STATE UNIVERSITY OF MOLDOVA
DOCTORAL SCHOOL IN BIOLOGICAL, GEONOMIC, CHEMICAL AND TECHNOLOGICAL SCIENCES

As manuscript
U.D.C.: 544.142.3:546.562:547.497.1(043)

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SYNTHESIS, STRUCTURE, AND BIOLOGICAL PROPERTIES OF COPPER COMPLEXES WITH POLIDENTATE LIGANDS BASED ON 4-ALLYLTHIOSEMICARBAZONES SOLUBLE IN WATER

141.02 – COORDINATION CHEMISTRY

Abstract of the doctoral thesis in chemical sciences

CHISINAU, 2023

The thesis was elaborated at the Doctoral School in Biological, Geonomic, Chemical and Technological Sciences ***of the Moldova State University, at the Faculty of Chemistry and Chemical Technology, Department of Chemistry, research laboratory «Advanced Materials in Biofarmaceutics and Technics».***

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The dissertation defense will take place on 20.10.2023 at 14:00 , in the meeting of the Doctoral Commission within the Doctoral School of in Biological, Geonomic, Chemical and Technological Sciences, Moldova State University (http://www.usm.md), 60, A. Mateevici str., Chisinau, room no. 317.

The PhD thesis and its summary may be consulted at the National Library of the Republic of Moldova, Central Scientific Library „Andrey Lupan" (Institute), Moldova State University Library (MD 2009, 60, A. Mateevici str., Chisinau), on the website of CNAA (http://www.cnaa.md) and on the website of the Moldova State University (http://www.usm.md).

Summary was sent on 19.09.2023.

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CONCEPTUAL GUIDELINES OF RESEARCH

Actuality and importance of the study. Coordination compounds are on the border between medicine and inorganic chemistry and are directly related to the discovery of new drugs. [1]. Our body and biological system contain hundreds of inorganic complexes and metals in the form of various enzymes and protein cofactors necessary for normal biological processes. It is the biological significance and their essential role in maintaining vital biological processes that have always attracted chemists to work in the field of synthesis and application of coordination compounds.

Thiosemicarbazones and their coordination compounds have structural diversity, different coordination patterns, and potential biological properties. Thiosemicarbazones have been used in medicine since the 20th century. In the 1950s, it has been reported that thiosemicarbazones are effective against tuberculosis and leprosy [2]. The antiviral properties of thiosemicarbazones led to the introduction of Metisazone for the treatment of smallpox on the market [3]. These ligands also exhibit antitumor properties, on the basis of which Triapin was developed (3-aminopyridine-2-carboxaldehyde thiosemicarbazone), an anticancer agent, which reached phase II trials on many cancer cell lines [4]. Metal coordination compounds with thiosemicarbazones manifest anticarcinogenic [5], antibacterial [6], anti-HIV [7], fungicidal [8], antiviral [9], antifungal [10], and antitumor [11] properties. The probable mechanism of action of such complexes includes a modification of lipophilicity, which regulates penetration into the cell, which changes when thiosemicarbazones are coordinated to metal ions. Therefore, in most cases, the coordination compounds are more active than the initial thiosemicarbazones.

Allyl isothiocyanate is a natural compound found in cruciferous plants such as horseradish and mustard and has antimicrobial activity. In addition, it is produced on an industrial scale, so its use is not difficult. Thiosemicarbazide, obtained on the basis of allyl isothiocyanate, easily enters into condensation reactions with various ketones and aldehydes, forming 4-allylthiosemicarbazones and their complexes. At the Laboratory of Advanced Materials for Biopharmaceutics and Technics at the Moldova State University, 4-allylthiosemicarbazone of salicylaldehyde and its mixed-ligand copper(II) coordination compounds were synthesized [12, 13]. The complexes showed a wide range of biological activity: anticancer, antimicrobial, antifungal and antioxidant. In all cases, they were superior in activity to 4-allylthiosemicarbazone of salicylaldehyde. However, thiosemicarbazone itself had low solubility in water, and its coordination to the copper(II) atom followed by the introduction of amines into the inner sphere of the complex did not lead to an increase in the solubility of the resulted complexes. Solubility in water is of top priority in the development of a sufficiently safe and effective dosage form, since the preparation, absorption and even biological activity of the

drug depend on its solubility. Therefore, it is of interest to study how the introduction of substituents into the benzylidene fragment of 4-allylthiosemicarbazone of salicylaldehyde will affect the activity of mixed-ligand copper(II) coordination compounds, as well as the water solubility of the obtained compounds.

Pyruvic acid is a natural compound found in all living organisms, as well as in *Populus tremula*, *Macrobrachium nipponense* and other plants that grow on the territory of the Republic of Moldova. At the Laboratory of Advanced Materials for Biopharmaceutics and Technics at the Moldova State University, pyruvic acid 4-allylthiosemicarbazone, its 3*d* metal complexes, as well as copper(II) mixed-ligand complexes were synthesized [14]. The study of their antimicrobial and antifungal activity showed that the compounds have low activity, the coordination of pyruvic acid 4-allylthiosemicarbazone to metal atoms leads to an increase in the activity of the complex, and the introduction of *N*-heteroaromatic bases into the inner sphere of copper(II) complexes leads to an even greater increase in activity. The solubility of pyruvic acid 4-allylthiosemicarbazone in water is more than 10 mg/mL, however, its coordination to metal atoms leads to a decrease in solubility up to its complete absence.

Pyruvic acid amides have various types of biological activity, for example, *N*,*N*-diethyl-2-oxopropanamide has an anti-inflammatory and anti-excitotoxic effect [15]. It effectively blocks neutrophils that build up around damaged brain tissue and exacerbate tissue damage during a stroke. *N*,*N*-diisopropyl-2-oxopropanamide exhibits anti-inflammatory and neuroprotective activity [16]. Pyruvic acid amides thiosemicarbazones and their complexes are little described in the literature, and their biological activity is practically not studied [17-19]. Therefore, it is of interest to study the biological activity of pyruvic acid amides 4-allylthiosemicarbazones and their complexes, to establish the effect of the appearance of an amide fragment in the composition of this thiosemicarbazone, and to study the change in the water solubility of the obtained compounds.

The aim of the study:

Discovery of new antimicrobial, antifungal and antioxidant agents with increased solubility based on mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives and 4-allylthiosemicarbazones of pyruvic acid amides.

The objectives of the thesis:

1. Synthesis of mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives;
2. Finding conditions for the synthesis of pyruvic acid amides;
3. Synthesis of 4-allylthiosemicarbazones of pyruvic acid amides;

4. Synthesis of coordination compounds of some 3*d* metals with 4-allylthiosemicarbazones of pyruvic acid amides;

5. Determination of the composition, structure, and physicochemical properties of the synthesized compounds;

6. Study of antioxidant, antimicrobial and antifungal activities of synthesized substances.

The research hypothesis. Based on the analysis of literature sources, it is assumed that the introduction of *N*-heteroaromatic bases into the inner sphere of copper(II) coordination compounds of 4-allylthiosemicarbazones of substituted salicylaldehyde, the introduction of substituents in the benzylidene fragment in the composition of 4-allylthiosemicarbazone of salicylaldehyde, the appearance of an amide fragment in the composition of 4-allylthiosemicarbazone of pyruvic acid will lead to an increase in biological activity of these thiosemicarbazones and their complexes. It will also affect the water solubility of the compounds obtained, making them more soluble.

Methodology and justification of chosen research methods

In the process of the study, 4-allylthiosemicarbazones of substituted salicylaldehyde were synthesized and conditions were found for the synthesis of pyruvic acid amides and 4-allylthiosemicarbazones of pyruvic acid amides. The purity and structure of the obtained compounds were determined by ^{1}H, ^{13}C NMR. NMR study was carried out at the Institute of Chemistry, Republic of Moldova. For all thiosemicarbazones, the melting point was determined by the capillary method. For fine crystals of 4-allylthiosemicarbazones and their coordination compounds obtained by recrystallization from methanol, ethanol, dimethylformamide and a mixture of acetone and acetonitrile, an X-ray diffraction analysis was carried out, which was performed at the Institute of Applied Physics, Republic of Moldova. For those substances for which fine crystals were not obtained, a comparative analysis of the FT-IR spectra for 4-allylthiosemicarbazones and their complexes was carried out. Registration of FT-IR spectra was carried out at the Laboratory of Advanced Materials in Biopharmaceutics and Technics at the Moldovan State University. To determine the composition of coordination compounds for each compound, an analysis for the metal was performed, the mass fraction of metals in the compounds was determined by the titrimetric method. The molar electrical conductivity of the complexes was determined in methanol or dimethylformamide in an electrochemical cell with platinum electrodes using a R-38 rheochord bridge. Antimicrobial, antifungal and antioxidant activity was studied for all synthesized compounds. The study of antimicrobial and antifungal activity was carried out in the Microbiological Laboratory of the National Agency of Public

Health, Republic of Moldova. The study of antioxidant activity was carried out at the Institute of Zoology, Republic of Moldova.

Novelty and scientific originality

The 89 new coordination compounds were synthesized and described; the influence of substituents in the benzylidene fragment, the nature of the central atom, the nature of the acid residue, the nature of *N*-heteroaromatic bases in the inner sphere of the complexes on the physicochemical properties and biological activity of the synthesized substances were studied.

Theoretical significance of the work

The results of this study can be used in the future to search for new coordination compounds with high antifungal, antimicrobial and antioxidant activity and solubility in water, by identifying the relationship between the structure of the substance and its activity, and determining the effect of an additional biologically active ligand in the composition of coordination compounds on the synergism of their biological properties. In the future, the results of this study can supplement the material of special courses on Biopharmaceutical Chemistry and Biochemistry.

The practical significance of the work is to obtain new potential antimicrobial, antifungal and antioxidant agents. The results of this study were included in **16 scientific publications**, of which **6 scientific articles** (4 articles in international journals with an impact factor and 2 scientific articles in a category B journal), **10 abstracts** at international and national conferences. **1 Patent** of the Republic of Moldova was received: a compound with a bacteriostatic effect against *Bacillus cereus* and *Bacillus subtilis*. **4** gold medals were received at the salons of inventions.

