

Synthesis, Structure and Biological Activity of Coordination Compounds of Copper, Nickel, Cobalt, and Iron with Ethyl *N'*-(2-Hydroxybenzylidene)-*N*-prop-2-en-1-ylcarbamohydrazonothioate

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Abstract—*N*-(Prop-2-en-1-yl)hydrazonocarbothioamide reacts with iodoethane in methanol with further addition of 2-hydroxybenzaldehyde to form hydroiodide of carbamohydrazonothioate (HL·HI). The coordination compounds were obtained by interaction of HL or HL·HI with copper, nickel, cobalt and iron salts CuLX·*n*H₂O [X = Cl⁻, Br⁻, NO₃⁻; *n* = 0–1], Ni(L)₂·HI·CH₃OH, Co(L)₂X [X = I⁻, NO₃⁻] and Fe(L)₂NO₃. The structures of three complexes were established by single crystal X-ray analysis. The synthesized complexes exhibit selective antimicrobial and antifungal activity against a series of standard microorganisms and fungi in the concentration range of 30–500 μg/mL. In addition, nickel and iron complexes selectively inhibit the growth and proliferation of cancer cells and do not adversely affect normal cells.

Keywords: coordination compounds, carbamohydrazonothioates, antimicrobial activity, anticancer activity

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Derivatives of thiosemicarbazides can be used for the synthesis of drugs [1–4]. Carbamohydrazonothioates exhibit various modes of coordination to metal ions and possess antimicrobial, antifungal, anticancer, and other types of biological activity [5–12]. In this regard, the synthesis and study of properties of carbamohydrazonothioates and their coordination compounds seem to be promising.

We have synthesized copper, nickel, cobalt, and iron coordination compounds with ethyl-*N'*-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)carbamohydrazonothioate (HL) and determined their composition, structure, physico-chemical, and biological properties.

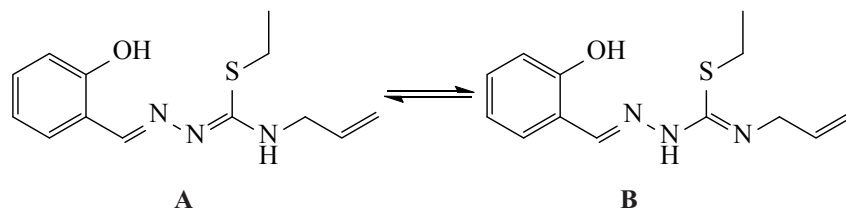
Ethyl *N'*-(2-hydroxybenzylidene)-*N*-prop-2-en-1-ylcarbamohydrazonothioate was obtained by the reaction of *N*-(prop-2-en-1-yl)hydrazinecarbothioamide

with iodoethane in methanol with following addition of 2-hydroxybenzaldehyde in the 1 : 1 molar ratio to the reaction mixture.

The structure of HL was determined by the NMR spectroscopy method. All signals in the spectrum are duplicated [13]. It points to the presence of tautomeric forms **A** and **B** of carbamohydrazonothioate in solution. The ratio of integral intensities of the signals of **A** and **B** forms is 1 : 0.4. The presence of tautomeric forms can be caused by the *syn/anti* isomerism of the C=N¹ double bond and the *cis/trans* isomerism of the C=N⁴ double bond (Scheme 1) [5, 14].

By the reaction of hot (50–55°C) ethanol solutions of copper, cobalt, and iron salts with the carbamohydrazonothioate HL in the mole ratio 1 : 1 in the case of copper and 1 : 2 in the case of cobalt and iron, small

Scheme 1.



crystal of compounds **1–3**, **6**, and **7** were obtained, for which the compositions $\text{Cu(L)X} \cdot n\text{H}_2\text{O}$ (**1–3**) [$\text{X} = \text{Cl}^-$ (**1**), Br^- (**2**), NO_3^- (**3**); $n = 0–1$] and $\text{Me(L)}_2\text{NO}_3$ [$\text{Me} = \text{Co}^{3+}$ (**6**), Fe^{3+} (**7**)] were proposed on the basis on the elemental analysis data (Table 1) Coordination compounds **4**, **5** were obtained by the reactions of $\text{HL} \cdot \text{HI}$ with nickel and cobalt acetates in the 2 : 1 mole ratio in methanol solutions. According to the elemental analysis, their compositions correspond to the formulae $\text{Ni(L)}_2 \cdot \text{HI} \cdot \text{CH}_3\text{OH}$ (**4**) and $\text{Co(L)}_2\text{I}$ (**5**). Coordination compounds **1–7** are insoluble in diethyl ether, poorly soluble in water, better—in alcohols, and highly soluble in DMF and DMSO.

