Molecules **2013**, *18*, 8812-8836; doi:10.3390/molecules18088812

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

Synthesis and Characterization of Some New Cu(II), Ni(II) and Zn(II) Complexes with Salicylidene Thiosemicarbazones: Antibacterial, Antifungal and *in Vitro* Antileukemia Activity

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Received: 29 May 2013; in revised form: 12 July 2013 / Accepted: 15 July 2013 / Published: 24 July 2013

Abstract: Thirty two new Cu(II), Ni(II) and Zn(II) complexes (**1**–**32**) with salicylidene thiosemicarbazones (**H_2L^1**–**H_2L^{10}**) were synthesized. Salicylidene thiosemicarbazones, of general formula (X)N-NH-C(S)-NH(Y), were prepared through the condensation reaction of 2-hydroxybenzaldehyde and its derivatives (X) with thiosemicarbazide or 4-phenylthiosemicarbazide (Y = H, C_6H_5). The characterization of the new formed compounds was done by ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy, elemental analysis, magnetochemical, thermoanalytical and molar conductance measurements. In addition, the structure of the complex **5** has been determined by X-ray diffraction method. All ligands and metal complexes were tested as inhibitors of human leukemia (HL-60) cells growth and antibacterial and antifungal activities.

Keywords: copper; nickel; zinc complexes; thiosemicarbazones; antimicrobial activity; antileukemia

1. Introduction

The design and study of well-arranged metal-containing Schiff bases with ONS – donor atoms is an interesting field of inorganic and bioinorganic chemistry [1–11]. *In-situ* one-pot template condensation reactions lie at the heart of the coordination chemistry. Transition metal complexes have also received great attention because of their biological interests, including antiviral, anticarcinogenic, antibacterial and antifungal activities [12–16]. Thiosemicarbazones and their Cu(II) complexes demonstrated potent cytotoxic activities against a series of murine and human tumor cells in culture [17–19].

In a recent study [20], we have concluded that the *in vitro* HL-60 leukemia cell growth inhibitory activity is influenced by the nature and geometric structure of copper complexes. Indeed, copper complexes containing tridentate ONS Schiff bases as well as salicyliden thiosemicarbazones have been found as effective inhibitors of cell proliferation. We have started a program directed toward the synthesis of different classes of anticancer, antibacterial and antifungal agents designed with complexes of a transition metal and an organic ligand [21–24].

In continuation of this approach, the present paper describes the synthesis, characterisation and *in vitro* evaluation of inhibitors of HL-60 cell proliferation, antibacterial and antifungal activity using thirty two novel Cu(II), Ni(II) and Zn(II) complexes with the salicylidene thiosemicarbazones (**H_2L^1**–**H_2L^{10}**), obtained from the condensation reaction of thiosemicarbazide or 4-phenylthiosemicarbazide with 2-hydroxybenzaldehyde derivatives. All ligands and metal complexes were tested as inhibitors of human leukemia (HL-60) cell growth. The Cu(II) complexes **21**–**25**, **30** have also been tested for their *in vitro* antibacterial activity against *Staphylococcus aureus (Wood-46, Smith, 209-P), Staphylococcus saprophyticus, Streptococcus (group A), Enterococcus faecalis* (Gram-positive)*, Escherichia coli (O-111), Salmonella typhimurium, Salmonella enteritidis, Klebsiella pneumoniaie, Pseudomonas aeruginosa, Proteus vulgaris and Proteus mirabilis* (Gram-negative) and antifungal activity against *Aspergillus niger, Aspergillus fumigatus, Candida albicans* and *Penicillium* strains.

2. Results and Discussion

2.1. Chemistry

The salicylidene thiosemicarbazones **H_2L^1**–**H_2L^{10}** used in this work were prepared by refluxing (for 30 min.) in ethanol an equimolar amount of aldehyde (salicylaldehyde or its derivatives, 5-chloro-, 5-bromo-, 5-nitro-, 5-methyl- and 3,5-dichlorosalicylaldehyde) and thiosemicarbazide or 4-phenylthiosemicarbazide. The structures of the Schiff bases **H_2L^1**–**H_2L^{10}** were established by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

These Schiff bases were further used for the complexation reaction with Cu^{2+}, Ni^{2+}, Zn^{2+} metal ions, using the following salts: $CuSO_4 \cdot 5H_2O$ (for complexes **1**–**7**), $Cu(NO_3)_2 \cdot 3H_2O$ (for **8**–**14**), $CuCl_2 \cdot 2H_2O$ (for **15**–**30**), $NiCl_2 \cdot 6H_2O$ (for **31**) and $ZnCl_2$ (for **32**). To metal salt (10 mmol) dissolved in distilled

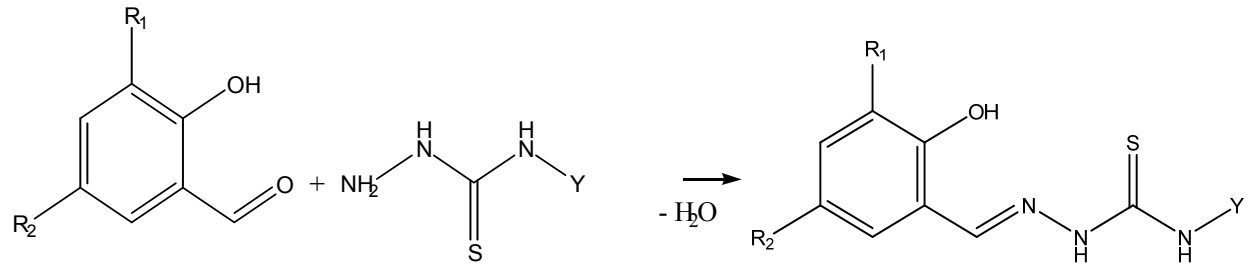
water was added salicylidene thiosemicarbazone, **HL**, (10 mmol) dissolved in ethanol. The reaction mixture was stirred and heated (50–55 °C) for 1.5 h. The precipitate was filtered, washed with ethanol, ether and dried in air.

The complexes obtained are microcrystalline solids which are stable in air and decompose above 310 °C (Table 1). They are insoluble in organic solvents such as acetone and chloroform but soluble in DMF and DMSO.

The molar conductance of the soluble complexes in DMF showed values indicating that **1**–**14** (80–100 ohm^{-1} cm^2 mol^{-1}) are electrolytes and **15**–**32** (10–20 ohm^{-1} cm^2 mol^{-1}) are non-electrolytes in nature [25].

The elemental analyses data of Schiff bases (reported in the Experimental section) and their complexes (Table 1) are in agreement with the proposed composition of the ligands as shown in Scheme 1 and with the formulas of the complexes as shown in Figure 1a,b.

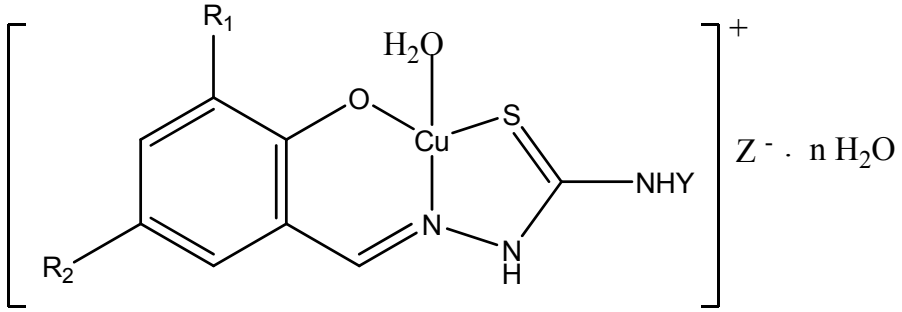
Scheme 1. General synthesis of organic ligands $\mathbf{H_2L^{1-10}}$.



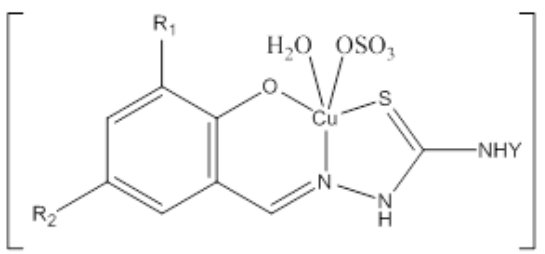
R_1 = H, R_2 = H, Y = H **(H_2L^1)**, R_1 = Cl, R_2 = Cl, Y = H **(H_2L^6)**
R_1 = H, R_2 = Cl, Y = H **(H_2L^2)**, R_1 = Br, R_2 = Br, Y = H **(H_2L^7)**
R_1 = H, R_2 = Br, Y = H **(H_2L^3)**, R_1 = H, R_2 = H, Y = C_6H_5 **(H_2L^8)**
R_1 = H, R_2 = NO_2, Y = H **(H_2L^4)**, R_1 = H, R_2 = Br, Y = C_6H_5 **(H_2L^9)**
R_1 = H, R_2 = CH_3, Y = H **(H_2L^5)**, R_1 = H, R_2 = NO_2, Y = C_6H_5 **(H_2L^{10})**

Figure 1. (**a**) General structure of complexes **1**–**14**. (**b**) General structure of complexes **15**–**32**.

(**a**)



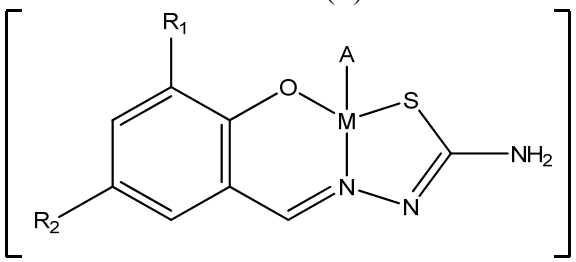
Z =



(1 – 7); Z = NO_3^- (8 – 14)

Figure 1. *Cont.*

(b)



M = Cu **(15–30)**, Ni **(31)**, Zn **(32);** R_1 = H (**1–19**, **30–32**), Cl (**20**), Br (**21–29**); R_2 = H (**1**, **2**, **8**, **9**, **15**, **30–32**), CH_3 (**19**), Cl (7, **14**, **16**, **20**), Br (**5**, **6**, **12**, **13**, **17**, **21–29**), NO_2 (**3**, **4**, **10**, **11**, **18**); Y = H (**1**, **3**, **5**, **7**, **8**, **10**, **12**, **14–32**), C_6H_5 (**2**, **4**, **6**, **9**, **11**, **13**).

