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POLYFUNCTIONAL INHIBITORS BASED ON COORDINATION COMPOUNDS OF SOME 3*d*-METALS WITH SALICYLIDENE- AND PICOLIDENE-4-ALLYL-S-ALKYLISOTHIOSEMICARBAZIDES AND THEIR SUBSTITUTES

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CONCEPTUAL MILESTONES OF RESEARCH

Relevance and importance of the problem:

Every day, the human body is exposed to various factors that can block the processes of DNA replication and transcription, which is the main cause of the development of cancer. The oxidative stress of the body is one of the mechanisms of the development of carcinogenesis. The oxidation processes play an important role in the cellular defense system, promote energy production in mitochondria, and are also a part of the inflammatory process. Thus, oxidative stress and chronic inflammation caused by a bacterial or viral infections can lead to the development of cancer.

The effectiveness of modern methods of cancer treatment increases with the use of antibiotics. Their use may decrease some side effects and reduce the risk of patients dying from infections. In most cases, bacterial and fungal infections are difficult to treat due to their high resistance to existing drugs. Currently, the search for effective anticancer, antimicrobial and antioxidant drugs is an actual vector of the development of modern chemistry. The principle of drug development is to transform the most studied and active molecules in order to obtain analogues that exhibit selective action and low toxicity.

Cisplatin and its analogues, as well as doxorubicin, are widely used as a part of combination chemotherapy regimens for the treatment of various tumors, but their action leads to severe side effects due to low selectivity towards healthy tissues and high toxicity. Based on the literature data, 3*d* metal complexes have a low toxicity and selective action, accordingly, open the field for further research. The thiosemicarbazides and their derivatives compouse a promising class of compounds with a wide spectrum of biological activity.

The Laboratory of Advanced Materials in Biopharmaceutics and Technics of the Moldova State University under the direction of Academician Gulea A.P. made a huge contribution to the development of innovative potential drugs based on coordination compounds of 3*d* metals with salicylidene- and picolidene-thiosemicarbazides [1-14]. The results of experimental researches in this area showed high biological activity. Multiple studies have shown that the introduction of a substituent in the fourth position of the thiosemicarbazone leads to a significant increase in biological activity.

The complexes with 4-allylthiosemicarbazones are of particular interest from the point of view of the introduction of an allyl group into the fourth position of thiosemicarbazone [5–8]. Several coordination compounds of biometals with these ligands and their derivatives, which

exhibit high biological activity and relatively low toxicity, have been patented [7, 8]. Despite the fact that thiosemicarbazides and thiosemicarbazones, along with their metal complexes, are widely represented in the literature, the coordination chemistry of *S*-substituted isothiosemicarbazides and their derivatives is much less studied. Thus, it was of interest to study how the alkylation of the thiosemicarbazide fragment of 4-allylthiosemicarbazones would affect the composition and structure of the coordination compounds of biometals with them, as well as the antimicrobial, antifungal, anticancer, and antioxidant properties. As a result, a wide range of salicylidene- and picoliden-4-allyl-S-alkylisothiosemicarbazides were obtained. It was determined that some of them exhibit promising biological activity and high selectivity. Also, various modes of coordination of these isothiosemicarbazones were identified. Thesis was elaborated in the research Laboratory of Advanced Materials in Biopharmaceutics and Technics of the Moldova State University.

The aim of this study:

finding of the new polyfunctional molecular inhibitors of cancer cells with selective activity and with antibacterial, antifungal and antioxidant properties; determination of the influence of the nature of the substituents at the sulfur atom and in the first position of isothiosemicarbazones, the nature of the central atom, the nature of the ligand, the introduction of amines into the inner sphere on the composition, structure, physicochemical and biological properties of the coordination compounds of some 3*d* metals with salicylidene- and picolidene-4-allylthiosemicarbazides.

Research objectives:

1. the alkylation of the sulfur atom in the composition of 4-allylthiosemicarbazones of various aromatic and heteroaromatic carbonyl compounds;
2. the synthesis of coordination compounds of some 3*d* metals with salicylidene- and picoliden-4-allyl-S-alkylisothiosemicarbazides and their derivatives;
3. the introduction of various amines into the inner sphere of the complex of copper(II) nitrate with salicylidene-4-allyl-S-methylisothiosemicarbazide;
4. establishing the influence of the nature of the central atom, ligand, anion of the acid residue, introduction of amines into the inner sphere on the composition, structure, physicochemical and biological properties of coordination compounds of some 3*d* metals with salicylidene- and picoliden-4-allyl-S-alkylisothiosemicarbazides and their derivatives.

Research hypothesis:

Based on the analysis of literature sources, it is assumed that 4-allyl-*S*-alkylisothiosemicarbazones of various aromatic and heteroaromatic carbonyl compounds, as well as coordination compounds of some 3*d* metals with these ligands, are of interest from the point of view of physicochemical and biological properties. These compounds are potential inhibitors of proliferation of cancer cells with selective activity and low toxicity, as well as antibacterial, antifungal and antioxidant properties.

Synthesis of the research methodology and justification of the chosen methods:

The structure and purity of the synthesized salicylidene- and picoliden-4-allyl-*S*-alkylisothiosemicarbazides and their derivatives were determined using ^{1}H and ^{13}C NMR spectroscopy. For the obtained isothiosemicarbazones and their hydrohalides, the melting points were determined by the capillary method, and nitrogen was analyzed by the Dumas method. The exact structure of a series of isothiosemicarbazones was determined by X-ray diffraction analysis, for which single crystals were obtained by recrystallization from such solvents as DMSO, DMF, chloroform, ethanol, and methanol.

The coordination compounds of some 3*d* metals were studied by such methods as elemental analysis, determination of magnetic susceptibility by the Gouy method, and molar electrical conductivity in methanol. A comparative analysis of the IR spectra of complexes and ligands was carried out in order to determine the coordination mode of isothiosemicarbazones to the central metal ions. The exact structure of single crystals for several coordination compounds was established by X-ray diffraction analysis.

The antiproliferative activity of the tested compounds against human myeloid leukemia HL-60 cancer cells, human cervical epithelial HeLa cells, human pancreatic epithelial adenocarcinoma BxPC-3 cells, rhabdomyosarcoma RD cells, and normal MDCK cells was investigated *in vitro* using resazurin and MTT cell proliferation assays. The antioxidant activity of the synthesized compounds has been determined using $ABTS^{\bullet+}$, $HO_2^{\bullet}$ radicals. Antimicrobial and antifungal activities were studied on a series of standard strains of gram-negative bacteria, gram-positive bacteria, and fungi by the serial dilution method.

The scientific problem:

The new molecular polyfunctional inhibitors of proliferation of cancer cells (HL-60, HeLa, BxPC-3, RD) based on salicylidene- and picoliden-4-allyl-*S*-alkylisothiosemicarbazides and their derivatives have been synthesized. These compounds have selective action. The antioxidant

activity of molecular inhibitors against ABTS $^{\bullet+}$ and $HO_2^{\bullet}$ radicals was determined. Several substances, that are superior in properties to commonly used drugs (doxorubicin, trolox, quercetin, nitrofurazone, nystatin), have been identified.

The theoretical importance of the work lies in the fact that the results of the research part can be used in the further study of potential anticancer, antimicrobial, antifungal and antioxidant drugs, due to the identified relationships between various structural fragments in salicylidene- and picoliden-4-allyl-*S*-alkylisothiosemicarbazides and their derivatives, coordination compounds and their biological activity. The results of this study are of scientific significance and can be used as a supplement to special courses in Biopharmaceutical Chemistry and Biochemistry.

The practical significance of the work lies in the synthesis of polyfunctional inhibitors with selective action. The research results of this work are presented in **35 scientific publications**, including **10 articles**, among which 3 articles with an impact factor above 3, 1 article with an impact factor of 0.1-1.0, 2 articles with one author, 3 articles of category B, **25 abstracts** in international and national conferences. The obtained results are protected by **5 patents** of the Republic of Moldova. Several compounds are of interest for further preclinical and clinical trials. Innovations were rewarded with **12** gold medals, **4** silver medals, and **1** bronze medal, as well as **35** diplomas.

The structure and scope of the thesis:

The thesis consists of an introduction, four chapters, general conclusions and recommendations, a list of references with 185 sources, and seven annexes. The material is presented on 159 pages of the main text and contains 132 figures and 36 tables (including the Annexes).