By recrystallization of complexes **3** and **7** from ethanol and of complex **4** from methanol, single crystals were obtained, the structure of which was determined by the X-ray structural analysis (Table 2, Figs. 1–3). In the crystal structure of compound **4** there are the iodide ion and methanol molecule in the in the outer sphere, whereas the outer sphere of complex **7** contains the nitrate ion. In each complex, the metal atom coordinates carbamothioate HL to form five- and six-membered metal cycles. In the studied complexes **3**, **4** and **7** five- and six-membered metal cycles. In complexes **3**, **4** and **7** five- and six-membered metal cycles lie almost in the same plane, with dihedral angles between them not exceeding 8.5° , and angles between the planes of six-membered metal cycles and benzene rings of salicylidene

fragments not exceeding 5.8° . In coordination compound **3** the dihedral angle between the five-membered metal cycle and the fragment $\text{S}^1\text{C}^5\text{C}^6$ takes a value of 2.9° , and the dihedral angle between the six-membered metal cycle and the fragment $\text{C}^2\text{C}^3\text{C}^4$ 70.86° , whereas for complexes **4** and **7** similar angles in the molecules of the both ligands are 23.5 (88.26°), 80.08 (85.91°), and 77.78 (87.29°), 65.4 (68.07°), respectively.

Coordination bonds of the copper atom in complex **3** form a tetragonal pyramid. The base of the pyramid consists of the O^1 , N^1 , and N^3 organic ligand atoms and the $\text{O}^{1\text{W}}$ oxygen atom of a water molecule (Table 3). Displacements of these donor atoms from the mean plane of the pyramid base are -0.019 , -0.02 , 0.021 , and 0.018 Å, respectively. The deviation of the copper atom from the pyramid base is equal to 0.116 Å towards the $\text{O}^{1\text{N}}$ nitrate group oxygen atom occupying the axial position with the $\text{Cu}^1\text{—O}^{1\text{N}}$ distance of $2.457(3)$ Å. In the complex **3** crystal nitrate groups combine complexes in centrosymmetric dimers by $\text{N}^2\text{—H} \cdots \text{O}^{1\text{N}}$, $\text{C}^5\text{—H} \cdots \text{O}^{2\text{N}}$ and $\text{C}^7\text{—H} \cdots \text{O}^{3\text{N}}$ hydrogen bonds. The dimers are connected with each other by the $\text{O}^{1\text{W}}\text{—H} \cdots \text{O}^{3\text{N}}$ hydrogen bonds in chains, which form layers parallel to the (001) plane, within which the layers are bound by the $\text{O}^{1\text{W}}\text{—H} \cdots \text{O}^1$ and $\text{C}^5\text{—H} \cdots \text{O}^{1\text{N}}$ hydrogen bonds (Table 4, Fig. 4). In the layers there is a $\pi\text{—}\pi$ stacking interaction between five- and six-membered metal cycles. The distance between

Table 1. Physico-chemical characteristics of coordination compounds **1–7**

Complex	Yield, %	μ_{ef} , ^a μ_{B}	χ , ^a $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$	Found, %			Formula	Calculated, %		
				M ^b	N	S		M ^b	N	S
1	82	1.75	103	17.45	11.47	8.81	$\text{C}_{13}\text{H}_{16}\text{ClCuN}_3\text{OS}$	17.59	11.63	8.87
2	79	1.78	108	15.61	10.27	7.79	$\text{C}_{13}\text{H}_{16}\text{BrCuN}_3\text{OS}$	15.66	10.35	7.90
3	81	1.83	112	15.58	13.71	7.81	$\text{C}_{13}\text{H}_{18}\text{CuN}_4\text{O}_5\text{S}$	15.65	13.80	7.90
4	76	2.85	85	7.78	11.17	8.45	$\text{C}_{27}\text{H}_{37}\text{IN}_6\text{NiO}_3\text{S}_2$	7.90	11.31	8.63
5	84	^c	90	8.20	11.72	8.96	$\text{C}_{26}\text{H}_{32}\text{CoIN}_6\text{O}_2\text{S}_2$	8.29	11.83	9.03
6	86	^c	86	9.02	15.11	9.79	$\text{C}_{26}\text{H}_{32}\text{CoN}_7\text{O}_5\text{S}_2$	9.13	15.19	9.93
7	75	5.93	105	8.59	15.19	9.87	$\text{C}_{26}\text{H}_{32}\text{FeN}_7\text{O}_5\text{S}_2$	8.69	15.26	9.98

^a At 294 K.

^b M – metal.

^c Diamagnetic.

Table 2. Crystallographic characteristics, experimental data, a structure refinement for compound **3**, **4**, **7**