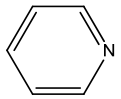
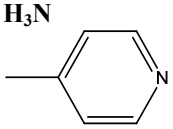
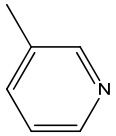
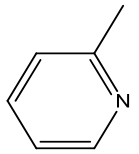
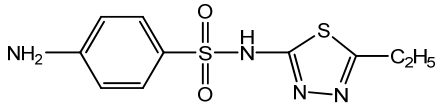
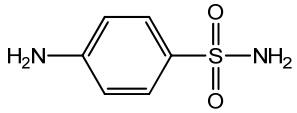
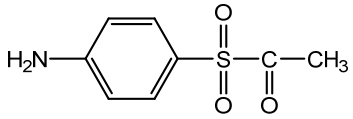
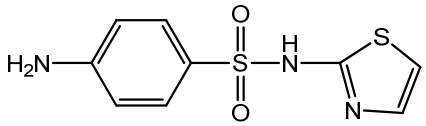
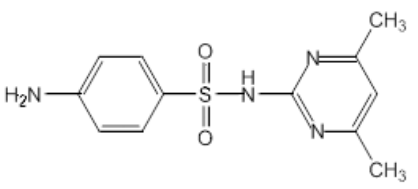
A–Structure	**Name**	**Complex**
	Py	15–20
H_3N	-	21
	4-MePy	22
	3-MePy	23
	2-MePy	24
	Etz	25, 30–32
	Str	26
	Sfc	27
	Nor	28
	Sdm	29

Table 1. Physical and analytical data of the metal complexes **1**–**32** [a].

Comp. No.	Molecular formula	Mr [b]	μ_{eff} [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, % [e]	T, C [f] dec
1	$C_{16}H_{24}Cu_2N_6O_{10}S_3$ $[Cu(H_2O)(HL^1)][Cu(H_2O)(HL^1)SO_4] \cdot 2H_2O$	684	2.14	C: 28.1(28.5); H: 3.5 (3.0); N: 12.3(12.5); S: 14.0 (13.7)	18.7 (18.6)	H_2O (3585, 1575, 920); NH_2 (3435, 3420); NH(3335, 3220, 3145); C= N (1605); C-O (1200); C = S (781); Cu-N (510, 415); Cu-O (470); Cu-S (450)	65	460
2	$C_{28}H_{30}Cu_2N_6O_9S_3$ $[Cu(H_2O)(HL^8)][Cu(H_2O)][(HL^8)SO_4] \cdot H_2O$	818	2.07	C: 41.1(41.4); H: 3.7 (3.4); N: 10.3(10.3); S: 11.7 (11.6)	15.6 (15.8)	H_2O (3580, 1570, 925); NH (3325, 3222, 3143); C = N (1600); C-0(1195); C = S (780); Cu-N(517, 428); Cu-O (472); Cu-S (445)	64	450
3	$C_{16}H_{22}Cu_2N_8O_{14}S_3$ $[Cu(H_2O)(HL^4)][Cu(H_2O)(HL^4)(SO_4)] \cdot H_2O$	774	1.98	C: 24.8 (24.5); H: 2.8(2.7); N: 14.5 (14.8); S: 12.4 (12.7)	16.5 (16.3)	H_2O (3575, 1570, 922); NH_2 (3445, 3425); NH (3330 3230, 3140); C = N (1590); C-O (1195); C = S (776); Cu-N (530, 410); Cu-O (470); Cu-S (465)	77	425
4	$C_{28}H_{30}Cu_2N_8O_{14}S_3$ $[Cu(H_2O)(HL^{1o})][Cu(H_2O)(HL^{1o})(SO_4)] \cdot 2H_2O$	926	2.09	C: 36.3 (36.5); H: 3.2 (3.0); N: 12.1 (12.4); S: 10.4 (10.1)	13.8 (14.1)	H_2O (3580, 1583, 915); NH (3315, 3230, 3138); C = N (1585); C-O (1197); C = S (779); Cu-N (525, 430); Cu-O (475); Cu-S(440)	72	410
5	$C_{16}H_{26}Br_2Cu_2N_6O_{12}S_3$ $[Cu(H_2O)(HL^3)][Cu(H_2O)(HL^3)(SO_4)] \cdot 4H_2O$	878	1.85	C: 21.9 (22.2); H: 3.3 (3.3); Br: 18.2 (18.4); N: 9.6 (9.4); S: 10.3 (10.5)	14.6 (14.4)	H_2O (3565, 1575, 935); NH_2 (3445, 3430); NH (3340, 3230, 3137); C = N (1590); C-O (1205); C = S (780); Cu-N (505, 430); Cu-O (485); Cu-S (462)	69	450

Table 1. *Cont.*

Comp. No.	Molecular formula	Mr [b]	μ_{eff} [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, % [e]	T, C [f] dec
6	$C_{28}H_{28}Br_2Cu_2N_6O_9S_3$ $[Cu(H_2O)(HL^9)][Cu(H_2O)(HL^9)(SO_4)] \cdot H_2O$	976	1.91	C: 34.4 (34.0); H: 2.9 (2.7); Br: 16.4 (16.5); N: 8.6 (8.4); S: 9.8 (9.9)	13.1 (12.8)	H_2O (3580, 1565, 930); NH (3330, 3225, 3145); C = N (1585); C-O (1203); C = S (778); Cu-N (525, 425); Cu-O (484); Cu-S (465)	56	435
7	$C_{16}H_{20}Cl_2Cu_2N_6O_9S_3$ $[Cu(H_2O)(HL^2)][Cu(H_2O)(HL^2)(SO_4)] \cdot H_2O$	735	1.79	C: 26.1 (26.3); H: 2.7 (2.4); Cl: 9.7 (10.0); N: 11.4 (11.5); S: 13.1 (13.3)	17.4 (17.7)	H_2O (3585, 1575, 920); NH_2 (3430, 3430); NH (3335, 3220, 3145); C = N (1595); C-0(1200); C = S(785); Cu-N (528, 410); Cu-O (482); Cu-S (464)	78	430
8	$C_8H_{12}CuN_4O_6S$ $[Cu(H_2O)\ (HL^1)\ ]NO_3 \cdot H_2O$	356	1.87	C: 27.0 (27.3); H: 3.4 (3.1); N: 15.7 (15.5); S: 9.0 (9.4)	18.0 (18.2)	H_2O (3580, 1574, 915); NH_2 (3440, 3430); NH (3325, 3230, 3140); C = N(1600); C-0(1200); C = S(776); Cu-N(530, 410); Cu-O(480); Cu-S(450)	70	390
9	$C_{14}H_{16}CuN_4O_6S$ $[Cu\ (H_2O)(HL^8)]NO_3 \cdot H_2O$	432	2.12	C: 38.9 (38.4); H: 3.7 (3.5); N: 13.0 (13.1); S: 7.4 (7.2)	14.8 (14.5)	H_2O (3576, 1570, 930); NH(3345, 3227, 3146); C = N(1595); C-O (1198); C = S (787); Cu-N (525, 430); Cu-O (465); Cu-S (440)	54	380
10	$C_8H_{11}CuN_5O_8S$ $[Cu\ (H_2O)(HL^4)]NO_3 \cdot H_2O$	401	1.85	C: 23.9 (24.2); H: 2.7 (2.5); N: 17.5 (17.1); S: 8.0 (8.3)	16.0 (16.3)	H_2O (3570, 1565, 925); NH_2 (3445, 3430); NH (3325, 3215, 3140); C = N (1598); C-O (1195); C = S (777); Cu-N (525, 410); Cu-O (475); Cu-S (440)	76	325

Table 1. *Cont.*

Comp. No.	Molecular formula	Mr [b]	μ_{eff} [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, % [e]	T, C [f] dec
11	$C_{14}H_{17}CuN_5O_9S$ $[Cu(H_2O)(HL^{1\circ})]NO_3 \cdot 2H_2O$	495	1.94	C: 33.9 (34.1); H: 3.4 (3.5); N: 14.1 (14.2); S: 6.5 (6.9)	12.9 (12.7)	H_2O (3590, 1585, 915); NH(3325, 3225, 3140); C = N(1593); C-0(1192); C = S(783); Cu-N(525, 430); Cu-O(480); Cu-S(455)	80	315
12	$C_8H_{11}BrCuN_4O_6S$ $[Cu(H_2O)(HL^{3})]NO_3 \cdot H_2O$	435	1.80	C: 22.1 (21.8); H: 2.5 (2.2); N: 12.9 (13.2); S: 7.4 (7.5)	14.7 (14.5)	H_2O (3585, 1575, 920); NH_2(3430, 3415); NH(3335, 3220, 3145); C = N(1595); C-0(1195); C = S(784); Cu-N(525, 425); Cu-O(475); Cu-S(460)	52	370
13	$C_{14}H_{19}BrCuN_4O_8S$ $[Cu(H_2O)(HL^{9})]NO_3 \cdot 3H_2O$	547	1.97	C: 30.7 (30.9); H: 3.4 (3.2); Br: 14.6 (14.4); N: 10.2 (9.9); S: 5.8 (5.7)	11.7 (11.5)	H_2O (3570, 1565, 925); NH(3330, 3210, 3135); C = N(1590); C-0(1197); C = S(780); Cu-N(530, 423); Cu-O(470); Cu-S(465)	65	360
14	$C_8H_{11}ClCuN_4O_6S$ $[Cu(H_2O)(HL^{2})]NO_3 \cdot H_2O$	390.5	2.03	C: 24.6 (24.6); H: 2.8 (2.5); Cl: 9.1 (9.3); N: 14.3 (14.5); S: 8.2 (8.5)	16.4 (16.1)	H_2O (3585, 1575, 920); NH_2(3435, 3425); NH(3335, 3220, 3145); C = N(1605); C-0(1193); C = S(780); Cu-N(515, 430); Cu-O(490); Cu-S(455)	75	365
15	$C_{13}H_{12}CuN_4OS$ $[Cu\ L^{1}Py]$	336	1.78	C: 46.4 (46.5); H: 3.6 (3.5); N: 16.7 (16.5); S: 9.5 (9.4)	19.0 (18.8)	NH_2(3440, 3425); C = N(1590, 1580, 1575, 1310); C-0 (1215); C-S (760); Cu-N(530, 425); Cu-O(475); Cu-S(460)	71	460