THESIS CONTENT

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

1. COORDINATION COMPOUNDS OF SOME *d* METALS WITH 4-ALLYLTHIOSEMICARBASONES AND *S*-ALKYLISOTHIO-SEMICARBAZONES OF AROMATIC CARBONYL COMPOUNDS

The **first chapter** is a literature review of 4 paragraphs, which describes the synthesis, structure, physicochemical and biological properties of 4-allylthiosemicarbazones and *S*-alkylisothiosemicarbazones of aromatic and heteroaromatic carbonyl compounds, as well as coordination compounds of biometals with these types of ligands. It is analyzed the influence of the introduction of amines into the inner sphere of some coordination compounds with thiosemicarbazones and isothiosemicarbazones on the biological activity.

2. METHODS OF SYNTHESIS, ANALYSIS, AND RESEARCH

The **second chapter** consists of 7 paragraphs, which describe the main methods used in the practical part of the research: the synthesis of salicylidene- and picolidene-4-allyl-*S*-alkylisothiosemicarbazides and their derivatives, as well as coordination compounds with some 3*d* metals, synthesis of coordination compounds with the introduction of amines into the inner sphere; elemental analysis for metals and nitrogen; NMR and IR spectroscopic studies; X-ray diffraction analysis; magnetochemical research; determination of molar electrical conductivity; determination of melting points.

The study of biological properties includes the *in vitro* determination of the antiproliferative activity of the tested compounds against human myeloid leukemia HL-60 cancer cells, human cervical epithelial HeLa cells, human pancreatic epithelial adenocarcinoma BxPC-3 cells, rhabdomyosarcoma RD cells, and normal MDCK cells using resazurin and MTT cell proliferation assays.

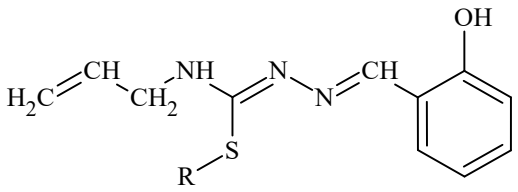
The antioxidant activity of the synthesized compounds has been determined using $ABTS^{\bullet+}$, $HO_2^{\bullet}$ radicals. Antimicrobial and antifungal activities were studied on a series of standard strains of gram-negative bacteria, gram-positive bacteria and fungi by the serial dilution method.

3. COORDINATION COMPOUNDS OF 3*d* METALS WITH 4-ALLYL-*S*-ALKYLISOTHIOSEMICARBAZONES OF AROMATIC CARBONYL COMPOUNDS

The **third chapter** consists of 5 paragraphs and is devoted to the synthesis, structure, and properties of salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones and their derivatives, as well as of coordination compounds of biometals with these ligands. The results of the study of antimicrobial, antifungal, anticancer and antioxidant activities of a number of synthesized compounds are described.

3.1. Complexes of 3*d* metals with salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones

The synthesis of salicylaldehyde 4-allyl-S-alkylisothiosemicarbazones **(HL^{1-4})** was carried out in several stages. At the first stage, the sulfur atom was alkylated by reaction of 4-allylthiosemicarbazide with iodomethane **(HL^{1})**, iodoethane **(HL^{2})**, benzyl chloride **(HL^{3})**, or 4-nitrobenzyl bromide (**HL^{4}**). At the second stage, hydrohalides of 4-allyl-*S*-alkylisothiosemicarbazones were obtained by adding salicylaldehyde, added to the reaction mixture in a 1:1 molar ratio. After that, the hydrohalides were neutralized to a weakly alkaline medium, followed by extraction of salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones using chloroform.



HL^{1}: *R*= CH_3;
HL^{2}: *R*= C_2H_5;
HL^{3}: *R*= $C_6H_5CH_2$;
HL^{4}: *R*= 4-$NO_2C_6H_4CH_2$.

Fig. 3.1.1. Structural formula of salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones

The structure of the synthesized salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones **(HL^{1-4})**, as well as their purity, were determined using ^{1}H and ^{13}C NMR spectroscopy. As a result of a comparative analysis of the NMR spectra of salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone and 4-allylthiosemicarbazone, it was found that the thiosemicarbazide fragment is alkylated. This is proved by the disappearance in the ^{13}C NMR spectrum of the signal in the range 177-179 ppm, which is characteristic for the carbon of the C=S group, as well as the appearance of a new signal in the region of 160-161 ppm, characteristic for the carbon of the C-S group of isothiosemicarbazides and the signal in the area of 10-35 ppm corresponding to the carbon of the CH_2-S group. As a result of recrystallization from various

solvents, single crystals of isothiosemicarbazones **HL^1·HI·C$_2$H$_5$**, **HL^3**, and **HL^4** were obtained and their structure was determined by X-ray diffraction analysis. These molecules are almost flat except for the allyl and benzyl radicals.



HL^1·HI·C$_2$H$_5$OH **HL^3**

Fig. 3.1.2. Molecular structure of salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones

The interaction of isothiosemicarbazones **HL$^{1-4}$** with copper(II), nickel(II), cobalt(II), iron(III), and chromium(III) salts taken in a 1:1 molar ratio in the case of copper(II) and 1:2 in other cases gives fine-crystalline substances of various shades of green in the case of copper(II), and brown in other cases. A magnetochemical study showed that copper(II) complexes have a monomeric structure, nickel(II), cobalt(III), iron(III), and chromium(III) complexes are in an octahedral ligand environment, and the central cobalt(II) ion is oxidized during synthesis and in the coordination compounds is in the +3 oxidation state. The values of molar electrical conductivity of copper(II), nickel(II), cobalt(III), iron(III) and chromium(III) coordination compounds with **HL$^{1-4}$** in methanol are in the range of 64-115 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$, which indicates that these substances belong to 1:1 type of binary electrolytes. A comparative analysis of the IR spectra of the complexes and ligands was carried out in order to determine the method of coordination of isothiosemicarbazones **HL$^{1-4}$** to the central metal ions. It was found that the azomethine and thiocarbamide nitrogen atoms, as well as the deprotonated phenolic oxygen atom, are involved in the coordination. The crystal structures of 11 complexes of copper(II), nickel(II), cobalt(III), iron(III), and chromium(III) with salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones (**HL$^{1-4}$**) were studied by X-ray diffraction analysis.

For a number of synthesized compounds, the antiproliferative activity against human myeloid leukemia HL-60 and cervical cancer HeLa cells was studied and it was found that they suppress cell growth at a concentration of 100 μM, but at lower concentrations (10–0.1 μM) the activity practically disappears. The **[Fe(L^1)$_2$]NO$_3$** complex showed the highest activity and selectivity. The substitution of the *S*-methyl group for the *S*-ethyl group in salicylaldehyde isothiosemicarbazone leads to an increase in activity of the complexes. The **[Fe(L^2)$_2$]NO$_3$** complex, having a high anticancer activity against HeLa and BxPC-3 cells, almost does not have

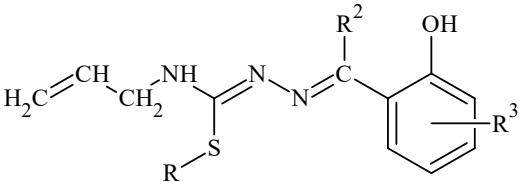
a negative effect on the proliferation of normal MDCK cells. The selectivity index of the **$[Fe(L^2)_2]NO_3$** complex is 64 times higher than the corresponding value for doxorubicine towards HeLa cells and 40 times higher towards BxPC-3 cells.

The study of antimicrobial and antifungal activities showed that complexes of biometals with isothiosemicarbazones **HL^{1-2}** selectively inhibit the growth and reproduction of certain types of microorganisms. The nature of the central atom influences the antimicrobial activity. The activity of coordination compounds decreases in the following order: **Cu(II)> Fe(III)> Co(III) ≈ Cr(III)**. The nature of the acid residue also affects the activity of substances and for the same type of complexes changes in the series **$Cl^- > Br^- > NO_3^-$**. It has been established that the substitution of the *S*-methyl group for the *S*-ethyl group in isothiosemicarbazone leads to an increase in the antimicrobial and antifungal activities of the complexes [9, 10].

The study of antioxidant properties showed that the activity of the tested isothiosemicarbazones towards radical cation $ABTS^{\bullet+}$ decreases in the series **$HL^3 > HL^4 > HL^2 \cdot HI > HL^1 \approx HL^1 \cdot HI \cdot C_2H_5OH$**. The activity significantly increases (IC_{50} = 0.5–0.7 μM) as a result of the complexation of salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone with salts of nickel(II), cobalt(II), iron(III), and chromium(III). The coordination compounds **$[Co(L^1)_2]NO_3$**, **$[Fe(L^1)_2]Cl$**, **$[Fe(L^1)_2]NO_3$**, **$[Cr(L^1)_2]NO_3$** have high antioxidant activity, exceeding 47–67 times the activity of Trolox [11]. The comparison of copper(II) chloride complexes with **HL^{1-4}** showed that the substitution of the *S*-methyl group for the *S*-ethyl group leads to a 3-fold increase in activity against $ABTS^{\bullet+}$ radicals, and in the case of cobalt(III) and iron(III) complexes the opposite effect is observed. The introduction of a benzyl or 4-nitrobenzyl radical into the thiosemicarbazide fragment leads to a loss of activity in most cases, except for the **$[Fe(L^3)_2]Cl$** complex (IC_{50} 0.22 μM) that exceeded the activity of Trolox by 151 times.