The results obtained by the author, which contribute to the solution of an important scientific problem

New potential antimicrobial, antifungal and antioxidant agents based on mixed-ligand coordination compounds of copper(II) 4-allylthiosemicarbazones of salicylaldehyde derivatives and coordination compounds of some 3*d* metals of 4-allylthiosemicarbazones of pyruvic acid amides were obtained. Compounds with high water solubility were identified, as well as compounds that are superior in activity to the substances that were used as standards (Tetracycline, Fluconazole and Trolox).

Implementation of scientific results. New compound with bacteriostatic action against *Bacillus cereus* and *Bacillus subtilis* was patented.

THESIS CONTENT

The **Introduction** describes the relevance of the research topic, the purpose and objectives of the research, scientific hypothesis, research methodology, scientific novelty, solved scientific problem, theoretical and practical significance of the work, approbation and implementation of the results.

1. COORDINATION COMPOUNDS OF SOME 3*d* METALS WITH THIOSEMICARBAZONES

The **first chapter** is a literature review, which consists of four paragraphs. The first paragraph provides an overview of thiosemicarbazones, with a focus on 4-allylthiosemicarbazones. The second paragraph describes some 3*d* metals coordination compounds with N^4-substituted thiosemicarbazones of substituted salicylaldehyde, their structure, synthesis, and various types of biological activity. The third paragraph describes mixed-ligand coordination compounds with N^4-substituted thiosemicarbazones of substituted salicylaldehyde, their preparation, structure, and the effect of introducing an *N*-heteroaromatic base into the inner sphere of the complexes on their biological activity. The fourth paragraph describes some 3*d* metals coordination compounds with oxoacids thiosemicarbazones; special attention is paid to pyruvic acid, its thiosemicarbazones, and their complexes. Pyruvic acid amides, thiosemicarbazones of pyruvic acid amides and their complexes are also described.

2. METHODS OF SYNTHESIS, ANALYSIS AND RESEARCH

The **second chapter** consists of 7 paragraphs, which describe the starting materials, methods for the synthesis of 4-allylthiosemicarbazones of substituted salicylaldehyde, pyruvic acid amides, 4-allylthiosemicarbazones of pyruvic acid amides, their 3*d* metals coordination compounds and mixed-ligand copper(II) coordination compounds. The methods for analyzing the obtained compounds are listed and described, such as metal analysis, spectral methods for NMR and FT-IR analysis, X-ray diffraction analysis, determination of molar electrical conductivity in solution, column chromatography, determination of melting point and determination of the solubility of substances in water.

Methods for determining antimicrobial activity against gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Acinetobacter baumannii* (ATCC BAA-747), *Enterobacter cloacae* (ATCC 13047), *Pseudomonas aeruginosa* (ATCC 853), *Bacillus cereus* (ATCC 11778), *Bacillus subtilis* (ATCC 6633), *Enterococcus faecium* (ATCC 6569) and antifungal activity against *Candida albicans* (ATCC 10231), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019),

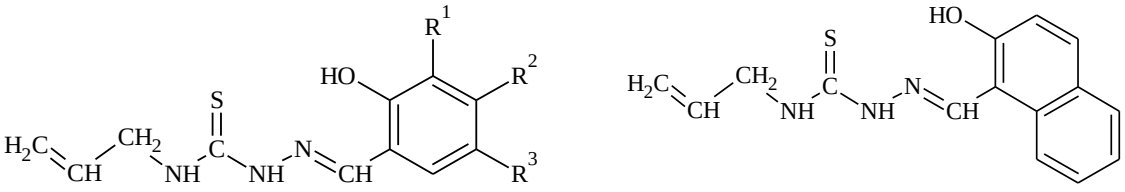
Cryptococcus neoformans (ATCC 34877) are described. The method for studying antioxidant activity against $ABTS^{\cdot+}$ radical cations is described. Antimicrobial, antifungal agents and antioxidants used in medicine were used as standards.

3. MIXED LIGAND COPPER(II) COORDINATION COMPOUNDS WITH 4-ALLYLTHIOSEMICARBAZONES OF SALICYL ALDEHYDE DERIVATIVES

The **third chapter** consists of 3 paragraphs and contains a description of the synthesis, structure, and physicochemical properties of the obtained 4-allylthiosemicarbazones of substituted salicylic aldehydes and their mixed-ligand copper(II) coordination compounds. The results of the study of antimicrobial, antifungal and antioxidant activities are given. The dependence of biological activity on the nature of the *N*-heteroaromatic base in the inner sphere of copper(II) complexes was studied, and the most active compounds were identified.

3.1 Synthesis and structure of mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives containing *N*-heteroaromatic bases

3-Methoxysalicylic aldehyde (**H_2L^1**), 2,4-dihydroxybenzaldehyde (**H_2L^2**), 3,5-dibromosalicylic aldehyde (**H_2L^3**), and 2-hydroxy-1-naphthaldehyde (**H_2L^4**) 4-allylthiosemicarbazones were obtained by the reaction of 4-allylthiosemicarbazide and the corresponding aldehyde in a molar ratio of 1:1 on heating in ethanol (Fig. 3.1**)**.



H_2L^1: R^1=OCH_3, R^2=H, R^3=H; H_2L^2: R^1=H, R^2=OH, R^3=H; H_2L^3: R^1=Br, R^2=H, R^3=Br

H_2L^4

Fig. 3.1. Structural formulas of 4-allylthiosemicarbazones of substituted salicylaldehyde (H_2L^1-H_2L^4)

The structure and purity of the synthesized 4-allylthiosemicarbazones were determined by ^1H and ^{13}C NMR spectroscopy. The spectra obtained, as well as the melting points of the substances, correspond to the literature data.

By the interaction of ethanol solutions of 4-allylthiosemicarbazones of salicylaldehyde derivatives **H_2L^{1-4}** with copper(II) acetate monohydrate in a molar ratio of 1:1, complexes of the composition $Cu(L^{1-4})\cdot H_2O$ are formed, and in the case of a similar interaction with copper(II)

nitrate trihydrate, complexes with the composition $Cu(HL^{1-4})NO_3 \cdot nH_2O$ (n=0-3) were obtained. The resulting complexes were filtered on a Schott filter and then used to obtain mixed-ligand complexes containing, in addition to the thiosemicarbazone ligand, various *N*-heteroaromatic bases in the inner sphere. For this purpose complexes $Cu(L^{1-4}) \cdot H_2O$ and $Cu(HL^{1-4})NO_3 \cdot nH_2O$ were dissolved in ethanol, and the corresponding *N*-heteroaromatic base (pyridine, 3-picoline, 4-picoline, 3,4-lutidine, imidazole, 2,2'-bipyridine, 1,10-phenanthroline) was added to the reaction mixture in a molar ratio of 1:1.

In addition to the method described above, a number of complexes with bidentate N-heteroaromatic bases were obtained by the second method, which consisted in the interaction of 4-allylthiosemicarbazones of salicylaldehyde derivatives $\mathbf{H_2L^{1-4}}$ with copper(II) acetate monohydrate or copper(II) nitrate trihydrate in an ethanol solution, followed by the addition of 2,2'-bipyridine or 1,10-phenanthroline to the reaction mixture in molar ratio 1:1:1. For these substances, based on elemental analysis for copper, the composition was determined $[Cu(A)(HL^{2-4})]NO_3$ and $[Cu(A)(L^{1-4})]$, A - 1,10-phenanthroline, 2,2'-bipyridine, 3,4-lutidine, 4-picoline, 3-picoline, pyridine and imidazole.

The studies of the molar electrical conductivity in dimethylformamide showed that the complexes obtained from copper(II) acetate are non-electrolytes, and the complexes of copper(II) nitrate are 1:1 type of the electrolytes.

To determine the method of coordination of ligands with central copper(II) atoms, a comparative analysis of the FT-IR spectra of $\mathbf{H_2L^{1-4}}$ and all synthesized mixed-ligand copper(II) coordination compounds was carried out, on the basis of which it was determined that 4-allylthiosemicarbazone in these complexes behaves as a tridentate ligand and is coordinated to the copper atom using the ONS set of donor atoms. In the composition of complexes obtained from copper(II) acetate, 4-allylthiosemicarbazone is double deprotonated, as confirmed by the disappearance of one absorption band ν(O–H), the absence of an absorption band ν(C=S), and the appearance of ν(C–S), from which we can conclude that the ligand has passed into the thiol form. In the composition of complexes obtained from copper(II) nitrate, 4-allylthiosemicarbazone is monodeprotonated, which is confirmed by the disappearance of one absorption band ν(O–H) and the presence of an absorption band ν(C=S) with a shift to the high-frequency region. This indicates that the deprotonization of the ligand occurs only through the phenolic OH group.

The structure of four mixed-ligand copper(II) coordination compounds, as well as the complex $[Cu(H_2O)(HL^3)](NO_3)$ was determined by X-ray diffraction analysis (Fig. 3.2).

