Synthesis, Structure, and Biological Activity of Copper and Cobalt Coordination Compounds with Substituted 2-(2-Hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamides

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Abstract—The reaction of *N*-(prop-2-en-1-yl)hydrazinecarbothioamide with substituted 2-hydroxybenzaldehydes afforded the corresponding Schiff bases which were used as ligands to obtain copper and cobalt coordination compounds $Cu(NL^{1-6})X \cdot n H_2O$ ($X = Cl^-$, NO_3^- ; n = 0-3), $Co(HL^2)_2NO_3$, and $Co(NL^6)_2Cl$. The structure of the isolated complexes was determined by NMR spectroscopy and X-ray analysis. The complexes were tested for antimicrobial and antifungal activity against *S. aureus*, *E. coli*, and yeast-like fungi. Inhibitory effect of the initial thioamides and their complexes against human myeloid leukemia HL-60 cancer cell line was also studied.

Keywords: coordination compounds, 2-hydroxybenzaldehyde, allylthiosemicarbazones, antimicrobial activity, anticancer activity

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2-(2-Hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide possesses a number of donor atoms and is capable of forming structurally diverse coordination compounds with transition metals [1–6]; such complexes showed selective anticancer activity [7, 8]. It was found that their biological activity correlates with their structure. Therefore, synthesis and study of new metal complexes with 2-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide and its derivatives attract interest from both theoretical and practical viewpoints.

The present work was aimed at synthesizing copper and cobalt coordination compounds with 2-(5-bromo-2hydroxybenzilidene)- (H_2L^1) , 2-(3,5-dibromo-2-hydroxybenzylidene)- (H_2L^2) , 2-(2,3-dihydroxybenzylidene)- (H₂L³), 2-(2,4-dihydroxybenzylidene)- (H₂L⁴), 2-(2-hydroxy-3-nitrobenzylidene)- (H₂L⁵), and 2-(2-hydroxy-3-methoxybenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothioamides (H₂L⁶) (Scheme 1) and studying their structure, physicochemical properties, and biological activity.

Thioamides $H_2L^1-H_2L^6$ were synthesized by condensation of equimolar amounts of *N*-(prop-2-en-1yl)hydrazinecarbothioamide (4-allylthiosemicarbazide) and substituted 2-hydroxybenzaldehydes in ethanol. The yields, melting points, and elemental analyses of ligands $H_2L^1-H_2L^6$ are given in Table 1, and their NMR spectral data are collected in Table 2. We succeeded in obtaining single crystals of $H_2L^4-H_2L^6$ suitable for X-ray analysis (Table 3) by recrystallization from ethanol.





 $R^{1} = R^{2} = H, R^{3} = Br (H_{2}L^{1}); R^{1} = R^{3} = Br, R^{2} = H (H_{2}L^{2});$ $R^{1} = OH, R^{2} = R^{3} = H (H_{2}L^{3}); R^{1} = R^{3} = H, R^{2} = OH (H_{2}L^{4});$ $R^{1} = NO_{2}, R^{2} = R^{3} = H (H_{2}L^{5}); R^{1} = OCH_{3}, R^{2} = R^{3} = H (H_{2}L^{6}).$

Figures 1 and 2 show the structures of hydrazinecarbothioamides $H_2L^4 - H_2L^6$ in crystal according to the X-ray diffraction data (arbitrary atom numbering). Unlike previously described thiosemicarbazides and thiosemicarbazones [12–15], the N¹–C¹ bond has Z configuration. However, the $N^3 = C^5$ bond has E configuration, which is consistent with published data. The $C^1N^1N^2N^3S^1C^5$ fragment (A) in thioamides H₂L⁴- H_2L^6 is almost planar; the maximum deviations of atoms from the corresponding mean-square planes are 0.053, 0.07, and 0.062 Å, respectively. On the other hand, the entire molecules $H_2L^4 - H_2L^6$ are non-planar. The mean-square planes of the benzene rings $(\overline{C^6}-C^{11})$ are turned through angles of 17.3°, 11.2°, and 10.7° with respect to the A planes, and the torsion angles $C^{1}N^{1}C^{2}C^{3}$ and $C^{1}C^{2}C^{3}C^{4}$ are 92.2, -134.7°, 109.6, 2.9°, and 142.1, 128.8°, respectively. The $S^{1}-C^{1}$ and N^1 - C^1 distances in H₂L⁶ are shorter than those in H₂L⁴ and H_2L^5 by 0.021, 0.026 Å and 0.024, 0.035 Å, respectively (Table 4).

