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ANTIBACTERIAL AND ANTIFUNGAL AGENTS BASED ON 3*d* METAL COORDINATION COMPOUNDS WITH 2-BENZOYLPYRIDINE 4-ALLYL/NORBORNYLTHIOSEMICARBAZONES

Vasilii GRAUR[1], Ianina GRAUR[1], Irina KRAVCHUK[1], Greta BALAN[2], Carolina LOZAN-TÎRȘU[2], Aurelian GULEA[1]

[1]*Laboratory of Advanced Materials in Biopharmaceutics and Technics, Institute of Chemistry, Moldova State University, Chisinau, Republic of Moldova*
[2]*Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova*

Abstract

Two 2-benzoylpyridine thiosemicarbazones (4-allylthiosemicarbazone – **HL[1]** and 4-norbornylthiosemicarbazone – **HL[2]**) and their 3*d* metal coordination compounds were synthesized and characterized. The complexes of Cu(II), Ni(II), Co(III), Fe(III), and Zn(II) were evaluated for antibacterial and antifungal activity against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Acinetobacter baumannii*, and *Candida albicans*. Biological activity was presented in form of MIC, MBC, and MFC values. Metal coordination significantly enhances antibacterial activity, with Cu(II) complexes showing the highest potency and the general activity trend Cu > Zn > Co > Fe > Ni. Gram-negative bacteria exhibit higher resistance than Gram-positive strains. **HL[2]** derivatives demonstrate superior antifungal activity compared to **HL[1]** and reference drugs, even without metal coordination. The most active copper complexes show up to 64-fold higher inhibitory activity against *Candida albicans* than fluconazole. The results highlight the importance of N^4-substitution and metal coordination in modulating antibacterial and antifungal properties.

Keywords: thiosemicarbazones; 2-benzoylpyridine; 3*d* metal coordination compounds; antibacterial activity; antifungal activity.

AGENȚI ANTIBACTERIENI ȘI ANTIFUNGICI PE BAZĂ DE COMPUȘI COORDINATIVI AI METALELOR 3*d* CU 4-ALIL/NORBORNILTIOSEMICARBAZONE 2-BENZOILPIRIDINEI

Rezumat

Două tiosemicarbazone de 2-benzoilpiridină (4-aliltiosemicarbazona – **HL[1]** și 4-norborniltiosemicarbazona – **HL[2]**) și compușii lor coordinativi cu metale 3*d* au fost sintetizați și caracterizați. Complecșii de Cu(II), Ni(II), Co(III), Fe(III) și Zn(II) au fost evaluați din punct de vedere al activității antibacteriene și antifungice împotriva tulpinilor *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Acinetobacter baumannii* și *Candida albicans*. Activitatea biologică a fost exprimată prin valorile MIC, MBC și MFC. Coordinarea la ionii de metal îmbunătățește semnificativ activitatea antibacteriană, complecșii de Cu(II) prezentând cea mai mare eficiență, iar tendința generală a activității este Cu > Zn > Co > Fe > Ni. Bacteriile Gram-negative prezintă o rezistență mai mare decât tulpinile Gram-pozitive. Derivații **HL[2]** manifestă o activitate antifungică superioară comparativ cu **HL[1]** și cu medicamentele de referință, chiar și în absența coordinării la ionii de metal. Cei mai activi complecși de cupru prezintă o activitate inhibitoare de până la 64 de ori mai mare împotriva *Candida albicans* decât fluconazolul. Rezultatele evidențiază importanța substituției N^4 și a procesului de coordinare în modularea proprietăților antibacteriene și antifungice.

Cuvinte-cheie: tiosemicarbazone, 2-benzoilpiridină, compuși coordinativi ai metalelor 3*d*; activitatea antimicrobiană; activitatea antifungică.

