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OF THE REPUBLIC OF KAZAKHSTAN

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SYNTHESIS, CHEMICAL TRANSFORMATIONS AND ANTIMICROBIAL ACTIVITY OF SOME THIOSEMICARBAZIDES OF *o*- AND *p*-HYDROXYBENZOIC ACID

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Key words: isothiocyanates, thiosemicarbazide, hydroxybenzoic acid, 1,2,4-triazol-5(4H)–thione, biological activity.

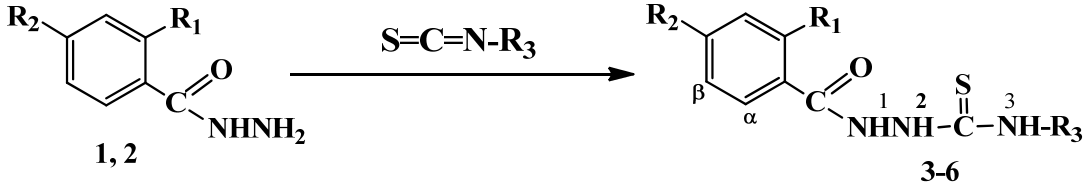
Abstract. The article describes information about synthesis of various thiosemicarbazide compounds obtained by reacting hydrazines of o- and p-hydroxybenzoic acids with various isothiocyanates and potassium thiocyanate. The optimal conditions for the reaction of glycosyl isothiocyanate with studied hydrazides were suggested. Intramolecular heterocyclisation of obtained thiosemicarbazide derivatives into 1,2,4-triazole-5(4H)-thiones was performed. It was found the expression and moderately expressed antimicrobial activity of the synthesized compounds. Composition and structure of the new obtained compounds were proved by elemental analysis and ^{1}H NMR spectroscopy.

At present time, the searching of chemical compounds having antibacterial activity is carried out on the basis of certain scientific principles and quantitative approaches that predicted structure of the compounds and lead, in essence, their purposeful synthesis. In the development of scientific researches in this area several trends can be traced, one of which is the introduction to the structure of the desired molecule pharmacophore fragments. Such fragments include thiosemicarbazide and hydrazide groups, and many of its derivatives [1-3]. It is also known that thiosemicarbazide derivatives have a wide range of biological activities: anticonvulsant, hypoglycaemic, anti-inflammatory and antibacterial [4, 5]. So, tibon (tioatsetazon or para-thiosemicarbazone *p*-acetaminobenzaldehyde), developed more in the laboratory of AUSRICP under the guidance of corr. AMS USSR G.N. Pershin, was one of the first antiviral drugs thiosemikarbazide fragment [5]. Thiosemicarbazide derivatives have become common among tuberculostatics [6-8].

In this regard, we are interested to synthesize new derivatives based on thiosemicarbazide hydrazides of *o*- and *p*-hydroxybenzoic (salicylic and nipagin) acids and studying their biological properties for the presence of antimicrobial activity. Special attention in this regard deserves hydrazide of salicylic acid derivatives, which are widely used as antipyretic, antirheumatic, anti-inflammatory, analgesic and anti-TB agents [4, 5]. Initial hydrazides (1, 2) were obtained hydrazinolysis methyl salicylate and nipagin (methyl ester of *o*- and *p*-hydroxybenzoic acid).

Joining hydrazides to various isothiocyanates is one of the most convenient methods for the synthesis of substituted thiosemicarbazide, which are of great interest not only in terms of the possible studying biological activity, but also are the starting synthons for the synthesis based on these pharmacologically important nitrogen-containing heterocycles. Thus, [9] we have described the synthesis of allyl(phenyl)thiosemicarbazide of N-morpholinyl acetic acid, and the possibility of its cyclization of 1,2,4-triazol-3(4H)-thione.