Molecules H₂L⁴ in crystal are linked through intermolecular hydrogen bonds $O^1 - H \cdots S^1$ i $C^2 - H \cdots O^1$ to form chains along the b axis due to double screw molecular axis (Fig. 3, Table. 5). Owing to the symmetry center, the chains are linked to each other through hydrogen bonds $N^2-H\cdots S^1$. Molecules H_2L^5 and H_2L^6 in crystal form centrosymmetric dimers through hydrogen bonds $N^2-H\cdots S^1$, $N^2-H\cdots O^1$, and O^1 -H···S¹ (Figs. 4, 5; Table 5). The dimers interact with each other mainly through van der Waals forces. In keeping with the criterion proposed in [16] (CgI···CgJ < 6.0 Å, β < 60.0°, where β is the angle formed by the CgICgJ vector and normal to the aromatic ring CgI), the crystal structure of thioamides $H_2L^4-H_2L^6$ is also characterized by $\pi-\pi$ stacking between the benzene rings (C^6-C^{11}) related to each other through the symmetry center in H_2L^4 and H_2L^5 or through the double screw axis in H_2L^6 . The distances between the centroids of these fragments are 5.334, 5.613, and 4.46 Å, and the angles β are 53.5°, 57.0°, and 12.2°, respectively. Apart from the above $\pi - \pi$ interactions, ligand H_2L^5 features Y-X...Cg (π -ring) interaction (X···Cg < 4.0 Å, γ < 30.0°, where γ is the angle between the XCg vector and normal to the aromatic ring), and X–H···Cg (π -ring) interaction (H···Cg < 3.0 Å, γ < 30.0°, where γ is the angle between the HCg vector and normal to the aromatic ring [16, 17]) is observed in the crystal structure of H_2L^6 . For the C¹-S¹...Cg (C⁶-C¹¹) interaction (-x, -y, 1-z), the distance between the S¹ atom and centroid of the benzene ring is 3.489 Å, and the angle γ is 2.7°. The C⁹-H···Cg (C⁶-C¹¹) (-x, 0.5 + y, 0.5 - z) interaction in H₂L⁶ is characterized by H...Cg 2.83 Å and γ 7.6°.

Thioamide	Yield, %	mp, °C	Found, %			Formula	Calculated, %			
		1,	С	Н	Ν		С	Н	N	
H_2L^1	87	172–174	41.82	3.73	13.21	C ₁₁ H ₁₂ BrN ₃ OS	42.05	3.85	13.37	
H_2L^2	90	210-212	33.72	2.65	10.93	$C_{11}H_{11}Br_2N_3OS$	33.61	2.82	10.69	
H_2L^3	75	198–200	52.76	5.35	16.44	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72	
H_2L^4	78	186–188	52.36	5.18	16.56	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72	
H_2L^5	85	151–153	47.00	4.02	20.24	$C_{11}H_{12}N_4O_3S$	47.13	4.32	19.99	
H_2L^6	92	225–227	54.14	5.54	15.77	$C_{12}H_{15}N_{3}O_{2}S$	54.32	5.70	15.84	

Table 1. Yields, melting points, and elemental analyses of substituted 2-(2-hydroxybenzylidene)-N-(prop-2-en-1-yl)hydra-zinecarbothioamides H₂L¹-H₂L^{6 a}

^a Some characteristics of thioamides H_2L^1 , H_2L^4 , and H_2L^6 were given in [9–11].

Thioamide	δ, ppm	δ _C , ppm
H_2L^1	10.56 br.s (1H, OH), 9.41 br.s (1H, NH), 8.47 br.s (1H, NH), 8.45 s (1H, CH=N), 7.90 d (1H, H _{arom} , $J = 2.5$ Hz), 7.38 m (1H, H _{arom}), 6.91 d (1H, H _{arom} , $J = 8.8$ Hz), 5.97 m (1H, CH=CH ₂), 5.15 m (2H, CH ₂ =), 4.35 m (2H, CH ₂ N)	177.42 (C=S); 155.74, 133.52, 129.87, 122.24, 118.30, 111.44 (C _{arom}); 139.48 (CH=N), 134.73 (CH=CH ₂), 115.24 (CH ₂ =), 46.37 (CH ₂ N)
H_2L^2	10.71 br.s (1H, OH), 9.88 br.s (1H, NH), 8.45 br.s (1H, NH), 8.40 s (1H, CH=N), 7.77 d (1H, H _{arom} , $J = 2.4$ Hz), 7.73 d (1H, H _{arom} , $J = 2.4$ Hz), 5.98 m (1H, CH=CH ₂), 5.16 m (2H, CH ₂ =), 4.37 m (2H, CH ₂ N)	177.43 (C=S); 152.49, 135.66, 131.14, 122.35, 111.49, 111.35 (C _{arom}); 141.38 (CH=N), 134.51 (CH=CH ₂), 115.41 (CH ₂ =), 46.58 (CH ₂ N)
H_2L^3	10.48 br.s (1H, OH), 8.73 br.s (1H, OH), 8.47 s (1H, CH=N), 8.27 br.s (2H, NH), 7.15 d (1H, H _{arom} , $J = 7.9$ Hz), 6.91 d (1H, H _{arom} , $J = 7.9$ Hz), 6.76 t (1H, H _{arom} , $J = 7.9$ Hz), 5.99 m (1H, CH=CH ₂), 5.17 m (2H, CH ₂ =), 4.36 m (2H, CH ₂ N)	178.32 (C=S); 145.31, 145.06, 142.92, 119.66, 119.61, 116.79 (C _{arom}); 142.96 (CH=N), 134.75 (CH=CH ₂), 115.26 (CH ₂ =), 46.40 (CH ₂ N)
H_2L^4	10.29 br.s (1H, OH), 9.44 br.s (1H, OH), 8.92 br.s (1H, NH), 8.35 s (1H, CH=N), 8.11 br.s (1H, NH), 7.38 d (1H, H _{arom} , $J =$ 8.5 Hz), 6.45 d (1H, H _{arom} , $J =$ 8.5 Hz), 6.41 s (1H, H _{arom}), 5.98 m (1H, CH=CH ₂), 5.15 m (2H, CH ₂ =), 4.35 m (2H, CH ₂ N)	177.85 (C=S); 160.84, 158.84, 131.50, 111.22, 108.10, 102.71 (C _{arom}); 145.01 (CH=N), 134.86 (CH=CH ₂), 115.15 (CH ₂ =), 46.41 (CH ₂ N)
H_2L^5	10.80 br.s (1H, OH), 10.69 br.s (1H, NH), 8.52 br.s (1H, NH), 8.58 s (1H, CH=N); 8.37 m, 8.16 m, 7.13 m (3H, H _{arom}); 5.98 m (1H, C H =CH ₂), 5.16 m (2H, CH ₂ =), 4.36 m (2H, CH ₂ N)	178.56 (C=S); 161.61, 135.83, 133.55, 126.21, 119.85, 116.74 (C _{arom}); 152.76 (CH=N), 134.63 (CH=CH ₂), 115.33 (CH ₂ =), 46.31 (CH ₂ N)
H ₂ L ^{6 b}	11.52 br.s (1H, OH), 9.23 br.s (1H, NH), 8.62 br.s (1H, NH), 8.42 s (1H, CH=N), 7.58 d (1H, H_{arom} , $J = 7.9$ Hz), 6.97 d (1H, H_{arom} , $J = 7.9$ Hz), 6.79 t (1H, H_{arom} , $J = 7.9$ Hz), 5.92 m (1H, CH=CH ₂), 5.13 m (2H, CH ₂ =), 4.22 m (2H, CH ₂ N), 3.82 s (3H, CH ₃)	177.46 (C=S); 148.39, 139.62, 121.30, 119.40, 118.57, 113.23 (C _{arom}); 146.42 (CH=N), 135.66 (CH=CH ₂), 115.94 (CH ₂ =), 56.35 (CH ₃), 46.22 (CH ₂ N)