Introduction

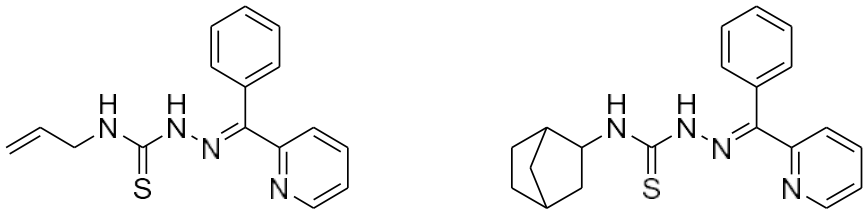
Bacterial resistance to antibiotics poses a major global public health challenge [1]. Resistant strains of pathogenic microorganisms emerge largely as a result of the excessive and improper use of antibiotics. Currently, the spread of resistance is progressing faster than the development of new antibacterial agents. Each year, approximately 1.3 million deaths are attributed to antibiotic resistance. To keep pace with this ongoing evolutionary process, continuous innovation in drug discovery is essential. Notably, around half of the antibiotics in use today were identified between the 1950s and 1970s [2], while since the late 20th century, research and development in this area have significantly declined. Consequently, the design and synthesis of new compounds with enhanced antibacterial activity remain highly relevant.

Thiosemicarbazones constitute an important class of organic compounds that often exhibit a wide range of biological activities, including antibacterial and antifungal [3] effects. Their coordination compounds with metal ions are considered promising candidates for biologically active agents. Furthermore, substitution at the N^4 position of the thiosemicarbazone fragment has been shown to enhance various types of biological activity in both the free ligands and their corresponding metal complexes [4]. Introducing bulky substituents at the N^4 position of the thiosemicarbazone fragment can significantly improve its biological activity [5].

2-Benzoylpyridine has recently emerged as a promising antibacterial compound with significant activity, primarily exerting its effect through disruption of the bacterial cell membrane. Its interaction with the membrane promotes the leakage of ions and low-molecular-weight components, resulting in an imbalance of cellular redox processes. Its structural features enable the formation of intermolecular hydrogen bonds within its coordination framework, which may partly explain its notable antibacterial performance.

In comparison with other pyridine-based derivatives, such as 2-acetylpyridine and 2-formylpyridine thiosemicarbazones, the corresponding 2-benzoylpyridine thiosemicarbazones are less extensively described in the literature. Nevertheless, available studies indicate that these compounds possess antibacterial [6] and antifungal [7] activities. Moreover, coordination of 2-benzoylpyridine thiosemicarbazones with metal ions generally results in enhanced biological activity.

Therefore, in this work the comparison of antibacterial and antifungal properties of two series of coordination compounds is made. The first series contains 2-benzoylpyridine 4-allylthiosemicarbazone as ligand [8] while the second series contains complexes of 2-benzoylpyridine 4-allylthiosemicarbazone (Figure 1) [9].



HL^1 **HL^2**

Figure 1. The structural formula of 2-benzoylpyridine 4-allyl/norbornylthiosemicarbazones (HL$^{1-2}$)

Materials and methods

Allyl and norbornyl isothiocyanates, hydrazine hydrate, 2-benzoylpyridine, hydrochloric acid, sodium carbonate, as well as 3d metal salts were obtained from Sigma-Aldrich. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 using $CDCl_3$ and aceton-d_6 as solvents.

FTIR spectra were obtained on a Bruker ALPHA FTIR spectrophotometer at room temperature in the range of 4000-400 cm^{-1}. The resistance of solutions of complexes in methanol (20°C, c 0.001 M) was measured using an R-38 rheochord bridge.

Synthesis of thiosemicarbazides

4-Allylthiosemicarbazide and 4-norbornylthiosemicarbazide were obtained by the following general procedure: 0.100 mol of corresponding isothiocyanate was added dropwise to 20 g of aqua solution of hydrazine (60% w/w). The resulting white precipitate of the corresponding thiosemicarbazide is filtered under vacuum and washed with water until a neutral or slightly alkaline reaction is achieved. [10]

Synthesis of thiosemicarbazones ***HL$^{1-2}$***

A two-step process was used for the synthesis of thiosemicarbazones **HL$^{1-2}$**. [11]

At first step 10.0 mmol of corresponding thiosemicarbazide was dissolved in 20 mL of ethanol with the constant steering. After that, the solution of 2-benzoylpyridine (1.83 g, 10.0 mmol) in 20 mL of ethanol was added. Concentrated hydrochloric acid (~10 g, 10.0 mmol) was added to the obtained solutions. These mixtures were steered and heated for 30 minutes. After cooling of the solutions, the yellow precipitates of corresponding hydrochlorides were formed. The precipitates were filtered and washed with small amounts of cold ethanol.

