DOI: 10.47743/achi-2025-1-0003 *ACTA CHEMICA IASI*, **33_1**, 43–60 (2025)

SYNTHESIS, ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY OF COORDINATION COMPOUNDS OF COPPER (II) WITH A THIOSEMICARBAZONE CONTAINING AN ACETANILIDE FRAGMENT

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Abstract: The synthesis of novel antibiotic compounds is a significant area of modern research. This paper describes a method for synthesizing a thiosemicarbazone containing the acetanilide fragment, as well as coordination compounds based on it. The structure of the thiosemicarbazone was confirmed using ^{1}H and ^{13}C NMR spectroscopy, while the structure of the coordination compounds was indirectly confirmed through FTIR spectroscopy and elemental metal analysis. Biological investigations revealed that compounds $[Cu(H_2O)(HL)Br]$ and $[Cu(H_2O)(HL)NO_3]$ exhibit 38 times and 19 times better antimicrobial activity against *Staphylococcus aureus* and *Bacillus cereus*, respectively, compared to Furacin.

***Keywords*:** coordination compound, thiosemicarbazones containing acetanilide fragment, antimicrobial activity, antifungal activity

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Introduction

Antimicrobials are crucial drugs for humans health. In fact, in 2022, healthcare professionals in the United States prescribed over 236 million antimicrobials for treatment.[1] However, there is a pressing global issue - the development of antimicrobial resistance by bacteria. It is estimated that by 2050, more than 8 million deaths will be caused by antimicrobial resistance, with 4.7 million already occurring in 2021[2] (figure 1).

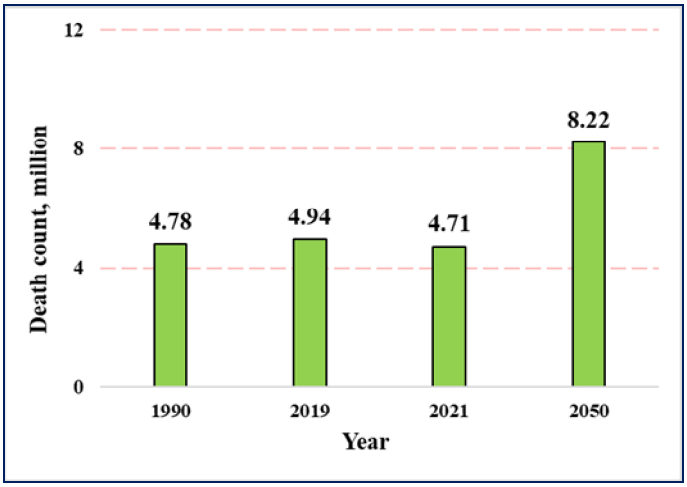


Figure 1. Deaths associated to antimicrobial resistance[2].

The fact that bacteria can develop resistance to drugs has been known since the first half of the last century. In 1940, a strain of *Staphylococcus aureus* was found to be resistant to penicillin, only 12 years after its discovery in 1928.[3] This occurred three years before penicillin purification methods were developed and production was scaled up.[4] A more recent example is levofloxacin, which was introduced in 1996 and in the same year, levofloxacin-resistant *pneumococcus* was discovered.[4] Additionally, many pharmaceutical companies with research departments have stopped developing new antimicrobials due to the inevitable development of resistance and low profitability.[4]

Thus, the development of new antimicrobial agents is a promising and necessary area for research. One potential class of organic compounds that shows promise in this field is thiosemicarbazones. These compounds are derivatives of Schiff bases and have been found to possess versatile biological properties. The literature reports various biological activities of thiosemicarbazones, including antioxidant,[5] antimicrobial,[6] antifungal,[7] anti-inflammatory,[8] antiviral,[9] and anticancer[10] properties. Additionally, thiosemicarbazones are known for their ability to form coordination compounds with 3*d* metals. Studies have shown that these coordination compounds also exhibit similar biological activities as free thiosemicarbazones,[11-13] but in many cases, they have even higher activity.