In continuation of our research and expand the arsenal of new biologically active compounds, we carried out the reaction of nucleophilic addition of hydrazides of *o*- and *p*-hydroxybenzoic acid (1, 2) to allylisothiocyanate. The reaction is carried out in an alcoholic medium at equimolar ratios of reagents according by the scheme:



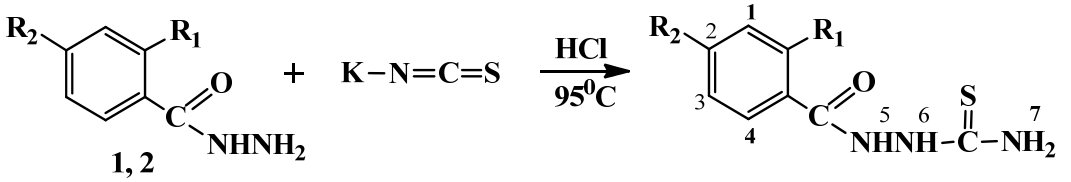
1, 2 **3-6**

R_1 = OH, R_2 = H, R_3 = CH_2=CH=CH_2- (1, 3); R_1= H, R_2 = OH, R_3 = CH_2=CH-CH_2- (2, 4); R_1= H, R_2 = OH, R_3 = CH_3CH_2- (2, 5); R_1= H, R_2 = OH, R_3 = C_6H_5- (2, 6).

In the IR-spectrum of the synthesized compounds (3-6) was shown the absorption band at 1330-1310 cm^{-1}, characteristic for the group -NH-CS thiosemicarbaze fragment of the absorption band of the amide group C(O)NH appear in the region 1690-1675 cm^{-1} and - NH-group in the 3390-3360 cm^{-1}.

In the ^{1}H NMR-spectrum allylthiosemicarbazide of *p*-hydroxybenzoic acid (4) signals α and β aromatic ring protons found in weak fields: a doublet H_α at 7.78 ppm ($J_{H\alpha H\beta}$= 8.7 Hz) and a doublet $H_\beta$at 6.81 ppm. Aromatic hydroxyl proton was shown singlet at 10.09 ppm. Amide and thioamide N-H protons are also written out in weak fields in the form of three singlets in 10.06 ppm (H_1), 9.25 ppm (H_2) and 8.2 ppm (H_3). Methine proton H_5 of vinyl fragment appears as a complex of multiplet at region of 5.82 ppm. Methylene protons H_{6a} and H_{6b} the same vinyl fragment manifest two doublets at region of 5.04 ppm and 5.14 ppm with constant spin-spin interaction J_{H6aH6b} = 17.27 Hz. Methylene protons NCH_2-fragment are shown in 4.09 ppm a broadened triplet.

In order to obtain new thiosemicarbazide derivatives we were also synthesized mono substituted thiosemicarbazide derivatives by reacting the corresponding hydrazide of *o*- and *p*-hydroxybenzoic acid (1, 2) with potassium thiocyanate according by the scheme:



1, 2 **7, 8**

R_1 = OH, R_2 = H (1, 7); R_1= H, R_2= OH (2, 8)

The reaction was performed in a dilute solution of hydrochloric acid at 95^{0}C during 4 hours. The main physico-chemical characteristics and the elemental analysis of the synthesized compounds (3-8) are shown in Table 1.

Table 1 – Physico-chemical constants, elemental analysis of the synthesized compounds (3-8)