On the second step, the obtained hydrochlorides were dissolved in minimal volume of ethanol with constant steering and neutralized with an aqueous solution of sodium carbonate. The resulting thiosemicarbazones were extracted with chloroform.

*2-benzoylpyridine 4-allylthiosemicarbazone (**HL^{1}**, 2-benzoylpyridine 4-(prop-2-en-1-yl)thiosemicarbazone)* [8]

Pale yellow solid. Yield: 84%; mp 125-127 °C. FW: 296.39 g/mol; Anal Calc. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82; found: C, 64.69; H, 5.37; N, 18.81; S, 10.75%. Main FTIR peaks (cm^{-1}): ν(N–H) 3368, 3135; ν (C=N) 1642, 1583; ν (C=S) 1314. ^{1}H NMR ($(CD_3)_2CO$, 400 MHz) 13.49 (br s, 1H; NH); 8.88 (d, 1H; CH (aromatic)); 8.59 (br s, 1H; NH); 8.02 (t, 1H; CH(aromatic)); 7.60 (m, 3H; CH(aromatic)); 7.47 (m, 3H; CH(aromatic)); 7.39 (d, 1H; CH(aromatic));5.99 (m, 1H; CH(allyl)); 5.17 (m, 2H; CH_2=C); 4.37 (m, 2H; CH_2-N). ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) 178.89 (C=S); 152.37, 142.63, 137.80, 137.73, 129.09, 128.77, 128.36, 126.23, 124.62 (C(aromatic)); 148.63 (C=N); 134.50 (CH_{allyl}); 115.46 (CH_2(allyl, sp^2)); 46.24 (CH_2(allyl, sp^3)).

*2-benzoylpyridine 4-norbornylthiosemicarbazone (**HL^{2}**, 2-benzoylpyridine 4-(bicyclo[2.2.1]hept-2-yl)thiosemicarbazone)* [9]

White solid. Yield: 94%; mp 189-191°C. FW: 350.48 g/mol; Anal Calc. for $C_{20}H_{22}N_4S$: C, 68.54; H, 6.33; N, 15.99; S, 9.15; found: C, 68.43; H, 6.23; N, 15.88; S, 9.05. Main FTIR peaks (cm^{-1}): ν(NH) 3368, 3151, ν(C=N) 1583, ν(C=S) 1313. ^{1}H NMR ($CDCl_3$, 400 MHz) 13.55 (s, 1H, NH), 8.82 (d, 1H, NH); 7.76 (t, 1H, CH(pyridine)); 7.60 (d, 1H, CH(pyridine)); 7.45 (m, 5H, CH(phenyl)); 7.37 (t, 1H, CH(pyridine)); 7.27 (d, 1H, CH (pyridine)); 4.23 (t, 1H, CH-N); 2.45, 2.32 (m, 2H, 2×CH (norbornyl); 2.0-1.1 (m, 8H, 4×CH_2 (norbornyl)). ^{13}C NMR ($CDCl_3$, 100 MHz) 177.03 (C=S); 152.41, 142.29, 137.72, 137.15, 129.69, 129.13, 128.59, 126.10, 124.13 (C aromatic); 148.68 (C=N); 57.35, 42.32, 40.36, 35.95, 35.88, 28.16, 26.40 (C from norbornyl fragment).

