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RUSNAC ROMAN

DESIGN AND SYNTHESIS OF BIOLOGICAL ACTIVE COMPOUNDS OF 3*d* METALS WITH THIOSEMICARBAZONE *N*(4)-SUBSTITUTES OF 2-FORMYLPYRIDINE DERIVATIVES

141.02 Coordination Chemistry

Summary of the doctoral submitted in chemical sciences

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Thesis was elaborated in research Laboratory of Advanced Materials in Biopharmaceutics and Technics of the Moldova State University

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Thesis defence will take place on April 7th, 2022 at 14:00 pm, in the meeting of the Doctoral Commission within the Doctoral School of Biological, Geonomic, Chemical and Technological Sciences, room no. 317 / IV of Moldova State University, 60, A. Mateevici str., Chisinau, MD-2009.

The PhD thesis and its summary may be consulted at the scientific library of the National Library of the Republic of Moldova, USM Library and at CNAA (http://www.cnaa.md) and (www.dspace.usm.md)

The summary was sent on March 7th, 2022

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CONCEPTUAL MILESTONES OF RESEARCH

Relevance and importance of the problem. The chemistry of coordination compounds is developing rapidly as methods of investigation modernize and the daily necessity of new innovative products/materials grows. Most coordination compounds show high physicochemical stability and are difficult to dissolve in water. The introduction of easily ionizable groups in the structure of the ligands that form the coordination compounds favors their solubilization in protic polar solvents such as: water, alcohols, etc., as well as aprotic polar solvents: CH_3CN, DMF, DMSO, etc. Thiosemicarbazones show a wide range of biological activities such as: antituberculosis, anticancer, antiviral, antimalarial, antifungal, anticonvulsant [1-5]. Interest in this family of compounds has increased significantly over the years since the first report in 1940 to the thousands of papers published by 2022. A particular manifestation of the biological property of thiosemicarbazones is the inhibition of ribonucleotide reductase (RR) synthesis [2].

The first drug approved for clinical trials in this class of compounds (introduced in the late 1940s) was thiosemicarbazone *p*-acetamidobenzaldehyde (*Thioacetazone*) which is used to treat multidrug-resistant tuberculosis [1-2]. Another thiosemicarbazone called Triapine which has been in more than 30 phase I and II clinical trials, Triapina® has shown excellent anticancer potential, which also increases the anticancer effects of other drugs of the same type, such as *cis*-Platinum, Gemcitabine, Doxorubicin, Irinotecan, minimizing the negative effects of radiation therapy [2, 5].

Although thiosemicarbazones show promising biological activities, they are predominantly advanced by the coordinative compounds that activate the biological properties of ligands and together form synergistic actions, which is very complex from a structural point of view and problematic to study. Modification of the substituent in position *N*(4) with lipophilic potential leads to an increase in biological activities [1-5].

The introduction of electron-donor substituents to nitrogen 4 from the thiosemicarbazide fragment, which would correspond to the *Lipinski* rule or the *Veber* rule, leads to an increased biological potential [2].

The aim: synthesis and physico-chemical characterization of some coordination compounds based on metals Cu, Ni, Fe, Co, Zn, Mn with different *N*(4)-*cyclohexyl (phenylacetamide; tert-butyl)* thiosemicarbazones derived from 2-formylpyridine; screening of antimicrobial-antifungal, anticancer and antioxidant activities of synthesized coordination compounds; analysis of the structure-activity relationship.

Research objectives:

- - Synthesis of *N*(4)-*cyclohexyl (phenylacetamide; tert-butyl)* thiosemicabases derived from 2-formylpyridine;
- Synthesis of the coordination compounds of Cu (II), Ni (II), Fe (III), Co (III), Zn (II), Mn(II) with *N*(4)-substituted thiosemicarbazones;
- Physico-chemical characterization of organic and inorganic compounds obtained through modern research methods: conductometry in solution; elementary analysis; MRI ^{1}H, ^{13}C, ^{15}N; REP; FT-IR spectroscopy; UV-vis spectrophotometry; mass spectroscopy; X-ray diffraction.
- Research of antimicrobial-antifungal and antioxidant properties.
- Study of the structure-activity correlation and the proposal of the most active compounds for the advanced study of anticancer properties.

The research hypothesis assumes that thiosemicarbazones, which contain electron-donor substituents in the *N*(4) position of the thiosemicarbazide fragment with lipophilic properties, may increase the probability of penetration of "target molecules" through cell membranes of various bacteria and fungi as well as tumor cells. Ensuring the transport of thiosemicarbazones through coordination compounds to the cell nucleus will be achieved by hydrolytic dissociation of coordination combinations into metal ions and free ligand, actively participating in the chelation of iron which is the key element in the synthesis of tumor cell DNA.

Synthesis of the research methodology and justification of the chosen methods

The research methodology involves the synthesis of coordination compounds by known methods. The investigation of the compounds obtained by means of modern spectral research methods ^{1}H, ^{13}C-(Dept 135), MRI was performed at the Institute of Chemistry. The recording of FT-IR spectra was performed in the scientific research laboratory "Advanced Materials in Biopharmaceuticals and Technology" of the State University of Moldova. Powder X-ray diffraction was performed at the Regional Interdisciplinary Scientific-Educational Center for the Study of Advanced Materials (CaRISMA) of the State University of Moldova. The UVDR analysis was performed within the Department of Materials Chemistry, Faculty of Chemistry, Alexandru Ioan Cuza University, Iași, Romania. Single crystal X-ray analysis was performed at the Institute of Applied Physics, Chisinau, Republic of Moldova, and the Institute of Macromolecular Chemistry "Petru Poni", Iasi, Romania. For a series of studied compounds, electronic paramagnetic resonance (EPR) was performed in the Coordinative Chemistry Laboratory of the National Center for Scientific Research, Toulouse, France. Electrospray mass spectra (ESI-MS) were collected using a Q-TOF instrument provided by WATERS, Chatenay-

Malabry, France. For the studied compounds, the elemental analysis was performed using the elemental analyzer "PERKIN ELMER 2400". Elemental analyses were performed by the BioCIS laboratory in Chatenay-Malabry, France. The antimicrobial and antifungal activity was performed in the Microbiology Laboratory of the National Agency for Public Health. The anticancer, antioxidant properties, and the study of *Eco*-toxicity were performed in the Laboratory of Systematics and Molecular Phylogeny, the Center for Biological Invasion Research of the Institute of Zoology, and the Biochemistry Laboratory of the State University of Medicine and Pharmacy "Nicolae Testemitanu".

The scientific problem that has been solved is: determining the optimal conditions for the synthesis of thiosemicarbazones *N*(4)-substituted based on 2-formylpyridine derivatives and coordination compounds with some ions of 3*d* metals; establishing the correlation between the structure of the coordination compounds, and the biological activity. The *Eco*-toxicity of a series of substituted *N(*4) thiosemicarbazones and their complexes has been determined for the first time.

The practical value consists in the synthesis of the coordination compounds of some 3*d* metals with thiosemicarbazones *N*(4)-substituted based on 2-formylpyridine derivatives which show an antimicrobial potential at concentrations of the order of nanograms.

The results presented in the paper were the subject of **30** scientific publications, including **7** scientific articles (**1** article in an international journal and **6** articles in national journals) and **23** abstracts at various national and international conferences; **2** patents and one patent application. Publications without co-authors - **1**.

The paper consists of an introduction, 3 chapters, general conclusions and recommendations, a bibliography with 180 titles. The thesis material is displayed on 123 pages of basic text and contains: 70 figures, 33 tables, and 10 annexes.

The work was carried out within the *institutional project* "Strategies for the development of molecular antitumor inhibitors of a new generation. Synthesis, properties and mechanisms of action"15.817.02.24F (2015-2019) and the *international project* "Synthèse et caractérisation de nouveaux composés de coordination des métaux de transition pour des applications en biologie" funded by AUF 2020.

PAPER CONTENTS

The introduction includes the relevance of the studied topic, the aim, the research objectives, the research hypothesis, being argued the research methodology and the justification of the chosen research methods. At the end of each chapter, the conclusions that give the generalized aspect of the elucidated information, as well as the most important results presented can be found.

1. COORDINATIVE COMBINATIONS OF SOME 3*d* METALS WITH THIO-SEMICARBAZONE *N*(4)-SUBSTITUTES OF 2-FORMYLPYRIDINE DERIVATIVES

Chapter 1 presents the general theoretical and practical approaches in the field of specialization concerned. Here are presented the investigation of the optimal methods of synthesis of thiosemicarbazones through the reactions of nucleophilic substitution, nucleophilic addition, and condensation. At the same time, various pathways for the synthesis of coordination compounds based on 3*d* metals with *N*(4) substituted thiosemicarbazones of 2-formylpyridine derivatives are described. The correlation of the structure of the coordination compounds with the biological activity is analyzed.

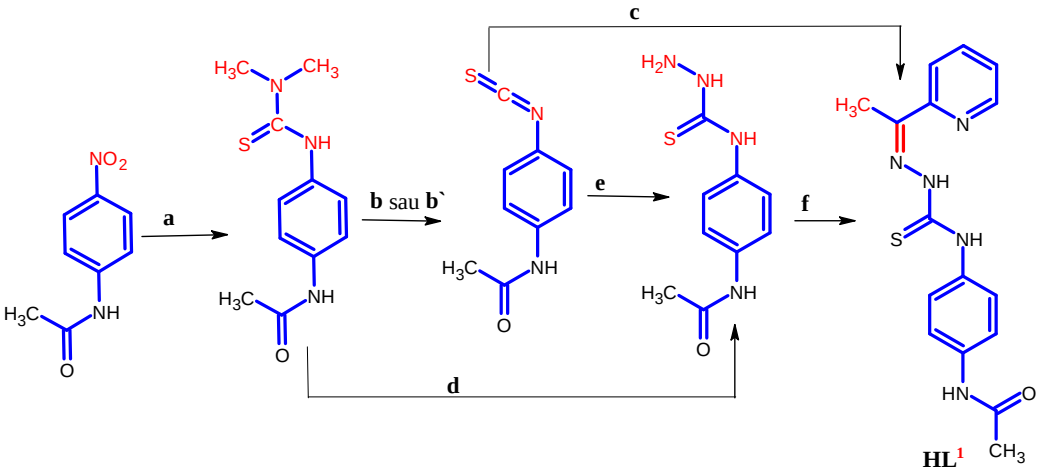
2. METHODS OF SYNTHESIS, ANALYSIS, AND RESEARCH

Chapter 2 includes methods for the synthesis of *N*(4)-substituted thiosemicarbazones HL^1-HL^{10} and coordination combinations with some 3*d* metals, physico-chemical research methods: FT-IR and ^1H, ^{13}C, ^{15}N NMR, etc. The paper used high purity chemical reagents sourced from Sigma-Aldrich®, Acros Organics®, and Alfa Aesar®.

