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FULL PAPER

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Novel 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone and Zn(II), Cu(II), Ni(II) and Co(III) complexes: Synthesis, characterization, crystal structure, antioxidant, antimicrobial and antiproliferative activity

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New zinc (II), copper (II), nickel (II) and cobalt (III) complexes, $[Zn(HL)_2]I_2$ **(1)**, $[Cu(HL)Cl_2]$ **(2)**, $[Cu(HL)Br_2]$ **(3)**, $[Cu(HL)(H_2O)_2](ClO_4)_2$ **(4)**, $[Ni(HL)_2]I_2 \cdot H_2O$ **(5)**, $[Co(L)_2]Cl$ **(6)**, $[Co(L)_2]NO_3$ **(7)**, $[Co(L)_2]I \cdot [Co(L)_2](I_3)$ **(8)** were obtained with 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone (**HL**). The isothiosemicarbazone ligand was characterized by NMR (^1H and ^{13}C), IR spectroscopy and X-ray diffraction. All the complexes were characterized by elemental analysis, IR, UV–Vis, ESI-MS spectroscopy, molar conductivity, magnetic susceptibility measurements. X-ray diffraction analysis on the monocrystal and powder elucidated the structure of the complexes **1**, **5**, **7** and **8**.

*T*he ligand and the complexes were tested for their antioxidant and antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans*. Also, the antiproliferative properties of these compounds on human leukemia HL-60, human cervical epithelial HeLa, human epithelial pancreatic adenocarcinoma BxPC-3, human muscle rhabdomyosarcoma spindle, large multinucleated RD cells and normal MDCK cells have been investigated. The nickel complex **5** and cobalt complexes **6**, **7** showed promising antiproliferative activity and low toxicity.

KEYWORDS

antimicrobial activity, antioxidant activity, antiproliferative activity, complexes, crystal structure

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1 | INTRODUCTION

Malignant tumors, antibiotic resistance are presently a global health problem urging the development of novel antitumor and antimicrobial agents.[1–3] Most of the medicines used in medical practice are organic substances. Recently, much attention has been paid to transition metal complexes as biologically active substances. The coordination compounds of 3*d* metals occupy an important place among them, since they have shown promising biological activity.[4–6]

The activity of these compounds depends on the structure of molecules and on the arrangement of functional groups. The study of the relationship between the chemical structure of substances and their biological activity allows for a purposeful synthesis of new drugs.[7–17]

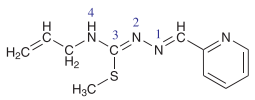
Thiosemicarbazones are of particular interest among a wide range of biologically active substances.[18–23]

The introduction of alkyl groups on the terminal N4 nitrogen atom and the moiety of 2-formylpyridine and their derivatives on the N1 position exert significant biological activity.[24]

Isothiosemicarbazones are of biological interest since thioalkylation leads to a change in the coordination mode.[25–29] Nevertheless, isothiosemicarbazones have not been studied extensively from a biological point of view. It is important to study the influence of thiosemicarbazide's alkylation on the geometry, physicochemical and biological properties of the corresponding coordination compounds.

Previously we have described 2-hydroxybenzaldehyde 4-allyl-*S*-methylisothiosemicarabzone and a series of its 3*d* metal coordination compounds.[30] These compounds exhibit moderate antimicrobial and antifungal activity, selective anticancer activity which in case of copper complex exceeds the activity of doxorubicine, and promising antioxidant activity. Since it is known that the substitution of 2-hydroxybenzaldehyde moiety with 2-formylpyridine moiety leads to a growth of biological activity of thiosemicarbazones and their coordination compounds,[28–32] the study of such substitution in case of isothiosemicarbazones is of interest.

Therefore, the present paper describes the chemical synthesis, characterization and *in vitro* biological evaluation of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone (Scheme 1) and its Zn (II), Cu (II), Ni (II) and Co (III) and coordination compounds.



SCHEME 1 Isothiosemicarbazone ligand **HL**

2 | EXPERIMENTAL

2.1 | Materials

All the reagents used were chemically pure. Zn $(CH_3COO)_2{\cdot}2H_2O$, $CuCl_2{\cdot}2H_2O$, $CuBr_2$, Cu $(ClO_4)_2{\cdot}6H_2O$, Ni $(CH_3COO)_2{\cdot}4H_2O$, $CoCl_2{\cdot}6H_2O$, Co $(NO_3)_2{\cdot}6H_2O$, Co $(CH_3COO)_2{\cdot}4H_2O$ (Merck, Darmstadt, Germany) were used as supplied. 2-Formylpyridine was used as received (Sigma-Aldrich, Munich, Germany). N(4)-Allyl-3-thiosemicarbazide was prepared similarly to the literature procedure[33,34] by reaction of the allylisothiocyanate and hydrazine hydrate. The solvents were purified and dried according to standard procedures.[35]

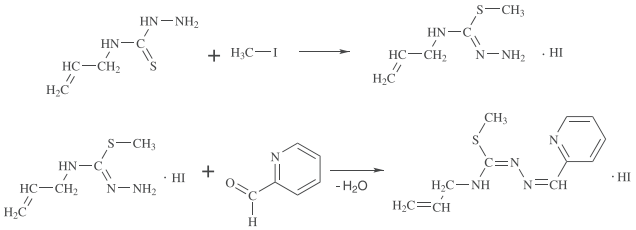
2.2 | Synthesis of the 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone (HL)

2-Formylpyridine 4-allyl-*S*-methylisothioseimicarbazone (**HL**) (Scheme 2) was obtained similarly to the method described in the literature.[21,30,36]

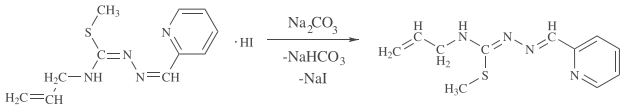
Sodium carbonate (1.06 g, 10 mmol) was added to the solution of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone hydroiodide (3.62 g, 10 mmol). The mixture is stirred for 30 min at 50 °C. By cooling to room temperature to give a yellow precipitate which was filtered, washed with ethanol and dried in vacuo (Scheme 3).

Yellow solid. Yield: 88%; m.p.: 75–77 °C; FW: 234.321 g/mol; Anal. Calc. for $C_{11}H_{14}N_4S$: C, 56.38; H, 6.02; N, 23.91; S, 13.68%. Found: C, 56.29; H, 6.14; N, 23.84; S, 13.59%.

Main IR peaks (cm^{-1}): $\nu(N^4H)$ 3010, $\nu(N^2\text{-}H)$ 3180, $\nu(C{=}C$ allyl) 1639, $\nu(C{=}N^1)$ 1614, $\nu(C = N_{pyr})$ 1560, $\nu(CH_3\text{–}S)$ 1093, $\nu(C\text{–}S)$ 643.

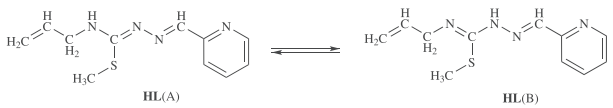


SCHEME 2 Synthesis of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone hydroiodide



SCHEME 3 Neutralization of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone hydroiodide

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SCHEME 4 The tautomeric forms of the ligand **HL**

1st tautomeric form (**HL**(A) on Scheme 4): ^{1}H NMR ($CDCl_3$; δ, ppm): 8.44 (s, 1H, CH=N); 8.64 (d, 1H, CH aromatic); 7.94 (d, 1H, CH aromatic); 7.70 (t, 1H, CH aromatic); 7.25 (t, 1H, CH aromatic); 6.81 (br, 1H, NH); 5.92 (m, 1H, CH from allyl moiety); 5.27 (m, 2H, CH_2 = C); 3.96 (t, 2H, CH_2-N); 2.52 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$; δ, ppm): 165.15 (C-S); 152.78, 154.32, 149.51, 123.64, 121.30 (C aromatic); 136.37 (CH=N); 134.38 (CH from allyl moiety); 116.63 (CH_2=); 45.75 (CH_2-N); 12.91 (CH_3).

2nd tautomeric form (**HL**(B) on Scheme 4): ^{1}H NMR ($CDCl_3$; δ, ppm): 8.38 (s, 1H, CH=N); 8.60 (d, 1H, CH aromatic); 8.07 (d, 1H, CH aromatic); 7.68 (t, 1H, CH aromatic); 7.22 (t, 1H, CH aromatic); 5.99 (m, 1H, CH from allyl moiety); 5.23 (m, 2H, CH_2 = C); 4.56 (br, 1H, NH); 4.14 (t, 2H, CH_2-N); 2.41 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$; δ, ppm): 163.65 (C-S); 154.84, 153.16, 149.35, 123.43, 120.78 (C aromatic); 136.11 (CH=N); 134.01 (CH from allyl moiety); 117.25 (CH_2=); 46.13 (CH_2-N); 13.18 (CH_3).

2.3 | GENERAL PROCEDURE FOR THE PREPARATION OF THE METAL COMPLEXES 1–8

Complexes **1–8** were synthesized by combining the ligand **HL** with the corresponding metal salts.