The biological properties of thiosemicarbazones and their derivatives are heavily influenced by the type of substituents used. Therefore, there is great interest in functionalizing natural or synthetic compounds thar already possess useful biological activity. One of such examples is the acetanilide fragment, which is present in some drugs with anti-inflammatory, antipyretic and analgesic effects[14] (figure 2). Our previous studies have also shown that thiosemicarbazones with an acetanilide moiety, as well as their coordination compounds with 3*d* metals, exhibit antimicrobial activity[14] and inhibition of some cancer cell lines growth.[14-15] Based on this information, we aimed to synthesize a novel thiosemicarbazone based on acetanilide moiety and its coordination compounds with various copper (II) salts. The antimicrobial and antifungal activity of these coordination compounds was then tested.

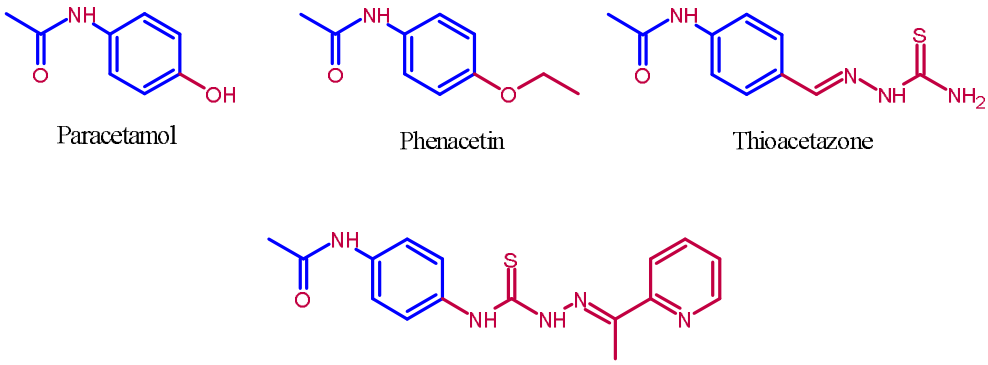
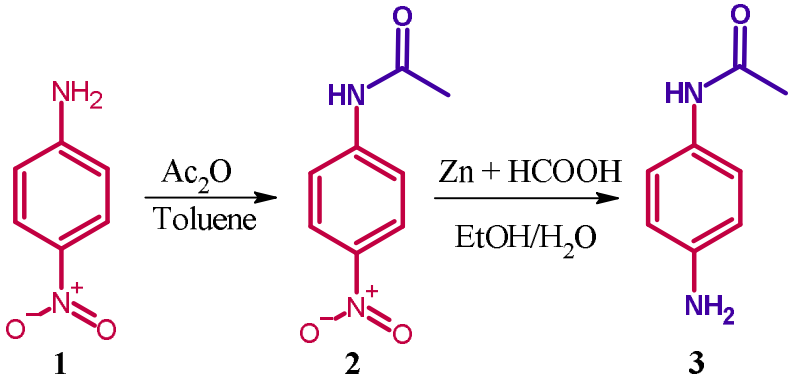


Figure 2. Compounds with acetanilide moiety, which exhibit biological properties.

Results and Discussion

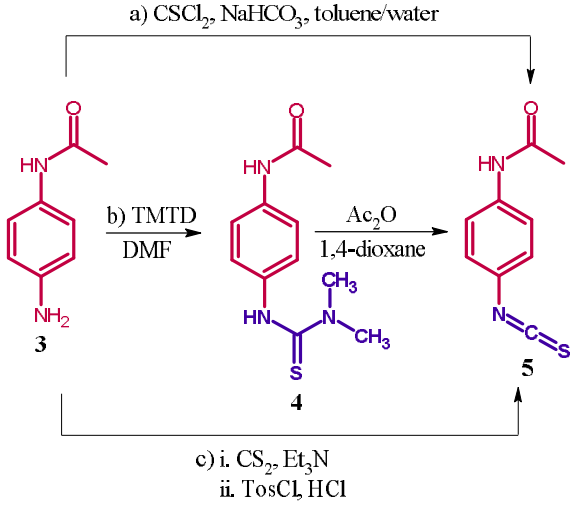
The synthesis of the desired compound (H_2L) began with the acetylation of 4-nitroaniline (compound **1**) using acetic anhydride, resulting in the formation of N-(4-nitrophenyl)acetamide (compound **2)**. Next, the nitro group was reduced to an amino group using zinc powder and formic acid, yielding compound **3** - N-(4-aminophenyl)acetamide (scheme 1).