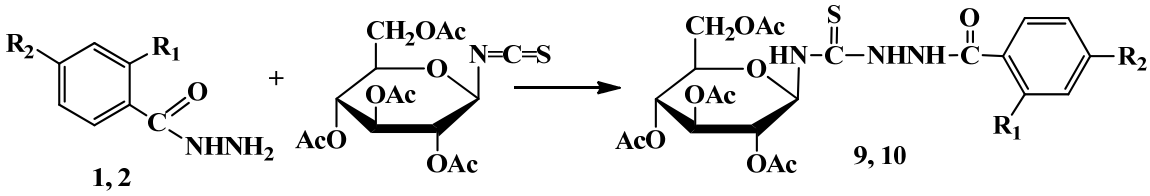
Comp.	Yield, %	$T_{m.p.}$,^{o}C	Found, %			Empirical Formula	Calculated, %		
			C	H	N		C	H	N
3	85.0	213-215	52.84	5.72	16.96	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72
4	53.0	215-216	52.90	5.80	17.12	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72
5	76.0	220-221	50.47	5.69	17.45	$C_{10}H_{13}N_3O_2S$	50.19	5.48	17.15
6	52.3	190-191	58.64	4.73	16.35	$C_{14}H_{13}N_3O_2S$	58.52	4.56	16.17
7	84.0	217-218	45.67	4.55	20.12	$C_8H_9N_3O_2S$	45.49	4.29	19.89
8	52.0	219-220	45.86	4.49	19.98	$C_8H_9N_3O_2S$	45.49	4.29	19.89
9	96.0	136-137	48.95	5.43	7.95	$C_{22}H_{27}N_3O_{11}S$	48.79	5.03	7.76
10	57.0	145-146	49.11	5.45	8.10	$C_{22}H_{27}N_3O_{11}S$	48.79	5.03	7.76
11	73.3	210-212	54.43	5.34	18.95	$C_{10}H_{11}N_3OS$	54.28	5.01	18.65
12	93.0	292-293	62.64	4.26	15.51	$C_{14}H_{11}N_3OS$	62.44	4.12	15.32
13	90.0	162-163	56.78	4.86	17.93	$C_{11}H_{11}N_3OS$	56.63	4.75	17.75

In the IR-spectrum of the thiosemicarbazide of *o*- and *p*-hydroxybenzoic acid (7, 8) there are absorption bands of stretching vibrations NH_2 group in the 3305-3240 cm^{-1}. In the 1660 cm^{-1} and 1270 cm^{-1} contains a carbonyl absorption bands (C=O) and thiocarbonyl (C=S) groups, respectively.

In the analysis ^1H NMR-spectrum of the compound (8) there are some characteristic signals of aromatic protons of the ring. Thus, the signals of aromatic protons H_1 - H_4 found in weak fields: a doublet H_1at 6.89 ppm, H_2 triplet at 7.42 ppm, doublet H_3at 6.93 ppm, H_4 doublet at 7.81 ppm. Aromatic hydroxyl proton singlet was shown at 9.42 ppm. Amide and thioamide N-H protons are shown in the form of three singlets in 11.89 ppm (H_5), 10.52 ppm (H_6) and 7.9 ppm (H_7).

As it is known, glycosyl isothiocyanates play an important role in carbohydrate chemistry, as synthons in the synthesis of various biologically active compounds [10]. Furthermore, it is known that the introduction of carbohydrate residues in the structure of biologically active substances lead to an increase in their solubility in water and a dramatic reduction in toxicity [11, 12].

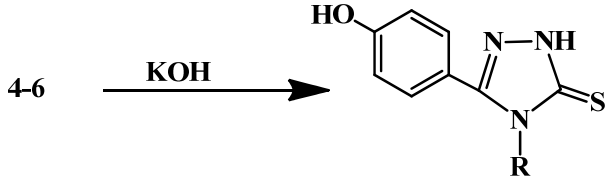
In this connection, the condensation of hydrazides (1, 2) with 1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranozyl isothiocyanate, obtained *in situ* from tetra-O-acetyl-α-D-glucopyranosyl bromide and lead thiocyanate were synthesized corresponding acetylated glycosyl derivatives containing thiosemicarbazide *o*- and *p*-hydroxybenzoic acid (9, 10), potentially possessing biological activity.



1, 2 **9, 10**

R_1 = OH, R_2 = H (1, 9); R_1 = H, R_2 = OH (2, 10)

Thiosemicarbazides are polyfunctional compounds; they can be used to generate a variety of heterocycles. Thus, the obtained boiling thiosemicarbazides (1-3, 4-6) with potassium hydroxide in aqueous solution for 2 hours and then acidified with acetic acid leads to novel cyclic products - 4-alkyl-3-(4-hydroxyphenyl)-1H-1,2,4-triazol-5(4H)–thione (4-6, 11-13).



11-13

R = CH_2=CH-CH_2- (4, 11) CH_2CH_3- (5, 12), C_6H_5- (6, 13).

The synthesized compounds (11-13) are white crystalline solids readily soluble in polar organic solvents.