Synthesis of the complex [Zn (HL)$_2$]I$_2$ ***1***

To an ethanolic solution (30 ml) of hydroiodide of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone **HL·HI** (0.724 g, 2 mmol) was added Zn $(CH_3COO)_2{\cdot}2H_2O$ (0.219 g, 1 mmol). The mixture was stirred for 1 hr at 70 °C. After filtration a yellow precipitate was obtained which was washed with cold ethanol and dried under vacuo.

Yield: 79%; FW: 787.86 g/mol; *Anal.* Calc. for $C_{22}H_{28}I_2N_8S_2Zn$: C, 33.50; H, 3.55; I, 32.22; N, 14.22; S, 8.14; Zn, 8.30; Found: C, 33.52; H, 3.51; I, 32.16; N, 14.17; S, 8.11; Zn, 8.24. Main IR peaks (cm^{-1}): ν(N^{4}H) 3071, ν(C=C allyl) 1637, ν(C=N^1) 1593, ν(C = N_{pyr}) 1499, ν (CH_3–S) 1093, ν(C–S) 667. μ_{eff} (292 ± 1 K): 0 μ_B; χ (CH_3OH): 173 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

Synthesis of the complex [Cu (HL)Cl$_2$] ***2***

The complex **2** was synthesized using $CuCl_2{\cdot}2H_2O$ (0.171 g; 1 mmol) and **HL** (0.234 g; 1 mmol).

Green solid. Yield: 81%; FW: 368.77 g/mol; *Anal.* Calc. for $C_{11}H_{14}Cl_2CuN_4S$: C, 35.83; H, 3.83; Cl, 19.23; Cu, 17.23; N, 15.19; S, 8.70; Found: C, 35.77; H, 3.76; Cl, 19.16; Cu, 17.15; N, 15.10; S, 8.62; Main IR peaks (cm^{-1}): ν(N^{4}H) 3104, ν(C=C allyl) 1645, ν(C=N^1) 1592, ν(C = N_{pyr}) 1524, ν (CH_3–S) 1095, ν(C–S) 646. μ_{eff} (292 ± 1 K): 1.48 μ_B; χ (CH_3OH): 170 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

Synthesis of the complex [cu (HL)Br$_2$] ***3***

The complex **3** was synthesized from $CuBr_2$ (0.224 g; 1 mmol) and **HL** (0.234 g; 1 mmol).

Green solid. Yield: 78%; FW: 457.68 g/mol; *Anal.* Calc. for $C_{11}H_{14}Br_2CuN_4S$: C, 28.87; H, 3.08; Br, 34.92; Cu, 13.88; N, 12.24; S, 7.01; Found: C, 28.81; H, 3.10; Br, 34.85; Cu, 13.79; N, 12.16; S, 6.97; Main IR peaks (cm^{-1}): ν(N^{4}H) 3143, ν(C=C allyl) 1645, ν(C=N^1) 1593, ν(C = N_{pyr}) 1525, ν (CH_3–S) 1095, ν(C–S) 648. μ_{eff} (292 ± 1 K): 1.37 μ_B; χ (CH_3OH): 202 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

Synthesis of the complex [cu (HL)(H$_2$O)$_2$](ClO$_4$)$_2$ ***4***

The complex **4** was synthesized from Cu $(ClO_4)_2{\cdot}6H_2O$ (0.370 g; 1 mmol) and **HL** (0.234 g; 1 mmol).

Green solid. Yield: 75%; FW: 532.80 g/mol; *Anal.* Calc. for $C_{11}H_{18}Cl_2CuN_4O_{10}S$: C, 24.80; H, 3.41; Cl, 13.31; Cu, 11.93; N, 10.52; S, 6.02; Found: C, 24.75; H, 3.35; Cl, 13.27; Cu, 11.88; N, 10.64; S, 6.10. Main IR peaks (cm^{-1}): ν(N^{4}H) 3071, ν(C=C allyl) 1637, ν(C=N^1) 1593, ν(C = N_{pyr}) 1505, ν (CH_3–S) 1093, ν(C–S) 667. μ_{eff} (292 ± 1 K): 1.80 μ_B; χ (CH_3OH): 207 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

Synthesis of the complex [Ni (HL)$_2$]I$_2{\cdot}H_2O$ ***5***

The complex **5** was synthesized from Ni $(CH_3COO)_2{\cdot}4H_2O$ (0.249 g; 1 mmol) and **HL·HI** (0.724 g; 2 mmol).

Brown solid. Yield: 70%; FW: 799.16 g/mol; *Anal.* Calc. for $C_{22}H_{30}I_2N_8NiOS_2$: C, 33.06; H, 3.78; I, 31.76; N, 14.02; Ni, 7.34; S, 8.02; Found: C, 32.98; H, 3.82; I, 31.85; N, 13.96; Ni, 7.28; S, 8.09. Main IR peaks (cm^{-1}): ν(N^{4}H) 3071, ν(C=C allyl) 1637, ν(C=N^1) 1593, ν(C = N_{pyr}) 1524, ν (CH_3–S) 1093, ν(C–S) 667. μ_{eff} (292 ± 1 K): 2.97 μ_B; χ (CH_3OH): 198 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

Synthesis of the complex [Co(L)$_2$]Cl ***6***

The complex **6** was synthesized from $CoCl_2{\cdot}6H_2O$ (0.238 g; 1 mmol) and **HL** (0.468 g; 2 mmol).

Brown solid. Yield: 82%; FW: 561.01 g/mol; *Anal.* Calc. for $C_{22}H_{26}ClCoN_8S_2$: C, 47.10; H, 4.67; Cl, 6.32; Co, 10.50; N, 19.97; S, 11.43; Found: C, 47.02; H, 4.58; Cl, 6.27; Co, 10.45; N, 19.88; S, 11.35. Main IR peaks (cm^{-1}): ν(N^{4}H) 3071, ν(C=C allyl) 1637, ν(C=N^1) 1593, ν(C = N_{pyr}) 1542, ν (CH_3–S) 1093, ν(C–S) 667. μ_{eff} (292 ± 1 K): 0 μ_B; χ (CH_3OH): 85 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

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Synthesis of the complex $[Co(L)_2]NO_3$ 7

The complex **7** was synthesized from Co $(NO_3)_2{\cdot}6H_2O$ (0.291 g; 1 mmol) and **HL** (0.468 g; 2 mmol).

Brown solid. Yield: 77%; FW: 587.56 g/mol; *Anal.* calc. For $C_{22}H_{26}CoN_9O_3S_2$ ($g{\cdot}mol^{-1}$): C, 44.97; H, 4.46; Co, 10.03; N, 21.45; S, 10.91; Found: C, 44.86; H, 4.37; Co, 9.93; N, 21.56; S, 10.81. Main IR peaks (cm^{-1}): $\nu(N^4H)$ 3070, ν(C=C allyl) 1637, $\nu(C{=}N^1)$ 1601, $\nu(C = N_{pyr})$ 1538, ν (CH_3–S) 1097, ν(C–S) 657. μ_{eff} (292 ± 1 K): 0 μ_B; χ (CH_3OH): 97 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

*Synthesis of the complex $[Co(L)_2]I{\cdot}[Co(L)_2](I_3)$ **8***

The complex **8** was synthesized from Co $(CH_3COO)_2{\cdot}4H_2O$ (0.249 g; 1 mmol) and **HL·HI** (0.724 g; 2 mmol).

Brown solid. Yield: 81%; FW: 1558.74 g/mol; *Anal.* Calc. for $C_{44}H_{52}Co_2I_4N_{16}S_4$: C, 33.90; H, 3.36; Co, 7.56; I, 32.57; N, 14.38; S, 8.23; Found: C, 33.98; H, 3.41; Co, 7.48; I, 32.47; N, 14.29; S, 8.31. Main IR peaks (cm^{-1}): $\nu(N^4H)$ 3070, $\nu(C{=}C$ allyl) 1640, $\nu(C{=}N^1)$ 1600, $\nu(C = N_{pyr})$ 1533, ν (CH_3–S) 1098, ν(C–S) 656. μ_{eff} (292 ± 1 K): 0 μ_B; χ (CH_3OH): 109 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$.

2.4 | Physical Measurements

Melting points, the determination of metal content, the chemical elemental analysis for the determination of C, H and N, molar conductivity, magnetic susceptibilities, were determined by specific methods.[37] Infrared spectra of the compounds were recorded on a Bruker ALPHA FTIR spectrophotometer at room temperature in the range of 4000–400 cm^{-1}. Electronic spectra were recorded using the JascoV-670 spectrophotometer (Tokyo, Japan), in diffuse reflectance, using MgO dilution matrices. UV–visible absorption spectra in DMSO solutions were measured on Agilent Cary 300 UV–Vis spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (Billerica, MA, USA), using $CDCl_3$ as a solvent. The chemical shifts (δ) in ppm were measured relative to tetramethylsilane (TMS). Electrospray Ionization Mass Spectrometry (ESI-MS) spectra were collected using a Q-TOF instrument supplied by WATERS. Samples were solubilized in methanol at a concentration of 5 mg. L^{-1} and were introduced into the spectrometer via an ACQUITY UPLC WATERS system whilst a Leucine Enkephalin solution was co-injected via a micro pump as internal standard. X-ray powder diffraction analysis was performed on Panalytical Empyrean diffractometer system using X-ray tube with copper anode in the range of 5–60 degrees 2θ. Similated powder X-ray diffractograms from single crystal X-ray data were generated using Mercury 4 software.

