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COPPER(II) COORDINATION COMPOUNDS WITH 2-ACETILPYRIDINE N⁴-(BICYCLO[2.2.1]HEPTAN-2-IL)TIOSEMICARBAZONA AS POTENTIAL ANTIBACTERIAL AGENTS

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The paper presents the synthesis of the new 2-acetylpyridine N⁴-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone (HL) and its three copper(II) coordination compounds: [Cu(L)X] (X = NO₃⁻ (I), Cl⁻ (II), CHCl₂COO⁻ (III)). The obtained compounds were studied by NMR and FTIR spectroscopies, elemental analysis, and molar electric conductivity. The antibacterial activity towards Gram-positive (*Staphylococcus aureus*, *Bacillus cereus*) and Gram-negative (*Escherichia coli*, *Acinetobacter baumannii*) standard strains was studied for the HL and complexes I-III. The coordination of the HL to the copper(II) atom leads to the increase of activity against almost all microorganisms. Complex I is the most active one towards Gram-positive microorganisms, while complex III is the most active one towards Gram-negative microorganisms. They in many cases surpass the activity of Furacillinum and are practically on the same level as Tetracycline towards Gram-positive microorganisms.

Keywords: *thiosemicarbazones, coordination compounds, copper, antibacterial activity.*

COMPUȘI COORDINATIVI AI CUPRULUI(II) CU N⁴-(BICICLO[2.2.1]HEPTAN-2-IL)TIOSEMICARBAZONA 2-ACETILPIRIDINEI CA POTENȚIALI AGENȚI ANTIBACTERIENI

Lucrarea conține descrierea sintezei N⁴-(bicyclo[2.2.1]hept-2-il)tiosemicarbazonei 2-acetilpiridinei (HL) și a trei compuși coordinativi ai cuprului cu acest ligand: [Cu(L)X] (X = NO₃⁻ (I), Cl⁻ (II), CHCl₂COO⁻ (III)). Compușii obținuți au fost studiați cu ajutorul spectroscopiei RMN și FTIR, analizei elementale și conductivității molare. Pentru HL și compușii coordinativi I-III a fost studiată activitatea antibacteriană față de microorganisme Gram-pozitive (*Staphylococcus aureus*, *Bacillus cereus*) și Gram-negative (*Escherichia coli*, *Acinetobacter baumannii*). Coordinarea HL la ion de cupru(II) duce la creșterea activității antimicrobiene practic asupra tuturor microorganismelor studiate. Complexul I este cel mai activ față de microorganismele Gram-pozitive, iar complexul III este cel mai activ față de microorganismele Gram-negative. Activitatea antimicrobiană a acestor complecși în multe cazuri depășește activitatea Furacilinei și este practic la același nivel cu Tetraciclina față de microorganismele Gram-pozitive.

Cuvinte-cheie: *tiosemicarbazone, compuși coordinativi; cupru; activitate antibacteriană*

Introduction

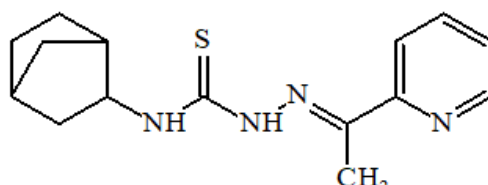
Bacterial resistance to antibiotics is a global threat for public health [1]. The resistant forms of pathogenic microorganisms develop due to the uncontrolled use of antibiotics. The resistance is outpacing new drug development now. Nearly 1.3 million people die every year because of antibiotic resistance. To stay ahead of this natural evolution, we must constantly innovate new drugs. Half of all antibiotics used today were discovered between the 1950s and 1970s [2]. Since the end of the 20th century, research and development

in this field have slowed down. Therefore, the synthesis of new substances with increased antibacterial properties remains an actual problem.

Thiosemicarbazones represent a class of organic substances which in many cases manifest biological properties such as antibacterial [3], antifungal [4], antiviral [5], and antimalarial [6]. The complexes of thiosemicarbazones with metal ions may be considered as the potential biological agents. Many studies have shown that copper(II) coordination compounds with thiosemicarbazones often display better selectivity than the initial thiosemicarbazones [7]. The substitution of the thiosemicarbazone moiety in the N^4 position leads to the increase of the different types of biological activity both in the initial thiosemicarbazone and in its complexes [8].