2.1 Synthesis of thiosemicarbazones *N*(4)- substituted HL^1-HL^{10}

Ten hiosemicarbazones **HL^{1-10}** were obtained, of which **6** are new, with four different substituents in position *N*(4) such as: phenylacetamide, cyclohexyl, hexyl, and *tert*-butyl. Thiosemicarbazone **HL^1**, unknown in the specialty literature, was obtained from 4-nitroacetanilide. It has been shown that *N*-{4-[(dimethylcarbonothioyl)amino]phenyl} acetamide can be obtained in a single step (**a**), without isolating the intermediate *N*-(4-aminophenyl) acetamide, having under chromatographic control the total transformation of *N*-(4-aminophenyl) acetamide in *N*-{4-[(hydrazinylcarbonyloyl)amino]phenyl}acetamide. Better results are obtained by treating *N*-{4-[(dimethylcarbamothioyl)amino]phenyl}acetamide (**b** or **b'**) with hydrogen chloride in 1,4-dioxane or acetic anhydride. Thus {4-[(hydrazinylcarbonyloyl)amino]phenyl} acetamide was obtained by the reaction of the addition (**s**) of hydrazine to *N*-(4-isothiocyanatophenyl)acetamide or by the direct method of *N*-{4-[(dimethylcarbamothioyl)amino]phenyl}acetamide by nucleophilic substitution reaction (**d**)

(Figure 2.1). Thiosemicarbazone **HL**^{1} was obtained by two methods: *condensation* - in the treatment of *N*-{4-[(hydrazinylcarbonyloyl)amino]phenyl}acetamide with 2-acetylpyridine and *addition* - 2-acetylpyridine hydrazone to *N*-(4-isothiocyanatophenyl)acetamide. Thiosemicarbazone **HL**^{1} is obtained in higher yield by the addition method (Figure 2.1).



Reagents and conditions: (**a**) Zn, NH_4Cl, DMF-H_2O (1:1), tetramethylthiuram disulfide, 1.5 hours, 93%; (**b**) HCl, 1,4-dioxane, one hour, 90%; (**b`**) Ac_2O, 1,4-dioxan, one hour, 95%; (**c**) 2-[1-hydrazinylideneethyl]pyridine, ethanol, 3 hours, 92%; (**d**) $N_2H_4 \cdot H_2O$, toluene, 2 ore, 86%; (**e**) $N_2H_4 \cdot H_2O$, benzene, o oră, 98%; (**f**) 2-acetylpyridine, AcOH glacial (4 drops), ethanol, 9 hours, 86%.

Fig. 2.1. The synthetic route for the preparation of the thiosemicarbazone derivatives HL^{1}

The purity and time of synthesis of the organic compound HL^{1} (R_f = 0.59 (ethyl acetate-benzene 2:1) was determined through thin layer chromatography. Using ^{1}H-NMR-DMSO-d_6 spectra which were recorded at room temperature, it has been noted that thiosemicarbazone **HL**^{1} is found in two tautomeric forms of thiol-thione, the thionic form is 95% predominant and the thiol tautomeric form is 5%. The molecular structure of thiosemicarbazone **HL**^{1} being confirmed by single-crystal X-ray diffraction is planar, it has been shown that **HL**^{1}**,** in the solid-state is found in the tautomeric form of the ionic tautomer with a C = S bond length of 1,672 Å. Following the recrystallization of **HL**^{1} from ethanol, it was possible to isolate the single crystals that were analyzed using X-ray diffraction, establishing the molecular structure (Figure 2.2). The synthesis of *N*(4)-substituted thiosemicarbazones **HL**^{2}**, HL**^{3}**, HL**^{4} was performed by classical methods according to the scheme in (Figure 2.3) of cyclohexylamine and corresponding reagents. Their purity is confirmed by thin layer chromatography on silufol plates. Retention factors are determined for **HL**^{2} (R_f = 0.71 (eluent:

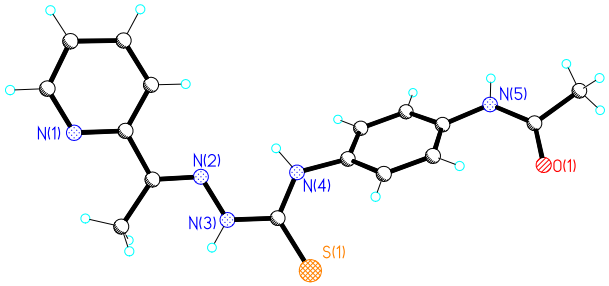
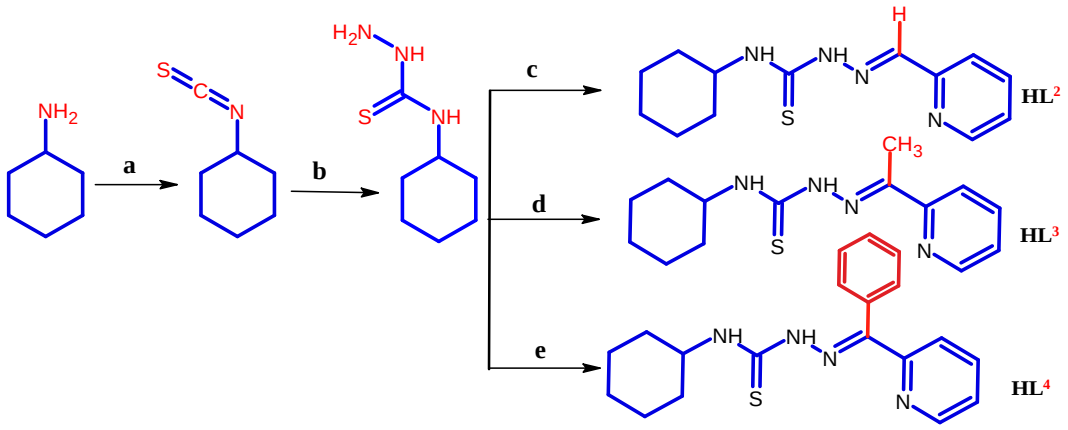


Fig. 2.2. Molecular structure of thiosemicarbazone HL^{1}

benzene-isopropanol, 1:1)) for **HL^3** (R_f = 0.71 (eluent: benzene-isopropanol, 1:1)) and for **HL^4** (R_f = 0.82 (eluent): benzene-ethyl acetate, 1:2)).

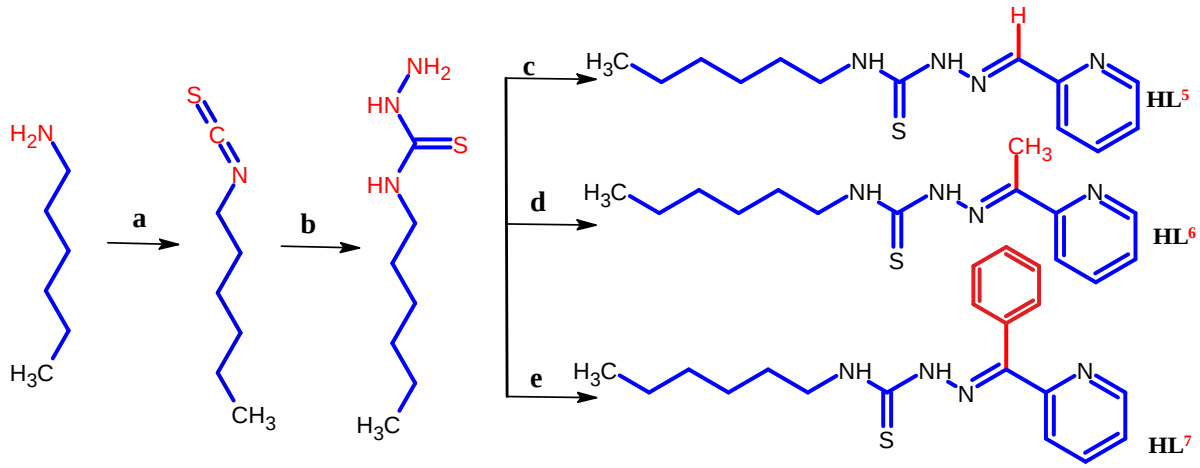


Reagents and conditions: (a) $CSCl_2$, $(C_2H_5)_3N$, benzene, 3.5 hours, 97%; (b) $N_2H_4 \cdot H_2O$, ethanol, one hour, 92%; (c) 2-formylpyridine, AcOH glacial (4 drops), ethanol, 5 hours, 91%; (d) 2-acetylpyridine, AcOH glacial (4 drops), ethanol, 7 hours, 94%; (e) 2-benzoylpyridine, AcOH glacial (4 drops), ethanol, 9 hours, 84%.

Fig. 2.3. Route of synthesis of the thiosemicarbazones HL^2; HL^3; HL^4

In the ^{1}H-NMR-DMSO-d_6 thiosemicarbazone spectra, **HL^2** is found in the thiol form 4.7% and for **HL^3** the thiol tautomeric form is 1%. For **HL^4**, the chemical shift of 12.81 ppm can be attributed to N-H, which forms intramolecular hydrogen bonds with pyridine nitrogen atoms, thus accentuating the acidic properties of the N-H hydrazine group. Such cases are found in the specialty literature when in the ^{1}H-NMR spectra of thiosemicarbazones based on 2-benzoylpyridine at the chemical shift of 12.0-14.6 ppm, the signals are attributed to N-H (hydrazine) in other words to the hydrogen atom in H-*N*(2) from thiosemicarbazone [1].

