MOLDOVA STATE UNIVERSITY

DOCTORAL SCHOOL OF NATURAL SCIENCES

Consortium: **Moldova State University, Institute for Development of the Information Society, State University "Bogdan Petriceicu Hasdeu" from Cahul**

As manuscript

C.Z.U: [546.56 + 546.87]-3:547.494.1(043)

NEGUTA ELENA

SYNTHESIS AND STUDY OF THE COORDINATION COMPOUNDS OF Cu(II) AND Bi(III) WITH AMINOPOLYCARBOXYLATE IONS AND THIOSEMICARBAZONE OF 2-FORMYLPYRIDINE AND ITS DERIVATIVES

141.01 INORGANIC CHEMISTRY

Symmary of the doctoral thesis in chemical sciences

CHISINAU, 2024

The thesis was realised at the Doctoral School of Natural Sciences of the Moldova State University, Department of Chemistry.

Scientific leader

BULIMESTRU Ion	doctor in chemistry, associate professor, Moldova State University

Composition of the Doctoral Committee for public defense of the thesis:

LOZAN Vasile	habilitated doctor of chemical sciences, research associate, Institute of Chemistry, Moldova State University – ***chairman***
BULIMESTRU Ion	doctor in chemistry, associate professor, Moldova State University - ***scientific leader***
GULEA Aurelian	habilitated doctor of chemical sciences, academician, university professor, Moldova State University - ***reviewer***
MELNIC Silvia	doctor in chemistry, associate professor, Nicolae Testemițanu University of Medicine and Pharmacy - ***reviewer***
COROPCEANU Eduard	doctor of chemical sciences, university professor, "Ion Creanga" State Pedagogical University from Chisinau - ***reviewer***

The presentation will take place on June 14, 2024 at 14:00 in the meeting of the Doctoral Commission for the public defense of the doctoral thesis within the Doctoral School of Natural Sciences, Moldova State University (http://www.usm.md), 65 A, M. Kogalniceanu str., IIIrd building, 332 auditorium, MD-2009, Chisinau, Moldova.

The doctoral thesis and the summary can be consulted at the National Library of the Republic of Moldova, „Andrei Lupan" Central Scientific Library (Institute), Central Library of Moldova State University (MD 2009, Chisinau, 60, Alexei Mateevici str.), on the ANACEC website (http://www.cnaa.md) and on the USM website (http://www.usm.md) .

The summary was sent on 07 of may, 2024.

The President of the Doctorate Commission
habilitated doctor of chemical sciences,
research associate — **LOZAN Vasile**

Scientific leader
doctor in chemistry, associate professor — **BULIMESTRU Ion**

Author: — **NEGUTA Elena**

TABLE OF CONTENTS:

CONCEPTUAL GUIDELINES OF THE RESEARCH

The actuality and the importance of the research topic. Antibiotic resistance is one of the greatest threats to global health and food security today, therefore the development of new antibiotics or molecules that exhibit activity against pathogenic strains is becoming increasingly important. The World Health Organization (WHO) reports that in European Union only, approximately 25,000 patients die from hospital-acquired resistant bacterial infections [1].

Majority of the drugs, used in medical practice, are organic substances. It has been demonstrated that coordination of certain organic molecules to ion metals generates a significant variety of biological activities. Thus, synthesis of antitumor and antimicrobial drugs, using metal complexes with organic ligands, emerges as an innovative strategy for researchers. Schiff bases, a vast class of organic compounds, are distinguished by the multitude of biological properties they exhibit: antifungal, antipyretic, antitumor, antiproliferative and antimicrobial properties. The chemistry of metal ion complexes with Schiff bases began to develop after the success of cisplatin [2]. Thiosemicarbazones have considerable interest due to their biological activities, such as antitumor, antibacterial, antiviral, antitubercular and antimalarial [3]. Medical applications of thiosemicarbazones began to develop in the 1950s and included applications against tuberculosis and leprosy [9]. In the 1960s, antiviral properties of thiosemicarbazones were discovered, and after additional investigations, Metisazone and Marboran started to be used in the treatment of smallpox [4]. During this period, the first results of the antitumor activity of thiosemicarbazones were published. The anticancer potential of Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) was discovered, which is currently undergoing Phase II clinical trials for several types of cancer [5]. Its antitumor activity is also very broad, but it is largely dependent on the type of tumour cells.

Copper(II) compounds have been investigated based on the assumption that endogenous metals may be less toxic to normal cells compared to cancer cells. However, copper(II) can also be toxic due to its redox activity and affinity for binding sites that should be occupied by other metal ions. Copper is an essential element for most aerobic organisms, used as a structural and catalytic cofactor and consequently is involved in many biological pathways [6]. Taking this into account, much attention has been paid to the research on the mechanisms of copper absorption, distribution, metabolism and excretion, as well as its role in the development of cancer and other diseases [7].

In recent years, considerable attention in the field of coordination chemistry has been focused on the medicinal chemistry of bismuth(III) ion-based therapeutic compounds. Bismuth is a heavy and relatively non-toxic metal. Due to its large ionic radius (1.16 Å) and $6s^2$ lone pair of electrons, Bi(III)

ions can form complexes with high coordination numbers [8] which are responsible for the high biological efficiency and low toxicity in the treatment of a variety of microbial infections, including syphilis, diarrhea, gastritis and colitis. Notably, bismuth(III) is an antimicrobial agent to which resistance has not yet developed and which has a synergistic effect with antibiotics. Among the antimicrobial properties of Bi(III) compounds, the activity against Helicobacter pylori in gastrointestinal diseases [9] and the inhibition of the SARS-CoV-2 virus and the attenuation of its consequences [10] can be highlighted. Moreover, many Bi(III) compounds have also been intensively investigated as potential antimicrobial and antileishmanial drugs [11]. A remarkable study demonstrated an 82% inhibition rate of cancer cells at a concentration of 0.25 μM of a Bi(III) coordination compound. The IC50 value of this complex is 41 nM, which is about 100 times lower than that of cisplatin [12].

In 2008, the researchers from the Department of Chemistry, Moldova State University, successfully synthesized a series of heterometallic coordination compounds of the Cu(II)-Bi(III)-APC type with salicylaldehyde thiosemicarbazone. These compounds have demonstrated remarkable efficiency in inhibiting the proliferation of human leukaemia HL-60 cells, achieving an inhibition rate of 99%, significantly higher than the one of the homometallic complex of Cu(II) with the same thiosemicarbazone (50%) [13].

Based on the foregoing, the **aim of this work** is the comparative structural and biological study of homo- and heterometallic complexes of Cu(II) and Bi(III) with mixed ligands: aminopolycarboxylates (APC) - thiosemicarbazones of 2-formylpyridine and its derivatives to elucidate the factors that amplify biological activity.

Research objectives:

- establishment of optimal synthesis conditions for homo- and heterometallic coordination compounds of Cu(II) and Bi(III) using $edta^{4-}$, $cdta^{4-}$, $dtpa^{5-}$ ions and thiosemicarbazones of 2-formyl-, 2-acetyl- and 2-benzoylpyridines with or without substituents in the 4N position.
- determination of the chemical composition, purity and structure of the obtained substances using various physicochemical analysis methods: elemental analysis, IR spectroscopy, single crystal X-ray diffraction and powder X-ray diffraction.
- determination of biological activity of the synthesized compounds to elucidate the influence of the following factors: the substituent (R1) on the carbonyl carbon; the thiol/thionic form of the ligand; the substituent (R2) in the 4N position of the thiosemicarbazone; the nature of the metal ion; the nature of the APC anion; the ligand ratio. In the heterometallic complexes, the influence of the second metal ion has also been analysed.

The research hypothesis is synthesis of new homo- and heterometallic compounds of Cu(II) and Bi(III) with aminopolycarboxylates (APC) ions in combination with different thiosemicarbazones. The obtained coordination compounds are of interest for the development of new antimicrobial, antifungal and anticancer drugs.

Protocol of the research methodology and justification of the chosen research methods.

The thiosemicarbazones were synthesized according to methodologies described in the literature [14]. The purity of the thiosemicarbazones was checked by thin-layer chromatography, IR, ^{1}H and ^{13}C NMR spectroscopies. The obtained homo- and heterometallic coordination compounds were characterized by various physicochemical analysis methods. Elemental analysis was performed using Vario-EL-III-CHNOS Elemental Analyser from GmbH, at the Physical and Inorganic Chemistry Centre of the Institute of Chemistry, USM. IR spectroscopy was performed on a BRUKER ALPHA spectrometer in the laboratory "Advanced Materials in Biopharmaceutics and Technology", MSU. Single crystal X-ray diffraction was performed at "Petru Poni" Macromolecular Chemistry Institute (Iasi, Romania) using a Bruker APEX II diffractometer and Xcalibur E with EOS CCD detector and Mo-K_α radiation. Powder X-ray diffraction was performed at the Regional Interdisciplinary Scientific-Educational Centre for Advanced Materials Research (CaRISMA), USM.

For some of the synthesized complexes, antimicrobial activity was determined against two Gram-positive bacterial strains: *Staphylococcus aureus* (ATCC 25923), *Bacillus cereus* (ATCC 11778) and two Gram-negative strains: *Escherichia coli* (ATCC 25922), *Acinetobacter baumannii* (BAA-747). Antifungal activity was also determined against *Candida albicans* strain (ATCC 10231). The research was carried out in the Microbiology Laboratory of the National Agency for Public Health, Chisinau, Moldova.

In addition to their antimicrobial and antifungal activities, the antioxidant properties of some of the synthesized coordination compounds have also been analysed. The research was carried out in the Laboratory of Molecular Systematics and Phylogeny at Institute of Zoology, Chisinau, Moldova.

Scientific novelty and originality.

Optimal synthesis conditions were determined and 57 coordination compounds with mixed polydentate ligands were obtained. These include 20 homometallic coordination compounds of Cu(II), 14 homometallic compounds of Bi(III) and 23 heterometallic Cu(II)-Bi(III) complexes, using aminopolycarboxylate ions and thiosemicarbazones of 2-formyl-, 2-acetyl- or 2-benzoylpyridine and their derivatives as ligands. The crystal structures of 22 complexes (10 homometallic Cu(II) compounds, 4 homometallic Bi(III) compounds and 8 heterometallic Cu(II)-Bi(III) complexes) were determined by single crystal X-ray diffraction. The antimicrobial, antifungal and antioxidant properties of the obtained coordination compounds were determined. A

heterometallic Cu(II)-Bi(III) compound was patented, which exhibits a 31.9 times higher fungistatic activity against *Candida albicans* than fluconazole and 1.4 times higher than the prototype [15].

The applied value of the thesis lies in the synthesis and characterization of homo- and heterometallic compounds of Cu(II) and Bi(III) with aminopolycarboxylate ions and with thiosemicarbazones of 2-formylpyridine and its derivatives. These compounds have demonstrated significant antimicrobial, antifungal and antioxidant activity. Among the obtained coordination compounds there are ones that are approximately 337 times more active than Furacilin and about 78 times more active than Nystatin.

The results obtained were valorised by publishing 5 articles in national category B journals, as well as by presenting 6 abstracts at national and international conferences. An invention patent was also obtained.

The volume and structure of the work.

The thesis is written on 123 pages of basic text, including 83 figures and 15 tables. Its structure consists of an introduction, the thesis summary written in 3 languages, the list of tables, the list of figures, the list of abbreviations, four basic chapters, conclusions and recommendations, 154 bibliographic resources, the statement of responsibility and the candidate's CV.

THESIS CONTENT

The thesis is presented on 123 pages of basic text, including 83 figures and 15 tables. Its structure consists of an introduction, the thesis summary written in 3 languages, a list of tables, a list of figures, a list of abbreviations, four basic chapters, conclusions and recommendations and 154 bibliographic resources. The total volume of the thesis is 181 pages.

1. COORDINATION COMPOUNDS OF Cu(II) AND Bi(III) WITH THIOSEMICARBAZONES OF 2-FORMYLPYRIDINE AND ITS DERIVATIVES

Chapter 1 is structured from 5 subchapters that present a literature review of the specialized literature. This chapter describes methods for obtaining coordination compounds, as well as some methods for their analysis and research. It also extensively describes the biological activities of coordination compounds.

2. SYNTHESIS AND RESEARCH METHODS

Chapter 2 presents the synthesis methods for 20 homometallic coordination compounds of Cu(II), 14 homometallic coordination compounds of Bi(III) and 23 Cu(II)-Bi(III) heterometallic coordination compounds with mixed ligands: thiosemicarbazone – APC ($edta^{4-}$, $cdta^{4-}$ and $dtpa^{5-}$). Determination of the chemical composition, purity, and structure of the obtained coordination compounds was carried out using elemental analysis, IR spectroscopy, single crystal and powder X-ray diffraction. The determination of antimicrobial activity was carried out by the method of serial dilutions of a liquid nutrient medium of 2% peptone meat broth, pH 7.0. Two Gram-positive strains: *Staphylococcus aureus* (ATCC 25923) and *Bacillus cereus* (ATCC 11778) and two Gram-negative strains: *Escherichia coli* (ATCC 25922) and *Acinetobacter baumannii* (BAA-747) were used as reference cultures in the in vitro experiment. The antifungal tests were performed on *Candida albicans* strain (ATCC 10231). The $ABTS^{\bullet+}$ method was used to determine the antioxidant property.

3. PHYSICAL-CHEMICAL ANALYSIS OF Cu(II) AND Bi(III) COORDINATION COMPOUNDS WITH AMINOPOLYCARBOXYLATE IONS AND THIOSEMICARBAZONES OF 2-FORMYLPYRIDINE AND ITS DERIVATIVES

3.1 Analysis of the IR spectra of the obtained coordination compounds

For Schiff bases, the most informative in IR spectra are the ν(C=N) and ν(C=S) or ν(C-S) valence vibrations. The characteristic signal of ν(C=N) vibrations in thiosemicarbazones, which appears in the range of 1638-1666 cm^{-1}, could not be identified for all complexes because, very often,

it is masked by the very strong and broad signals of the ν_{as}(COO) vibrations of the carboxylate groups from APC (Tables 3.1 and 3.2).