Parameter	Value		
	3	4	7
Chemical formula	C ₁₃ H ₁₈ CuN ₄ O ₅ S	C _{26.89} H ₃₂ IN ₆ NiO _{2.89} S ₂	C ₂₆ H ₃₂ FeN ₇ O ₅ S ₂
<i>M</i>	405.91	735.30	642.56
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	<i>P</i> -1	<i>C</i> 2/ <i>c</i>	<i>P</i> 21/ <i>c</i>
<i>Z</i>	2	8	4
<i>a</i> , Å	7.4464(9)	18.3136(8)	8.2137(8)
<i>b</i> , Å	9.9324(7)	18.9679(10)	16.1962(7)
<i>c</i> , Å	12.1455(9)	20.1004(8)	22.5614(11)
α , deg	92.397(6)	90	90
β , deg	101.133(8)	99.982(5)	94.714(5)
γ , deg	105.318(8)	90	90
<i>V</i> , Å ³	845.98(13)	6876.6(6)	2991.2(3)
<i>d</i> _{calc} , g/cm ³	1.594	1.420	1.427
λ , Å	0.71073	0.71073	0.71073
μ , cm ⁻¹	1.445	1.618	0.692
<i>T</i> , K	293(2)	293(2)	293(2)
Crystal size, mm	0.40×0.22×0.04	0.50×0.35×0.20	0.36×0.181×0.003
Limits of <i>h</i> , <i>k</i> , <i>l</i>	-8 ≤ <i>h</i> ≤ 8 -8 ≤ <i>k</i> ≤ 11 -14 ≤ <i>l</i> ≤ 13	-22 ≤ <i>h</i> ≤ 22 -22 ≤ <i>k</i> ≤ 17 -24 ≤ <i>l</i> ≤ 14	-6 ≤ <i>h</i> ≤ 9 -19 ≤ <i>k</i> ≤ 12 -26 ≤ <i>l</i> ≤ 19
Number of reflections measured/independent	4510 (<i>R</i> _{int} = 0.0217)/2974	11301 (<i>R</i> _{int} = 0.0238)/6321	10057 (<i>R</i> _{int} = 0.0829)/5233
Number of parameters	226	390	378
<i>R</i> ₁ / <i>wR</i> ₂ by <i>N</i> ₁	0.0542/0.0989	0.0828/0.1460	0.1993/0.1167
<i>R</i> ₁ / <i>wR</i> ₂ by <i>N</i> ₂	0.0413/0.0916	0.0510/0.1286	0.0780/0.0889
<i>S</i>	1.034	0.986	0.897
Δr	0.687/-0.381	0.525/-0.277	0.391/-0.495

the centroids of the corresponding cycles is 3.861 Å and the angle $\beta = 26.1^\circ$.

Coordination polyhedra of the nickel and iron atoms in compounds **4** and **7** are distorted octahedra (Figs. 2, 3). The octahedral volumes of these atoms are 11.435 and 10.918 Å³, respectively. In the crystal of complex **4** there are only Van der Waal's interactions between molecules (Fig. 5), whereas nitrate groups in the crystalline structure of complex **7** combine molecules in chains along the *c* axis due to hydrogen bonds. Such chains are bound with each other by the C^{5A}-H...O^{1N} hydrogen bonds (Table 4, Fig. 6). In complex **7** a π - π stacking interaction arises between benzene rings of different chains. The distance between centroids of the corresponding cycles is 3.777 Å with the angle $\beta = 27.4^\circ$. In complexes **3**, **4**, and **7** there are intramolecular hydrogen bonds C-H...S.

The methods of elemental analysis, molar electrical conductivity, magnetochemistry, and IR spectroscopy

were used to determine the composition and structure of the remaining complexes. It was found on the basis of the data on the molar electrical conductivity (κ) in methanol that complexes **1-7** are binary electrolytes ($\kappa = 85-112 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$).

The magnetochemical study of complexes **1-7** at room temperature (294 K) has shown (Table 1) that cobalt complexes **5** and **6** are diamagnetic. It indicates that of central atoms of cobalt are in the oxidation state +3 in the pseudo-octahedral ligand environment. For the copper compounds the values of effective magnetic moments correspond to one unpaired electron. These experimental data suggest that they have a monomeric structure. The nickel complex has the octahedral structure with the effective magnetic moment $\mu_{\text{eff}} = 2.85 \mu_{\text{B}}$ characteristic of two unpaired electrons. The iron complex is paramagnetic with $\mu_{\text{eff}} = 5.93 \mu_{\text{B}}$, which corresponds to the metal atom high-spin state, whereas the cobalt atom in the complex

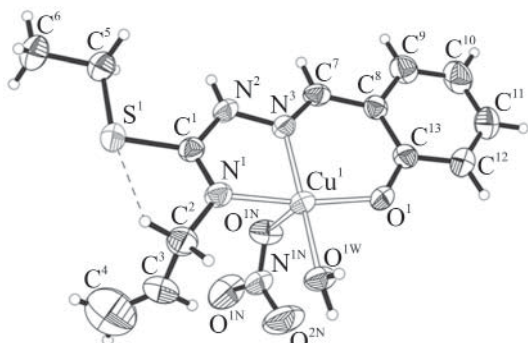


Fig. 1. General view of the complex **3** molecule in the crystal.

is in the low-spin state. These data point to a medium ligand field strength.