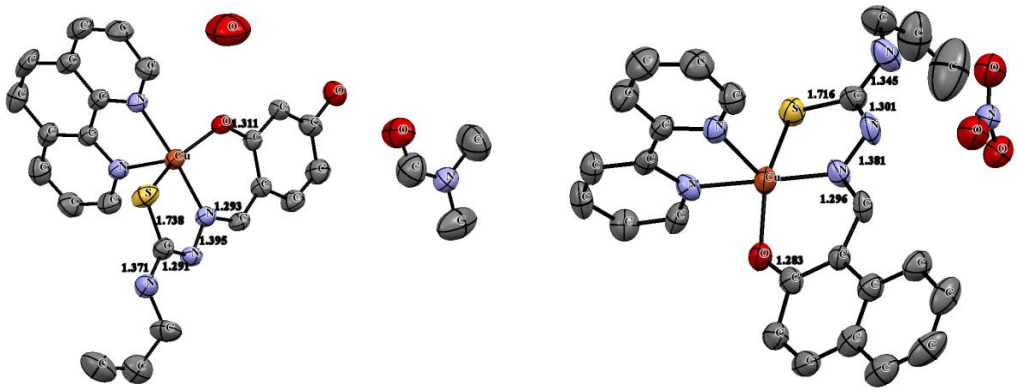


Fig. 3.2. The structure of the complexes [Cu(1,10-Phen)(L^2)]·DMF·H_2O and [Cu(2,2'-Bpy)(HL^4)]NO_3

The complexes have a monomeric structure. The coordination polyhedron is a distorted square pyramid. The central copper atom has a coordination number of 5. In the complex **[Cu(1,10-Phen)(L^2)]·DMF·H_2O** 2,4-dihydroxybenzaldehyde 4-allylthiosemicarbazone acts as a tridentate, double deprotonated ligand, coordinating to the central copper atom via the O,N,S set of donor atoms. The fourth coordination place at the base of the pyramid and the apical position are occupied by the nitrogen atoms of 1,10-phenanthroline. The outer sphere contains a molecule of crystallization water and a molecule of dimethylformamide - a solvent used in recrystallization. In the complex **[Cu(2,2'-Bpy)(HL^4)]NO_3** 2-hydroxy-1-naphthaldehyde 4-allylthiosemicarbazone **H_2L^4** behaves as a tridentate monodeprotonated ligand, coordinating to the central copper atom using the O,N,S set of donor atoms, and forming one five-membered and one six-membered metallocycles. The outer sphere of the complex contains the nitrate ion.

The complex without an *N*-heteroaromatic base in the inner sphere **[Cu(H_2O)(HL^3)]NO_3** has an almost planar structure. Thiosemicarbazone H_2L^3 is in the monodeprotonated form $(HL^3)^-$ and occupies three coordination sites of the copper atom, while the fourth coordination site is occupied by the water molecule. As a result, a complex cation is formed, for the neutralization of the charge of which the nitrate ion is located in the outer sphere. Deprotonization of oxygen occurs due to the phenolic oxygen atom, while the thiosemicarbazide fragment remains in the thione form, as indicated by the bond lengths: C-O 1.324 Å and C=S 1.692 Å.

3.2 Biological properties of mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives H_2L^{1-4}

For all synthesized compounds, antimicrobial activity was studied against gram-positive, gram-negative microorganisms and fungi.

Of all the synthesized 4-allylthiosemicarbazones of substituted salicylaldehyde, 3,5-dibromosalicylicaldehyde 4-allylthiosemicarbazone (**H_2L^3**), exhibits the highest antimicrobial activity against gram-positive microorganisms, its concentration values are in the range 0.9766 - 3.906 μg/mL. As a result of the coordination of 4-allylthiosemicarbazones to the copper atom,

the activity of the obtained coordination compounds increases in all cases. The activity of mixed-ligand copper(II) coordination compounds is affected by the nature of the *N*-heteroaromatic base in the inner sphere of the complex. The introduction of bidentate amines (1,10-phenanthroline and 2,2'-bipyridine) into the inner sphere of copper(II) coordination compounds obtained from copper(II) nitrate did not lead to an increase in the biological activity of the resulting complexes. In the case of complexes derived from copper(II) acetate, most complexes with amines in the inner sphere outperform the activity of copper(II) complexes without amines. The resulting compounds are more active against Gram-positive microorganisms. The synthesized compounds are superior in activity to Tetracycline, which is used as an antibiotic in medicine, against to Gram-positive microorganisms, and in relation to fungi, only the **[Cu(3,4-Lut)(L^2)]** complex is more active than Fluconazole, which is an antifungal agent. Among the mixed-ligand copper(II) coordination compounds, the complex **[Cu(Py)(L^3)]** is the most active against Gram-positive microorganisms, and complex **[Cu(3,4-Lut)(L^2)]** is the most active against fungi.

A wider range of its activity was studied for the complex **[Cu(3,4-Lut)(L^2)]**. The coordination compound **[Cu(3,4-Lut)(L^2)]** exhibits the highest activity against *Enterococcus faecium*. It exceeds the activity of Tetracycline against *Enterobacter cloacae*, as well as the activity of Fluconazole against *Cryptococcus neoformans*.

Summarizing the results of the study of the antimicrobial and antifungal activities of all synthesized compounds, we can conclude that the activity of the compounds is influenced by several factors at once: the introduction of substituents into the benzylidene fragment in the composition of 4-allylthiosemicarbazones of substituted salicylic aldehyde, the nature of *N*-heteroaromatic bases in the inner sphere of mixed-ligand copper(II) coordination compounds, the presence or absence of the nitrate ion in the outer sphere of the complexes, and the presence of monodeprotonated ligand or double deprotonated ligand in the composition of complexes.

For all the synthesized compounds, the antioxidant activity against $ABTS^{\cdot+}$ radical cation was studied. All the synthesized 4-allylthiosemicarbazones **H_2L^{1-4}** exhibit antioxidant activity in the concentration range 6.30-12.45 μM. Coordination of 4-allylthiosemicarbazones **H_2L^{1-4}** to the copper atom did not lead to an increase in activity in most cases, as did the introduction of *N*-heteroaromatic bases into the inner sphere of the coordination compounds. However, in the case of 3-methoxysalicylic aldehyde 4-allylthiosemicarbazone **H_2L^1** the appearance of an amine in the inner sphere of copper(II) nitrate and acetate coordination compounds made these complexes more active. The antioxidant activity of the complexes is influenced by the nature of the *N*-heteroaromatic base. For all mixed-ligand complexes obtained from copper(II) acetate, there is no common dependence, therefore, it is necessary to consider a series of complexes of each 4-allylthiosemicarbazone separately. Antioxidant activity decreases according to the following

series for amine-containing copper(II) coordination compounds with 3-methoxysalicylic aldehyde 4-allylthiosemicarbazone **H_2L^1**: 1,10-Phen > Im > 3,5-Br_2Py > 2,2'-Bpy > 3,4-Lut > Py > 3-Pic > 4-Pic; for complexes with 2,4-dihydroxybenzaldehyde 4-allylthiosemicarbazone **H_2L^2**: 3,4-Lut > 2,2'-Bpy > 3-Pic > 4-Pic >1,10-Phen; for complexes with 3,5-dibromsalicylic aldehyde 4-allylthiosemicarbazone **H_2L^3**: 1,10-Phen > 4-Pic > Py > 2,2'-Bpy > 3-Pic > 3,4-Lut; for complexes with 2-hydroxy-1-naphthaldehyde 4-allylthiosemicarbazone **H_2L^4**: 3,4-Lut > Py > 2,2'-Bpy > 3-Pic > 1,10-Phen > 4-Pic.

The most active complex is **[Cu(3,4-Lut)(HL^1)]NO_3**, with IC_{50} values 3.15 μM. Almost all synthesized compounds exhibit activity higher than Trolox, which is used in medicine as an antioxidant.

For comparison, the values of the antioxidant activity of 4-allylthiosemicarbazone of salicylaldehyde and its mixed ligand copper(II) coordination compounds published in the literature are given (Fig. 3.3).

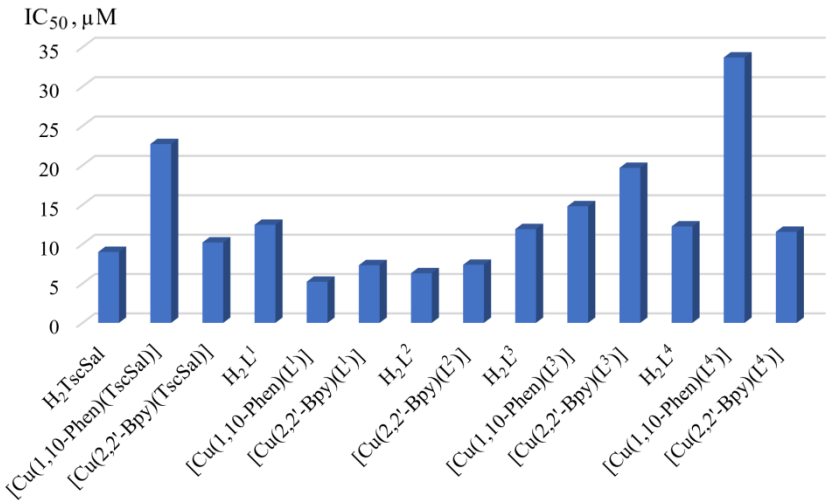


Fig. 3.3. Comparison of antioxidant activity against $ABTS^{\cdot+}$ of some synthesized substances with literature data

It can be seen from the above diagram that 2,4-dihydroxybenzaldehyde 4-allylthiosemicarbazone **H_2L^2** exhibits higher antioxidant activity than salicylaldehyde 4-allylthiosemicarbazone H_2TscSal. Also, the activity of mixed-ligand copper(II) coordination compounds **[Cu(2,2'-Bpy)($L^{1,2}$)]** and **[Cu(1,10-Phen)(L^{1-3})]** exceeds the activity of similar coordination compounds of salicylaldehyde 4-allylthiosemicarbazone. So we can conclude that the hydroxyl group as a substituent in the benzylidene fragment in the composition of 4-allylthiosemicarbazone increases the antioxidant activity of both: the uncoordinated ligand and its mixed ligand compounds.

4. COORDINATION COMPOUNDS OF SOME 3*d* METALS WITH PYRUVIC ACID AMIDES 4-ALLYLTHIOSEMICARBAZONES

The **fourth chapter** consists of 4 paragraphs, which describe pyruvic acid amides, synthesis, structure and physicochemical properties of their 4-allylthiosemicarbazones and coordination compounds of some 3*d* metals based on them. The results of the study of antimicrobial, antifungal and antioxidant activities are presented. The dependence of the biological activity and the influence of the nature of the central atom, the acid residue and the *N*-heteroaromatic base in the inner sphere of the copper(II) complexes was studied, and the most active compounds were identified and compared with the substances that were used as standards.