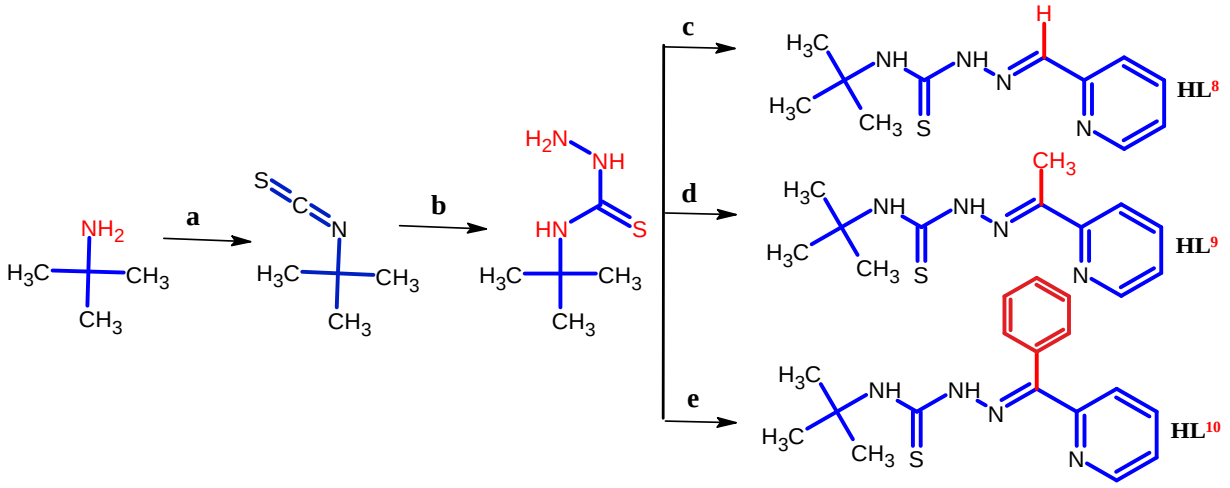
The synthesis of thiosemicarbazones **HL$^{5-7}$** took place according to the classical methods of synthesis following condensation reactions between the corresponding thiosemicarbazide and aldehyde or heterocyclic ketone. Thus thiosemicarbazones **HL$^{5-7}$** were obtained and their purity was confirmed by thin-layer chromatography: HL^5 (R_f = 0.65 (eluent: benzene-ethyl acetate, 3:1)), HL^6 (R_f = 0.70 (eluent: benzene-ethyl acetate, 3:1)) and HL^7 (R_f = 0.68 (eluent: benzene-ethyl acetate, 3:1)). In the ^{1}H-NMR-DMSO-d_6 spectra of **HL^5** thiosemicarbazone recorded at room temperature, it was found that it is found in two tautomeric forms thiol-thione, the thionic form is predominant 96% and the thiol tautomeric form is 4%. At 14.17 ppm, the characteristic proton is present for SH thiol groups in carbothioamide groups. For HL6 the thiol tautomeric form is more accentuated being 17% and the thionic form 83%. In the case of thiosemicarbazone **HL^7**, it was possible to confirm by ^{1}H-NMR spectra the presence of the Z form at the azomethine bond by assigning the 13.65 ppm peak to the proton in the hydrazine group that binds to the basic center of the pyridine ring, thus emphasizing the property of thiosemicarbazone to form intramolecular hydrogen bonds.



Reagents and conditions: (a) $CSCl_2$, $(C_2H_5)_3N$, THF, 45 minutes, 97%; (b) $N_2H_4 \cdot H_2O$, ethanol, one hour, 98%; (c) 2-formylpyridine, AcOH glacial (4 drops), ethanol, 8 hours, 96%; (d) 2-acetylpyridine, AcOH glacial (4 drops), ethanol, 12 hours, 97%; (e) 2-benzoylpyridine, AcOH glacial (4 drops), ethanol, 15 hours, 92%.

Fig. 2.4. Route of synthesis of the thiosemicarbazones HL[5]; HL[6]; HL[7]

Synthesis of *N*(4) thiosemicarbazones-substituted **HL[8], HL[9], HL[10]** required to obtain the coordination compounds, were obtained from 2-methylpropane-2-amine by classical methods according to the scheme:



Reagents and conditions: (a) $CSCl_2$, $NaHCO_3$, H_2O-Hexane (10:1), 2 hours, 96%; (b) $N_2H_4 \cdot H_2O$, ethanol, one hour, 94%; (c) 2-formylpyridine, AcOH glacial (4 drops), ethanol, 6 hours, 90%; (d) 2-acetylpyridine, AcOH glacial (4 drops), ethanol, 8 hours, 88%; (e) 2-benzoylpyridine, AcOH glacial (4 drops), ethanol, 11 hours, 96%;

Fig. 2.5. Route of synthesis of the thiosemicarbazones HL[8], HL[9] și HL[10]

The purity and time of synthesis of thiosemicarbazones **HL[8-10]** were determined by thin-layer chromatography. For HL^8 R_f = 0.51 (eluent: benzene-ethyl acetate, 3:1) and for HL^9 R_f= 0.59 (eluent: benzene-ethyl acetate, 3:1) and HL^{10} R_f = 0.63 (eluent: benzene-ethyl acetate, 3:1). In the ^{1}H-NMR spectrum of HL^8, we observe 71% thiol form and 29% thionic form. For HL^9 32% thiol form and 68% thionic form. For HL^{10}, the presence of the ionic form is mainly observed, but in the *cis/trans* equilibrium conformation concerning the azomethine bond, hence

the signals doubled by NH-hydrazine. But most of them are found in the *E* configuration of thiosemicarbazone **HL**[10].

2.2 Methods of preparation of coordination compounds

Based on copper(II), nickel(II), cobalt(III), iron(III), manganese(II), and zinc(II) ions, **55** coordination combinations were obtained, of which **42** are new, including **6** binuclear coordination compounds and **49** mononuclear coordination compounds.

The coordination compounds of some 3*d* metals were obtained by the direct interaction of the respective metal salts with the substituted *N*(4) thiosemicarbazones of the 2-formylpyridine derivatives. The classical method applied to the synthesis of all coordination compounds is reflux in ethanolic solution. Applying this synthesis method, Cu(II), Ni(II), Co(III), Fe(III), Mn(II), and Zn(II) complexes were obtained.

General method of synthesis of coordination combinations in a molar ratio of 1: 1 or 1: 2.

The complexes were obtained by the interaction of a metal salt dissolved in a hydroalcoholic mixture with slight heating in a water bath, then added (1 equivalent / 2 equivalents) of thiosemicarbazone dissolved in EtOH. The mixture obtained is homogenized and refluxed with a magnetic stirrer. A microcrystalline solid substance is deposited from the reaction mixture, which is filtered through the Schott funnel under reduced pressure, then dried in a vacuum desiccator in the presence of anhydrous $CaCl_2$ to a constant mass. The pH of the solution was measured during the syntheses. In the case of copper(II) salts and Cl^-; Br^-; NO_3^-; ClO_4^- anions pH is located in the range 0.91-2.10; in the case of CH_3COO^- salts pH being in the range 4.09-5.02.

2.3 Research methods

^1H, ^{13}C, ^{15}N NMR spectroscopy; FT-IR spectroscopy; single-crystal X-ray diffraction; powder X-ray diffraction (XRD); conductometry in solution; determination of melting point; mass spectroscopy; elementary analysis; REP spectroscopy; thin-layer chromatographic analysis; research on antimicrobial and antifungal activity; research of antioxidant activities by the $ABTS^{\bullet+}$ method; anticancer analysis; determination of toxicity (*Paramecium caudatum*); determination of *in vivo* Eco-toxicities (*Daphnia magna*).

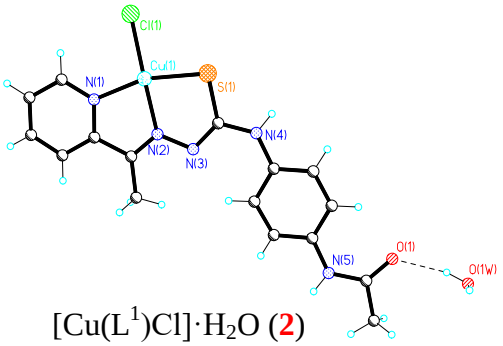
3. COORDINATIVE COMPOUNDS OF SOME 3*d* ELEMENTS WITH *N*(4)-(ARYL/ALKYL) THIOSEMICARBASONES BASED ON 2-FORMYLPIRDINE DERIVATIVES. BIOLOGICAL PROPERTIES

The physico-chemical properties of thiosemicarbazones based on 2-formylpyridine derivatives are suitable both for chelating 3*d* metal ions and for various other applications. Thiosemicarbazones show a wide range of biological properties such as: antifungal, antimicrobial, antioxidant, anticancer, etc. Following the complexation of thiosemicarbazones to 3*d* metal ions, new molecular structures with classical or less ordinary geometries are obtained. According to the crystallographic database (The Cambridge Crystallographic Data Center (CCDC)), the coordination combinations of thiosemicarbazones **HL^1-HL^{10}** with the metal ions of Cu(II), Ni(II), Co(III), Fe(III), Mn(II) and Zn(II) are in small numbers or even missing. Thus, our interest was focused on obtaining a series of 3*d* metal ion complexes with thiosemicarbazones HL$^{1\text{-}10}$. In order to determine the composition and chelation of 3*d* metal ions, the structure was determined using single-crystal X-ray diffraction as well as other modern research methods.

