CZU: 544.142.3:547-304.6 **https://doi.org/10.59295/sum1(171)2024_28**

EXPLORING THE ANTIOXIDANT ACTIVITY OF 1-(PIPERIDIN-1-YL) PROPANE-1,2-DIONE 4-PHENYLTHIOSEMICARBAZONE AND 3*d* METAL COORDINATION COMPOUNDS WITH THIS LIGAND

Ianina GRAUR, Mihail MAXIM, Vasilii GRAUR, Victor TSAPKOV, Aurelian GULEA,

Laboratory of Advanced Materials in Biopharmaceutics, Institute of Chemistry, Moldova State University

Olga GARBUZ,

Laboratory of Systematics and Molecular Phylogenetics, Institute of Zoology, Moldova State University

The new 1-(piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone (HL) and its 7 coordination compounds [Cu(L)X] (X = Br^- (I); Cl^- (II); NO_3^- (III); CH_3COO^- (IV); Cl_2CHCOO^- (V)), $[Co(L)_2]NO_3$ (VI), $[Fe(L)_2]NO_3$ (VII) have been synthesized and characterized by elemental analysis, FTIR, ^1H, ^{13}C NMR spectra and molar electric conductibility. For the obtained compounds it was studied the antioxidant activity towards $ABTS^{\bullet+}$ radical cation. Uncoordinated 4-phenylthiosemicarbazone HL is the most active one with IC_{50} 14.1 μM. Its activity is higher than that of Trolox which is used in medicine as an antioxidant. Among all the synthesized coordination compounds, the iron(III) complex VII showed the greatest activity. The antioxidant activity of metal complexes is influenced by the anion and the nature of the central metal atom.

Keywords: *coordination compounds, 4-phenylthiosemicarbazone, pyruvamide, antioxidant activity.*

STUDIUL ACTIVITĂȚII ANTIOXIDANTE A 4-FENILTIOSEMICARBAZONEI 1-(PIPERIDIN-1-IL)PROPAN-1,2-DIONEI ȘI A COMPUȘILOR COORDINATIVI AI METALELOR 3d CU ACEST LIGAND

Un ligand nou, 4-feniltiosemicarbazonă 1-(piperidin-1-il)propan-1,2-dionei (HL) și 7 compuși coordinativi [Cu(L)X] (X = Br^- (I); Cl^- (II); NO_3^- (III); CH_3COO^- (IV); Cl_2CHCOO^- (V)), $[Co(L)_2]NO_3$ (VI), $[Fe(L)_2]NO_3$ (VII) au fost sintetizați și caracterizați prin analiză elementală, spectroscopia FTIR, ^1H, ^{13}C RMN și conductibilitatea electrică molară. Pentru compușii obținuți a fost studiată activitatea antioxidantă față de cation-radical $ABTS^{\bullet+}$. 4-Feniltiosemicarbazona HL necoordonată este cea mai activă cu IC_{50} 14.1 μM, activitatea ei este mai mare decât cea a Troloxului, care este folosit în medicină ca antioxidant. Dintre toți compușii coordinativi sintetizați, complexul de fier(III) VII posedă cea mai pronunțată activitate. Activitatea antioxidantă a complecșilor metalici este influențată atât de anion, cât și de natura atomului central.

Cuvinte-cheie: *compuși coordinativi, 4-feniltiosemicarbazonă, amidă acidului pyruvic, activitatea antioxidantă.*

Introduction

Thiosemicarbazones are a group of compounds usually obtained by the condensation reaction between a thiosemicarbazide and an aldehyde or ketone [1]. For many years scientists focused on thiosemicarbazone derivatives, considering them not only as potential ligands but also as compounds displaying a wide spectrum of biological activities [2-6]. In recent decades, thiosemicarbazones have undergone clinical development for a variety of diseases, including tuberculosis, viral infections, malaria and cancer [7]. Certain derivatives of thiosemicarbazones demonstrated notable inhibition of tumor cell growth in Hep3B, A549, and MCF-7 cell lines [8]. 4-Phenylthiosemicarbazone and its 3*d* metal complexes manifest antibacterial [9], antioxidant [10-11] and anticancer [12] activities.

Pyruvic acid is a compound formed during the metabolism of carbohydrates, proteins, and fats. It

is a component of a blood cell processing solution utilized to revitalize a unit of red blood cells before transfusion. Pyruvic acid is recognized for its diverse pharmacological effects, including anti-inflammatory, neuroprotective, and anticancer properties. These effects are believed to stem from its antioxidant and free radical scavenging capabilities [13]. Piperidine can be obtained from plant sources or synthesized through various chemical reactions. Piperidine scaffold has been utilized in numerous pharmaceutical drugs that are currently available in the market [14]. Piperidine is employed as agent against cancer, viruses, malaria, microbes, fungi, hypertension, inflammation, Alzheimer's disease, psychiatric disorders, and blood clotting [15]. Therefore, it is assumed that piperidine-based pyruvic acid amide can impart interesting biological properties in the composition of thiosemicarbazones and their complexes.