Table 1. *Cont.*

Comp. No.	Molecular formula	Mr[b]	μ_{eff} [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, % [e]	T, C [f] dec
16	$C_{13}H_{11}ClCuN_4OS$ [Cu L^2Py]	370.5	1.78	C: 42.1 (42.0); H: 3.0 (2.9); Cl: 9.6 (9.5); N: 15.1 (15.0); S: 8.6 (8.4)	17.3 (17.0)	NH_2 (3435, 3420); C = N (1585, 1580, 1570, 1305); C-O (1225); C-S (750); Cu-N (510, 405); Cu-O (470); Cu-S (465)	72	440
17	$C_{13}H_{11}BrCuN_4OS$ [Cu L^3Py]	415	1.93	C: 37.6 (37.5); H: 2.7 (2.5); Br: 19.3 (19.0); N: 13.5 (13.3); S: 7.7 (7.5)	15.4 (15.5)	NH_2 (3430, 3420); C = N (1585, 1580, 1575, 1300); C-O (1210); C-S (750); Cu-N (515, 410); Cu-O (475); Cu-S (465)	75	450
18	$C_{13}H_{11}CuN_5O_3S$ [Cu L^4Py]	381	1.84	C: 40.9 (40.8); H: 2.9 (2.8); N: 18.4 (18.2); S: 8.4 (8.3)	16.8 (16.7)	NH_2 (3440, 3425); C = N (1585, 1580, 1570, 1315); C-O (1220); C-S (770); Cu-N (525, 410); Cu-O (470); Cu-S (465)	69	400
19	$C_{14}H_{14}CuN_4OS$ [Cu L^5Py]	350	1.75	C: 48.0 (47.8); H: 4.0 (3.9); N: 16.0 (15.9); S: 9.1 (9.0)	18.3 (18.0)	NH_2 (3430, 3425); C = N (1590, 1585, 1570, 1315); C-O (1220); C-S (770); Cu-N (520, 415); Cu-O (470); Cu-S (465)	70	460
20	$C_{13}H_{10}Cl_2CuN_4OS$ [Cu L^6Py]	405	1.80	C: 38.5 (38.3); H: 2.5 (2.4); Cl: 17.5 (17.4); N: 13.8 (13.6); S: 7.9 (7.8)	15.8 (15.7)	NH_2 (3435, 3425); C = N (1585, 1580, 1575, 1305); C-O (1205); C-S (770); Cu-N (515, 430); Cu-O (485); Cu-S (47 0)	76	410
21	$C_8H_{12}Br_2CuN_4O_3S$ [Cu $L^7(NH_3)$] · $2H_2O$	468	1.87	C: 20.5 (20.4); H: 2.6 (2.5); Br: 34.2 (34.0); S: 6.8(6.7)	11.9 (1.7)	NH_2 (3440, 3425); NH (3330, 3215, 3150); C = N (1582, 1585); C-O (1225); C-S (748); Cu-N (540, 425); Cu-O (490); Cu-S (410);	78	310

Table 1. *Cont.*

Comp. No.	Molecular formula	Mr [b]	μ_{eff} [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, % [e]	T, °C [f] dec
22	$C_{14}H_{14}Br_2CuN_4O_2S$ [Cu L^7(4-MePy)] · H_2O	526	1.79	C: 31.9 (31.8); H: 2.7 (2.5); Br: 31.5(31.3); S: 6.3(6.0)	12.2 (12.3)	NH_2 (3435,3430); C = N (1580,1585); C-O (1225); CNC (1042); C-S (748); Cu-O (540); Cu-O (490); Cu-S (410)	77	380
23	$C_{14}H_{12}Br_2CuN_4OS$ [Cu L^7(3-MePy)]	508	1.99	C: 33.1 (33.0); H: 2.4 (2.2); Br: 31.5(31.4); S: 6.3(6.1)	12.6 (12.4)	NH_2 (3440,3425); C = N (1580,1585); C-O (1225); CNC (1042); C-S (748); Cu-O (540); Cu-O (490); Cu-S (410)	76	390
24	$C_{14}H_{12}Br_2CuN_4OS$ [Cu L^7(2-MePy)]	508	1.92	C: 33.1 (32.9); H: 2.4 (2.5); Br: 31.5(31.4); S: 6.3(6.0)	12.6 (12.3)	NH_2 (3440,3430); C = N (1580,1585); C-O (1225); CNC (1042); C-S (748); Cu-O (540); Cu-O (490); Cu-S (410)	71	345
25	$C_{18}H_{17}Br_2CuN_7O_3S_3$ [Cu L^7(Etz)]	699	1.35	C: 30.9 (31.0); H: 2.4 (2.2); Br: 22.9 (22.7); N: 14.0(13.9); S: 13.7(13.5)	9.2 (8.6)	NH_2 (3435,3425, 3420, 3410); C = N (1610, 1600, 1585); SO_2 (1320, 1140), C-O (1215); Cu-N (540, 415); Cu-O (490); Cu-S (440)	81	470
26	$C_{14}H_{13}Br_2CuN_5O_3S_2$ [Cu L^7(Str)]	587	1.28	C: 28.6 (28.5); H: 2.2 (2.0); Br: 27.3 (27.0); N: 11.9 (12.0); S: 10.9 (10.7)	10.9 (11.0)	NH_2 (3415,3420,3405,3415); C = N (1600, 1585); SO_2 (1325, 1140); C-O (1210); Cu-N (525, 410); Cu-O (475); Cu-S (455)	68	430
27	$C_{16}H_{15}Br_2CuN_5O_4S_2$ [Cu L^7(Sfc)]	629	1.31	C: 30.5 (30.3); H 2.4 (2.5); Br: 25.4 (25.3); N: 11.1 (11.0); S: 10.2 (10.0)	10.2 (10.1)	NH_2 (3420,3415,3415,3405); C = N (1605, 1590); SO_2 (1320, 1145); C-O (1215); Cu-N (530, 425); Cu-O (480); Cu-S (465);	63	450

Table 1. *Cont.*

Comp. No.	Molecular formula	Mr [b]	μ eff [c] B.M.	C, H, N, calc (found) %	M(3d) [d] %	IR (cm^{-1})	η, %[e]	T, C [f] dec
28	$C_{17}H_{14}Br_2CuN_6O_3S_3$ [Cu L^7(Nor)]	670	1.35	C: 30.4 (30.2); H: 2.1 (2.0); Br: 23.9 (24.0); N: 12.5 (12.3); S: 14.3 (14.2)	9.6 (9.5)	NH_2 (3430, 3425, 3415, 3410); C = N (1610, 1605, 1590); SO_2 (1315, 1145); C-O (1210); Cu-N (530, 420); Cu-O (480); Cu-S (455);	69	470
29	$C_{20}H_{19}Br_2CuN_7O_3S_2$ [Cu L^7(Sdm)]	693	1.22	C: 34.6 (34.5); H: 2.7 (2.5); Br: 23.1 (23.0); N: 14.1 (14.0); S: 9.2 (9.0)	9.2 (9.1)	NH_2 (3440, 3430, 3425, 3415); C = N (1610, 1600, 1595); SO_2 (1310, 1150); C-O (1215); Cu-N (510, 425); Cu-O (475); Cu-S (450);	68	460
30	$C_{18}H_{19}CuN_7O_3S_3$ [Cu L^1(Etz)]	541	1.45	C: 39.9 (40.0); H: 3.5 (3.4); N: 18.1 (17.9); S: 17.7(17.5)	11.8 (11.6)	NH_2 (3435, 3430, 3425, 3415); C = N (1600, 1595, 1590); SO_2 (1310, 1140); C-O (1225); Cu-N (515, 410); Cu-O (470); Cu-S (465)	70	500
31	$C_{18}H_{23}NiN_7O_5S_3$ [Ni L^1(Etz)] · $2H_2O$	572	dia	C: 37.8 (37.5); H: 4.0 (3.8); N: 17,1 (17.0); S: 16.8 (16.6)	10.3 (10.2)	NH_2 (3430, 3430, 3420, 3410); C = N (1605, 1595, 1590); SO_2 (1315, 1145); C-O (1220); Cu-N (525, 415); Cu-O (475); Cu-S (460)	80	380
32	$C_{18}H_{19}N_7O_3S_3Zn$ [Zn L^1(Etz)]	542	dia	C: 39.9 (40.0); H: 3.5 (3.4); N: 18.1 (18.0); S: 17.7 (17.5)	12.0 (11.8)	NH_2 (3430, 3430, 3420, 3415); C = N (1605, 1595, 1585); SO_2 (1315, 1140); C-0 (1215); Cu-N (525, 425); Cu-O (480); Cu-S (470)	75	490

[a] **H_2L^{10}**, used in the preparation of complexes are reported in Scheme 1. [b] Mr: relative molecular mass. [c] μ eff: magnetic moment. [d] M (3d): metal 3d. [e] η: yield. [f] T_{dec} .: decomposition temperature.

2.1.1. X-ray Structure of $[Cu(H_2O)(HL^3)][Cu(H_2O)(HL^3)(SO_4)]\cdot 4H_2O$ (**5**)

The structure of crystals, obtained from ethanolic solution after recrystallization of (**5**), has been determined by means of X-ray analysis and is similar to the structure described in [26].

2.1.2. IR Spectra and Coordination Mode

The tentative assignments of the significant IR spectral bands of $\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$ and their Cu(II), Ni(II) and Zn(II) complexes are presented in Table 1. It has been established that the substituted salicylaldehyde thiosemicarbazones of complexes **1**–**14** behave as monodeprotonated tridentate ligands and are coordinated to the central ions through deprotonated phenolic oxygen atom, azomethinic nitrogen atom and sulphur atom forming five- and six-membered metalocycles [9,20,21].

The IR spectra of the free ligands shows a broad band at *ca*. 3600 cm^{-1} attributed to phenolic group, δ(OH). This band disappeared from IR spectra of complexes **1**–**14** [22,23,27]. Moreover, this is confirmed by the shift of ν(C-O) stretching vibration bands observed in the range of 1250-1240 cm^{-1} in the spectra of the free ligands, to lower frequency at around 1225–1210 cm^{-1} in the spectra of the complexes. This is further confirmed by the presence of the band appearing in the region 500-470 cm^{-1} assigned to the ν(M-O) frequency [28].

Likewise, the IR spectra of the ligands exhibits a strong band in the range 1620–1610 cm^{-1} assignable to ν(C = N). In the spectra of the complexes **1**–**14** this band is shifted to lower frequencies by ca. 25–15 cm^{-1} suggesting the coordination of the azomethine nitrogen to the central metal atom. Also, this coordination is supported of ν(M-N) vibration around 515–540 cm^{-1} [29].

