, Stuart, 2004).

Antimicrobial screening: Estimation of the Minimum Inhibitory Concentration (MIC) of GKP-F-67 and GKP-245 was carried out with the method of serial dilution in the Mueller-Hinton Broth inoculated with 1 ml of the test organism and after incubation the presence or absence of visible growth was evaluated. 6-hour broth cultures of microorganisms were used for the preparation of the inoculum. The concentration of the microbial suspension was equivalent to the 0.5 McFarland turbidity standard. Different concentrations of GKP-F-67 and GKP-245 compounds were added to each tube: 3000.0; 1500.0; 750.0; 375.0; 187.5; 93.8; 46.9; 23.4; 11.8; 5.9 mkg/ml. Purified water was used to dilute the compounds. One tube with a nutrient medium was left to control the growth activity of the culture. We considered MIC the maximum dilution of the compound at which visually no microbial growth was observed. In the disc diffusion test, paper disks impregnated with 0.5%, 1% and 3% solutions of these compounds were used as the carriers of the GKP-F-67 and GKP-245 compounds. The disks were placed with tweezers on the surface of the contaminated nutrient medium at the equal distances from each other and approximately at the distance of 2 cm from the edge of the cup. As test cultures we used 18-hour agar or broth cultures of museum strains of *S. aureus ATCC 25923, E. coli ATCC 25922, E. faecalis ATCC 29212, C. albicans CCM 885* and clinical strains of *P. haemolytica, Enterobacter spp., Proteus spp., Staph. spp., S. pyogenes.* Microorganisms were considered sensitive to the test compounds if the ingibition zone was larger than 10 mm.

The upside-down cups were incubated in a thermostat for 18-20 hours, at a temperature of 35-37°C. Preparation of inocula and nutrient media was carried out with standard methods according to the methodological guidelines 9.9.5-143-2007 "Estimation of microorganisms' sensitivity to antibacterial drugs".

RESULTS

At the first stage of our work, we determined optimal conditions for obtaining the compounds 5.9, 5.10 (Gotsulia *et al*, 2014). The synthesis was performed through a series of successive steps: preparation of an ester, its hydrazinolysis, interaction with ethyl or phenyl isothiocyanate and intramolecular cyclization in an alkaline medium. The reaction of the obtained thiol with the monochloroacetic acid in an aqueous solution of the doubled amount of alkali followed by neutralization with hydrochloric acid resulted in the corresponding carboxylic acid (5.7, 5.8). The neutralization reaction resulted in salts with piperazine in an aqueous medium (5.9, 5.10).