2.5 | X-ray Crystallography

The main crystallographic data together with refinement details of **HL**, **1**, **5**, **7** and **8** compounds are summarized in Table 1. Data collection and unit cell determination: CrysAlis PRO CCD (Oxford Diffraction), programs used to solve and refine structures: SHELXS-97 and SHELXL-97.[38,39] All atomic displacements for non-hydrogen atoms were refined using an anisotropic model.

The structures of **1** and **7** displayed the disorder of the C_2H_3 groups which was refined with the help of PART instruction dividing the disordered atoms into two groups. Selected bond lengths, angles and hydrogen bonds are presented in Table 2 and Table 3 respectively. The geometric parameters were calculated with the help of the PLATON program.[40] Analysis of found X-H...Cg (π ring) interactions were performed by the following criteria: H··· Cg < 3.0 Å, γ < 30.0°, where γ is the angle between the H··· Cg vector and the normal to the aromatic ring. The hydrogen atoms that are not involved in the hydrogen bonding were omitted from the generation of the packing diagrams. Mercury software[41] was used for visualization of the studied structures.

2.6 | Biological Studies

2.6.1 | Antibacterial and antifungal activity

The antimicrobial activities of the free ligand and complexes were evaluated against three bacterial strains, *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 13883) and fungal strain, *Candida albicans* (ATCC 10231). Determination of the MIC (minimum inhibitory concentration, µg/ml) and MBC (minimum bactericidal concentration, µg/ml) was done using the serial dilutions in liquid broth method.[30,42] The tested substances were dissolved in DMSO in concentration of 10 mg/ml. The next dilutions were made using 2% of peptonate bullion. Furacillinum was used as the standard antibacterial drug while nystatine was used as the standard antifungal drug.

2.6.2 | Antiproliferative activity

Cell cultures

BxPC-3 (ATCC CRL-1687) and HL-60 (ATCC CCL-240) lines were cultured as monolayer in Roswell Park Memorial Institute (RPMI) 1640 medium containing L-glutamine (2 nM), antibiotics penicillin–streptomycin (final concentration 100 IU/ml penicillin and 100 µg

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TABLE 1 Crystallographic data, details of data collection and structure refinement parameters for compounds **HL**, **1** and **5**

Compound	HL	1	5
Chemical formula	$C_{11}H_{15}N_4S$	$C_{22}H_{25}I_2N_8S_2Zn$	$C_{44}H_{56}I_4N_{16}Ni_2OS_4$
M (g mol^{-1})	234.32	784.79	631.32
Temperature, (K)	293(2)	293(2)	293(2)
Wavelength, (Å)	0.71073	0.71073	0.71073
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	*P-1*	$P2_1/c$
a (Å)	13.3581(7)	8.6878(8)	8.8120(3)
b (Å)	9.7224(6)	9.2783(8)	17.7401(6)
c (Å)	9.7046(4)	19.1777(16)	20.4101(5)
α (^{0})	90	99.670(7)	90
β (^{0})	91.744(4)	93.314(7)	107.177(2)
γ (^{0})	90	93.453(8)	90
V (Å^3)	1259.78(11)	1517.5(2)	3048.31(17)
D_{calc} (g cm^{-3})	1.241	1.718	1.720
μ (mm^{-1})	0.237	3.006	2.826
F(0 0 0)	500	762	1544
Goodness-of-fit on F^2	1.024	1.027	1.046
Final R_1, wR_2 [$I > 2\sigma(I)$]	0.0548, 0.1205	0.0388, 0.0914	0.0376, 0.0856
R_1, wR_2 (all data)	0.0972, 0.1406	0.0558, 0.0993	0.0538, 0.0937
Largest difference in peak and hole (e Å^{-3})	0.205, −0.402	0.549, −0.522	0.716, −0.669

Crystallographic data, details of data collection and structure refinement parameters for compounds 7, 8

Compound	7	8
Chemical formula	$C_{22}H_{24}CoN_9O_3S_2$	$C_{44}H_{51}Co_2I_4N_{16}S_4$
M (g mol^{-1})	585.55	1557.71
Temperature, (K)	293(2)	293(2)
Wavelength, (Å)	0.71073	0.71073
Crystal system	triclinic	triclinic
Space group	*P-1*	*P-1*
a (Å)	8.8203(4)	9.1984(2)
b (Å)	10.1890(3)	17.7683(7)
c (Å)	14.8156(8)	19.7114(7)
α (^{0})	90.362(3)	110.651(4)
β (^{0})	100.013(4)	99.664(3)
γ (^{0})	90.763(3)	99.054(3)
V (Å^3)	1311.02(10)	2888.78(17)
D_{calc} (g cm^{-3})	1.483	1.791
μ (mm^{-1})	0.857	2.902
F(0 0 0)	604	1514
Goodness-of-fit on F^2	1.070	1.044
Final R_1, wR_2 [$I > 2\sigma(I)$]	0.0450, 0.1182	0.0526, 0.1082
R_1, wR_2 (all data)	0.0579, 0.1274	0.0870, 0.1211
Largest difference in peak and hole (e Å^{-3})	0.356, −0.555	1.351, −1.003

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TABLE 2 Selected bond lengths and angles for **HL**, **1**, **5**, **7** and **8**

	***d*, Å**					
Bond lengths	**HL**	**1**	**5**	**7**	**8**	
Zn(1)[Ni(1),Co(1)]-N(1A)		2.113(4)	1.991(3)	1.863(2)	1.868(5)	1.858(5)
Zn(1)[Ni(1),Co(1)]-N(1)		2.119(3)	2.002(3)	1.867(2)	1.878(5)	1.865(5)
Zn(1)[Ni(1),Co(1)]-N(3A)		2.125(4)	2.082(4)	1.919(3)	1.928(5)	1.918(5)
Zn(1)[Ni(1),Co(1)]-N(3)		2.137(4)	2.104(3)	1.923(2)	1.941(5)	1.947(5)
Zn(1)[Ni(1),Co(1)]-N(4A)		2.198(4)	2.131(4)	1.950(3)	1.949(4)	1.946(5)
Zn(1)[Ni(1),Co(1)]-N(4)		2.267(4)	2.110(3)	1.951(2)	1.945(5)	1.962(5)
S(1)-C(1)	1.750(3)	1.757(5)	1.756(4)	1.752(3)	1.744(7)	1.750(7)
S(1)-C(11)	1.785(2)	1.787(6)	1.772(6)	1.777(3)	1.790(9)	1.781(9)
S(1A)-C(1A)		1.752(5)	1.757(4)	1.757(3)	1.756(6)	1.762(6)
S(1A)-C(11A)		1.800(6)	1.785(6)	1.793(4)	1.739(10)	1.769(9)
N(1)-C(5)	1.279(3)	1.266(6)	1.277(5)	1.298(3)	1.289(8)	1.293(8)
N(1)-N(2)	1.383(3)	1.357(5)	1.360(4)	1.352(3)	1.356(7)	1.360(7)
N(2)-C(1)	1.303(3)	1.367(6)	1.382(5)	1.344(4)	1.332(9)	1.334(8)
N(3)-C(1)	1.332(3)	1.279(6)	1.284(5)	1.316(4)	1.356(9)	1.329(8)
N(3)-C(2)	1.436(3)	1.463(6)	1.472(6)	1.464(4)	1.388(9)	1.410(8)
N(4)-C(10)		1.310(6)	1.335(5)	1.335(4)	1.335(7)	1.334(8)
N(4)-C(6)		1.342(5)	1.345(5)	1.359(4)	1.358(8)	1.373(8)
C(2)-C(3)		1.483(9)	1.411(8)	1.491(5)	1.528(12)	1.505(10)
C(3)-C(4)		1.182(9)	1.229(9)	1.303(5)	1.211(14)	1.209(11)
C(5)-C(6)		1.467(7)	1.448(6)	1.444(4)	1.455(9)	1.436(9)
I(1)-I(2)					2.9218(8)	
I(2)-I(3)					2.8942(8)	
Bond angles	***ω*, deg.**					
N(1A)-Zn(1)[Ni(1),Co(1)]-N(1)		163.42(15)	173.99(14)	178.93(11)	179.5(3)	177.8(3)
N(1A)-Zn(1)[Ni(1),Co(1)]-N(3A)		73.85(15)	77.16(14)	80.73(11)	80.9(2)	80.8(2)
N(1)-Zn(1)[Ni(1),Co(1)]-N(3A)		115.04(16)	104.12(14)	99.98(11)	99.0(2)	99.1(2)
N(1A)-Zn(1)[Ni(1),Co(1)]-N(3)		120.05(14)	109.02(14)	98.44(10)	99.4(2)	101.0(2)
N(1)-Zn(1)[Ni(1),Co(1)]-N(3)		74.08(14)	76.77(14)	80.76(10)	81.1(2)	81.2(2)
N(3A)-Zn(1)[Ni(1),Co(1)]-N(3)		97.00(16)	96.66(14)	91.51(10)	92.2(2)	90.7(2)
N(1A)-Zn(1)[Ni(1),Co(1)]-N(4A)		73.48(14)	76.85(14)	82.96(11)	82.3(2)	83.0(2)
N(1)-Zn(1)[Ni(1),Co(1)]-N(4A)		97.20(14)	101.80(14)	96.34(11)	97.8(2)	97.1(2)
N(3A)-Zn(1)[Ni(1),Co(1)]-N(4A)		147.25(14)	154.00(14)	163.68(11)	163.1(2)	163.5(2)
N(3)-Zn(1)[Ni(1),Co(1)]-N(4A)		97.29(15)	91.20(13)	91.39(11)	92.0(2)	89.4(2)
N(1A)-Zn(1)[Ni(1),Co(1)]-N(4)		93.21(13)	97.12(13)	98.05(10)	96.6(2)	94.9(2)
N(1)-Zn(1)[Ni(1),Co(1)]-N(4)		72.84(14)	77.03(13)	82.75(10)	82.8(2)	82.9(2)
N(3A)-Zn(1)[Ni(1),Co(1)]-N(4)		93.54(15)	91.74(13)	91.32(10)	90.7(2)	91.3(2)
N(3)-Zn(1)[Ni(1),Co(1)]-N(4)		146.71(14)	153.71(14)	163.51(10)	164.0(2)	164.1(2)
N(4A)-Zn(1)[Ni(1),Co(1)]-N(4)		90.45(13)	92.04(13)	90.44(10)	89.82(19)	93.1(2)
C(1)-S(1)-C(11)	102.2(1)	104.5(3)	104.4(2)	103.63(15)	103.3(4)	102.0(4)
C(1A)-S(1A)-C(11A)		104.9(3)	103.7(3)	102.31(19)	104.4(4)	103.3(4)
I(3)-I(2)-I(1)					178.99(2)	