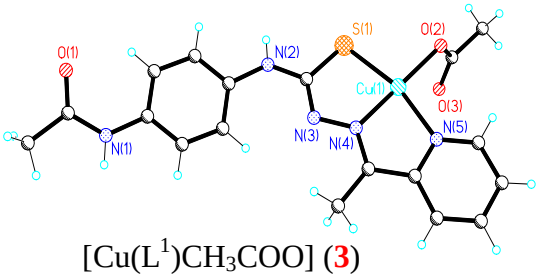
3.1 Structure and biological properties of copper(II) complexes with *N*(4)-phenylacetamide-3-thiosemicarbazones

As a result of the reaction between the Cu(II) salts with **HL^1**, a series of single crystals were isolated and investigated (Figure 3.1) for which the molecular structure was determined. All Cu(II)-based coordination compounds with HL^1 are monomers.

The coordination number of Cu(II) is 4 or 5 and thiosemicarbazone **HL^1** behaves in all cases as a tridentate, monodeprotonated ligand coordinating through the pyridine nitrogen donor atoms, azomethine nitrogen, and the thiol sulfur atom. The length of the C-S bonds in the ligand in these complexes is located in the range 1,745-1,758 Å, which corresponds to the data in the specialty literature.



[Cu(L^1)Cl]·H$_2$O (**2**)

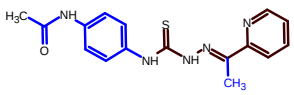


[Cu(L^1)CH$_3$COO] (**3**)

Fig. 3.1. Molecular structures of coordination compounds based on Cu (II) with HL^1

The study of antioxidant activity was performed by the ABTS method to identify the antioxidant potential of the synthesized coordination compounds. Thus the most active complex established **is** $[Cu(L^1)(H_2O)_2]ClO_4$ (**5**) with perchlorate ion, which is 3.3 times more active than Trolox which served as a reference substance (Table 3.1).

Table 3.1. Antioxidant and antimicrobial activities of coordination compounds (1-5) based on *N*(4) phenylacetamide thiosemicarbazone-2-acetylpyridine (HL^1)

Ligand	Compounds	*ABTS*		*S.aureus*
		***IC_{50}, µM**	***SD*, µM**	**MIC, µg/mL**(µM)
 **HL^1**	*$[Cu(L^1)Br(H_2O)]$* (**1**)	47.44	1.06	**3.90**(8.29)
	$[Cu(L)^1Cl]$ (**2**)	**24.30**	1.28	**3.90**(8.80)
	$[Cu(L)^1CH_3COO]$(**3**)	32.43	1.40	**15.62**(34.79)
	$[Cu(L^1)(H_2O)]NO_3$ (**4**)	**23.30**	0.92	**7.81**(16.62)
	$[Cu(L^1)(H_2O)_2]ClO_4$ (**5**)	**10.11**	0.30	**3.90**(7.69)
	HL^1	**8.5**	1.4	**250.0**(765.0)
****Trolox**		**33.3**	**1.03**	*****4.67**(23.6)

Antioxidant activity
**IC_{50}- semiminimal concentration of cation radical inhibition of $ABTS^{\cdot+}$*
*** Trolox IC_{50}=33.3±1.03 µM,*
Antimicrobial activity
**** Furaciline*
MIC- minimum inhibitory concentration

Table 3.1 shows that most copper(II) complexes with thiosemicarbazone **HL^1** show antioxidant activity. Antimicrobial analysis on gram-positive microorganisms *Staphylococcus aureus ATCC 25923 (Gr.* +) was studied using the modern standard method for determining the sensitivity of *S.aureus* microorganisms - serial dilution method. The most active coordination compounds are those of Cu(II) with chlorine and bromine ions as well as perchlorate with a concentration of 3.90 µg/mL which exceeds the antimicrobial activity of the reference substance Furacilline.

3.2 Coordination compounds of some 3*d* metals with *N*(4)-cyclohexyl-3-thiosemicarbazone

The synthesis of the chloride compounds of some 3*d* metals with thiosemicarbazones HL^2-HL^4 was performed according to the classical synthesis procedures at the interaction of the metal salt with the alcoholic solution of thiosemicarbazone. From the obtained or last recrystallization solutions, a series of single crystals were isolated and characterized.

All complexes are mononuclear and have the geometry of the central atom flat-square, the length of the bonds C-S 1,734-1,753 Å. In the series of **HL$^{2-4}$** complex compounds with 3*d* metal salts, single crystals were obtained only based on Cu(II) complexes, for the other metals, this was impossible due to high solubilities. An unusual case is the molecular structure of the ionic complex (**16**). The bromine ion is in the outer sphere and compensates for the charge of the cationic complex, the ligand coordinates tridentate through the set of NNS atoms, **HL^{3}** behaves as a neutral ligand, the length of C-S bonds is 1,696 Å.

Most **HL$^{2-4}$**-based complexes are monomers, with the exception of the coordination compound (**24**) in which it is a dimer assembled via the coordinated sulfur atom bridge. Of the thiosemicarbazones functionalized in position *N*(4) with the cyclohexane ring, the best antioxidant potential was recorded in HL^{2} which is 7 times more active than Trolox. The coordination compounds of Mn(II), Zn(II), and Ni(II) with **HL^{2}** showed an antioxidant potential 2-5 times higher than Trolox. The best antimicrobial activity was recorded for thiosemicarbazone **HL^{3}** with a MIC value of **0.061 µg/mL**, which is 77 times more active than Furacillin. The most prominent antimicrobial activity is in the coordination compound [Cu(L^{2}) H_2O]ClO_4 (**10**) with the value of the minimum inhibition concentration of **0.060 µg/ mL** which is 78 times more active than the comparator substance.

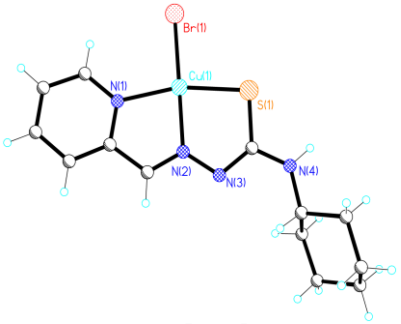


Fig. 3.2. Molecular structure of [Cu(L^{2})Br] (6) based on HL^{2}

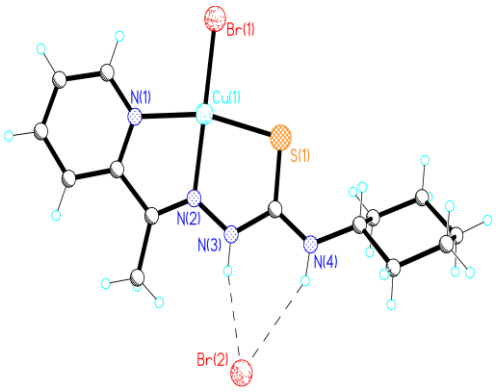


Fig. 3.3. Molecular structure of [{Cu(HL^{3})Br]Br (16) based on HL^{3}

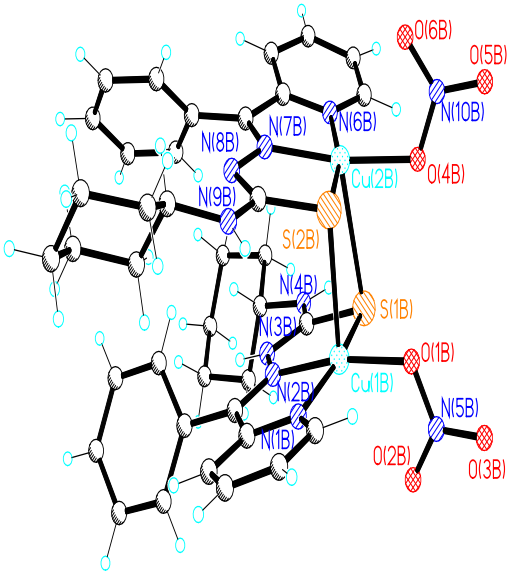
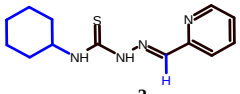
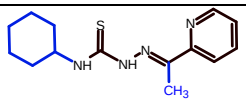
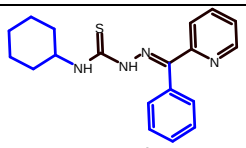


Fig. 3.4. Structura moleculară a [{Cu(L^{4})NO_3}$_2$] (24) în baza HL^{4}

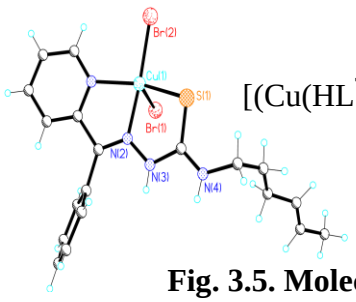
Table 3.2. Antioxidant and antimicrobial activity of coordination compounds of some 3*d* metals (6-25) based on *N*(4)cyclohexyl thiosemicarbazones (HL^{2-4})

Ligand	Compounds	ABTS		*S.aureus*
		IC_{50}, μM	SD, μM	MIC, μg/mL(μM)
 HL^2	$[Cu(L^2)Br]$ (**6**)	100	-	**0.48**(1.20)
	$[Cu(L^2)Cl(H_2O)]$(**7**)	**25.12**	2.23	**0.48**(1.291)
	$[Cu(L^2)CH_3COO]$ (**8**)	**25.53**	2.12	**0.97**(2.542)
	$[Cu(L^2)NO_3]$ (**9**)	100	-	**0.12**(0.315)
	$[Cu(L^2)H_2O]ClO_4$ (**10**)	72.14	1.29	**0.06**(0.138)
	$[Ni(L^2)Cl]$(**11**)	**11.73**	0.66	**62.50**(175.60)
	$[Co(L^2)_2]Cl$ (**12**)	100	-	**0.97**(1.58)
	$[Fe(L^2)_2]Cl$ (**13**)	38.96	5.30	**31.25**(50.90)
	$[Mn(L^2)_2]$ (**14**)	**6.74**	0.64	**31.25**(54.07)
	$[Zn(L^2)(H_2O)Cl]$ (**15**)	**14.09**	2.14	**7.81**(20.55)
	HL^2	**5.1**	0.8	**250.0**(765.0)
 HL^3	$[Cu(HL^3)Br]Br$ (**16**)	100	-	**0.24**(0.48)
	$[Cu(L^3)Cl]$ (**17**)	100	-	**0.24**(0.65)
	$[Cu(L^3)CH_3COO]$ (**18**)	100	-	**1.95**(4.90)
	$[Cu(L^3)NO_3]$ (**19**)	100	-	**0.97**(2.43)
	$[Cu(L^3)H_2O]ClO_4$ (**20**)	100	-	**0.97**(2.14)
	HL^3	**27.4**	2.0	**0.0610**(0.2328)
 HL^4	$[Cu(L^4)Br]$ (**21**)	69.77	5.3	**0.48**(1.01)
	$[Cu(L^4)Cl]$ (**22**)	53.93	3.15	**0.48**(1.11)
	$[Cu(L^4)CH_3COO]$ (**23**)	100	-	**1.95**(4.24)
	$[\{Cu(L^4)NO_3\}_2]$ (**24**)	**18.08**	1.96	**0.97**(1.05)
	$[Cu(L^4)H_2O]ClO_4$ (**25**)	100	-	**0.24**(0.47)
	HL^4	82.5	6.5	*-
Trolox		**33.3**	**1.03**	
Furacilline				**4.67**(23.60)