4.1 Synthesis and structure of pyruvic acid amides 4-allylthiosemicarbazones HL$^{5-10}$

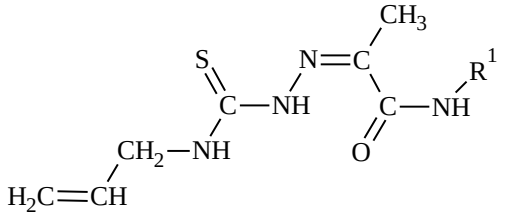
Pyruvic acid amides were obtained by reaction between pyruvic acid with oxalyl chloride in a molar ratio of 1:1.2 in dichloromethane as solvent. The reaction took place in the presence of catalytic amounts of *N*,*N*-dimethylformamide. The reaction mechanism involves the reaction of oxalyl chloride with dimethylformamide, forming a cationic intermediate with high electrophilicity, which further reacts with pyruvic acid, forming an acid chloride. At the end of the reaction of formation of pyruvic acid chloride, the resulting acid chloride was added dropwise with constant cooling and stirring into a flask containing the corresponding amine (4-methoxyaniline, piperidine, morpholine, hexamethyleneimine, cyclohexylamine, 3-methoxypropane-1-amine) and anhydrous sodium carbonate, which is added to neutralize the released hydrogen chloride. The resulting amides, with the exception of *N*-(4-methoxyphenyl)-2-oxopropanamide and *N*-cyclohexyl-2-oxopropanamide, are oily liquids.

In all cases, the preparation of pyruvic acid amides was confirmed by a comparative analysis of the FT-IR spectra of the starting reagents and the reaction product. The spectra show the appearance in the obtained amides of pyruvic acid of two absorption bands of C=O groups, amide and carbonyl, which are shifted to the low-frequency region compared to the absorption bands of C=O groups from pyruvic acid. In the obtained FT-IR spectra of some pyruvic acid amides, the disappearance of the absorption band characteristic of the NH group is observed, which indicates the formation of an amide bond C-N. One of the two absorption bands υ(N-H) disappears in the case of *N*-(4-methoxyphenyl)-2-oxopropanamide, *N*-cyclohexyl-2-oxopropanamide and *N*-(3-methoxypropyl)-2-oxopropanamide compared to 4-methoxyaniline, cyclohexylamine and 3-methoxypropan-1-amine, accordingly.

4-Allylthiosemicarbazones of *N*-(4-methoxyphenyl)-2-oxopropanamide (**HL^5**), 1-(piperidin-1-yl)propan-1,2-dione (**HL^6**), 1-(morpholin-4-yl)propan-1,2-dione (**HL^7**), 1-(azepan-1-yl)propan-1,2-dione (**HL^8**), *N*-cyclohexyl-2-oxopropanamide (**HL^9**) and *N*-(3-methoxypropyl)-

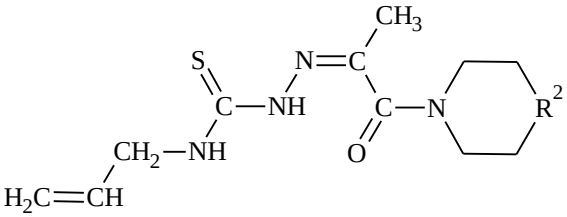
2-oxopropanamide (**HL^{10}**) were obtained by the interaction of 4-allylthiosemicarbazide and the corresponding pyruvic acid amide in ethanol in a molar ratio of 1:1 (Fig. 4.1).

The result of the condensation reaction was confirmed by a comparative analysis of the FT-IR spectra of the reagents and the reaction product. The spectra of synthesized 4-allylthiosemicarbazones show two absorption bands characteristic of NH groups from the 4-allylthiosemicarbazide fragment. The disappearance of the carbonyl absorption band C=O and the shift of the absorption band of the amide group C=O to the low-frequency region are also observed.

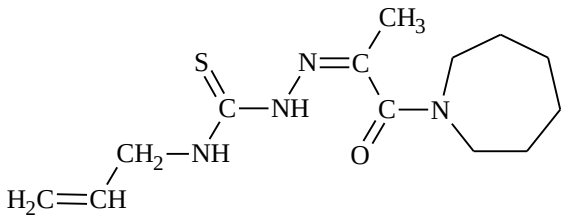


HL^{5}: R^{1}= $C_6H_5OCH_3$; HL^{9}: R^{1}= C_6H_{12};

HL^{10}: R^{1}= $C_4H_{10}O$.



HL^{6}: R^{2}= H; HL^{7}: R^{2}=O.



HL^{8}

Fig. 4.1. Structural formulas of pyruvic acid amides 4-allylthiosemicarbazones (HL^{5}-HL^{10})

The structure and purity of the synthesized 4-allylthiosemicarbazones were determined by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of 4-allylthiosemicarbazones contains multiplets at 6.0 – 4.3 ppm, which correspond to the allyl fragment in the molecule of 4-allylthiosemicarbazones. There are also singlets at 8.8–7.4 ppm, which correspond to hydrogen atoms from the NH group of the thiosemicarbazide fragment, and a peak at 2.11–2.13 ppm, which is characteristic of the methyl group in the composition of the pyruvic acid fragment at the spectra. The ^{13}C NMR spectrum has a characteristic peak at 178 ppm, which corresponds to the C=S group, and indicates that all pyruvic acid amides 4-allylthiosemicarbazones are in the thionic form.

The structures of five pyruvic acid amides 4-allylthiosemicarbazones were studied by X-ray diffraction analysis (**HL$^{5,6-10}$**) (Fig. 4.2).

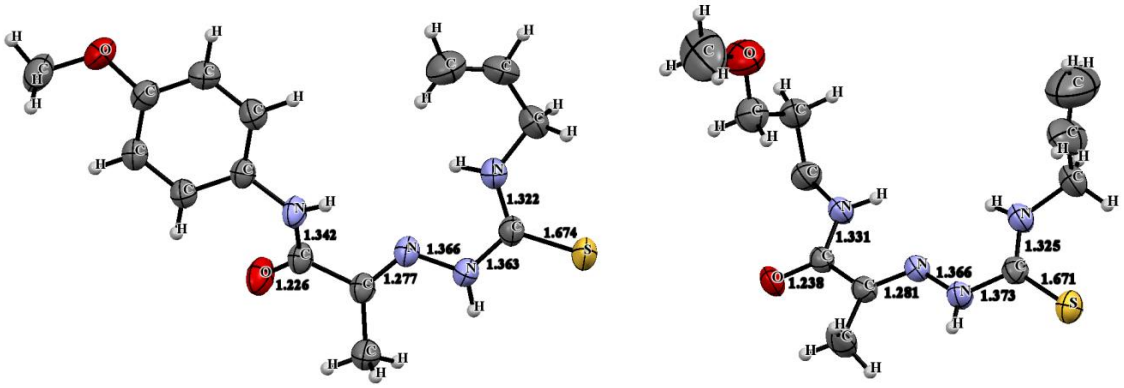


Fig. 4.2. The structure of the HL^5 and HL^{10}

All 4-allylthiosemicarbazones are in the thione form, that is confirmed by the C=S bond length in the range of 1.671-1.681 Å, and the C-NH bond in the range of 1.312-1.373 Å.

The solubility in water was studied for all synthesized pyruvic acid amides 4-allylthiosemicarbazones **HL^{5-10}** (Table 4.1).

Table 4.1. The solubility in water of pyruvic acid amides 4-allylthiosemicarbazones HL^{5-10}

Compound	HL^5	HL^6	HL^7	HL^8	HL^9	HL^{10}
Solubility, mg/mL	1.0	2.5	10	2.5	<0.2	5.0

Solubility is affected by the nature of the amide moiety in 4-allylthiosemicarbazones. Solubility decreases according to the following series of amide moieties: 1-(morpholin-4-yl)propan-1,2-dione > *N*-(3-methoxypropyl)-2-oxopropanamide > 1-(piperidin-1-yl)propan-1, 2-dione ~ 1-(azepan-1-yl)propan-1,2-dione > *N*-(4-methoxyphenyl)-2-oxopropanamide > *N*-cyclohexyl-2-oxopropanamide.

4.2 Synthesis and structure of coordination compounds of some 3*d* metals with pyruvic acid amides 4-allylthiosemicarbazones HL^{5-10}

Coordination compounds of 4-allylthiosemicarbazones were obtained as a result of the interaction of various salts of some 3*d* metals with the corresponding 4-allylthiosemicarbazones. Copper(II) complexes were obtained by the reaction of 4-allylthiosemicarbazone with copper(II) salts in a molar ratio of 1:1 in ethanol, while cobalt(III), iron(III), and zinc(II) complexes were obtained by the reaction in a molar ratio of 2:1. The synthesis of nickel(II) complexes was carried out both in a molar ratio of 1:1 and 2:1. Mixed ligand copper(II) coordination compounds were obtained both: by the reaction of the prepared complex of copper(II) nitrate with heteroaromatic amines and by the template method. General formula of synthesized compounds: $[M(L^{5-10})X]$ (M = Cu^{2+}, Ni^{2+}; X = NO_3^-, Cl^-, Br^-, OAc^-, Cl_2CHCOO^-), $[M(L^{5-10})_2]X$ (M = Co^{3+},

Fe^{3+}; X = Br^-, Cl^-, NO_3^-, OAc^-), $Zn(L^5)_2$, $[Ni(HL^{4-9})_2](NO_3)_2$, $[Cu(A)(L^{5-7})]NO_3$ (A = 1,10-Phen, 2,2'-Bpy, 3,4-Lut, 4-Pic, 3-Pic, Py, Im).

The study of the molar electrical conductivity in methanol showed that all the synthesized complexes are 1:1 electrolytes, except for the nickel(II) nitrate complexes, **$[Ni(HL^5)_2]Cl_2$** and **$[Cu(1,10\text{-}Phen)(HL^6)](NO_3)_2$** – they are 1:2 electrolytes.