Table 3.1 Maxima (cm^{-1}) of characteristic oscillations in IR spectra of some homometallic complexes of Bi(III)

Compound	νC=N Schiff base	$\nu_{as}COO^-$ APC	$\nu_{sym}COO^-$ APC	$\Delta\nu_{as}COO^- - \nu_sCOO^-$	νC=S Schiff base	νC-C (CH_2COO^-) (CH_2-CH_2) νC-C (cyclohexane)
{[Bi(Hedta)]·HFoPyTSC-4Et}$_n$ **(23)**	1638	1594 1573	1393 1381	201 192	1298	912 883
{[Bi(Hcdta)](HFoPyTSC-4Et)}$_n$ **(27)**	1653 1619	1596 1559	1394 1370	202 189	1302	917 (878)
[Bi(Hedta)(HAcPyTSC-4Et)$_2$]·7.25H_2O **(31)**	-	1584	1374 1357	210 227	1314 1289	916 844
[Cu(HFoPyTSC-4Et)(H_2O)Cu(edta)(H_2O)]·1.5H_2O **(3)**	-	1581 1558	1390	191 168	1321	-
[Cu_2(FoPyTSC-4Et)$_2$Cu(cdta)] **(7)**	-	1602 1562	1367	235 195	-	767 737
{[Cu_2(AcPyTSC-4Me)$_2$Cu(edta)]·H_2O}$_n$ **(10)**	1644	1615 1562	1389 1361	226 201	-	779
{[Cu(HAcPyTSC)Cu(cdta)]·3H_2O}$_2$ **(12)**	-	1595	1363 1334	232 261	1334	-
[Cu_2(AcPyTSC-4Me)$_2$(H_2O)Cu(cdta)]·4,5H_2O **(13)**	-	1607 1562	1377	230 185	-	778
{[Cu_2(AcPyTSC-4Et)$_2$Cu(cdta)]·5.5H_2O}$_n$ **(14)**	-	1606 1563	1372	234 191	-	774 757
{[Cu_2(AcPyTSC-4Ph)$_2$Cu(cdta)]·H_2O}$_n$ **(15)**	-	1598 1558	1413 1371	185 187	-	749 733
{[Cu_2(BzPyTSC)$_2$Cu(cdta)]·6H_2O}$_n$ **(17)**	-	1592 1559	1394	198 165	-	784
{[Cu_4(BzPyTSC-4Me)$_4$$Cu_2$(cdta)$_2$]·11,65$H_2O$}$_n$ **(18)**	-	1591	1393	198	-	784
{[Cu_2(BzPyTSC-4Et)$_2$Cu(cdta)]·3.95H_2O}$_n$ **(19)**	-	1594 1553	1419 1369	175 184	-	789

The shift of the characteristic ν(C=S) oscillation signals in noncoordinated thiosemicarbazones (1301-1324 cm^{-1}) towards higher wavenumbers (1314-1338 cm^{-1}) indicates the coordination of sulphur atoms to Cu(II) ions in homometallic complexes (Table 3.2). In complexes with monodeprotonated thiosemicarbazone in the thiolic form, a new signal appears with a maximum at 733-784 cm^{-1}, attributed to ν(C-S) oscillations, while the signal characteristic to ν(C=S) oscillations disappears. In complexes **42** and **51**, with both deprotonated and monodeprotonated thiosemicarbazone, both ν(C-S) signal and the characteristic signal of the thione form, ν(C=S) are present (Table 3.2). According to literature data [16], $\Delta\nu_{as}$-ν_s differences of COO^- oscillations greater than 200 cm^{-1}, in the IR spectra of complexes, indicate the presence of monodentately coordinated

carboxylate groups, and in the case of differences of around 200 cm^{-1} or less, it can be assumed that the carboxylate groups are mainly coordinated in a bidentate-bridge mode, which was eventualy confirmed by the structural study of the coordination compounds (compounds **7**, **15**, **17**, **18**, **19**), in which all four carboxylate groups coordinate in a bidentate-bridge mode to Bi(III) and Cu(II) ions.

Table 3.2 Maxima (cm^{-1}) of characteristic oscillations in the IR spectra of some Cu(II)-Bi(III) heterometallic complexes

Compound	νC=N Schiff base	ν_{asCOO-} APC	$\nu_{symCOO-}$ APC	$\Delta(\nu_{asCOO^-}-\nu_{sCOO-})$	νC=S Schiff base	νC-S Schiff base	νC-C (CH_2COOH) (CH_2COO^-) νC-C (cyclohexane)
{[Cu(H_2O)(FoPyTSC)Bi(edta)]·H_2O}$_n$ **(35)**	-	1574	1406 1362	168 212	-	757	918 859
{[Cu(FoPyTSC-4Ph)Cu(HFoPyTSC-4Ph)Bi_3(cdta)$_3$]·nH_2O}$_n$ **(42)**	-	1582 1537	1420 1386	162 151	1338	753	922 (881)
[Cu(H_2O)(HFoPyTSC)Bi(dtpa)-(H_2O)]·5H_2O **(43)**	-	1576	1385 1368	191 208	1333	-	921 894_u 862
{[Cu(H_2O)(AcPyTSC)Bi(edta)]·2H_2O}$_n$ **(45)**	-	1578	1421 1358	157 220	-	765	916 859
{[Cu(AcPyTSC-Me)Bi(edta)]·H_2O} **(46)**	1666	1576	1446 1434 1360	130 142 216	-	789	916 855
{[Cu(H_2O)(AcPyTSC-Et)Bi(edta)]·4H_2O}$_n$ **(47)**	-	1570	1433 1363	137 207	-	771	917 853
{[Cu(AcPyTSC-4Ph)Cu(HAcPyTSC-4Ph){Bi(cdta)}$_3$]·8H_2O}$_n$ **(51)**	1638	1585 1532	1422 1389	163 143	1323	779	923 (882)
{[Cu_2(BzPyTSC-Et)$_2$$Bi_2$(cdta)$_2$($H_2O$)$_2$]·13.25$H_2O$}$_n$ **(56)**	-	1585	1432 1382	153 203	-	787	924 (880)

The signals from 912-926 cm^{-1} were attributed to the νC-C vibrations of the carboxylate groups of the APC. The signals of the ethylene/cyclohexane groups from APC can serve as an analytical signal for the identification of coordinated aminopolycarboxylates. Thus, similar to the literature data [17], in case of $edta^{4-}$ ligands, the νC-C signal from the ethylene fragment appears at 844-871 cm^{-1}, while the $dtpa^{5-}$ ligand can be unambiguously distinguished due to the presence of a shoulder at 894 cm^{-1}. The presence of the cyclohexane ring in the $cdta^{4-}$ ligand is confirmed by the νC-C oscillations at ~878-886 cm^{-1}.

3.2 Single crystal X-ray analysis of Cu(II) homometallic coordination compounds with APC ions and thiosemicarbazones of 2-formylpyridine and its derivatives

Homometallic Cu(II) compounds with mixed ligands (thiosemicarbazone – APC) were obtained in two steps. In the first step, Cu_2APC·4H_2O (deep blue in both cases) were synthesized by

the interaction of malachite with the corresponding aminopolycarboxylic acids [18,19]. In the second step, methanolic solutions of 2-formyl-, 2-acetyl- or 2-benzoylpyridines with, or without, 4N substituents were added to an aqueous solution of Cu_2APC. Thus, 20 homometallic coordination compounds of Cu(II) with $edta^{4-}$ and $cdta^{4-}$ ions and 2-formylpyridine thiosemicarbazones with two derivatives were obtained.

The compound $[Cu(HFoPyTSC\text{-}4Et)(H_2O)Cu(edta)(H_2O)]\cdot 1.5H_2O$ **(3)** crystallizes in the triclinic system, space group $P\bar{1}$, with unit cell parameters a=7.659131; b=12.541856; c=14.13501; α=79.7385; β=89.7207; γ = 88.1179. The structure of **3** is formed by anionic $\{Cu(edta)\}^{2-}$ and cationic $\{Cu(HFoPyTSC\text{-}4Et)(H_2O)\}^{2+}$ entities, linked through O8 oxygen atom of a carboxylate group, generating a monomeric structure. The Cu^{2+} ion has a coordination number of five and adopts a distorted square pyramidal geometry (Figure 3.1).

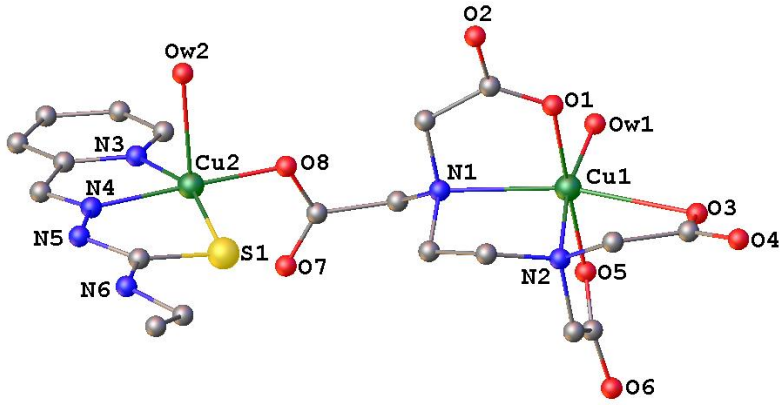


Figure 3.1. Molecular structure of homometallic complex 3

The coordination polyhedron base is formed by the donor atoms (N3, N4, S1) of the non-deprotonated thiosemicarbazone and O8 oxygen atom of a carboxylate group, while Ow2 oxygen atom of a water molecule is at the apex of the pyramid. The Cu1 ion is hexacoordinated, adopting a distorted tetragonal-bipyramidal geometry. The base of the pyramid is formed by Ow1 oxygen atom of a water molecule, two nitrogen atoms (N1 and N2) and O3 oxygen atom of a carboxylate group, while the apical positions are occupied by O1 and O5 oxygen atoms.

The complex $[Cu_2(FoPyTSC\text{-}4Et)_2Cu(cdta)]$ **(7)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=15.288; b=12.2306; c=22.773; β=91.53. In complex 7, an anionic entity $\{Cu(cdta)\}^{2-}$ and two cationic entities $\{Cu(FoPyTSC\text{-}4Et)\}^{+}$ (Figure 3.2) can be distinguished, linked through O8 and O6 oxygen atoms of the bridging carboxylate groups, generating a monomeric structure. There are two Cu(II) ions with different coordination numbers in the structure. The Cu1 ion has a coordination number of six, adopting a distorted tetragonal bipyramidal geometry. The $cdta^{4-}$ anion coordinates hexadentately Cu1 ion through two nitrogen atoms (N1 and N2) and four oxygen atoms (O1, O3, O5 and O7) of four carboxylate groups. The Cu2 and Cu3 ions have

coordination numbers four and adopt tetragonal geometries, coordinating the NNS atoms of the thiosemicarbazones and one oxygen atom (O6 and O8, respectively) of the bridging carboxylate groups from the neighbouring anionic entity $\{Cu(cdta)\}^{2-}$. The 4-ethylthiosemicarbazone of 2-formylpyridine is in monodeprotonated form.

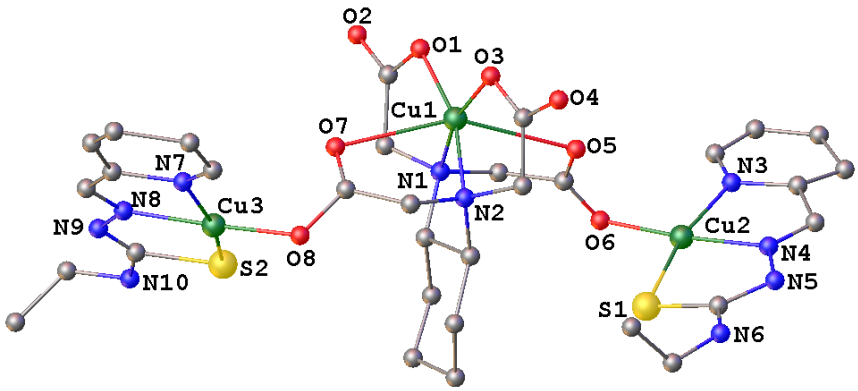


Figure 3.2. Molecular structure of homometallic complex 7

Complex $\{[Cu(HAcPyTSC)Cu(cdta)]\cdot 3H_2O\}_2$ **(12)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=4.2766; b=14.1177; c=14.5139; β=107.151. The structure of compound **12** is formed by cationic $\{Cu(HAcPyTSC)\}^{2+}$ and anionic $\{Cu(cdta)\}^{2-}$ fragments (Figure 3.3).