In the IR-spectrum of the obtained new triazoles (11-13) no absorption band characteristic of an amide carbonyl (C=O) and in the region 1272 cm^{-1} absorption band is present to a thiocarbonyl group (C=S).

In the analysis of the ^1H NMR-spectrum of compound (12) the proton signals characteristic of the aromatic ring had observed. So, α and β signals of protons of the aromatic ring at 7.48 ppm prescribed ($J_{H\alpha H\beta}$8.6 Hz) and 6.93 ppm as two doublets respectively. In a weak field prescribed aromatic hydroxyl proton signals at 9.10 ppm and thioamide N-H proton at 13.79 ppm in the form of a small two broad singlet. Proton signals of the methyl group resonate at 1.15 ppm (J_{HH}7.1 Hz) as a triplet and methylene group at 4.01 ppm (J_{HH}7.2 Hz) as a quartet.

Physico-chemical constants, elemental analysis of the synthesized triazoles (11-13) are presented in Table 1.

In order to detect among synthetic derivatives of substances with a pronounced biological activity, the primary screening were conducted tests of compounds 3, 4, 7, 9 for antimicrobial activity against Gram-positive (Staphylococcus aureus, Bacillus subtilis) and gram-negative (Pseudomonas aeruginosa, Escherichia coli) strains by diffusion agar. Preparations comparison - gentamicin for bacteria and fungi to

nystatin. The antimicrobial activity of the compounds 3, 4, 7, 9 assessed by growth inhibition zone diameter of the test strains (mm). As a result of bioscreening it was found that the investigated compounds (3) show pronounced activity against Gram-positive strains (Staphylococcus aureus, Bacillus subtilis) (Table 2). Compounds (4), (7) and (9) exhibit moderate antibacterial activity, expressed as only against Gram-positive (Staphylococcus aureus, Bacillus subtilis) strain. Compounds (3) and (9) show moderately pronounced activity against gram-negative strains Escherichia coli and yeast fungus Candida albicans. Table 2 shows the numerical values of the diameters of zones of growth inhibition of test-strains (mm).

Table 2 – Information about antimicrobial activity test samples (3, 4, 7, 9)

Compound	S. aureus 505	Bacillus Subtilis	Pseudomonas aeruginosa	E. coli M-17	Candida Albicans
3	24 ± 0.1	26 ± 0.1	14 ± 0.2	20 ± 0.1	18 ± 0.2
4	18 ± 0.1	20 ± 0.1	–	14 ± 0.1	11 ± 0.3
7	20 ± 0.1	20 ± 0.2	–	11 ± 0.2	–
9	23 ± 0.2	22 ± 0.1	–	17 ± 0.1	16 ± 0.1
Gentamicin	26 ± 0.1	24 ± 0.1	24 ± 0.1	23 ± 0.2	–
Nystatin	–	–	–	–	22 ± 0.1

Note: "-" - a zone of growth inhibition is absent. The diameters of the zones of growth inhibition lower than 10 mm and the continuous growth in the absence of the cup was evaluated as antibacterial activity, 10-15 mm - weak activity 15-20 mm - moderately expressed activity of over 20 mm - expressed.

Thus, we have obtained based on hydrazides of *o*- and *p*-hydroxybenzoic acids are promising biologically thiosemicarbazide derivatives, which are found among the substances with moderate and marked antimicrobial activity.

Experimental part

IR-spectra were recorded on a spectrometer with Fourier transformer «AVATAR-320" company NICOLET tablets with KBr. ^{1}H NMR-spectra were recorded on a Bruker DRX500 spectrometer 500 MHz in DMSO-d_6 solution, relative to internal TMS (measurement error ±0.05ppm). Melting point defined on the device «Boetius» (measurement error ±0.1^{o}C). Control of the reaction and purity of the obtained compounds was monitored by thin layer chromatography plates «Silufol UV-254" in the system isopropanol-benzene- ammonia (25%) - 10:5:2. The plates showed iodine vapor.