The aim of this work is the synthesis of 2-acetylpyridine N^4 -(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone (HL, Fig. 1), that contains a bicyclic fragment which is present in the natural biological active substance Camphor, as well as Cu(II) complexes with this thiosemicarbazone as ligand, and the determination of their antibacterial properties.

Fig. 1. 2-Acetylpyridine N^4 -(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone.



Materials and methods

N^4 -(bicyclo[2.2.1]heptan-2-yl)thiosemicarbazide was synthesized by the reaction between 2-isothiocyanatobicyclo[2.2.1]heptane and hydrazine hydrate as described in [9]. 2-Acetylpyridine (Sigma-Aldrich) and copper salts were used as received.

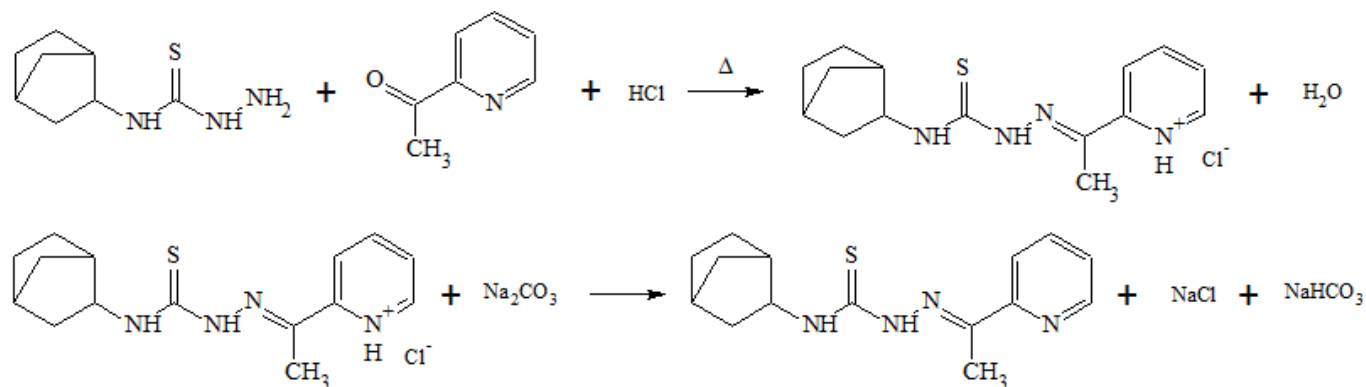
Infrared spectra of the compounds were recorded on a Bruker ALPHA FTIR spectrophotometer at room temperature in the range of 4000-400 cm^{-1} .

The determination of copper content in the synthesized coordination compounds, using titration methods, was performed similarly to the literature procedures [10, 11]. Melting point of the thiosemicarbazone was measured using capillary method [12]. Molar conductivity values of the 1 mM methanol solutions were measured using portable conductivity meter.

Synthesis of the 2-acetylpyridine N^4 -(bicyclo[2.2.1]heptan-2-yl)thiosemicarbazone (HL)

2-Acetylpyridine N^4 -(bicyclo[2.2.1]heptan-2-yl)thiosemicarbazone (HL) was prepared using a two-step process (Fig. 2).

Fig. 2. Synthesis of the 2-acetylpyridine N^4 -(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone.



At first step N^4 -(bicyclo[2.2.1]hept-2-yl)thiosemicarbazide (0.500 g, 2.70 mmol) was dissolved in 20 mL of ethanol with the constant stirring. After that, the solution of 2-acetylpyridine (0.327 g, 2.70 mmol) in 20 mL of ethanol was added. Concentrated hydrochloric acid (0.274 g, 2.70 mmol) was added to the obtained

solution. This mixture was stirred and heated for 30 minutes. After cooling of the solution, the yellow precipitate of 2-acetylpyridine *N*⁴-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone hydrochloride was formed. The precipitate was filtered and washed with small amounts of cold ethanol.