Synthesis of coordination compounds ***1-14***

General procedure for copper(II) coordination compounds ***1–2 and 8–9***

A hot ethanolic solution (20 mL, 65 °C) containing one of the thiosemicarbazones **HL$^{1-2}$** (1.00 mmol) was treated with corresponding copper(II) salt (1.00 mmol). The reaction mixture was stirred and maintained at 65 °C for 40 minutes using a magnetic stirrer. Upon cooling to room temperature, a green solid precipitate was collected by filtration, washed with ethanol, and dried.

*Synthesis of mixed-ligand complexes **3** and **10***

1,10-Phenanthroline (1.00 mmol) was added to a hot ethanolic solutions of complex **2** or **9** (1 mmol). The green precepitates were formed upon cooling. The formed compounds were isolated by filtration, washed with ethanol, and dried.

*Synthesis of nickel, cobalt, iron and zinc complexes (**4**–**7** and **11**–**14**)*

A hot ethanolic solution (20 mL, 65 °C) containing one of the thiosemicarbazones $\mathbf{HL^{1\text{-}2}}$ (1.00 mmol) was treated with corresponding 3d metal salt (0.50 mmol). The reaction mixture was stirred and heated at 65 °C for 40 minutes. Upon cooling to room temperature, a solid precipitate was collected by filtration, washed with ethanol, and dried.

Table 1. Physical and analytical data of the metal complexes 1–14

#	Compound	Formula	Yield, %	Found/calculated, metal %	Molar conductivity, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$
1	$[Cu(L^1)Cl]_2$	$C_{32}H_{30}Cl_2Cu_2N_8S_2$	76	16.04/16.11	98
2	$[Cu(L^1)(NO_3)]_2$	$C_{32}H_{30}Cu_2N_{10}O_6S_2$	89	15.01/15.10	80
3	$[Cu(phen)(L^1)]NO_3$	$C_{28}H_{23}CuN_7O_3S$	76	10.48/10.57	83
4	$[Ni(HL^1)_2]Cl_2$	$C_{32}H_{32}Cl_2N_8NiS_2$	84	8.02/8.13	148
5	$[Co(L^1)_2]NO_3$	$C_{32}H_{30}CoN_9O_3S_2$	72	8.18/8.28	98
6	$[Fe(L^1)_2]NO_3$	$C_{32}H_{30}FeN_9O_3S_2$	74	7.82/7.88	105
7	$[Zn(L^1)_2]\cdot 0.125H_2O$	$C_{32}H_{30.25}N_8O_{0.125}S_2Zn$	88	9.81/9.93	7
8	$[Cu(L^2)Cl]$	$C_{20}H_{21}ClCuN_4S$	76	14.05/14.17	46
9	$[Cu(L^2)NO_3]$	$C_{20}H_{21}CuN_5O_3S$	80	13.26/13.38	80
10	$[Cu(phen)(L^2)]NO_3$	$C_{32}H_{29}CuN_7O_3S$	78	9.79/9.71	86
11	$[Ni(HL^2)_2](NO_3)_2$	$C_{40}H_{44}N_{10}NiO_6S_2$	72	6.55/6.64	134
12	$[Co(L^2)_2]NO_3$	$C_{40}H_{42}CoN_9O_3S_2$	71	7.08/7.19	70
13	$[Fe(L^2)_2]NO_3$	$C_{40}H_{42}FeN_9O_3S_2$	70	6.73/6.84	70
14	$[Zn(L^2)_2]$	$C_{40}H_{42}N_8S_2Zn$	86	8.43/8.55	5

Antibacterial and antifungal activity

The antibacterial and antifungal properties of thiosemicarbazones $\mathbf{HL^{1\text{-}2}}$ and their coordination compounds **1**–**14** were evaluated against standard strains of Gram-positive bacteria (Staphylococcus aureus (ATCC 25923), Bacillus cereus (ATCC 11778)), Gram-negative bacteria (Escherichia coli (ATCC 25922), Acinetobacter baumannii (BAA-747)), and Candida albicans (ATCC 10231). Minimum inhibitory concentrations (MIC, μg mL^{-1}), minimum bactericidal concentrations (MBC, μg mL^{-1}), and minimum fungicidal concentrations (MFC, μg mL^{-1}) were determined using the broth microdilution method. Stock solutions of the investigated compounds were prepared in DMSO at 10 mg mL^{-1} concentration, and subsequent dilutions were carried out with 2% peptone broth. Furacillinum and Tetracycline [12, 13] served as the antibacterial reference drugs, while Nystatin [12] and Fluconazole [14] were employed as standard antifungal agents.