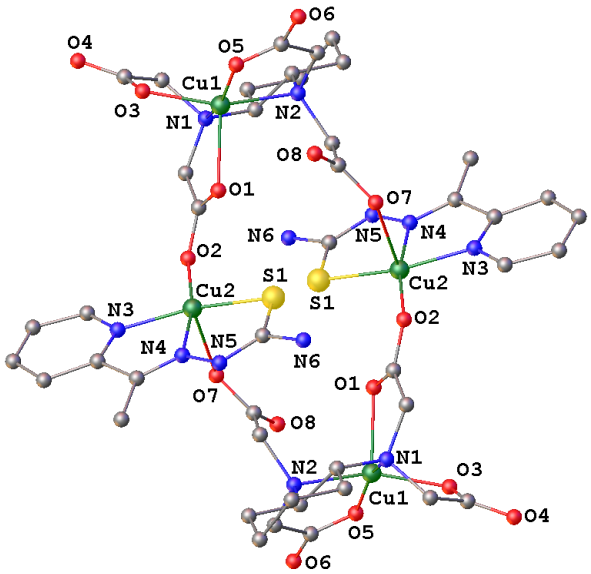


Figure 3.3. Molecular structure of the homometallic complex 12

These are linked through O2 and O7 oxygen atoms of the bridging carboxylate groups, generating separate tetrametallic units, generated by symmetry. The Cu2 ion, which coordinates the tridentate thiosemicarbazone, has a coordination number five, and the coordination polyhedron is a tetragonal pyramid. The deprotonated thiosemicarbazone is coordinated by three atoms (N3, N4 and S1) forming the equatorial plane of the coordination polyhedron. In the same plane there is a

coordination bond with O2 oxygen atom of a carboxylate group. At the top of the pyramid is O7 oxygen atom of a bridging carboxylate group from another $\{Cu(cdta)\}^{2-}$ entity, generated by symmetry. The $cdta^{4-}$ anion pentadentately coordinates to Cu1 ion through two nitrogen atoms (N1 and N2) and three oxygen atoms (O1, O3 and O5) of three carboxylate groups. The coordination number of Cu1 ion is five and the coordination geometry is a tetragonal pyramid.

The complex $\{[Cu_2(AcPyTSC\text{-}4Me)_2Cu(edta)]\cdot H_2O\}_n$ **(10)** crystallizes in the orthorhombic system, space group *Pbcn*, and unit cell parameters a=16.9492, b=9.6355, and c=21.604. The structure of compound **10** (Figure 3.4) is composed of centrosymmetric dimeric cationic entities $\{[Cu(AcPyTSC\text{-}4Me)\}_2^{2+}$ and anionic entities $\{Cu(edta)\}^{2-}$, bridged by O2 oxygen atoms of the carboxylate groups to the $\{Cu(edta)\}^{2-}$ anionic entities. As a result, the structure represents a 1D coordination polymer.

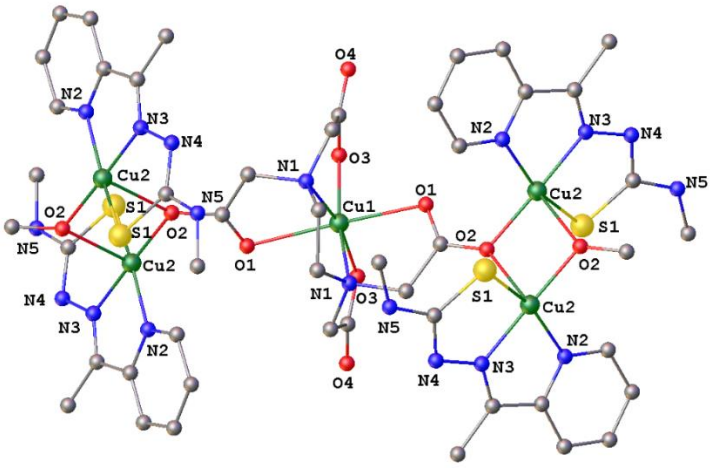


Figure 3.4. Crystal structure of homometallic complex 10

The $edta^{4-}$ anion hexadentately coordinates the Cu1 ion, which occupies a special position on the centre of symmetry, through two nitrogen atoms (N1, N1) and four oxygen atoms of the carboxylate groups (O1, O3, O1`, O3`). As a result, Cu1 has a coordination number of six and a distorted tetragonal-bipyramidal geometry. The Cu2 ions, in the centrosymmetric dimers, have the coordination number of five and a tetragonal-pyramidal geometry. The base of the coordination polyhedron is formed by N2, N3 and S1 donor atoms of the monodeprotonated thiosemicarbazone and by O2 bridging oxygen atom of a carboxylate group from $\{Cu(edta)\}^{2-}$anionic fragment. The apex of the pyramid is occupied by the bridging oxygen atom O2 of a carboxylate group from $\{Cu(edta)\}^{2-}$ anionic entities.

Compound $[Cu_2(AcPyTSC\text{-}4Me)_2(H_2O)Cu(cdta)]\cdot 4.5H_2O$ **(13)** crystallizes in the orthorhombic system, space group *P*2, with unit cell parameters a=14.3463, b=17.5896, and c=20.7623. The structure of compound **13** (Figure 3.5) is formed of $\{Cu(cdta)\}^{2-}$ anionic fragments and centrosymmetric cationic dimers $\{[Cu(AcPyTSC\text{-}4Me)(H_2O)\}_2]^{2+}$, linked through S1 sulphur

atoms of the $\{Cu(AcPyTSC\text{-}4Me)(H_2O)\}^+$ entity, generated by symmetry. As a result, a monomeric structure is formed. The Cu1 ion in the $\{Cu(cdta)\}^{2-}$ anionic fragments, which occupies a special position on the centre of symmetry, has a coordination number of six with a distorted tetragonal-bipyramidal geometry. The coordination sphere includes the set of 2N+4O atoms of the $edta^{4-}$ ligand. The base of the bipyramid is formed by N1, N1`, O3 and O3` atoms, while the apical positions are occupied by O1 and O1` oxygen atoms

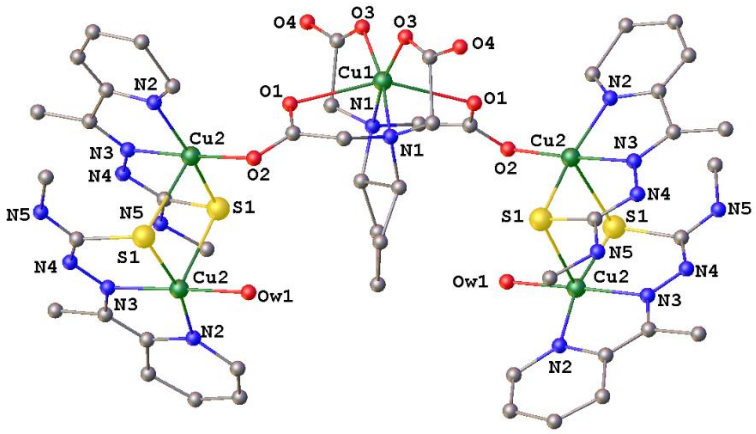


Figure 3.5. Crystal structure of homometallic complex 13

The assembly of centrosymmetric cationic dimers $\{[Cu(AcPyTSC\text{-}4Me)(H_2O)\}_2]^{2+}$ takes place through the bridging sulphur atoms (S1 and S1) of the monodeprotonated thiosemicarbazone. The coordination number of the Cu^{2+} ions is five and the coordination polyhedron is a tetragonal pyramid. In the equatorial plane of the coordination sphere of the Cu^{2+} ion are the donor atoms of the thiosemicarbazone (N2, N3 and S1), as well as the oxygen atom O2 of the carboxylate groups from the anionic entity $\{Cu(cdta)\}^{2-}$. The tip of the pyramid is occupied by the bridging sulphur atom S1 from the coordination sphere of the cationic entity $\{Cu(AcPyTSC\text{-}4Me)(H_2O)\}^+$, generated by symmetry.

The complex $\{[Cu_2(AcPyTSC\text{-}4Et)_2Cu(cdta)]\cdot 5.5H_2O\}_n$ **(14)** crystallizes in an orthorhombic system, space group *Pnna*, with unit cell parameters a=17.0881; b=13.8949; c=21.1916. The structure of complex **14** (Figure 3.6) is very similar to that of complex **13** (Figure 3.5). The two differences between these structures include the absence of the water molecule (Figure 3.6), coordinated to the Cu(II) ions, as well as the formation of 1D coordination polymers in the structure of complex **14**, compared to the structure of complex **13**.

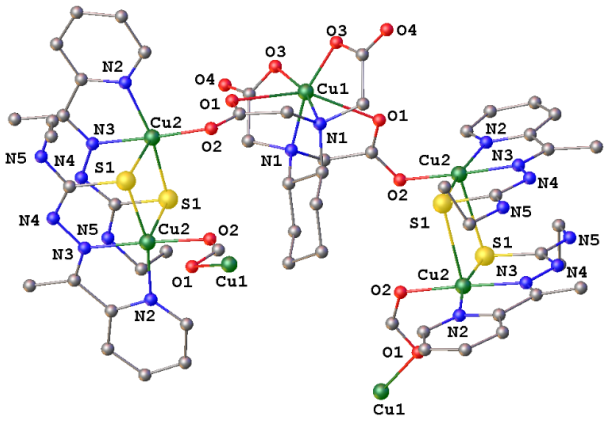


Figure 3.6. Crystal structure of homometallic complex 14

3.3 X-ray analysis of homometallic coordination compounds of Bi(III) with APC ions and 2-formylpyridine thiosemicarbazones and its derivatives

Homometallic Bi(III) compounds with mixed ligands, thiosemicarbazone - APC, were obtained by mixing aqueous solutions of Bi(HAPC) [20,21] and methanolic solutions of the corresponding thiosemicarbazones. Thus, the synthesis of 13 homometallic coordination compounds of Bi(III) with APC ions ($edta^{4-}$, $cdta^{4-}$) and thiosemicarbazones of 2-formylpyridine and its derivatives was carried out.

The compound $\{[Bi(Hedta)]\cdot HFoPyTSC\text{-}4Et\}_n$ **(23)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=11.9542; b=22.1135; c=8.5894; β=94.519. The structure of complex 23 (Figure 3.7), consists of dimeric units $\{[Bi(Hedta)]\}_2$, assembled through oxygen atoms O1 and thiosemicarbazone molecules, which are not involved in coordination.

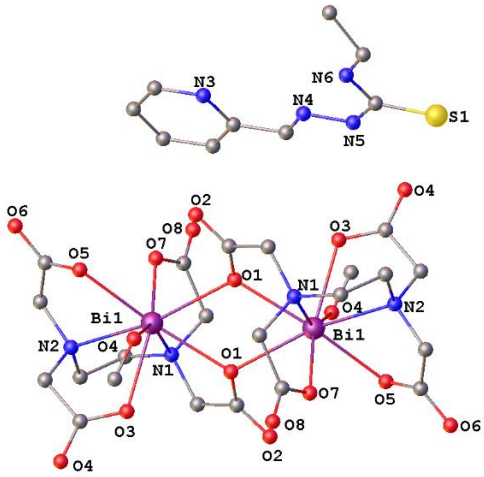


Figure 3.7. A fragment of the crystal structure of homometallic complex 23

The dimers $\{Bi(Hedta)\}_2$, in turn, are linked in infinite chains through O4 oxygen atoms, forming a 1D coordination polymer. The $Hedta^{3-}$ ligand coordinates to Bi(III) ions through two nitrogen atoms (N1, N2) and through O1, O3, O5 and O7 oxygen atoms of four carboxylate groups. The Bi1 ions complete their coordination sphere to eight by O1 and O4 bridging oxygen atoms of

two carboxylate groups from two neighbouring {Bi(Hedta)} fragments. The coordination geometry of the Bi(III) ions is dodecahedral.

Compound [Bi(Hcdta)(H_2O)]·2H_2O·HFoPyTSC-4Ph **(28)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=11.8618; b=14.9605; c=17.5694; β=91.479. The structure of complex **28** (Figure 3.8) consists of noncordinated thiosemicarbazone molecules and centrosymmetric dimers {[Bi(Hcdta)(H_2O)]}$_2$, generated by means of O1 oxygen atoms of the bridging carboxylate groups.

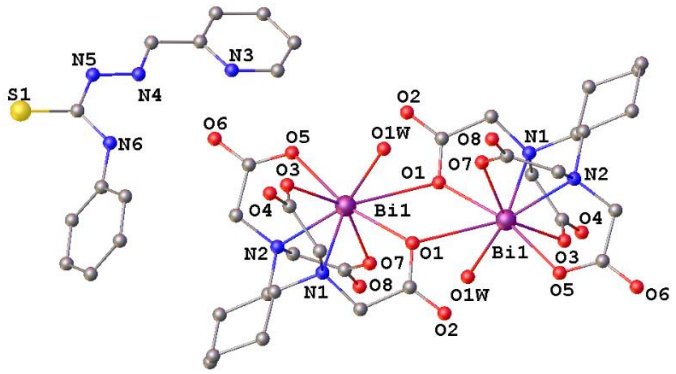


Figure 3.8. Molecular structure of homometallic complex 28

The Bi1 ion has a coordination number of eight and adopts a dodecahedral geometry. The $cdta^{4-}$ anion coordinates to the Bi(III) ion through two nitrogen atoms (N1, N2), O1, O3, O5 and O7 oxygen atoms of four carboxylate groups and two coordination positions are occupied by Ow1 oxygen atom of a water molecule and by O1 oxygen atom of a bridged carboxylate group from the neighbouring {Bi(Hcdta)} entity, generated by symmetry.

The compound [Bi(Hedta)(HAcPyTSC-4Et)$_2$]·7.25H_2O **(31)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=12.4441; b=14.9124; c=23.3797; β=92.95. The structure of complex **31** consists of separate [Bi(Hedta)(HAcPyTSC-4Et)$_2$] entities, in which the $edta^{4-}$ ligand is hexadentately coordinated to Bi(III) ion through two nitrogen atoms (N1 and N2) and O1, O3, O5, and O7 oxygen atoms of four carboxylate groups (Figure 3.9).