Scheme 1. Preparation of N-(4-aminophenyl)acetamide.

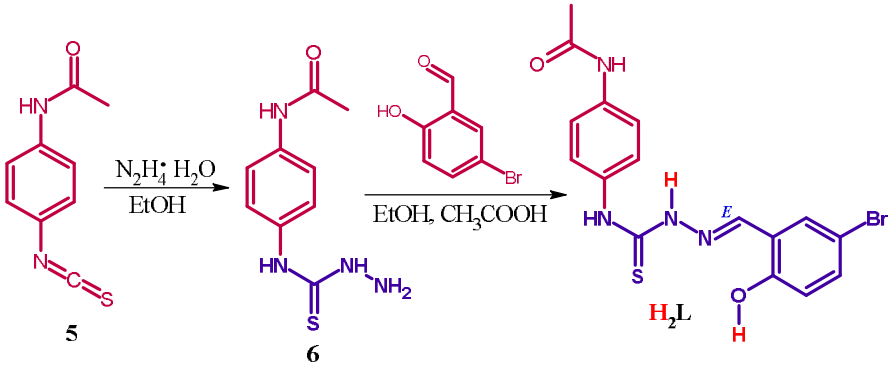
In the subsequent step N-(4-aminophenyl)acetamide (compound **3**) was converted to N-(4-isothiocyanatophenyl)acetamide (compound **4**). Following synthesis methods of N-(4-isothiocyanatophenyl)acetamide

(***a*** and ***b***) were performed according to the procedures described in source[15], with some minor changes (scheme 2).



Scheme 2. Synthesis N-(4-isothiocyanatophenyl)acetamide.

In the final step, N-(4-isothiocyanatophenyl)acetamide (compound **5**) was treated with hydrazine to obtain N-{4-[(hydrazinecarbothioyl) amino]phenyl}acetamide (compound **6**), which was then condensed with 5-bromosalicylaldehyde to form the desired thiosemicarbazone **H_2L** (scheme 3).



Scheme 3. Synthesis of N-(4-(2-(5-bromo-2-hydroxybenzylidene)hydrazinecarbothioamido)phenyl)acetamide.

In total four coordination compounds were synthesised. These compounds were synthesized using a procedure[14,15] that we have previously. The composition of the synthesized compounds was determined through metal analysis, FTIR spectroscopy, and comparison to the structures of similar compounds confirmed through single-crystal XRD.[16-17]

