ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 6, pp. 1198–1201. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © E. Pakhontsu, V.I. Tsapkov, D. Poirier, A.P. Gulya, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 6, pp. 1020–1024.

Coordination Compounds of Copper and Nickel with *N,N*'-[4,4'-(Perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]-bis[2-(pyridin-2-ylmethylidene)hydrazinecarbothioamide] and Its Derivatives

E. Pakhontsu[a], V. I. Tsapkov[b], D. Poirier[c], and A. P. Gulya[b]

[a] *Carol Davila University of Medicine and Pharmacy, Bucharest*
[b] *Moldova State University, ul. Mateevicha 60, Chisinau, 2009 Moldova*
e-mail: gulea@usm.md
[c] *Laval University, Québec, Canada*

Received October 10, 2013

Abstract—*N,N*'-[4,4'-(Perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis[2-(pyridin-2-ylmethylidene)-hydrazinecarbothioamide] as well as its methyl and phenyl derivatives react with copper and nickel chlorides in ethanol to form coordination compounds. In the products, the hydrazinecarbothioamides act as doubly deprotonated bridging ligands. The prepared complexes have been found to inhibit in vitro the growth and propagation of the myeloid human leukemia HL-60 cancer cells at the 10^{-5}–10^{-7} mol/L concentration.

Keywords: coordination compound, hydrazinecarbothioamide, anticancer activity

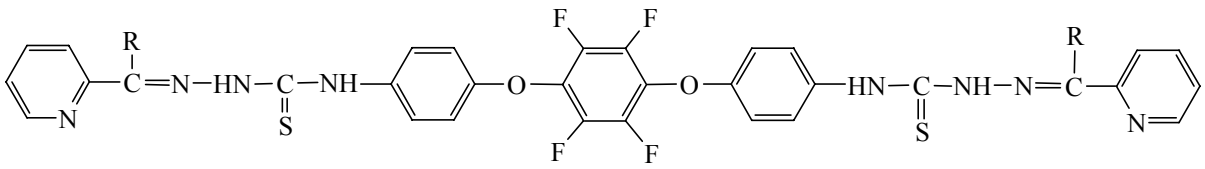
DOI: 10.1134/S1070363214060231

Thiosemicarbazide derivatives are widely used in medicine for cancer treatment [1, 2]. As they contain different types of donor atoms, they form a variety of coordination compounds with metal ions, differing in the composition, structure, and properties [3–7]. In many cases the biological activity of the compounds is in line with their complex formation ability [8–10]. In view of that, studies of preparation and properties of new coordination compounds of metal ions with such Schiff's bases are of significant academic and practical importance.

In this work we elaborated the optimal preparation conditions and the composition, structure, physicochemical properties, and anticancer activity of copper and nickel complexes with *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis[2-(pyridin-2-ylmethilidene)hydrazinecarbothioamide] (H_2L^1), *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis{2-[1-(pyridin-2-yl)ethylidene]hydrazinecarbothioamide} (H_2L^2), and *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis{2-[(pyridin-2-yl(phenyl)methilidene]hydrazinecarbothioamide} (H_2L^3) (Scheme 1).

Interaction of hot (50–55°C) ethanolic solutions of copper or nickel chloride with the hydrazinecarbothioamides ($H_2L^{1–3}$) taken in the 2 : 1 molar ratio

Scheme 1.



$H_2L^{1–3}$

R = H (H_2L^1), CH_3 (H_2L^2), C_6H_5 (H_2L^3).

Table 1. Physicochemical parameters of the studied coordination compounds **I–VI**

Comp. no.	Yield, %	μ_{eff}, [a] μ_B	æ, [a] Ω^{-1} cm^2 mol^{-1}	Found, %				Formula	Calculated, %			
				Cl	M[b]	N	S		Cl	M[b]	N	S
I	72	1.81	4	7.81	14.07	12.50	6.99	$C_{32}H_{20}Cl_2Cu_2F_4N_8O_2S_2$	8.00	14.33	12.64	7.23
II	70	1.97	4	7.49	13.61	12.00	6.75	$C_{34}H_{24}Cl_2Cu_2F_4N_8O_2S_2$	7.75	13.89	12.25	7.01
III	65	2.04	2	6.58	11.94	10.45	5.97	$C_{44}H_{28}Cl_2Cu_2F_4N_8O_2S_2$	6.83	12.23	10.79	6.17
IV	70	[c]	3	7.82	13.11	12.47	7.05	$C_{32}H_{20}Cl_2F_4N_8Ni_2O_2S_2$	8.09	13,38	12.78	7.31
V	67	[c]	3	7.59	12.75	12.14	6.79	$C_{34}H_{24}Cl_2F_4N_8Ni_2O_2S_2$	7.83	12.97	12.38	7.08
VI	64	[c]	4	6.67	11.18	10.61	6.00	$C_{44}H_{28}Cl_2F_4N_8Ni_2O_2S_2$	6.89	11.41	10.89	6.23