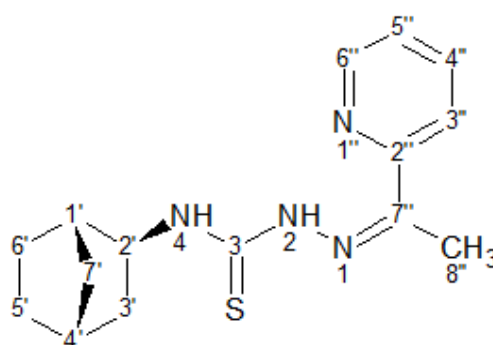
On the second step, the obtained 2-acetylpyridine *N*⁴-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone hydrochloride was dissolved in 20 mL ethanol with the constant stirring and heating. The obtained solution was neutralized with an aqueous solution of Na₂CO₃. The resulting thiosemicarbazone was extracted with chloroform.

White solid. Yield: 89%; m.p.: 154-156 °C; FW: 288.41 g/mol.

Main IR peaks (cm⁻¹): ν(NH) 3329, 3185; ν(C=N) 1581, 1516; ν(C=S) 1302.

NMR spectroscopy (Fig. 3)

Fig. 3. Numbering of atoms in NMR spectra



¹H NMR (CDCl₃; δ, ppm): 8.64, 8.59 (br, 2×1H, NH(2,4)); 7.88 (d, 1H, CH(6'')); 7.72 (t, 1H, CH(4'')); 7.46 (d, 1H, CH(3'')); 7.28 (t, 1H, CH(5'')); 4.21 (t, 1H, CH(2')); 2.46 (m, 1H, CH(1')); 2.38 (s, 3H, CH₃); 2.36 (m, 1H, CH(4')); 2.0-1.1 (m, 8H, CH₂ (3', 5', 6', 7')).

¹³C NMR (CDCl₃; δ, ppm): 176.72 (C(3)=S); 154.57, 148.89, 147.32, 123.95, 120.08 (C from pyridine fragment); 136.34 (C(7'')=N); 57.66, 42.35, 40.47, 36.02, 35.90, 28.08, 26.37 (C from bicycle fragment), 11.41 (CH₃(8'')).