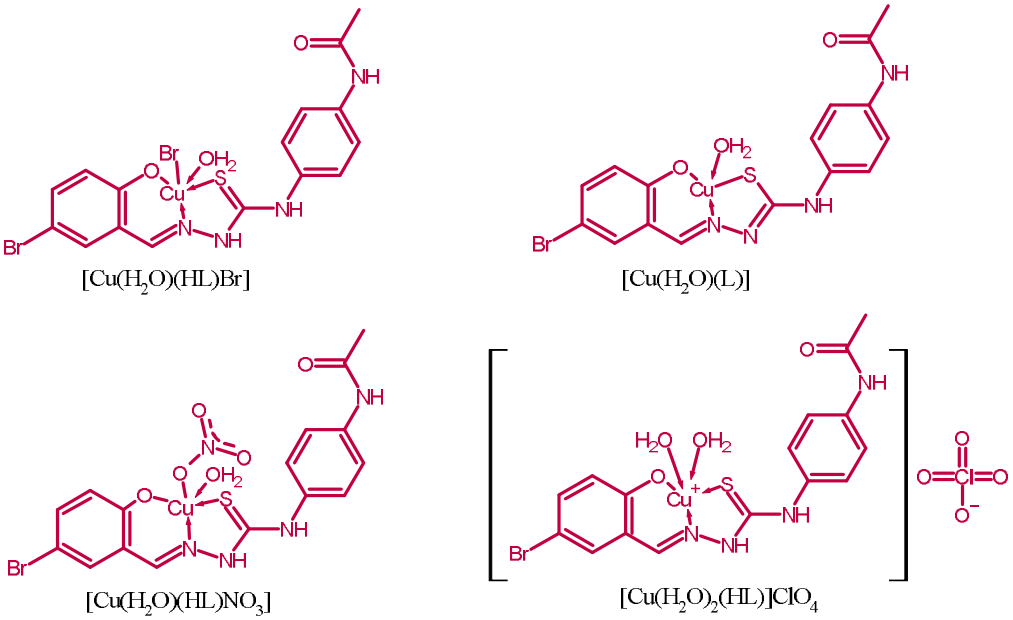


Figure 3. Proposed structure for synthesised coordination compounds.

Antimicrobial activity

All synthesized coordination compounds were tested on 4 bacterial strains: *Staphylococcus aureus* ATCC 25923; *Bacillus cereus* ATCC 11778; *Acinetobacter baumannii* BAA-747 and *Escherichia coli* ATCC 25922. The data obtained are given in Table 1. Ciprofloxacin and Furacin were used as reference substances.

Table 1. Antimicrobial activity of synthesised coordination compounds *("n.a "– "not active", "-" – not tested, MIC – minimal inhibitory concentration and MBC – minimal bactericide concentration).*

Compound	*Staphylococcus aureus* ATCC 25923		*Bacillus cereus* ATCC 11778		*Acinetobacter baumannii* BAA-747		*Escherichia coli* ATCC 25922	
	MIC µg/mL	MBC µg/mL	MIC µg/mL	MBC µg/mL	MIC µg/mL	MBC µg/mL	MIC µg/mL	MBC µg/mL
$[Cu(H_2O)(HL)Br]$	0.122	0.244	0.244	0.488	250	500	n.a.	n.a.
$[Cu(H_2O)(L)]$	1.953	3.906	0.976	1.953	250	500	n.a.	n.a.
$[Cu(H_2O)(HL)NO_3]$	0.122	0.244	0.244	0.488	250	500	n.a.	n.a.
$[Cu(H_2O)_2(HL)]ClO_4$	0.976	1.953	0.976	1.953	250	500	n.a.	n.a.
Ciprofloxacin	1.000	-	-	-	1.000	-	0.250	n.a.
Furacin	4.670	9.350	4.670	4.670	-	-	4.670	4.670

As shown in Table 1 and Figure 5, the compounds $[Cu(H_2O)(HL)Br]$ and $[Cu(H_2O)(HL)NO_3]$ exhibit the lowest MIC (minimal inhibitory concentration) against *Staphylococcus aureus* and *Bacillus cereus*, indicating the strongest antimicrobial activity against these strains. They are 8 times more effective than Ciprofloxacin and 38 times more effective than Furacin against *Staphylococcus aureus*. In case of *Bacillus cereus*, they are 19 times more effective than Furacin. However, the synthesized compounds show weak antimicrobial activity against *Acinetobacter baumannii*, which cannot be compared to the reference substances. Additionally, synthesized compounds showed no significant activity against *Escherichia coli*.