To determine the mode of carbamohydrazone-thioate HL coordination to metal central atoms, a comparative analysis of the IR spectra of complexes **1–7** and the ligand was carried out. Absorption bands in the ranges 3400–3100, 1660–1580, and 700–600 cm^{-1} are present in the IR spectra, which characterize stretching vibrations of coordinated carbamohydrazone-thioate HL molecules. The absorption band $\nu(\text{O}-\text{H}_{\text{phenol}})$ in the range of 3400–3100 cm^{-1} disappears from the IR spectra of all the complexes, which points to the deprotonation of the phenol OH group in the ligand molecules. The same conclusion can be drawn on the basis of the $\nu(\text{C}-\text{O})$ band position, which is observed in the range of 1230–1250 cm^{-1} in the HL spectrum, whereas in the spectra of the complexes it is shifted by 40–50 cm^{-1} to the low-frequency region. The band in the range of 3000–3400 cm^{-1} , which relates to the stretching $\nu(\text{N}^4-\text{H})$ vibrations in the HL molecule, undergoes a significant change. In the spectra of the complex compounds it is shifted to the high-frequency region by 50–70 cm^{-1} . In addition, the absorption band $\nu(\text{C}=\text{N})$ is shifted to the low-frequency region by 20–30 cm^{-1} . All of this point to the HL compound coordination to the metal atoms through the oxygen atom of deprotonated phenol and the nitrogen atoms of azomethine and thiocarbamide. The above coordination of HL carbamohydrazone-thioate is also confirmed by the fact that in the IR spectra of all the complexes a number of new absorption bands appear in the range of 530–405 cm^{-1} , which relate to the $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ (M is a metal) vibrations. The

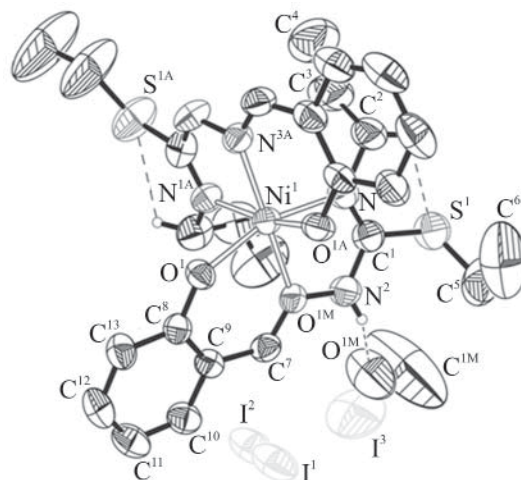


Fig. 2. General view of the complex **4** molecule in the crystal (hydrogen atoms are omitted).

$\nu(\text{C}=\text{S})$ absorption band is absent from the HL spectrum, because the sulfur atom is alkylated by iodoethane, and a new absorption band corresponding to $\nu(\text{C}-\text{S})$ appears at 682 cm^{-1} [12]. This band is not shifted on the complex formation, which indicates that the sulfur atom is not involved in the coordination with the metal ion.

The above-mentioned physico-chemical data allow us to present the distribution of chemical bonds [**B** (**1**, **2**) and **D** (**5**, **6**)] in the complexes (Scheme 2).

The complexes of biometals with methyl-*N'*-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)carbamohydrazone-thioate selectively inhibit the growth and reproduction of certain types of cancer cells and certain types of microorganisms [12]. In this regard we studied in vitro the antimicrobial and antifungal activity of

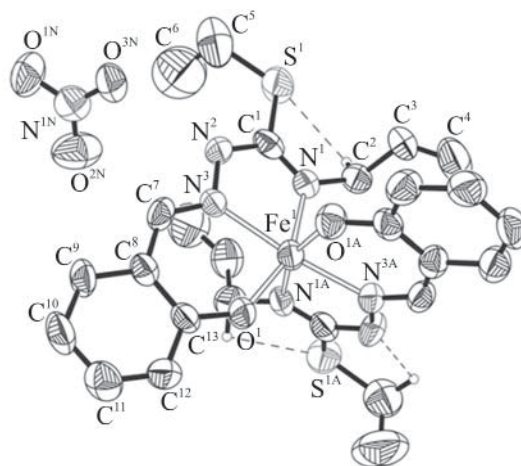


Fig. 3. General view of the complex **7** molecule in the crystal (hydrogen atoms are omitted).

Table 3. Certain interatomic distances and valence angles in molecules of complexes **3**, **4**, **7**