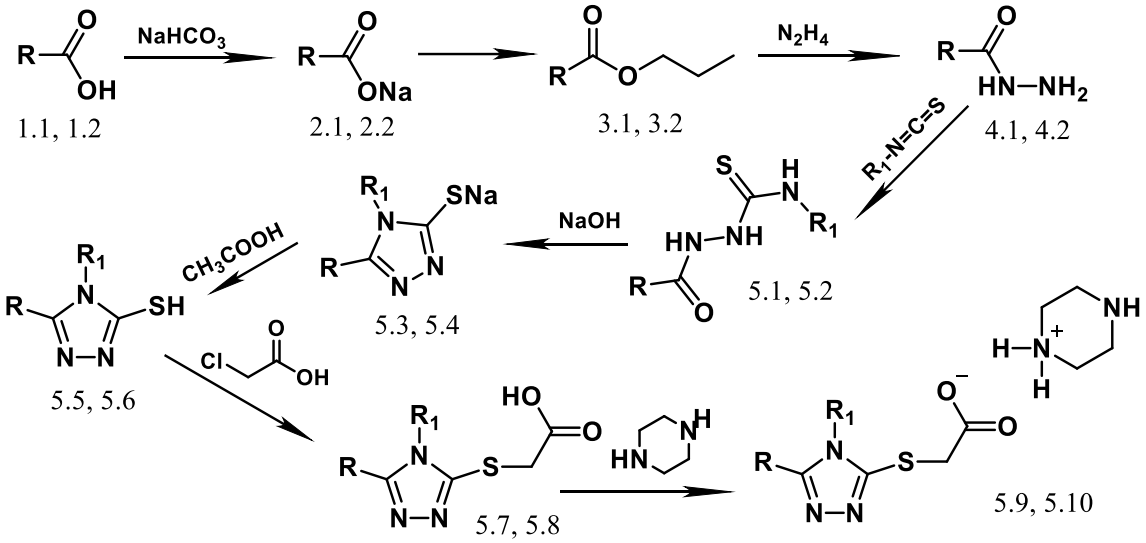
Piperazin-1-ium 2-((5-((theophylline-7-yl) methyl)-4-ethyl-1,2,4-triazol-3-yl)thio)acetate (5.9) (GKP-F-67): The formation of the salt was confirmed with the protonated piperazine signals and the absence of a proton signal of the carboxyl group. The piperazinedium cation is described by the presence of proton signals in the form of doublet of doublets at 2.88-2.85 ppm and 3.27-3.24 ppm with the corresponding spin-spin interaction constants. The methyl group proton signal at the first Nitrogen atom of the xanthine fragment is fixed as a singlet (3.37 ppm), the one at the third Nitrogen atom is fixed as a multiplet together with the proton of the piperazine fragment (3.55-3.52 ppm). The singlet proton of the thiomethylene fragment is registered at 4.08 ppm. The proton signals of the ethyl substituent of the triazole fragment form a multiplet at 4.13-4.10 ppm (-CH_2-CH_3) and a triplet at 1.36-1.32 ppm (-CH2-CH3) respectively. The methine proton of the theophylline fragment forms a singlet at 8.03 ppm. The signal of the methylene group, which combines the triazole and theophylline fragments, also manifests itself in the form of a singlet at 5.15 ppm. In the weak field at 9.71-9.67 ppm there is evident a two-proton signal of the H_2N^+-group of the piperazinedium fragment (Breitmaier, 2002).

^1H NMR (400 MHz, dimethyl sulfoxide d_6), δ, ppm: 9.71-9.67 (m, 2H, H_2N^+), 8.03 (s, 1H, =CH-), 5.15 (s, 2H, -CH_2-).

4.13-4.10 (m, 2H, -$\underline{CH_2}$-CH_3), 4.08 (s, 2H, S-$\underline{CH_2}$-), 3.55-3.52 (m, 4H, NH-piperazine, CH_3 theophylline), 3.37 (s, 3H, CH_3 theophylline) , 3.27-3.24 (dd, *J* = 11.9, 5.7 Hz, 2H, -CH_2-piperazine), 2.88-2.85 (dd, *J* = 6.8, 5.4 Hz, 2H, -CH_2-piperazine), 1.37-1.31 (m, 3H).

In the IR spectrum of the piperazinedium salt under study there are three valence vibration bands in the 1740-1665 cm^{-1} region. Wide absorption bands in the 3050-2900 cm^{-1} or 2710-2250 cm^{-1} region are also fixed as well as deformation fluctuations in the 1610-1565 cm^{-1} region (Stuart, 2004).

Piperazin-1-ium 2-((4-phenyl-5-((((5-(phenylamino)-1,3,4-thiadiazol-2-yl)thio)methyl)-4H-1,2,4-triazole-3-yl)thio)acetate (5.10) (GKP-245): The ^1H NMR spectrum of the compound 5.10 is also characterized by the presence of proton signals of the piperazinedium fragment in the form of doublets of doublets that resonate at 2.90-2.87 ppm and 3.29-3.26 ppm. The protons of the thiomethylene fragments produce in the strong field intense singlets, which are fixed at 4.07 ppm and at 4.43 ppm. The "aromatic" region is represented by a triplet, two double proton doublets of doublets and a multiplet in the range of 7.58-7.95 ppm, which confirms the presence of phenyl substituents. In the weak field at 9.65-9.62 ppm there is evident a two-proton signal of the H_2N^+-group of the piperazinedium fragment (Breitmaier, 2002)