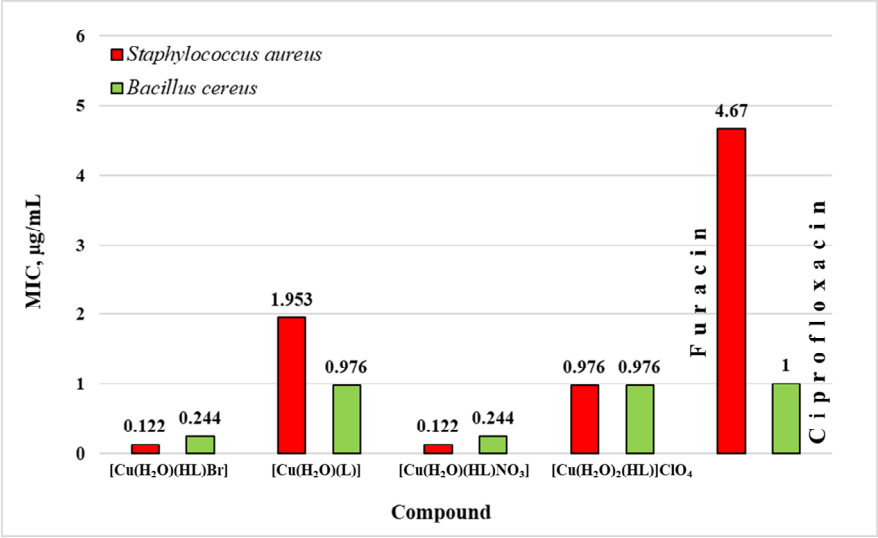


Figure 4. Minimal inhibitory concentration (MIC) of coordination compounds.

Antifungal activity

The synthesized coordination compounds were tested for antifungal activity, but of the compounds have non significant antifungal activity.

Table 2. Antifungal activity of synthesised coordination compounds *("n.a "– "not active", "-" – not tested, MIC – minimal inhibitory concentration and MFC – minimal fungicide concentration).*

Compound	*Candida albicans* ATCC 10231		*Candida krusei* ATCC 6258		*Cryptococcus neoformans* CECT 1043	
	MIC µg/mL	MFC µg/mL	MIC µg/mL	MFC µg/mL	MIC µg/mL	MFC µg/mL
$[Cu(H_2O)(HL^1)Br]$	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
$[Cu(H_2O)(L^1)]$	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
$[Cu(H_2O)(HL^1)NO_3]$	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**	**n.a.**
$[Cu(H_2O)_2(HL^1)]ClO_4$	**n.a.**	**n.a.**	**n.a.**	**n.a.**	500	**n.a.**
Nystatin	32	-	32	-	8	-

Experimental

Synthesis of N-(4-aminophenyl)acetamide (3)

In a round-bottom flask, 4-nitroaniline (10 g, 0.0724 mol) was dissolved in toluene. To this solution, acetic anhydride (7.4 g, 0.0725 mol) was added. The mixture was stirred at room temperature for 1 hour (or heated up to 45-50 °C if necessary). Once the reaction was complete, the solution was concentrated using a rotary evaporator under reduced pressure. The resulting solid was washed with water and recrystallized from methanol, to yield a pale-yellow solid (compound **2**) with a yield of 89%.

Next, the N-(4-nitrophenyl)acetamide (1.0 eq., compound **2**) was dissolved in a mixture of ethanol and water. To this solution, HCOOH (85%) (3.0 eq.,) and zinc powder (1.2 eq.,) were added. The solution was heated up to 50 °C and stirred for 2 hours. It was then filtered while still hot and cooled to 0-5 °C. The resulting crystalized product was separated, washed with water and cold diethyl ether, and dried under vacuum. The slightly-pink solid (compound **3**) was obtained with a yield of 96 %.

Synthesis of *N-(4-isothiocyanatophenyl)acetamide (5)*[a]

A mixture of $NaHCO_3$ (4.67 g, 0.0556 mol) and N-(4-aminophenyl)acetamide (5.00 g, 0.0278 mol, compound **3**) was dissolved in a mixture of water and toluene. Thiophsogen (3.20 g, 0.0278 mol) dissolved in toluene was then added dropwise to the resulting solution. After its addition, the mixture was stirred for 2 hours. The organic layer was then separated and washed with a saturated solution of $NaHCO_3$ (3x20 mL), water (3x20 mL), and brine (2x15 mL). It was then dried over anhydrous $MgSO_4$. The resulting solution was concentrated using a rotary evaporator under reduced pressure. The solid obtained was twice

recrystallized from 1,4-dioxane to yield a white solid of N-(4-isothiocyanatophenyl)acetamide (compound **5**) with a yield of 86 %.

Synthesis of N-(4-isothiocyanatophenyl)acetamide (5)[b]

In a round-bottom flask, 5.00 g (0.0333 mol) of N-(4-aminophenyl) acetamide (compound **3**), 8.00 g (0.0333 mol) of tetramethyl thiuram disulphide, and 15 mL of isopropanol were added. The mixture was refluxed for 6 hours. The completion of the reaction was determined by TLC, and the synthesis solution was then poured into cold distilled water. The resulting precipitate was recrystallized from benzene to obtain a light-grey solid of the N-{4-[(dimethylcarbamothioyl)amino] phenyl}acetamide (compound **4**) with a yield of 80%.