3.2. Complexes of 3*d* metals with substituted salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones

In this paragraph, it was studied the effect of introducing substituents —Br, —OH, —OCH_3 into the benzene ring of the salicylidene fragment of 4-allyl-*S*-alkylisothiosemicarbazones on the composition, structure, and biological activity.



HL^5: *$R=CH_3$; $R^2=H$; $R^3=OCH_3$;*

HL^6: *$R=C_2H_5$; $R^2=H$; $R^3=OCH_3$;*

HL^7: *$R= CH_3$; $R^2=H$; $R^3=OH$;*

HL^8: *$R= CH_3$; $R^2=H$; $R^3=2Br$;*

Fig. 3.2.1. Structural formula of substituted salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones (HL^{5-8})

The experiment showed that fine-crystalline substances of various shades of green, with the general formula $\mathbf{CuL^{5-8}X}$ (X=Cl^-, Br^-, NO_3^-, CH_3COO^-) are formed by the interaction of copper(II) salts with alcoholic solutions of 4-allyl-*S*-alkylisothiosemicarbazones $\mathbf{HL^{5-8}}$. As a result of interaction of 4-allyl-*S*-alkylisothiosemicarbazones $\mathbf{HL^{5-8}}$ with nickel(II), cobalt(II) and iron(III) salts under similar conditions, brown substances are formed with general formulas $\mathbf{Ni(L^{5,6})_2}$; $\mathbf{Ni(L^{6,8})X}$, where X= I^-, CH_3COO^-; $\mathbf{Co(L^{5-8})_2X}$, where X=I^-, Br^-, NO_3^-, CH_3COO^-; $Fe(L^{5-8})_2NO_3$.

The study of anticancer activity against cervical HeLa cancer cells showed that the introduction of the methoxy group into position 3 of the salicylidene fragment leads to an increase in the activity of isothiosemicarbazone and its copper(II) complexes. The results of the study of antimicrobial and antifungal properties showed that the synthesized compounds exhibit antimicrobial activity against all studied bacterial strains in the concentration range of 0.97-500 μg/mL and antifungal activity against *Candida albicans* in the concentration range of 15.63-500 μg/mL. The complexes of copper(II) halides with 3,5-dibromosalicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone showed the highest activity. The minimum inhibitory concentration of $\mathbf{[Cu(L^8)]Cl}$, $\mathbf{[Cu(L^8)]Br}$ complexes was 0.97 μg/mL against gram-positive bacteria *Staphylococcus aureus*, which is 19 times higher than the activity of nitrofurazone used as a standard antimicrobial agent. It has been established that the introduction of substituents in positions 3 and 5 of the salicylidene fragment leads to an increase of the antimicrobial and antifungal activities of both the initial isothiosemicarbazone and its complexes.

The antioxidant activity of a number of compounds increases significantly with the introduction of an additional —OH group into the 4th position of the salicylidene fragment of 4-allyl-*S*-methylisothiosemicarbazone. The activity against $ABTS^{\bullet+}$ radical cations of isothiosemicarbazones decreases in the following order: $\mathbf{HL^7 > HL^6 > HL^8 > HL^5}$. The half-maximal inhibitory concentrations were 0.4 μM for $\mathbf{[Co(L^7)_2]I}$ and 0.65 μM for $\mathbf{[Fe(L^7)_2]NO_3}$, which are 83 and 51 times higher than the activity of Trolox.

3.3. Complexes of 3*d* metals with 2-hydroxyacetophenone and 2-hydroxy-1-naphthaldehyde 4-allyl-*S*-alkylisothiosemicarbazones

In this paragraph, it was studied the effect of substitution of the salicylidene fragment with 2-hydroxyacetophenone and 2-hydroxy-1-naphthalidene fragments on the composition, structure, and properties of 4-allyl-*S*-alkylisothiosemicarbazones and their complexes. For this, 2-

hydroxyacetophenone 4-allyl-*S*-methylisothiosemicarbazone **(HL^{9})**, 2-hydroxy-1-naphthaldehyde 4-allyl-*S*-methylisothiosemicarbazone **(HL^{10})** and 2-hydroxy-1-naphthaldehyde 4-allyl-*S*-ethylisothiosemicarbazone **(HL^{11})** were synthesized.

The single crystals **HL^{10}** and **HL^{11}·HI·H$_2$O** were obtained as a result of recrystallization from chloroform. Their structures were established by X-ray diffraction analysis (**Fig. 3.3.1.**). The thiosemicarbazone molecules in both cases is practically planar, except for the ethyl fragment.

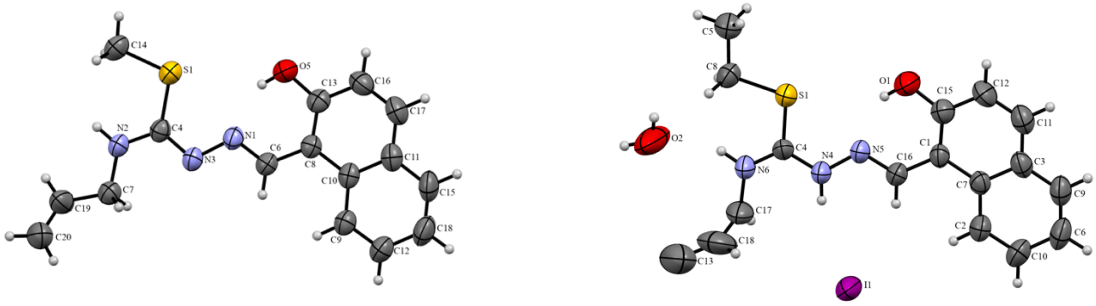


Fig. 3.3.1. Molecular structures of 2-hydroxy-1-naphthaldehyde 4-allyl-*S*-methyl/ethylisothiosemicarbazones

During interaction of hot ethanol solutions of copper(II), nickel(II), cobalt(II), iron(III), and chromium(III) salts with isothiosemicarbazones **HL$^{9\text{-}11}$** fine-crystalline compounds were obtained, for which, based on the results obtained in the course of elemental analysis, the following composition was established: **Cu(L$^{9\text{-}11}$)X·nH$_2$O**, where X = Cl^-, Br^-, NO_3^-, ClO_4^-, CH_3COO^-, n=1-2; **Ni(HL^{10})(L^{10})ClO$_4$**; **Ni(L^{11})$_2$**; **M(L$^{9\text{-}11}$)X**, where X = Br^-, I^-, NO_3^-, M=Co^{3+}, Fe^{3+}. The magnetochemical research showed that copper(II) complexes have a monomeric structure, nickel(II), cobalt(III), iron(III), and chromium(III) complexes are in an octahedral ligand environment, and the central cobalt(II) ion is oxidized during synthesis and in coordination compounds is in the +3 oxidation state. The molar conductivity values of the complexes in methanol indicate that these compounds are binary electrolytes (λ = 70-89 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$). As a result of a comparative analysis of the IR spectra, it was found that isothiosemicarbazones **(HL$^{9\text{-}11}$)** are coordinated to the central metal ions by NNO donor atoms.

The activity of the studied compounds against human myeloid leukemia cells HL-60 varies in the range of concentrations 10^{-5}-10^{-7} mol/L. The anticancer activity significantly increases as a result of the complexation reaction of isothiosemicarbazones with some 3*d* metals. The **[Cu(L^{11})Cl]** and **[Cu(L^{11})NO$_3$]** complexes showed the highest selectivity against the BxPC-3 cancer cells, thus proving that the substitution of the *S*-methyl radical of isothiosemicarbazone for *S*-ethyl leads to an increase in anticancer activity.

In the course of studying the antimicrobial and antifungal properties of a number of compounds, it was found that substitution of the salicylidene fragment with 2-

hydroxyacetophenone leads to a significant increase in activity, reaching 60 μg/mL, and subsequent substitution for the 2-hydroxy-1-naphthaldehyde fragment leads to a $1.4 \cdot 10^3$ times increase in activity comparing to the original isothiosemicarbazones against *Staphylococcus aureus* and 66 times higher against *Candida albicans*. The antifungal activity of **HL^{10}** was 0.7 μg/mL, which is 114 times higher than the activity of nystatin against *Candida albicans*. The antimicrobial and antifungal activities of isothiosemicarbazones increase in the following order: **$HL^1 \approx HL^2 < HL^9 < HL^{10}$**.