Table 2. ¹H and ¹³C NMR spectra (acetone- d_6) of thioamides H₂L¹-H₂L^{6 a}

^a Some characteristics of thioamides H_2L^1 , H_2L^4 , and H_2L^6 were given in [9–11].

^b In DMSO- d_6 .

By mixing hot (50–55°C) ethanolic solutions of copper and cobalt chlorides or nitrates and thioamides $H_2L^1-H_2L^6$ at a molar ratio of 1:1 or 1:2 and subsequent heating for 50–60 min we obtained coordination compounds 1–10 whose elemental

compositions (Table 6) corresponded to the formulas $Cu(HL^{1-6})X \cdot nH_2O(1, 3-9) [X = Cl^-(1, 5, 7, 8), NO_3^-(3, 4, 6, 9); n = 0 (1, 5, 7, 8), 1 (3, 4, 6), 3 (9)], Co(HL^2)_2NO_3$ (2), and Co(HL⁶)_2Cl (10). Complexes 1–10 are insoluble in diethyl ether, poorly soluble in



Fig. 1. Structure of the molecule of 2-(2,4-dihydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide (H_2L^4) in crystal according to the X-ray diffraction data.



Fig. 2. Structure of the molecule of 2-(2-hydroxy-3-methoxybenzyl-idene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide (H_2L^6) in crystal according to the X-ray diffraction data.

Parameter	H_2L^4	H_2L^5	H_2L^6	9
Formula	$C_{11}H_{13}N_3O_{2.75}S$	$C_{11}H_{12}N_4O_3S$	$C_{12}H_{15}N_3O_2S$	$C_{12}H_{20}N_4O_8SCu$
M	263.30	280.31	265.33	443.92
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_{1}/c$	$P2_{1}/c$	$P2_{1}/c$	<i>P</i> -1
Ζ	4	4	4	4
<i>a</i> , Å	15.236(4)	8.9728(5)	13.661(14)	6.8720(7)
<i>b</i> , Å	4.5098(13)	16.6764(7)	5.978(4)	14.0564(18)
<i>c</i> , Å	20.553(5)	8.8395(5)	16.834(6)	18.901(2)
α, deg	90	90	90	79.178(10)
β, deg	95.65(2)	104.396(6)	108.17(6)	89.523(9)
γ, deg	90	90	90	87.640(10)
<i>V</i> , Å ³	1405.4(6)	1281.16(12)	1306.2(17)	1791.8(4)
$d_{\rm calc}, {\rm g/cm}^3$	1.244	1.453	1.349	1.646
λ, Å	0.71073	0.71073	0.71073	0.71073
μ , cm ⁻¹	0.232	0.263	0.246	1.384
Temperature, K	293(2)	293(2)	293(2)	293(2)
Crystal dimensions, mm	$0.80 \times 0.05 \times 0.02$	0.20×0.18×0.30	0.40×0.03×0.01	0.50×0.27×0.04
θ_{max} , deg	25.05	25.04	28.96	25.05
h, k, l	$-16 \le h \le 18$ $-3 \le k \le 5$ $-24 \le l \le 15$	$-7 \le h \le 10$ $-17 \le k \le 19$ $-9 \le l \le 10$	$ \begin{array}{r} -18 \le h \le 18 \\ -7 \le k \le 7 \\ -22 \le l \le 22 \end{array} $	$-8 \le h \le 8$ $-16 \le k \le 15$ $-22 \le l \le 14$
Number of independent	4482/2409	2785/1926	4767/4915	9835/6197
reflections (R_{int}) Number of reflections with $I > 2\sigma(I)$	0.0699	0.0186	0.00	0.0507
Number of refined parameters	156	172	150	485
R_1/wR_2 (independent reflections)	0.0739/0.1345	0.0425/0.0851	0.0736/0.1064	0.0866/0.1625
R_1/wR_2 (reflections with $I > 2\sigma(I)$]	0.1822/0.1703	0.0657/0.0960	0.2974/0.2091	0.1751/0.2013
Goodness of fit S	0.883	1.004	0.828	0.962
$\Delta \rho_{max} / \Delta \rho_{min}, \bar{e} / A^3$	0.291/-0.224	0.144/-0.201	0.310/-0.304	1.776/-0.473