Bond	<i>d</i> , Å		
	3	4	7
Cu ¹ [Ni ¹]{Fe ¹ }–O ¹	1.893(3)	2.083(2)	1.923(4)
Ni ¹ {Fe ¹ }–O ^{1A}		2.090(2)	1.905(4)
Cu ¹ [Ni ¹]{Fe ¹ }–N ¹	1.959(3)	2.076(3)	2.109(5)
Ni ¹ {Fe ¹ }–N ^{1A}		2.082(3)	2.119(4)
Cu ¹ [Ni ¹]{Fe ¹ }–N ³	1.941(3)	2.025(3)	2.120(4)
Ni ¹ {Fe ¹ }–N ^{3A}		2.018(3)	2.116(4)
Cu ¹ –O ^{1N}	2.457(3)		
Cu ¹ –O ^{1W}	1.975(3)		
S ¹ –C ¹	1.744(4)	1.788(4)	1.754(6)
S ¹ –C ⁵	1.807(4)	1.802(8)	1.828(8)
O ¹ –C ¹³	1.325(5)	1.346(4)	1.309(6)
N ¹ –C ¹	1.289(5)	1.266(5)	1.286(6)
N ² –C ¹	1.363(5)	1.364(5)	1.358(7)
N ² –N ³	1.389(4)	1.378(4)	1.377(6)
N ³ –C ⁷	1.285(5)	1.278(4)	1.307(6)
C ² –C ³	1.503(8)	1.520(7)	1.497(7)
C ³ –C ⁴	1.221(8)	1.284(10)	1.284(10)
C ⁵ –C ⁶	1.514(6)	1.472(12)	1.465(9)
C ⁷ –C ⁸	1.435(5)	1.437(5)	1.429(7)
Angle	ω , deg		
O ¹ Cu ¹ [Ni ¹]{Fe ¹ }N ³	92.29(12)	85.75(11)	83.67(18)
N ^{3A} Ni ¹ {Fe ¹ }O ¹		96.70(11)	104.65(17)
O ¹ Cu ¹ [Ni ¹]{Fe ¹ }N ¹	171.56(12)	163.15(11)	155.64(18)
N ^{1A} Ni ¹ {Fe ¹ }O ¹		91.77(11)	90.31(18)
N ^{3A} Ni ¹ {Fe ¹ }O ^{1A}		86.01(11)	84.13(18)
N ³ Cu ¹ [Ni ¹]{Fe ¹ }N ¹	81.14(13)	79.41(12)	73.80(19)
N ^{3A} Ni ¹ {Fe ¹ }N ¹		98.73(12)	97.41(19)
N ¹ Ni ¹ {Fe ¹ }N ^{1A}		97.74(13)	86.05(18)
N ³ Ni ¹ {Fe ¹ }O ^{1A}		98.59(11)	98.39(17)
N ¹ Ni ¹ {Fe ¹ }O ^{1A}		89.44(12)	95.05(18)
N ^{3A} Ni ¹ {Fe ¹ }N ³		174.99(13)	171.00(19)
N ³ Ni ¹ {Fe ¹ }N ^{1A}		96.49(12)	103.26(18)
N ^{3A} Ni ¹ {Fe ¹ }N ^{1A}		79.10(13)	73.66(18)
N ^{1A} Ni ¹ {Fe ¹ }O ^{1A}		164.27(11)	157.71(18)
O ¹ Ni ¹ {Fe ¹ }O ^{1A}		84.91(10)	97.32(17)
O ¹ Cu ¹ O ^{1W}	91.60(13)		
N ³ Cu ¹ O ^{1W}	170.95(14)		
N ¹ Cu ¹ O ^{1W}	94.16(13)		
O ¹ Cu ¹ [Ni ¹]O ^{1N}	94.68(12)		
N ³ Cu ¹ [Ni ¹]O ^{1N}	80.91(12)		
N ¹ Cu ¹ [Ni ¹]O ^{1N}	89.55(12)		
O ^{1W} Cu ¹ O ^{1N}	106.91(14)		

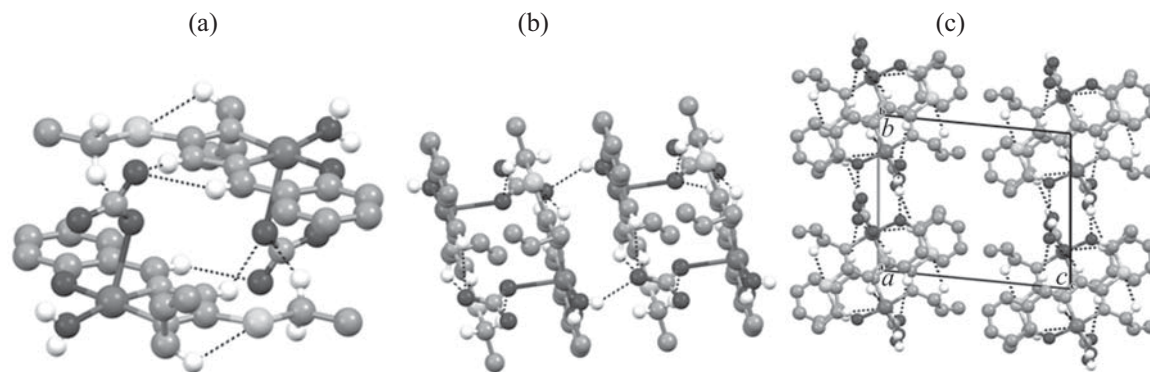


Fig. 4. General view of (a) dimer, (b) chain, and (c) fragment of molecules packaging in the complex 3 crystal.

coordination compounds 1–7 in relation to a series of standard strains of gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli* and *Klebsiella pneumoniae*) bacteria and of the representative of yeast-like fungi *Candida albicans*. The experimental data obtained are presented in Table 5, which shows that all the copper, nickel, cobalt, and iron initial salts and carbamohydranonioate HL do not show antimicrobial activity in relation to the above microorganisms. Complexes 1 and 3–7 show selective, both bacteriostatic

and bactericide, activity in the concentration range of 30–500 $\mu\text{g/mL}$ in relation to the microbes and in the range of 30–60 $\mu\text{g/mL}$, in relation to the *Candida albicans*. The nature of the central atom has the main influence on the minimal suppressive (MSC) and the minimal microbicide (MMC) concentrations of complexes 1 and 3–7. Complex 7 is the most active against gram-positive microorganisms, and complex 4, against gram-negative microorganisms. The proximity of MSC and MMC values