The study of the antioxidant activity of some synthesized substances containing isothiosemicarbazones **$HL^{9\text{-}11}$** toward to the $ABTS^{\bullet+}$ radical cation showed that the substitution of the *S*-methyl radical for the *S*-ethyl radical in 2-hydroxy-1-naphthaldehyde 4-allyl-*S*-alkylisothiosemicarbazones leads to an increase in activity. It was also possible to establish that the substitution of the 2-hydroxy-1-naphthaldehyde fragment for 2-hydroxyacetophenone in the hydroiodides of 4-allyl-*S*-methylisothiosemicarbazones leads to an almost twofold increase in activity.

3.4. Copper(II) complexes with salicylaldehyde 4-allyl-*S*-alkylisothiosemicarbazones and amines

In order to study the effect of introducing amines into the structure of copper(II) complexes with salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone **(HL^1)**, a number of mixed-ligand compounds were synthesized. During the experiment, it was found that in the interaction of ethanol solutions of salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone and copper(II) nitrate trihydrate, followed by the addition of various monodentate amines (pyridine, 3-picoline, 4-picoline, 3,4-lutidine, imidazole) taken in a 1:1 molar ratio, fine-crystalline substances of various shades of green are formed, with a composition determined on the basis of elemental analysis **$Cu(A)(L^1)NO_3 \cdot nH_2O$**, where A – pyridine (Py), 3-picoline (3-Pic), 4-picoline (4-Pic), 3,4-lutidine (3,4-Lut), imidazole (Im); n=0.1.

The synthesis of a mixed-ligand complex of copper(II) with 1,10-phenanthroline was carried out in two stages. Initially, an intermediate complex of copper(II) nitrate with salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone was isolated from the ethanol medium,. The dried complex was then dissolved in a mixture of methanol and acetonitrile, and 1,10-phenanthroline was added in a 1:1 molar ratio. As a result, a complex was formed for which, based on elemental analysis, the composition **$Cu(1,10\text{-}Phen)(L^1)NO_3$** was determined. The magnetochemical research of the synthesized mixed-ligand complexes showed that these complexes are monomers (1.79–2.10 MB). The molar conductivity values of the methanol solutions of complexes (λ = 78-96 $\Omega^{-1} \cdot cm^2 \cdot mol^{-1}$)

indicate that **Cu(A)(L^1)NO_3·nH_2O** compounds are electrolytes of the 1:1 type. As a result of recrystallization from ethanol solutions, single crystals of three mixed-ligand coordination compounds were obtained **[Cu(3,4-Lut)(L^1)NO_3]**, **[Cu(1,10-Phen)(L^1)]NO_3**, **[Cu(4-Pic)(L^1)(NO_3)]$_n$**. Copper(II) coordination compounds with 3,4-lutidine and 1,10-phenanthroline have a monomeric structure. The coordination polyhedrons are a distorted square pyramid. The salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone **HL^1** in complexes behave like a NNO – tridentate monodeprotonated ligands. The fourth and fifth coordination sites are occupied by the nitrogen atoms of amines and oxygen atom of the nitrate ion, in the case of complex with 3,4-lutidine. In the case of the **[Cu(4-Pic)(L^1)(NO_3)]$_n$** complex, a polymer structure was established. The coordination polyhedron of the compound is a distorted square bipyramid. The salicylic aldehyde 4-allyl-*S*-methylisothiosemicarbazone **HL^1** as part of the complex, is located at the base of the bipyramid and acts as a NNO – tridentate, monodeprotonated ligand. The fourth coordination site at the base of the bipyramid is occupied by the nitrogen atom of 4-picoline. Apical positions are occupied by oxygen atoms of bridging nitrate ions.

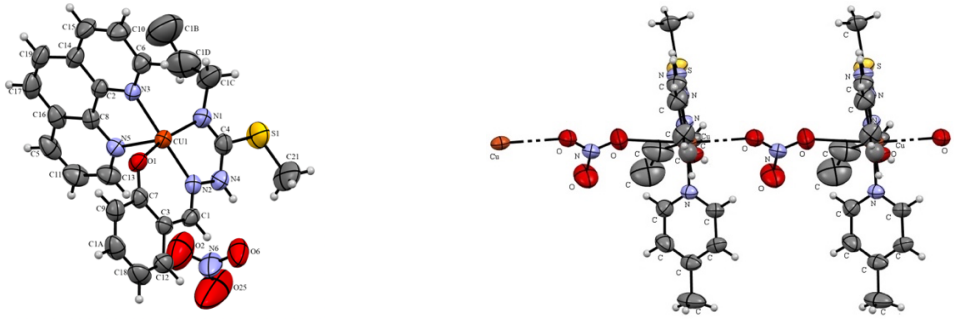


Fig. 3.4.1. Molecular structure [Cu(1,10-Phen)(L^1)]NO_3 and [Cu(4-Pic)(L^1)(NO_3)]$_n$

The study of the anticancer activity of the synthesized substances against HeLa, BxPC-3, and RD cancer cells showed that copper(II) complexes with amines have an inhibitory effect on the proliferation of cancer cells in the range of concentrations 100–0.1 μM. The **Cu(Im)(L^1)NO_3·H_2O** complex exhibits activity against HeLa cancer cells 6 times higher than the other studied compounds of this group, as well as doxorubicin, with a selectivity index value of 4.48. It has been established that the introduction of additional methyl groups into the pyridine ring of the amine leads to a decrease in activity against cervical HeLa cancer cells. The complexes with pyridine and 3-picoline have the most selective effect on BxPC-3 cancer cells, for which the inhibitory effect on normal MDCK cells is 10 times lower than on cancer cells. The **Cu(3-Pic)(L^1)NO_3·H_2O** and **Cu(Im)(L^1)NO_3·H_2O** complexes have the highest selectivity among the series of mixed-ligand coordination compounds studied for rhabdomyosarcoma RD cells, exceeding the selectivity of doxorubicin.

The study of antioxidant properties showed that the introduction of amines into the inner sphere of the complexes of copper(II) nitrate with salicylaldehyde 4-allyl-*S*-methylisothiosemicarbazone leads to a significant increase in antioxidant activity in comparison with the activity of **HL^{1}**. The greatest suppression of $ABTS^{\bullet+}$ radical cations occurs in the presence of the copper(II) complex with the bidentate amine 1,10-phenanthroline **[Cu(1,10-Phen)(L^{1})]NO$_3$**.

4. COORDINATION COMPOUNDS OF SOME 3*d* METALS WITH 4-ALLYL-*S*-ALKYLISOTHIOSEMICARBAZONES OF HETEROAROMATIC CARBONYL COMPOUNDS

The **fourth chapter** consists of 3 paragraphs, which present the results of chemical, physical, physicochemical and biological studies of 2-formylpyridine and its derivatives 4-allyl-*S*-alkylisothiosemicarbazones, as well as complexes of some 3*d* metals with these ligands.

4.1. Coordination compounds of 3*d* metals with 2-formylpyridine 4-allyl-*S*-alkyliso-thiosemicarbazones

The synthesis of isothiosemicarbazones of heteroaromatic carbonyl compounds was carried out similarly to the synthesis of salicylidene-4-allyl-*S*-alkylisothiosemicarbazides. As a result of recrystallization from chloroform, single crystals were obtained, and the structure of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone **(HL^{12})** and 2-formylpyridine 4-allyl-*S*-(4-nitrobenzyl)isothiosemicarbazone **(HL^{15}·HBr)** was determined by X-ray diffraction analysis. Molecules of isothiosemicarbazones are practically flat except for the methyl and 4-nitrobenzyl radicals.