In the IR spectra of the $\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$, the ν(S-H) band at 2570 cm^{-1} [30–33] was absent, but the ν(C = S) bands at about 1560 and 822 cm^{-1} were present. These bands were shifted to lower wavenumbers in complexes **1**–**14** and this shift can be assigned to the thiocarbonyl ν(C = S) stretching and bending modes of vibrations and to the coordination of sulfur atom to metal ion [34–36].

In complexes **15**–**32**, thiosemicarbazones behave as double deprotonated tridentate ligands, coordinating to the central ion through phenolic oxygen atom, azomethinic nitrogen atom and sulphur atom forming two five- and six-membered heterocycles. As much, the absorption bands ν(C-OH), ν(N-NH) and ν(C=S), observed in the spectra of the free thiosemicarbazones, in the range 1245–1240, 1540–1535 and 1125–1120 cm^{-1}, respectively, were shifted to lower frequencies in the spectra complexes. In the spectra complexes the absorption band ν(C-S) is observed in the range 750–740 cm^{-1} and the band ν(C-N) is shifted to small frequencies with 35-30 cm^{-1}, being accompanied by the splitting into two components [27–29].

In the IR spectra of complexes **15**–**32**, an absorption band is observed in the range 1520–1518 cm^{-1}, conditioned by valence oscillations >C = N-N = C<. This character of IR spectra demonstrates the thiosemicarbazone enolization in the process of synthesized complexes formation [30–33].

The nitrate complexes **8**–**14** shows a single band at around 1345-1340 cm^{-1}. It is attributable to ionic NO_3^- [37].

In compounds **1**–**14** the absorption bands characteristic to the water molecule from the inner sphere are observed: $\nu(H_2O)$ = 3595–3585 cm^{-1}, $\delta(H_2O)$ = 1590–1585 cm^{-1}, $\gamma(H_2O)$ = 920–915 cm^{-1},

$w(H_2O)$ = 640–615 cm^{-1} due to OH stretching, HOH deformation, H_2O rocking and H_2O wagging, respectively [38].

The presence of sulphanilamides in complexes **25–32** is confirmed by the characteristic absorption bands observed in IR spectra: $\nu_{as}(NH_2)$, $\nu_s(NH_2)$: ≈ 3400 cm^{-1}; ν(N-H): 3330 ± 20 cm^{-1}, $\nu(C\text{-}N)_{(arom)}$: 1305 ± 55 cm^{-1}, $\nu(C = N)_{(arom)}$ 1580 ± 30 cm^{-1}; $\nu_{as}(SO_2)$, $\nu_s(SO_2)$: 1320 ± 20 cm^{-1}, 1100 ± 20 cm^{-1}. It has been established that the investigated sulphanilamides of the given complexes behave as monodentate ligands and are coordinated to the central atom through nitrogen atoms and amino groups in the case of streptocide (Str) and sulphacil (Sfc), thiadiazolic nitrogen atom in the case of ethazole (Etz) and norsulphazole (Nor) one of the pyrimidinic nitrogen atoms in the case of sulphadimezine (Sdm) [38].

2.1.3. Magnetochemistry

The room temperature magnetic moment of the solid copper (II) complexes **1-24** was found in the range 1.75–2.00 BM, indicative one unpaired electron per Cu(II) ion [39]. These experimental data allow us to suppose that in these compounds the spin-spin interaction lacks and probably the investigated complexes have monomer structure. Also, the magnetic moment values in the range 1.22–1.45 BM for the copper (II) complexes **25–30** are of indicative anti-ferromagnetic spin-spin interaction through molecular association [40]. Complex **31** is diamagnetic and the central Ni^{2+} ion is in a square planar environment [40].

2.1.4. Thermal Decomposition

All complexes studied were investigated by thermogravimetry analysis. The TG thermograms of complexes **1–14** are characterized by three degradation steps (50–100, 130–170, 310–530 °C). The weight loss between 50 and 100 °C corresponds to the elimination of water molecules of dehydration and is an endothermic effect. The second step, also an endothermic effect, corresponds to the elimination of coordinated water molecules (Table 1). The following effect on DTA curve is exothermic and corresponds to the complete decomposition (TG, TGD curves) of the organic part of the complexes.

The TG and TGD curves of the complexes **15–32** are characterized by two steps of weight loss united (350–480 °C, 480–620 °C) and corresponds to the complete decomposition of the ligands. In addition, the TG and TGD curves of the complexes **21**, **22** and **31** are characterized by a weight loss in the renge 50–100 °C.

By replacing the sulphate ion from complexes with nitrate ion or by changing the thiosemicarbazide fragment with 4-phenylthiosemicarbazide fragment, TG and TGD curves show weight loss at lower temperatures. The final residues were identified by IR spectroscopy as CuO, which provides %Cu values in the initial samples, by quantitative analyses. They were in agreement wich the theoretical obtained %Cu values.

2.1.5. NMR Spectra

The NMR spectra of ligands $\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$ were recorded in DMSO-d_6. The ^{1}H-NMR and ^{13}C-NMR spectral data are reported along with the possible assignments [41]. All the protons were found to be in

the expected regions. It was observed that DMSO did not have any coordinating effect on the ligands or their metal complexes.

2.1.6. Mass Spectra

The FAB mass spectra of Cu(II), Ni(II) and Zn(II) complexes with salicyliden thiosemicarbazones (**H_2L^1**–**H_2L^{10}**) have been recorded (Table 2). The molecular ion $[M]^+$ peaks obtained from Cu(II), Ni(II) and Zn(II) complexes are as follows: *m/z* = 274.8 (**1**), *m/z* = 319.7 (**3**), *m/z* = 309.6 (**7**), *m/z* = 350.9 (**9**), *m/z* = 395.6 (**11**), *m/z* = 429.8 (**13**), *m/z* = 369.8 (**16**), *m/z* = 349.3 (**19**), *m/z* = 506.8 (**22**), *m/z* = 698.2 (**25**), *m/z* = 586.1 (**26**), *m/z* = 536 (**31**), *m/z* = 541.4 (**32**). The data obtained are in good agreement with the proposed molecular formula for Cu(II), Ni(II) and Zn(II) complexes. The FAB mass spectra of these complexes shows peaks assignable to various fragments arising from the thermal cleavage of the complexes.

Table 2. FAB mass spectral data of Cu(II) Ni(II) and Zn(II) complexes.

Molecular formula	Mw (g/mol)	Molecular ion peak $[M]^+$	The peaks due to complex fragmentation			
$[Cu(H_2O)(HL^1)][Cu(H_2O)(HL^1)SO_4] \cdot 2H_2O$ (**1**)	684	274.8	101.2	170.3	203.4	
$[Cu(H_2O)(HL^4)][Cu(H_2O)(HL^4)(SO_4)] \cdot H_2O$ (**3**)	774	319.7	147.3	216.5	296.3	
$[Cu(H_2O)(HL^2)][Cu(H_2O)(HL^2)(SO_4)] \cdot H_2O$ (**7**)	735	309.6	136.7	206.3	287.5	
$[Cu(H_2O)(HL^8)]NO_3 \cdot H_2O$ (**9**)	432	350.9	101.7	171.4	203.8	320.2
$[Cu(H_2O)(HL^{1\circ})]NO_3 \cdot 2H_2O$ (**11**)	495	395.6	147.7	220.2	286.3	372.1
$[Cu(H_2O)(HL^9)]NO_3 \cdot 3H_2O$ (**13**)	547	429.8	181.2	229.1	295.2	398.8
$[Cu\ L^2Py]$ (**16**)	370.5	369.8	136.7	207.5	292.1	322.6
$[Cu\ L^5Py]$ (**19**)	350	349.3	132.1	203.3	289.2	318.5
$[Cu\ L^7(4\text{-MePy})] \cdot H_2O$ (**22**)	526	506.8	262.3	327.8	403.2	498.8
$[Cu\ L^7(Etz)]$ (**25**)	699	698.2	296.3	357.5	434.4	544.2
$[Cu\ L^7(Str)]$ (**26**)	587	586.1	284.1	345.6	422.1	532.4
$[Ni\ L^1(Etz)] \cdot 2H_2O$ (**31**)	572	536	269.5	330.6	401.3	517.8
$[Zn\ L^1(Etz)]$ (**32**)	542	541.4	282.2	344.2	416.1	527.4

2.2. Biological Activity

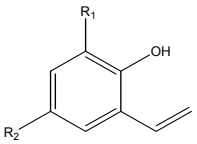
2.2.1. Antiproliferative Activity of Human Leukemia HL-60 Cells

All ligands (Table 3) and their metal complexes (Table 4) were tested as inhibitors of HL-60 cells proliferation using three concentrations: 0.1, 1.0 and 10 μmol/L. At 0.1 and 1.0 μmol/L the ligands have unsignificant inhibitor activity, but at 10 μmol/L **H_2L^8** (salicylidene-4-phenylthiosemicarbazone), **H_2L^9** (5-Br-salicylidene-4-phenylthiosemicarbazone) and **H_2L^1** (5-NO_2-salicyliden-4-phenylthiosemicarbazone) inhibit the cell proliferation (90, 75 and 70%, respectively). So, we can assert that the presence of phenyl-radical in the Schiff bases composition is important. The same fact is confirmed for copper complexes, but in the enforced variant. So, copper complexes act selectively in this biological

process [23,42–44]. In fact, copper complexes, including inner sphere water and tridentate ONS ligands, are more active than those containing inner sphere amine, which blocked the metal active centre. Complexes **1–14** are thus better inhibitors of cell proliferation than complexes **15–30**.

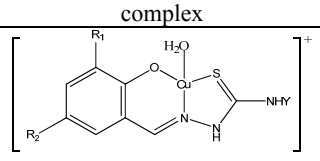
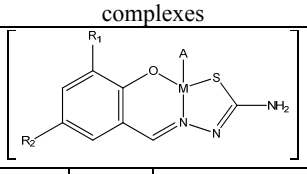
If copper is capsulated with amine, the antiproliferative activity change in dependence of substituents R_1 and R_2 in the same series Y = H or Y = -C_6H_5. The following three examples illustrate our SAR results. If A = Py, Y = H and R_1 = H, the antiproliferative activity varies (from 60% to 10%) depending on R_2: H (**15**) > CH_3 (**19**) > Br (**17**) > Cl (**16**) > NO_2 (**18**). If Y = H, R_1 = R_2 = Br and A - is variable, the moderate influence of amine nature can be observed depending on the ability of amine(N)-copper bond force: **25** > **28** > **26 = 27 = 29 > 23 = 24 > 21 > 22**. If Y = H, R_1 = R_2 = H, A = ethazole and copper ion is replaced by nickel or zinc (**31**, **32**), the antiproliferative activity dramatically decreases.