A comparative analysis of the FT-IR spectra of **$HL^{5\text{-}10}$** and all synthesized coordination compounds was carried out to determine the mode of coordination of ligands with the central atoms of some 3*d* metals. It has been established that in the composition of complexes 4-allylthiosemicarbazones behave as tridentate monodeprotonated ligands, coordinating to the central atom through the oxygen atom of the amide group, the nitrogen atom of the azomethine group, and the sulfur atom. This was confirmed by the disappearance of one of the two absorption bands of NH groups, as well as the disappearance of the absorption band ν(C=S), and the appearance of a new absorption band ν(C-S) at 780-791 cm^{-1}. The disappearance of the absorption band ν(C=S) means the transition of 4-allylthiosemicarbazone from the thione to the thiol form. The exceptions are nickel(II) nitrate complexes, **$[Ni(HL^5)_2]Cl_2$** and **$[Cu(1,10\text{-}Phen)(HL^6)](NO_3)_2$**, in which the ligands are not deprotonated. In the spectra of these substances, the absorption bands of NH and ν(C=S) do not disappear, which means that 4-allylthiosemicarbazone is in the thione form in the composition of these complexes.

The structure of 10 copper(II) and nickel(II) coordination compounds with 4-allylthiosemicarbazones **$HL^{5\text{-}7,9}$** was determined by X-ray diffraction analysis. The coordination numbers of the central atoms vary from four to six.

The resulting complexes have both dimeric and monomeric structures (Fig. 4.3). The central copper atom has a coordination number 5 in the complex **$[\{Cu(L^7)Br\}_2]$**. The coordination polyhedron is a distorted square pyramid. There are ONS donor atoms of 4-allylthiosemicarbazone at the base of the pyramid. The fourth position at the base of the pyramid and the apical position are occupied by bromine atoms, which act as a bridge. The complex **$[Cu(L^6)Cl]$** has a monomeric, almost planar structure. The central copper atom has a coordination number 4. In the complex 4-allylthiosemicarbazone is monodeprotonated, that is confirmes by the bond lengths C-S 1.738 Å, C=N 1.329 Å.

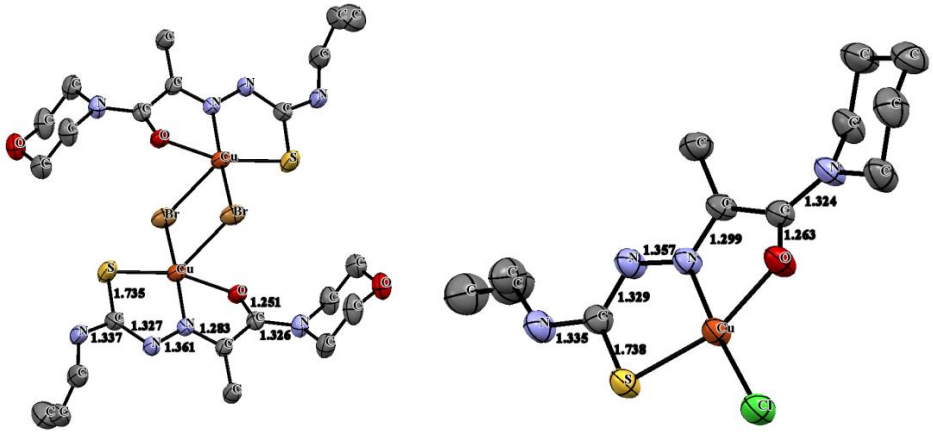


Fig. 4.3. The structure of the [{Cu(L^7)Br}$_2$] and [Cu(L^6)Cl]

4-Allylthiosemicarbazone is also monodeprotonated and is in the thiol form in the composition of mixed-ligand copper(II) coordination compounds (Fig. 4.4)

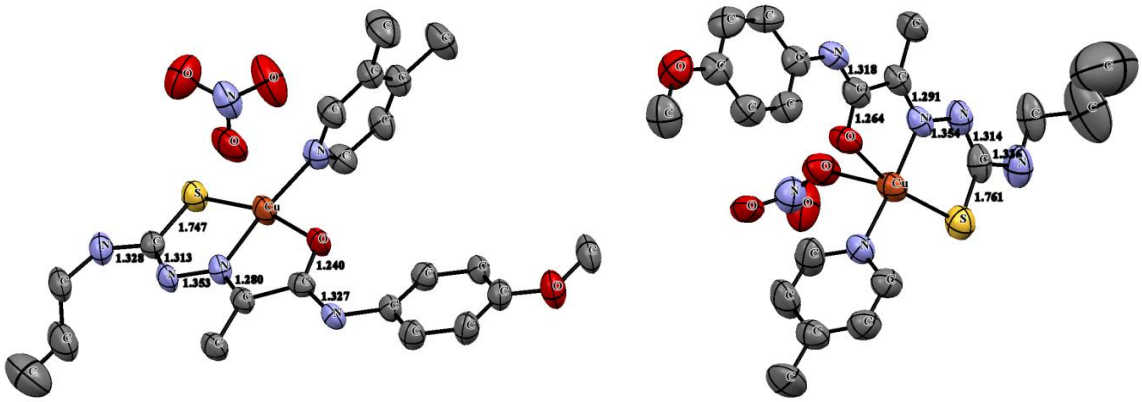


Fig. 4.4. The structure of the [Cu(3,4-Lut)(L^5)]NO_3 and [Cu(4-Pic)(L^5)NO_3]

In all cases, the outer sphere contains a nitrate ion to compensate for the charge. The exception is the **[Cu(4-Pic)(L^5)NO_3]** complex, in which the nitrate ion is located in the inner sphere. The coordination number of the central copper atom in the case of complexes with monodentate amines is four, except for the complex **[Cu(4-Pic)(L^5)NO_3]**, in which it is five, and in the case of complexes with bidentate amines (1,10-phenanthroline and 2,2'-bipyridine) the coordination number of the central copper atom is five. As part of complexes with bidentate amines, 4-allylthiosemicarbazone is coordinated to the copper atom with the help of nitrogen, oxygen, and sulfur donor atoms, forming two five-membered metallocycles. The fourth coordination site at the base of the pyramid and the apical position are occupied by the nitrogen atoms of the bidentate amine.

The complexes obtained from nickel(II) chloride and nitrate have a monomeric structure, and 4-allylthiosemicarbazone in these complexes is coordinated to the central nickel atom in the non-deprotonated thione form. This is confirmed by the C-S bond length, that is equal to 1.678 Å in the case of the **[Ni(HL^5)$_2$]Cl$_2$** and 1.676 Å for the **[Ni(HL^9)$_2$](NO$_3$)$_2$**, which corresponds to a

double bond and practically does not differ from the length of this bond in uncoordinated thiosemicarbazone. There are two ions of the acid residue in the outer sphere of these complexes.

4.3 Biological activity of coordination compounds of some 3*d* metals with pyruvic acid amides 4-allylthiosemicarbazones HL^{5-10}

For a number of synthesized compounds, antimicrobial and antifungal activities were studied against Gram-positive, Gram-negative microorganisms and fungi. The studied 4-allylthiosemicarbazones do not show antimicrobial and antifungal activity against the tested microorganisms. Among the copper(II) coordination compounds of *N*-(4-methoxyphenyl)-2-oxopropanamide 4-allylthiosemicabazone HL^5 the complex **$[Cu(L^5)Cl]$** is the most active one against *Bacillus cereus*. The activity of these compounds is influenced by the nature of the rest acid, the activity decreases according to the following series **$Cl^- > NO_3^- > CH_3COO^- > Br^- > Cl_2CHCOO^-$**. The introduction of heteroaromatic amines into the inner sphere of the copper(II) nitrate coordination compound $[Cu(L^5)NO_3]$ did not lead to an increase in the activity of the resulting substances. In the case of mixed-ligand copper(II) coordination compounds, the activity is influenced by *N*-heteroaromatic base in the inner sphere of these complexes. Complexes with bidentate amines exhibit higher activity than complexes with monodentate amines.

Among the complexes of 1-(piperidin-1-yl)propan-1,2-dione 4-allylthiosemicarbazone (**HL^6**), its complex with copper(II) chloride is the most active against Gram-positive microorganisms. The activity of copper(II) coordination compounds can be traced depending on the nature of the rest acid. The complex with copper(II) bromide showed the average activity, and the complex obtained from copper(II) nitrate showed the lowest activity. The introduction of 1,10-phenanthroline into the inner sphere of the complex **$[Cu(L^6)NO_3]$** led to an increase in the activity of the resulting coordination compound **$[Cu(1,10\text{-}Phen)(HL^6)](NO_3)_2$** against *Bacillus cereus* and *Candida albicans*.

From the series of studied substances of 1-(morpholin-4-yl)propan-1,2-dione 4-allylthiosemicarbazone HL^7 and its coordination compounds, the complex **$[Cu(L^7)(CH_3COO)]$** is the most active against Gram-positive microorganisms.

Among all the studied substances, the complex **$[Cu(L^6)Cl]$** is the most active against Gram-positive microorganisms, and against fungi - **$[Cu(1,10\text{-}Phen)(L^7)]NO_3$**, their activity is on the same level as Tetracycline and Furacilin, which were used as standards.

The resulting substances were also tested for antioxidant activity against $ABTS^{\cdot+}$ radical cation. Among the 4-allylthiosemicarbazones, 1-(azepan-1-yl)propan-1,2-dione 4-allylthiosemicarbazone (**HL^8**) exhibits the highest activity, its value IC_{50} 3.85 μM. The most active complexes are complexes of Ni(II) and Fe(III) in most cases, among the coordination compounds of 3*d* metals. The activity of mixed-ligand copper(II) coordination compounds is

affected by the nature of the *N*-heteroaromatic base in the inner sphere of the complex. The copper(II) coordination compound with 1,10-phenanthroline **[Cu(1,10-Phen)(HL^{6})](NO$_3$)$_2$**, in which 4-allylthiosemicarbazone is not deprotonated, is inactive, and a complex similar in structure, but with monodeprotonated 4-allylthiosemicarbazone its activity is 89.55 μM. The dependence of activity on the nature of the rest acid can be traced for copper(II) complexes with 1-(morpholin-4-yl)propan-1,2-dione 4-allylthiosemicarbazone HL^{7}. The complex obtained from copper(II) chloride showed the highest activity, the complexes of copper(II) bromide and nitrate showed average activity, and the complexes of copper(II) acetate and dichloroacetate were inactive.