Table 3. Crystallographic data and parameters of X-ray diffraction experiments and structure refinement for compounds $H_2L^4 - H_2L^6$ and 9

water, better soluble in alcohols, and readily soluble in DMF, DMSO, and acetonitrile. Their yields and some physicochemical characteristics are given in Table 6.

The structure of copper complex 9 was determined by X-ray analysis of its single crystal which was obtained by recrystallization from ethanol (Table 3). A unit cell of **9** contains two nonequivalent $[Cu(HL^6)H_2O]^+$ cations, two nitrate ions, and four water molecules. The copper atom in each cation coordinates singly deprotonated H_2L^6 molecule acting as a tridentate ligand to form two chelate rings, as well

as a water molecule (Fig. 6). The lengths of the coordination bonds are as follows: Cu^1-O^1 1.9152(2) $[1.9112(2)], Cu^1-S^1 2.2636(3) [2.2591(3)], Cu^1-N^3$ 1.9270(2) [1.9331(2)], and Cu^1-O_W 1.9430(2) Å [1.9605(3) Å] (Table 7). The six- and five-membered chelate rings lie virtually in one plane; the corresponding dihedral angles are 3.83 and 3.79°. Molecules 9 in crystal are linked to each other through the nitrate anions and water molecules to form a threedimensional intermolecular hydrogen bond system (Fig. 7). In keeping with the above noted criterion $(CgI \cdots CgJ < 6.0 \text{ Å}, \beta < 60.0^{\circ}, \text{ where } \beta \text{ is the angle}$ between the CgICgJ vector and normal to the aromatic ring CgI) [16], there exists π - π -stacking interaction between the $Cu^2O^{1A}C^{11A}C^{6A}C^{5A}N^{3A}$ metallacycles related through a symmetry center. The distance $Cg^1 \cdots Cg^1 (1 - x, 1 - y, -z)$ between the centroids of these fragments is 3.513 Å, and the angle β is equal to 13.8°. Apart from the π - π stacking, metal-Cg (π -ring) interaction (Cu···Cg < 4.0 Å) is observed in the crystal structure of complex 9. The Cu-Cg distances for the Cu¹...Cg (C⁶C⁷C⁸C⁹C¹⁰C¹¹) (-*x*, 1 - *y*, 1 - *z*) and Cu²...Cg (C^{6A}C^{7A}C^{8A}C^{9A}C^{10A}C^{11A}) (1 - *x*, 1 - *y*, -*z*) interactions are 3.517 and 3.487 Å, respectively.

Complexes 1–10 were characterized by elemental analyses, molar electrical conductivities, magneto-



Fig. 3. A fragment of crystal packing of 2-(2,4-dihydroxybenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothioamide (H₂L⁴).

Table 4. Selected bond lengths and bond angles in molecules H_2L^4 - H_2L^6 in crystal

Dond	d, Å					
Bond	H_2L^4	H_2L^5	H_2L^6			
S^1-C^1	1.687(5)	1.683(3)	1.662(7)			
C^5-N^3	1.283(5)	1.276(3)	1.264(7)			
$C^{5}-C^{6}$	1.460(6)	1.461(3)	1.448(8)			
N^3-N^2	1.397(5)	1.374(3)	1.399(6)			
N^1-C^1	1.330(5)	1.325(3)	1.295(8)			
N^1-C^2	1.437(5)	1.455(3)	1.476(9)			
N^2-C^1	1.355(5)	1.354(3)	1.356(8)			
C^2-C^3	1.463(7)	1.478(4)	1.462(10)			
Angle		ω, deg				
$N^{3}C^{5}C^{6}$	122.0(4)	121.4(2)	121.0(6)			
$C^5N^3N^2$	115.9(4)	115.4(2)	115.9(5)			
$C^1N^1C^2$	125.3(4)	123.9(2)	124.2(7)			
$C^1N^2N^3$	120.1(4)	121.1(2)	122.4(5)			
$N^1C^1N^2$	117.0(4)	115.7(2)	115.5(6)			
$N^1C^1S^1$	123.9(4)	125.43(19)	125.0(6)			
$N^2C^1S^1$	119.1(4)	118.87(18)	119.5(5)			
$C^9C^8C^7$	119.3(5)	119.6(2)	119.8(6)			
$N^1C^2C^3$	115.6(5)	112.3(2)	112.3(7)			
$C^4C^3C^2$	127.2(5)	126.0(3)	125.7(10)			

chemical data, and IR spectra (Table 6). According to the molar conductivity measurements, compounds 1, 5, 7, and 8 in DMF solution are nonelectrolytes ($\alpha = 2-4 \ \Omega^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$), and complexes 2–4, 6, 9, and 10 are binary electrolytes ($\alpha = 54-70 \ \Omega^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$). Cobalt complexes 2 and 10 are diamagnetic at room