Results and discussion

Synthesis and characterization

Two 2-benzoylpyridine thiosemicarbazones $\mathbf{HL^{1\text{-}2}}$ were obtained using a two-step process (Figure 2). In the first step, condensation between 2-benzoylpyridine and corresponding thiosemicarbazide took place in presence of equimolar amount of hydrochloric acid. In these conditions, this condensation takes place rapidly without need of 6-8 hours of heating. In the second step, the obtained hydrochlorides of thiosemicarbazones were neutralized with sodium

carbonate solution. The composition and structure of the resultant thiosemicarbazones were proved using ^{1}H and ^{13}C NMR spectroscopies. [8, 9]

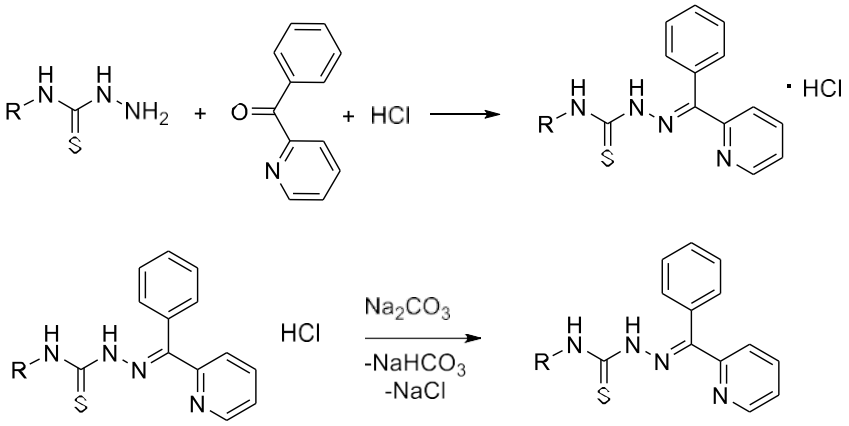


Figure 2. Synthesis of thiosemicarbazones HL^1 (R = allyl) and HL^2 (R = norbornyl)

Coordination compounds were obtained upon interaction of corresponding copper salts and **HL$^{1-2}$** in a 1:1 molar ration, while interaction between HL^{1-2} and other 3*d* metal salts took place in a 2:1 molar ratio: $[Cu(L^1)Cl]_2$ (**1**), $[Cu(L^1)(NO_3)]_2$ (**2**), $[Cu(phen)(L^1)]NO_3$ (**3**), $[Ni(HL^1)_2]Cl_2$ (**4**), $[Co(L^1)_2]NO_3$ (**5**), $[Fe(L^1)_2]NO_3$ (**6**), $[Zn(L^1)_2]\cdot 0.125H_2O$ (**7**), $[Cu(L^2)Cl]$ (**8**), $[Cu(L^2)NO_3]$ (**9**), $[Cu(phen)(L^2)]NO_3$ (**10**), $[Ni(HL^2)_2](NO_3)_2$ (**11**), $[Co(L^2)_2]NO_3$ (**12**), $[Fe(L^2)_2]NO_3$ (**13**), $[Zn(L^2)_2]$ (**14**).

Copper(II), cobalt(III), and iron(III) complexes behave as 1:1 electrolytes with the measured molar conductivity values in the range of 46-105 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$. Zinc complexes **7** and **14** obtained from zinc acetate are non-electrolytes while nickel(II) complexes behave as 1:2 electrolytes.

Antibacterial activity against Gram-positive microorganisms

Antibacterial properties were studied on two strains of Gram-positive microorganisms, namely: *Staphylococcus aureus* (ATCC 25923) and *Bacillus cereus* (ATCC 11778), The values for minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) are provided in the table 2.