Table 3. Schiff bases $\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$ and their antiproliferative activity on human leukemia (HL-60) cells at three concentrations.

Schiff base	**(X)N-NH-C(S)-NH(Y)**			**Inhibition of cell proliferation (%)**		
	X		Y	10 μM	1 μM	0.1μM
						
	R_1	R_2				
H_2L^1	H	H	H	20	10	0
H_2L^2	H	Cl	H	0	0	0
H_2L^3	H	Br	H	5	0	0
H_2L^4	H	NO_2	H	0	0	0
H_2L^5	H	CH_3	H	5	0	0
H_2L^6	Cl	Cl	H	10	0	0
H_2L^7	Br	Br	H	0	0	0
H_2L^8	H	H	C_6H_5	90	0	0
H_2L^9	H	Br	C_6H_5	75	0	0
H_2L^{10}	H	NO_2	C_6H_5	70	0	0

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

Table 4. Antiproliferative activity of complexes **1**–**32** on human leukemia (HL-60) cells at three concentrations.

Complex [a]	Structural formula of copper complex			Inhibition of cell proliferation (%) [b]			Complex [a]	Structural formula of metal complexes			Inhibition of cell proliferation (%) [b]		
				10 μM	1 μM	0.1 μM					10 μM	1 μM	0.1 μM
	R_1	R_2	Y					R_1	R_2	A			
1	H	H	H	98	50	0	15	H	H	Py	-	35	10
2	H	H	$-C_6H_5$	100	90	0	16	H	Cl	Py	-	25	5
3	H	NO_2	H	90	70	0	17	H	Br	Py	-	50	0
4	H	NO_2	$-C_6H_5$	96	78	0	18	H	NO_2	Py	-	10	0
5	H	Br	H	95	90	0	19	H	CH_3	Py	-	55	0
6	H	Br	$-C_6H_5$	90	90	0	20	Cl	Cl	Py	-	60	10
7	H	Cl	H	95	95	0	21	Br	Br	NH_3	-	25	0
8	H	H	H	100	95	0	22	Br	Br	4-MePy	-	20	0
9	H	H	$-C_6H_5$	100	100	0	23	Br	Br	3-MePy	-	30	15
10	H	NO_2	H	100	90	0	24	Br	Br	2-MePy	-	30	5
11	H	NO_2	$-C_6H_5$	100	90	0	25	Br	Br	Ethazole	-	60	15
12	H	Br	H	98	95	0	26	Br	Br	Streptocide	65	40	5
13	H	Br	C_6H_5	100	80	0	27	Br	Br	Sulfocile	65	40	5
14	H	Cl	H	100	90	0	28	Br	Br	Norsulfosole	65	55	5
							29	Br	Br	Sulfadimizine	65	40	5
DOX				100	100	30	30	H	H	Ethazole	60	65	0
							31	H	H	Ethazole	5	5	5
							32	H	H	Ethazole	10	5	0

[a] The molecular formula of complexes are reported in Table 1. [b] SEM < ± 4% of a single experiment in triplicate. DOX = Doxorubicine.

2.2.2. Antibacterial Activity

Experimental results obtained from the study of antimicrobial activity (Table 5) demonstrate that compounds **21**–**25** and **30** display bacteriostatic and bactericide activity in the concentration range 0.03-4000 μg/mL towards both Gram-positive as well as Gram-negative bacteria. In comparison, the antimicrobial data characteristic for *furacillinum* used in medical practice are given. The antimicrobial activity displayed by the above mentioned compounds is 32–260 times higher towards staphylococcus and streptococcus than *furacillinum* and exceeds by 2–260 times her bacteriostatic activity towards the majority of Gram-negative bacteria. The minimum inhibitory concentration (MIC) and minimum bactericide concentration (MBC) are influenced by the nature of thiosemicarbazone and amine of the inner sphere of the coordination compound.

The data concerning the study of antimycotic properties of compounds **22**–**24** show that they also display selective bacteriostatic and bactericide activity in the concentration range 9.3–600 μg/mL towards investigated fungi stems. In order to make a comparison, we also added data regarding the activity of nystatine, a compound used in medicine at mycoses treatment. The results show that the synthesized substances have antimycotic activity against most fungi, higher than nystatine activity. Aspergillus fumigatus is an exception, being less sensible towards mentioned substances. The toxicity (LD_{50}) of complexes **24** and **30** (some of the most active in this group of substances) is 1,420 mg/kg and 4,250 mg/kg so it is 8.6–25.5 times lower than that of furacillinum (LD_{50} = 166.7 mg/kg).

Table 5. Antimicrobial or antifungal activity (MIC [a]/MBC [b]) (μg/mL) of some copper complexes.

Stem			Complexes [c]							
			21	**22**	**23**	**24**	**25**	**30**	**Furacillinum**	**Nystatin**
Staphylococcus aureus	Wood-46	MIC	0.29	0.145	0.145	0.29	0.06	0.03	9.35	-
		MBC	0.29	0.145	0.145	0.29	0.06	0.03	9.35	-
	Smith	MIC	0.29	0.145	0.29	0.29	-	-	9.35	-
		MBC	0.58	0.29	0.29	0.58	-	-	9.35	-
	209-P	MIC	0.58	0.29	0.29	0.29	0.06	0.03	18.7	-
		MBC	0.58	1.16	1.16	0.58	0.06	0.03	18.7	-
Staphylococcus saprophyticus		MIC	0.29	0.29	0.145	0.29	0.12	0.03	9.35	-
		MBC	0.29	0.58	0.145	0.29	0.24	0.06	18.7	-
Streptococcus(group A)		MIC	0.036	0.009	1.16	0.29	0.12	0.06	-	-
		MBC	0.072	0.036	2.33	0.58	0.24	0.06	-	-
Enterococcus faecalis		MIC	-	-	-	-	0.06	0.03	37.5	-
		MBC	-	-	-	-	0.06	0.097	37.5	-
Escherichia coli, O-111		MIC	1.16	9.35	18.7	4.67	15.6	15.6	18.7	-
		MBC	37.5	9.35	18.7	9.35	31.2	15.6	37.5	-
Salmonella typhimurium		MIC	2.33	4.67	4.67	0.29	1.95	7.8	75	-
		MBC	9.35	4.67	1000	75	62.5	31.2	150	-
Salmonella enteritidis		MIC	2.33	9.35	4.67	1.16	-	-	9.35	-
		MBC	600	9.35	2000	300	-	-	9.35	-
Klebsiella pneumoniae		MIC	0.58	1.16	0.29	0.29	1.95	7.8	>300	-
		MBC	600	300	400	300	62.5	15.6	>300	-
Pseudomonas aeruginosa		MIC	2000	1000	2000	>4000	1000	250	>300	-
		MBC	>4000	1000	4000	>4000	>4000	250	>300	-
Proteus vulgaris		MIC	0.29	1000	1.16	1.16	0.49	7.8	150	-
		MBC	2000	>4000	4000	150	7.8	15.6	300	-
Proteus mirabilis		MIC	2.33	1000	9.35	1.16	-	-	150	-
		MBC	1000	>4000	>4000	>4000	-	-	300	-
Aspergillus niger		MIC	-	150	9.3	18.7	-	-	-	240
		MBC	-	150	9.3	18.7	-	-	-	240

Table 5. *Cont.*

Stem		Complexes [c]							
		21	**22**	**23**	**24**	**25**	**30**	**Furacillinum**	**Nystatin**
Aspergillus fumigatus	MIC	-	300	300	300	-	-	-	240
	MBC	-	300	300	300	-	-	-	240
Candida albicans	MIC	-	37.5	37.5	37.5	-	-	-	80
	MBC	-	37.5	37.5	37.5	-	-	-	80
Penicillium	MIC	-	18.7	37.5	37.5	-	-	-	80
	MBC	-	18.7	37.5	37.5	-	-	-	80
LD_{50}, mg/kg		-	-	-	1420	-	4250	166.7	-

[a] MIC – minimum inhibitory concentration. [b] MBC – minimum bactericide concentration. [c] The molecular formula of complexes are reported in Table 1.

3. Experimental

3.1. Chemistry

All commercially available reagents and chemicals were of analytical- or reagent-grade purity and used as received. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer in DMSO-d_6, using TMS as the internal standard. IR spectra were recorded on a Specord-M80 spectrophotometer in the 4000–400 cm^{-1} region using KBr pellets. The chemical elemental analysis for the determination of C, H, N and Br was done the Carlo-Erba LA-118 microdosimeter. Metal ions were determined following the method described by G. Schwarenbach and H. Flaschka [45]. The complexes were studied by thermogravimetry (TG), in a current of air, with a sample heating rate of 1 °C/min, using a SETARAM 92-1600 thermo-balance. Magnetic measurements were carried out on solid complexes using the Gouy's method [39].

X-ray diffraction analysis of compound **5** was carried out on a Nonius KappaCCD diffractometer (MoK_α radiation, λ = 0.71069 Å) at room temperature. The structures of complex **5** was solved by the direct method using SHELXS-86 [46] and SIR-97 [47] software and refined by least squares in the anisotropic approximation for nonhydrogen atoms (CRYSTALS) [48]. The hydrogen atoms were refined isotropically. In complex **5**, all hydrogen atoms were included in the refinement in geometrically calculated positions (except for water molecules in which hydrogen atoms were not located). The C–H and N–H bond lengths varied in the 0.93–0.98 and 0.86–0.89 Å ranges, respectively. The thermal factors U_H were taken to be 1.2–1.5 times as high as the U_{eq} values of the carbon and nitrogen atoms.

3.1.1. General Procedures for the Synthesis of the Schiff Bases $\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$

A hot solution of salicylaldehyde (10 mmol) in ethanol (20 mL, 50 °C) was added to a magnetically stirred solution of H_2N-NH-C(S)-NH(Y) (10 mmol), where Y = H, in warm ethanol (20 mL). The mixture was refluxed for 1–2 h. The resulting precipitate was filtered, washed with cold ethanol, then with diethyl ether, and dried under vacuum. Crystallization from ethanol gave $\mathbf{H_2L^1}$. The same method was applied for the synthesis of $\mathbf{H_2L^2}$–$\mathbf{H_2L^{10}}$ by using 2-hydroxybenzaldehyde and its derivatives (X) with thiosemicarbazide or 4-phenylthiosemicarbazide.