4-Allylthiosemicarbazone of pyruvic acid amide based on piperidine and its copper(II), nickel(II) and iron(III) complexes were previously synthesized and described [16]. The antioxidant activity against $ABTS^{\bullet+}$ cation radicals was studied for these substances and it was concluded that the activity is influenced by the nature of the central metal atom.

Based on the foregoing, it is of interest to study how the replacement of the radical in the fourth position with the phenyl group in thiosemicarbazone will affect its antioxidant activity and the activity of its complexes. So, the aim of this work is synthesis of 1-(piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone and its 3*d* metal coordination compounds and study of their antioxidant activity.

Materials and methods

Pyruvic acid, 4-phenylthiosemicarbazide, oxalyl chloride, sodium carbonate, dichloromethane, dimethylformamide, piperidine, copper(II) chloride dihydrate, copper(II) bromide, copper(II) nitrate trihydrate, copper(II) dichloroacetate, copper(II) acetate monohydrate, cobalt(II) nitrate hexahydrate, iron(III) nitrate hexahydrate were obtained from Sigma-Aldrich and used without further purification.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400, using $CDCl_3$ as a solvent.

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

The determination of copper, cobalt and iron content in the synthesized coordination compounds, using titration methods, performed similarly to the literature procedures [17-18].

The resistance of solutions of complexes in methanol (20°C, 0.001 M) was measured using an R-38 rheochord bridge.

1-(Piperidin-1-yl)propane-1,2-dione

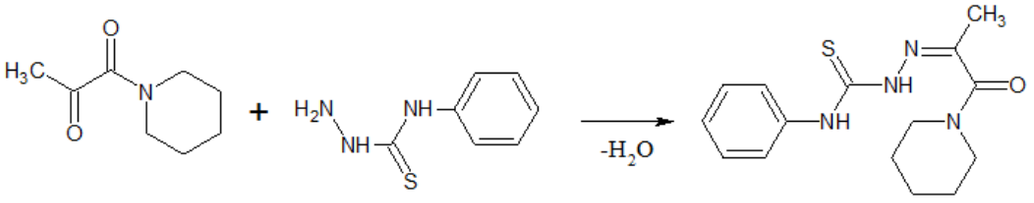
1-(Piperidin-1-yl)propane-1,2-dione was synthesized by the method described in [16]. Pyruvic acid (8.80 g, 0.100 mol) was dissolved in 5 mL CH_2Cl_2 and placed in a flat-bottomed flask. Oxalyl chloride (15.24 g, 0.120 mol) was dissolved in 10 mL CH_2Cl_2 and was added dropwise to the reaction mixture with stirring at the 0°C. Following this, 3 drops of dimethylformamide were introduced as a catalyst and the condenser with drying tube containing calcium chloride was fitted onto the flask. The reaction mixture was stirred and heated for 1.5 hours, yielding a yellow oil. A suspension of piperidine (8.50 g, 0.100 mol), sodium carbonate (10.60 g, 0.100 mol) and 10 mL CH_2Cl_2 was stirred at 0°C. The obtained yellow oil, that contains 2-oxopropanoyl chloride, was added dropwise to the cooled suspension and the mixture was stirred at rt for 1 h. The mixture was filtered and filtrate that contains 1-(piperidin-1-yl)propane-1,2-dione in CH_2Cl_2 was air-dried resulting the crude product in the form of a mobile, yellow oil.

1-(Piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone (HL)

1-(Piperidin-1-yl)propane-1,2-dione (3.10 g, 20.0 mmol) was dissolved in 25 mL of ethanol, followed by the addition of 4-phenylthiosemicarbazide (3.34 g, 20.0 mmol) was added to the reaction mixture under stirring and heating (Scheme 1). The obtained pale-yellow precipitate was filtered, washed with small amount of ethanol and dried on air. Yield: 82%. m.p. 130-131°C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.13 (s, 1H, NH); 8.81 (s, 1H, NH); 7.60 (d, 2×1H, CH_{phenyl}); 7.37 (t, 2×1H, CH_{phenyl}); 7.23 (t, 1H, CH_{phenyl}); 3.55 (m, 2×2H, $CH_{2piperidine}$); 2.15 (s, 3H, CH_3); 1.69 (m, 2H, $CH_{2piperidine}$); 1.62 (m, 2×2H, $CH_{2piperidine}$); ^{13}C NMR (100 MHz,

$CDCl_3$): 176.42 (C=S); 165.23 (C=O); 143.72 (C=N); 137.51, 128.85, 126.36, 124.10 (C_{phenyl}); 45.62, 26.06, 24.50 ($C_{piperidine}$); 14.39 (CH_3). FTIR data (cm^{-1}): 3276, 3199 (NH), 1616 (C=O), 1591 (C=N), 1363 (C=S).