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TABLE 3 Hydrogen bonds of HL, 1, 5, 7 and 8 compounds

D-H···A	d(D···H), Å	d(H···A), Å	d(D···A), Å	∠(DHA), deg.	Symmetry transformation for H-acceptor.
HL					
N(3)-H(3)...N(1)	0.86	2.24	2.5778	103	x,y,z
N(3)-H(3)...N(4)	0.86	2.33	3.0740	145	x,1/2-y,-1/2 + z
C(2)-H(2B)...S(1)	0.97	2.56	2.9694	106	x,y,z
1					
N(2)-H(2)...I(2)	0.86	2.88	3.5574	137	-x,1-y,-z
N(2A)-H(2A)...I(1)	0.86	3.01	3.5234	120	x,y,z
C(2A)-H(2AA)... S(1A)	0.97	2.50	2.9834	111	x,y,z
C(2)-H(2C)... S(1)	0.97	2.46	2.9812	113	x,y,z
C(11)-H(11C)...I(2)	0.96	3.05	3.9439	155	-x,1-y,-z
5					
N(2)-H(2)...I(2)	0.86	2.95	3.5603	130	1-x,-1/2 + y,1/2-z
N(2A)-H(2A)...I(1)	0.86	2.83	3.5288	140	x,1/2-y,-1/2 + z
C(2A)-H(2AB)...S(1)	0.97	2.63	3.0203	104	x,y,z
C(2)-H(2B)...S(1A)	0.97	2.42	2.9990	118	x,y,z
C(10)-H(10)...I(1)	0.93	2.97	3.8094	151	1-x,-1/2 + y,1/2-z
C(11)-H(11B)...O(1 W)	0.96	2.51	3.4027	154	x,y,z
7					
C(2A)-H(2AB)... S(1A)	1.03	2.51	3.0066	109	x,y,z
C(2)-H(2B)... S(1)	0.97	2.55	2.9767	106	x,y,z
C(2)-H(2C)... O(2 N)	0.97	2.43	3.2641	144	x,y,z
C(5)-H(5)... O(2 N)	0.93	2.57	3.1704	123	x,-1 + y,z
C(8A)-H(8A)... O(3 N)	0.93	2.43	3.3140	160	1-x,1-y,-z
C(9)-H(9)... O(1 N)	0.93	2.55	3.4478	161	-x,1-y,-z
C(10)-H(10)... O(3 N)	0.93	2.46	3.1521	131	-x,1-y,-z
C(11A)-H(11F)... O(2 N)	0.96	2.49	3.3783	154	-1 + x,y,z
8					
C(2A)-H(2AA)... S(1A)	0.97	2.56	3.0000	108	x,y,z
C(2)-H(2B)... S(1)	0.97	2.55	2.9678	106	x,y,z
C(2B)-H(2BB)... S(1B)	0.97	2.57	2.9972	107	x,y,z
C(9)-H(9)...I(1)	0.93	3.01	3.7550	138	x,y,1 + z
C(2C)-H(2CB)... S(1C)	0.97	2.57	2.9782	105	x,y,z
C(10)-H(10)...I(4)	0.93	3.00	3.7578	140	-x,1-y,1-z
C(11B)-H(11H)...N(2B)	0.96	2.43	2.8036	103	x,y,z

streptomycin/ml) and supplemented with fetal bovine serum (FBS) (10% *v*/v).

Cell lines HeLa (ATCC CCL-2), RD (ATCC CCL-136) and MDCK (ATCC CCL-34) were cultured in the Dulbecco's Modified Essential Medium (DMEM) with L-glutamine (4 mM), glucose (4.5 g/l), bovine albumin fraction (0,2% v/v), HEPES buffer (20 mM), antibiotics penicillin–streptomycin (final concentration 100 U/ml penicillin and 100 μg streptomycin/ml) and supplemented with FBS (10% v/v).

Cells were maintained at 37 °C in a 2–5% humidified CO_2 atmosphere in the incubator in 75-cm^2 culture dishes, and used for experiments between passage 5 and 16. The compounds were dissolved at the time of the experiments.

Cell proliferation Resazurin assay

The number of viable HeLa, BxPC-3, RD and MDCK cells were measured using resazurin sodium salt (MERCK) as a reagent.

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Triplicate cultures of $1{\cdot}10^4$ cells in 100 μL of stated above medium were incubated at 37 °C, 2% CO_2 in 96-well microtiter plates. Tested compounds were dissolved in dimethyl sulfoxide in order to prepare $1{\cdot}10^{-2}$ M solutions. After that these solutions were diluted with corresponding media, added to each well and incubated for 24 hr. Subsequently 20 μL resazurin indicator solution was added to each well and incubated for 4 hr. At last, the absorbance was read at 570 nm and 600 nm.

The percentage inhibition was calculated according to the formula:

$$100-\frac{Abs_{570nm}(sample)-Abs_{600nm}(sample)}{Abs_{570nm}(control)-Abs_{600nm}(contol)}\times 100$$

where Abs_{570nm} and Abs_{600nm} stand for absorbance at 570 and 600 nm.

The IC_{50} values were evaluated by statistical software.

Cell proliferation MTS assay

The number of viable HL-60 cells was measured using Owen's Reagent (MTS, CAS#138169–43-4) (Cell Titer 96 Aqueous, Promega, Madison, Wisconsin, USA). Triplicate cultures of $1{\cdot}10^4$ cells in 100 μL of stated above medium were incubated at 37 °C, 5% CO_2 in 96-well microtiter plates. The $1{\cdot}10^{-2}$ M solutions of the tested compounds were obtained by dissolving them in ethanol. After that these solutions were diluted with culture media and added to each well and incubated for 3 days. Following each treatment, 20 μL of Owen's Reagent was added to each well and incubated for 4 hr. At last, the plates were read at 490 nm using a microplate reader (Molecular Devices, Sunnyvale, CA, USA).

2.6.3 | Antioxidant activity

The ABTS free radical-scavenging activity was determined according to Re et al.[43] A mixture (1:1, *v*/*v*) of ABTS (7 mM) and potassium persulfate (4.95 mM) was incubated at 25 °C overnight in the dark to prepare the stock solution. The $ABTS^{\bullet+}$ solution was diluted with acetate-buffered saline (0.02 M, pH 6.5) to give an absorbance of 0.7 ± 0.01 at 734 nm. Solutions in DMSO of Trolox, **HL** and complexes **1**–**8** were prepared. Then, 20 μl of each dilution was transferred to a 96-well microtiter plate and 180 μl of working solution of $ABTS^{\bullet+}$ was dispensed with the dispense module of hybrid reader (BioTek) and shaken for 15 s. After 30 min of incubation was measured the decrease in absorbance at 734 nm. Blank samples do not contain $ABTS^{\bullet+}$. The decrease in absorbance is expressed as % inhibition and is calculated according to the following formula:

$$\left(\left(Abs_{control}-Abs_{sample}\right)/Abs_{control}\right)\cdot 100.$$

3 | RESULTS AND DISCUSSION

The ligand **HL** was synthesized in good yield and characterized by FT-IR, UV–Vis, ^{1}H NMR and ^{13}C NMR spectroscopy and X-ray diffraction. The complexes **2**–**4**, **6**, **7** were obtained by combining the isothiosemicarbazone **HL** with various metal salts, but complexes **1**, **5**, **8** were synthesized using **HL**·**HI** and acetates of corresponding metals. Coordination compounds of copper were synthesized in 1:1 molar ratio [Cu:**HL**], zinc, nickel and cobalt coordination compounds were synthesized similarly, but in 1:2 molar ratio. The synthesis of the complexes is reproducible and 2-formilpyridine 4-allyl-*S*-methylisothio -semicarbazone coordinates as a tridentate ligand through the NNN chelating system, which was confirmed by the X-ray structure determinations for complexes **1**, **5**, **7**, and **8**.