Fig. 4. H-Bonded chains in the crystal structure of 2-(2-hydroxy-3-nitrobenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothioamide (H₂L⁵).

Dond D. H. A		Distance, Å		DUA dog	Coordinates of A						
Bolid D-H***A	D–H	H…A	D···A	ZDNA, deg							
		H ₂ L	4								
O^1 – H ···· N^3	0.82	1.95	2.672	147	<i>x</i> , <i>y</i> , <i>z</i>						
$N^2 \cdots H \cdots S^1$	0.86	2.60	3.448	171	1- <i>x</i> , 2- <i>y</i> , 1- <i>z</i>						
$N^1 \cdots H \cdots N^3$	0.86	2.26	2.659	108	<i>x</i> , <i>y</i> , <i>z</i>						
$C^2 \cdots H \cdots S^1$	0.97	2.61	3.109	112	<i>x</i> , <i>y</i> , <i>z</i>						
	H_2L^5										
$O^1 \cdots H \cdots O^3$	0.82	1.90	2.594	142	<i>x</i> , <i>y</i> , <i>z</i>						
$O^1 \cdots H \cdots S^1$	0.82	2.82	3.367	126	-x, -1/2+y, 1/2-z						
$N^1 \cdots H \cdots N^3$	0.86	2.25	2.638	107	<i>x</i> , <i>y</i> , <i>z</i>						
$N^2 \cdots H \cdots S^1$	0.86	2.72	3.479	148	-x, -y, -z						
$C^2 \cdots H \cdots O^1$	0.97	2.46	3.349	153	-x, $1/2+y$, $1/2-z$						
		H ₂ L	6								
$N^2 \cdots H \cdots O^1$	0.86	2.19	2.978	151	-x, 2-v, -z						
$O^1 \cdots H \cdots O^2$	0.82	2.18	2.637	116	x, y, z						
$O^1 \cdots H \cdots S^1$	0.82	2.52	3.184	139	-x, 2-v, -z						
$N^1 \cdots H \cdots N^3$	0.86	2.26	2.664	109	x, v, z						
$C^5 \cdots H \cdots O^1$	0.93	2.43	2.754	100	x, y, z						
$C^2 \cdots H \cdots S^1$	0.97	2.64	3.081	108	x, y, z						
		9									
$N^1 \cdots H \cdots O^{2N2}$	0.86	2.04	2.897	174	<i>x</i> , <i>v</i> , <i>z</i>						
$N^{1A}\cdots H\cdots O^{2N1}$	0.86	2.02	2.870	169	1-x, 1-y, -z						
$N^2 \cdots H \cdots O^{1N2}$	0.86	1 93	2 783	169	x y z						
$N^{2A}\cdots H\cdots O^{1N1}$	0.86	1.96	2.815	170	1-x 1-y -z						
$O^{1W} \cdots H \cdots O^{4W}$	0.85	2.21	2.685	115	-x, 1-v, 1-z						
$O^{1W} \cdots H \cdots O^{4W}$	0.85	2.41	2.685	100	-x, 1-y, 1-z						
$O^{1WA} \cdots H \cdots O^{2W}$	0.87	1.88	2.743	171	x, y, z						
$O^{1WA} \cdots H \cdots O^{5W}$	0.87	190	2.655	144	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{2W} \cdots H \cdots O^{1N1}$	0.85	2.34	3.090	148	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{2W} \cdots H \cdots O^{1A}$	0.85	2.22	2.926	141	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{2W} \cdots H \cdots O^{2A}$	0.85	2.27	3.022	147	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{3W} \cdots H \cdots O^{5W}$	0.85	2.51	3.343	167	-1+x, y, z						
$O^{4W} \cdots H \cdots O^{1A}$	0.85	2.23	2.977	146	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{4W} \cdots H \cdots O^{2A}$	0.85	2.48	3.233	147	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{5W} \cdots H \cdots O^{1N2}$	0.85	206	2.893	167	<i>x</i> , <i>y</i> , <i>z</i>						
$O^{5W} \cdots H \cdots O^{1}$	0.85	2.18	3.005	163	1-x, 1-y, 1-z						
$C^{2A}\cdots H\cdots S^{1A}$	0.97	2.62	3.089	110	<i>x</i> , <i>y</i> , <i>z</i>						
$C^2 \cdots H \cdots S^1$	0.97	2.60	3.112	113	<i>x</i> , <i>y</i> , <i>z</i>						

Table 5. Geometric parameters of hydrogen bonds in the crystal structures of compounds $H_2L^4-H_2L^6$ and **9**