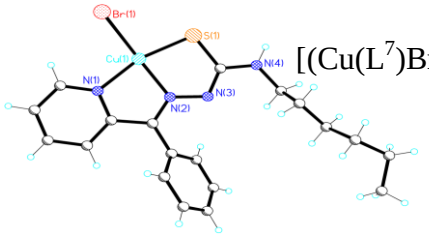
* * has no bactericidal or bacteriostatic effect at a concentration of 0.5 mg / mL

3.3 Coordination compounds of copper(II) with *N*(4)hexyl-3-thiosemicarbazone

The coordination combinations of Cu(II) and the thiosemicarbazones HL^5-HL^7 allowed to elucidate the mechanism of formation of the coordination compounds based on the thiosemicarbazones derived from the substituted 2-formylpyridine *N*(4). Thus, in the first stage of synthesis, the addition of thiosemicarbazones to the metal ion takes place, resulting in the successful isolation of a series of single crystals of coordination compounds **26, 32, 36 A,** and **37A** which demonstrate the first stage of the proposed synthesis mechanism (Figure 3.5 and 3.6).



$[(Cu(HL^7)Br_2]$ (36 A)



$[(Cu(L^7)Br]$ (36)

Fig. 3.5. Molecular structures of Cu (II) complexes based on HL^7

According to the proposed mechanism, in phase II the removal of the acid residue takes place simultaneously with the deprotonation of the corresponding thiosemicarbazone. As a result of the same series of complexes, it was possible to isolate single crystals after heating, adjust the pH or recrystallize from DMF (Figure 3.6).

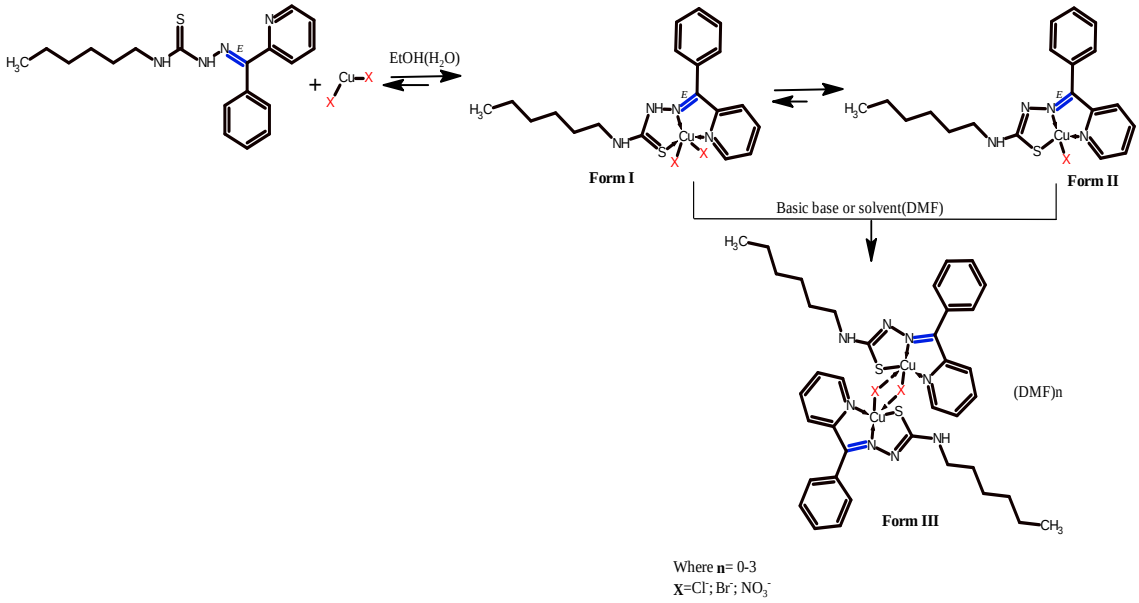


Fig. 3.6. The hypothetical mechanism for the formation of coordinating compounds 36/37 și 36. A/37.A

The tendency to form final structures is increased in the case of syntheses in which the temperature is higher than 60-75 °C, by using a reflux system. In such conditions, the optimal synthesis time varies from 60 minutes to 3 hours. The structure of the monomeric compounds obtained demonstrates that thiosemicarbazones behave as monodeprotonated tridentate ligand, coordinating to the central atom through the N-pyridine, N-azomethine, and S-thiol groups of atoms. After the elemental analysis of the coordination compounds, other physico-chemical analyzes were performed, which occurred in the confirmation of the monomeric structures. The study of single-crystal X-ray diffraction allowed the determination of the structures of all intermediate and final forms of addition products and in the form of corresponding coordination compounds.

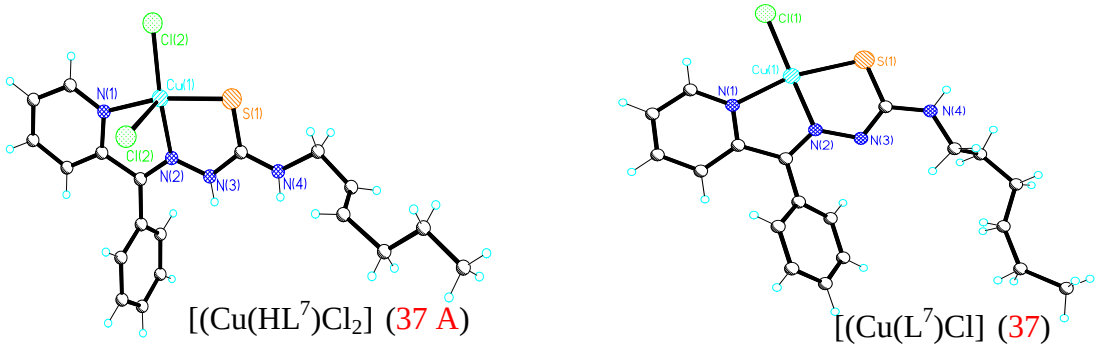
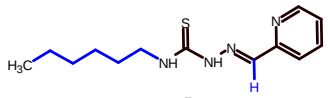
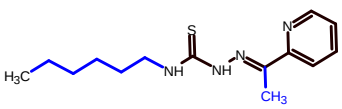
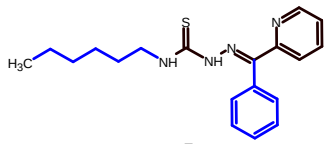


Fig. 3.7. Molecular structures of Cu (II) complexes based on HL^7

The study of the antioxidant properties of the complexes in question showed that the introduction of the hexyl fragment into the *N*(4) position of thiosemicarbazones did not lead to an improvement in antioxidant activity compared to cyclohexyl fragment analogues (Table 3.3).

Table 3.3. Antioxidant and antimicrobial activity of Cu(II) coordination compounds (26-40) based on *N*(4) hexyl thiosemicarbazones (HL^{5-7})

Ligand	Compounds	ABTS		*S.aureus*
		IC_{50}, μM	**SD, μM**	**MIC, μg/mL**(μM)
 **HL^5**	*$[Cu(HL^5)Br_2]$* (**26**)	100	-	**62.5**(128.1)
	$[Cu(HL^5)Cl_2]$ (**27**)	100	-	**31.25**(78.321)
	$[Cu(L^5)CH_3COO]$ (**28**)	91.3	8.0	**1.95**(5.05)
	$[Cu(L^5)NO_3]$ (**29**)	72.60	1.39	**1.95**(5.02)
	$[Cu(L^5)(H_2O)]ClO_4$ (**30**)	100	-	**0.48**(1.09)
	HL^5	**17.9**	4.2	**1.953**(7.397)
 **HL^6**	*$[Cu(HL^6)Br_2]$* (**31**)	100	-	**31.25**(62.25)
	$[Cu(HL^6)Cl_2]$ (**32**)	100	-	**15.62**(37.83)
	$[Cu(L^6)(H_2O)CH_3COO]$ (**33**)	88.6	0.69	**1.95**(4.67)
	$[\{Cu(L^6)NO_3\}_2]$ (**34**)	100	-	**1.95**(2.42)
	$[Cu(L^6)(H_2O)]ClO_4$ (**35**)	100	-	**0.97**(2.13)
	HL^6	**10.9**	0.6	**3.906**(14.050)
 **HL^7**	*$[Cu(L^7)Br]$* (**36**)	100	-	***-**
	$[Cu(L^7)Cl]$ (**37**)	100	-	-
	$[Cu(L^7)CH_3COO]$ (**38**)	100	-	-
	$[Cu(L^7)NO_3]$ (**39**)	100	-	**1.95**(4.20)
	$[Cu(L^7)(H_2O)]ClO_4$ (**40**)	100	-	**0.48**(0.93)
	HL^7	**23.3**	0.4	-
Trolox		**33.3**	**1.03**	
Furacilline				**4.67**(23.60)

** has no bactericidal or bacteriostatic effect at a concentration of 0.5 mg/mL*

3.4 Coordination compounds of copper(II) with *N*(4)*tert*-butyl-3-thiosemicarbazone

The synthesis of coordination compounds based on thiosemicarbazones **HL^{8-10}** highlighted the stereochemical possibility of ligands to form dimers through the non-participating electron pairs of the sulfur atom of the neighboring ligand, which is stabilized by hydrogen bonds.