R = theophylline (1.1, 2.1, 3.1, 4.1, 5.1, 5.3, 5.5, 5.7, 5.9), 5-phenylamino-1,3,4-thiadiazole (1.2, 2.2, 3.2, 4.2, 5.2, 5.4, 5.6, 5.8, 5.10)

Figure 1.
The synthetic route of title compounds

Table 1
Antimicrobial activity of GKP-F-67 and GKP-245 solutions

Compounds and their concentration	Types of microorganisms and inhibition zone, mm								
	S. aureus ATCC 25923	*E. coli ATCC 25922*	*E. faecalis ATCC 29212*	*C. albicans CCM 885*	*P. haemolytica (n=4)*	*E. spp. (n=7)*	*P. spp.(n=3)*	*S. spp. (n=6)*	*S. pyogenes (n=3)*
GKP-F-67 0.5 %	5	-	-	8	-	10±1.0	5±0.7	12±0.54	9±0.9
1%	8	6	16	24	10±1.23	18±2.3	20±2.3	20±0.7	15±1.2
3%	15	6	24	36	12±1.54	26±2.7	26±3.0	24±0.9	30±2.3
GKP-245 0.5 %	-	-	-	10	-	8±0.9	4±0.4	8±0.5	14±1.0
1 %	-	-	14	14	-	12±1.6	16±1.9	13±1.2	20±1.2
3 %	-	6	20	18	-	15±2.8	28±4.6	18±1.2	25±2.0

The minimum inhibitory concentration of GKP-F-67 and GKP-245 solutions for most microorganisms tested was 750.0 mkg/ml (Table 2). The MIC of GKP-245 solution for S. aureus ATCC 2592, E. coli ATCC 25922 and P. haemolytica was not determined. The MIC of the GKP-F-67 solution for E. coli ATCC 25922 was 3000.0 mkg/ml, for C. albicans CCM 885 – 93.8 mkg/ml and for P. haemolytica – 1500.0 mkg/ml. The MIC of GKP-245 solution for E. faecalis ATCC 29212 was 1500.0 mkg/ml, for C. albicans CCM 885 – 187.5 mkg/ml and for S. spp. – 1500.0 μkg/ml.

^{1}H NMR (400 MHz, dimethyl sulfoxide d_6), δ, ppm: 9.65-9.62 (m, 2H, H_2N^+), 7.58 - 7.49 (m, 5H, C_6H_5), 7.35 - 7.27 (dd, 2H, C_6H_5). 7.25-7.17 (dd, 2H, C_6H_5), 7.05-6.97 (t, 1H, C_6H_5), 4.43 (s, 2H, S-C*H2*-), 4.07 (s, 2H, S-C*H2*-), 3.50-3.46 (m, 1H, NH-piperazine), 3.29-2.26 (dd, 2H, -CH_2- piperazine), 2.90-2.87 (dd, 2H, -CH_2- piperazine).

Sensitivity to 0.5% GKP-F-67 solution showed E. spp. – 10±1.0 mm and S. spp. – 12±0.54 mm (Table 1). Sensitivity to 1% GKP-F-67 solution showed E. faecalis ATSC 29212 – 16 mm, C. albicans CCM 885 – 24 mm, P. haemolytica – 10±1.23 mm, E. spp. – 18±2.3 mm, P. spp. – 20±2.3 mm, S. spp. – 20±0.7 mm, S. pyogenes – 15±1.2 mm.

Sensitivity to 3% GKP-F-67 solution showed S. aureus ATCC 25923 – 15 mm, E. faecalis ATCC 29212 – 24 mm, C. albicans CCM 885 – 36 mm, P. haemolytica – 12±1.54 mm, E. spp. – 26±2.7 mm, P. spp. – 26±3.0 mm, S. spp. – 24±0.9 mm, S. pyogenes – 30±2.3 mm.