Synthesis of Cu(II) coordination compounds

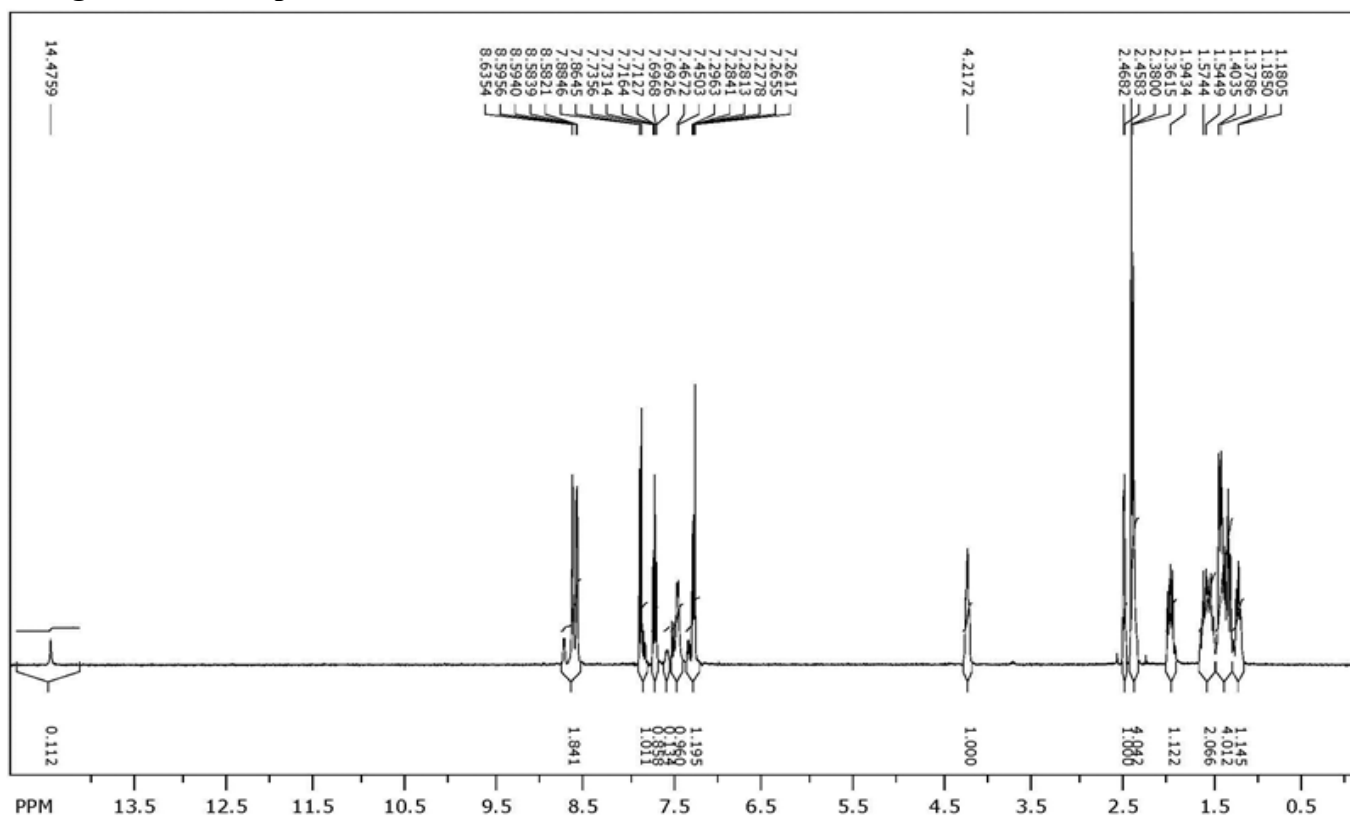
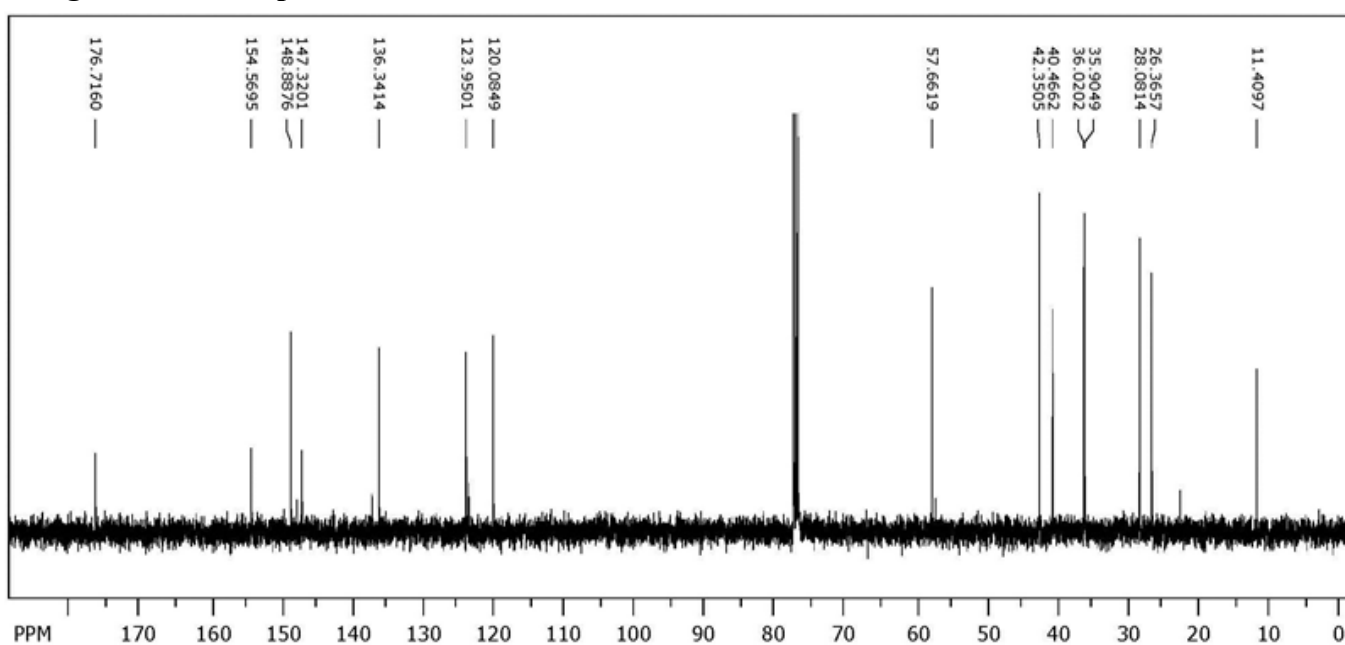
The complexes [Cu(L)X] (X = NO₃⁻ (I), Cl⁻ (II), CHCl₂COO⁻ (III)) were obtained by reaction between hot ethanolic solution of HL and corresponding copper salt (copper(II) nitrate trihydrate, copper(II) chloride dihydrate, and copper(II) dichloroacetate, correspondingly) in 1:1 molar ratio. The green precipitates have formed during stirring. They were filtered, washed with a small amount of ethanol and allowed to dry at room temperature.