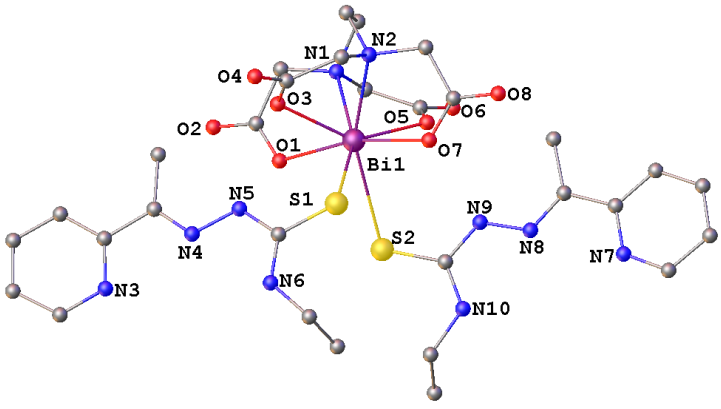


Figure 3.9. Molecular structure of homometallic complex 31

The Bi(III) ion completes its coordination number to eight with the sulfur atoms S1 and S2 of two molecules of non-deprotonated thiosemicarbazone. It is noteworthy that this is the only structure of homometallic Bi(III) complexes in this work where the thiosemicarbazone is coordinated to the Bi(III) ions.

3.4 X-ray analysis of heterometallic coordination compounds of Cu(II) and Bi(III) with APC ions and thiosemicarbazones of 2-formylpyridine and its derivatives

Cu(II)-Bi(III) heterometallic compounds, with mixed thiosemicarbazone-APC ligands, were synthesized in several steps. In the first step, by using methods described in the literature, were obtained the coordination compounds $Cu\{Bi(edta)\}_2 \cdot 9H_2O$ [22], $Cu\{Bi(cdta)\}_2 \cdot 5H_2O$ and $Cu\{Bi(dtpa)\}_2 \cdot 8H_2O$ [23] in crystalline form, as well as the *in situ* aqueous solution of the $Ba\{Bi(edta)\}_2$ complex. Initially, the heterometallic complexes were obtained by two different routes. The first method involved the reaction between $Ba[Bi(edta)]_2$ and copper(II) complex sulphates, while the second method involved the reaction of aqueous solutions of the respective aminopolycarboxylates of copper(II) with alcoholic solutions of the corresponding thiosemicarbazones. Thus, it was carried out the synthesis of 23 heterometallic Cu(II)-Bi(III) coordination compounds with APC ions ($edta^{4-}$, $cdta^{4-}$, $dtpa^{5-}$) and 2-formylpyridine thiosemicarbazones and its derivatives. The composition of these complexes was established on the basis of the results of elemental analysis and IR spectroscopy, while 8 compounds have been investigated by using single crystal X-ray diffraction study.

Complex $\{[Cu(H_2O)(FoPyTSC)Bi(edta)] \cdot H_2O\}_n$ **(35)** crystallizes in the monoclinic system, space group $P2_1/c$, with unit cell parameters a=8.302; b=25.6771; c=10.8597, β=91.231. The structure of complex **35** (Figure 3.10) is formed by infinite chains of complex anions $\{Bi(edta)\}^-_n$, connected through O2 and O7 oxygen atoms of carboxylate groups and cationic fragments $\{Cu(H2O)(FoPyTSC)\}^+$, which are coordinated on both sides of the anionic chains through O5 bridging oxygen atoms of the carboxylate groups, forming a 2D coordination polymer. The 2-formylpyridine thiosemicarbazone is coordinated to Cu1 ion through the classical set of atoms (N3, N4 and S1) which, together with O5 bridging oxygen atom of a carboxylate group, forms the equatorial plane of the tetragonal pyramid. The the top position of the pyramid is occupied by Ow1 oxygen atom of a water molecule. The coordination number of the Bi1 ions is eight and its coordination polyhedron is a dodecahedron. The $edta^{4-}$ anion is coordinated to Bi1 through two nitrogen atoms (N1 and N2) and O1, O4, O6 and O8 oxygen atoms of four carboxylate groups. Two more coordination positions are occupied by O2 and O7 bridging oxygen atoms of two carboxylate groups from neighbouring $\{Bi(edta)\}^-$ anionic entities, generated by symmetry.

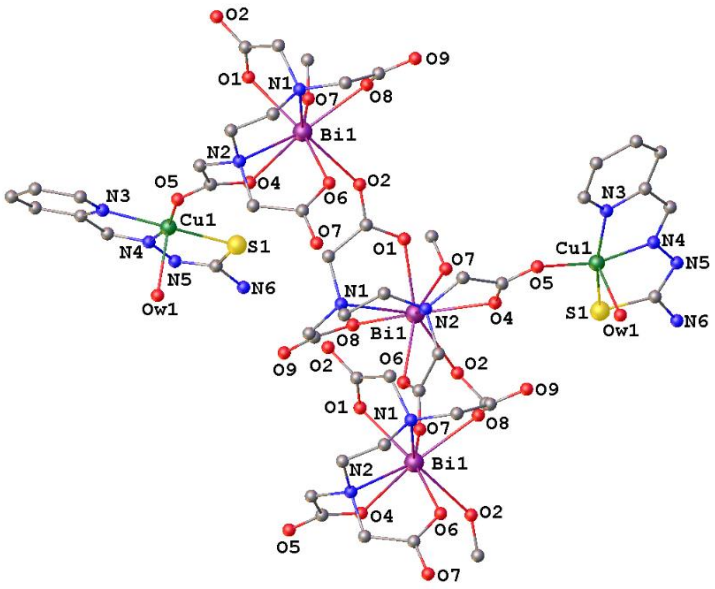


Figure 3.10. Crystal structure of the heterometallic complex 35

Complex $[Cu(H_2O)(HFoPyTSC)Bi(dtpa)(H_2O)]\cdot 5H_2O$ **(43)** crystallizes in a monoclinic system, space group $P2_1/c$, with unit cell parameters a = 14.2116; b = 8.2505; c = 27.19; β = 99.082. The structure of compound **43** (Figure 3.11) consists of cationic $\{Cu(H_2O)(HFoPyTSC)\}^{2+}$ and anionic $\{Bi(dtpa)\}^{2-}$ fragments, assembled into bimetallic entities separated by O8 bridging oxygen atoms of carboxylate groups.

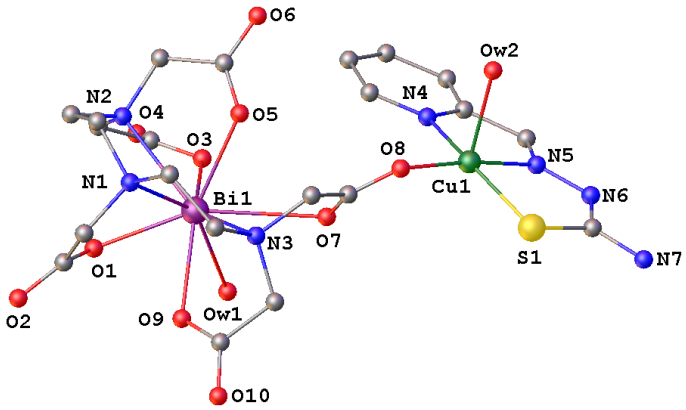


Figure 3.34. Molecular structure of heterometallic complex 43

It is noteworthy that, in this case, the 2-formylpyridine thiosemicarbazone is not deprotonated. The Cu1 ion has a coordination number of five and adopts a tetragonal pyramidal geometry. In the equatorial plane are situated the thiosemicarbazone donor atoms (N4, N5 and S1) and the oxygen atom O8 of a carboxylate group from the anionic entity $\{Bi(dtpa)\}^{2-}$, while in the apical position is occupied by Ow1 oxygen atom of a water molecule. The Bi1 ion has a coordination number of nine and a capped tetragonal antiprism geometry. The coordination sphere includes the set of eight atoms (3N+5O) of the $dtpa^{5-}$ ligand and the oxygen atom Ow2 of a water molecule.

Complex $\{[Cu(AcPyTSC\text{-}Me)Bi(edta)]\cdot H_2O\}_n$ **(46)** crystallizes in the orthorhombic system, space group $Pna2_1$, with unit cell parameters a=26.3837; b=11.1997; c=7.93034. The structure of compound **46** (Figure 3.12) is very similar to the structure of compound **35** (Figure 3.10). The difference consists in the coordination number of the Cu(II) ion, which is four, and the tetragonal geometry, formed by the thiosemicarbazone atoms (N3, N4 and S1) and the oxygen atom O2 of a carboxylate group from the anionic entity $\{Bi(EDTA)\}^-$.

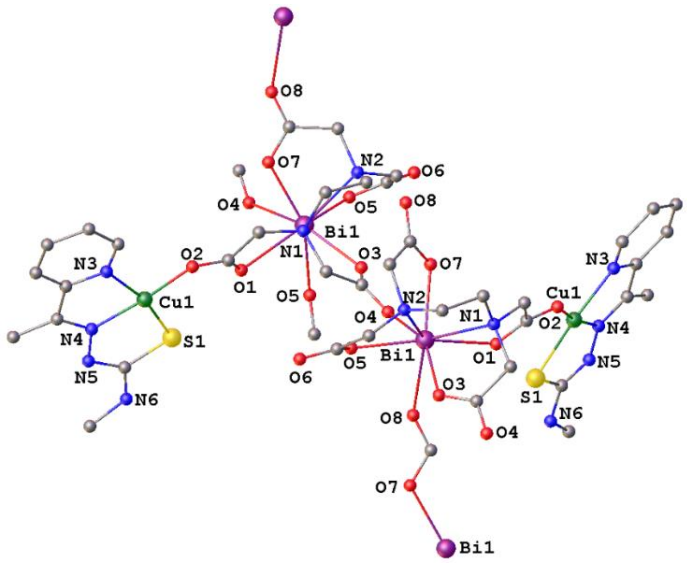


Figure 3.12. Crystal structure of heterometallic complex 46

The coordination compound $\{[Cu(AcPyTSC\text{-}4Ph)Cu(HAcPyTSC\text{-}4Ph)Bi3(cdta)_3]\cdot 8H_2O\}_n$ **(51)** crystallizes in the triclinic system, space group $P\bar{1}$, with unit cell parameters a=17.155; b=18.136; c=20.841; α=69.25; β=87.638; γ=67.881. The structure of compound **51** (Figure 3.13) consists of trimetallic anionic units $\{Bi3(cdta)_3\}^{3-}$ and two types of cationic entities: $\{Cu1(AcPyTSC\text{-}4Ph)\}^+$ and $\{Cu2(HAcPyTSC\text{-}4Ph)\}^{2+}$, coordinated on both sides of the anionic units through O2 and O16 oxygen atoms (in the case of Cu1) and O5 and O21 (in the case of Cu2) forming a 1D polymeric structure. The Cu1 and Cu2 ions have a coordination number of five and adopt a tetragonal pyramidal geometry. The base of the coordination polyhedron is formed by the donor atoms of the thiosemicarbazone (N7, N8, S1) and an oxygen atom of a carboxylate group (O2), while the apex of the pyramid is occupied by an oxygen atom (O16) of a carboxylate group from a neighboring $\{Bi(cdta)\}^-$ entity. The base of the coordination polyhedron of the Cu2 atom is formed by the donor atoms of the thiosemicarbazone (N11, N12, S2) and an oxygen atom of a carboxylate group (O5), while the apex of the pyramid is occupied by an oxygen atom (O21) of a carboxylate group belonging to a neighboring $\{Bi(cdta)\}^-$ anionic entity. Bismuth(III) ions have a coordination number of eight and a dodecahedral geometry. The $cdta^{4-}$ anion coordinates to the bismuth(III) ions through two

nitrogen atoms, four oxygen atoms of four carboxylate groups, and two coordination positions are occupied by two oxygen atoms of two neighboring $\{Bi(cdta)\}^-$ entities.

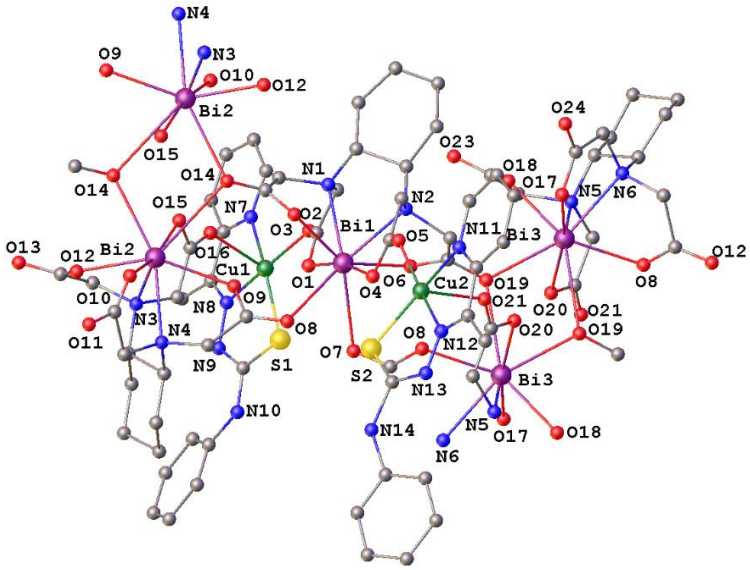
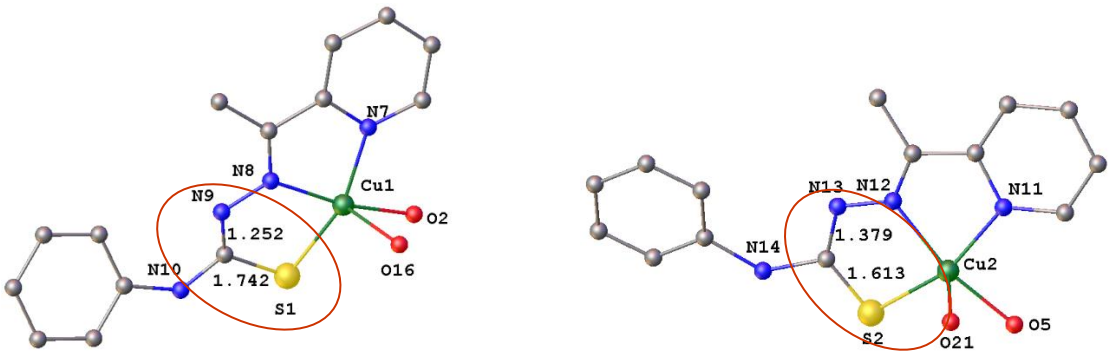


Figure 3.13. Crystal structure of heterometallic complex 51

It is remarkable that in the structure of compound **51**, there are cationic fragments with thiosemicarbazone in both deprotonated (Figure 3.14a) and non-deprotonated (Figure 3.14b) forms. This is confirmed by the C-S (1.742 Å) and C-N (1.379 Å) or C=S (1.613 Å) and C=N (1.252 Å) bond lengths in the corresponding modifications. In this case, the ratio of the cationic fragments of Cu(II) to the anionic fragments of Bi(III) is 2:3, compared to 1:1 for the other structures of the heterometallic complexes.