In the next step, 5 g (0.021 mol) of N-{4-[(dimethylcarbamothioyl) amino]phenyl}acetamide (compound **4**) was mixed with 2.15 g (0.021 mol) of acetic anhydride and refluxed for 4 hours in 1,4-dioxane. The resulting precipitate was recrystallized from benzene, and then twice from 1,4-dioxane to yield a white solid (compound **5**) with a yield of 45%.

Synthesis of N-(4-isothiocyanatophenyl)acetamide (5)[c]

In a round-bottom flask N-(4-aminophenyl)acetamide (5 g, 0.0278 mol, compound **3**) was dissolved in toluene and triethylamine (12 mL, 0.086 mol) was added. A solution of CS_2 (1.72 mL, 2.17 g, 0.0285 mol) in toluene was then added dropwise to the mixture over a period of 30-40 minutes. The solution was stirred for 24 hours. After this, tosyl chloride (5.83 g, 0.0306 mol) was added in three portions and the solution was stirred for an additional 24 hours. Then, 10 mL of 1 N HCl solution was added and the solution was mixed for 1 hour. Then, 15 mL of diethyl ether was added and the organic layer was separated. The organic layer was washed with three portions of 20 mL of distilled water and twice

with 15 mL of brine. The solution was dried over anhydrous $MgSO_4$. The resulting solution was concentrated using a rotary evaporator under reduced pressure. Precipitated solid was recrystallized twice from 1,4-dioxan to result a white solid (compound **5**) with a yield of 65%.

Synthesis of N-(4-(2-(5-bromo-2-hydroxybenzylidene)hydrazine-carbothioamido)phenyl)acetamide (H_2L)

Previously obtained N-(4-isothiocyanatophenyl)acetamide (1.00 g, 0.0052 mol, compound **5**) was dissolved in ethanol and slowly added to an ethanolic solution of hydrazine monohydrate (0.26 g, 0.0052 mol). The synthesis solution was stirred for an additional 2 hours after the addition was complete. The resulting solid was filtered and washed with ethanol and diethyl ether. This resulted a white solid of N-{4-[(hydrazinecarbothioyl)amino]phenyl}acetamide (**6**) with a 78% yield.

In a round-bottom flask, 5-bromo-2-hydroxybenzaldehyde (0.60 g, 0.003 mol) and N-{4-[(hydrazinecarbothioyl)amino]phenyl}acetamide (0.67 g, 0.003 mol, compound **6**) where mixed. Ethanol (15 mL) was added as a solvent and 500-700 μL of glacial acetic acid was added as a catalyst. The mixture was refluxed for approximatively 6 hours, with TLC monitoring of the initial compounds. After the reaction was complete, the resulting solid was filtered and washed with water and ethanol. This resulted in a pale yellow solid of N-(4-(2-(5-bromo-2-hydroxybenzylidene)hydrazinecarbothioamido)phenyl)acetamide (H_2L) with an 89% yield. M.p.= 213-215°C, R_f = 0.83 (eluent: benzene-isopropanol 3:1). FTIR (ν_{max}, cm^{-1}): ν(OH) – 3357; ν(N-H) - 3286; ν(C-H) - 3118; ν(C=C) – 1515-1471; ν(C=S) - 1273; ν(1,3,5-substitution) – 754; ν(C-Br) - 693. ^{1}H RMN (400 MHz, DMSO-d_6) δ(ppm): 2.06 s 3H (37, 38, 39); 6.83-6.86 d 1H (29); 7.34-7.40 m 3H (30, 26, 28); 7.56-7.58 m 2H (25, 27); 8.33-8.34 d

1H (31); 8.41 s 1H (32); 10.0 s 1H (35); 10.13 s 1H (36); 10.37 s 1H (34); 11.76 s 1H (33). ^{13}C RMN (100 MHz, DMSO-d_6) δ(ppm): 24.42 (from -CH_3); 111.60 (aromatic); 118.63 (aromatic); 119.09 (aromatic); 123.20 (aromatic); 127.41 (aromatic); 128.95 (aromatic); 133.92 (aromatic); 134.61 (aromatic); 137.30 (from C=N); 156.20 (aromatic C-OH); 168.76 (C=O); 176.72 (C=S).