Scheme 1. Synthesis of 1-(piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone (HL).



Synthesis of coordination compounds

[Cu(L)Br] (**I**)

The ethanol solution containing 4-phenylthiosemicarbazone **HL** (0.304 g, 1.00 mmol) was combined with an ethanol solution of copper(II) bromide (0.224 g, 1.00 mmol). A green precipitate formed upon stirring. The resulting precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 86%. FTIR data (cm^{-1}): 3199, 1626, 1589, 1559, 755; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 90; copper content (%): 14.15; calcd (%) for $C_{15}H_{19}BrCuN_4OS$: 14.22.

[Cu(L)Cl] (**II**)

The reaction was carried out as described above, but copper(II) chloride dihydrate (0.171 g, 1.00 mmol) was used instead of copper(II) bromide. A green precipitate formed upon stirring. The resulting precipitate was filtered off, washed with a small amount of ethanol and then dried. Yield: 72%. FTIR data (cm^{-1}): 3272, 1603, 1589, 1575, 757; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 79; copper content (%): 15.62; calcd (%) for $C_{15}H_{19}ClCuN_4OS$: 15.79.

[Cu(L)NO_3] (**III**)

The reaction was carried out as described above, but copper(II) nitrate trihydrate (0.242 g, 1.00 mmol) was used instead of copper(II) chloride dihydrate. A green precipitate formed upon stirring. The resulting precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 78%. FTIR data (cm^{-1}): 3246, 1596, 1587, 1561, 749; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 72; copper content (%): 14.74; calcd (%) for $C_{15}H_{19}CuN_5O_4S$: 14.81.

[Cu(L)CH_3COO] (**IV**)

The reaction was carried out as described above, but copper(II) acetate monohydrate (0.200 g, 1.00 mmol) was used instead of copper(II) nitrate trihydrate. A green precipitate formed upon stirring. The resulting precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 80%. FTIR data (cm^{-1}): 3254, 1630, 1593, 1581, 1544, 753; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 67; copper content (%): 14.86; calcd (%) for $C_{17}H_{22}CuN_4O_3S$: 14.92.

[Cu(L)(Cl_2CHCOO)] (**V**)

The reaction was carried out as described above, but copper(II) dichloroacetate (0.321 g, 1.00 mmol) was used instead of copper(II) acetate monohydrate. A green precipitate formed upon stirring. The resulting precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 81%. FTIR data (cm^{-1}): 3272, 1638, 1587, 1546, 755; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 68; copper content (%): 12.74; calcd (%) for $C_{17}H_{20}Cl_2CuN_4O_3S$: 12.84.

[$Co(L)_2$]NO_3 (**VI**)

The ethanol solution containing 4-phenylthiosemicarbazone **HL** (0.304 g, 1.00 mmol) was combined with an ethanol solution of cobalt(II) nitrate hexahydrate (0.146 g, 0.50 mmol). A reddish brown precipitate formed upon stirring. The resulting precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 70%. FTIR data (cm^{-1}): 3246, 1601, 1576, 1557, 755; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 90; cobalt content (%): 7.97; calcd (%) for $C_{30}H_{38}CoN_9O_5S_2$: 8.10.

[$Fe(L)_2$]NO_3 (**VII**)

The reaction was carried out as described above, but iron(III) nitrate hexahydrate (0.175 g, 0.50 mmol) was used instead of cobalt(II) nitrate hexahydrate. A brown precipitate formed upon stirring. The resulting

precipitate was filtered, washed with a small amount of ethanol and then dried. Yield: 70%. FTIR data (cm^{-1}): 3244, 1601, 1575, 1546, 755; λ (MeOH, $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$): 80; iron content (%): 7.63; calcd (%) for $C_{30}H_{38}FeN_9O_5S_2$: 7.71.