4-Allylthiosemicarbazone **HL^1** shows antibacterial properties against *S. aureus* and *B. cereus* and even surpasses Furacillinum by this type of activity while 4-norbornylthiosemicarbazone **HL^2** does not affect these bacteria in the studied range of concentrations. An increase in activity is observed upon coordination of **HL^1** to the ions of all studied metals, except for nickel(II) ions, where the activity decreases significantly. The activity decreases in the following order: Cu > Zn > Co > Fe > Ni. The additional introduction of 1,10-phenanthroline reduced the antibacterial activity.

A similar trend is observed in the case of coordination of **HL^2** to the studied 3d metal ions. For the 4-norbornylthiosemicarbazone, the activity of the complexes decreases in the same order, Cu > Zn > Co > Fe > Ni; however, the MIC and MBC values span a wider range. The introduction of 1,10-phenanthroline did not enhance the activity of the copper complexes.

A comparison of analogous complexes with HL^1 and HL^2 shows that coordination compounds of 4-allylthiosemicarbazone exhibit higher activity than the complexes of 4-norbornylthiosemicarbazone.

The most active complexes, 1, 2, 7, and 8, surpass not only Furacillinum but also Tetracycline, commonly used in medical practice, in activity against *Staphylococcus aureus*.

Table 2. Antibacterial activity of the tested compounds against Gram-positive microorganisms.

Compound	*Staphylococcus aureus* ATCC 25923		*Bacillus cereus* ATCC 11778	
	MIC, μg/mL	MBC, μg/mL	MIC, μg/mL	MBC, μg/mL
HL[1]	1.95	3.91	1.95	1.95
1	0.122	0.244	0.122	0.122
2	0.244	0.488	0.244	0.244
3	0.977	1.95	0.977	1.95
4	250	500	>1000	>1000
5	0.488	0.977	0.488	0.977
6	0.977	0.977	0.488	0.977
7	0.244	0.488	0.244	0.244
HL[2]	>1000	>1000	>1000	>1000
8	0.244	0.488	0.488	0.488
9	0.977	1.95	0.244	0.244
10	0.977	1.95	0.977	0.977
11	>1000	>1000	500	>1000
12	1.95	3.91	0.488	1.95
13	7.81	15.6	7.81	7.81
14	0.977	1.95	0.977	0.977
Furacillinum	9.3	9.3	4.7	4.7
Tetracycline	0.25	1.96	0.06	-

Antibacterial activity against Gram-negative microorganisms

Antibacterial properties were studied on two strains of Gram-negative microorganisms, namely: *Escherichia coli* (ATCC 25922) and *Acinetobacter baumannii* (BAA-747), The values for minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) are provided in the table 3.

If the antibacterial activity of the studied compounds is compared against Gram-positive and Gram-negative bacteria, it becomes evident that they exhibit significantly lower activity against Gram-negative bacteria, which in no case exceeded that of the reference drugs. However, it is noteworthy that, in the case of *Escherichia coli*, the introduction of 1,10-phenanthroline enhanced the antimicrobial activity fourfold.

Antifungal activity against Candida albicans

Antifungal activity of tested substances against *Candida albicans* in the form of minimal inhibitory concentration (MIC) and minimal fungicidal concentration (MFC) are given in table 4.

In terms of antifungal activity, the 4-norbornylthiosemicarbazone **HL[2]** exhibits higher activity than the 4-allylthiosemicarbazone. Even without coordination to 3d metals, **HL[2]** surpasses the reference antifungal agents nystatin and fluconazole in activity. The most active compounds are the copper complexes, with complexes **8** and **9** being more active than complexes **1** and **2**. The most active complex, **8**, is 64 times more potent than fluconazole in inhibiting *Candida albicans*.

Table 3. Antibacterial activity against Gram-negative microorganisms.