(a) **(b)**

Figura 3.14. Differences in bond lengths in deprotonated (a) and non-deprotonated (b) ligands in the crystal structure of complex 51

The compound $\{[Cu_2(BzPyTSC\text{-}Et)_2Bi_2(cdta)_2(H_2O)_2]\cdot 13.25H_2O\}_n$ **(56)** crystallizes in the triclinic system, space group $P\bar{1}$, with unit cell parameters a = 4.3081; b = 16.8577; c = 19.136; α = 106.242; β = 106.068; γ = 100.305. The structure of complex **56** (Figure 3.15) consists of symmetry-generated tetrametallic anionic aggregates, $\{Bi_2(cdta)_2\}_2^{4-}$, and dimeric cationic fragments

$\{Cu_2(BzPyTSC\text{-}Et)_2\}^{2+}$, which are coordinated to both sides of the tetramers through oxygen atoms O2 and O14, generating a 1D polymeric structure. The coordination number of the two crystallographically independent Bi(III) ions is eight, and the coordination geometries are, in both cases, dodecahedral. The coordination polyhedra are formed by the nitrogen and oxygen atoms belonging to the $cdta^{4-}$ ligands. As a result, the Bi1 and Bi2 ions coordinate one $cdta^{4-}$ ligand each through the 2N+4O donor set, and the coordination polyhedra are completed to eight in different ways. Thus, Bi1 coordinates two additional O5 atoms, which belong to the carboxylate groups of two neighboring ligands, and the Bi2 ion forms coordination bonds with the oxygen atom O9, which belongs to a carboxylate group of a neighboring $cdta^{4-}$ ligand and the oxygen atom Ow1 of a water molecule.

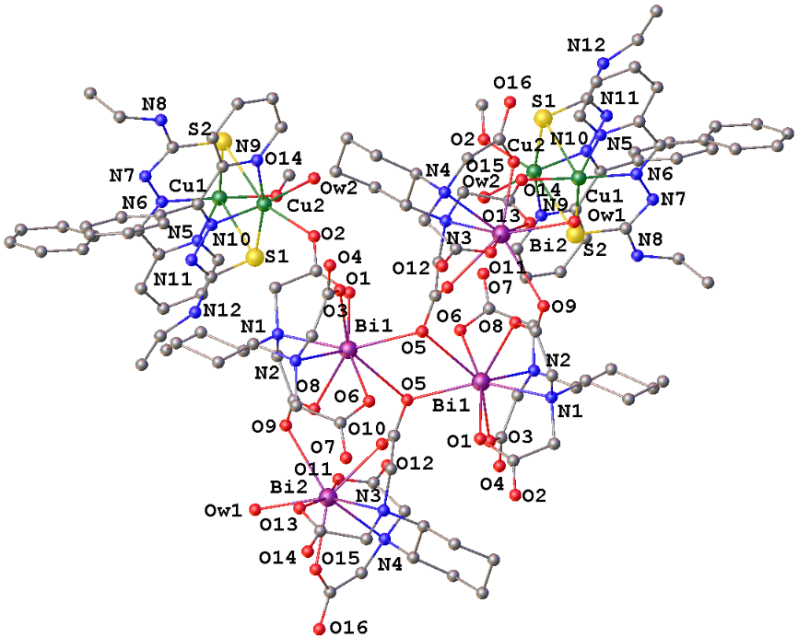


Figure 3.15. Crystal structure of heterometallic complex 56

The two copper(II) ions have different geometries and coordination numbers. The Cu1 ion, with a coordination number of five, has a slightly distorted tetragonal pyramidal coordination polyhedron, with the base formed of the NNS atoms of the thiosemicarbazone and the oxygen atom O14 of a bridging carboxylate group. The apical position of the pyramid is occupied by another sulfur atom, S1, belonging to the neighboring entity $\{Cu(BzPyTSC\text{-}4Et)\}^{+}$ in the dimer. The Cu2 ion has a coordination number of six, the coordination polyhedron in this case being a distorted tetragonal bipyramid. The base of the coordination polyhedron is formed by atoms N9, N10 and S1 of the thiosemicarbazone and an oxygen atom Ow2 of a water molecule, while in the apical positions are situated an oxygen atom O2 of a carboxylate group from the neighboring anionic entity $\{Bi_2(cdta)_2\}_2^{4-}$ and the bridging sulfur atom S2 from the neighboring cationic entity $\{Cu(BzPyTSC\text{-}4Et)\}^{+}$ of the dimer.

4. BIOLOGICAL PROPERTIES OF HOMO- AND HETEROMETALLIC COMPLEXES OF CU(II) AND BI(III) WITH APC IONS AND 2-FORMYLPYRIDINE THIOSEMICARBAZONES AND THEIR DERIVATIVES

4.1 Antimicrobial activity of homo- and heterometallic coordination compounds of Cu(II) and Bi(III) with mixed ligands: thiosemicarbazone – APC

Homo- and heterometallic coordination compounds of Cu(II) and Bi(III) with mixed ligands were tested against the following bacterial strains: *Staphylococcus aureus* (ATCC 25923), *Bacillus cereus* (ATCC 11778), *Escherichia coli* (ATCC 25922), and *Acinetobacter baumannii* (BAA-747).

Antimicrobial properties test results have demonstrated that, under similar conditions, the antibacterial activity of metal ion complexes is superior to that of the corresponding noncoordinated thiosemicarbazones. This could be due to the fact that the metal ions, Cu(II) and Bi(III), can interact with bacterial cell structures more efficiently than organic ligands. The Cu_2edta·$4H_2O$ complex, which contains the APC ligand but does not contain thiosemicarbazone, and which served as a precursor for the synthesis of homometallic Cu(II) complexes with mixed ligands, exhibits very low biological activity. The synthesized coordination compounds, both homo- and heterometallic, exhibited higher antimicrobial activity against Gram-positive species (MIC = 0.07 - 77.14 μM) compared to Gram-negative species (MIC = 1.58 - 632 μM).

The highest antimicrobial activity was exhibited by the complexes against the *Staphylococcus aureus* strain (ATCC 25923) in the range of minimum inhibitory concentration 0.07 - 77.14 μM (Table 4.1). The most active compound against the *Staphylococcus aureus* strain was found to be the heterometallic complex [Cu(AcPyTSC-4Et)Bi(edta)]·$5H_2O$ **(47)** with MIC = 0.07 μM, a value approximately 337 times higher than Furacilin used in medicine (MIC = 23.56 μM).

The most active compound against *Bacillus cereus* strain was also a ***heterometallic complex***, Cu(AcPyTSC-4Ph)Bi(edta)·$6H_2O$ **(48)**, with MIC = 0.13 μM, a value approximately 181 times higher than Furacilin (Table 4.1). This could be explained both by the fact that different metal ions can have complementary effects on bacterial cell structures and by the synergistic effect caused by the simultanious presence of two different types of metal ions.

The results of the antimicrobial study suggest that both homometallic Cu(II)-APC and heterometallic Cu(II)-Bi(III)-APC coordination compounds with 2-formylpyridine thiosemicarbazones and their derivatives can be potentially useful antibacterial agents.

The antibacterial activity of coordination compounds depends on a number of factors, as follows: *nature of the R fragment in the ketone/aldehyde:* Ac > Fo; *nature of the substituent in the 4N*

position of the thiosemicarbazone: Ph > Et > Me > H; *nature of the APC ions:* $edta^{4-}$ > $cdta^{4-}$; *nature of the metal ion:* homometallic Cu(II) coordination compounds > homometallic Bi(III) coordination compounds; *presence of a second metal ion:* heterometallic Cu(II)-Bi(III) compounds > homometallic Cu(II) or Bi(III) compounds.

Table 4.1. Antimicrobial activity results of the synthesized coordination compounds

Nr.	Compound	*Staphylococcus aureus* ATCC 25923			*Bacillus cereus* ATCC 11778		
		MIC, μg/mL	MIC, μM	MBC, μg/mL	MIC, μg/mL	MIC, μM	MBC, μg/mL
1	$\{Cu(FoPyTSC\text{-}4Me)\}_2Cu(edta)\cdot 2H_2O$ **(2)**	15,62	17,33	15,62	31,25	34,67	31,25
2	$[Cu(HFoPyTSC\text{-}4Et)Cu(edta)]\cdot H_2O$ **(3)**	3,90	6,07	3,90	1,95	3,03	1,95
3	$\{Cu(HFoPyTSC\text{-}4Ph)\}_2Cu(edta)\cdot 2H_2O$ **(4)**	0,97	0,95	1,95	0,48	0,44	0,97
4	$\{Cu(AcPyTSC)\}_2Cu(edta)\cdot 4H_2O$ **(9)**	7,81	8,35	7,81	3,90	4,17	3,90
5	$[\{Cu(AcPyTSC\text{-}4Me)\}_2Cu(edta)]\cdot H_2O$ **(10)**	1,95	2,14	1,95	0,97	1,06	0,97
6	$\{Cu(AcPyTSC\text{-}4Et)\}_2Cu(edta)\cdot H_2O$ **(11)**	0,24	0,26	0,48	0,24	0,26	0,48
7	$Cu(HAcPyTSC)Cu(cdta)\cdot 3H_2O$ **(12)**	1,95	2,72	7,81	15,62	21,81	31,25
8	$[\{Cu(AcPyTSC\text{-}4Ph)\}_2Cu(cdta)]\cdot H_2O$ **(15)**	0,24	0,22	0,48	0,48	0,44	0,97
9	$Bi(Hedta)(HFoPyTSC\text{-}4Ph)\cdot 2H_2O$ **(24)**	7,81	9,88	15,62	3,90	4,93	3,90
10	$Bi(Hcdta)(H_2O)]\cdot 2H_2O\cdot HFoPyTSC\text{-}4Ph$ **(28)**	15,62	18,12	31,25	15,62	18,12	15,62
11	Bi(Hedta)(HAcPyTSC) **(29)**	7,81	11,28	7,81	15,62	22,57	31,25
12	Bi(Hedta)(HAcPyTSC-4Me) **(30)**	0,97	1,37	0,97	0,48	1,37	0,97
13	$[Bi(Hedta)(HAcPyTSC\text{-}4Et)_2]\cdot 7.25H_2O$ **(31)**	0,97	0,91	0,97	0,97	0,91	0,97
14	$[Cu(FoPyTSC)Bi(edta)]\cdot H_2O$ **(35)**	7,81	1,21	31,25	15,62	20,61	31,25
15	$[Cu(FoPyTSC\text{-}4Me)Bi(edta)]\cdot 3H_2O$ **(36)**	31,25	9,67	62,50	15,62	19,35	15,62
16	$Cu(FoPyTSC\text{-}4Et)Bi(edta)\cdot 2H_2O$ **(37)**	0,97	1,21	1,95	1,95	2,42	3,90
17	$Cu(FoPyTSC\text{-}4Ph)Bi(edta)\cdot 6H_2O$ **(40)**	0,97	1,05	1,95	0,97	1,05	3,90
18	$[Cu(FoPyTSC\text{-}4Ph)Cu(HFoPyTSC\text{-}4Ph)Bi_3(cdta)_3]\cdot H_2O$ **(42)**	1,95	2,07	1,95	0,48	0,51	0,97
19	$[Cu(AcPyTSC)Bi(edta)]\cdot 3H_2O$ **(45)**	15,62	19,33	15,62	15,62	19,33	15,62
20	$[Cu(AcPyTSC\text{-}4Me)Bi(edta)]\cdot H_2O$ **(46)**	3,90	4,97	7,81	1,95	2,48	1,95
21	$[Cu(AcPyTSC\text{-}4Et)Bi(edta)]\cdot 5H_2O$ **(47)**	0,06	0,07	0,06	0,24	0,28	0,24
22	$Cu(AcPyTSC\text{-}4Ph)Bi(edta)\cdot 6H_2O$ **(48)**	0,12	0,13	0,12	0,12	0,13	0,12
23	$[Cu(AcPyTSC\text{-}4Ph)Cu(HAcPyTSC\text{-}4Ph)Bi_3(cdta)_3]\cdot 8H_2O$ **(51)**	0,97	0,39	3,90	0,97	0,39	1,95
24	$Cu(BzPyTSC\text{-}4Me)Bi(edta)\cdot 4H_2O$ **(53)**	0,24	0,27	0,24	0,97	1,07	0,97
25	$Cu(BzPyTSC\text{-}4Et)Bi(edta)\cdot 7H_2O$ **(54)**	0,24	0,25	0,24	0,97	0,99	0,97
	FURACILIN	4,67	23,56	9,35	4,67	23,56	4,67

4.2 Antifungal activity of homo- and heterometallic coordination compounds of Cu(II) and Bi(III) with mixed ligands: thiosemicarbazone – APC

The coordinative compounds exhibited antifungal activity in the range of 0.44 - 354.03 μM (Table 4.2). The highest antifungal activity was shown by the homometallic Cu(II) compound, [{Cu(AcPyTSC-4Ph)}$_2$Cu(cdta)]·H$_2$O **(15)**, with a minimum inhibitory concentration of 0.44 μM, which is approximately 78 times more active than Nystatin (MIC = 34.35 μM).