Antioxidant activity

The antioxidant activity of the synthesized compounds was investigated using the $ABTS^{\bullet+}$ method described by Re *et al.* [19] with modifications. The $ABTS^{\bullet+}$ radical was produced by mixing a 7 mM solution of ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)) from Sigma with a 2.45 mM solution of potassium persulfate ($K_2S_2O_8$), also from Sigma, at 25°C in the dark for 12-20 hours at room temperature. The resulting solution was diluted by combining it with acetate-buffered saline (0.02 M, pH 6.5) until an absorbance of 0.70 ± 0.01 units at 734 nm was attained. The studied compounds were diluted in DMSO, with concentrations ranging from 1 to 100 μM. Next, 20 μL of each compound's dilution was added to a 96-well microtiter plate, followed by the addition of 180 μL of the $ABTS^{\bullet+}$ working solution was dispensed using the dispense module of the hybrid reader (BioTek). The reduction in absorbance at 734 nm was accurately measured after a 30-minute incubation at 25°C. All measurements were conducted in triplicate, with DMSO serving as the negative control, and blank samples were run using solvent without $ABTS^{\bullet+}$. The hybrid reader used for the measurement was the Synergy H1 from BioTek. Each experiment was repeated three times, and the resulting data were averaged.

Results and discussion

The new 1-(piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone (**HL**) was obtained through a two-stage process. In the initial stage, 1-(piperidin-1-yl)propane-1,2-dione was produced by interaction of pyruvic acid, oxalyl chloride, and piperidine in CH_2Cl_2. In the subsequent phase, the obtained 1-(piperidin-1-yl)propane-1,2-dione reacted with 4-phenylthiosemicarbazide in ethanol, with both compounds utilized in equal molar proportions. Its structure was confirmed via NMR spectroscopy (Fig.1, 2).

Fig. 1 ^{1}H NMR spectrum of HL.