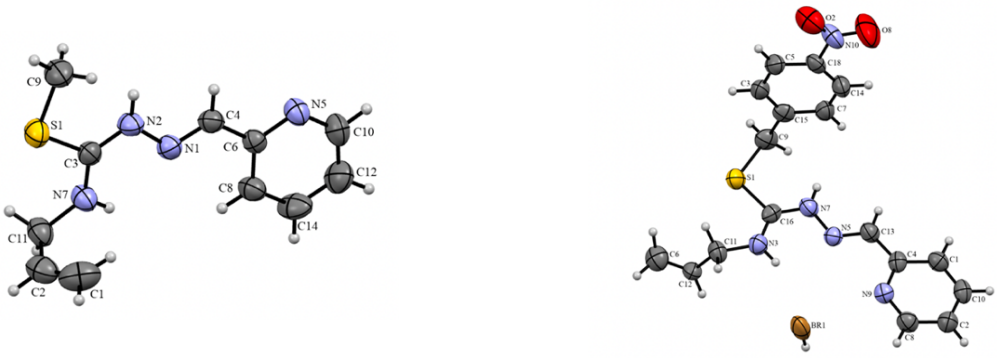


Fig. 4.1.1. Molecular structures of 2-formylpyridine 4-allyl-*S*-alkylisothiosemicarbazones HL^{12} and HL^{15}·HBr

The synthesis of copper(II) coordination compounds was carried out in a 1:1 molar ratio. The ligand in the complex of 2-formylpyridine 4-allyl-S-alkylisothiosemicarbazones with

copper(II) acetate is deprotonated, as indicated by the value of molar electrical conductivity that is in the range of 60-90 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$. In other cases, the molar conductivity values correspond to the 1:2 type electrolytes. The magnetochemical study of the synthesized compounds showed that most of the copper(II) complexes have a monomeric structure, except for the polynuclear complexes **[Cu(HL^{12})Cl$_2$]**, **[Cu(HL^{12})Br$_2$]** (1.48 and 1.37 MB).

Nickel complexes were obtained by interaction of 2-formylpyridine isothiosemicarbazone hydrohalides with nickel(II) acetate or by interaction of isothiosemicarbazones with the corresponding nickel(II) salts in a 2:1 molar ratio. These substances are 1:2 type electrolytes. Nickel(II) complexes have effective magnetic moments (2.87-2.97 MB) characteristic of two unpaired electrons, which indicates an octahedral structure. Cobalt(III) complexes are diamagnetic, iron(III) complexes are paramagnetic with effective magnetic moments in the range of 5.65-5.94 MB, characteristic for 5 unpaired electrons in an octahedral ligand environment.

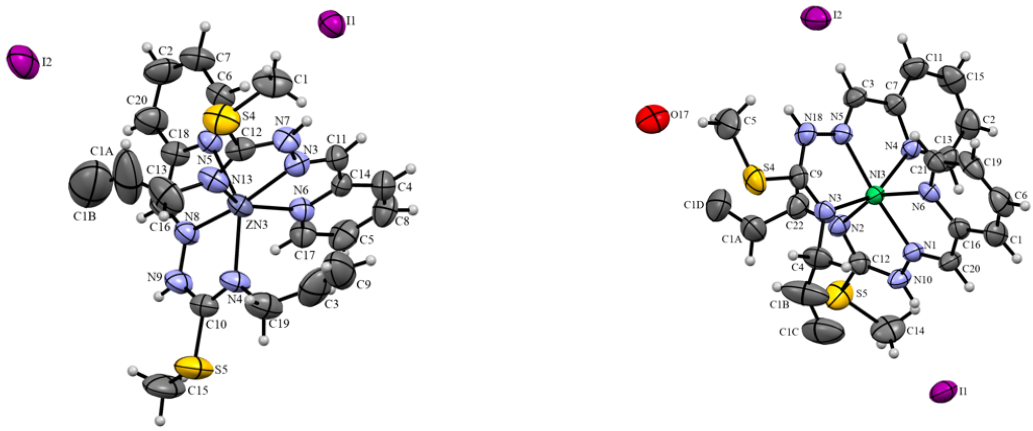


Fig. 4.1.2. Molecular structures of complexes [Zn(HL^{12})$_2$]I$_2$ and [Ni(HL^{12})$_2$]I$_2\cdot$H$_2$O

The single crystals of 8 coordination compounds were obtained as a result of recrystallization from ethanol, the structure of which was established by X-ray diffraction analysis. Zinc(II) and nickel(II) complexes have a similar monomeric structure. The coordination polyhedron is an octahedron. Picolidene-4-allyl-*S*-methylisothiosemicarbazide is coordinated to the metal ions by the NNN-set of donor atoms. The outer sphere contains iodide ions and a water molecule, in the case of the nickel(II) complex.

The antitumor activity was studied for a number of synthesized compounds on a series of cancer cells: human myeloid leukemia HL-60; human cervical epithelium HeLa; human pancreatic epithelial adenocarcinoma BxPC-3; human rhabdomyosarcoma RD. The studied compounds inhibit the growth of HL-60 and HeLa cancer cells at the range of concentrations 1-100 μM. The activity of the studied complexes practically disappears at a concentration of 0.1 μM. The isothiosemicarbazone **HL^{12}** selectively inhibits only RD cells. The cobalt(III) complex **[Co(L^{12})$_2$]Cl** is highly selective toward HeLa cervical cancer cells, since the value of the

selectivity index is more than 60 times higher than the selectivity index of doxorubicin, which is used in medical practice [12].

The results of the study of antimicrobial and antifungal activities showed that **HL^{12}** and its coordination compounds exhibit bacteriostatic and bactericidal properties in the range of concentrations 0.7-500 μg/mL. It has been established that the substitution of the 2-hydroxybenzaldehyde fragment for the 2-formylpyridine fragment in 4-allyl-*S*-alkylisothiosemicarbazone leads to a significant increase in antimicrobial activity, especially against gram-positive microorganisms *Staphylococcus aureus*. The cobalt(III) complex **[Co(L^{12})$_2$]Cl** exhibits the highest antifungal activity against *Candida albicans*, exceeding the activity of nystatin and other synthesized substances. The substitution of the *S*-methyl group to the S-allyl group in the copper complexes **[Cu(HL^{14})Cl$_2$]**, **[Cu(HL^{14})Br$_2$]** leads to an increase of antimicrobial activity against gram-negative microorganisms *Escherichia coli* with values of MIC = 15.63 μg/mL and MBC = 31.25 μg/mL, as well as antifungal activity against *Candida albicans* with values of MIC = 3.906-7.813 μg/mL and MBC=7.813-15.63 μg/mL.

The study of antioxidant properties toward ABTS$^{\bullet+}$ radical cation showed that the activity values of this series of compounds are comparable with the activity of Trolox used in medical practice. Hydrohalides exhibit higher activity than free isothiosemicarbazones. The substitution of the *S*-methyl radical for *S*-allyl or 4-nitrobenzyl radicals leads to an increase in the activity of the free ligand and its complexes. The activity completely disappears upon the formation of coordination bonds of isothiosemicarbazones **HL$^{12\text{-}13}$** with copper(II) and cobalt(II) salts. The **[Zn(L^{15})Cl]** complex showed the highest activity against ABTS$^{\bullet+}$ radicals, with an IC_{50} value 7 times more active than activity of Trolox.

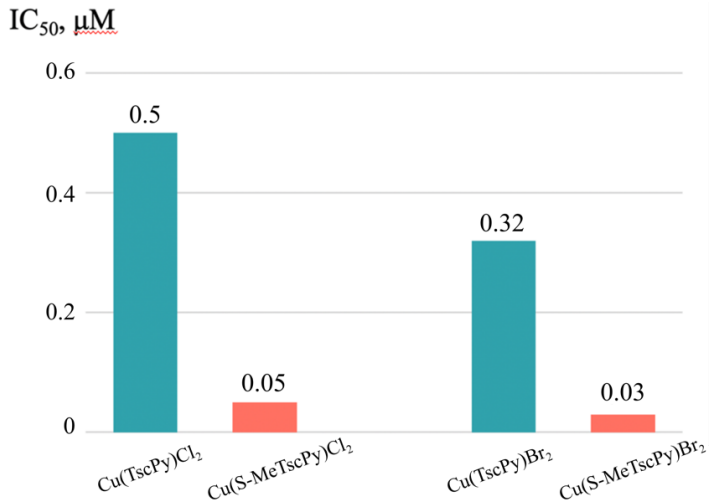
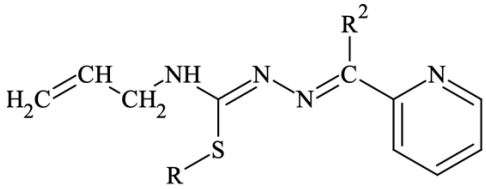


Fig. 4.1.3. Comparative diagram of IC_{50} of some synthesized substances based on 2-formylpyridine thiosemicarbazones and isothiosemicarbazones toward superoxide radicals

The alkylation of the sulfur atom leads to a significant increase in activity against superoxide radicals. The diagram **(Fig. 4.1.3.)** shows a comparison of copper(II) chloride and bromide complexes with 2-formylpyridine 4-allylthiosemicarbazone (TscPy) and 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone (S-MeTscPy). In both cases, the activity of alkylated thiosemicarbazones in the composition of complexes leads to a tenfold increase in activity.