[a] At 294 K. [b] M is the metal. [c] Diamagnetic.

yielded fine crystalline compounds **I–VI**. The $M_2L^{1-3}Cl_2$ composition of the complexes was concluded from the elemental analysis data (Table 1) [M = Cu (**I–III**) and Ni (**IV–VI**); H_2L^{1-3} = H_2L^1 (**I** and **IV**), H_2L^2 (**II** and **V**), and H_2L^3 (**III** and **VI**)]. The prepared coordination compounds were poorly soluble in water and in alcohols, but were readily soluble in dimethylformamide (DMF), dimethylsulfoxide, and acetonitrile. The products yield and selected physicochemical parameters are collected in Table 1.

The products purity was assessed by elemental analysis, IR spectroscopy, and molar electric conductance as well as magnetic susceptibility measurements.

From the molar electric conductance values in DMF all prepared compounds were nonelectrolytes (æ = 2–4 Ω^{-1} cm^2 mol^{-1}).

The effective magnetic moment of compounds **I–VI** at 294 K (Table 1) corresponded to the value for one unpaired electron. The result suggested the absence of electron exchange between the paramagnetic central atoms in the prepared coordination compounds. Nickel complexes were diamagnetic; hence, the metal ion was likely in the square plane ligand surrounding.

Type of the ligands coordination with the central ions was elucidated from comparative analysis of IR spectra of complexes **I–VI**, the free ligands H_2L^{1-3}, and coordination compounds of copper salts with 2-formylpyridine thiosemicarbazone, structure of the latter being previously established by X-ray diffraction study [11] (Table 2). The results revealed that the azomethines H_2L^{1-3} acted as bridging *N,N* ,S ligands in the studied complexes, being coordinated with the metal ion via nitrogen atoms of pyridine ring and azomethine group and via sulfur atom, to form four five-membered cycles. That conclusion was confirmed by disappearance of the ν(NH), δ(NH), and ν(C=S) absorption bands in the spectra of the complexes; in the spectra of the free ligands these bands were found at 3500–2800, 1540–1535, and 1125–1120 cm^{-1}, respectively. Furthermore, a new band, ν(C–S), appeared in the complexes spectra at 750–730 cm^{-1}, and the ν(C=N) band was split into two components and shifted towards lower frequency by 25–20 cm^{-1} as compared with the free ligands spectra. At 1570–1560 cm^{-1}, the IR spectra of the complexes contained a band assigned to >C=N–N=C< stretching vibration [12–14]. The observed spectral features indicate the presence of the enolization of hydrazinecarbothioamides H_2L^{1-3} upon formation of complexes **I–VI**. The above-described type of the ligands coordination was confirmed by the appearance of the new bands at 530–405 cm^{-1} in the spectra of all the studied complexes, assigned to the stretching vibrations of M–N (525–505, 430–405 cm^{-1}) and M–S (475–470 cm^{-1}) bonds. The participation of the other functional groups of the ligands in the coordination with the central metal ion was improbable, because their characteristic bands were not shifted upon the complexes formation.

The collected physicochemical data allowed to present the chemical structure of complexes **I–VI** as showed in Scheme 2.

Many coordination compounds of 3*d* elements with pyridine derivatives as ligands are known to selectively inhibit the cancer tumors growth [15–17]. In view of that, we performed in vitro test of anticancer activity of compounds **I–VI** towards

Table 2. Selected absorption bands (cm^{-1}) in the IR spectra of the studied coordination compounds **I–VI** and the free ligands