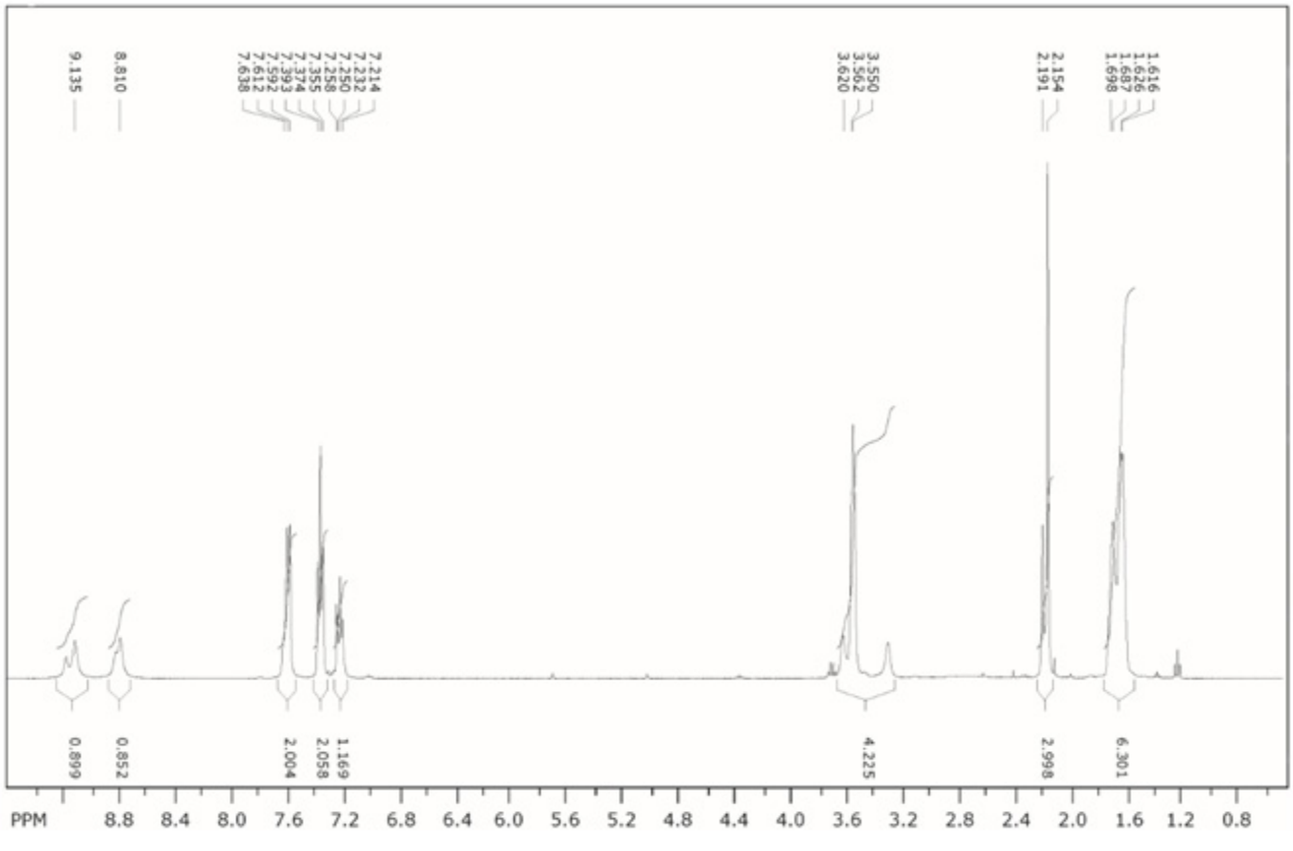
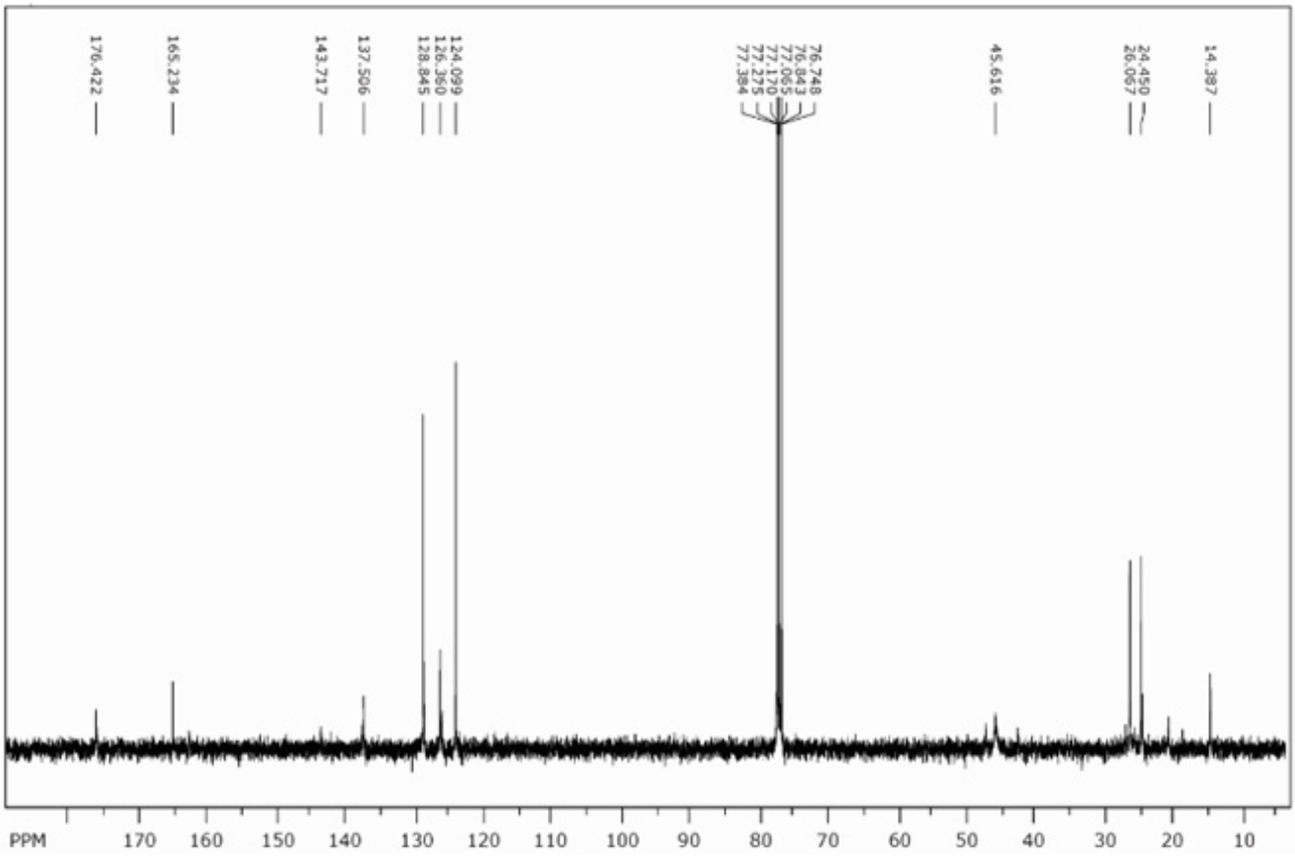