4-(Allyl)-1-[2-hydroxybenzoyl]thiosemicarbazide (3). To a stirred solution of hydrazide 1.52 g (0.01 mol) of *o*-hydroxybenzoic acid in 20 ml of ethanol was added bydropwise 1.1 ml (0.011 mol) allylisocyanate. The mixture was stirred for 60 minutes at a temperature of 50-60^{0}C. Completion of the reaction was monitored by TLC. Upon cooling, powdery white crystalline solid fell. Recrystallization from 2-propanol, yielding 2.14 g (85.0%) of the compound (3) with $T_{m.p.}$ 213 -215^{0}C.

4-(Allyl)-1-[4-hydroxybenzoyl]thiosemicarbazide (4) was obtained analogously to compound **(3)** in yield of 53%, $T_{m.p.}$215 -216^{0}C (2-propanol).

4-Ethyl-2-(4-hydroxybenzoyl)thiosemicarbazide (5). To a stirred solution of hydrazide 1.52 g (0.01 mol) of *p*-hydroxybenzoic acid in 20 ml of ethanol was added bydropwise 0.95 g (0.011 mol) ethylisotiocyanate. The mixture was stirredduring 10 hours at temperature of 50-60^{0}C. Completion of the reaction was monitored by TLC. The solution was cooled; the precipitate fine crystalline sediment was filtered, washed with a small amount of cold ethanol. Recrystallization from 2-propanol was obtained 1.81 g (76.0%) with $T_{m.p}$220-221^{o}C.

^{1}H NMR, δ, ppm, J/Hz: 1.05 t (3H, CH_3, J_{HH} 7.1), 2.50 q (2H, CH_2), 6.81 d (1H, $CH_{aromatic}$), 7.78 d (1H, $CH_{aromatic}$, J_{HH}8.7 Hz), 8.02 s (1H, NH_3), 10.06 s (1H, NH_2), 9.13 s (1H, NH^1), 10.04 s (1H, OH). Found,%: C 50.47; H 5.69. $C_{10}H_{13}N_3O_2S$. Calculated,%: C 50.19; H 5.48.

N-Phenyl-2-(4-hydroxybenzoyl)hydrazinecarbothioamido (4) was prepared analogously to compound **(5)**. Yield is 2.09 g (52.3%), $T_{m.p}$190-191^{o}C (2-propanol).

1-(2-hydroxybenzoyl)thiosemicarbazide (7). The mixture of hydrazide 1.66 g (0.01 mol) of *o*-hydroxybenzoate acid (1), 1.4 g (0.015 mol) of potassium thiocyanate, 1.5 ml of hydrochloric acid in

20 ml of water was heated with stirring for 4 hours at 95°C. The reaction mixture was allowed to stand at room temperature overnight. The solution was basified until pH = 6-7 and the precipitate formed is filtered off. After it was recrystallized by ethanol and yield was 1.78 g (84.0%) with $T_{m.p}$ 217-218 °C.

1- (4-hydroxybenzoyl) thiosemicarbazide (8) is obtained analogously to compound (5) with yield of 52% and $T_{m.p}$ 219-220 °C (2-propanol).

4-[2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl]-1-[2-hydroxybenzoyl]thiosemicarbazide (9). To the solution of 1-isothiocyano-1-deoxy-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose in o-xylene obtained *in situ*, during 8 hours by refluxing 1.32 g (3.2 mmol) of acetobromoglucose, 1.61 g (5 mmol) of acetobromoglucose lead thiocyanate, lead thiocyanate, was added hydrazide0.5 g (0.003 mol) of *o*-hydroxybenzoic acid and stirred at room temperature for about 2 hours to the lack of glucosylisothiocyanate by TLC. The solution was evaporated and obtained a white powdery substance. Crude yield was 1.72 g (96.0%). After two recrystallizations from benzene to give a crystalline product with $T_{m.p}$136-137°C.

4-[2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl]-1-[4-hydroxybenzoyl]thiosemicarbazide (10) is obtained analogously to compound **(7)** in a yield of 57.0%, $T_{m.p}$145-146°C (2-propanol).