Compound	ν(NH), δ(NH)	ν(C=N)	ν(>C=N–N=C<)	δ(C–N)	ν(C=S)	ν(C–N)	ν(C–S)	ν(M–N), ν(M–S)
H_2L^1	3512, 3405, 3302, 3130, 3007, 2970, 2815, 1540	1605, 1585	–	1190, 1145	1125	997, 950	–	–
I	–	1590, 1575	1565	1180, 1157	–	985, 945	737	535,475, 425
IV	–	1592, 1572	1568	1175, 1155	–	987, 944	735	530, 465, 415
H_2L^2	3504, 3408, 3310, 3133, 3001, 2968, 2821, 1535	1602, 1583	–	1188, 1146	1120	998, 947	–	–
II	–	1593, 1570	1569	1177, 1153	–	987, 946	730	510, 470, 425
V	–	1590, 1560	1559	1175, 1125	–	985, 941	735	524, 475, 435
H_2L^3	3295, 3220, 3194, 3097, 3065, 3026, 2958, 1535	1610, 1587	–	1185, 1147	1120	996, 940	–	–
III	–	1598, 1569	1568	1167, 1145	–	987, 933	737	525, 470, 430
VI	–	1595, 1560	1558	1165, 1135	–	985, 930	736	530, 470, 415

myeloid human leukemia HL-60 cells. The inhibiting activity of the studied complexes (Table 3) was similar to that of the known drug Doxorubicin, the latter being used for leucosis treatment [7]. At 10^{-5} to 10^{-6} mol/L, complexes **I–VI** inhibited growth and proliferation of 5.1 to 100% of the cancer cells, the effect being less prominent at 10^{-7} mol/L (4.5–10%); no anticancer activity was observed at lower concentration. As seen from Table 3, the anticancer activity depended on the nature of both metal ion and R substituent, decreasing in the following series: Cu ≥ Ni and C_6H_5 > H > CH_3.

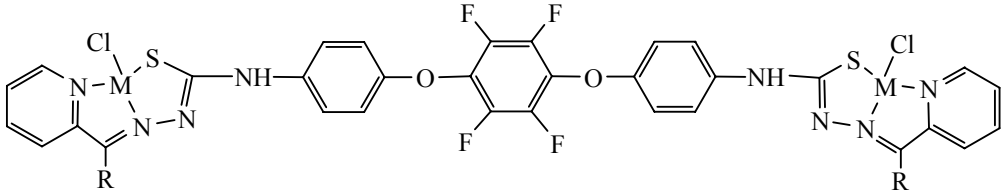
EXPERIMENTAL

Resistivity of the solutions of complexes **I–VI** in DMF (20°C, *c* 0.001 mol/L) was measured with the R-39 rheochord bridge. IR spectra of the compounds were recorded on a Specord M-80 spectrophotometer (mineral oil suspension). Effective magnetic moments of complexes **I–VI** were determined using the Gui method. Molar magnetic susceptibility accounting for the diamagnetism was calculated from theoretical magnetic susceptibility of organic compounds. The ligands $H_2L^{1–3}$ were prepared as described elsewhere [18].

Anticancer activity of the prepared complexes was tested in vitro with myeloid human leukemia cells HL-60 as described elsewhere [19].

μ-{*N*,*N*'-[4,4'-(Perfluoro-1,4-phenylene)bis(oxy)-bis(4,1-phenylene)]bis[2-(pyridin-2-ylmethylidene)-

Scheme 2.



I–VI

Table 3. Fraction (%) of the myeloid human leukemia HL-60 cancer cell with growth and proliferation inhibited by the studied compounds **I–VI** and doxorubicin[a]

Compound	10^{-5} mol/L	10^{-6} mol/L	10^{-7} mol/L
I	17.7	16.1	10.0
II	100.0	78.4	10.0
III	100.0	100.0	4.5
IV	13.2	5.1	4.5
V	14.2	6.5	5.0
VI	15.9	8.0	6.4
Doxorubicin	76.4	73.9	15.7

[a] Each experiment was run in triplicate; the estimated error is ±4%.

hydrazinecarbothioamido]}di(chlorocopper) (I). Solution of 10 mmol of copper chloride dihydrate in 20 mL of ethanol was added at continuous stirring and heating (50–55°C) to ethanol solution of 5 mmol of *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis[2-(pyridin-2-ylmethilidene)hydrazine-carbothioamide] H_2L^1 in 30 mL of ethanol. Then the reaction mixture was heated during 50–60 min. After cooling to room temperature and slow evaporation of the solvent a dark-green precipitate was formed; it was filtered off on a glass filter, washed with a little of ethanol, diethyl ether, and finally dried in air till constant mass.