Bond	d, Å	Bond	<i>d</i> , Å	Angle	ω, deg	Angle	ω, deg
$Cu^1 - O^1$	1.915(5)	S^1-C^1	1.705(8)	O ¹ Cu ¹ N ³	93.6(3)	O ^{1WA} Cu ² S ^{1A}	92.68(18)
Cu ¹ –N ³	1.927(6)	C^5-N^3	1.277(9)	$O^1Cu^1O^{1W}$	86.6(2)	$N^3C^5C^6$	126.1(8)
$Cu^1 - S^1$	2.264(2)	$C^{5}-C^{6}$	1.458(10)	$N^{3}Cu^{1}O^{1W}$	175.4(3)	$C^5N^3N^2$	116.5(6)
$Cu^1 - O^{1W}$	1.943(5)	$N^3 - N^2$	1.393(8)	$O^1Cu^1S^1$	173.98(19)	$C^1N^1C^2$	125.6(8)
$Cu^2 - O^{1A}$	1.911(5)	N^1-C^1	1.325(9)	$N^{3}Cu^{1}S^{1}$	86.7(2)	$C^1N^2N^3$	118.7(7)
Cu ² –N ^{3A}	1.933(6)	N^1-C^2	1.472(10)	$O^{1W}Cu^1S^1$	93.54(17)	$N^1C^1N^2$	116.1(8)
Cu ² –S ^{1A}	2.259(2)	$N^2 - C^1$	1.325(9)	$O^{1A}Cu^2N^{3A}$	93.8(2)	$N^1C^1S^1$	122.6(7)
$Cu^2 - O^{1WA}$	1.961(6)	$C^2 - C^3$	1.389(14)	O ^{1A} Cu ² O ^{1WA}	86.8(2)	$N^2C^1S^1$	121.3(6)
				$N^{3A}Cu^2O^{1WA}$	176.8(3)	$C^{9}C^{8}C^{7}$	120.7(8)
				$O^{1A}Cu^2S^{1A}$	174.74(17)	$N^1C^2C^3$	113.2(9)
				$N^{3A}Cu^2S^{1A}$	86.99(19)	$C^4C^3C^2$	125.7(13)

Table 6. Selected bond lengths and bond angles in molecule 9

temperature (294 K), and the central metal atom therein has a degree of oxidation of 3+ and a pseudooctahedral ligand environment (Table 6). The effective magnetic moments of the copper complexes correspond to spin values for one unpaired electron. These findings suggest monomeric structure of the complexes. The mode of ligand coordination to the central metal ion in complexes 1-10 was determined by comparing their IR spectra with the spectra of initial thioamides $H_2L^1-H_2L^6$ with account taken of the X-ray diffraction data for compound 9. The IR spectra of initial ligands $H_2L^1-H_2L^6$ contained absorption bands



Fig. 5. A fragment of crystal packing of 2-(2-hydroxy-3-methoxybenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothio-amide (H₂L⁶).



Fig. 6. Structure of the molecule of complex 9 in crystal according to the X-ray diffraction data.

no.	Viold	a	m ^a		Four	nd, %			Calculated, %			
Comp.	%	$\mu_{ef,}$ B.M.	Ω^{-1} cm ² mol ⁻¹	Cl	М	Ν	S	Formula	Cl	М	N	S
1	80	1.75	4	8.47	15.19	9.90	7.48	C ₁₁ H ₁₁ BrClCuN ₃ OS	8.60	15.42	10.19	7.78
2	75	б	70	_	6.25	10.57	6.94	$C_{22}H_{20}Br_4CoN_7O_5S_2$	_	6.51	10.83	7.09
3	82	1.82	57	_	11.60	10.17	5.70	$C_{11}H_{12}Br_2CuN_4O_5S$	_	11.86	10.46	5.99
4	67	1.81	65	_	15.87	13.98	7.91	$C_{11}H_{14}CuN_4O_6S$	_	16.13	14.22	8.14
5	78	1.92	4	9.88	17.93	11.94	8.89	C ₁₁ H ₁₂ ClCuN ₃ O ₂ S	10.15	18.19	12.03	9.18
6	69	1.83	67	_	15.87	14.01	7.99	$C_{11}H_{14}CuN_4O_6S$	_	16.13	14.22	8.14
7	77	1.79	2	9.14	16.59	14.60	8.31	C ₁₁ H ₁₁ ClCuN ₄ O ₃ S	9.37	16.80	14.81	8.48
8	73	1.78	3	9.55	17.32	11.39	8.74	C ₁₂ H ₁₄ ClCuN ₃ O ₂ S	9.76	17.49	11.57	8.83
9	69	1.87	61	_	14.17	12.47	6.98	$C_{12}H_{20}CuN_4O_6S$	-	14.31	12.62	7.22
10	72	b	54	5.47	9.17	13.32	10.07	$\mathrm{C}_{24}\mathrm{H}_{28}\mathrm{ClCoN}_6\mathrm{O}_4\mathrm{S}_2$	5.69	9.46	13.49	10.29

 Table 7. Yields, effective magnetic moments, electrical conductivities, and elemental analyses of copper and cobalt coordination compounds 1–10

^a At 294 K.