The molar conductivity values of the coordination compounds **1–5** are in the range 170–207 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$ that indicates that these complexes represent 1:2 electrolytes. The corresponding anion (Cl^-, Br^-, I^-, ClO_4^-) can be either in the outer sphere or in the inner sphere as it can be easily substituted by the solvent molecule during dissolution process. The data obtained (85–104 $\Omega^{-1}{\cdot}cm^2{\cdot}mol^{-1}$) for cobalt complexes **6**–**8** demonstrates their electrolotic nature (1:1).[44]

The elemental analyses data (reported in Experimental Section) confirm the stoichiometry of the ligand and the corresponding coordination compounds.

3.1 | ^{1}H-NMR and ^{13}C-NMR Spectra

The purity and structure of isothiosemicarbazone **HL** was determined using ^{1}H and ^{13}C NMR spectroscopy. The alkylation of the sulfur atom is demonstrated using NMR spectra of 2-formylpyridine 4-allylthiosemicarbazone and 4-allyl-*S*-methylisothiosemicarbazone. The ^{13}C NMR spectrum of ligand, the characteristic peak (179–180 ppm) is not observed for the C = S. Is remarkable in the range 12–14 ppm characteristic peaks of the carbon atom in the methyl group (Figure S1).

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In the ^{1}H NMR spectrum of the ligand **HL** (Figure S2), the double peaks of methyl protons in the range of 2.41–2.52 ppm are observed.[36,45] Consequently, two tautomeric forms in the integral ratio of 1: 0.4 (**HL** (A): **HL** (B)) are present in the solution. Tautomerism can be explained by syn/anti isomerism around C=N^1 double bond, and *cis/trans* isomerism around C=N^4 double bond (Scheme 4).[21,46]

3.2 | Infrared Spectra

The IR spectra of the complexes (Figure S3) were compared with the ligand (Figure S4) in order to determine the changes that may occur during their formation. It was observed that three donor nitrogen atoms of the ligand involved in the coordination to the metal center.

The pyridine $\upsilon(C = N_{pyr})$ stretching vibration in the free ligand is observed at 1560 cm^{-1}, which is shifted by 18–60 cm^{-1} towards lower wavenumbers in the complexes, thus indicating coordination of the pyridine nitrogen atom to the metal ion.[47,48]

A significant change is observed in the area 3010 cm^{-1}, relating to the ν(N^{4}H) stretching vibrations of the isothiosemicarbazone molecule. It is shifted to the high-frequency region by 60–130 cm^{-1} in coordination compounds. Such changes in the spectra are the result of participation in the formation of the bond of the azomethine nitrogen atom.

The intense bands in the spectrum of ligand at 1638 and 1585 cm^{-1} assigned to ν(C=N) and is shifted with up to 15–27 cm^{-1},[49–51] in all the complexes, suggesting the coordination of the azomethine nitrogen.

An absorption band is observed at 661 cm^{-1} in the ligand spectrum that corresponds to ν(C-S), which is not displaced in the spectra of coordination compounds.[52] Consequently, the sulfur atom is not involved in the coordination of the central ion.

The presence of the NO_3^- anion is demonstrated by the appearance in the IR spectrum of complex **7** of an absorption band extended at 1354 cm^{-1}.[30]

The complex **4** exhibits ν (OH) and $\gamma(H_2O)$ bands at 3404 and 1157 cm^{-1} which are indicative for the coordinated water molecules [53] and broad band in the region 1100–1000 cm^{-1} that is characteristic for perchlorate ion.

3.3 | Electronic Spectra and Magnetic Studies

The geometry of the complexes has been deduced from electronic spectra and magnetic moment data (Figure S5). The electronic spectra in the polycrystalline state of **HL** show the intraligand absorption maxima corresponding to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions: 30,769 and 26,315 cm^{-1}. In the spectra of the complexes these bands are shifted to lower energies (Table 4).

Magnetic moments values for copper complexes **2**, **3** are in the range of 1.37–1.48 B.M.These may indicate their polynuclear structure, because the values are understated in comparison with spin value for one unpaired electron 1.73 B.M. Effective magnetic moment of the copper complex **4** is 1.80 B.M., indicate the presence of an unpaired electron on Cu (II) ion, consequently is a monomer.[53] The electronic spectra of complexes **2**–**4** exhibit d-d bands at 14,280, 14,490 and 15,380 cm^{-1}, respectively corresponding to the transitions specific to the square-pyramidal geometry.[54]

The electronic spectrum of the nickel complex **5** shows three spin-allowed bands at 11,290 14,380 and 19,410 cm^{-1} respectively. These absorption bands may be assigned to the $^3A_{2g} \rightarrow {}^3T_{2g}(F)$, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$, $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ transitions respectively, and reflect Ni (II) d^8 ions in an octahedral geometrical environment.[55] The magnetic moment value, 3.20 BM corresponds to two unpaired electrons per metal ion.

The cobalt complexes **6–8** are diamagnetic, therefore cobalt ion is in the +3 oxidation state. These complexes show absorption bands in the area 13,980 – 14,920, 16,390–16,800 and 20,000–22,470 cm^{-1} that were assigned to the d–d transitions $^1A_{1g} \rightarrow {}^3T_{2g}$, $^1A_{1g} \rightarrow {}^1T_{1g}$, $^1A_{1g} \rightarrow {}^1T_{2g}$, suggesting a octahedral geometry.[56]

UV–Vis spectrum of DMSO solution of **HL** contains maximum at 30,581 cm^{-1} while corresponding spectra of coordination compounds **1–8** contain two maximums in the regions 30,959–32,894 cm^{-1} and 22,123–22,727 cm^{-1}. It proves that these coordination compounds are stable in DMSO solutions.

3.4 | Mass spectra

The ESI-MS spectra of the ligand and complexes **1–8** were recorded to determine molecular species in solution (Figure S6).

The mass spectra of these complexes show peaks assignable to various fragments arising from the thermal cleavage of the complexes (Table S1). The molecular ion peaks obtained from complexes are as follow: m/z = 532.1 (**1**), m/z = 333.9 (**2**), m/z = 487.1 (**3**), m/z = 533.1 (**4**), m/z = 527.1 (**5**), m/z = 525.1 (**6–8**). The data obtained provide good agreement for the molecular formula of these complexes.

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TABLE 4 Electronic spectral assignments (cm^{-1}) for the complexes **2–8**

Compound	Transitions d–d (cm^{-1})	μ_{eff} (MB)	Geometry
[Cu (HL)Cl_2] **(2)**	$^2B_{1g} \rightarrow {}^2B_{2g}$ $^2B_{1g} \rightarrow {}^2E_g$ $^2B_{1g} \rightarrow {}^2A_{1g}$ - 14,280 -	1.37	Square-pyramidal
[Cu (HL)Br_2] **(3)**	$^2B_{1g} \rightarrow {}^2B_{2g}$ $^2B_{1g} \rightarrow {}^2E_g$ $^2B_{1g} \rightarrow {}^2A_{1g}$ - 14,490 -	1.48	Square-pyramidal
[Cu (HL)$(H_2O)_2$]$(ClO_4)_2$ **(4)**	$^2B_{1g} \rightarrow {}^2B_{2g}$ $^2B_{1g} \rightarrow {}^2E_g$ $^2B_{1g} \rightarrow {}^2A_{1g}$ - 15,380 -	1.80	Square-pyramidal
[Ni $(HL)_2$]$I_2 \cdot H_2O$ **(5)**	$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ 11,290 14,380 19,410	3.20	Octahedral
[$Co(L)_2$]Cl **(6)**	$^1A_{1g} \rightarrow {}^3T_{2g}$ $^1A_{1g} \rightarrow {}^1T_{1g}$ $^1A_{1g} \rightarrow {}^1T_{2g}$ 14,290 16,390 20,000	*	Octahedral
[$Co(L)_2$]NO_3 **(7)**	$^1A_{1g} \rightarrow {}^3T_{2g}$ $^1A_{1g} \rightarrow {}^1T_{1g}$ $^1A_{1g} \rightarrow {}^1T_{2g}$ 16,390 19,607 22,470	*	Octahedral
[$Co(L)_2$]I·[$Co(L)_2$](I_3) **(8)**	$^1A_{1g} \rightarrow {}^3T_{2g}$ $^1A_{1g} \rightarrow {}^1T_{1g}$ $^1A_{1g} \rightarrow {}^1T_{2g}$ 13,980 16,806 20,400	*	Octahedral

*diamagnetic.

3.5 | Structural Characterization of Ligand HL and Complexes 1, 5, 7, 8

The X-ray structures of **HL**, **1**, **5**, **7** and **8** are *shown* on the Figures 1–4.