Table 4.2. Antifungal activity results of the synthesized coordination compounds

Nr.	Compound	*Candida albicans* ATCC 10231		
		MIC, μg/mL	MIC, μM	MFC, μg/ml
1	{Cu(HFoPyTSC-4Ph)}$_2$Cu(edta)·2H$_2$O **(4)**	3,90	3,81	31,25
2	Cu(HFoPyTSC)Cu(cdta)·7H$_2$O **(5)**	15,62	20,18	15,62
3	{Cu(AcPyTSC)}$_2$Cu(edta)·4H$_2$O **(9)**	15,62	16,71	31,25
4	{Cu(AcPyTSC-4Et)}$_2$Cu(edta)·H$_2$O **(11)**	0,97	1,04	1,95
5	Cu(HAcPyTSC)Cu(cdta)·3H$_2$O **(12)**	15,62	21,81	15,62
6	[{Cu(AcPyTSC-4Ph)}$_2$Cu(cdta)]·H$_2$O **(15)**	0,48	0,44	1,95
7	Bi(Hedta)(HFoPyTSC-4Ph)·2H$_2$O **(24)**	15,62	19,77	31,25
8	Cu(FoPyTSC-4Et)Bi(edta)·2H$_2$O **(37)**	1,95	2,43	7,81
9	Cu(FoPyTSC-4Ph)Bi(edta)·6H$_2$O **(38)**	1,95	2,11	7,81
10	[Cu(FoPyTSC-4Ph)Cu(HFoPyTSC-4Ph)Bi$_3$(cdta)$_3$]·H$_2$O **(42)**	3,90	4,14	62,50
11	[Cu(AcPyTSC)Bi(edta)]·3H$_2$O **(45)**	3,90	4,83	7,81
12	[Cu(AcPyTSC-4Me)Bi(edta)]·H$_2$O **(46)**	15,62	19,90	500,0
13	Cu(AcPyTSC-4Ph)Bi(edta)·6H$_2$O **(48)**	0,48	0,512	0,97
14	[Cu(AcPyTSC-4Ph)Cu(HAcPyTSC-4Ph)Bi$_3$(cdta)$_3$]·8H$_2$O **(51)**	3,90	1,58	15,62
15	Cu(BzPyTSC-4Me)Bi(edta)·4H$_2$O **(53)**	7,81	8,65	15,62
16	Cu(BzPyTSC-4Et)Bi(edta)·7H$_2$O **(54)**	15,62	20,26	31,25
	NYSTATIN	32,0	34,55	64,0

The antifungal activity of coordination compounds is influenced by a number of factors, including: *the nature of the R fragment in the ketone/aldehyde:* Ac > Fo; *the nature of the substituent in the 4N position of the thiosemicarbazone:* Ph > Et > Me > H; *the nature of the APC ions:* edta^{4-} > cdta^{4-}; *the nature of the metal ion:* homometallic coordination compounds of Cu(II) are more active than those of Bi(III); *the presence of a second metal ion:* heterometallic Cu(II)-Bi(III) > homometallic compounds of Cu(II) or Bi(III).

4.3 Antioxidant properties of homo- and heterometallic coordination compounds of Cu(II) and Bi(III) with mixed ligands: thiosemicarbazone – APC

Antioxidant activity of coordination compounds was evaluated by determining the half-maximal inhibitory concentration (IC_{50}). The IC_{50} determination was carried out by the $ABTS^+$ free radical scavenging method. It was observed that some coordination compounds in the work have

antioxidant properties comparable to the activity of the reference substance, Trolox (Table 4.3). Table 4.3 shows that five of the obtained coordination compounds exhibit antioxidant activity with IC_{50} values ranging from 5.36 to 10.5 μM, which are 2.96 to 1.5 times higher than the activity of Trolox (IC_{50} = 15.86 μM).

Table 4.3 Results of the antioxidant properties of the obtained coordination compounds

Nr.	Compound	C, μM	%, Inh. ABTS	SD, %	IC_{50} μM	SD
1	{Cu(HFoPyTSC-4Ph)}$_2$Cu(edta)·2H$_2$O **(4)**	100	90,76	0,12	10,15	0,03
2	{Cu(FoPyTSC-4Ph)}$_2$Cu(cdta)·H$_2$O **(8)**	100	93,23	0,10	5,91	0,03
3	[{Cu(AcPyTSC-4Et)}$_2$Cu(cdta)]·5H$_2$O **(14)**	100	69,48	0,65	48,12	0,34
4	[{Cu(AcPyTSC-4Ph)}$_2$Cu(cdta)]·H$_2$O **(15)**	100	59,41	0,81	73,86	0,72
5	[{Cu(BzPyTSC-4Me)}$_4${Cu(cdta)}$_2$]·11.65H$_2$O **(18)**	100	80,90	1,22	28,95	0,38
6	[{Cu(BzPyTSC-4Et)}$_2${Cu(cdta)}]·3.95H$_2$O **(19)**	100	72,12	0,71	45,58	0,05
7	[Bi(Hedta)](HFoPyTSC-4Et) **(23)**	100	86,74	0,63	36,35	0,72
8	[Bi(Hcdta)(HFoPyTSC-4Et)] **(27)**	100	78,68	0,91	56,65	0,40
9	[Bi(Hedta)(HAcPyTSC-4Et)$_2$]·7.25H$_2$O **(31)**	100	95,97	0,06	10,50	0,08
10	Bi(Hcdta)(HAcPyTSC-4Et)·2H$_2$O **(34)**	100	95,59	0,30	8,63	0,05
11	Cu(FoPyTSC-4Ph)Bi(edta)·6H$_2$O **(38)**	100	74,51	0,43	23,46	0,24
12	[Cu(FoPyTSC-4Ph)Cu(HFoPyTSC-4Ph)Bi$_3$(cdta)$_3$]·H$_2$O **(42)**	100	71,60	0,06	31,56	0,10
13	Cu(HFoPyTSC-4Ph)Bi(dtpa)·5H$_2$O **(44)**	100	77,43	1,90	5,36	0,58
14	[Cu(AcPyTSC-4Ph)Cu(HAcPyTSC-4Ph){Bi(cdta)}$_3$]·8H$_2$O **(51)**	100	74,53	1,53	17,43	1,02
15	Cu(BzPyTSC-4Ph)Bi(cdta)·H$_2$O **(57)**	100	54,13	0,50	78,43	3,31
	Trolox	100	87,13	0,88	15,86	1,53

The study of the antioxidant properties of the obtained coordination compounds has shown that they depend on a number of factors, including: *the nature of the substituent in the 4N position of the thiosemicarbazone* : Ph > Et > Me > H; *the nature of the R fragment in the ketone/aldehyde*> Fo > Ac > Bz; *the nature of the APC ions*: dtpa^{5-} > cdta^{4-} > edta^{4-}; and *the nature of the metal ion*: homometallic Bi(III) compounds > homometallic Cu(II) compounds.

The most active compound was found to be the heterometallic complex **44**, with IC_{50}=5.36 μM, which is about 3 times more active than Trolox.

CONCLUSIONS AND RECOMMENDATIONS

1. Optimal synthesis conditions were established and accornig to which there were obtanied 57 new coordination compounds with mixed polydentate ligands: thiosemicarbazone - aminopolycarboxylate, among them 20 homometallic coordination compounds of Cu(II), 14 homometallic compounds of Bi(III) and 23 Cu(II) - Bi(III) heterometallic complexes with the following general formulas: $Cu(HL)Cu(APC)\cdot nH_2O$, $Cu(L)_2Cu(APC)\cdot nH_2O$, $Bi(HL)m(HAPC)\cdot nH_2O$, $Cu(L)Bi(APC)\cdot nH_2O$ and $Cu(L)Cu(HL)\{Bi(APC)\}_3\cdot nH_2O$ (n = 0 – 13.25), (m = 1, 2) and APC = $edta^{4-}$, $cdta^{4-}$ and $dtpa^{5-}$. The thiosemicarbazones of 2-formyl-, 2-acetyl- and 2-benzoylpyridine are in the deprotonated (HL) or monodeprotonated (L^-) form.

2. The IR study results confirmed the coordination of non-deprotonated or monodeprotonated thiosemicarbazones to Cu(II) ions through sulfur atoms. $\Delta\nu_{as}(COO)$-$\nu_s(COO)$ differences greater than 200 cm^{-1} in the IR spectra of the complexes indicate monodentate coordination of the carboxylate groups, while differences smaller than this value indicate bidentate or bidentate-bridge coordination of the carboxylate fragments to the metal ions.

3. The crystal structures of 22 complexes were determined by single crystal X-ray diffraction: (10 homometallic Cu(II) compounds, 4 homometallic Bi(III) compounds, and 8 heterometallic Cu(II)-Bi(III) complexes).

4. In the structures of homometallic Cu(II) complexes, the molar ratio between the cationic fragments $\{Cu(HL)\}^{2+}$ or $\{Cu(L)\}^{+}$ and the anionic ones $\{Cu(APC)\}^{2-}$ is 1:1 or 2:1, respectively. These fragments are assembled into bi-, tetra- or polynuclear aggregates with the help of the oxygen-bridging atoms of the carboxylate groups in the APC ligands. Cu(II) ions have coordination numbers of four, five or six.

5. Single crystal X-ray diffraction of the homometallic Bi(III) complexes revealed that the complex structures are either monomeric or polymeric. In only one case, the thiosemicarbazone is coordinated to Bi(Hedta), while in three cases the thiosemicarbazone is co-crystallized. The coordination number of the Bi(III) ions in all four structures is eight.

6. The structures of six heterometallic Cu(II)-Bi(III) complexes consist of cationic fragments $\{Cu(L)\}^{+}$ or $\{Cu(HL)\}^{2+}$ and anionic fragments $\{Bi(APC)\}^{-}$ in a 1:1 molar ratio. In two complexes (**42**, **51**) this ratio is 2:3 due to the concomitant presence of $\{Cu(L)\}^{+}$ and $\{Cu(HL)\}^{2+}$ fragments with monodeprotonated or non-deprotonated thiosemicarbazone, respectively. The structures represent, in one case, separate molecules (with $dtpa^{5-}$), and in the rest – 1D or 2D coordination polymers, assembled by bridging oxygen atoms of the carboxylate groups of the APC ligands. The coordination

number of Cu(II) ions is 4, 5 or 6. The coordination number of Bi(III) ions is eight, while in the complex with the $dtpa^{5-}$ ligand - nine.

7. In homo- and heterometallic coordination compounds of Cu(II) with 4-methyl and 4-ethylthiosemicarbazones of 2-acetyl and 2-benzoylpyridine with $cdta^{4-}$ ligands, Cu(II) complex dimers are present, assembled through the sulphur atoms of the thiosemicarbazones.

8. **The antimicrobial activity** of coordination compounds is higher against Gram-positive strains compared to Gram-negative strains. The complexes have proven to be more effective antibacterial agents against the *Staphylococcus aureus* strain, with values in the concentration range of 0.07 - 77.14 μM. The antimicrobial activity of the complexes decreases according to the following sequences:

- *the nature of the substituent in the 4N position of thiosemicarbazone:* Ph > Et > Me > H;
- *the nature of the R fragment from ketone/aldehyde:* Ac > Fo > Bz;
- *the nature of APC ions:* $edta^{4-}$ > $cdta^{4-}$;
- *the nature of the metal ion:* homometallic compounds of Cu(II) > homometallic compounds of Bi(III);
- *the presence of the second metal ion:* heterometallic compounds Cu(II)-Bi(III) > homometallic compounds of Cu(II) or Bi(III);
- the highest antimicrobial activity against the *Staphylococcus aureus* strain was manifested by the compound [Cu(AcPyTSC-4Et)Bi(edta)]·$5H_2O$ **(47)** with MIC = 0.07 μM, a value approximately 337 times higher than Furacilin - used in medicine (MIC = 23.56 μM);
- the most active compound against the *Bacillus cereus* strain was Cu(AcPyTSC-4Ph)Bi(edta)·6H2O **(48)** with MIC = 0.13 μM, a value approximately 181 times higher than Furacilin.

9. **Antifungal activity** of coordination compounds, determined in the range of 0.44 - 354.03 μM, decreases as follows:

- *the nature of the substituent in the 4N position of the thiosemicarbazone:* Ph > Et > Me > H;
- *the nature of the R fragment in the ketone/aldehyde:* Ac > Fo > Bz;
- *the nature of the APC ions:* $edta^{4-}$ > $cdta^{4-}$;
- *the nature of the metal ion:* homometallic Cu(II) compounds > homometallic Bi(III) compounds;
- *presence of a second metal ion:* heterometallic Cu(II)-Bi(III) compounds > homometallic Cu(II) or Bi(III) compounds;

- The highest antifungal activity was exhibited by the compound [{Cu(AcPyTSC-4Ph)}$_2$Cu(cdta)]·H_2O **(15)** with MIC = 0.44 μM, being about 78 times more active than Nystatin (MIC = 34.35 μM).

10. The study of the **antioxidant properties** of the synthesized compounds has shown that the activity of some complexes is 2.96 - 1.5 times higher than that of Trolox, while other compounds did not exhibit antioxidant activity. The antioxidant properties of the compounds decrease according to the following series:

- *the nature of the substituent in the 4N position of thiosemicarbazone:* Ph > Et > Me > H;
- *the nature of the R fragment in ketone/aldehyde:* Fo > Ac> Bz;
- *the nature of APC ions:* $dtpa^{5-}$ > $cdta^{4-}$ > $edta^{4-}$;
- *the nature of the metal ion:* homometallic Bi(III) compounds > homometallic Cu(II) compounds;
- *presence of a second metal ion:* homometallic Cu(II) or Bi(III) compounds > heterometallic Cu(II)-Bi(III) compounds;
- The most active was the heterometallic complex Cu(HFoPyTSC-4Ph)Bi(dtpa)·$5H_2O$ **(44)**, with IC_{50}=5.36 μM, which is about 3 times more active than Trolox.