Analysing Figure 3.6, it can be seen that in complexes **42-44** and **47** the central ion has a distorted square-pyramidal environment. The monodeprotone ligands **HL**^{8} and **HL**^{9} coordinate the tridentate, through the set of NNS atoms, in the case of the complexes **43** and **44**, the acetate ion and, respectively, the nitrate coordinate cleanliness the Cu(II) ion.

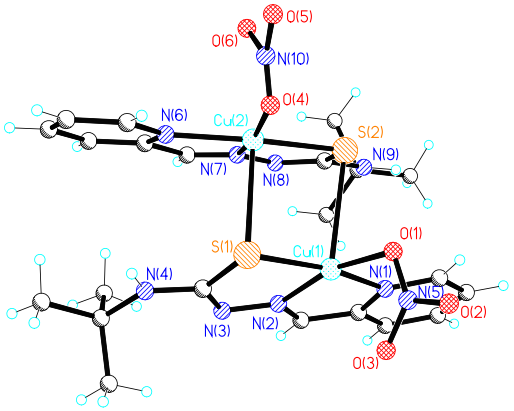


Fig. 3.8. Molecular structures of [{Cu(L^{8})NO$_3$}$_2$] (44)

For the coordination compounds **48** and **52,** it was possible to isolate the single crystals, for which with the X-ray diffraction on the single crystal the mononuclear structure in which the monodeprotonated ligand is coordinated tridentate to the Cu(II) ion was confirmed. The coordination number of the central ion is four and the geometry is square (Figure 3.10). The molar conductivity analysis (20-45 μS/cm) also confirms the non-electrolytic shape of complexes **48** and **52**. In the FT-IR spectra, there are asymmetric vibration bands of the COO^- monocoordinate groups at the central ion at 1601 cm^{-1} and vibration symmetrical COO^- at 1362 cm^{-1}. The difference between ν_{as} (COO^-) and ν_{as} (COO^-) is 239 cm^{-1}, which corresponds to the monodentate coordination of carboxylate clusters (Nakamoto, p. 258).

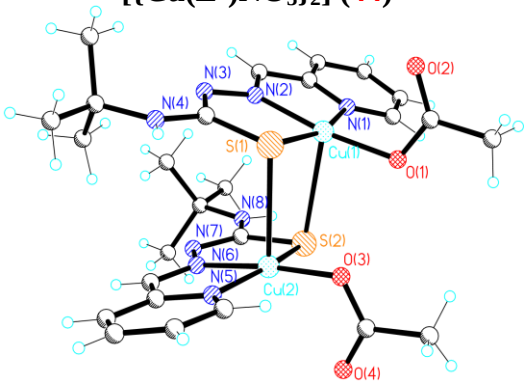


Fig. 3.9. Molecular structures of [{Cu(L^{8})CH$_3$COO}$_2$] (43)

The study of the antioxidant properties of the complexes in this series showed that the best antioxidants are **47** and **49** based on thiosemicarbazone HL^{9} with chloride ions or nitrate coordinated to metal ions.

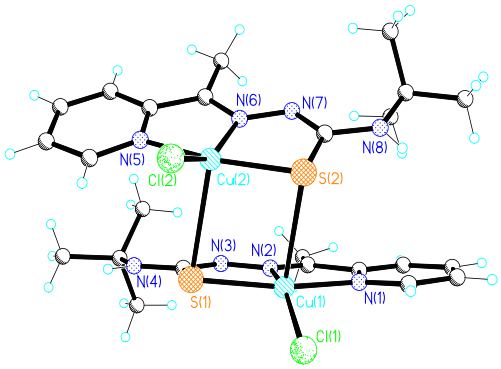


Fig. 3.10. Molecular structures of [{Cu(L^{9})Cl}$_2$] (47)

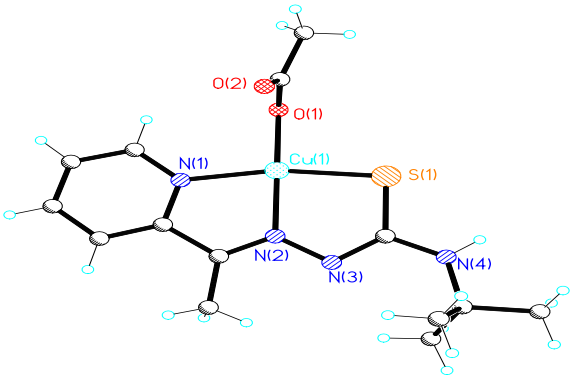
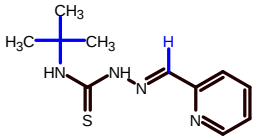
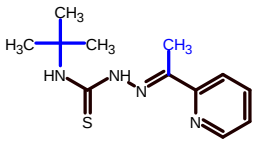
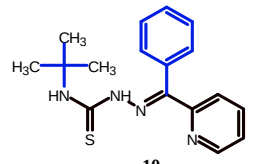


Fig. 3.11. Molecular structures of [(Cu(L^{9})CH$_3$COO] (48)

Table 3.4. Antioxidant and antimicrobial activity of Cu(II) coordination compounds (41-55) based on *N*(4) *tert*-butyl thiosemicarbazones (HL^{8-10})

Ligand	Compounds	ABTS		*S.aureus*
		IC_{50}, μM	SD, μM	MIC, μg/mL(μM)
 **HL^8**	*[{Cu(L^8)Br}$_2$]* (**41**)	75.40	1.75	**0.97**(1.28)
	[{Cu(L^8)Cl}$_2$] (**42**)	89.90	1.55	**1.95**(2.92)
	[{Cu(L^8)CH_3COO}$_2$] (**43**)	71.10	2.80	**1.95**(2.72)
	[{Cu(L^8)NO_3}$_2$] (**44**)	100	-	**0.48**(0.67)
	[Cu(L^8)(H_2O)]ClO_4 (**45**)	100	-	**1.95**(4.69)
	HL^8	**18.50**	2.2	**0.97**(3.71)
 **HL^9**	*[{Cu(L^9)Br}$_2$]* (**46**)	100	-	**1.95**(2.48)
	[{Cu(L^9)Cl}$_2$] (**47**)	**16.40**	0.90	**1.95**(2.80)
	[Cu(L^9)CH_3COO] (**48**)	48.90	1.80	**1.95**(5.25)
	[Cu(L^9)NO_3] (**49**)	**23.80**	1.90	**0.48**(1.30)
	[Cu(L^9)(H_2O)]ClO_4 (**50**)	100	-	**1.95**(4.54)
	HL^9	**12.20**	0.70	**3.90**(15.62)
 **HL^{10}**	*[Cu(L^{10})Br]* (**51**)	97.70	7.70	**0.97**(2.14)
	[Cu(L^{10})Cl] (**52**)	98.90	12.70	**0.97**(2.38)
	[Cu(L^{10})CH_3COO] (**53**)	55.30	5.40	**1.95**(4.50)
	[Cu(L^{10})NO_3] (**54**)	66.20	4.10	**0.48**(1.11)
	[Cu(L^{10})(H_2O)]ClO_4 (**55**)	100	-	**1.95**(3.97)
	HL^{10}	**26.10**	0.80	**7.81**(25.03)
Trolox		**33.30**	**1.03**	
Furacilline				**4.67**(23.60)

In the series of complexes with thiosemicarbazones **HL^{8-10}** the tendency to IC_{50} of inhibition of cation-radicals of $ABTS^{\cdot+}$ between mononuclear and binuclear complexes was not observed.

In the study of gram-positive and gram-negative microorganisms, thiosemicarbazones **HL^{1-10}** showed a different behavior of inhibiting the multiplication of microorganisms. One of the defining factors significantly affecting antibacterial activity is the *N*(4) thiosemicarbazone substituent.

The influence of the anion in the studied complexes (**1-55**) is decisive in terms of biological antimicrobial and antifungal activities and decreases in the following sequence of the acid residue: $Br^- \sim Cl^- > ClO_4^- > NO_3^- > CH_3COO^-$.

The results of the anticancer activity by the MTT method, referring to the initial thiosemicarbazones, are presented in tables 3.11 and 3.12.

Tablel 3.11 Anticancer activity of complexes 5, 7 și HL^1

Compound	MDCK	HeLa	BxPc-3	RD
	%, inhibition	%, inhibition	%, inhibition	%, inhibition
$[Cu(L^1)(H_2O)_2]ClO_4$ (**5**)	**14.8**±8.3	**-5.5**±9.4	**18.9**±6.8	**14.4**±3.4
$[Cu(L^2)(H_2O)Cl]$(**7**)	**0.4**±3.2	**7.6**±0.5	**14.6**±4.6	**-8.9**±0.1
HL^1	**93.7**±6.5	**84.0**±6.2	**60.4**±3.6	**99.6**±1.0
DOX	56.0±2.6	49.8±6.6	76.6±0.9	47.3±1.6

Note: the values are represented as the average of the experiments repeated three times; The analysis was performed at a concentration of 100 μM; DOX- Doxorubicin

Table 3.12 Anticancer analysis of Cu(II) coordination compounds based on thiosemicarbazones (HL^{1-2})

Compound	HEp-2	BxPC-3
	%*, inhibition	%, inhibition
$[Cu(L)^1Cl]$ (**2**)	44.1±1.8	58.1±5.1
$[Cu(L^1)(H_2O)]NO_3$ (**4**)	23.7±6.1	44.7±2.8
$[Cu(L^1)(H_2O)_2]ClO_4$ (**5**)	19.7±1.5	3.9±0.5
$[Cu(L^2)Br]$ (**6**)	18.6±1.5	13.3±0.6
$[Cu(L^2)(H_2O)Cl]$(**7**)	16.0±2.1	3.4±0.7
$[Cu(L^2)(H_2O)]ClO_4$ (**10**)	18.9±3.2	21.9±1.1
HL^1	**64.9**±3.2	**60.4**±3.6
HL^2	**66.1**±2.8	**61.6**±2.2
HL^3	**82.8**±3.7	**97.8**±4.9
cis-platin	68.2±1.9	78.5±1.2