^b Diamagnetic.

at 3450–3100, 1660–1580, and 1400–1100 cm⁻¹. The IR spectra of all complexes lacked absorption in the region 3450–3100 cm⁻¹, which is typical of phenolic O–H stretchings of the free ligands. This indicates deprotonation of the OH group upon coordination. The same conclusion follows from the 40–50 cm⁻¹ low-frequency shift of the v(C–O) band observed at 1260–1190 cm⁻¹ in the spectra of $H_2L^1-H_2L^6$. In addition, the

complexation is accompanied by low-frequency shift of the v(C=N) band (by 20–30 cm⁻¹) and highfrequency shift of the v(C=C) band (by 25–40 cm⁻¹). These data suggest coordination of deprotonated ligands HL^1-HL^6 to the metal ion through phenolic oxygen atom, nitrogen atom of the azomethine group, and thionic sulfur atom. This coordination mode is also supported by the appearance in the IR spectra of all



Fig. 7. A fragment of crystal packing of complex 9.

Compound	Staphylococcus aureus ATCC 25923		Bacillus cereus GISK 8035		Escherichia coli ATCC 25922		Salmonella abony GISK 03/03		<i>Candida albicans</i> ATCC 90028	
••••••	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Initial salts ^a	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
H_2L^1	15	60	1.5	15	>1000	>1000	>1000	>1000	3	3
1	3	15	1.5	3	>1000	>1000	>1000	>1000	3	30
H_2L^2	1.5	3	1.5	3	>1000	>1000	>1000	>1000	1.5	3
2	3	7	>1000	>1000	>1000	>1000	>1000	>1000	1.5	3
3	1.5	1.5	1.5	3	>1000	>1000	>1000	>1000	1.5	3
H_2L^3	15	30	30	60	120	250	250	500	30	120
4	7	15	7	15	30	60	60	120	7	7
H_2L^4	3	15	30	60	>1000	>1000	>1000	>1000	3	15
5	7	15	7	15	500	500	250	500	3	7
6	3	7	3	7	12	250	12	60	3	7
H_2L^5	60	250	15	120	120	500	120	500	3	30
7	15	120	1.5	15	15	120	120	120	3	15
H_2L^6	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
8	7	60	7	30	30	120	15	60	15	60
9	7	7	120	120	500	500	500	500	7	7

Table 8. Minimum inhibitory concentrations (MIC, $\mu g/mL$) and minimum bactericidal concentrations (MBC, $\mu g/mL$) of ligands $H_2L^1-H_2L^6$ and coordination compounds 1–10

^a CuCl₂·2H₂O; Cu(NO₃)₂·3H₂O; CoCl₂·6H₂O; Co(NO₃)₂·6H₂O.

complexes of new bands in the region 530–405 cm⁻¹, in particular v(M–N) bands at 525–505 and 430– 405 cm⁻¹ and v(M–S) bands at 450–440 cm⁻¹. The other functional groups of thioamides $H_2L^1-H_2L^6$ are not involved in the complexation since the corresponding characteristic bands of the complexes are observed in the same regions as in the spectra of the initial thiosemicarbazones. On the basis of the obtained data, the synthesized complexes were assigned structures **A** (1, 5, 7, 8), **B** (3, 4, 6, 9), and **C** (2, 10) (Scheme 2).

As shown in [7, 8] complexes of biometals with 2-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide selectively inhibit the growth and proliferation of some cancer cell lines and some microorganisms. In this work we tested initial metal salts and ligands and coordination compounds **1–10** for *in vitro* antimicrobial and antifungal activities against standard strains of gram-positive (*Staphylococcus*) aureus, Bacillus cereus) and gram-negative bacteria (Escherichia coli, Salmonella abony) and yeast-like fungi (Candida albicans). The results are summarized in Table 8. It is seen that all initial copper and cobalt salts showed no activity against the above listed microorganisms and that ligands H_2L^1 , H_2L^2 , and H_2L^4 were active only against gram-positive bacteria and fungi and low active against gram-negative bacteria. Complexes 1-10 showed selective bacteriostatic and and bactericidal activities against S. aureus and C. albicans in the concentration range 1.5-120 µg/mL and against E. coli in the concentration range 15-500 µg/mL. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the complexes depended on the nature of the central metal ion and substituents in thiosemicarbazones $H_2L^1-H_2L^6$. Complex 3 turned out to be the most active against gram-positive bacteria, and complex 8, against gramnegative bacteria. Furthermore, similarity of the MIC





Table 9. Antiproliferation activity of ligands $H_2L^1-H_2L^6$ and coordination compounds **1–10** against cancer (HL-60) and healthy cells (MDCK)

Compound	IC ₅₀ , µM				
Compound	HL-60	MDCK			
H_2L^1	8.0	>100			
1	1.8	18			
H_2L^2	>10	> 100			
2	>10	>100			
3	3.8	92			
H_2L^3	>10	>100			
4	3.8	4.8			
H_2L^4	>10	>100			
6	>10	50			
H_2L^5	>10	>100			
7	0.6	>100			
H_2L^6	7.2	>100			
8	0.4	>100			
10	>10	>100			

and MBC values for many compounds indicated bactericidal character of their action.