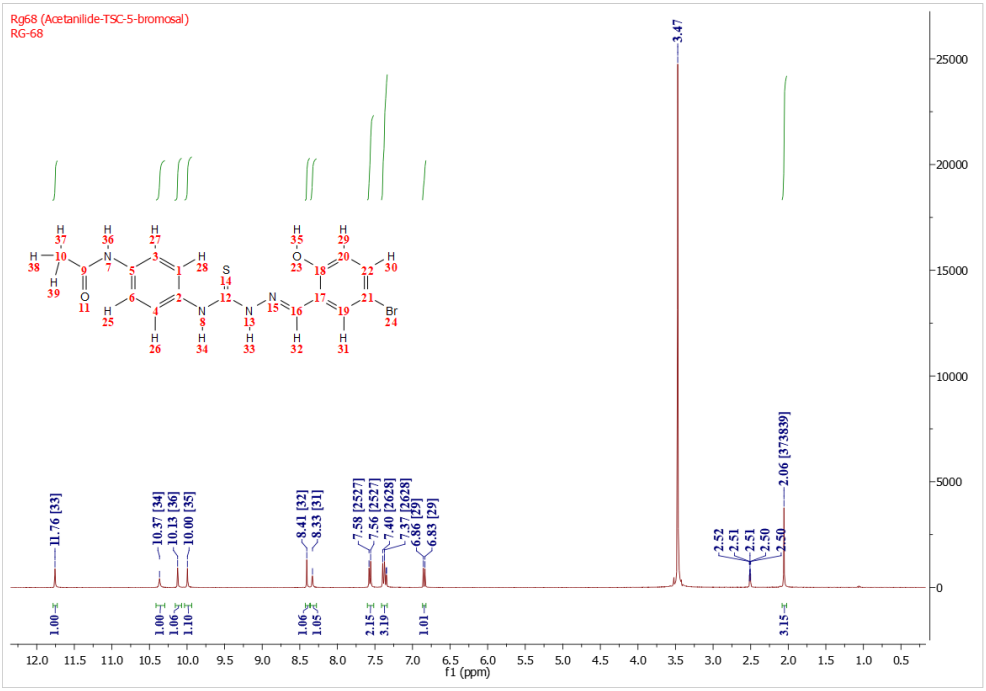


Figure 5. ^{1}H NMR spectrum of H_2L.

Synthesis of coordination compounds

[Cu(H_2O)(HL)Br]

In a conical flask ligand H_2L (0.4082 g, 1 mmol) and ethanol (10 mL) were added and stirred continuously as the temperature was raised to 75-78 ºC. Next, a pre-heated ethanolic solution of $CuBr_2$ (0.1117 g, 1 mmol), was added to the ligand solution. The resulting mixture was stirred at 75-78 ºC for 2 hours. The solid product was then filtered, washed with diethyl ether and dried under the vacuum. Dark brown solid. Yield:

52%. Melting point: 270-272 °C. Mass part of metal: theoretic 11.18%, determined 11.19%. FTIR (ν_{max}, cm^{-1}): ν(H-OH) – 3670; ν(N-H) - 3285; ν(C-H) - 3117; $\nu((C\text{-}H)\text{-}CH_3)_{sy}$ - 2933; ν(C=N)- 1610; ν(C=C) – 1473; ν(C-O) - 1220; ν(C=S) – 1209; ν(M-O) – 575; ν(M-N) – 461; ν(M-S) – 339.