Table 4. Geometric parameters of hydrogen bonds in complexes 3, 4, 7

D–H...A bond	Distance, Å			DHA angle, deg	Atom A coordinates
	D–H	H...A	D...A		
3					
O ^{1W} –H ^{1WA} ...O ¹	0.86	1.83	2.6886	174	1–x, 1–y, –z
N ² –H ² ...O ^{1N}	0.86	2.17	2.8752	139	2–x, 2–y, –z
O ^{1W} –H ^{1WB} ...O ^{3N}	0.72	2.11	2.7186	143	–1+x, y, z
C ² –H ^{2A} ...S ¹	0.97	2.55	2.9778	107	x, y, z
C ⁵ –H ^{5A} ...O ^{2N}	0.97	2.52	3.2026	127	x, 1+y, z
C ⁵ –H ^{5B} ...O ^{1N}	0.97	2.48	3.2692	139	2–x, 2–y, –z
C ⁷ –H ⁷ ...O ^{3N}	0.93	2.47	3.3217	153	2–x, 2–y, –z
4					
C ^{2A} –H ^{2AA} ...S ^{1A}	0.97	2.54	3.0016	109	x, y, z
C ² –H ^{2B} ...S ¹	0.97	2.57	3.1022	115	x, y, z
7					
N ² –H ² ...O ^{3N}	0.86	2.09	2.9163	162	1–x, –1/2+y, 1/2–z
N ^{2A} –H ^{2A} ...O ^{1N}	0.86	2.38	2.8483	115	1–x, 1–y, –z
C ^{2A} –H ^{2AB} ...S ^{1A}	0.97	2.61	2.9880	103	x, y, z
C ² –H ^{2B} ...S ¹	0.97	2.57	2.9557	104	x, y, z
C ^{5A} –H ^{5AA} ...O ^{1N}	0.97	2.55	3.4892	162	x, y, z
C ^{5A} –H ^{5AB} ...N ^{2A}	0.97	2.60	2.9726	103	x, y, z
C ^{5A} –H ^{5AB} ...O ^{1N}	0.97	2.58	3.4848	155	1–x, 1–y, –z
C ⁵ –H ^{5A} ...O ^{3N}	0.97	2.47	3.2257	134	1–x, –1/2+y, 1/2–z
C ⁷ –H ⁷ ...O ^{3N}	0.93	2.54	3.3447	134	1–x, –1/2+y, 1/2–z
C ^{7A} –H ^{7A} ...O ^{2N}	0.93	2.56	3.4300	155	1–x, 1–y, –z

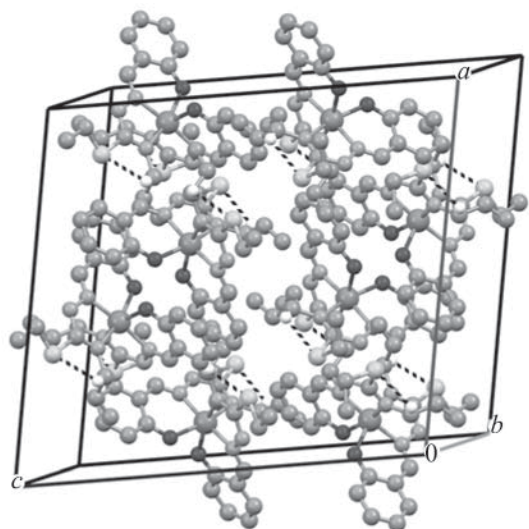


Fig. 5. Fragment of molecules packaging in the complex 4 crystal.

for many of compounds points to the anti-bacterial nature of their action.

The study of anti-proliferative activity of complexes 1–7 in relation to the cells of cervical cancer HeLa, pancreatic BxPC-3, and muscle tissue RD showed that, as in the case of 3*d*-metal complexes with methyl-*N'*-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)carbamohydrazonotioate [12], compounds 1–7 show anti-cancer activity in the concentration range of 0.1–100 μM . Table 6 presents concentrations of the semi-maximum inhibition (IC_{50}), which are indicators of the inhibitory action effectiveness of the substances under study in relation to the above-mentioned cells. The experimental data indicates that complex 7 exhibits a higher anti-cancer activity in relation to the HeLa and BxPC-3 cells than the anti-cancer drug doxorubicine used in the medical practice.

To determine the selectivity of the anti-proliferative action of carbamohydrazonothioate HL and complexes 1–7, their inhibiting activity in relation to the model line of normal mammalian cells MDCK was determined. As can be seen from Table 6, complex 7, having a high anti-cancer activity in relation to HeLa and BxPC-3 cells, scarcely affects negatively the growth and reproduction of normal MDCK cells.

The above experimental data point to the prospect of further search for antimicrobial, antifungal, and anti-cancer substances among coordination compounds of biometals with bioligands based on carbamohydrazonothionates.