Salicylidene thiosemicarbazone **(H_2L^1)**. Yield: 75%. Anal. Calc. (%) for $C_8H_9N_3OS$ (195 g/mol): C, 49.23; H, 4.61; N, 21.53; S, 16.41. Found: C, 49.40; H, 4.52; N, 21.35; S,16.28. IR (cm^{-1}, KBr): 3600 (m, OH), 3058 (m, NH), 1560 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 822 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.39 (s, 1H, NNH); 9.88 (s, 1H, OH); 8.37 (s, 1H, HC=N); 7.93, 7.91 (2s, 1H+1H, NH_2); 8.20, 7.21, 6.85, 6.80 (m, 4H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 177.6 (C=S); 156.4 (HC=N); 139.6 (C-OH); 116.0, 131.1 120.4, 126.7, 118.9 (benzene).

5-*Chlorosalicylidene thiosemicarbazone* **(H_2L^2)**. Yield: 70%. Anal. Calc. (%) for $C_8H_8ClN_3OS$ (229.5 g/mol): C, 41.83; H, 3.48; N, 18.30; S, 13.94. Found: C, 42.26; H, 3.34; N, 18.15; S, 13.79. IR (cm^{-1}, KBr): 3600 (m, OH), 3058 (m, NH), 1565 (s, C=S), 1585 (w, C=N), 1535 (m, NNH), 820 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.44 (s, 1H, NNH); 10.21 (s, 1H, OH); 8.30 (s, 1H, HC=N); 8.16, 8.11 (2s, 1H+1H, NH_2); 8.10, 7.21, 6.86 , (m, 3H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 177.8 (C=S); 155.1 (HC=N); 137.7 (C-OH); 117.7, 132.6, 130.4, 122.4, 123.5, 126.5 (benzene).

5-*Bromosalicylidene thiosemicarbazone* **(H_2L^3)**. Yield: 71%. Anal. Calc. (%) for C_8H_8 BrN_3OS (274 g/mol): C, 35.03; H, 2.91; N, 15.32; Br, 29.19; S, 11.67. Found: C, 34.89; H, 2.78; N, 15.25; Br, 28.91; S, 11.45. IR (cm^{-1}, KBr): 3600 (m, OH), 3055 (m, NH), 1562 (s, C=S), 1584 (w, C=N), 1535 (m, NNH), 823 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.42 (s, 1H, NNH); 10.23 (s, 1H, OH); 8.29 (s, 1H, HC=N); 8.21, 8.17 (2s, 1H+1H, NH_2); 8.21, 7.32, 6.81 (m, 3H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 177.8 (C=S); 155.6 (HC=N); 137.2 (C-OH); 118.2, 133.2, 111.2, 128.3, 122.9 (benzene).

5-*Nitrosalicylidene thiosemicarbazone* **(H_2L^4)**. Yield: 62%. Anal. Calc. (%) for $C_8H_8N_4O_3S$ (240 g/mol): C, 40.00; H, 3.33; N, 23.33; S, 13.33. Found: C, 40.46; H, 3.12; N, 23.16; S, 13.10. IR (cm^{-1}, KBr): 3600 (m, OH), 3058 (m, NH), 1559 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 821 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.53 (s, 1H, NNH); 11.55 (s, 1H, OH); 8.37 (s, 1H, HC=N; 8.29, 8.24 (2s 1H+1H, NH_2); 8.86, 78.11, 7.04 (m, 3H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 178.0 (C=S); 161.9 (HC=N); 136.8 (C-OH); 116.5, 126.3, 140.3, 122.2, 121.4 (benzene).

5-Methylsalicylidene thiosemicarbazone **(H_2L^5)**. Yield: 68%. Anal. Calc. (%) for $C_9H_{11}N_3OS$ (209 g/mol): C, 51.67; H, 5.26; N, 20.09; S, 15.31. Found: C, 52.02; H, 5.00; N, 19.83; S, 15.04. IR (cm^{-1}, KBr): 3600 (m, OH), 3058 (m, NH), 1558 (s, C=S), 1583 (w, C=N), 1535 (m, NNH), 824 (m, C=S). ^{1}H-NMR (DMSO-$d_{6,}$ δ, ppm): 11.50 (s, 1H, NNH); 9.85 (s, 1H, OH); 8.31 (s, 1H, HC=N); 8.02, 8.07 (2s 1H+1H, NH_2); 7.22, 6.85, 6.62 (m, 3H, benzene); 2.30 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6, δ, ppm): 178.2 (C=S); 153.4 (HC=N); 140.3 (C-OH); 116.0, 133.4, 130.8, 130.5, 118.0 (benzene); 20.9 (CH_3).

3,5-Dichlorosalicylidene thiosemicarbazone **(H_2L^6)**. Yield: 75%. Anal. Calc. (%) for C_8H_7 Cl_2N_3OS (264 g/mol): C, 36.36; H, 2.65; N, 15.90; Cl, 26.89; S, 12.12. Found: C, 36.53; H, 2.48; N, 15.73; Cl, 26.57; S, 11.98. IR (cm^{-1}, KBr): 3600 (m, OH), 3058 (m, NH), 1558 (s, C=S), 1587 (w, C=N), 1535 (m, NNH), 822 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.48 (s, 1H, NNH); 10.3 (s, 1H, OH); 8.35 (s, 1H, HC=N); 7.98, 7.93 (2s 1H+1H, NH_2); 7.28, 7.13, (m, 2H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 177.9 (C=S); 154.0 (HC=N); 140.5 (C-OH); 123.0, 133.1, 126.9, 127.1, 121.5 (benzene).

*3,5-Dibromosalicylidene thiosemicarbazone (***H_2L^7***)*. Yield: 72%. Anal. Calc. (%) for $C_8H_7Br_2N_3OS$ (353 g/mol): C, 27.19; H, 1.98; N, 11.89; Br, 45.32; S, 9.06. Found: C, 27.40; H, 1.78; N, 11.68; Br, 45.03; S, 8.83. IR (cm^{-1}, KBr): 3650 (m, OH), 3058 (m, NH), 1560 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 819 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.45 (s, 1H, NNH); 10.55 (s, 1H, OH); 8.29 (s, 1H, HC=N); 8.10, 8.01 (2s, 2H, NH_2); 8.20, 7.56 (d, 2H, benzene). ^{13}C-NMR (DMSO-d_6, δ, ppm): 178.5 (C=S); 155.4 (HC=N); 150.2 (C-OH); 118.1, 137.5, 111.2, 130.8, 123.0 (benzene).

Salicylidene-4-phenylnthiosemicarbazone **(H_2L^8)**. Yield: 58%. Anal. Calc. (%) for $C_{14}H_{13}N_3OS$ (271 g/mol): C, 61.99; H, 4.79; N, 15.49, S, 11.80. Found: C, 62.27; H, 4.58; N, 15.28; S, 11.73. IR (cm^{-1}, KBr): 3600 (m, OH), 3060 (m, NH), 1565 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 823 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.78 (s, 1H, NNH); 9.98 (s, 1H, OH); 8.50 (s, 1H, HC=N); 10.06 (1s 1H, NH-C_6H_5); 8.10, 7.22, 6.90, 6.88 (m, 4H, benzene-OH); 7.38, 7.34, 7.34, 7.25, 7.25 (m, 5H-benzene-NH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 177.2 (C=S); 157.1 (HC=N); 140.5 (C-OH); 116.5, 131.8, 120.7, 128.5, 118.4 (benzene-OH); 139.6 (C-NH); 127.5, 127.5, 126.1, 126.1, 127.7 (benzene-NH).

5-Bromosalicylidene-4-phenylthiosemicarbazone **(H_2L^9)**. Yield: 70%. Anal. Calc. (%) for $C_{14}H_{12}BrN_3OS$ (350 g/mol): C, 48.00; H, 3.42; N, 12.00; Br, 22.85; S, 9.14. Found: C, 48.39; H, 3.25; N, 11.80; Br, 22.63; S, 9.00. IR (cm^{-1}, KBr): 3600 (m, OH), 3060 (m, NH), 1565 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 822 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.82 (s, 1H, NNH); 10.32 (s, 1H, OH); 8.42 (s, 1H, HC=N); 10.20 (1s 1H, NH-C_6H_5); 8.35, 7.35, 6.85 (m, 3H, benzene-OH); 7.38, 7.39, 7.52, 7.51, 7.24 (m, 5H-benzene-NH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 176.6 (C=S); 156.2 (HC=N); 139.7 (C-OH); 118.6, 138.4, 111.6, 133.9, 123.2 (benzene-OH); 139.4 (C-NH); 128.5, 128.5, 126.9, 126.9, 125.9 (benzene-NH).

5-*Nitrosalicylidene-4-phenylthiosemicarbazone* **(H_2L^{10})**. Yield: 76%. Anal. Calc. (%) for $C_{14}H_{12}N_4O_3S$ (316 g/mol): C, 53.16; H, 3.79; N, 17.72; S, 10.12. Found: C, 53.34; H, 3.57; N, 17.58; S, 9.97. IR (cm^{-1}, KBr): 3600 (m, OH), 3060 (m, NH), 1565 (s, C=S), 1586 (w, C=N), 1535 (m, NNH), 822 (m, C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 11.91 (s, 1H, NNH); 11.67 (s, 1H, OH); 8.49 (s, 1H, HC=N); 10.35 (1s 1H, NH-C_6H_5); 8.98, 8.15, 7.06 (m, 3H, benzene-OH); 7.37, 7.39, 7.31, 7.52, 7.21 (m, 5H-benzene-NH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 176.6 (C=S); 156.2 (HC=N); 139.7 (C-OH); 118.6, 138.4, 111.6, 133.9, 123.2 (benzene-OH); 139.4 (C-NH); 128.5, 128.5, 126.9, 126.9, 125.9 (benzene-NH).

3.1.2. General Procedure for the Preparation of Complexes **1**–**32**

Synthesis of compound **1**. 30 mL of ethanolic solution, which contains 10 mmol of salicyliden thiosemicarbazone is mixed with 10 mmol of $CuSO_4 \cdot 5H_2O$, dissolved in 20 mL of distilled water. The reaction mixture is heated (50–55 °C) and stirred continuously for 1.5 h. The green colored solid, which separated on cooling, was filtered, washed with ethanol, diethyl ether and dried in air. Method for the synthesis of compound **1** is similar to that of work [26] but were modified working conditions.
Synthesis of Compounds **2**–**14**. This compounds have been synthesized according to the above described procedure, using $CuSO_4 \cdot 5H_2O$ or $Cu(NO_3)_2 \cdot 3H_2O$ and salicyliden thiosemicarbazone, 5-chloro-, 5-bromo-, 5-nitro- salicyliden thiosemicarbazones or 5-bromo-, 5-nitro-salicyliden-4-phenylthiosemicarbazones, in 1:1 molar ratio.