4.2. Coordination compounds of 3*d* metals with derivatives of 2-formylpyridine 4-allyl-*S*-alkylisothiosemicarbazones

In this paragraph, it was studied the effect of substitution of 2-formylpyridine with 2-acetylpyridine and 2-benzoylpyridine on the composition, structure, and properties of 4-allyl-*S*-alkylisothiosemicarbazones and its complexes.



HL^{16}: $R=CH_3$; $R^2=CH_3$;
HL^{17}: $R= C_2H_5$; $R^2=CH_3$;
HL^{18}: $R= CH_2=CH-CH_2$; $R^2=CH_3$;
HL^{19}: $R= 4\text{-}NO_2C_6H_4CH_2$; $R^2=CH_3$;
HL^{20}: $R=CH_3$; $R^2=C_6H_5$;

Fig. 4.2.1. Structural formula of derivatives of 2-formylpyridine 4-allyl-*S*-alkylisothiosemicarbazone

The isothiosemicarbazones **$HL^{16\text{-}20}$** were obtained in two stages: the synthesis of hydrohalides of the corresponding isothiosemicarbazones and their further neutralization.

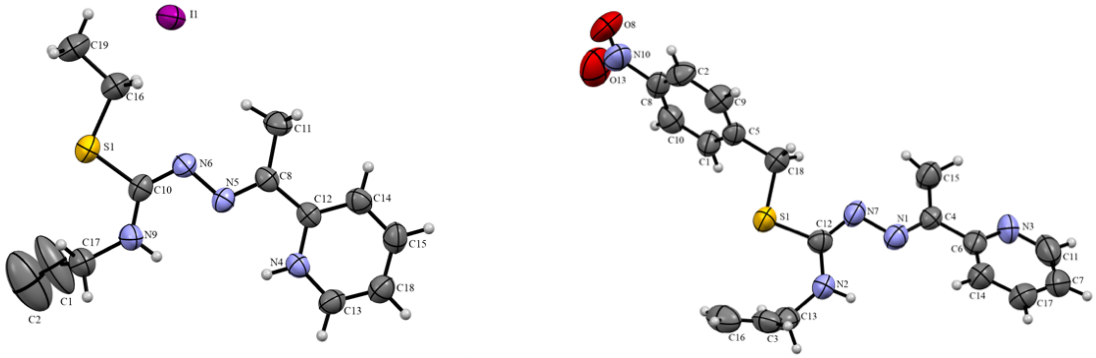


Fig. 4.2.2. Molecular structures of 4-allyl-*S*-alkylisothiosemicarbazones $[H_2L^{17}]I$ and HL^{19}

Recrystallization of six coordination compounds from chloroform gave single crystals of 4-allylisothiosemicarbazones, the structure of which was determined by X-ray diffraction.

The coordination compounds were synthesized by reaction of isothiosemicarbazones **HL$^{16-20}$** and the corresponding copper(II) salts in a 1:1 molar ratio or nickel(II), cobalt(II) and iron(III) in a 2:1 molar ratio. The complexes were also synthesized by the interaction of hydrohalides of isothiosemicarbazones **HL$^{16-20}$** with zinc(II) acetates in a 1:1 molar ratio, nickel(II) or cobalt(II) acetates in a 2:1 molar ratio. The zinc(II), copper(II) and nickel(II) coordination compounds are the 1:2 type electrolytes, since the values of their molar electrical conductivity vary in the range of 146–192 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$. In the case of zinc(II) and copper(II) coordination compounds, the corresponding anions (I^-, Cl^-, Br^- and NO_3^-) are replaced by solvent molecules during dissolution. The coordination compounds of cobalt(III) and iron(III) are the 1:1 type electrolytes with molar electrical conductivity values λ = 82 - 103 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$. The effective magnetic moments of copper(II) coordination compounds are in the range 1.75 – 1.93 MB, which indicates a monomeric structure. The values of magnetic moments of nickel(II) coordination compounds (2.92 – 2.94 MB) correspond to two unpaired electrons and an octahedral ligand environment. The iron(III) coordination compounds are in the high-spin state (5.82 MB). The cobalt complexes are diamagnetic, indicating that cobalt(II) is oxidized to the +3-oxidation state during synthesis. The IR spectra of coordination compounds were compared with the corresponding spectra of isothiosemicarbazones **HL$^{16-20}$** to determine the changes that occur during the formation of coordination compounds. The NNN-set of donor atoms is involved in the coordination of isothiosemicarbazones **HL$^{16-20}$** with central metal ions.

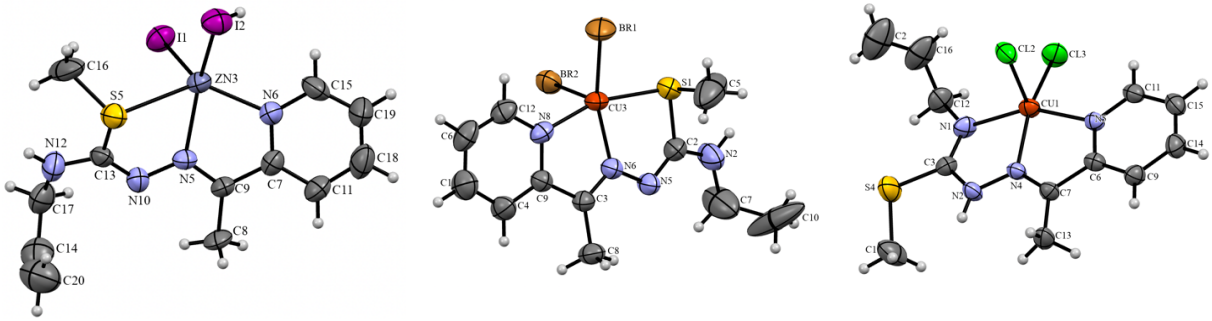


Fig. 4.2.3. Molecular structures of [Zn(HL^{16})I$_2$], [Cu(HL^{16})Br$_2$] and [Cu(HL^{16})Cl$_2$]

In most cases, the coordination of 2-formylpyridine isothiosemicarbazones and its derivatives to the central metal ions occurs along the NNN set of donor atoms. However, in the case of the **[Zn(HL^{16})I$_2$]**, **[Cu(HL^{16})Br$_2$]** complexes, isothiosemicarbazone is coordinated through the methylated sulfur atom. Previously, the coordination of *S*-alkylisothiosemicarbazones through alkylated sulfur atom was observed only in case of some palladium coordination compounds. The crystal structures of these complexes demonstrate the first examples of SNN coordination of isothiosemicarbazones to zinc(II) and copper(II) ions [13].

These compounds exhibit a distorted square pyramidal geometry of metal provided by SNN donor atoms of the ligand and one halogen anion in basal plane ligand and another halogen anion in apical position, but involvement in coordination alkylated sulfur atom differs by orientation of attached to sulfur atoms methyl group. The replacement of bromide ions with chloride ions in **[Cu(HL^{16})Cl$_2$]** leads to the traditional NNN mode of isothiosemicarbazone coordination. Moreover, the coordination mode of **[Cu(HL^{16})Br$_2$]** also change from NNS to NNN mode in the process of its dissolution when the bromide ions are washed out from the inner sphere. Thus, it can be assumed that the presence of bulky anions in the inner sphere leads to the stabilization of coordination through the methylated sulfur atom.

Some synthesized compounds **HL$^{16\text{-}20}$** and their complexes were tested for antiproliferative activity against HeLa, BxPC-3, RD cancer cells and normal MDCK cells. The replacement of hydrogen in the azomethine group by a methyl group leads to an increase in antiproliferative activity; the most active and selective complexes are copper(II) halide complexes, the selectivity index of which toward BxPC3 cells is greater than 12.

The inhibitory activity of novel coordination compounds **[Cu(HL^{18})Cl$_2$]** and **[Cu(HL^{18})Br$_2$]** was tested and compared with the corresponding activities of complexes with 2-acetylpyridine 4-allyl-*S*-methylisothiosemicarbazone. The inhibitory activity toward the normal MDCK cell line decreased. Their IC_{50} values are in the range of 1.2–1.4 μM, while the corresponding complexes with **HL^{16}** have IC_{50} values of 0.35–1.0 μM. Therefore, the novel complexes have a lower impact on normal cells. At the same time, the inhibitory activity toward the human pancreatic cancer cell line (BxPC-3) increased 2.5–18 times. The IC_{50} values of the novel complexes toward BxPC-3 cells are in the range of 5–8 nM. This means that the selectivity indexes (the ratio between IC_{50} values of normal cells and cancer cells) of the novel complexes are in the range of 150–280, which is very promising for further study of these complexes as potent selective anticancer drugs [14].