Fig. 2 ^{13}C NMR spectrum of HL

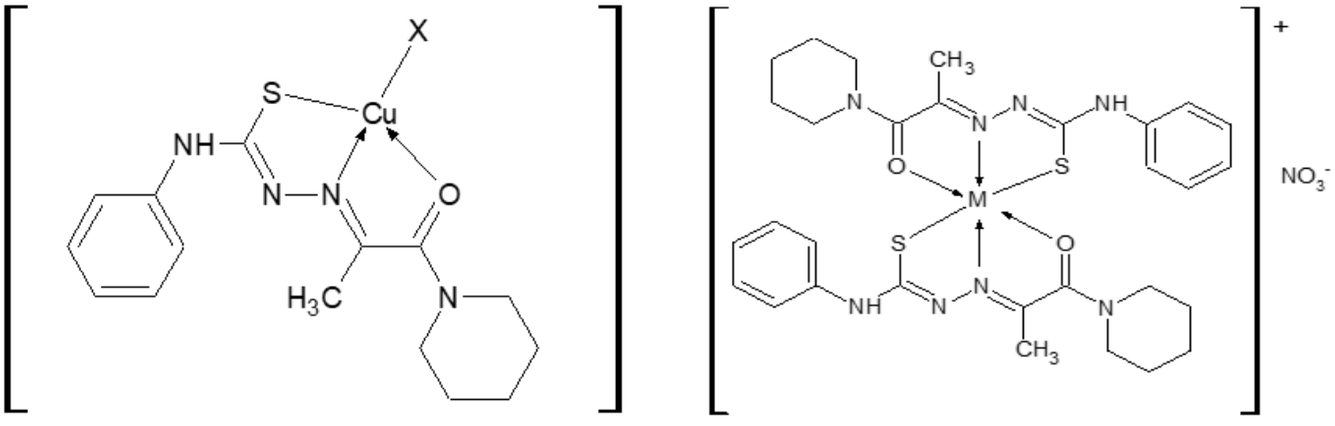


Seven new coordination compounds were synthesized based on 4-phenylthiosemicarbazone **HL**. Copper(II) complexes **I-V** were obtained by the reaction between **HL** and copper(II) salts in molar ratio 1:1 in hot ethanolic solutions. Cobalt(III) and iron(III) complexes were synthesized by heating a mixture of **HL** and metal salt in a 2:1 molar ratio. Elemental analyses on copper, cobalt, and iron of the complexes suggest the general formulas [Cu(L)X] (X = Br^- (**I**); Cl^- (**II**); NO_3^- (**III**); CH_3COO^- (**IV**); Cl_2CHCOO^- (**V**)), $[Co(L)_2]NO_3$ (**VI**), $[Fe(L)_2]NO_3$ (**VII**). The molar conductivity values of the synthesized complexes **I-VII** are in the range 67-90 $\Omega^{-1}\cdot cm^2\cdot mol^{-1}$ suggesting that these complexes are 1:1 electrolytes.

In the FTIR spectra of **HL** are presented the absorption bands at 3276 and 3199 cm^{-1} that indicate two NH groups, ν(C=O) absorption band at 1616 cm^{-1}, ν(C=N) absorption band at 1591 cm^{-1} and ν(C=S) absorption band at 1363 cm^{-1}. The spectra of the obtained complexes **I-VII** exhibit absorption bands ranging from 3199–3272, 1589–1638, and 1575-1589 cm^{-1}, representing the stretching vibrations specific to the coordinated molecules of **HL**. The changes occurring in the FTIR spectrum during the coordination of 4-phenylthiosemicarbazone **HL** to the central metal atoms are similar to those that were previously published for 1-(piperidin-1-yl)propane-1,2-dione 4-allylthiosemicarbazone and its complexes [16]. In the FTIR spectra of complexes **I-VII**, the disappearance of one of the ν(N-H) absorption bands indicates the deprotonation of the **HL**. Furthermore, the spectra indicate shifts to the lower frequency region for the ν(C=O) absorption band and for the ν(C=N) absorption band. Also, the disappearance of the ν(C=S) absorption band was noted, along with the appearance of the ν(C–S) absorption bands in the region of 749-757 cm^{-1}. The absence of the ν(C=S) group suggests that the **HL** has transformed from the thione form to a thiol form followed by deprotonation. Based on these findings, it can be proved that **HL** coordinates with the metal ions in a mono-deprotonated thiol form using the oxygen atom of the amide group, nitrogen atom of the azomethine group, and deprotonated sulfur atom and forms five- and six-membered metallacycles.

Scheme 2 illustrates the suggested distribution of chemical bonds in the coordination compounds **I-VII**.

Scheme 2. Proposed distribution of chemical bonds in the complexes I-VII.