Synthesis of Compound **15**. To $CuCl_2 \cdot 2H_2O$ (10 mmol) dissolved in 20 mL ethanol was added salicyliden thiosemicarbazone (10 mmol) dissolved in 15 mL hot ethanol.The mixture was stirred continuously (1 h) and then pyridine alcoholic solution is added till pH=7.5–8. The dark green microcrystals was filtered, washed with ethanol, diethyl ether and dried in air.

Synthesis of Compound **16**–**32**. This compounds have been synthesized according to the above described procedure, using as initial substances $CuCl_2 \cdot 2H_2O$, thiosemicarbazones $\mathbf{H_2L^{2-7}}$ and ethanolic solution of pyridine, 2-, 3-, 4-picoline, streptocide (Str), sulphacil (Sfc), norsulphazol (Nor), ethazol (Etz) or sulphadimezine (Sdm), in 1:1:1 molar ratio. The elemental analysis confirms the molecular formula. The physical and analytical data are presented in Table 1.

3.2. Cytotoxicity Assay

3.2.1. Preparation of Test Solutions

Stock solutions of the investigated compounds ($\mathbf{H_2L^1}$–$\mathbf{H_2L^{10}}$) and copper complexes **1**–**30** were prepared in dimethylsulfoxide (DMSO) at a concentration of 10 mM and diluted with nutrient medium to various working concentrations. DMSO was used instead of ethanol due to solubility problems.

3.2.2. Cell Culture

Human promyelocytic leukemia cells HL-60 (ATCC, Rockville, MD, USA) were routinely grown in suspension in 90% RPMI-1640 (Sigma, Saint Louis, USA) containing *L*-glutamine (2 nM), antibiotics (100 IU penicillin/mL, 100 μg streptomycin/mL) and supplemented with 10% (v/v) foetal bovine serum (FBS), in a 5% CO_2 humidified atmosphere at 37 °C. Cells were currently maintained in continuous exponential growth with twice a week dilution of the cells in culture medium [9].

3.2.3. Cell Proliferation Assay

The cell proliferation assay was performed using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)2-(4-sulfophenyl)-2H-tetrazolium (MTS) (Cell Titer 96 Aqueous, Promega, Madison, Wi, USA), which allowed us to measure the number of viable cells. In brief, triplicate cultures of 1 x 10^4 cells in a total of 100 μL medium in 96-well microtiter plates (Becton Dickinson and Company, Lincoln Park, NJ, USA) were incubated at 37 °C, 5% CO_2. Compounds were dissolved in DMSO to prepare the stock solution of 1×10^{-2} M. These compounds were diluted at the appropriate concentration (1 or 10 μM) with culture media, added to each well and incubated for 3 days. Following each treatment, 20 μL MTS was added to each well and incubated for 4 h. MTS is converted to water-soluble coloured formazan by dehydrogenase enzymes present in metabolically active cells. Subsequently, the plates were read at 490 nm using a microplate reader (Molecular Devices, Sunnyvale, CA). The results were reported as the percentage of cell proliferation inhibition compared to the control (basal cell proliferation=100%).

3.3. Antibacterial Activity

The antibacterial activity of complexes and also of their prototype Furaciline has been determined under liquid nutritive environment [2% of peptonate bullion (pH 7.0)] using successive dilutions method [36–38]. *Staphylococcus aureus (Wood-46, Smith, 209-P), Staphylococcus saprophyticus, Streptococcus faecalis, Escherihia coli (O-111), Salmonella typhimurium, Salmonella enteritidis, Klebsiella pneumoniaie, Pseudomonas aeruginosa, Proteus vulgaris* and *Proteus mirabilis* standard stems were used as reference culture for *in vitro* experiments. The dissolution of studied substances in dimethylformamide, microorganisms cultivation, suspension obtaining, determination of minimal inhibition concentration (MIC) and minimal bactericide concentration (MBC) have been carried out according to the method previously reported [39].

3.4. Antifungal Bioassay

Antimycotic properties of the complexes were investigated *in vitro* on laboratory stems: *Aspergillus niger, Aspergillus fumigatusi, Candida albicans* and *Penicillium.* The activity has been determined in liquid Sabouroud nutritive environment (pH 6.8). The inoculates were prepared from fungi stems which were harvested during 3–7 days. Their concentration in suspension is (2–4) $\times 10^6$ colonies form unities in milliliter. Sowings for levures and micelles were incubated at 37 °C during 7 and 14 days, respectively.

4. Conclusions

Ten new salicyliden thiosemicarbazones ligands and their corresponding Cu(II), Ni(II) and Zn(II) complexes have been synthesized and characterized. The molecular structure of the complex **5** has been determined by single crystal X-ray diffraction method. The IR, ^{1}H-NMR and ^{13}C-NMR data were successfully used to elucidate the formation of the salicyliden thiosemicarbazones ligands. All ligands and their metal complexes were tested as inhibitors of HL-60 cells proliferation. The ligands have unsignificant inhibitor activity at 0.1 and 1.0 μmol/L, but at 10 μmol/L $\mathbf{H_2L^8}$, $\mathbf{H_2L^9}$ and $\mathbf{H_2L^{10}}$ inhibit the cell proliferation. The copper complexes, including inner sphere water and tridentate ONS ligands, are more active than those containing inner sphere amine, which blocked the metal active centre. The most indicative criteria for future synthesis of biological active coordination compounds from the viewpoint of the inhibition of HL-60 cell proliferation, antibacterial and antifungal activity: use of copper (II) complexes and presence of sulphur atom in the tridentate organic ligand.

Supplementary Data

CCDC 623449 contain the supplementary crystallographic data for $C_{16}H_8Br_2Cu_2N_6O_{12}S_3$ (**5**). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgements

The authors wish to thank the CHUQ (CHUL) Research Center at Québec City (Canada) and State University of Medicine and Pharmacy of Chisinau (Moldova) for their help in carrying out biological studies. The authors thank the Academy of Sciences of Moldova (Institute of Chemistry), for their help in carrying out C, H, N and Br elemental analyses. Also authors thank the FQRNT grant funding project 115825 for financial support.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Rosu, T.; Pahontu, E.; Pasculescu, S.; Georgescu, R.; Stanica, N.; Curaj, A.; Popescu, A.; Leabu, M. Synthesis, characterization antibacterial and antiproliferative activity of novel Cu(II) and Pd(II) complexes with 2-hydroxy-8-R-tricyclo[7.3.1.0.2,7] tridecane-13-one thiosemicarbazone. *Eur. J. Med. Chem.* **2010**, *45*, 1627–1634.
2. Leovac, V.M.; Bogdanović, G.A.; Jovanović, L.S.; Joksović, L.; Marcović, V.; Joksovic, M.D.; Denčić S.M.; Isaković, A.; Marković, I.; Heinemann, F.W.; *et al.* Synthesis, characterization and antitumor activity of polymeric copper (II) complexes with thiosemicarbazones of 3-methyl-5-oxo-1-phenyl-3-pyrazolin-4-carboxaldehyde and 5-oxo-3-phenyl-3-pyrazolin-4-carboxaldehyde. *J. Inorg. Biochem.* **2011**, *105*, 1413–1421.
3. Hanafy, A.I.; Maki, A.B.K.T.; Mostafa, M.M. Synthesis, structural and catalytic activity of binaphthyl macrocyclic complexes.*Transition Met. Chem.* **2007**, *32*, 960–966.
4. Fernandez, M.C.; Basitida, R.; Macias, A.; Valencia L.; Lourida, P.P. Different nuclearities of M(II) nitrate complexes (M=Co, Ni, Cu and Cd) with a tetrapyridyl pendant-armed hexaazamacrocyclic ligand. *Polyhedron* **2006**, *25*, 783–792.
5. Ilhan, S.; Temel, H. Synthesis and spectral studies of macrocyclic Pb(II), Zn(II), Cd(II) and La(III) complexes derived from 1,4-bis(3-aminopropoxy)butane with metal nitrate and salicylaldehyde derivatives. *Transition Met Chem.* **2007**, *32*, 1039–1046.
6. Casas, J.S.; García-Tasende, M.S.; Sánchez, A.; Sordo, J.; Touceda, A. Coordination modes of 5-pyrazolones: A solid-state overview. *Coord. Chem. Rev.* **2007**, *251*, 1561.
7. Lindoy, L.F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, UK, 1989.
8. Ali, M.A.; Mirza, A.H.; Abu Bakar, H.J.H.; Bernhardt, P.V. Preparation and structural characterization of nickel(II), cobalt(II), zinc(II) and tin(IV) complexes of the isatin Schiff bases of S-methyl and S-benzyldithiocarbazates. *Polyhedron* **2011**, *30*, 556–564.
9. Youssef, N.S.; El-Seidy, A.M.A.; Schiavoni, M.; Castano, B.; Ragaini, F.; Gallo, E.; Caselli, A. Thiosemicarbazone copper complexes as competent catalysts for olefin cyclopropanations. *J. Organometallic Chem.* **2012**, doi:10.1016/j.jorganchem.2012.03.018.
10. Pathan, A.H.; Bakale, R.P.; Naik, G.N.; Frampton, C.S. Synthesis, crystal structure, redox behavior and comprehensive studies on DNA binding and cleavage properties of transition metal

complexes of a fluoro substituted thiosemicarbazone derived from ethyl pyruvate. *Polyhedron* **2012**, *34*, 149–156.