Antibacterial bioassay

The antimicrobial activities of the pro-ligand and complexes were evaluated *in vitro* against *Staphylococcus aureus* (ATCC 25923), *Bacillus cereus* (ATCC 11778), *Escherichia coli* (ATCC 25922), and *Acinetobacter baumannii* (BAA-747) standard strains. Determination of the MICs (minimum inhibitory concentrations) and MBCs (minimum bactericidal concentrations) was done using the serial dilutions in liquid broth method [13].

Results and discussion

The process of condensation of thiosemicarbazides with ketones usually requires 5-8 hours of heating in presence of the catalytic amount of acetic acid [14, 15]. So, a modified two-step mechanism was developed in order to obtain the required thiosemicarbazone. As a result of reaction between *N*⁴-(bicyclo[2.2.1]heptan-2-yl)thiosemicarbazide, 2-acetylpyridine, and hydrochloric acid in molar ratio 1:1:1 hydrochloride of 2-acetylpyridine *N*⁴-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone (HL·HCl) was easily obtained in 30 minutes. Reaction between ethanol solution of HL·HCl and aqua solution of sodium carbonate was used to obtain 2-acetylpyridine *N*⁴-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone (HL) which was extracted from the reaction mixture with chloroform and then purified by recrystallization from ethanol. Its structure was proven using NMR spectroscopy (Fig. 4 and 5).

Fig. 4. ^1H NMR spectrum of HLFig. 5. ^{13}C NMR spectrum of HL

^1H NMR spectrum contains corresponding peaks of hydrogen atoms from bicyclo[2.2.1]heptan-2-yl fragment (1.18-4.21 ppm), methyl group (2.38 ppm), pyridine moiety and NH-groups (7.26-8.63 ppm). Also there is a small peak at 14.48 ppm which corresponds to the hydrogen of the SH-group. It indicates the presence of an equilibrium between thion and thiol tautomeric forms of this thiosemicarbazone in the chloroform solution.

^{13}C NMR also contains all the characteristic peaks of sp^3 -hybrid carbon atoms from bicyclic fragment (26.37-57.66 ppm), methyl group (11.41 ppm), and sp^2 -hybrid carbon atoms (120.08-176.72 ppm) including characteristic peak at 176.72 ppm of the C=S carbon atom.

Three new copper coordination compounds were obtained as a result of interaction between $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and $\text{Cu}(\text{CHCl}_2\text{COO})_2$ with ethanol solution of thiosemicarbazone HL. The obtained coordination compounds are green microcrystalline solids and are stable in air. The elemental analysis on copper suggest the general formula $\text{Cu}(\text{L})\text{X}$ ($\text{X} = \text{NO}_3^-$ (I), Cl^- (II), $\text{CHCl}_2\text{COO}^-$ (III)) (Table 1).

Table 1. Physical and analytical data of the metal complexes (I-III).

#	Compound	Formula	η^a , %	Found/calculated, metal %	λ^b
I	$[\text{Cu}(\text{L})\text{NO}_3]$	$\text{C}_{15}\text{H}_{19}\text{CuN}_5\text{O}_3\text{S}$	78	16.01/15.39	86
II	$[\text{Cu}(\text{L})\text{Cl}]$	$\text{C}_{15}\text{H}_{19}\text{ClCuN}_4\text{S}$	87	16.94/16.45	108
III	$[\text{Cu}(\text{L})(\text{CHCl}_2\text{COO})]$	$\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{CuN}_4\text{O}_2\text{S}$	82	13.06/13.27	60

a – yield; *b* – molar conductivity in methanol at room temperature, $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$.