EXPERIMENTAL

The X-ray structural analysis of compounds 3, 4, and 7 was fulfilled on an Oxford Diffraction diffractometer [15]. The structures were solved by direct methods and refined for non-hydrogen atoms by the least square method in anisotropic approximation according to the SHELX-97 programs [16]. Hydrogen atoms were included in the refinement in geometrically calculated positions, and their temperature factors U_{H} were taken to be 1.2 times greater than those of carbon, nitrogen, and oxygen atoms bound with them. The refinement of positions of the CH_3OH and HI molecules in compound 4 was fulfilled in view of their disordering. The basic experimental parameters and also the solution and refinement of the structures are presented in Table 2, and some interatomic distances, valence angles, and hydrogen bonds, in Tables 3 and 4. Coordinates of the basic atoms of the studied structures are deposited in the Cambridge Data Bank (CCDC 1944047–1944049).

Geometric parameters of the compounds under study were analyzed using the Platon program [17], and the observed π - π stacking interactions between cycles were

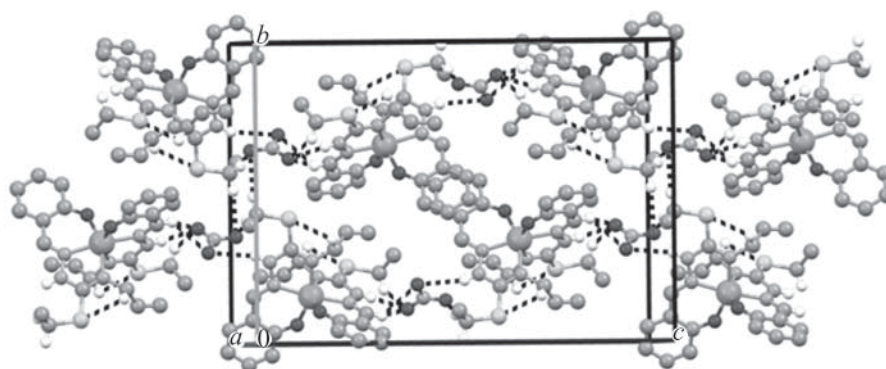


Fig. 6. Fragment of molecules packaging in the complex 7 crystal.

Table 5. Minimal suppressive (MSC) and microbicide (MMC) concentrations of coordination compounds **1** and **3–7** in relation to test-microbes ($\mu\text{g/mL}$)

Compound	<i>Staphylococcus aureus</i> , ATCC 25923		<i>Escherichia coli</i> , ATCC 25922		<i>Klebsiella pneumoniae</i>		<i>Candida albicans</i> , ATCC 90028	
	MSC	MMC	MSC	MMC	MSC	MMC	MSC	MMC
Initial salts ^a	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
HL	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
1	30	60	500	500	500	500	60	60
3	30	60	500	500	500	500	60	60
4	30	60	120	120	120	120	30	30
5	30	60	500	500	500	500	60	60
6	30	60	500	500	500	500	30	30
7	30	30	500	500	250	500	30	30

^a $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, CuBr_2 , $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, $\text{Ni}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$, $\text{Co}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$, $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Fe}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$.

Table 6. Semi-maximum inhibition of HeLa, BxPC-3, RD and MDCK cell growth by compounds **1–7**

Compound	IC_{50} , $\mu\text{mol/L}$				Compound	IC_{50} , $\mu\text{mol/L}$			
	HeLa	BxPC-3	RD	MDCK		HeLa	BxPC-3	RD	MDCK
HL	>100	88	>100	>100	5	>100	19	37	29
1	14	>100	13	12	6	>100	>100	>100	>100
2	37	22	12	33	7	2.2	1.3	>100	>100
3	13	1.1	5.5	1.6	Doxorubicine	10	3.7	16	7.1
4	83	69	57	>100					

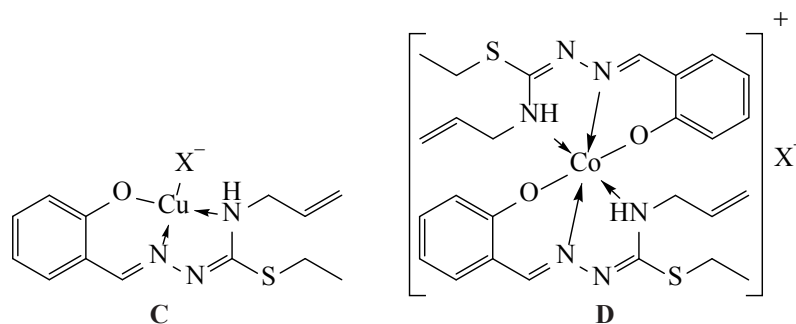
evaluated according to the criterion proposed in this program ($\text{CgI} \cdots \text{CgJ} < 6.0 \text{ \AA}$, $\beta < 60.0^\circ$, where β is the angle between the CgICgJ vector and the normal to the CgI aromatic cycle). Geometric calculations and figures were fulfilled with the Mercury program [18], and only those hydrogen atoms that participate in hydrogen bonds were left to represent the packaging of structures.

Electrical resistance of complexes **1–7** solutions in methanol (20°C , $c = 0.001 \text{ M}$) was measured with a P-38 reochord bridge. The IR spectra were recorded on a Bruker ALPHA spectrophotometer ($4000\text{--}400 \text{ cm}^{-1}$).