In **HL** the substituents at the N(2)–C(1) bond are in the *E* position. The *A*(S(1)-N(1)-N(2)-N(3)-C(1)-C(5)) core is practically planar within 0.028 Å and the dihedral angle between given core and pyridine ring is equal to 4.1°. However the given molecule is nonplanar because the presence of C_3H_5 substituent in the thiosemicarbazone moiety, the dihedral angle between the best planes of *A* and (C(2)–C(4)) fragment is equal to 88.8°. In the crystal the ligand **HL** forms the chains along the *c*-axis where the molecules are linked by N(3)-H... N(4) (*x,1.2-y,-1/2 + z)* hydrogen bonds (HB) (Table 2, Figure 2).

In these complexes, the isothiosemicarbazone coordinates to the metal atom in a tridentate manner using its the NNN set of donor atoms. They exhibit a distorted octahedral geometry by the involvement of two ligand molecules (Tables 3, 4, Figures 1, 3, 4). The octahedral volumes of Co atoms in **7** and **8** are equal to 9.122 and 9.213 $Å^3$ whereas for Zn and Ni (**1**, **5**) atoms the corresponding values are 12.111, and 11.178 $Å^3$ respectively.

In the crystal the complexes of **1** form the hydrogen bonds with iodine atoms (Table 2, Figure 3a) while in the crystal structure of **5** the iodine atoms I(1) join the complexes into the dimers *via* (2A)-H...I(1) (x,1/2-y,-1/2 + z) and C(10)-H...I(1) (1-x,-1/2 + y,1/2-z) HB. In the dimers each of complexes are liked by hydrogen bonds with another iodine atoms I(2) and water molecules (Table 2, Figure 3b). In crystal packing, it is observed that cobalt complexes **7** are linked to C (2) -H ... S (1) HB in centrosimetric dimers which are bound by the nitrate groups in the bridge, forming the 3D hydrogen bonding networks (Table 2, Figure 4). The crystal structure of **8** contains two independent molecules. But only the first complex forms the hydrogen bonds with triiodide and iodine ions through C(9)-H(9)...I(1) and C(10)-H(10)... I(4) HB (Table 2, Figure 3c). The C(3)–H ... π and C(8)–H ... π interactions were observed for compounds of **HL** and **7** with H ... *Cg (pyridine)* distances 2.91 and 2.71 Å respectively. All studied compounds are stabilized by C-H...S intramolecular HB.

The performed powder X-ray diffractograms of these compounds correspond to the simulated ones from single crystal X-ray data (Figure S7).

3.6 | Biological Activity

3.6.1 | Antibacterial and antifungal activity

In a microdilution *in vitro* assay, ligand and their complexes were tested against Gram-positive (*Staphylococcus aureus ATCC 25923*), Gram-negative (*Escherichia coli ATCC 25922*, *Klebsiella pneum*oniae ATCC 13883) bacterial strains and fungal strain (*Candida albicans* ATCC 10231). Data interpretation was made using furacillinum and nystatine as standards drugs.

The results of the antimicrobial activity study (Table 5) showed that **HL** and its complexes manifest bacteriostatic and bactericidal properties. Activity of

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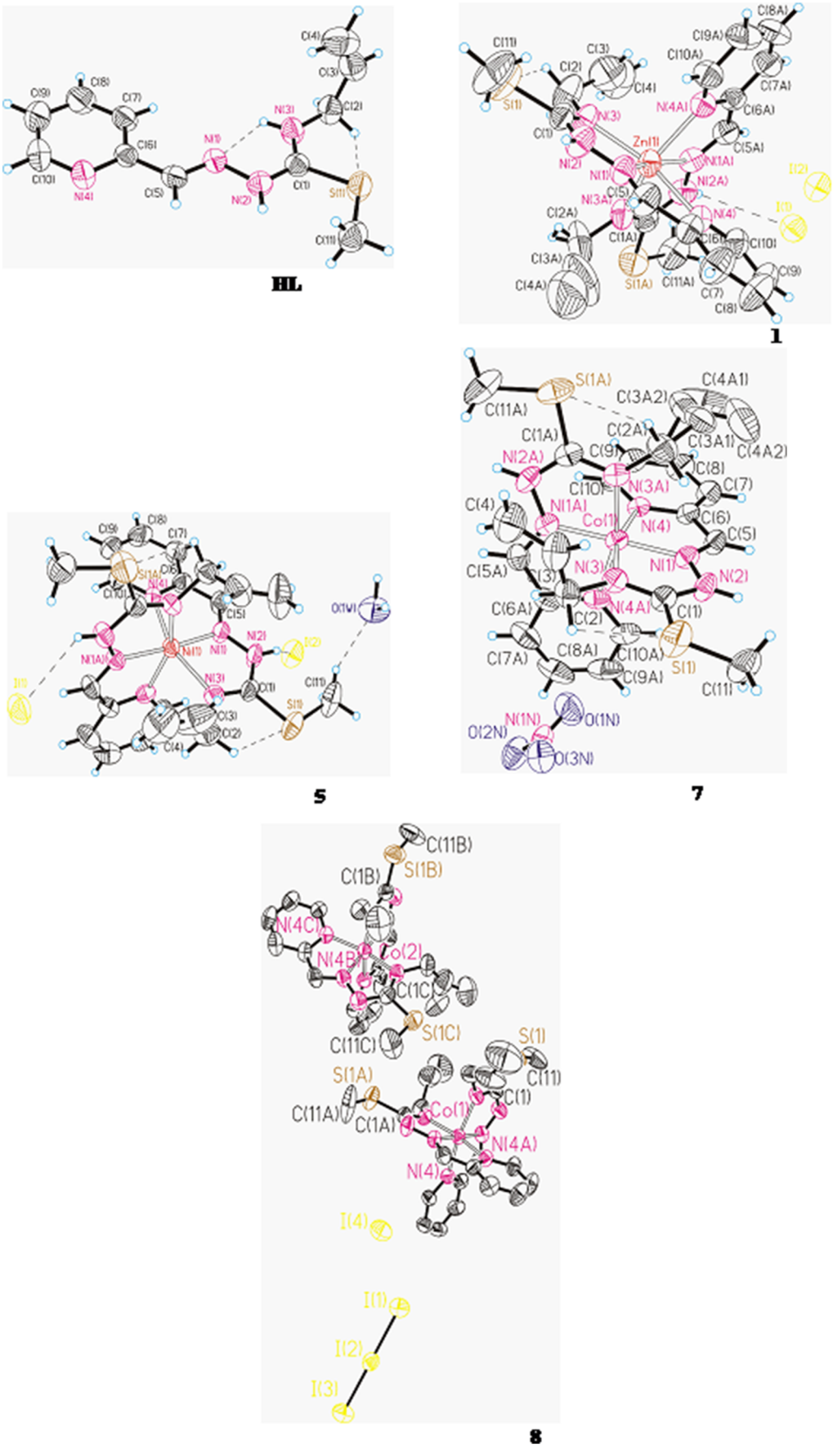


FIGURE 1 View of **HL**, **1**, **5**, **7**, **8** compounds with atom numbering. Thermal ellipsoids are drawn at 50% probability level

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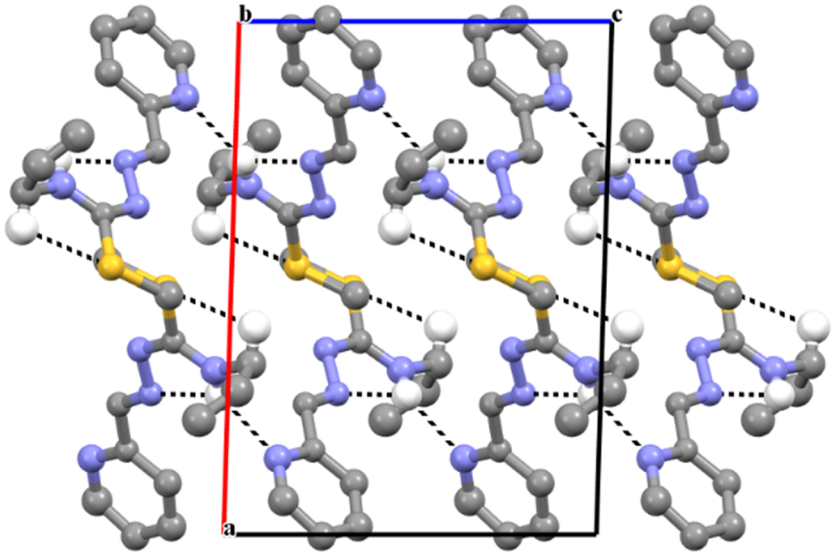