4-Ethyl-3-(4-hydroxyphenyl)-1H-1,2,4-triazol-5(4H)-thione (12). To the alkaline aqueous solution 0.40 g (0.01 mol) of NaOH in 30 ml distilled water was added 2.39 g (0.01 mol) of the compound (1). The reaction mixture was heated at 85 °C for 2 hours, then cooled and neutralized with hydrochloric acid to pH=7. The precipitate was filtered off and recrystallized by 2-propanol. Yield was 1.62 g (73.3%) with $T_{m.p}$ 210-212°C. ^{1}H NMR, δ, ppm, *J*/Hz: 1.15 t (3H, CH_3, J_{HH} 7.1), 4.01 q (2H, CH_2), 6.93 d (1H, $CH_{aromatic}$) d 7.48 (1H, $CH_{aromatic}$, J_{HH} 8.6 Hz), 10.09 s (1H, OH), 13.79 s (1H, NH). Found, %: C 54.43; H 5.34. $C_{10}H_{11}N_3OS$. Calculated,%: C 54.28; H 5.01.

4-Allyl-3-(4-hydroxyphenyl)-1H-1,2,4-triazol-5(4H)-thione (11) was prepared analogously. Yield was 2.09 g (90.0%), $T_{m.p}$ 162-163°C (ethanol).

4-Phenyl-3-(4-hydroxyphenyl)-1H-1,2,4-triazol-5(4H)-thione (13) was prepared analogously. Yield was 2.5 g (93.0%), $T_{m.p}$ 292-293°C (ethanol).

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СИНТЕЗ, ХИМИЯЛЫҚ ТҮРЛЕНДІРУЛЕР ЖӘНЕ КЕЙБІР о- ЖӘНЕ п-ГИДРОКСИБЕНЗОЙҚЫШҚЫЛ ТИОСЕМИКАРБАЗИДТЕРІНІҢ МИКРОБҚА ҚАРСЫ БЕЛСЕНДІЛІГІ

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Тірек сөздер: изотиоцианаттар, тиосемикарбазидтер, гидроксибензой қышқылы, 1,2,4-триазол-5(4*H*)-тион, биологиялық белсенділік.

Аннотация. Мақалада *о*- и *п*-гидроксибензой қышқыл гидразидтерінің әртүрлі изотиоцианаттармен және калий роданидімен әрекеттесуі арқылы алынатын тиосемикарбазидтердің синтездерін зерттеу нәтижелері қарастырылған. Гликозилизотиоцианаттың зерттелуші гидразидтермен әрекеттесу реакциясының тиімді жағдайлары ұсынылған. Алынған тиосемикарбазидтердің ішкімолекулалық гетероциклизацияға түсуі нәтижесінде 1,2,4-триазол-5(4*H*)-тиондарға айналуы іске асырылды. Синтезделінген жаңа заттардың жоғары және қалыпты-әсерлі антимикробты белсенділігі бар екендігі анықталды. Жаңа заттардың құрамы мен құрылысы элементті анализ бен ЯМР ^{1}Н-спектроскопия арқылы дәлелденді.

СИНТЕЗ, ХИМИЧЕСКИЕ ПРЕВРАЩЕНИЯ И ПРОТИВОМИКРОБНАЯ АКТИВНОСТЬ НЕКОТОРЫХ ТИОСЕМИКАРБАЗИДОВ о- И п-ГИДРОКСИБЕНЗОЙНЫХ КИСЛОТ

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Ключевые слова: изотиоцианаты, тиосемикарбазиды, гидроксибензойная кислота, 1,2,4-триазол-5(4*H*)-тион, биологическая активность.

Аннотация. В статье описаны результаты исследования по синтезу различных тиосемикарбазидных соединений, получаемых взаимодействием гидразидов *о*- и *п*-гидроксибензойных кислот с различными изотиоцианатами и роданидом калия. Предложены оптимальные условия реакции взаимодействия гликозилизотиоцианата с изучаемыми гидразидами. Проведена внутримолекулярная гетероциклизация полученных тиосемикарбазидных производных в 1,2,4-триазол-5(4*H*)-тионы. Установлена выраженная и умеренно-выраженная антимикробная активность синтезированных соединений. Состав и строение полученных новых соединений доказаны элементным анализом и ЯМР ^{1}Н-спектроскопией.

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