The initial 4-allylthiosemicarbazones are in most cases more active than their coordination compounds, so below is Figure 4.5 that shows a comparison diagram of antioxidant activity values for HL$^{5-10}$.

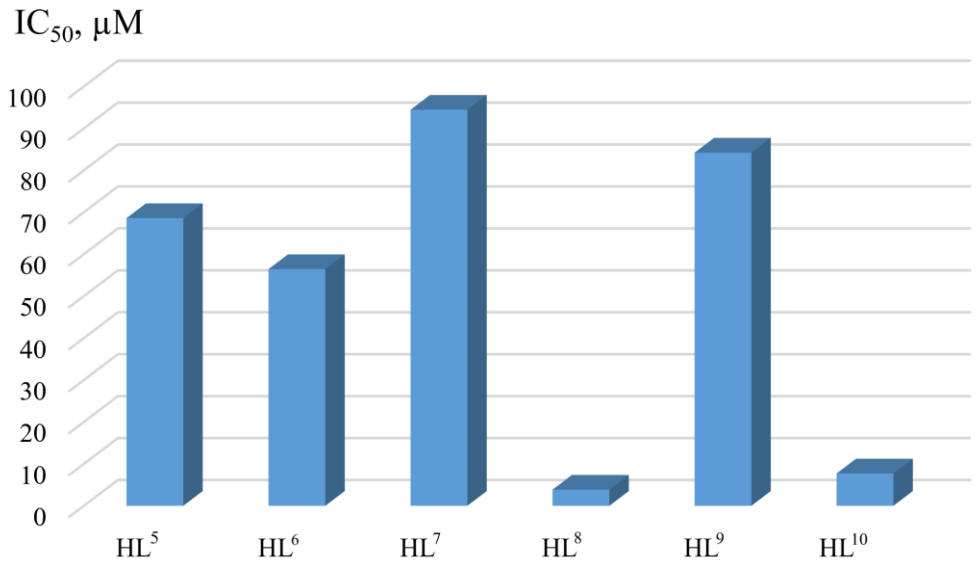


Fig. 4.5. Comparison of the antioxidant activity of 4-allylthiosemicarbazones HL$^{5-10}$ against ABTS$^{\cdot+}$

This diagram shows the influence of the amide fragment in the composition of 4-allylthiosemicarbazones **HL$^{5-10}$** on their antioxidant activity. 4-Allylthiosemicarbazone 1-(azepan-1-yl)propan-1,2-dione (**HL^{8}**) showed the highest activity, **HL^{10}** was in second place in activity. The weakest antioxidant is 4-allylthiosemicarbazone, which contains morpholine.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. Based on 4-allylthiosemicarbazones of substituted salicylaldehyde (3-methoxysalicylic aldehyde (**H_2L^1**), 2,4-dihydroxybenzaldehyde (**H_2L^2**), 3,5-dibromsalicylic aldehyde (**H_2L^3**) and 2-hydroxy-1-naphthaldehyde (**H_2L^4**)) 40 copper(II) coordination compounds were obtained, including mixed-ligand copper(II) coordination compounds, for which, based on the analysis for copper, composition was determined.

2. The procedure for the synthesis of pyruvic acid amides was modified, according to which 6 pyruvic acid amides were obtained, the melting point and IR spectra of which coincide with the literature data.

3. Six new 4-allylthiosemicarbazones were synthesized **HL^{5-10}**, for which FT-IR and NMR (^{1}H and ^{13}C) spectroscopic study was carried out.

4. 49 New coordination compounds were obtained, on the basis of pyruvic acid amides 4-allylthiosemicarbazones **HL^{5-10}** for which, based on the analysis for the metal, the composition was determined.

5. The method of X-ray diffraction analysis established:

   - structure of 5 new pyruvic acid amides 4-allylthiosemicarbazones;
   - all 4-allylthiosemicarbazones are in ionic form;
   - structure of 15 coordination compounds of some 3*d* metals, including mixed-ligand copper(II) coordination compounds;
   - complexes have both monomeric and dimeric structures;
   - in complexes, 4-allylthiosemicarbazones are coordinated to the central atoms using the ONS set of donor atoms and can be non-deprotonated, mono-deprotonated or in doubly deprotonated form;
   - the coordination number of the central atom in the composition of the complexes varies from four to six;

6. The ONS mode of coordination of 4-allylthiosemicarbazones to the central metal atom was established, based on a comparative analysis of the FT-IR spectra of ligands and their complexes, for which the structure was not determined by X-ray diffraction analysis.

7. The study of antimicrobial activity showed:

   - 3*d* metal coordination compounds are more active than the initial 4-allylthiosemicarbazones;
   - the introduction of substituents in the benzylidene fragment in the composition of salicylaldehyde 4-allylthiosemicarbazone leads to an increase in biological activity;

- the introduction of *N*-heteroaromatic bases into the inner sphere of copper(II) coordination compounds leads to a significant increase in the activity of the formed substances;
- the appearance of an amide fragment in the pyruvic acid 4-allylthiosemicarbazone leads to an increase in the activity of coordination compounds with the formed 4-allylthiosemicarbazone;
- copper(II) complexes are the most active ones among all studied 3*d* metals complexes;
- mixed-ligand copper(II) coordination compounds with salicylaldehyde derivatives 4-allylthiosemicarbazones exhibit antimicrobial and antifungal activity higher than the coordination compounds of pyruvic acid amides 4-allylthiosemicarbazones;

8. The study of antioxidant activity showed:
- 3*d* metal coordination compounds are more active than the initial 4-allylthiosemicarbazones in most cases;
- the introduction of substituents in the benzylidene fragment in the composition of salicylaldehyde 4-allylthiosemicarbazone leads to an increase in biological activity;
- introduction of *N*-heteroaromatic bases into the inner sphere of copper(II) nitrate and acetate coordination compounds increases the antioxidant activity of the formed compounds;
- the appearance of an amide fragment in the pyruvic acid 4-allylthiosemicarbazone leads to an increase in the activity of coordination compounds with the formed 4-allylthiosemicarbazone;
- nickel(II) complexes are the most active, among all studied 3*d* metals;
- coordination compounds with pyruvic acid amides 4-allylthiosemicarbazones exhibit antioxidant activity higher than mixed-ligand copper(II) coordination compounds with salicylic aldehyde derivatives 4-allylthiosemicarbazones.

A number of **recommendations** can be made for further research, based on the obtained results:

1. to continue the search for new antimicrobial, antifungal, and antioxidant agents among mixed-ligand copper(II) coordination compounds, replacing substituents in the benzylidene fragment in the composition of 4-allylthiosemicarbazones of substituted salicylic aldehyde, as well as the amide fragment in the composition of 4-allylthiosemicarbazones of pyruvic acid amides;
2. to continue the studies of coordination compounds with similar 4-allylthiosemicarbazones in order to search for biologically active and at the same time water-soluble substances;

3. to continue the introduction of natural compounds that can be produced on the territory of the Republic of Moldova, in the composition of 4-allylthiosemicarbazones in order to create local biologically active agents;

4. to supplement the results of the study of materials of special courses on Biopharmaceutical Chemistry and Biochemistry;

5. the introduction and use of a patented compound with bacteriostatic activity against *Bacillus cereus* and *Bacillus subtilis*.

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LIST OF PUBLICATIONS ON THE THEME OF THE THESIS

Articles in scientific journals from the Web of Science and SCOPUS databases

1. CHUMAKOV, Y., GRAUR, V., **ULCHINA (GRAUR), Y.**, SMAGLII, V., GULEA, A., GARBUZ, O., TSAPKOV, V. Crystal structures of [*N*′-(2-oxidobenzylidene)-*N*-(prop-2-en-1-yl)-carbamohydrazonothioato (2-)](1, 10-phenanthroline) copper and [N′-(2-oxidobenzylidene)-*N*-(prop-2-en-1-yl)-carbamohydrazonothioato (2-)](2, 2′-bipyridine) copper hemihydrates. In: *Journal of Structural Chemistry*. 2022, nr. 6 (63), pp. 905-913. ISSN 0022-4766. **IF 1.004** DOI: https://doi.org/10.1134/S0022476622060075

2. GULEA, A., GRAUR, V., **ULCHINA (GRAUR), IA.**, BOUROSH, P., SMAGLII, V., GARBUZ, O., TSAPKOV, V. Synthesis, Structure, and Biological Activity of Mixed-Ligand Amine-Containing Copper(II) Coordination Compounds with 2-(2-Hydroxybenzylidene)-N-(prop-2-en-1-yl)hydrazinecarbothioamide. In: *Russian Journal of General Chemistry*. 2021, nr. 1 (91), pp. 98–107. ISSN 1608-3350. **IF 0.716** DOI: https://doi.org/10.1134/S1070363221010114

3. GULEA, A., TODERAS, I., GARBUZ, O., **ULCHINA (GRAUR), I.**, GRAUR, V., RAILEAN, N. Biological Evaluation of a Series of Amine-Containing Mixed-Ligand Copper(II) Coordination Compounds with 2-(2-hydroxybenzylidene)-*N*-(prop-2-en-1-yl) hydrazinecarbothioamide. In: *Microscopy and Microanalysis*. 2022, nr. 5 (28), pp. 1696 - 1702. ISSN 1431-9276 **IF 4.099** DOI: https://doi.org/10.1017/S1431927622000733