In the course of the study of antioxidant properties, in almost all cases, nickel(II) complexes exhibit activity higher than Trolox. Among the complexes with 2-benzoylpyridine 4-allyl-*S*-methylisothiosemicarbazone, the highest activity was shown by zinc complexes **Zn(HL^{18})I$_2$**, **[ZnL^{20}Cl]**, exceeding the activity of Trolox by 8 times. The studying of antioxidant properties toward superoxide radicals, it was found that the replacement of the hydrogen of the azomethine group with a methyl fragment leads to a 12-fold decrease in activity, but significantly exceeds the activity of quercetin.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. **20** new salicylidene- and picolidene-4-allyl-S-alkylisothiosemicarbazides and their derivatives and **149** new coordination compounds of chromium(III), iron(III), cobalt(III), nickel(II), copper(II) and zinc(II) with these ligands were synthesized. The conditions for the alkylation of the sulfur atom in the composition of thiosemicarbazone and the introduction of heteroaromatic amines into the inner sphere of copper(II) coordination compounds with salicylidene-4-allyl-S-methylisothiosemicarbazide were found.
2. The isothiosemicarbazones **HL$^{1\text{-}20}$** were studied using IR and NMR (^{1}H and ^{13}C) spectroscopic studies. Two tautomeric forms are present in the solutions of 4-allyl-S-alkylisothiosemicarbazones **HL$^{1\text{-}20}$**.
3. X-ray diffraction analysis established the structure of **13** 4-allyl-S-alkylisothiosemicarbazones and **29** coordination compounds of zinc(II), copper(II), nickel(II), cobalt(III), iron(III) and chromium(III). In the coordination compounds analyzed, the 4-allyl-S-alkylisothiosemicarbazones **HL$^{1\text{-}20}$** behave as tridentate ligands with the set of NNO, NNN or NNS donor atoms, forming metallocycles with the central metal ions, composed of five and six atoms.
4. For the coordination compounds whose structure was not determined by the X-ray diffraction analysis, the coordination mode of 4-allyl-S-alkylisothiosemicarbazone at the central metal ions was established based on the comparative analysis of the IR spectra of the respective ligands and complexes. The 4-allyl-S-alkylisothiosemicarbazone of salicylic aldehyde coordinates to the central metal ions through the set of NNO donor atoms, and in the case of compounds with the 4-allyl-S-alkylisothiosemicarbazone of 2-formylpyridine through the set of NNN donor atoms.
5. The composition of the coordination compounds was determined based on elemental analysis. The magnetochemical study showed that copper(II) complexes can have a monomeric and polynuclear structure, nickel(II), cobalt(III), iron(III), and chromium(III) complexes are in an octahedral ligand environment, the central cobalt(II) ion is oxidized during synthesis and in coordination compounds is in the oxidation state +3.

The study of antiproliferative activity showed:

1. in the most cases, 2-formylpyridine 4-allyl-S-alkylisothiosemicarbazones HL$^{12\text{-}20}$ and its coordination compounds of some 3*d* metals exhibit higher antiproliferative activity against

HeLa, BxPC-3 and RD cancer cells than the corresponding compounds of salicylic aldehyde isothiosemicarbazones and its derivatives;

2. the nature of the central metal ion has the main influence on the antiproliferative activity of the complexes, the most active are copper(II) complexes;
3. The antiproliferative effect of the complexes is selective, copper(II) complexes suppress the growth and reproduction of BxPC-3 cancer cells up to 280 times stronger than normal MDCK cells;
4. The most promising molecular inhibitors of BxPC-3 cancer cells from the synthesized series of substances are the $[Cu(HL^{18})Cl_2]$ and $[Cu(HL^{18})Br_2]$ complexes, whose selectivity indices for BxPC-3 cancer cells and normal MDCK cells exceed the corresponding indicator DOXO 80-145 times.

The study of antimicrobial and antifungal activity showed:

1. Copper(II) complexes with 2-formylpyridine 4-allyl-S-alkylisothiosemicarbazones and its derivatives exhibit higher antimicrobial and antifungal activity than the corresponding complexes with salicylic aldehyde isothiosemicarbazones and its derivatives and are superior in activity to nitrofurazone and nystatin;
2. The range of concentrations in which these substances exhibit antimicrobial and antifungal activity is close to the range of concentrations in which their antiproliferative effect is manifested.

The study of antioxidant activity showed:

1. in most cases, the salicylic aldehyde 4-allyl-S-alkylisothiosemicarbazones HL^{1-11} and its coordination compounds of some 3*d* metals exhibit higher activity towards $ABTS^{\bullet+}$ radical cations than the corresponding 2-formylpyridine 4-allyl-S-alkylisothiosemicarbazones HL^{12-20} and its derivatives, as well as Trolox;
2. The Co(III) and Fe(III) complexes in most cases are superior in antioxidant activity compared with Cu(II) complexes; the introduction of amines into the inner sphere of the Cu(II) complex leads to an increase in antioxidant properties, the acid residue has little effect;
3. antioxidant activity is enhanced by replacing the S-methyl fragment with S-ethyl, S-benzyl and S-p-nitrobenzyl fragments in 4-allyl-S-alkylisothiosemicarbazones;
4. the introduction of additional hydroxy-, methoxy-groups or bromine atoms into the salicylidene fragment leads to an increase of antioxidant activity;

5. the alkylation of thiosemicarbazone led to an increase of antiradical activity towards superoxide radicals; the studied class of compounds exhibits activity significantly higher than quercetin.

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

1. continuation of the study of the structure-property dependence of compounds of the class of various aldehydes and ketones 4-allyl-S-alkylisothiosemicarbazones, since the study revealed active and selective substances that are potential for preclinical and clinical trials, as well as the study of the toxicity of these compounds, in order to a broader view of their action;
2. the introduction of research results into supplements of special courses in Biopharmaceutical Chemistry and Biochemistry;
3. the introduction and application of a number of patented compounds.

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ADNOTARE

Usataia Irina, "Inhibitori polifunctionali în baza compușilor coordinativi ai unor metale 3*d* cu saliciliden- și picoliden-4-alil-S-alchilizotiosemicarbazide substituite", teză de doctor în științe chimice, Chișinău, 2023.

Structura tezei: introducere, patru capitole, concluzii generale şi recomandări, bibliografie din 185 de titluri, 7 anexe, 159 de pagini de text de bază (până la Bibliografie), 132 figuri, 36 tabele (inclusiv Anexe). Rezultatele obţinute sunt publicate în 40 lucrări ştiinţifice (10 articole, 25 teze la conferințe, 5 brevete de invenție).

Cuvinte-cheie: compuşi coordinativi, metale 3*d*, 4-alil-S-alchilizotiosemicarbazone, activitate antiproliferativă, activitate antimicrobiană, activitate antifungică, activitate antioxidantă.

Scopul lucrării: Studiul influenţei alchilării atomului de sulf în saliciliden- și picoliden-4-aliltiosemicarbazide și derivații lor, naturii atomului central, introducerii aminelor în sfera interioară a complecșilor asupra compoziției, structurii, proprietăților fizico-chimice și biologice ale compușilor coordinativi ai unor metale *3d*; găsirea substanțelor cu activitatea antitumorală selectivă, antimicrobiană, antifungică, antioxidativă.

Obiectivele cercetării: sinteza saliciliden- și picoliden- 4-aliltiosemicarbazide și derivaților lor; sinteza compușilor coordinativi ai unor metalelor *3d* cu aceşti liganzi; introducerea aminelor în sfera interioară a complecşilor; determinarea compoziţiei, structurii, activităţilor anticanceroase, antimicrobiene, antifungice și antioxidante pentru compuşii sintetizaţi.

Noutatea şi originalitatea ştiinţifică: Au fost sintetizați și descriși 20 de precursori organici noi și 129 de compuși coordinativi noi. Au fost studiate efectul alchilării atomului de sulf în saliciliden- și picoliden-4-aliltiosemicarbazide și derivații lor, naturii atomului central, introducerii aminelor în sfera interioară a complecșilor asupra proprietăților fizico-chimice și biologice ale compușilor coordinativi ai unor metalele *3d.*

Problema științifică importantă soluționată: Au fost sintetizați inhibitori moleculari noi de proliferare a celulelor canceroase bazate pe saliciliden- și picoliden- 4-alil-S-alchilisotiosemicarbazide și derivații lor cu activitate antiproliferativă selectivă înaltă, antimicrobiană, antifungică. Au fost determinate valorile concentrațiilor de inhibiție semimaximală asupra radicalilor $ABTS^{\bullet+}$, $HO_2^{\bullet}$.