Complexes II–VI were prepared similarly from *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis[2-(pyridin-2-ylmethilidene)hydrazine-carbothioamide] (H_2L^1), *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis[2-(1-(pyridin-2-ylethylidene)hydrazinecarbothioamide] (H_2L^2), or *N,N*'-[4,4'-(perfluoro-1,4-phenylene)bis(oxy)bis(4,1-phenylene)]bis{2-[pyridin-2-yl(phenyl)methylidene]-hydrazinecarbothioamide} (H_2L^3) and copper or nickel chloride hydrates (1 : 2 molar ratio). Yields and physicochemical parameters of the compounds **I–VI** are given in Tables 1 and 2.

ACKNOWLEDGMENTS

This work was performed in the frame of the 13.820.08.01/RoF international project.

REFERENCES

1. Mashkovskij, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2008.
2. Zhungietu, G.I. and Granik, V.G., *Osnovnye printsipy konstruirovaniya lekarstv* (General Principles for Constructing of Drugs), Chisinau: IPK MoldGU, 2000.
3. Gerbeleu, N.V., Arion, V.B., and Burges, J., *Template Synthesis of Macrocyclic Compound*, Wiley-VCH: Weinheim, 1999.
4. Samus', N.M., Chumakov, Yu.M., Tsapkov, V.I., Bocelli, G., Simonov, Yu.A., Gulya, A.P., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 3, p. 428.
5. Chumakov, Yu.M., Tsapkov, V.I., Zhanno, E., Bairak, N.N., Bocelli, G., Puar'e, D., Rua, Zh., and Gulya, A.P., *Crystallograph. Rep*., 2008, vol. 53, no. 5, p. 786.
6. Gulya, A., Poirier, D., Roy, J., Stavila, V., Bulimestru, I., Tapcov, V., Birca, M., and Popovschi, L., *J. Enzyme Inhib. Med. Chem*., 2008, vol. 23, no. 6, p. 806.
7. Pahontu, E., Fala, V., Gulea, A., Poirier, D., Tapcov, V., and Rosu, T., *Molecules*, 2013, no. 18, p. 8812.
8. Gulya, A.P., Prisakar', V.I., Tsapkov, V.I., Buracheva, S.A., Spynu, S.N., and Bezhenar', N.P., *Chem. Pharm. J.,* 2008, vol. 42, no. 6. p. 326.
9. Rosu, T., Gulea, A., Nicolae, A., and Georgescu, R., *Molecules*, 2007, no. 12, p. 782.
10. Ilies, D.C., Pahontu, E., Shova, S., Gulea, A., and Rosu, T., *Polyhedron*, 2013, vol. 51, no. 3, p. 307.
11. Chumakov, Yu.M., Tsapkov, V.I., Zhanno, E., Bairak, N.N., Bochelli, G., Puar'e, D., Rua, Zh., and Gulya, A.P., *Crystallograph. Rep*., 2008, vol. 53, no. 5, p. 786.
12. Arion, V.B., Gerbeleu, N.V., and Indrichan, K.M., *Zh. Neorg. Khim*., 1985, vol. 30, no. 1, p. 126.
13. Gulya, A.P., Spynu ,S.N., Tsapkov, V.I., and Poirier, D., *Russ. J. Gen. Chem*., 2008, vol. 78, no. 5, p. 984.
14. Gulya, A.P.., Prisakar', V.I., Tsapkov, V.I., Buracheva, S.A., Spynu, S.N., Bezhenar', N.P., Puar'e, D., and Roi, Zh., *Chem. Pharm. J*., 2007, vol. 41, no. 11, p. 596.
15. Gulya, A.P., Tsapkov, V.I., Straistar', T., and Puar'e, D., Patene MD no. 4132, 2011, *Byull. Izobret.,* I. MD. BOPI no. 10/2011, p. 24.
16. Ferrari, M.B., Bisceglie, F., and Pelosi, G., *J. Inorg. Biochem*., 2004, vol. 98, p. 301.
17. Gulya, A.P., Tsapkov, V.I., Puar'e, D., and Pahoncu, E., Patent MD no. 3996, 2009, *Byull. Izobret.,* MD. BOPI no. 12/2009, p. 30.
18. Gulya, A.P., Zhalb'e, A.V., Barba, N.A., Tsapkov, V.I. Sofroni, L.S., and Puar'e, D., Patent MD no. 4126, 2011, *Byull. Izobret., MD.* BOPI no. 9/2011, p. 24.
19. Gulya, A.P., Puar'e, D., Rua, Zh., Stavil'e, V.G, and Tsapkov, V.I., Patent MD no. 2786, 2005, *Byull. Izobret.,* MD. BOPI no. 6/2005, p. 22.