Sensitivity to 0.5% GKP-245 solution showed C. albicans CCM 885 – 10 mm and S. pyogenes – 14±1.0 mm. Sensitivity to 1% GKP-245 solution showed E. faecalis ATSC 29212 – 14 mm, C. albicans CCM 885 – 14 mm, E. spp. – 12±1.6 mm, P. spp. – 16±1.9 mm, S. spp. – 13±1.2, S. pyogenes – 20±1.2 mm. Sensitivity to 3% GKP-245 solution showed E. faecalis ATCC 29212 – 20 mm, C. albicans CCM 885 – 18 mm, E. spp. – 15±2.8 mm, P. spp. – 28±4.6 mm, S. spp. – 18±1.2, S. pyogenes – 25±2.0 mm.

Table 2
Minimum Inhibitory Concentration of GKP-F-67 and GKP-245 solutions

Types of microorganisms	MIC mkg/ml	
	GKP-F-67	GKP-245
S. aureus ATCC 25923	750.0	-
E. coli ATCC 25922	3000.0	-
E. faecalis ATCC 29212	750.0	1500.0
C. albicans CCM 885	93.8	187.5
P. haemolytica	1500.0	-
E. spp.	750.0	750.0
P. spp.	750.0	750.0
S. spp.	750.0	1500.0
S. pyogenes	750.0	750.0

DISCUSSION

1,2,4-triazole derivatives are widely used in medicine and pharmacy. Among them there are simple molecules containing 1,2,4-triazole ring, as well as bi- and polyheterocyclic compounds containing triazole ring or compounds consisting of one 1,2,4-triazole ring and one 1,3,4-thiadiazole ring or of two 1,2,4-triazole rings (Demirbas *et al*., 2004).

We synthesized in one structure a heterocycle with fragments of theophylline and 1,3,4-thiadiazole with the following study of their biological properties. The azoles are widely used as antimicrobial and antifungal agents (Bayrak *et al*., 2009; Ceylan *et al*., 2014; Cui *et al*., 2005; Demirbas *et al*., 2009; Yu *et al*., 2007). Literature tells us that piperazine and morpholine rings have antimicrobial activity (Foroumadi *et al*., 2006). At the moment, the number of commercially registered antimicrobial drugs is rather small among the derivatives of triazole. These are such antibiotics as eperezolid, which consists of a morpholine and an oxazolidine ring linked together by a fluorophenylene bond, linezolid, which contains a piperazine ring instead of a morpholine one and cefozopran, which is a 1,2,4-thiadiazole derivative (Dixit *et al*., 2006, Demirbas *et al*., 2009). Our research has confirmed that the compounds Piperazin-1-ium 2-((5-((theophylline-7-yl)methyl)-4-ethyl-1,2,4-triazol-3 yl)thio) acetate and Piperazin-1-ium 2-((4-phenyl-5-(((5-(phenylamino)-1,3,4-thiadiazol-2-yl)thio)methyl)-4H-1,2,4-triazol-3-yl)thio)acetate display activity against such microorganisms as S. aureus, E. faecalis, P. haemolytica, E. spp., P. spp., S. spp., S. pyogenes and such fungi as C. albicans. Nowadays, the resistance of microorganisms and fungi to a wide range of known drugs makes relevant a search for new antimicrobial and fungicidal agents, which would have a different chemical structure from the usually used ones (Ceylan *et al*., 2014). The compounds we synthesized can potentially become such agents and therefore require further detailed study.

In conclusion, GKP-F-67 and GKP-245 solutions exhibited best antimicrobial activity at 1% and 3% concentrations. Sensitivity to GKP-F-67 solutions was found in S. aureus ATCC 25923, E. faecalis ATCC 29212, C. albicans CCM 885, P. haemolytica, E. spp., P. spp., S. spp., S. pyogenes. Sensitivity to GKP-245 solutions was found in E. faecalis ATCC 29212, C. albicans CCM 885, E. spp., P. spp., S. spp., S. pyogenes. The minimum inhibitory concentration of GKP-F-67 and GKP-245 solutions was 750.0 mkg/ml for most of the microorganisms tested.

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