Semnificaţia teoretică a lucrării și valoarea aplicativă:

Au fost sintetizați inhibitori polifuncționali moleculari noi cu activitate selectivă, care prezintă interes pentru studiile preclinice. S-a stabilit influenţa diferitor fragmente structurale din compoziția izotiosemicarbazonelor asupra proprietăţilor anticanceroase, antimicrobiene, antifungice și antioxidante.

Implementarea rezultatelor ştiinţifice: Au fost brevetați un inhibitor molecular nou al proliferării celulelor canceroase RD, 3 compuși coordinativi cu activitate antioxidantă ridicată asupra radicalilor superoxizi și $ABTS^{\bullet+}$, un precursor organic care prezintă activitate antifungică ridicată împotriva *Candida albicans*.

АННОТАЦИЯ

Усатая Ирина, "Полифункциональные ингибиторы на основе координационных соединений некоторых 3*d*-металлов с салицилиден- и пиколиден-4-аллил-S-алкилизотиосемикарбазидами и их замещенными", диссертация доктора химических наук, Кишинэу, 2023.

Структура диссертации: введение, 4 главы, общие выводы и рекомендации, библиография из 185 наименований, 7 приложений, 159 страниц основного текста (до Библиографии), 132 рисунка, 36 таблицы (включая Приложение). Полученные результаты опубликованы в 40 научных работах (10 статей, 25 тезисов на конференциях, 5 патентов).

Ключевые слова: координационные соединения, 3*d* металлы, 4-аллил-S-алкилизотиосемикарбазоны, антипролиферативная активность, противомикробная активность, противогрибковая активность, антиоксидантная активность.

Цель работы: изучение влияния алкилирования атома серы в салицилиден- и пиколиден- 4-аллилтиосемикарбазидах и их производных, природы центрального атома, аминов во внутренней сфере комплексов на состав, строение, физико-химические и биологические свойства координационных соединений некоторых 3*d*-металлов; выявление веществ, обладающих селективной противораковой, противомикробной, противогрибковой и антиоксидантной активностями.

Задачи исследования: синтез салицилиден- и пиколиден- 4-аллил-S-алкилизотиосемикарбазидов и их производных; синтез координационных соединений некоторых 3*d* металлов с вышеуказанными соединениями в качестве лигандов; введение аминов во внутреннюю сферу комплексов; установление состава и строения, антипролиферативной, противомикробной, противогрибковой и антиоксидантной активностей синтезированных веществ.

Научная новизна и оригинальность: синтезированы и описаны 20 новых органических прекурсоров и 129 новых координационных соединений; изучено влияние алкилирования атома серы в салицилиден- и пиколиден- 4-аллилтиосемикарбазидах и их производных, природы центрального атома, введения аминов во внутреннюю сферу комплексов на физико-химические и биологические свойства координационных соединений некоторых 3*d*-металлов.

Решенная научная проблема: Синтезированы новые молекулярные ингибиторы пролиферации раковых клеток на основе салицилиден- и пиколиден- 4-аллил-S-алкилизотиосемикарбазидов и их производных, обладающие селективной противораковой, противомикробной и противогрибкой активностями. Установлены значения концентраций полумаксимального ингибирования в отношении радикалов $ABTS^{\bullet+}$, $HO^{2\bullet}$.

Теоретическая и практическая значимости работы: Синтезированы новые молекулярные полифункциональные ингибиторы, обладающие селективной активностью и представляющие интерес для предклинических испытаний. Установлено влияние различных фрагментов в составе изотиосемикарбазонов на противораковые, противомикробные, противогрибковые и антиоксидантные свойства. Результаты данного исследования имеют научную значимость и могут быть использованы в качестве дополнения спецкурсов по Биофармацевтической химии и Биохимии.

Внедрение полученных научных результатов: Запатентованы молекулярный ингибитор пролиферации раковых клеток RD, 3 координационных соединения, обладающих высокой антиоксидантной активностью в отношении супероксид радикалов и $ABTS^{\bullet+}$, органический прекурсор, проявляющий высокую противогрибковую активность в отношении *Candida albicans*.

ANNOTATION

Usataia Irina, "Polyfunctional inhibitors based on some 3*d* metal coordination compounds with substituted salicylidene- and picolidene-4-allyl-S-alkylisothiosemicarbazides", thesis for PhD in chemical sciences, Chisinau, 2023.

Thesis structure: introduction, four chapters, general conclusions and recommendations, 185 references, 7 annexes, 159 pages of main text (before Bibliography), 132 figures, 36 tables (including applications). The results are published in 40 scientific publications (10 articles, 5 patents, 25 theses at conferences).

Keywords: coordination compounds, 3*d* metals, 4-allyl-S-alchylisothiosemicarbazones, antiproliferative activity, antimicrobial activity, antifungal activity, antioxidant activity.

The aim of the thesis: Determination of the influence of alkylation of sulfur atom in salicylidene- and picolidene-4-allylthiosemicarbazides and their derivatives, nature of central atom, nature of ligands, introduction of amines into the inner sphere of complexes on the composition, structure, physical, chemical and biological properties of the coordination compounds of some *3d*-metals; finding substances with selective antiproliferative, antimicrobial, antifungal, antioxidant activities.

The objectives of the thesis: Synthesis of salicylidene- and picolidene- 4-allyl-S-alkylisothiosemicarbazides and their derivative; synthesis of coordination compounds of some 3d metals with these ligands; introduction of amines into the inner sphere of complexes; determination of composition, structure and antiproliferative, antimicrobial, antifungal and antioxidant activities of the synthesized substances.

Novelty and relevance of the study: The 20 new organic precursors and 129 new coordination compounds were synthesized and described; the effects of alkylation of sulfur atom in salicylidene- and picolidene- 4-allylthiosemicarbazides and their derivatives, the nature of the central atom, the introduction of amines into the inner sphere of the complexes on the physicochemical and biological properties of the coordination compounds of some 3*d*-metals were studied.

Scientific problem solved in this thesis: New molecular inhibitors of cancer cells proliferation based on salicylidene- and picolidene- 4-allyl-S-alkylisothiosemicarbazides and their derivatives, with selective anticancer, antimicrobial and antifungal activities were synthesized. The values of the half maximal inhibitory concentration on $ABTS^{\bullet+}$, $HO_2^{\bullet}$ radicals were determined.

The theoretical importance and potential application value of the work: New molecular polyfunctional inhibitors with selective activity, which are of interest for preclinical trials, were synthesized. The influence of different fragments in composition of isothiosemicarbazones on the antitumor, antimicrobial, antifungal and antioxidant properties was established. The results of this study are of scientific importance and can be used as a supplement to special courses in Biopharmaceutical Chemistry and Biochemistry.

Implementation of scientific results: New molecular inhibitor of RD cancer cells proliferation, 3 coordination compounds with high antioxidant activity against superoxide radicals and $ABTS^{\bullet+}$, an organic precursor showing high antifungal activity against *Candida albicans* were patented.

UNIVERSITATEA DE STAT DIN MOLDOVA

ȘCOALA DOCTORALĂ ȘTIINȚE BIOLOGICE, GEONOMICE, CHIMICE ȘI TEHNOLOGICE

Consorțiu: Universitatea de Stat din Moldova, Institutul de Zoologie, Institutul de Microbiologie și Biotehnologie, Institutul de Genetica, Fiziologie și Protecție a Plantelor, Institutul de Fiziologie și Sanocreatologie, Institutul de Ecologie si Geografie, Gradina Botanică națională (Institut) „Alexandru Ciubotaru", Institutul de Geologie și Seismologie, Institutul de Chimie, Universitatea de Stat din Tiraspol

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USATAIA IRINA

INHIBITORI POLIFUNCTIONALI ÎN BAZA COMPUȘILOR COORDINATIVI AI UNOR METALE 3*d* CU SALICILIDEN- ȘI PICOLIDEN-4-ALIL-S-ALCHILIZOTIOSEMICARBAZIDE SUBSTITUITE

141.02 – CHIMIE COORDINATIVĂ

Rezumatul tezei de doctor în ştiinţe chimice

CHIŞINĂU, 2023

USATAIA IRINA

POLYFUNCTIONAL INHIBITORS BASED ON COORDINATION COMPOUNDS OF SOME 3*d*-METALS WITH SALICYLIDENE- AND PIKOLIDEN-4-ALLYL-S-ALKYLISOTHIOSEMICARBAZIDES AND THEIR SUBSTITUTES

141.02 – COORDINATION CHEMISTRY

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