[$Cu(H_2O)(L)$]

In a conical flask ligand H_2L (0.4082 g, 1 mmol) and ethanol (10 mL) were added and stirred continuously as the temperature was raised to 75-78 °C. Next, a pre-heated water solution of $Cu(CH_3COO)_2 \cdot H_2O$ (0.1996 g, 1 mmol), was quantitatively added to the ligand solution. The resulting mixture was stirred at 75-78 °C for 2 hours. The solid product was then filtered, washed with diethyl ether and dried under the vacuum. Dark brown solid. Yield: 66%. Melting point: 304-306 °C. Mass part of metal: theoretic 13.01%, determined 13.05%. FTIR (ν_{max}, cm^{-1}): ν(H-OH) – 3540; ν(N-H) - 3253; ν(C-H) - 2999; $\nu((C\text{-}H)\text{-}CH_3)_{sy}$ - 2935; ν(C=N)- 1608; ν(C=C) – 1496 ; ν(C-O) - 1228; ν(C=S) – 1202; ν(M-O) – 579; ν(M-N) – 467; ν(M-S) – 388.

[$Cu(H_2O)(HL)NO_3$]

In a conical flask ligand H_2L (0.4082 g, 1 mmol) and ethanol (10 mL) were added and stirred continuously as the temperature was raised to 75-78 °C. Next, a pre-heated ethanolic solution of $Cu(NO_3)_2 \cdot 3H_2O$ (0.2416 g, 1 mmol), was quantitatively added to the ligand solution. The resulting mixture was stirred at 75-78 °C for 2 hours. The solid product was then filtered, washed with diethyl ether and dried under the vacuum. Dark green solid. Yield: 94%. Melting point: 300-302 °C. Mass part of metal: theoretic 11.54%, determined 11.38%. FTIR (ν_{max}, cm^{-1}): ν(H-OH) – 3640;

ν(N-H) - 3265; ν(C-H) - 2994; ν((C-H)-CH_3)$_{sy}$ - 2922; ν(C=N)- 1514; ν(C=C) – 1496; ν(C-O) - 1220; ν(C=S) – 1210; ν(M-O) – 582; ν(M-N) – 466; ν(M-S) – 389.

$[Cu(H_2O)_2(HL)]ClO_4$

In a conical flask ligand H_2L (0.4082 g, 1 mmol) and ethanol (10 mL) were added and stirred continuously as the temperature was raised to 75-78 ºC. Next, a pre-heated ethanolic solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.3705 g, 1 mmol), was quantitatively added to the ligand solution. The resulting mixture was stirred at 75-78 ºC for 2 hours. The solid product was then filtered, washed with diethyl ether and dried under the vacuum. Dark brown solid. Yield: 43%. Melting point: 280-282 ºC Mass part of metal: theoretic 10.49%, determined 10.74%. FTIR (ν_{max}, cm^{-1}): ν(H-OH) – 3648; ν(N-H) - 3285; ν(C-H) - 2978; ν((C-H)-CH_3)$_{sy}$ - 2920; ν(C=N) - 1618; ν(C=C) – 1473 ; ν(C-O) - 1198; ν(C=S) – 1213; ν(M-O) – 577; ν(M-N) – 460; ν(M-S) – 338.

Conclusions

A novel thiosemicarbazone: N-(4-(2-(5-bromo-2-hydroxy-benzylidene)hydrazinecarbothioamido)phenyl)acetamide containing the acetanilide fragment was synthesized. Its structure was confirmed by ^1H, ^{13}C NMR and FTIR spectroscopy. Additionally, four new coordination compounds were synthesized and their structures were indirectly confirmed by FTIR and elemental analysis. Biological studies demonstrated that compounds $[Cu(H_2O)(HL)Br]$ and $[Cu(H_2O)(HL)NO_3]$ exhibit 38 and 19 times better the antimicrobial activity against *Staphylococcus aureus* and *Bacillus cereus,* respectively, compared to Furacin. No significant activity was found against *Acinetobacter baumannii* and *Escherichia coli* strains,

indicating a selective activity of the synthesized compounds towards *Staphylococcus aureus* and *Bacillus cereus*. Furthermore, the antifungal activity of the synthesized coordination compounds was investigated, but this compounds not showed any significant antifungal activity.

Acknowledgements

This research was fulfilled with the financial support of the" young researchers 2024-2025" project 24.80012.5007.14TC, and subprogram 010602 of the institutional project, National Agency for Research and Development (NARD).

The authors thank to Greta Balan and Olga Burduniuc for the help in performing antimicrobial and antifungal assays.

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