Recommendations

1. The patented compound [Cu(AcPyTSC-4Ph)Bi(edta)]·$4H_2O$ **(48)**, which exhibits antifungal activity against *Candida albicans* 31.9 times higher than fluconazole, could be used in medicine and veterinary medicine for the prophylaxis and treatment of mycoses.
2. It is recommended to carry out the research on the anticancer activity of the obtained homo- and heterometallic coordination compounds.

BIBLIOGRAPHY

1. BISCEGLIE, F., BACCI, C., VISMARRA, A., BARILLI, E., PIOLI, M., ORSONI, N., PELOSI, G. Antibacterial activity of metal complexes based on cinnamaldehyde thiosemicarbazone analogues. In: *Journal of Inorganic Biochemistry*. 2020, vol. 203, pp. 1-22. DOI: 10.1016/j.jinorgbio.2019.110888.

2. TANAKA, K., TENGEIJI, A., KATO, T., TOYAMA, N., SHIRO, M., SHIONOYA, M. Efficient Incorporation of a Copper Hydroxypyridone Base Pair in DNA. In: *Journal of the American Chemical Society*. 2002, vol. 124(42), pp. 12494-12498. DOI: 10.1021/ja027175o.

3. MA, D.L., CHE, C.M. A Bifunctional Platinum(II) Complex Capable of Intercalation and Hydrogen-Bonding Interactions with DNA: Binding Studies and Cytotoxicity. In: *Chemistry - A European Journal*. 2003, vol. 9(24), pp. 6133-6144. DOI: 10.1002/chem.200304964.

4. ALAHARI, A., TRIVELLI, X., GUÉRARDEL, Y., DOVER, L.G., BESRA, G.S., SACCHETTINI, J.C., REYNOLDS, R.C., COXON, G.D., KREMER, L. Thiacetazone, an Antitubercular Drug that Inhibits Cyclopropanation of Cell Wall Mycolic Acids in Mycobacteria. In: *PLoS ONE*. 2007, vol. 2(12), pp. 1-12. DOI: 10.1371/journal.pone.0001343.

5. BAVIN, E.M., REES, R.J.W., ROBSON, J.M., SEILER, M., SEYMOUR, D.E., SUDDABY, D. The Tuberculostatic Activity of Some Thiosemicarbazones. In: *Journal of Pharmacy and Pharmacology*. 2011, vol. 2(1), pp. 764-772. DOI: 10.1111/j.2042-7158.1950.tb12999.x.

6. YANG, J., KONG, J., LI, B., JI, Z., LIU, A., CHEN, J., LIU, M., FAN, Y., PENG, L., SONG, J., WU, X., GAO, L., MA, W., DONG, Y., LUO, S., BAO, F. Seventy years of evidence on the efficacy and safety of drugs for treating leprosy: a network meta-analysis. In: *Journal of Infection*. 2023, vol. 86(4), pp. 338-351. DOI: 10.1016/j.jinf.2023.02.019.

7. LI, X., MU, J., LIU, F., TAN, E.W.P., KHEZRI, B., WEBSTER, R.D., YEOW, E.K.L., LIU, F. Human Transport Protein Carrier for Controlled Photoactivation of Antitumor Prodrug and Real-Time Intracellular Tumor Imaging. In: *Bioconjugate Chemistry*. 2015, vol. 26(5), pp. 955-961. DOI: 10.1021/acs.bioconjchem.5b00170.

8. STAVILA, V., DAVIDOVICH, R.L., GULEA, A., WHITMIRE, K.H. Bismuth(III) complexes with aminopolycarboxylate and polyaminopolycarboxylate ligands: Chemistry and structure. In: *Coordination Chemistry Reviews*. 2006, vol. 250(21–22), pp. 2782-2810. DOI: 10.1016/j.ccr.2006.02.032.

9. CHEY, W.D., LEONTIADIS, G.I., HOWDEN, C.W., MOSS, S.F. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. In: *American Journal of Gastroenterology*. 2017, vol. 112(2), pp. 212-239. DOI: 10.1038/ajg.2016.563.

10. YUAN, S., WANG, R., CHAN, J.F.-W., ZHANG, A.J., CHENG, T., CHIK, K.K.-H., YE, Z.-W., WANG. S., LEE, A.C.-Y., JIN, L., LI, H., JIN, D.Y., YUEN, K.Y., SUN, H. Metallodrug ranitidine bismuth citrate suppresses SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters. In: *Nature Microbiology*. 2020, vol. 5(11), pp. 1439-1448. DOI: 10.1038/s41564-020-00802-x.

11. ANDREWS, P.C., FRANK, R., JUNK, P.C., KEDZIERSKI, L., KUMAR, I., MACLELLAN, J.G. Anti-Leishmanial activity of homo- and heteroleptic bismuth(III) carboxylates. In: *Journal of Inorganic Biochemistry*. 2011, vol. 105(3), pp. 454-461. DOI: 10.1016/j.jinorgbio.2010.08.007.

12. WANG, X., ZHANG, X., LIN, J., CHEN, J., XU, Q., GUO, Z. DNA-binding property and antitumor activity of bismuth(III) complex with 1,4,7,10-tetrakis(2-pyridylmethyl)-1,4,7,10-tetraazacyclododecane. In: *Dalton Transactions*. 2003, vol. 12, pp. 2379-2380. DOI: 10.1039/b305290g.

13. GULEA, A., POIRIER, D., ROY, J., STAVILA, V., BULIMESTRU, I., TAPCOV, V., BIRCA, M., POPOVSCHI, L. *In vitro* antileukemia, antibacterial and antifungal activities of some 3d metal complexes: Chemical synthesis and structure – activity relationships. In: *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2008, vol. 23(6), pp. 806-818. DOI: 10.1080/14756360701743002.

14. BERMEJO, E., CARBALLO, R., CASTIÑEIRAS, A., DOMÍNGUEZ, R., MAICHLE-MÖSSMER, C., STRÄHLE, J., WEST, D.X. Synthesis, characterization and antifungal activity of group 12 metal complexes of 2-acetylpyridine-^{4}N-ethylthiosemicarbazone (H4EL) and 2-acetylpyridine-N-oxide-^{4}N-ethylthiosemicarbazone (H4ELO). In: *Polyhedron*. 1999, vol. 18(27), pp. 3695-3702. DOI: 10.1016/S0277-5387(99)00309-5.
15. GULEA, A., BURDUNIUC, O., BĂLAN, G., RUSNAC, R., ȚAPCOV, V., RUDIC, V. Utilizare a N-ciclohexil-2-[1-(piridin-2-il)]hidrazincarbotioamidei în calitate de inhibitor al proliferării microorganismelor gram-pozitive și fungilor Candida albicans. Brevet de invenție 4648, Nr. depozit a 2018 0079. Data depozit 12.09.2018. Publicat 30.09.2019.
16. BULIMESTRU, I., MENTRÉ, O., TANCRET, N., ROLLE, A., DJELAL, N., BURYLO, L., CORNEI, N., POPA, N., GULEA, A. Heterobimetallic Ba-Co aminopolycarboxylate complexes as precursors for $BaCoO_{3-\delta}$ oxides; towards a one-stage-deposition of cobaltite films. In: *Journal of Materials Chemistry*. 2010, vol. 20(47), pp. 10724-10734. DOI: 10.1039/c0jm01012j.
17. NELEA, P. *Sinteza și proprietățile combinațiilor heterometalice ale lantanidelor cu bismutul(III)*: teză de doctor în științe chimice. Chișinău, 2023, 162 p.
18. ANTSYSHKINA, A.S., SADIKOV, G.G., POZNYAK, A.L., SERGIENKO, V.S. Crystal structure of $[Cu_2(Edta)(Py)_2(H_2O)_2]\cdot 2H_2O$ and $[Cu(Im)_6]\{Cu(Im)_4[Cu(Edta)(Im)]_2\}\cdot 6H_2O$, Products of the interaction of (Ethylenediaminetetraacetato)diaquadicopper(II) with pyridine and imidazole. In: *Russian Journal of Inorganic Chemistry*. 2006, vol. 51(2), pp. 241-252. DOI: 10.1134/S0036023606020124.
19. FUERTES, A., MIRAVITLLES, C., ESCRIV, E., CORONADO, E., BELTRN, D. Crystal structure and magnetic properties of the alternating chain $[Cu_2(cdta)]\cdot 4H_2O$. In: *Journal of the Chemical Society, Dalton Transactions.* 1986, vol. 9, pp. 1795-1800. DOI: 10.1039/dt9860001795
20. SUMMER, S.P., ABBOUD, K.A., FARRAH, S.R., PALENIK, G.J. Syntheses and Structures of Bismuth(III) Complexes with Nitrilotriacetic Acid, Ethylenediaminetetraacetic Acid, and Diethylenetriaminepentaacetic Acid. In: *Inorganic Chemistry*. 1994, vol. 33(1), pp. 88-92.
21. WULLENS, H., DEVILLERS, M., TINANT, B., DECLERCQ, J.-P. Synthesis, characterization and crystal structures of bismuth(III) complexes with triethylenetetraaminehexaacetic acid and trans-cyclohexane-1,2-diaminetetraacetic acid. In: *Journal of the Chemical Society, Dalton Transactions*. 1996, vol. 10, pp. 2023-2029. DOI: 10.1039/dt9960002023.
22. SOBANSCA, S., WIGNACOURT, J.–P, CONFLANT, P., DRACHE, M., BULIMESTRU, I., GULEA, A. A new $CuBi_2O_4$ precursor: Synthesis, crystal structure and thermal behaviour of $Cu(BiEDTA)_2, 9H_2O$. In: *European Journal of Solid State and Inorganic Chemistry*. 1996, vol. 33(8), pp. 701-711.
23. BULIMESTRU, I., SHOVA, S., POPA, N., ROUSSEL, P., CAPET, F., VANNIER, R.-N., DJELAL, N., BURYLO, L., WIGNACOURT, J.-P., GULEA, A., WHITMIRE, K.H. Aminopolycarboxylate Bismuth(III)-Based Heterometallic Compounds as Single-Source Molecular Precursors for $Bi_4V_2O_{11}$ and Bi_2CuO_4 Mixed-Oxides. In: *Chemistry of Materials*. 2014, vol. 26(21), pp. 6092-6103. DOI: 10.1021/cm502009y.

LIST OF PUBLICATIONS OF THE AUTHOR ON THE THEME OF THE THESIS

SCIENTIFIC JOURNAL ARTICLES:

1) **NEGUȚA, E**. Compuși coordinativi ai cuprului(II) cu tiosemicarbazone ale 2-formilpiridinei și derivaților ei. In: *Studia Universitatis Moldaviae (Seria Ştiinţe Reale şi ale Naturii)*, 2020, nr. 6(136), pp. 127-139. DOI: 10.5281/zenodo.4431717
2) **NEGUȚA, E**. Compuși coordinativi ai cuprului(II) cu tiosemicarbazone ale 2-acetil/2-benzoilpiridinei și derivații lor. . In: *Studia Universitatis Moldaviae (Seria Ştiinţe Reale şi ale Naturii)*, 2021, nr. 1(141), pp. 195-212. DOI: 10.5281/zenodo.4981593

3) **NEGUȚA, E.**, NEGUȚA, A., GARBUZ, O., GULEA, A., BULIMESTRU, I. Combinații coordinative ale Cu(II) și Bi(III) cu liganzi aminopolicarboxilat și 4-etil-,4-feniltiosemicarbazone ale 2-acetilpiridinei . In: *Revista de Ştiinţă, Inovare, Cultură şi Artă „Akademos”,* 2023, nr. 3(70), pp. 71-75. DOI: 10.52673/18570461.23.3-70.04

4) **NEGUȚA, E.**, BĂLAN, G., ȘOVA, S., GULEA, A., COTOVAIA, A., BULIMESTRU, I. Sinteza și studiul compușilor coordinativi homo- și heterometalici ai Cu(II) și Bi(III) cu 4-etiltiosemicarbazonele 2-formil și 2-acetilpiridinei. În: *Studia Universitatis Moldaviae, Revista științifică a Universtității de Stat din Moldova*, 2023, nr. 6(166), pp. 118-125. DOI: 10.59295/sum6(166)2023_16

5) **NEGUȚA, E.**, BĂLAN, G., ȘOVA, S., GULEA, A., COTOVAIA, A., BULIMESTRU, I. Compuși coordinativi homo- și heterometalici ai Cu(II) și Bi(III) cu aminopolicarboxilați și tiosemicarbazone ale 2-benzoilpiridinei. In: *Revista de Ştiinţă, Inovare, Cultură şi Artă „Akademos”,* 2023, nr. 4(71), pp. 40-46. DOI: 10.52673/18570461.23.4-71.03

PARTICIPATION IN SCIENTIFIC EXHIBITIONS (NATIONAL AND INTERNATIONAL)

1) **NEGUȚA, E.**, LAZAR, G., BULIMESTRU, I. Compuşi coordinativi homo- și heterometalici ai Cu(II) și Bi(III) cu ioni aminopolicarboxilat și semi/tiosemicarbazone ale 2-formilpiridinei. In: *Integrare prin cercetare și inovare.: Ştiinţe ale naturii și exacte*, 10-11 noiembrie 2020, Chișinău, Republica Moldova, pp. 234-237. ISBN 978-9975-152-50-1.