4. **ULCHINA (GRAUR), I.**, GRAUR, V., TSAPKOV, V., CHUMAKOV, Y., GARBUZ, O., BURDUNIUC, P., CEBAN, E., GULEA, A. Introducing *N*-Heteroaromatic Bases into Copper(II) Thiosemicarbazone Complexes: A Way to Change their Biological Activity. In: *Chemistry Open*. 2022, nr. 12 (11), pp. 1-7. ISSN 2191-1363. **IF 2.63**. DOI: https://doi.org/10.1002/open.202200208

Category B articles:

1. **УЛЬКИНА (ГРАУР), Я.**, ГРАУР, В., ГУЛЯ, А. Синтез и биологическая активность смешаннолигандных координационных соединений меди(II) с 4-аллилтиосемикарбазонами замещенных салицилового альдегида. In: *Studia Universitatis Moldaviae (Seria Ştiinţe Reale şi ale Naturii)*. 2021, nr. 6 (146), pp. 126-131. ISSN 1814-3237. DOI: https://doi.org/10.5281/zenodo.5702067

2. **ULCHINA (GRAUR), I.**, TSAPKOV, V., GRAUR, V., GULEA, A. Synthesis and biological activity of copper(II) coordination compounds with 2-hydroxy-1-naphthaldehyde *N*(4)-allyl-3-thiosemicarbazone. In: *Studia Universitatis Moldaviae (Seria Ştiinţe Reale şi ale Naturii)*. 2020, nr. 6 (136), pp. 113-118. ISSN 1814-3237. DOI: https://doi.org/10.5281/zenodo.4431698

Scientific abstracts in book of abstracts, with posters, presented and published at international conferences:

1. GARBUZ, O., TODERAS, I., **ULCHINA (GRAUR), I.**, GRAUR, V., RAILEAN, N., GULEA, A. The antiproliferative, antioxidant activities and toxicity of mixed-ligand amine-containing copper(II) coordination compounds with 2-(2-hydroxybenzylidene)-n-(prop-2-en-1-yl)hydrazinecarbothioamide. In: *X-th International Conference of Zoologists. "SUSTAINABLE USE AND PROTECTION OF ANIMAL WORLD IN THE CONTEXT OF CLIMATE CHANGE" dedicated to the 75th anniversary from the creation of the first research subdivisions and 60th from the foundation of the Institute of Zoology*, 16-17 sept. 2021. Chișinău: S. n., 2021, pp. 123-129. ISBN 978-9975-157-82-7. DOI: https://doi.org/10.53937/icz10.2021.20

2. **ULCHINA (GRAUR), I.**, GRAUR, V., TSAPKOV, V., BESPALOVA, T., GARBUZ, O., GULEA, A. Synthesis and characterization of novel coordination compounds with 1-(piperidin-1-yl)propane-1,2-dione 4- allylthiosemicarbazone. In: *Conferința Națională de Chimie – CNChim – 2022, ediția a XXXVI – a*, October 4 – 7, 2022, Călimănești-Căciulata, România, p. 97. Disponibil: https://ibn.idsi.md/sites/default/files/imag_file/97-97_43.pdf

3. **ULCHINA (GRAUR), I.**, GRAUR, V., GARBUZ, O., TSAPKOV, V., GULEA, A. Coordination Compounds of Cu(II) and Ni(II) with 1-(Morpholin-4-yl) propane-1, 2-dione 4-allylthiosemicarbazone: A Protection from Free Radical Damage. In: *8th International Electronic Conference on Medicinal Chemistry*, November 1-30, 2022, Online, p. 32. ISSN 2673-9992. DOI: https://doi.org/10.3390/ECMC2022-13252

4. **ULCHINA (GRAUR), I.**, GRAUR, V., TSAPKOV, V., GARBUZ, O., GULEA, A. Synthesis and antioxidant activity of mixed-ligand copper(II) coordination compounds with 1-(piperidin-1-yl)propane-1,2-dione 4- allylthiosemicarbazone. In: *"International scientific and practical conference on „MODERN PROBLEMS OF THE CHEMISTRY OF COORDINATION COMPOUNDS"*, December 22-23, 2022, Bukhara, Uzbekistan, pp. 67-68. Disponibil: https://uniwork.buxdu.uz/resurs/13317_1_A655CEA9E5140E872A6DAFD62B5B16919F2C5F7B.pdf

5. **ULCHINA (GRAUR), I.**, GRAUR, V., BALAN, G., TSAPKOV, V., GULEA, A. Biological investigation of copper mixed ligand coordination compounds with 3,5-dibromosalicylaldehyde 4-allylthiosemicarbazone and N-heteroaromatic bases in the search of new antimicrobial agents. In: *Antimicrobial Chemotherapy Conference 2023*, February 1-2, 2023, Online. Disponibil: https://az659834.vo.msecnd.net/eventsairwesteuprod/production-bsac-public/7c38451a4f864ab1bda1979e621db410

6. **ULCHINA (GRAUR), IA.**, GRAUR, V., TSAPKOV, V., BESPALOVA, T., GARBUZ, O., GULEA, A. Antioxidant activity of some 3d metal coordination compounds with 1-(piperidin-1-yl)propane-1,2-dione 4-allylthiosemicarbazone. In: *XXVI Всероссийская конференция молодых учёных-химиков (с международным участием) 2023*, 18-20 april. 2023, Nijni Novgorod, Rusia, p. 246. ISBN 978-5-91326-796-2. Disponibil: http://www.youngchem-conf.unn.ru/wp-content/uploads/2023/04/%D1%81%D0%B1%D0%BE%D1%80%D0%BD%D0%B8%D0%BA2023.pdf

7. **ULCHINA (GRAUR), I.** Синтез, строение и биологическая активность смешаннолигандных координационных соединений меди(II) с птиосемикарбазонами замещенных салицилового альдегида. In: *Conferință stiințifică națională cu participare Internațională MATERIALE AVANSATE ÎN BIOFARMACEUTICĂ ȘI TEHNICĂ. Dedicată aniversărilor a 75-a de la nașterea academicianului AURELIAN GULEA și de fondare a Universității de Stat din Moldova*, 26 mai 2021. Chișinău: S. n., 2021, pp. 424-440 ISBN 978-9975-89-216-2. Disponibil: https://usm.md/wp-content/uploads/Invitatia-Program-A.Gulea-75-ani.pdf

8. **УЛЬКИНА (ГРАУР), Я.** Синтез, противомикробная и противогрибковая активности смешаннолигандных координационных соединений меди(II) с 4-аллилтиосемикарбазонами замещенных салицилового альдегида. In: *Conferința științifică națională cu participare internațională „Integrare prin cercetare și inovare”*, USM, 10-11 noiembrie 2021. Chișinău: CEP USM, 2021, pp.176-178. ISBN 978-9975-62-469-5. Disponibil: https://ibn.idsi.md/sites/default/files/imag_file/176-178_18.pdf

9. **УЛЬКИНА (ГРАУР), Я.** Синтез и противомикробные свойства координационных соединений некоторых 3*d* металлов с 4-аллилтиосемикарбазоном N-(4-метоксифенил)-2-оксопропанамидом. In: *Conferinţa ştiinţifică naţională cu participare internaţională „Integrare prin cercetare şi inovare” dedicată Zilei internaționale a Științei pentru Pace și Dezvoltare*, 10-11 noiembr. 2022. Chişinău: CEP USM, 2022, pp. 212-214. ISBN 978-9975-158-60-2. Disponibil: https://ibn.idsi.md/sites/default/files/imag_file/212-214_13.pdf

10. **ULCHINA (GRAUR), Ia.**, GRAUR, V., TSAPCOV, V., CELAC, M., GARBUZ, O., GULEA, A. Cu(II) complexes with 4-allylthiosemicarbazone as possible antioxidant agents. In: *The National Conference with international participation “Dialogul generațiilor-2022”*, 29-30 sept. 2022. Chișinău : Editura USM, 2022., p. 227. ISBN 978-9975-159-80-7. Disponibil: https://ibn.idsi.md/sites/default/files/imag_file/227_6.pdf

Invention patents:

1. GULEA Aurelian, BĂLAN Greta, **ULCHINA (GRAUR) Ianina,** GRAUR Vasilii, ȚAPCOV Victor. *[N'-(3,5-dibromo-2-oxidobenziliden)-N-prop-2-en-1-ilcarbamo-hidrazontioato]piridincupru, care manifestă activitate bacteriostatică față de bacteriile din speciile Bacillus cereus și Bacillus subtilis.* Brevet de invenție 4707 (2006.01); C07C 47/55 (2006.01); C07C 47/56 (2006.01); C07C 337/08 (2006.01); (2006.01); A61K 31/30 (2006.01); A61K 31/175 (2006.01); A61P 31/04 (2006.01). Universitatea De Stat Din Moldova. Nr. deposit A2019 0051. Data deposit 20.06.2019. 2020. Publicat 2020.08.31. In: BOPI. 2020, nr. 8, pp. 52-53. Disponibil: https://www.agepi.gov.md/sites/default/files/bopi/BOPI_08_2020.pdf

ADNOTARE

Graur Ianina, "Sinteza, structura și proprietățile biologice ale complecșilor cuprului cu liganzi polidentați în baza 4-aliltiosemicarbazonelor solubile în apă", Teză de doctor în științe chimice, Chișinău, 2023

Structura tezei: introducere, patru capitole, concluzii generale și recomandări, 161 referințe bibliografice, 5 anexe, 136 pagini text de bază, 27 tabele, 109 figuri (inclusiv anexe). Rezultatele obținute sunt publicate în 17 lucrări științifice (4 articole în reviste internaționale cu IF, 2 articole în reviste naționale, 10 rezumate de conferințe, 1 brevet).

Cuvinte-cheie: compuși coordinativi, metale 3*d*, baze *N*-heteroaromatice, 4-aliltiosemicarbazone, piruvamide substituite, activitate antimicrobiană și antifungică, activitate antioxidantă.