The molar conductivity values of the synthesized complexes I-III are in the range 60 - 108 $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ that indicates that these complexes are 1:1 type of electrolytes.

The FTIR spectrum of HL contains the absorption bands at 3329 and 3185 cm^{-1} that correspond to two NH groups, $\nu(\text{C}=\text{N})$ absorption bands at 1581 and 1516 cm^{-1} and $\nu(\text{C}=\text{S})$ absorption band at 1302 cm^{-1} . One of the $\nu(\text{N}-\text{H})$ absorption bands disappears from the FTIR spectra of the complexes I-III, which points to deprotonation of the HL in the process of coordination (Fig. 6, Table 2).

Fig. 6. FTIR spectra of HL (blue) and $[\text{Cu}(\text{L})\text{Cl}]$ (II) (green).

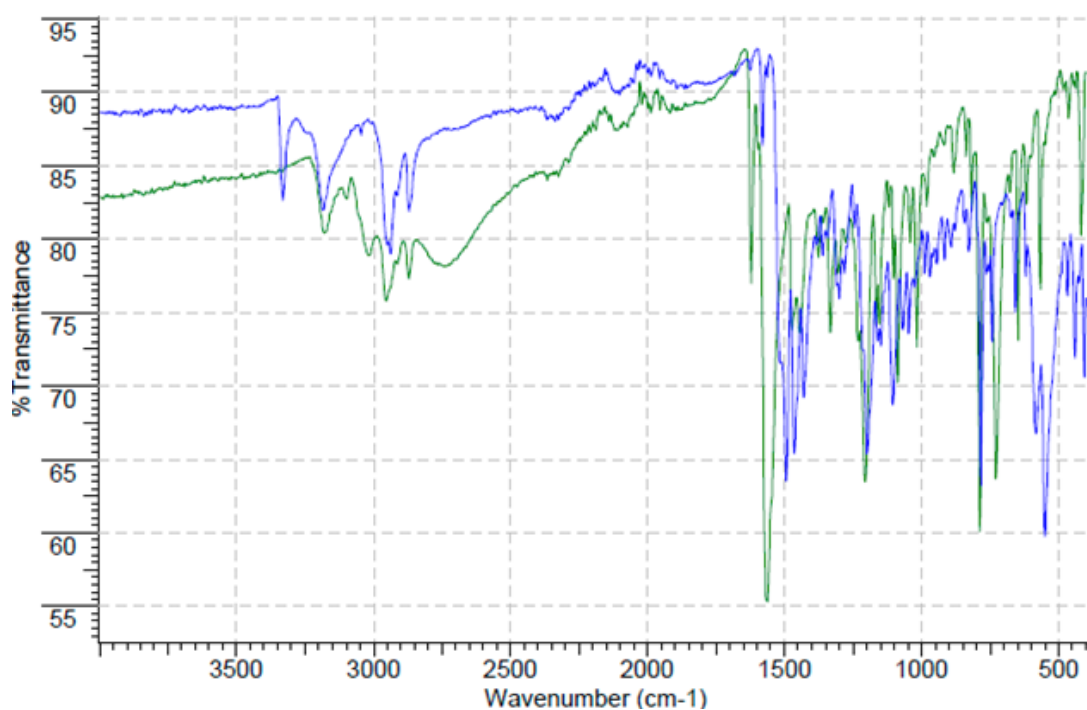


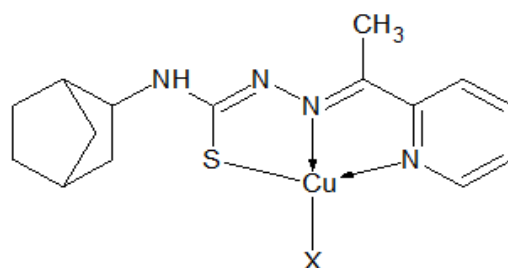
Table 2. Some frequencies (cm^{-1}) of the FTIR spectra of the thiosemicarbazone HL and complexes I-III.