FIGURE 2 The crystal packing of the ligand **HL**, showing the chains formation

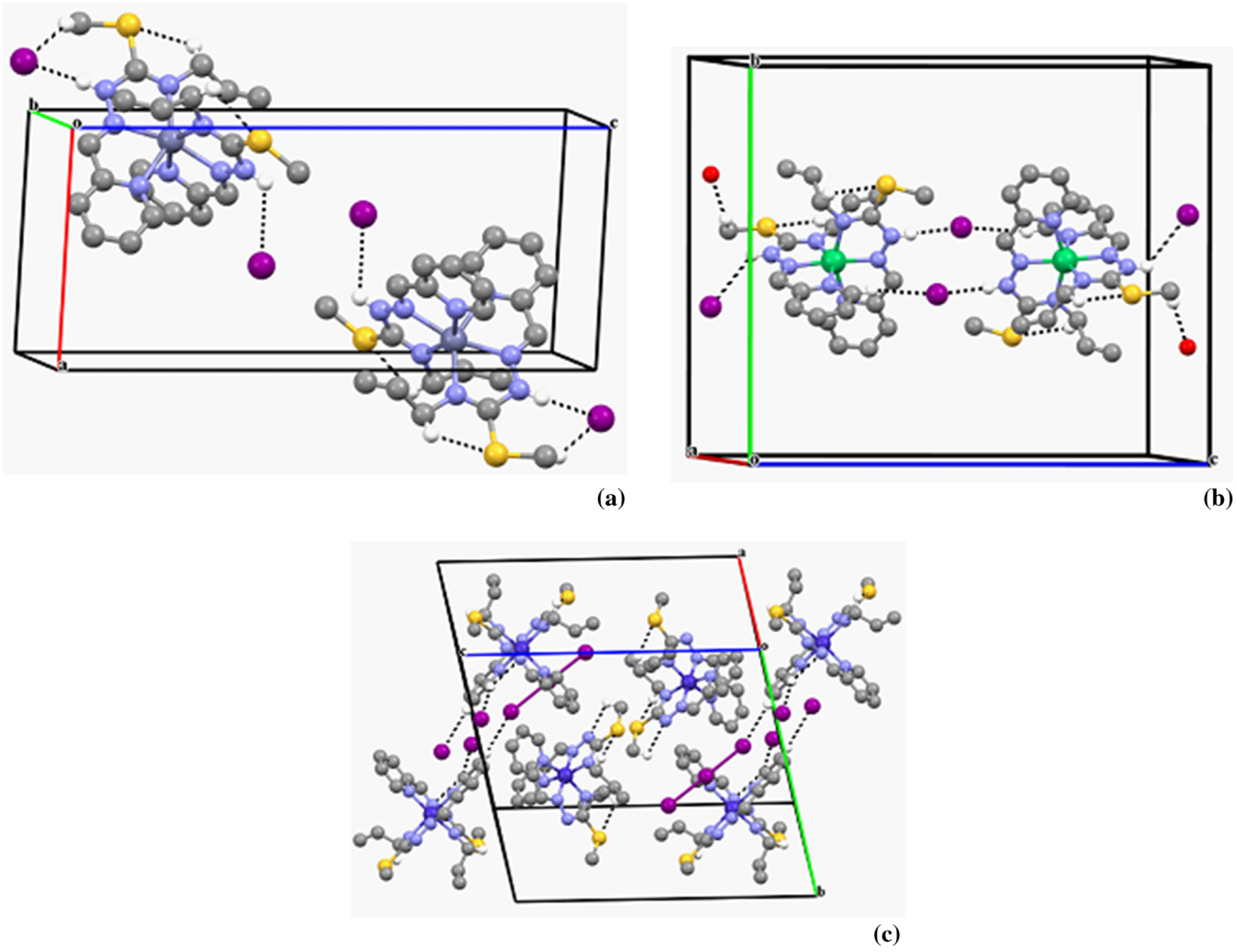


FIGURE 3 The crystal packing fragments of (a)**1**, (b) **5**, (c) **8**

these compounds towards gram-negative bacteria is lower than towards gram-positive bacteria and fungi.

It has been observed, that the isothiosemicarbazone **HL** and studied coordination compounds manifest

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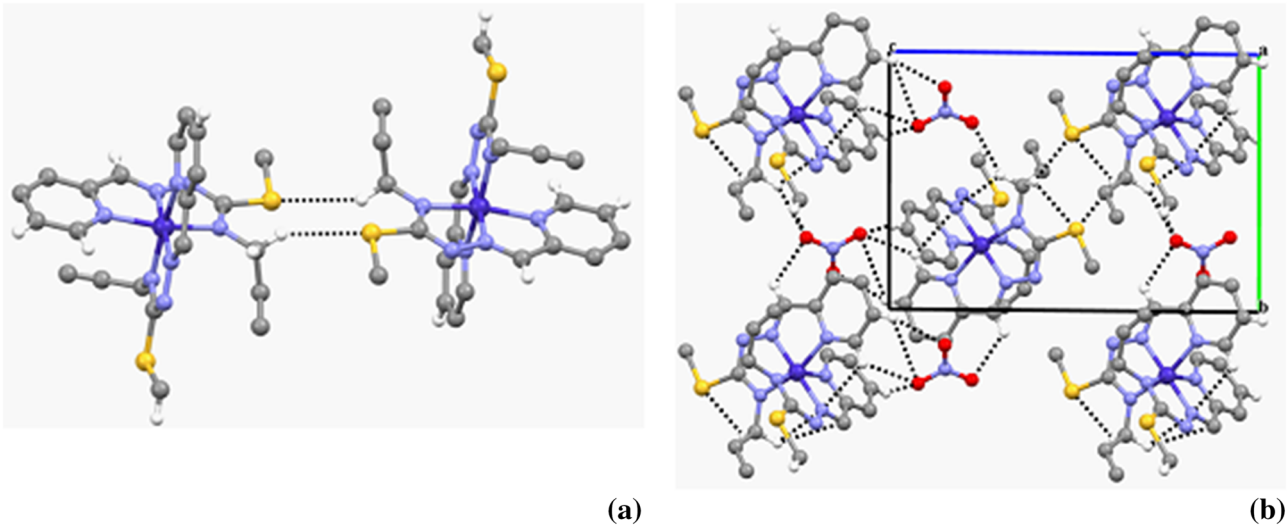


FIGURE 4 The crystal packing of **7**, showing the (a) formation of centrosymmetric dimers and (b) 3D molecular network

TABLE 5 Antibacterial and antifungal activities of ligand **HL**, **HL·HI** and complexes **1–4**, **6**, **7** as MIC[a]/MBC[b]/MFC[c] values (μg/ml)

	E. coli (G-)		*K. pneumoniae (G-)*		*S. aureus (G+)*		*C. albicans*	
Compound	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MFC**
HL	500	500	500	500	0.7	1.5	250	500
HL·HI	250	250	500	1000	1.5	3	500	1000
$[Zn(HL)_2]I_2$ **(1)**	60	120	120	120	0.7	0.7	60	60
$[Cu(HL)Cl_2]$ **(2)**	60	60	60	60	0.7	0.7	30	30
$[Cu(HL)Br_2]$ **(3)**	60	60	120	120	0.7	0.7	30	30
$[Cu(HL)(H_2O)_2](ClO_4)_2$ **(4)**	60	60	250	250	1.5	1.5	60	60
$[Co(L)_2]Cl$ **(6)**	250	250	120	250	3	3	7	30
$[Co(L)_2]NO_3$ **(7)**	120	250	60	120	0.7	0.7	120	250
Furacillinum	18.5	37.5	75	150	9.3	9.3	-	-
Nystatine	-	-	-	-	-	-	80	80

E. coli (*Escherichia coli*, ATCC 25922); K. pneumoniae (*Klebsiella pneumoniae*, ATCC 13883); S. Aureus (*Staphylococcus aureus*, ATCC 25923); C. albicans (*Candida albicans*, ATCC 10231).
[a]MIC–minimum inhibitory concentration;
[b]MBC—minimum bactericide concentration;
[c]MFC, minimum fungicidal concentration. G(−): Gram-negative bacteria; G(+): Gram-positive bacteria.

antimicrobial activities within the concentration limits 0.7–500 μg/ml.

The most vulnerable to the studied substances was *Staphylococcus aureus*. In this case, the values of minimum inhibitory and minimum bactericide concentrations vary in the range of concentrations 0.7–3 μg/ml, which indicate the high activity of synthesized compounds. These values are several times higher than activity of furacillinum that is used in medical practice.

The comparison of the activity of **HL** with the activity of 2-hydroxybenzaldehyde 4-allyl-*S*-methylisothiosemicarbazone[30] shows that the substitution of 2-hydroxybenzaldehyde moiety with 2-formylpyridine moiety leads to a significant intensification of antimicrobial activity especially towards Gram-positive *Staphylococcus aureus*.

The results show that copper complexes **2**–**4** are the most active toward gram-negative bacteria *Escherichia coli*. The attention deserve complexes **2** and **7**, because its activity towards gram-negative bacteria *Klebsiella pneumoniae* exceedes the activity of furacillinum. The cobalt complex **6** exhibits the greatest antifungal activity that exceeding the activity of nystatine and other synthesized substances.

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The activity of this series of complexes exceeds the activity of corresponding complexes of 2-hydroxybenzaldehyde 4-allyl-*S*-methylisothiosemicarbazone.[30] The activity of copper (**2**–**4**) and cobalt (**6**–**7**) complexes is 2–8 times higher towards gram-negative *Escherichia coli* than the activity of corresponding copper and cobalt complexes of 2-hydroxybenzaldehyde 4-allyl-*S*-methylisothiosemicarbazone. Therefore, the the substitution of 2-hydroxybenzaldehyde moiety with 2-formylpyridine moiety leads to a significant growth of antimicrobial activity of coordination compounds towards gram-negative microorganisms.

The present experimental results show that these complexes display the potential application in the antibacterial and antifungal arias.