Compound	*Escherichia coli* ATCC 25922		*Acinetobacter baumannii* BAA-747	
	MIC, μg/mL	MBC, μg/mL	MIC, μg/mL	MBC, μg/mL
HL[1]	>1000	>1000	>1000	>1000
1	125	125	125	125
2	125	250	62.5	62.5
3	31.3	62.5	31.3	62.5
4	>1000	>1000	>1000	>1000
5	250	>1000	250	>1000
6	500	500	250	250
7	>1000	>1000	>1000	>1000
HL[2]	>1000	>1000	>1000	>1000
8	500	>1000	31.3	125
9	500	>1000	7.81	15.6
10	62.5	62.5	31.3	62.5
11	500	500	250	500
12	500	500	250	250
13	>1000	>1000	500	>1000
14	>1000	>1000	250	250
Furacillinum	18.5	37.5	4.7	9.4
Tetracycline	0.98	3.91	0.5	5.66

Table 4. Antifungal activity of the tested compounds

Compound	*Candida albicans* ATCC 90028	
	MIC, μg/mL	MFC, μg/mL
HL[1]	125	500
1	0.977	1.95
2	1.95	1.95
3	15.6	31.3
4	7.81	7.81
5	31.3	250
6	7.81	31.3
7	>1000	>1000
HL[2]	0.977	0.977
8	0.244	1.95
9	0.977	0.977
10	0.977	1.95
11	125	>1000
12	15.6	31.3
13	250	500
14	250	>1000
Nystatin	80	80
Fluconazole	15.6	31.3

Conclusion

This work reports the synthesis and evaluation of antibacterial and antifungal properties of two 2-benzoylpyridine thiosemicarbazones and 14 coordination compounds. The obtained results clearly demonstrate that both substituent in the 4th position of the thiosemicarbazide moiety of the ligand and the nature of the central atom of the coordination compound play decisive roles in tuning the biological properties. Coordination to the 3d metal ions leads to a pronounced enhancement of antibacterial activity, with copper(II) derivatives consistently showing superior performance across all investigated strains. Overall, this study highlights the combined importance of N^4-substitution and metal coordination in controlling activity of 3d metal thiosemicarbazone-based complexes.

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Date despre autori:



Vasilii GRAUR, doctor în ştiinţe chimice, cercetător ştiinţific coordonator, Universitatea de Stat din Moldova.
e-mail: vasilii.graur@usm.md
ORCID: 0000-0001-8153-2153



Ianina GRAUR, doctor în ştiinţe chimice, cercetător ştiinţific superior, Universitatea de Stat din Moldova.
e-mail: ulchina.ianina@usm.md
ORCID: 0000-0002-3345-7539



Irina KRAVCHUK, doctor în ştiinţe chimice, cercetător ştiinţific superior, Universitatea de Stat din Moldova.
e-mail: irynakravchuk67@gmail.com
ORCID: 0000-0002-6749-0687



Greta BALAN, doctor habilitat în ştiinţe medicale, conferenţiar universitar, Șef Disciplina de microbiologie şi imunologie, Departamentul Medicină Preventivă, Universitatea de Stat de Medicină şi Farmacie „Nicolae Testemiţanu” Chişinău, Republica Moldova
e-mail: greta.balan@usmf.md
ORCID: 0000-0003-3704-3584



Carolina LOZAN-TÎRȘU, doctor în ştiinţe medicale, conferenţiar universitar, Disciplina de microbiologie şi imunologie, Departamentul Medicină Preventivă, Universitatea de Stat de Medicină şi Farmacie „Nicolae Testemiţanu” Chişinău, Republica Moldova
e-mail: carolina.lozan@usmf.md
ORCID: 0000-0003-3831-2758



Aurelian GULEA, doctor habilitat în ştiinţe chimice, profesor universitar, academician, Șef de laborator. Laboratorul Materiale Avansate în Biofarmaceutică şi Tehnică, Institutul de Chimie, Universitatea de Stat din Moldova, Chişinău, Republica Moldova
E-mail: guleaaurelian@gmail.com
ORCID: 0000-0003-2010-7959

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