Scopul tezei: descoperirea de noi agenți antimicrobieni, antifungici și antioxidanti cu solubilitate crescută pe baza compușilor coordinativi ai cuprului(II) cu liganzi micști cu 4-aliltiosemicarbazonele derivaților aldehidei salicilice și 4-aliltiosemicarbazonele amidelor acidului piruvic.

Obiectivele tezei: sinteza compușilor coordinativi ai cuprului(II) cu liganzi micști cu 4-aliltiosemicarbazone derivaților aldehidei salicilice; sinteza amidelor acidului piruvic; sinteza 4-aliltiozemicarbazonelor amidelor acidului piruvic; sinteza compușilor coordinativi ai unor metale 3*d* cu 4-aliltiozemicarbazonele amidelor acidului piruvic; determinarea compoziției, structurii, proprietăților fizico-chimice, activităților antioxidante, antimicrobiene și antifungice ale compușilor sintetizați.

Noutatea și originalitatea științifică: au fost sintetizați și descriși 89 de compuși coordinativi noi; s-a studiat influența substituenților din fragmentul benziliden, natura atomului central, natura resturilor acide, natura bazelor *N*-heteroaromatice din sfera interioară a compușilor coordinativi asupra proprietăților fizico-chimice și activității biologice.

Problema științifică rezolvată în această teză: au fost obținuți noi agenți cu potențial antimicrobian, antifungic și antioxidativ în baza compușilor coordinativi ai cuprului(II) cu liganzi micști cu 4-aliltiosemicarbazonele derivaților aldehidei salicilice și compușilor coordinativi ai unor metale 3*d* ai 4-aliltiosemicarbazonelor amidelor acidului piruvic. Au fost identificați compuși cu solubilitate ridicată în apă, precum și compuși cu activitate superioară substanțelor care au fost utilizate ca standarde (Tetraciclină, Fluconazol și Trolox).

Semnificația teoretică a lucrării și valoarea aplicativă. Rezultatele acestui studiu pot fi utilizate în viitor pentru a căuta noi compuși coordinativi cu activitate antifungică, antimicrobiană și antioxidantă ridicată precum și solubilitate ridicată în apă, prin identificarea relației dintre structura substanței și activitatea acesteia și determinarea efectului unui ligand suplimentar activ din punct de vedere biologic în compoziția compușilor coordinativi privind sinergia proprietăților lor biologice. Substanțele sintetizate pot fi apoi supuse unor studii preclinice. În viitor, rezultatele acestui studiu pot completa materialul cursurilor speciale de Chimie Biofarmaceutică și Biochimie.

Implementarea rezultatelor științifice. A fost brevetat un nou compus cu acțiune bacteriostatică împotriva *Bacillus cereus* și *Bacillus subtilis*.

ANNOTATION

Graur Ianina, "Synthesis, structure and biological properties of copper complexes with polydentate ligands based on water-soluble 4-allylthiosemicarbazones", PhD thesis in chemical sciences, Chisinau, 2023

Thesis structure: introduction, four chapters, general conclusions and recommendations, 161 bibliographic references, 5 annexes, 136 pages of main text, 27 tables, 109 figures (including annexes). The obtained results are published in 17 scientific publications (4 articles in international journals with IF, 2 articles in national journals, 10 conference abstracts, 1 patent).

Keywords: coordination compounds, 3*d* metals, *N*-heteroaromatic bases, 4-allylthiosemicarbazones, substituted pyruvamides, antimicrobial and antifungal activity, antioxidant activity.

The aim of the thesis: discovery of new antimicrobial, antifungal and antioxidant agents with increased solubility based on mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives and 4-allylthiosemicarbazones of pyruvic acid amides.

The objectives of the thesis: synthesis of mixed-ligand copper(II) coordination compounds with 4-allylthiosemicarbazones of salicylaldehyde derivatives; synthesis of pyruvic acid amides; synthesis of 4-allylthiosemicarbazones of pyruvic acid amides; synthesis of coordination compounds of some 3*d* metals with 4-allylthiosemicarbazones of pyruvic acid amides; determination of the composition, structure, physicochemical properties, antioxidant, antimicrobial and antifungal activities of the obtained substances.

The novelty and relevance of the study: 89 new coordination compounds were synthesized and described; the influence of substituents in the benzylidene fragment, the nature of the central atom, the nature of the acid residue, the nature of *N*-heteroaromatic bases in the inner sphere of the complexes on the physicochemical properties and biological activity of the synthesized substances were studied.

The scientific problem solved in this thesis: new potential antimicrobial, antifungal and antioxidant agents based on mixed-ligand coordination compounds of copper(II) 4-allylthiosemicarbazones of salicylaldehyde derivatives and coordination compounds of some 3*d* metals of 4-allylthiosemicarbazones of pyruvic acid amides were obtained. Compounds with high water solubility were identified, as well as compounds that are superior in activity to the substances that were used as standards (Tetracycline, Fluconazole and Trolox).

The theoretical importance and potential application value of the work. The results of this study can be used in the future to search for new coordination compounds with high antifungal, antimicrobial and antioxidant activity and solubility in water, by identifying the relationship between the structure of the substance and its activity, and determining the effect of an additional biologically active ligand in the composition of coordination compounds on synergism their biological properties. The synthesized substances can then undergo preclinical trials. In the future, the results of this study can supplement the material of special courses on Biopharmaceutical Chemistry and Biochemistry.

Implementation of scientific results. New compound with bacteriostatic action against *Bacillus cereus* and *Bacillus subtilis* was patented.

АННОТАЦИЯ

Граур Янина, “Синтез, структура и биологические свойства комплексов меди с полидентатными лигандами на основе 4-аллилтиосемикарбазонов растворимых в воде”, Диссертация доктора химических наук, Кишинэу, 2023.

Структура диссертации: введение, 4 главы, общие выводы и рекомендации, библиография из 161 наименований, 5 приложения, 136 страниц основного текста (до библиографии), 109 рисунков, 27 таблиц (включая Приложения). Полученные результаты опубликованы в 17 научных работах (4 статьи в международных журналах, 2 статьи в национальных журналах, 10 тезисов на конференциях, 1 патент).

Ключевые слова: координационные соединения, $3d$ металлы, N-гетероароматические основания, 4-аллилтиосемикарбазоны, замещенные пирувамиды, противомикробная и противогрибковая активность, антиоксидантная активность.

Цель работы: нахождение новых противомикробных, противогрибковых и антиоксидантных агентов с повышенной растворимостью на основе смешаннолигандных координационных соединений меди(II) с 4-аллилтиосемикарбазонами замещенных салицилового альдегида и 4-аллилтиосемикарбазонами амидов пировиноградной кислоты.

Задачи исследования: синтез смешаннолигандных координационных соединений меди(II) с 4-аллилтиосемикарбазонами замещенных салицилового альдегида; нахождение условий синтеза амидов пировиноградной кислоты; синтез 4-аллилтиосемикарбазонов амидов пировиноградной кислоты; синтез координационных соединений некоторых $3d$ металлов с 4-аллилтиосемикарбазонами амидов пировиноградной кислоты; установление состава, строения и физико-химических свойств синтезированных соединений; исследование антиоксидантной, противомикробной и противогрибковой активностей синтезированных веществ.

Научная новизна и оригинальность: синтезированы и описаны 89 новых координационных соединений; изучено влияние заместителей в бензилиденовом фрагменте, природы центрального атома, природы кислотного остатка, природы N-гетероароматических оснований во внутренней сфере комплексов на физико-химические свойства и биологическую активность синтезированных веществ.

Решенная научная проблема: получены новые потенциальные противомикробные, противогрибковые и антиоксидантные агенты на основе смешаннолигандных координационных соединений меди(II) 4-аллилтиосемикарбазонов замещенных салицилового альдегида и координационных соединений некоторых $3d$ металлов 4-аллилтиосемикарбазонов амидов пировиноградной кислоты. Были выявлены соединения, обладающие высокой растворимостью в воде, а также соединения, которые превосходят по активности вещества, которые были использованы в качестве стандартов (Тетрациклин, Флуконазол и Тролокс).

Теоретическая и практическая значимость работы: результаты данного исследования могут быть использованы в дальнейшем для поиска новых координационных соединений, обладающих высокой противогрибковой, противомикробной и антиоксидантной активностью и растворимостью в воде, за счет выявления взаимосвязи структуры вещества и его активности, и определения влияния дополнительного биологически активного лиганда в составе координационных соединений на синергизм их биологических свойств. Синтезированные вещества в дальнейшем могут пройти предклинические испытания. В дальнейшем результаты данного исследования могут дополнить материал спецкурсов по Биофармацевтической Химии и Биохимии.

Внедрение полученных научных результатов: Запатентовано соединение, обладающее бактериостатическим действием в отношении *Bacillus cereus* и *Bacillus subtilis*.

UNIVERSITATEA DE STAT DIN MOLDOVA
ȘCOALA DOCTORALĂ ȘTIINȚE BIOLOGICE, GEONOMICE, CHIMICE ȘI TEHNOLOGICE

Cu titlu de manuscris
C.Z.U.: 544.142.3:546.562:547.497.1(043)

GRAUR IANINA

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141.02 – CHIMIE COORDINATIVĂ

Rezumatul tezei de doctor în ştiinţe chimice

CHISINAU, 2023

GRAUR IANINA

SYNTHESIS, STRUCTURE, AND BIOLOGICAL PROPERTIES OF COPPER COMPLEXES WITH POLIDENTATE LIGANDS BASED ON 4-ALLYLTHIOSEMICARBAZONES SOLUBLE IN WATER

141.02 – COORDINATION CHEMISTRY

Abstract of the doctoral thesis in chemical sciences

Approved for printing: 18.09.2023 Paper size 60x84 1/16

Offset paper. Offset printing. Edition 10 ex.

Printing sheets.: 2.0 Order № 179

Typography: Centrul Editorial-Poligrafic al USM
Mateevici 60 str., Chișinau, MD-2009, Republic of Moldova