Compound	$\nu(\text{NH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{S})$	$\nu(\text{C}-\text{S})$
HL	3329 3185	1581 1516	1302	-
$[\text{Cu}(\text{L})\text{NO}_3]$ (I)	3350	1601 1499,1475	-	777

[Cu(L)Cl] (II)	3180	1621 1563,1546	-	787
[Cu(L)(CHCl ₂ COO)] (III)	3321	1599 1505, 1495	-	787

The results showed the appearance of new $\nu(\text{C}=\text{N})$ absorption band, and the disappearance of $\nu(\text{C}=\text{S})$ absorption band from all the spectra of copper(II) coordination compounds. The new absorption band appears in the spectra at $777\text{-}787\text{ cm}^{-1}$ that correspond to $\nu(\text{C}-\text{S})$. All these results confirm that HL acts as a mono-deprotonated tridentate ligand, that coordinates to the copper(II) atom by pyridine nitrogen atom, azomethine nitrogen atom, and sulfur atom in the thiol form. The proposed distribution of chemical bonds in the coordination compounds is shown in Figure 7.

Fig. 7. Proposed distribution of chemical bonds in the complexes. ($\text{X}=\text{NO}_3^-$ (I), Cl^- (II), $\text{CHCl}_2\text{COO}^-$ (III)).



For the synthesized compounds the antibacterial activity was studied *in vitro* on a series of standard strains. The obtained results in terms of minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) are presented in Table 2.

Table 2. Antibacterial activity of thiosemicarbazone HL and copper(II) complexes I-III.

Compound	Staphylococcus aureus ATCC 25923		Bacillus cereus ATCC 11778		Escherichia coli ATCC 25922		Acinetobacter baumannii BAA-747	
	MIC, $\mu\text{g/mL}$	MBC, $\mu\text{g/mL}$	MIC, $\mu\text{g/mL}$	MBC, $\mu\text{g/mL}$	MIC, $\mu\text{g/mL}$	MBC, $\mu\text{g/mL}$	MIC, $\mu\text{g/mL}$	MBC, $\mu\text{g/mL}$
HL	0.244	0.244	0.122	0.244	>1000	>1000	500.0	>1000
I	0.244	0.488	0.031	0.061	31.25	62.50	1.953	7.813
II	0.488	0.977	0.061	0.061	62.50	250.0	3.906	15.63
III	0.977	1.953	0.244	0.244	125.0	500.0	1.953	3.906
Furacillinum [16, 17]	9.3	9.3	4.7	4.7	18.5	37.5	4.7	9.4
Tetracycline [18-21]	0.25	1.96	0.06	-	0.98	3.91	0.5	-

The HL and its copper(II) coordination compounds manifest antibacterial activity towards a series of Gram-positive (*Staphylococcus aureus* (ATCC 25923), *Bacillus cereus* (ATCC 11778)) and Gram-negative (*Escherichia coli* (ATCC 25922), *Acinetobacter baumannii* (BAA-747)) standard strains in the range of concentrations $0.031\text{-}1000\text{ }\mu\text{g/mL}$. The HL is active only towards Gram-positive microorganisms, but towards Gram-negative microorganisms it is inactive. The coordination of the HL to the copper(II) ion does not lead to the increase of antibacterial activity only in the case of *Staphylococcus aureus*. Nevertheless, in the case of others microorganisms the results showed the significant increase of the activity. Complex I is the most active one towards Gram-positive microorganisms, its activity is up to 150 times greater than the activity of Furacillinum, and is on the same level of activity with Tetracycline, that are used in medicine as an antibiotic. Complex III is the most active one towards *Acinetobacter baumannii* and it exceeds the activity of Furacillinum in 2.4 times.

Conclusions

The new 2-acetylpyridine N^4 -(bicyclo[2.2.1]heptan-2-yl)thiosemicarbazone (HL) and its 3 copper(II) coordination compounds were prepared and characterized using such methods as NMR and FTIR spectroscopies, elemental analysis and molar conductivity. The antimicrobial activity towards Gram-positive and Gram-negative microorganisms was studied for all the obtained substances. The results showed that in almost all cases the coordination of the HL to the copper atom leads to the increase of such type of activity. Complex I is the most active one towards Gram-positive microorganisms and complex III is the most active one towards Gram-negative *Acinetobacter baumannii*. The most active complexes surpass in many cases the activity of Furacillinum and are practically on the same level as Tetracycline towards Gram-positive microorganisms.

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