TABLE 6 Antiproliferative activity of ligand and metal complexes on human leukaemia HL-60 cells at three concentrations and IC_{50} values

Compound	Inhibition of cell proliferation (%)[a]			IC_{50}, μM
	10 μM	1 μM	0.1 μM	
HL	0	0	0	>100
HL·HI	0	0	0	>100
$[Zn(HL)_2]I_2$ **(1)**	0	0	0	>100
$[Cu(HL)Cl_2]$ **(2)**	100	30.1	0	3.3
$[Cu(HL)Br_2]$ **(3)**	99.5	96.0	0	0.4
$[Cu(HL)(H_2O)_2](ClO_4)_2$ **(4)**	100	7.6	5.0	5.2
$[Ni(HL)_2]I_2·H_2O$ **(5)**	94.7	5.7	1.1	5.5
$[Co(L)_2]NO_3$ **(7)**	77.7	10.0	4.1	6.3
Doxorubicin	99	98	15	0.2

[a]SEM < ±4% of a single experiment in triplicate. The IC_{50} values were calculate using statistical software.

3.6.2 | Antiproliferative activity

The compounds have been tested for antiproliferative activity on the following cancer cells: human leukemia (HL-60), human cervical epithelial (HeLa), human epithelial pancreatic adenocarcinoma (BxPC-3), human muscle rhabdomyosarcoma spindle and large multinucleated (RD) cells.

The isothiosemicarbazone and six coordination compounds were tested as inhibitors of HL-60 cells proliferation. These human promyelocytic leukemia cells were incubated for three days in the presence of synthesized compounds (ligand and complexes) and the number of viable cells was measured using the MTS assay. The results are expressed as the percentage of cell growth inhibition at three concentrations.

The **HL**, **HL·HI** and zinc complex **1** do not manifest inhibitor activity in the concentration range 10–0.1 μM. Copper, nickel and cobalt complexes with this ligand possess anticancer activity with IC_{50} values 0.4–6.3 μM (Table 6). The nature of the metal ion, the number and nature of the donor atoms, the stereochemistry of the coordination polyhedral, seem to influence cellular proliferation.

The copper complex **3** manifests the highest activity in comparison to all studied coordination compounds with this ligand and approaches to the activity of doxorubicin, which is used in medicine. The activity of the studied complexes practically disappears at 0.1 μM concentration.

The search for novel biologically active substances with more selectivity and lower toxicity continues to be an area of intensive investigation. So that, the activity of these compounds was tested on normal MDCK cells. Experimental data indicate that the ligand **HL** does not

TABLE 7 Antiproliferative activity of ligand and metal complexes on MDCK cells at three concentrations and IC_{50} values

Compound	Inhibition of cell proliferation (%)[a]				IC_{50}, μM
	100 μM	10 μM	1 μM	0.1 μM	
HL	0	0	0	0	>100
$[Zn(HL)_2]I_2$ **(1)**	96.7	0	0	0	68
$[Cu(HL)Cl_2]$ **(2)**	100	79.5	2.4	0	5.0
$[Cu(HL)Br_2]$ **(3)**	100	100	7.3	0	1.5
$[Ni(HL)_2]I_2·H_2O$ **(5)**	57.4	0	0	0	95
$[Co(L)_2]Cl$ **(6)**	45.8	0	0	0	>100
$[Co(L)_2]NO_3$ **(7)**	23.8	0	0	0	>100
$[Co(L)_2]I·[Co(L)_2](I_3)$ **(8)**	31.0	0	0	0	>100
Doxorubicin	-	56.0	25.1	19.1	7.1

[a]SEM < ±4% of a single experiment in triplicate.

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TABLE 8 IC_{50} values of ligand and metal complexes towards MDCK, HL-60, HeLa, BxPC-3 and RD cells

	MDCK	HL-60		HeLa		BxPC-3		RD	
Compound	**IC_{50}, μM**	**IC_{50}, μM**	**SI[a]**	**IC_{50}, μM**	**SI[a]**	**IC_{50}, μM**	**SI[a]**	**IC_{50}, μM**	**SI[a]**
HL	>100	>100	-	>100	-	>100	-	16.1	>6.2
$[Zn(HL)_2]I_2$ **(1)**	68	>100	-	>100	-	>100	-	10.9	6.24
$[Cu(HL)Cl_2]$ **(2)**	5.0	3.3	1.52	7.92	0.63	1.08	4.63	1.16	4.31
$[Cu(HL)Br_2]$ **(3)**	1.5	0.4	3.75	1.25	1.20	0.36	4.17	0.68	2.21
$[Ni(HL)_2]I_2 \cdot H_2O$ **(5)**	95	5.5	17.3	54.0	1.76	51.6	1.84	14.1	6.74
$[Co(L)_2]Cl$ **(6)**	>100	-	-	2.1	>47	48.2	>2.1	15.9	6.29
$[Co(L)_2]NO_3$ **(7)**	>100	6.3	>16	>100	-	>100	-	57.0	>1.7
$[Co(L)_2]I \cdot [Co(L)_2](I_3)$ **(8)**	>100	-	-	>100	-	>100	-	>100	-
Doxorubicin	7.1	0.2	35.5	10.0	0.71	3.7	1.92	16.2	0.44

[a]SI – selectivity index $SI = \frac{IC_{50}(MDCK)}{IC_{50}(cancer\ cell)}$.

inhibit proliferation of these normal cells (Table 7). Cobalt coordination compounds also do not affect the growth and multiplication of MDCK cells.

By performing primary screening on several cancer cells, the selectivity of antiproliferative activity was determined for some of the synthesized complexes (Table 8).

The isothiosemicarbazone **HL** selectively inhibits only RD cells. The copper complex **3** is the most active towards all studied cancer cells, but it also affects proliferation of normal cells, so it is not enough selective (SI (selectivity index) = 1.2–4.2). Copper complexes **2**, **3** have selectivity indexes towards BxPC-3 and RD cells that exceed corresponding SI values of doxorubicin in 2.2–9.8 times. Cobalt complex **6** selectively inhibits proliferation of HeLa cells (SI > 47) and practically does not influence the growth of normal cells. Its SI value towards this cancer cell is more than 60 times higher than the corresponding SI value of doxorubicin that is used in medical practice.

Copper coordination compound **3** is more active than corresponding copper complex of 2-hydroxybenzaldehyde 4-allyl-*S*-methylisothiosemicarbazone[30] but it is less selective at the same time. So the subtituition of 2-hydroxybenzaldehyde moiety with 2-formylpyridine moiety leads to a decrease of selectivity.

3.6.3 | Antioxidant activity

The antioxidant activity of the compounds was determined by the ABTS• + method. Experimental data revealed that ligand **HL** and complexes **1**–**8** show moderate antioxidant activity against $ABTS^{\bullet+}$ with an $IC_{50} \geq 100$ μM.

4 | CONCLUSIONS

Physico-chemical analyses confirmed the composition and structures of the newly obtained complexes. The coordination ability of the isothiosemicarbazone **HL** has been proved in complexation reaction with Zn (II), Ni (II), Cu (II) and Co (III) ions. The structure of the **HL** and complexes **1**, **5**, **7** and **8** has been elucidated by single-crystal X-ray diffraction analysis. These studies demonstrate the nonplanar configuration of the ligand by the presence of the C_3H_5 radical in the isothiosemicarbazone structure.

Depending on the metal salt used, the isothiosemicarbazone act as ligand tridentate through deprotonated N^4 nitrogen atom (when we used $CoCl_2 \cdot 6H_2O$, Co $(NO_3)_2 \cdot 6H_2O$, Co $(CH_3COO)_2 \cdot 4H_2O$), nondeprotonated N^4 (when we used Zn $(CH_3COO)_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, $CuBr_2$, Cu $(ClO_4)_2 \cdot 6H_2O$, Ni $(CH_3COO)_2 \cdot 4H_2O$), N^1 and pyridine nitrogen atoms.

The antimicrobial activity of the ligand and its complexes was evaluated on a series of standard strains of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans* and antiproliferative activity was investigated using HL-60, HeLa, BxPC-3, RD cancer cell lines and normal MDCK cell.

The quantitative antimicrobial activity test results proved that the complexes have specific antimicrobial activity, depending on the microbial species tested, in the range of concentration 0.7–500 μg/ml.

The screening results showed that the synthesized substances inhibit proliferation of the studied cancer cells at concentrations 100–0.1 μM. The study of the influence of synthesized compounds on healthy MDCK cells

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showed that in many cases they have lower cytotoxic effect on healthy cells of human organism. Copper complexes **2**, **3** show the highest antiproliferative towards the studied cancer cells, but they are still less active than doxorubicin. At the same time they do not show high selectivity with selectivity index values 0.63–4.63. On the other hand, the cobalt complexes **6**, **7** and nickel complex **5** are more selective ones. They show promising antiproliferative activity and low toxicity with SI towards HeLa more than 47 for the cobalt complex **6**. It makes these substances perspective for their use as anticancer drugs.

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SUPPLEMENTARY DATA

CCDC 1915015, 1915016, 1915017, 1915018, 1915019 contains the supplementary crystallographic data for **HL**, **1**, **5**, **7** and **8**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44–1223–336-033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk

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SUPPORTING INFORMATION

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