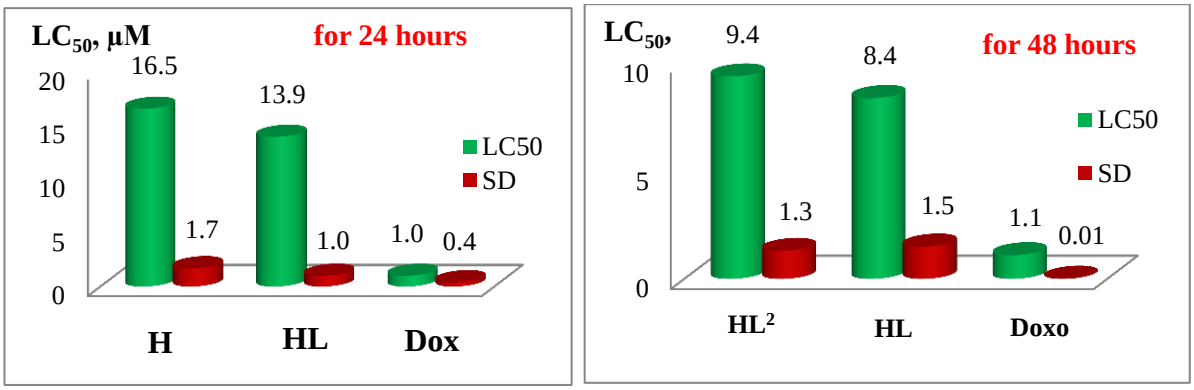
*Concentration 100 μM; *Values are average (standard deviations obtained from at least three independent experiments).*

The sequence of decreasing anticancer activities for the series of coordination compounds of Cu(II) with thiosemicarbazone **HL^2** depending on the rest of the acid is as follows: $Cl^- > Br^- > NO_3^- > ClO_4^-$.

Table 3.10. Anticancer activity of the coordination compound $[Cu(L^3)Cl]$ (**17**)

Compound	IC_{50}, μM				
	HEp-2	BxPC-3	RD	L20B	MDCK
$[Cu(L^3)Cl]$ (**17**)	**1.09**±0.01	**0.170**±0.002	**0.70**±0.02	**0.30**±0.10	**1.00**±0.50
cis-platin	**60**±9	**11.2**±1.2	**13.4**±2.0	**16.3**±1.8	**30.9**±1.1

The study of the toxicity of organic compounds is essential in order to be able to draw conclusions about the possibility of being recommended for preclinical practice. Thus, the most active compounds that show antifungal and antimicrobial activities in *in vivo* studies and significant antioxidant potential in relation to Trolox are selected.



LC_{50}- semimaximal lethal killing concentration of 50% of Paramecium caudatum.

Fig. 3.12. Determination of toxicity (*Paramecium caudatum*) at 24 h and 48 h

Table 3.14. Eco-toxicity of thiosemicarbazones HL^1-HL^{10} and of some coordination compounds of 3*d* metal ions

Thiosemicarbazone	LC_{50}, µM	SD
HL^1	**15.55**	1.45
HL^2	0.12	0.05
HL^3	3.53	0.80
HL^4	0.29	0.01
HL^5	0.67	0.01
HL^6	0.16	0.01
HL^7	1.52	0.32
HL^8	1.23	0.08
HL^9	0.58	0.04
HL^{10}	3.27	0.10
Doxo	**3.27**	**0.30**

Compound	LC_{50}, µM	SD
*[**Cu**$(L)^1Cl]$* (**2**)	**100**	-
*[**Cu**$(L^1)(H_2O)]NO_3$* (**4**)	**100**	-
*[**Cu**$(L^2)Br]$* (**6**)	4.40	0.96
*[**Cu**$(L^2)(H_2O)Cl]$*(**7**)	3.50	0.91
*[**Cu**$(L^2)NO_3]$* (**9**)	2.60	0.74
*[**Cu**$(L^2)(H_2O)]ClO_4$* (**10**)	1.40	0.24
*[**Co**$(L^2)_2]Cl$* (**12**)	0.60	0.13
*[**Ni**$(L^2)Cl]$*(**11**)	6.10	0.42
*[**Fe**$(L^2)_2]Cl$*(**13**)	4.60	0.62
*[**Mn**$(L^2)_2]$* (**14**)	0.090	0.001
*[**Zn**$(L^2)(H_2O)Cl]$* (**15**)	0.30	0.01
Doxo	**3.27**	**0.30**

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. Ten thiosemicarbazones **HL$^{1-10}$** were obtained, of which **6** are new, with four different substituents in position *N*(4) such as: phenylacetamide, cyclohexyl, hexyl, and *tert*-butyl. Based on copper(II), nickel(II), cobalt(III), iron(III), manganese(II), and zinc(II) ions, **55** coordination combinations were obtained, of which **42** are new, including **6** binuclear coordination compounds and **49** mononuclear complexes. Thiosemicarbazones **HL$^{1-10}$** coordinate at the central ion through the pyridine nitrogen atom, of azomethine nitrogen and thionic or thiol sulfur atom, behaving as an **NNS**-type tridentate ligand. In the series of coordination compounds of Cu(II), **21** molecular structures were determined and characterized. For the first time, the molecular structure was determined for **5** thiosemicarbazones by single-crystal X-ray diffraction.

2. For almost all copper(II) chlorides and bromides, the tendency to form non-electrolyte mononuclear compounds based on *N*(4)-hexylthiosemicarbazones has been demonstrated, in which the ligands are unprotonated. The exception is the coordination compound **16**, which is of the cation-anion type, having a bromide ion in the outer sphere.

3. For the *N*(4)-hexylthiosemicarbazone-based coordination compounds, a two-step synthesis mechanism has been demonstrated: the initial addition of thiosemicarbazone to the metal ion and the subsequent removal of the acid residue.

4. The antioxidant activity of the **HL$^{1-10}$** series of thiosemicarbazones was first investigated by the $ABTS^{\cdot+}$ method, the results of which showed that the most notable antioxidant potential is the **HL^{2}** ligand (IC_{50} =5.1±0.8μM), which is 7 times more active compared to the reference substance Trolox. Coordination compounds with the same thiosemicarbazones have comparable antioxidant properties, the highest value being found in complexes **14** (IC_{50}= 6.7±0.6μM) and **5** (IC_{50}=10.1±0.3μM). The correlated antioxidant activity according to the four analyzed factors decreases as follows:

- central ion: Mn^{2+}> Ni^{2+}> Zn^{2+}> Cu^{2+}>> Fe^{3+}> >>> Co^{3+}.
- acid residue: Br^{-} ~ Cl^{-}> CH_3COO^{-}> ClO_4^{-}> NO_3^{-}.
- substitute in position *N*(4) of 2-acetylpyridine thiosemicarbazones: phenylacetamide> hexyl> *tert*-butyl> cilohexyl
- substitute in position *N*(1) of thiosemicarbazones: CH_3 > H> C_6H_5.

5. Antimicrobial analysis of ligands showed that the most active thiosemicarbazone is **HL^{3}** based on cyclohexyl with 2-acetylpyridine (MIC of 0.061 μg/mL (0.2328 μM)), which is 76 times more active than Furacillin on *S. Aureus*, and the antifungal activity of **HL^{3}** is 18 times higher than Miconasol.

In the thiosemicarbazone series, the antimicrobial activity on *S.aureus* decreases in the following series: HL^3> HL^8> HL^5> HL^6 = HL^9> HL^{10}> HL^1 = HL^2> HL^4 = HL^7. The antimicrobial activity of the complexes with these thiosemicarbazones according to the four factors analyzed decreases as follows:

- central ion: Cu^{2+}> Co^{3+}> Zn^{2+}> Fe^{3+} ~ Mn^{2+}> Ni^{2+}.
- acid residue: Br^- ~ Cl^-> NO_3^- ~ ClO_4^-> CH_3COO^-.
- substitute in position *N*(4) of 2-acetylpyridine thiosemicarbazones: cilohexyl> *tert*-butyl> hexyl> phenylacetamide
- substitute in position *N*(1) of thiosemicarbazones: H ~ CH_3> C_6H_5.

6. The anticancer activity of copper(II) complexes according to the three factors analyzed decreases as follows:

- acid residue: Cl^-> Br^-> ClO_4^-> NO_3^-.
- substitute in position *N*(4) of 2-acetylpyridine thiosemicarbazones: cilohexyl> phenylacetamide
- substitute in position *N*(1) of thiosemicarbazones: CH_3> H> C_6H_5.

7. The toxicity analysis showed that the least toxic is thosemicarbazone HL^1 which is LC_{50} = 15.5 μM, compared to Doxorubicin LC_{50} = 3.2 μM. In the thiosemicarbazone series, toxicity increases in the following range: HL^1 <HL^3 <HL^{10} <HL^7 = HL^8 <HL^5 <HL^9 <HL^4 <HL^6 <HL^2. The determination of the toxicity of the coordination compounds according to the four factors analyzed increases as follows:

- central ion: Zn^{2+}>> Ni^{2+}> Fe^{3+}> Cu^{2+}> Co^{3+}> Zn^{2+} >>> Mn^{2+}
- acid residue: Br^->>> CH_3COO^-> NO_3^-> ClO_4^-> Cl^- ~ Br^-
- substitute in position *N*(4) of 2-acetylpyridine thiosemicarbazones: phenylacetamide> cilohexyl> tert-butyl> hexyl
- substitute in position *N*(1) of thiosemicarbazones: H ~ CH_3> C_6H_5.