X = Cl^-, Br^-, NO_3^-, CH_3COO^-, Cl_2CHCOO^- M=Co^{3+}, Fe^{3+}

The antioxidant activity of the synthesized compounds **HL** and complexes **I-VII** was investigated using the $ABTS^{\bullet+}$ method (Table 1). Almost all copper(II) complexes showed no activity, except for the complex [Cu(L)CH_3COO] with IC_{50} 30.2 μM. This shows that the anion in the complexes affects their antioxidant activity. The cobalt(III) complex showed no activity, but the iron(III) complex showed activity with IC_{50} 20.7 μM. 4-Phenylthiosemicarbazone **HL** is the most active substance among all synthesized compounds. Its activity also surpasses that of trolox which was used as a standard antioxidant for comparison.

Table 1. IC_{50} values of the synthesized substances towards $ABTS^{\bullet+}$ radical cation.

Compound	IC_{50}, μM
HL	14.1
I	≥100
II	≥100
III	≥100
IV	30.2
V	≥100
VI	≥100
VII	20.7
Trolox	33.0

The obtained results can be compared with previously published data with the antioxidant activity of similar complexes based on 1-(piperidin-1-yl)propane-1,2-dione 4-allylthiosemicarbazone [16]. The activity of the thiosemicarbazone **HL** is higher than that of its 4-allylthiosemicarbazone analogue, which means that the appearance of a phenyl fragment in the fourth position of this thiosemicarbazone increased its antioxidant activity. Iron(III) complex with **HL** also surpasses the corresponding iron(III) complex with 4-allylthiosemicarbazone analogue.

Conclusions

The new 1-(piperidin-1-yl)propane-1,2-dione 4-phenylthiosemicarbazone and its 7 coordination compounds were synthesized and characterized using NMR, FTIR spectroscopy, elemental analysis and molar conductivity. It was determined that the non-coordinated 4-phenylthiosemicarbazone **HL** exhibits the greatest activity against $ABTS^{\bullet+}$ radical cation. Among the synthesized coordination compounds, only the copper(II) and iron(III) complexes show activity that is slightly higher than the activity of Trolox. However, the results showed that the thiosemicarbazone containing a phenyl radical in the fourth

position is more active in comparison with the previously published 1-(piperidin-1-yl)propane-1,2-dione 4-allylthiosemicarbazone. It was also determined that the antioxidant activity of the synthesized substances is significantly influenced by the nature of the central metal atom.

References:

1. HASSAN, A., SHAWKY, A., SHEHATTA, H. *Chemistry and heterocyclization of thiosemicarbazones*. In: *J Heterocyclic Chem.* 2012. nr. 49, p. 21–37.
2. ARORA, S., AGARWAL, S., SINGHAL, S. *Anticancer activities of thiosemicarbazides/thiosemicarbazones: a review.* In: *International Journal of Pharmacy and Pharmaceutical Sciences*, 2014, Vol. 6(9), p. 34-41.
3. LIBERTA, A. E., WEST, D. X. *Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status.* In: *Biometals*, 1992, Nr. *5*, p. 121-126.
4. SHIM, J., JYOTHI, N. R., FAROOK, N. M. (2013). *Biological applications of thiosemicarbazones and their metal complexes.* In: *Asian Journal of Chemistry*, 2013, Vol. 25(10), p. 5838.
5. SIDDIQUI, E. J., AZAD, I., KHAN, A. R., KHAN, T. *Thiosemicarbazone complexes as versatile medicinal chemistry agents: a review*. In: *Journal of drug delivery and therapeutics,* 2019, Vol. 9(3), p. 689-703.
6. PAHONTU, E., JULEA, F., ROSU, T., PURCAREA, V., CHUMAKOV, Y., PETRENCO, P., GULEA, A. *Antibacterial, antifungal and in vitro antileukaemia activity of metal complexes with thiosemicarbazones*. In: *Journal of cellular and molecular medicine*, 2015,Vol. 19(4), p. 865-878.
7. SINGHAL, S., ARORA, S., AGARWAL, S., SHARMA, R., SINGHAL, N. *A review on potential biological activities of thiosemicarbazides*. In: *World J Pharm and Pharm Sci.* 2013, Vol. 2, p. 4661–4481.
8. PHAM, V., PHAN, T., PHAN, D., VU, B. *Synthesis and bioactivity of thiosemicarbazones containing adamantane skeletons.* In: *Molecules*, 2020, Vol. 25(2), p. 324.
9. KIZILCIKLI, İ., KURT, Y. D., AKKURT, B., GENEL, A. Y., BIRTEKSÖZ, S., ÖTÜK, G., ÜLKÜSEVEN, B. *Antimicrobial activity of a series of thiosemicarbazones and their Zn II and Pd II complexes.* In: *Folia microbiologica*, 2007, Vol. 52, p. 15-25.
10. ILIES, D. C., SHOVA, S., RADULESCU, V., PAHONTU, E., ROSU, T. *Synthesis, characterization, crystal structure and antioxidant activity of Ni (II) and Cu (II) complexes with 2-formilpyridine N(4)-phenylthiosemicarbazone.* In: *Polyhedron*, 2015, Vol. 97, p. 157-166.
11. KUMAR, V. A., SIDDIKHA, A., SEKHAR, A. R., KUMAR, A. S., BABU, S., RAO, C. A., REDDY, A. V. *Synthesis, Characterization, Antimicrobial and Antioxidant Activity of 2-Hydroxy-3-Methoxybenzaldehyde-4-Phenylthiosemicarbazone and its Pd (II) Complex, Ni (II) Mixed Ligand Complex and Cu(II) Complex having Heterocyclic Bases.* In: *World Journal of Pharmaceutical Sciences*, 2017, Vol. 8(4), p. 127-138.
12. HOSSEINI-YAZDI, S. A., MIRZAAHMADI, A., KHANDAR, A. A., EIGNER, V., DUŠEK, M., MAHDAVI, M.,WHITE, J. *Reactions of copper (II), nickel (II), and zinc (II) acetates with a new water-soluble 4-phenylthiosemicarbazone Schiff base ligand: Synthesis, characterization, unexpected cyclization, antimicrobial, antioxidant, and anticancer activities*. In: *Polyhedron*, 2017, Vol. 124, p. 156-165.
13. KŁADNA, A., MARCHLEWICZ, M., PIECHOWSKA, T., KRUK, I., ABOUL-ENEIN, H. Y. *Reactivity of pyruvic acid and its derivatives towards reactive oxygen species*. In: *Luminescence*, 2015, Vol. 30(7), p. 1153-1158.
14. NAICKER, L., VENUGOPALA, K. N., SHODE, F., ODHAV, B. *Antimicrobial and antioxidant activities of piperidine derivatives.* In: *African Journal of Pharmacy and Pharmacology*, 2015, Vol. 9(31), p. 783-792.
15. ABDELSHAHEED, M. M., FAWZY, I. M., EL-SUBBAGH, H. I., YOUSSEF, K. M. *Piperidine nucleus in the field of drug discovery.* In: *Future Journal of Pharmaceutical Sciences*, 2021, Nr. 7, p. 1-11.
16. GRAUR, I., BESPALOVA, T., GRAUR, V., TSAPKOV, V., GARBUZ, O., MELNIC, E., BOUROSH, P., GULEA, A. *A new thiosemicarbazone and its 3d metal complexes: Synthetic, structural, and antioxidant studies*. In: *Journal of Chemical Research*, 2023, Vol. 47(6).
17. ПОДЧАЙНОВА, В. Н., СИМОНОВА, Л. Н. *Медь. Аналитическая химия элементов.* Москва: Наука, 1990, с. 78-80.
18. БЕЛЯВСКАЯ, Т. А. *Практическое руководство по гравиметрии и титриметрии.* Москва : Издательство Московского Университета, 1986, с. 123.

19. RE, R., PELLEGRINI, N., PROTEGGENTE, A., PANNALA, A., YANG, M., RICE-EVANS, C. *Antioxidant activity applying an improved ABTS radical cation decolorization assay.* In: *Free radical biology and medicine*. 1999, Vol. 26(9-10), p. 1231-1237.

Notă: *Lucrarea a fost efectuată în cadrul subprogramelor 010602 și 010701 a proiectului institutional.*

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

Mihail MAXIM, masterand, Facultatea de Chimie și Tehnologie Chimică, Universitatea de stat din Moldova.
ORCID: 0009-0006-3417-1133
E-mail: ch20maxim.mihail@gmail.com

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

Victor TSAPKOV, doctor în ştiinţe chimice, conferenţiar universitar, Universitatea de stat din Moldova.
ORCID: 0000-0003-1732-3116
E-mail: victor.tapcov@usm.md

Aurelian GULEA, doctor habilitat, profesor universitar, academician al Academiei de Științe a Moldovei, Universitatea de stat din Moldova.
ORCID: 0000-0003-2010-7959
E-mail: aurelian.gulea@usm.md

Olga GARBUZ, doctor în ştiinţe biologice, Institutul de Zoologie, Universitatea de stat din Moldova.
ORCID: 0000-0001-8783-892X
E-mail: olga.garbuz@sti.usm.md

Prezentat la 28.03.2024