As reported previously for 3d metal complexes with 2-(2-hydroxybenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothioamide, complexes 1-10 at a concentration of 0.1-10 µM showed antiproliferative activity against HL-60 human myeloid leukemia cancer cell line and model MDCK (Madin-Darby canine kidney) normal cell line (Table 9). The activity of both ligands and complexes derived therefrom strongly depended on the substituent in the salicylidene fragment. For example, introduction of two bromine atoms into the benzene ring (H_2L^2) led to complete loss of activity. The highest activity was observed for the ligands containing a bromine atom in the 5-position and a methoxy group in the 3-position, which inhibited cancer cell proliferation by more than 50% at a concentration of 10 µM. Copper complexes with these ligands showed the highest activity in the examined series. The activity of the copper complexes was higher than that of the corresponding ligand, whereas the cobalt complexes were low active. The highest

cytostatic activity was found for complex **8** which completely inhibited proliferation of cancer cells at concentrations of 10 and 1 μ M; however, it showed almost no activity at lower concentrations.

The selectivity of action of thioamides $H_2L^1-H_2L^6$ and complexes **1–10** was assayed by estimating their antiproliferative activity healthy MDCK cells. Table 9 contains IC₅₀ values characterizing the cytostatic effect of these compounds with respect to HL-60 and MDCK cells. It is seen that in most cases the antiproliferative activity against healthy cells is lower by a factor of 10 and more than their effect on HL-60 cancer cells. Thus, the synthesized compounds selectively inhibit proliferation of HL-60 cancer cells without appreciable negative effect on healthy cells.

Our results indicate promise of further search for antimicrobial, antifungal, and anticancer agents among coordination compounds of biometals with thioamidebased ligands.

EXPERIMENTAL

The X-ray diffraction data for compounds H_2L^4 - H_2L^6 and 9 were obtained with an Oxford Diffraction Xcalibur diffractometer [18]. The structures were solved by the direct method and were refined by the least-squares method in anisotropic approximation for non-hydrogen atoms using SHELX-97 software [19]; the crystal structure of H_2L^4 was refined as racemic twin. Hydrogen atoms were placed in geometrically calculated positions, and their temperature factors $U_{\rm H}$ were assumed to be higher by a factor of 1.2 than those of the corresponding carbon and oxygen atoms. The principal crystallographic data and parameters of X-ray diffraction experiments and structure refinement are given in Table 1, and selected interatomic distances and bond angles are given in Table 2. The coordinates of atoms in structures $H_2L^4-H_2L^6$ and 9 were deposited to the Cambridge Crystallographic Data Centre (CCDC entry nos. 929459-929461, 1872426). The geometry calculations and were performed, and the molecular structures were plotted, using PLATON [16]; only those hydrogen atoms which are involved in hydrogen bonds are shown in the crystal packing images. The structures were analyzed using the CCDC data (versiin 5.39) [20, 21].

The electrical conductivity of solutions of complexes 1-10 in DMF with a concentration of 0.001 M were measured at 20°C with an R-38 rheochord bridge. The IR spectra (4000–400 cm⁻¹) were recorded on an Bruker ALPHA spectrometer. The effective magnetic moments were measured by the Gouy method. The molar magnetic susceptibilities were calculated with a correction for diamagnetism on the basis of theoretical magnetic susceptibilities of organic compounds.

The antimicrobial, antifungal, and anticancer activities were assessed according to standard procedures [22].

2-(5-Bromo-2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide (H₂L¹) was synthesized as described in [9].

2-(3,5-Dibromo-2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide (H₂L²). A solution of 10 mmol of *N*-(prop-2-en-1-yl)hydrazinecarbothioamide in 35 mL of ethanol was added to a hot (55–60°C) solution of 10 mmol of 3,5-dibromo-2hydroxybenzaldehyde in 15 mL of ethanol. After cooling, light yellow solid precipitated and was filtered off on a glass filter, washed with a small amount of ethanol, and dried in air.

Ligands H_2L^3 i H_2L^5 were synthesized in a similar way from *N*-(prop-2-en-1-yl)hydrazinecarbothioamide and 2,3-dihydroxy- or 2-hydroxy-3-nitrobenzaldehyde, respectively, at a molar ratio of 1:1. Compounds H_2L^4 and H_2L^6 were prepared according to the procedures described in [10, 11]. Some characteristics of thioamides $H_2L^1-H_2L^6$ are given in Tables 1 and 2. Thioamides $H_2L^1-H_2L^6$ are readily soluble in DMF and DMSO, as well as in alcohols on heating.

[2-(5-Bromo-2-hydroxybenzylidene)-*N*-(prop-2en-1-yl)hydrazinecarbothioamido]chlorocopper(II) (1). A solution of 10 mmol of ligand H_2L^1 in 50 mL of ethanol was heated to 50–55°C, and a solution of 10 mmol of copper(II) chloride dihydrate in 20 mL of ethanol was added with continuous stirring. The mixture was refluxed for 50–60 min. After cooling to room temperature, the precipitate was filtered on a glass filter, washed with small amounts of alcohol and diethyl ether, and dried in air until constant weight.

Complexes 2–10 were synthesized in a similar way from thioamides $H_2L^2-H_2L^6$ and the corresponding cobalt(II) and copper(II) salts taken at a ratio of 2:1 or 1:1.

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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