2) **NEGUȚA, E.**, BULIMESTRU, I. Combinații coordinative ale Cu(II) și Bi(III) cu liganzi aminopolicarboxilat și tiosemicarbazone ale 2-acetilpiridinei. In: *Conferință stiințifică națională cu participare Internațională Materiale Avansate în Biofarmaceutică și Tehnică*. Dedicată aniversării a 75-a de la nașterea academicianului AURELIAN GULEA și de la fondare a Universității de Stat din Moldova, 26.05.2021, pp. 178-182

3) **NEGUȚA, E.**, BULIMESTRU, I. Combinaţii coordinative ale Cu(II) şi Bi(III) cu liganzi aminopolicarboxilat şi tiosemicarbazone ale 2-benzoilpiridinei. In: *Integrare prin cercetare și inovare.: Ştiinţe ale naturii și exacte*, 10-11 noiembrie 2021, Chișinău, Republica Moldova, pp. 159-161. ISBN 978-9975-158-60-2.

4) **NEGUTA, E.**, BALAN, G., GULYA, A., BULIMESTRU, I. Antimicrobial and antifungal activity of Cu(II) and Bi(III) complexes based on aminopolycarboxylate ions and 2-formyl and 2-acetylpyridine thiosemicarbazones. In: *One Health and Risk Management*, 2021, nr. 2(4-S), p. 52. ISSN 2587-3458.

5) **NEGUTA, E.**, BALAN, G., GULYA, A., BULIMESTRU, I. Coordination Compounds of Cu(II) and Bi(III) with Ethylenediaminetetraacetate Ions and 2-Acetylpyridine Thiosemicarbazones. In: *Applications of Chemistry in Nanosciences and Biomaterials Engineering: . NanoBioMat 2022*, Ed. 2, 22-24 iunie 2022, Bucharest, pp. 146-147.

6) **NEGUȚA, E.**, BALAN, G., GULEA, A., BULIMESTRU, I. Activitatea biologică a compușilor coordinativi ai Cu(II) și Bi(III) cu ioni aminopolicarboxilat și tiosemicarbazone ale 2-formil și 2-acetilpiridinei. In: *Integrare prin cercetare și inovare.: Ştiinţe ale naturii și exacte*, 10-11 noiembrie 2022, Chișinău, Republica Moldova, pp. 201-204. ISBN 978-9975-62-469-5.

PATENT OF INVENTION

BULIMESTRU, I., **NEGUȚA, E.**, NEGUȚA, A., BĂLAN, G., LOZAN-TÎRȘU, C., ȚAPCOV, V., GULEA, A. (μ_2-Etilendiamin-N,N,N',N'-tetraacetato)-{N-fenil-N'-[1-(piridin-2-il)etiliden]-carbamohidrazontioatocupru(II)}-di(aqua)bismut(III) tetrahidrat, care manifestă activitate antimicotică față de *Candida albicans* // Brevet de invenție MD nr. 4880. Publicat BOPI nr.12/2023, pp. 22-23.

ADNOTARE

NEGUȚA Elena "Sinteza și studiul compușilor coordinativi ai Cu(II) și Bi(III) cu ioni aminopolicarboxilat și tiosemicarbazone ale 2-formilpiridinei și derivaților ei", teză de doctor în științe chimice, la specialitatea 141.01 "Chimie Anorganică", Chișinău, 2024

Structura tezei: lucrarea constă din introducere, 4 capitole, concluzii generale și recomandări, bibliografie din 154 de surse, 123 pagini de text de bază, 83 figuri și 15 tabele. Rezultatele obținute la tema tezei au fost publicate în 12 lucrări științifice, inclusiv 5 articole categoria B, 6 rezumate la conferințe și un brevet de invenție.

Cuvinte cheie: cupru(II), bismut(III), complecși homometalici, complecși heterometalici, aminopolicarboxilat (APC), tiosemicarbazone, activitate antimicrobiană și antifungică, propietăți antioxidative.

Scopul lucrării: studiul comparativ structural și biologic al complecșilor homo- și heterometalici ai Cu(II) și Bi(III) cu liganzi micști: aminopolicarboxilat (APC) - tiosemicarbazone ale 2-formilpiridinei și derivaților ei pentru elucidarea factorilor care amplifică activitatea biologică.

Obiectivele cercetării: stabilirea condițiilor optime de sinteză a compușilor coordinativi homo- și heterometalici ai Bi(III) și Cu(II) folosind în calitate de agenţi de chelatare ionii APC şi tiosemicarbazonele 2-formil-, 2-acetil- și 2-benzoilpiridinei (HL); determinarea compoziţiei chimice, purităţii şi structurii substanţelor obţinute cu ajutorul diferitor metode fizico-chimice de analiză; determinarea activității biologice a compușilor sintetizați pentru elucidarea influenței următorilor factori: a) substituentul (R^1) de la carbonul carbonilic; b) forma tiolică/tionică a ligandului; c) substituentul (R^2) în poziția 4N a tiosemicarbazonei; d) natura ionului metalic; e) natura anionului APC; f) raportul dintre liganzi. În complecșii heterometalici, suplimentar, a fost analizată și influența celui de-al doilea ion metalic.

Noutatea și originalitatea științifică: sinteza a 57 combinații coordinative homo- și heterometalice ai Cu(II) și Bi(III) cu ioni aminopolicarboxilat și tiosemicarbazone ale 2-formilpiridinei și derivaților ei. Determinarea compoziției, purității și structurii compușilor sintetizați cu ajutorul spectroscopiei IR, spectroscopiei de Rezonanță Magnetică Nucleară ^{1}H-RMN, ^{13}C-RMN, analizei elementelor și analizei cu raze X pe monocristal/pulbere; cercetarea activității antibacteriene, antifungice și antioxidative.

Problema ştiinţifică soluționată: au fost obținuți noi agenți cu proprietăți antibacteriene, antifungice și antioxidative în baza compușilor coordinativi ai Cu(II) și Bi(III) cu ioni aminopolicarboxilat și tiosemicarbazone ale 2-formilpiridinei și derivaților ei.

Semnificația teoretică: rezultatele obținute pot fi utilizate pentru a sintetiza noi compuși coordinativi homo- și heterometalici cu proprietăți biologice înalte.

Valoarea aplicativă: au fost obținute combinații coordinative care sunt de aproximativ 337 mai active decât Furacilina și de cca 78 de ori mai active decât Nistatina.

Implementarea rezultatelor ştiinţifice: a fost brevetat un compus heterometalic al Cu(II)-Bi(III) ce manifestă activitate antimicotică înaltă faţă de fungile din specia *Candida albicans* şi datorită acestor proprietăţi poate găsi aplicare în medicină şi veterinărie la profilaxia şi tratarea micozelor.

ANNOTATION

NEGUTA Elena "Synthesis and study of the coordination compounds of Cu(II) and Bi(III) with aminopolycarboxylate ions and thiosemicarbazone of 2-formylpyridine and its derivatives", PhD thesis in chemical sciences, specialty 141.01 "Inorganic Chemistry", Chisinau, 2024

Thesis structure: the paper consists of introduction, 4 chapters, general conclusions and recommendations, bibliography from 154 sources, 123 pages of basic text, 83 figures and 15 tables. The results obtained on the thesis topic were published in 12 scientific papers, including 5 category B articles, 6 conference abstracts and an invention patent.

Key words: copper(II), bismuth(III), homometallic complexes, heterometallic complexes, aminopolycarboxylate (APC), thiosemicarbazones, antimicrobial and antifungal activity, antioxidant properties.

The aim of the work: comparative structural and biological study of the homo- and heterometallic complexes of Cu(II) and Bi(III) with small ligands: aminopolycarboxylate (APC) - thiosemicarbazones of 2-formylpyridine and its derivatives to elucidate the factors that amplify the biological activity.

Research objectives: establishing the optimal conditions for the synthesis of homo- and heterometallic coordination compounds of Bi(III) and Cu(II) using APC ions and 2-formyl-, 2-acetyl- and 2-benzoylpyridine (HL) thiosemicarbazones as chelating agents; determination of the chemical composition, purity and structure of the substances obtained with the help of different physico-chemical methods of analysis; determination of the biological activity of the synthesized compounds to elucidate the influence of the following factors: a) the substituent (R^1) from the carbonyl carbon; b) the thiol/ionic form of the ligand; c) the substituent (R^2) in the 4N position of the thiosemicarbazone; d) the nature of the metal ion; e) the nature of the APC anion; f) the ratio between the ligands. In the heterometallic complexes, additionally, the influence of the second metal ion was analyzed.

Scientific novelty and originality: synthesis of 57 homo- and heterometallic coordination combinations of Cu(II) and Bi(III) with aminopolycarboxylate ions and thiosemicarbazones of 2-formylpyridine and its derivatives. Determination of the composition, purity and structure of the synthesized compounds using IR spectroscopy, Nuclear Magnetic Resonance spectroscopy ^{1}H-NMR, ^{13}C-NMR, elemental analysis and single crystal/powder X-ray analysis; antibacterial, antifungal and antioxidant activity research.

The scientific problem solved: new agents with antibacterial, antifungal and antioxidant properties were obtained based on the coordination compounds of Cu(II) and Bi(III) with aminopolycarboxylate and thiosemicarbazone ions of 2-formylpyridine.

Theoretical significance: the obtained results can be used to obtain new homo- and heterometallic coordination compounds with high biological properties.

Application value: coordinative combinations were obtained which are approximately 337 times more active than Furacilin and approx. 78 times more active than Nystatin.

Implementation of the scientific results: a heterometallic compound of Cu(II) and Bi(III) was patented, which exhibits high antimycotic activity against fungi of the *Candida albicans* species and, thanks to these properties, can find application in medicine and veterinary medicine for the prophylaxis and treatment of mycoses.

АННОТАЦИЯ

НЕГУЦА Елена “Синтез и исследование координационных соединений Cu(II) и Bi(III) с ионами аминополикарбоксилатов и тиосемикарбазонов 2-формилпиридина и его производных”, кандидатская диссертация по химическим наукам по специальности 141.01 “Неорганическая химия”, Кишинёв, 2024 г.

Структура диссертации: статья состоит из введения, 4 глав, общих выводов и рекомендаций, библиографии из 154 источников, 123 страниц основного текста, 83 рисунков и 15 таблиц. Результаты, полученные по теме диссертации, опубликованы в 12 научных работах, в том числе 5 статьях категории Б, 6 тезисах конференций и патенте на изобретение.

Ключевые слова: медь(II), висмут(III), гомометаллические комплексы, гетерометаллические комплексы, аминополикарбоксилат (АПК), тиосемикарбазоны, противомикробная и противогрибковая активность, антиоксидантные свойства.

Цель работы: сравнительное структурно-биологическое исследование гомо- и гетерометаллических комплексов Cu(II) и Bi(III) со смешанными лигандами: аминополикарбоксилатом (АПК) - тиосемикарбазонами 2-формилпиридина и его производных для выяснения факторов, вызывающих усиливают биологическую активность.

Задачи исследования: установление оптимальных условий синтеза гомо- и гетерометаллических координационных соединений Bi(III) и Cu(II) с использованием ионов АПК и 2-формил-, 2-ацетил- и 2-бензоилпиридиновых (HL) тиосемикарбазонов в качестве хелатирующих агентов; определение химического состава, чистоты и строения полученных веществ с помощью различных физико-химических методов анализа; определение биологической активности синтезированных соединений с целью выяснения влияния следующих факторов: а) заместителя (R^1) у карбонильного углерода; б) тиоловая/тионная форма лиганда; в) заместитель (R^2) в положении 4N тиосемикарбазона; г) природа иона металла; д) природа аниона АПК; е) соотношение между лигандами. В гетерометаллических комплексах, дополнительно, анализировали влияние иона второго металла.

Научная новизна и оригинальность: синтез 57 гомо- и гетерометаллических координационных соединений Cu(II) и Bi(III) с аминополикарбоксилат-ионами и тиосемикарбазонами 2-формилпиридина и его производными. Определение состава, чистоты и структуры синтезированных соединений методами ИК-спектроскопии, спектроскопии ядерного магнитного резонанса ^{1}H-ЯМР, ^{13}C-ЯМР, элементного анализа и рентгеноструктурного анализа монокристаллов/порошков; исследование антибак-териальной, противогрибковой и антиоксидантной активности.

Решаемая научная задача: получены новые средства с антибактериальными, противогрибковыми и антиоксидантными свойствами на основе координационных соединений Cu(II) и Bi(III) с аминополикарбоксилатными и тиосемикарбазон-ионами 2-формилпиридина.

Теоретическая значимость: полученные результаты могут быть использованы для получения новых гомо- и гетерометаллических координационных соединений с высокими биологическими свойствами.

Прикладное значение: получены координационные комбинации, которые примерно в 337 раз активнее Фурацилина и примерно в 78 раз активнее Нистатина.

Внедрение научных результатов: запатентовано гетерометаллическое соединение Cu(II) и Bi(III), которое проявляет высокую антимикотическую активность в отношении грибов вида *Candida albicans* и благодаря этим свойствам может найти применение в медицине и ветеринарии для профилактика и лечение микозов.

NEGUTA ELENA

SYNTHESIS AND STUDY OF THE COORDINATION COMPOUNDS OF CU(II) AND BI(III) WITH AMINOPOLYCARBOXYLATE IONS AND THIOSEMICARBAZONE OF 2-FORMYLPYRIDINE AND ITS DERIVATIVES

141.01 INORGANIC CHEMISTRY

Summary of the doctoral thesis in chemical sciences

Approved for printing: 02.05.2024
Offset paper. Offset printing.
Printing sheets: 2.0

Paper size: 60×84 1/16
Copies 10 ex.
Command nr. 56/24

Moldova State University, Editorial-Printing Center
60, Al. Mateevici str., Chisinau, MD, 2009