Effective magnetic moments of compounds **1–7** were determined by the Gouy method. The molar magnetic susceptibility corrected for diamagnetism was calculated on the based on the theoretical values of magnetic susceptibility of organic compounds.

Antimicrobial, antifungal, and anti-cancer activities were studied using the standard procedures [19].

Ethyl-*N'*-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)carbamohydranotioate (HL). To a methanol solution of 1.31 g (10 mmol) of *N*-(prop-2-en-1-yl)-hydrazinecarbothioamide, 1.71 g (11 mmol) of iodoethane

Scheme 2.

$\text{X} = \text{Cl}, \text{Br} \text{ (C)}; \text{NO}_3, \text{I} \text{ (D)}$.

was added. The resulting solution was stirred with continuous heating up to 60°C for 7 h, then 1.22 g (10 mmol) of 2-hydroxybenzaldehyde was added. The resulting solution was stirred with heating for 30 min. Resulting carbamohydrazone thionate hydroiodide was neutralized with sodium carbonate to a low-alkaline medium (pH=7–8). Then the liquid extraction with chloroform was carried out. The resulting yellow substance was dried in air. **Form A.** ¹H NMR spectrum (CDCl₃), δ, ppm: 1.38 t (3H, CH₃, *J* = 7.3 Hz), 2.90 q (2H, SCH₂, *J* = 7.3 Hz), 4.09 t (2H, CH₂N, *J* = 5.6 Hz), 4.49 br. s (1H, NH), 5.24 m (2H, CH₂=C), 5.98 m (1H_{Allyl}), 6.88 t (1H, CH_{Ar}, *J* = 7.5 Hz), 6.99 d (1H, CH_{Ar}, *J* = 7.5 Hz), 7.25 t (1H, CH_{Ar}, *J* = 7.5 Hz), 7.26 d (1H, CH_{Ar}, *J* = 7.5 Hz), 8.40 s (1H, CH=N), 11.85 br. s (1H, OH). ¹³C NMR spectrum (CDCl₃), δ_C, ppm: 14.56 (CH₃), 17.26 (CH₂=), 24.75 (SCH₂), 45.94 (CH₂N); 116.59, 118.88, 119.07, 130.75, 130.80 (C_{Ar}), 133.89 (CH_{Allyl}), 158.77 (CS), 160.54 (C_{Ar}). **Form B.** ¹H NMR spectrum (CDCl₃), δ, ppm: 1.38 t (3H, CH₃, *J* = 7.3 Hz), 3.11 q (2H, SCH₂, *J* = 7.3 Hz), 3.92 t (2H, CH₂N, *J* = 5.8 Hz), 5.23 m (2H, CH₂=C), 5.65 br. s (1H, NH), 5.87 m (1H, CH_{Allyl}), 6.91 t (1H, CH_{Ar}, *J* = 7.4 Hz), 6.97 d (1H, CH_{Ar}, *J* = 7.4 Hz), 7.24 t (1H, CH_{Ar}, *J* = 7.4 Hz), 7.29 d (1H, CH_{Ar}, *J* = 7.4 Hz), 8.43 s (1H, CH=N), 11.41 br. s (1H, OH). ¹³C NMR spectrum (CDCl₃), δ_C, ppm: 14.52 (CH₃), 24.79 (SCH₂), 45.80 (CH₂N), 116.32 (C_{Ar}), 116.81 (CH₂=), 118.79, 119.50, 131.14, 131.23 (C_{Ar}); 134.07 (CH_{Allyl}), 156.84 (CH=N), 158.50 (CS), 161.32 (C_{Ar}).

Chloro[2-((ethylsulanyl)(prop-2-en-1-ylamino)methylidene]hydrazinylidene}methylphenolato]-copper (1). To an ethanol solution of 10 mmol of ethyl-*N'*-(2-hydroxybenzylidene)-*N*-prop-2-en-1-yl)carbamohydrazone thionate, 10 mmol of copper(II) chloride dihydrate was added with continuous stirring and heating (50–55°C). After cooling to room temperature a fine crystalline precipitate was formed, which was filtered off on a glass filter, washed with small amounts of alcohol and ether, and dried in air to a constant weight.

Similarly, using copper(II) bromide and hydrates of copper(II), cobalt(II), and iron(III) nitrates as initial compounds taken in the mole ratios 1 : 1 and 1 : 2, compounds **2**, **3**, **6**, and **7** were synthesized.

Bis[2-((ethylsulanyl)(prop-2-en-1-ylamino)methylidene]hydrazinylidene}methylphenolato]-cobalt(III) iodide (5). To a methanol solution of 20 mmol of ethyl-*N'*-(2-hydroxybenzylidene)-*N*-prop-2-en-1-yl)carbamohydrazone thionate hydroiodide, 10 mmol of

cobalt(II) acetate tetrahydrate was added with continuous stirring and heating (50–55°C). After cooling the reaction mixture to room temperature, a fine crystalline precipitate was formed, which was filtered off on a glass filter, washed with small amounts of alcohol and ether, and dried in air to a constant weight.

Similarly, using nickel(II) tetrahydrate and HL·HI as initial compound taken in the mole ratio 1 : 2, complex **4** was synthesized.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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