Recommendations

- It is proposed to use the coordination compounds of some 3*d* metals with thiosemicarbazones *N*(4) -substituted based on 2-formylpyridine derivatives, which show an antimicrobial potential at concentrations of ng / mL.
- The implementation of the results of the 2 patents as well as of the patent application for the expansion of the arsenal of inhibitors of the fungi of the species *Candida albicans* and inhibitors of the gram-negative bacteria *Acinetobacter baumannii* with high antifungal and antimicrobial activity.
- It is recommended to carry out a more in-depth study of the anticancer and antimicrobial activities of the substances studied in order to exclude mutagenic, teratogenic effects *in vivo*.
- The results of the thesis can be used in the normative courses within the undergraduate cycle (Organic Chemistry II, Heterocyclic Compounds, Biopharmaceutical Chemistry) and the master cycle.

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Brevete și cereri de brevet

1. GULEA, Aurelian; **RUSNAC, Roman**; BĂLAN, Greta; RUSNAC, Anna; NICOLENCO, Nicoleta; ȚAPCOV, Victor. *Utilizarea nitrato-[N-ciclohexil-N'-(piridin-2-ilmetiliden)carbamohidrazontioato]cupru în calitate de inhibitor al proliferării bacteriilor din specia Acinetobacter baumannii*. Brevet de invenție 4761(13)B1, Int. Cl.: A61K 31/30, A61K 31/4402, A61K 31/175, A61P 31/04, C07F 1/08, C07D 213/48, C07C 337/08. Universitatea de Stat din Moldova. Nr. depozit a 2020 0019. Data depozit 05.03.2020. Publicat 31.07.2021. In: BOPI. 2021, nr. 7, pp. 37. Disponibil: http://www.db.agepi.md/Inventions/details/a%202020%200019
2. GULEA, Aurelian; BURDUNIUC Olga; BALAN, Greta; **RUSNAC, Roman**; ȚAPCOV Victor; RUDIC, Valeriu. *Utilizare a N-ciclohexil-2-[1-(piridin-2-il)]hidrazincarbotioamidei în calitate de inhibitor al proliferării microorganismelor gram-pozitive și fungilor Candida albicans.* Brevet de invenție 4648(13) B1, Int.Cl: A61K 31/175, A61K 31/4402, A61P 31/10, A61P 31/04, C07C 337/08, C07D 213/16. Universitatea de Stat din Moldova. Nr. depozit a 2018 0079. Data depozit 12.09.2018. Publicat 30.09.2019. In: BOPI. 2019, nr. 9, pp. 40-41. Disponibil: http://www.db.agepi.md/Inventions/details/a%202018%200079

3. GULEA, Aurelian; **RUSNAC, Roman**; ȚAPCOV, Victor; BĂLAN, Greta. Nitratul de bis{[(ciclohexilamino)fenil(piridin-2-il)metilidenhidrazono]metansulfinato-*N,N',S*}fier(III), care manifestă activitate antimicrobiană față de bacteriile din specia *bacillus cereus*. Cerere de brevet. Nr. A 2021 0015 din 2021.03.29.

ADNOTARE

Rusnac Roman: ”Designul și sinteza compușilor biologic activi ai unor metale 3*d* cu tiosemicarbazone *N*(4)-substituite ale derivaților 2-formilpiridinei”, teză de doctor în științe chimice, Chișinău, 2022. Teza constă din: introducere, 3 capitole, concluzi generale și recomandări, referințe bibliografice cu 181 surse, 10 anexe, 123 pagini, 70 figuri, și 33 de tabele. Rezultatele obținute sunt publicate în 30 de lucrări științifice (6 articole în reviste naționale, 1 articol în revistă internațională, 23 teze la conferințe și 2 brevete de invenție și 1 cerere de brevet de invenție).

Cuvinte-cheie: tiosemicarbazone, compuși coordinativi, metale 3*d*, activitate biologică, RMN-FTIR, difracție cu raze X pe monocristal.

Domeniul de studiu: chimie coordinativă

Scopul și obiectivele tezei: sinteza și caracterizarea fizico-chimică a unor compuși coordinativi în baza ionilor Cu(II), Ni(II), Fe(III), Co(III), Zn(II), Mn(II) cu diferite *N*(4)-*ciclohexil (fenilacetamidă; terț-butil*) tiosemicabazone derivate de la 2-formilpiridină; *screening-ul* activităţilor antimicrobiene și antifungice, anticancer și antioxidative a compușilor coordinativi sintetizați precum și determinarea relației structură-activitate; sinteza *N*(4)-*ciclohexil (fenilacetamidă; terț-butil*) tiosemicabazonelor derivate de la 2-formilpiridină; sinteza compușilor coordinativi ai Cu(II), Ni(II), Fe(III), Co(III), Zn(II), Mn(II) cu tiosemicarbazone *N*(4)-substituite; caracterizarea fizico-chimică compușilor organici și anorganici obținuți prin intermediul metodelor moderne de cercetare: spectroscopia RMN ^{1}H, ^{13}C, ^{15}N, REP, FT-IR, spectrofotometria UV-vis, difracția cu raze X, spectroscopia de masă, codunctometria în soluție, analiza elementală; cercetarea proprietăților antimicrobiene, antifungice și antioxidative ale compușilor atât intermediari cât și finali ; Elucidarea corelației structură-activitate și propunerea unor compușii sintetizați spre studiul biologice avansat .

Noutatea și originalitatea ştiințifică constă în sinteza a 55 compuși coordinativi, inclusiv 6 complecși binucleari și 49 de compuși coordinativi mononucleari. Pentru prima dată au fost propus un mecanism al formări combinațiilor coordinative în baza ionuluii de cupru(II) și studiate proprietățile antimicrobiene și antifungice ale tuturor compușior sintetizați atât intermediari cât și finali.

Problema științifică soluționată. Au fost stabilite procedee optime de obținere a compușilor coordinativi prin metode clasice optimizate de sinteză. Au fost obținute tiosemicarbazone funcționazite cu diferiți substituenți în poziția *N*(4) cu lipofilitate majorată. Majoritatea compușilor coordinativi sintetizați manifestă o solubilitate bună în etanol și apă.

Semnificația teoretică și valoarea aplicativă a lucrării. Teza data contribuie la: lărgirea clasei de substanțe biologic active pe baza tiosemicarbazonelor *N*(4) substituite; identificarea influenței ionului central asupra proprietăților biologice; înțelegerea corelației dintre lipofilitatea radicalilor în poziția *N*(4) a tiosemicarbazonelor derivate de la 2-formilpiridină.

Aplicabilitatea acestei lucrări o reprezintă compușii coordinativi cu activitate antimicrobiană selectivă asupra microorganismelor gram-pozitive.

АННОТАЦИЯ

Руснак Роман: «Дизайн и синтез биологически активных соединений 3*d*-металлов с тиосемикарбазонами *N*(4)-замещенных производных 2-формилпиридина», диссертация на соискание ученой степени доктора химических наук, Кишинев, 2022. Диссертация состоит из введения, трех глав, в которых представлены обзор исследований, имеющихся в литературе, и собственный вклад, основывающийся на экспериментально полученных результатах, общих выводов и рекомендаций, библиографии из 183 наименований, 123 страницы основного текста, 33 таблиц, 10 приложений и 70 рисунков. Полученные результаты опубликованы в 30 научных работах (6 статей в национальных журналах, 1 статья в международном журнале, 23 тезиса конференций, 2 патента и 1 заявка на патенты).

Ключевые слова: тиосемикарбазоны, координационные соединения, 3d-металлы, биологическая активность, ИК-Фурье спектроскопия, ЯМР спектроскопия, дифракция рентгеновских лучей на монокристаллах.

Область исследования: Координационная Химия.

Цель и задачи работы: синтез и физико-химическая характеристика некоторых координационных соединений на основе ионов металлов Cu(II), Ni(II), Fe(III), Co(III), Zn(II), Mn(II) с различными *N*(4)-циклогексил (фенилацетамидом; *трет*-бутил) тиосемикабазонами производных 2-формилпиридина; скрининг антимикробной,противогрибковой, противоопухолевой и антиоксидантной активности синтезированных координационных соединений; выявление взаимосвязи структура-активность; синтез *N*(4) -циклогексил (фенилацетамида; *трет*-бутил) тиосемикабазонов, производных от 2-формилпиридина; синтез координационных соединений Cu(II), Ni(II), Fe(III), Co(III), Zn(II), Mn(II) с *N*(4) -замещенными тиосемикарбазонами; физико-химическая характеристика полученных органических и неорганических соединений современными методами анализа: спектроскопия ЯМР ^{1}H, ^{13}C, ^{15}N, ЭПР; ИК, УФ-видимая спектрофотометрия, дифракция рентгеновского излучения, масс-спектроскопия, кодунктометрия в растворе, элементный анализ; исследование противомикробных, противогрибковых и антиоксидантных свойств как промежуточных, так и конечных полученных соединений; выявление корреляции структура-активность и предложение некоторых синтезированных соединений для углубленного изучения биологических исследований.

Научная новизна и оригинальность заключается в синтезе 55 координационных соединений, в том числе 6 биядерных координационных соединений и 49 одноядерных координационных соединений. Впервые предложен механизм образования координационных соединений на основе ионов меди(II) и изучены антимикробные и противогрибковые свойства всех синтезированных соединений, как промежуточных, так и конечных. **Научная проблема решена.** Установлены оптимальные условия получения координационных соединений классическими методами синтеза. Были получены тиосемикарбазоны, функционализированные различными заместителями в положении *N*(4) с повышенной липофильностью. Большинство синтезированных координационных соединений обладают хорошей растворимостью в этаноле и воде.

Теоретическая значимость и прикладное значение работы. Диссертацияспособствует: выделению класса биологически активных веществ на основе замещенных тиосемикарбазонов *N*(4); выявление влияния центрального атома на биологические свойства; понимание корреляции между радикальной липофильностью в положении *N*(4) и тиосемикарбазонами, производными 2-формилпиридина.

Область применения этой работы - координационные соединения с селективной антимикробной активностью в отношении грамположительных микроорганизмов.

RUSNAC ROMAN

DESIGN AND SYNTHESIS OF BIOLOGICAL ACTIVE COMPOUNDS OF 3*d* METALS WITH THIOSEMICARBAZONE *N*(4)-SUBSTITUTES OF 2-FORMYLPYRIDINE DERIVATIVES

141.02 Coordination Chemistry

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