11. Saif, M.; Mashaly, M.M.; Eid, M.F.; Fouad, R. Synthesis, characterization and thermal studies of binary and/or mixed ligand complexes of Cd(II), Cu(II), Ni(II) and Co(III) based on 2-(Hydroxybenzylidene) thiosemicarbazone: DNA binding affinity of binary Cu(II) complex. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2012**, *92*, 347–356.
12. Chandra, S.; Gupta, N.; Gupta, R.; Bawa, S.S. Biologically Relevent Macrocylic Complexes of Copper Spectral, Magnetic Thermal and Antibactrial Approach. *Transition Met Chem.* **2006**, *31*, 147–151.
13. Tan, K.W.; Seng, H.L.; Lim, F.S.; Cheah, Sh.-Ch.; Ng, C.H.; Koo, K.S.; Mustafa, M.R.; Ng, S.W.; Maah, M.J. Towards a selective cytotoxic agent for prostate cancer: Interaction of zinc complexes of polyhydroxybenzaldehyde thiosemicarbazones with topoisomerase. *Polyhedron* **2012**, *38*, 275–284.
14. Raja, D.S.; Bhuvanesh, N.S.P.; Natarajan, K. Biological evaluation of a novel water soluble sulphur bridged binuclear copper(II) thiosemicarbazone complex. *Eur. J. Med. Chem.* **2011**, *46*, 4584–4594.
15. Ramachandran, E.; Thomas, S.P.; Poornima, P.; Kalaivani, P.; Prabhakaran, R.; Padma, V.V.; Natarajan, K. Evaluation of DNA binding, antioxidant and cytotoxic activity of mononuclear Co(III) complexes of 2-oxo-1,2-dihydrobenzoh]quinoline-3-carbaldehyde thiosemicarbazones. *Eur. J. Med. Chem.* **2012**, *50*, 405–415.
16. Chohan, Z.H.; Pervez, H.; Rauf, A.; Khan, K.M.; Supuran, C.T. Antibacterial cobalt (II), copper (II), nickel (II) and zinc (II) complexes of mercaptothiadiazole--derived furanyl, thienyl, pyrrolyl, salicylyl and pyridinyl Schiff bases. *J. Enz. Inh. Med. Chem.* **2006**, *21*, 193.
17. Hall, I.H.; Lackey, C.B.; Kistler, T.D.; Durham,R.W., Jr.; Jouad, E.M.; Khan, M.; Thanh, X.D.; Djebbar-Sid, S.; Benali-Baitich, O.; Bouet, G.M. Cytotoxicity of copper and cobalt complexes of furfural semicarbazone and thiosemicarbazone derivatives in murine and human tumor cell lines. *Pharmazi*e **2000**, *55*, 937–941.
18. Baldini, M.; Belicchi-Ferrari, M.; Bisceglie, F.; Dall'Aglio, P.P.; Pelosi, G.; Pinelli, S.; Tarasconi, P. Copper (II) complexes with substituted thiosemicarbazones of α-ketoglutaric acid: synthesis, X-ray structures, DNA binding studies, and nuclease and biological activity. *Inorg. Chem.* **2004**, *43*, 7170–7179.
19. Belicchi, F.M.; Bisceglie, F.; Pelosi, G.; Tarasconi, P.; Albertini, R.; Dall'Aglio, P.P.; Pinelli, S.; Bergamo, A.; Sava, G.A.J. Synthesis, characterization and biological acvity of copper complexes with pyridoxal thiosemicarbazone derivatives. X-ray crystal structure of three dimeric complexes. *Inorg. Biochem.* **2004**, *98*, 301–312.
20. Gulea, A.; Poirier, D.; Roy, J.; Stavila, V.; Bulimestru, I.; Țapcov, V.; Bârcă, V.M.; Popovschi, L. In vitro antileukemia, antibacterial and antifungal activities of some 3d metal complexes: Chemical synthesis and structure–activity relationships. *J. Enz. Inh. Med. Chem.* **2008**, *23*, 806–818.
21. Gulea, A.P.; Samusi, N.M.; Prisacari, V.I.; Țapcov, V.I.; Buraciov, S.A.; Spinu, S.N.; Bejenari, N.P.; Poirier, D.; Roy, J. Synthesis and antibacterial activity of Copper and Nickel saliciliden thiosemicarbazidates. *Pharm. Chem. J.* **2007**, *41*, 114–117.

22. Stavila, V.; Davidovich, R.L.; Gulea, A.; Whitmire, K.H. Bismuth(III) complexes with aminopolycarboxylate and polyaminopolycarboxylate ligands: Chemistry and structure. *Coord. Chem. Rev.* **2006**, *250*, 2782–2793.
23. Gulea, A.; Poirier, D.; Roy, J.; Tapcov, V. Inhibitors of enzyme 17β-HSD proliferation. Patent of invention MD 3771. BOPI 12. 2008.
24. Samusi, N.M.; Prisacari, V.I.; Ţapcov, V.I.; Buraciov, S.A.; Gulea, A.P. Synthesis and antimicrobial activity of the complexes of 3d-metals with substituted salicylaldehyde benzoylhydrazones. *Pharm. Chem. J.* **2004**, *38*, 373–377.
25. Geary, W.J. The use of conductivity measurements in organic solvents for the characterisation of coordination compounds. *Coord. Chem. Rev.* **1971**, *7*, 81–122.
26. Chumakov, M.Yu.; Janneau, E.; Bejenari, P.N.; Tsapkov, I.V.; Gulea, P.A. Crystal Structure of Cooper Sulfate and Thiocyanate Complexes with 5-Bromo-and 5-Nitrosalicylaldehyde Thiosemicarbazones. *Koordinatsionnaya Khimiya* **2008**, *34*, 46–54.
27. Saydam, S.; Yilmaz, E. Synthesis, characterization and thermal behavior of 4-chloromethyl-2-(2-hydroxybenzilidenehydrazino) thiazole and its complexes with Cr(III), Co(II), Ni(II) and Cu(II). *Spectrochim. Acta A* **2006**, *63*, 506–510.
28. Larabi, L.; Harek, Y.; Reguig, A.; Mostafa, M.M. Synthesis, structural study and electrochemical properties of copper(II) complexes derived from benzene- and p-toluenesulphonylhydrazones. *J. Serb. Chem. Soc.* **2003**, *68*, 85–95.
29. Gupta, L.; Chandra, S. Spectroscopy: the study of DNA cleavage by newly synthesized polydentate macrocyclic ligand and its copper(II) complexes. *Spectrochim. Acta A* **2008**, *71*, 496–501.
30. El-Reash, G.M.A.; Ibrahim, K.M.; Bekheit, M.M. Synthesis, characterization and thermal analysis of new Cu(II) complexes with hydrazide ligands. *E-J. Chem.* **2010**, doi:10.1155/2010/605947.
31. Jouad, E.M.; Riou, A.; Allain, M.; Khan, M.A.; Bouet, G.M. Synthesis, structural and spectral studies of 5-methyl 2-furaldehyde thiosemicarbazone and its Co, Ni, Cu and Cd complexes. *Polyhedron* **2001**, *20*, 67–74.
32. Chandra, S.; Sangeetika, X. Spectroscopic, redox and biological activities of transition metal complexes with ons donor macrocyclic ligand derived from semicarbazide and thiodiglycolic acid. *Spectrochim. Acta A* **2004**, *60*, 147–153.
33. Chanrda, S.; Pundir, M. Spectral studies of cobalt(II) complexes of 12-membered macrocyclic ligands having thiosemicarbazone moieties. *Spectrochim. Acta A* **2007**, *68*, 833–840.
34. Goel, S.; Pandey, O.P.; Sengupta, S.K. Synthesis and physico-chemical studies on neodymium(III) and samarium (III) derivatives with mercapto triazoles. *Thermochim. Acta* **1988**, *133*, 359–364.
35. Raphae, P.F.; Manoj, E.; Kurup Prathapachandra, M.R. Copper(II) complexes of N(4)-substituted thiosemicarbazones derived from pyridine-2-carbaldehyde: Crystal structure of a binuclear complex. *Polyhedron* **2007**, *26*, 818–828.
36. Kostas, I.D.; Andreadaki, F.J.; Demertzi, D.K.; Prentjas, C.; Demertzis, M.A. Suzuki-Miyaura cross-coupling reaction of aryl bromides and chlorides with phenylboronic acid under aerobic conditions catalyzed by palladium complexes with thiosemicarbazone ligands. *Tetrahedron Lett.* **2005**, *46*, 1967–1970.

37. Belicchi-Ferrari, M.; Bisceglie, F.; Cavalieri, C.; Pelosi, G.; Tarasconi, P. Bis(triphenylphosphine)4-fluorobenzaldehyde thiosemicarbazone copper(I): Forcing chelation through oxoanions. *Polyhedron* **2007**, *26*, 3774–3782.
38. Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds Part B. Applications in Coordination, Organometallic and Bioinorganic Chemisrty*, 6th ed.; Wiley-Interscience: Hoboken, NJ, USA, **2008**, p.384.
39. Drago, R.S. *Physical Methods in Chemistry*; W.B. Saunders Company: Philadelphia, PA, USA, 1977.
40. Carlin, R.L. *Transition Metal Chemistry*, 2nd ed.; Marcel Decker Inc.: New York, NY, USA, 1965.
41. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds* ^{13}*C-NMR,* ^{1}*H-NMR, IR, MS, UV/VIS*; Springer-Verlag: Berlin, Gemany 1989.
42. Raja, D.S.; Paramaguru, G.; Bhuvanesh, N.S.P.; Reibenspies, J.H.; Renganathan,R.; Natarajan, K,; Effect of terminal N- substitution in 2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone on the mode of ccordination, structure, interaction with protein, radical scavenging and cytotoxic activity of copper(II) complexes. *Dalton Trans.* **2011**, *40*, 4548–4559.
43. Mohan, M.; Gupta, N.S.; Kumar, A.; Kumar, M. Synthesis, characterization and antitumor activity of iron (II) and iron (III) complexes of 3- and 5- substituted salicylaldehyde benzoyl hydrazones. *Inorg. Chim. Acta.* **1987**, *135*, 167–171.
44. Mohan, M.; Kumar, A.; Kumar, M.K. Synthesis, characterization and antitumor activity of manganese(II), cobalt(II), nickel(II), copper(II), zinc(II) and platinum complexes of 3- and 5-substituted salicylaldehide benzoylhydrazones. *Inorg. Chim. Acta* **1987**, *136*, 65–70.
45. Schwarenbach, G.; Flaschka, H. *Die Komplexometrische Titration*; Ferdinand Euke: Verlag Stuttgart, Germany, 1956.
46. Sheldrick, G.M. A short history of SHELX. Acta Crystallogr. 2008, *A64*, 112–122.
47. Altomare, A.; Burla, M.C.; Camalli, M.; Cascarano, G.L.; Giacovazzo C.; Guagliardi, A.G.; Moliterni, G.; Polidori, G.; Spagna, R. SIR97: A new tool for crystal structure determination and refinement. *J. App. Cryst.* **1999**, *32*, 115–119.
48. Betteridge, P.W.; Carruthers, J.R.; Cooper, R.I.; Prout, K.; Watkin, D.J. CRYSTALS version 12: software for guided crystal structure analysis. *J. Appl. Cryst.* **2003**, *36*, 1487–1452.

Sample Availability: Not available.