

# Synthesis, Characterization and Toxicity Evaluation of Cu(II), Mn(II), Co(II), Ni(II), Pd(II) Complexes with Ligand Derived from Hydrazinecarbothioamide

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*New copper(II), manganese(II), cobalt(II), nickel(II) and palladium(II) complexes, [Cu(L)(X)(H<sub>2</sub>O)] [X= OAc (1), Cl (3), ClO<sub>4</sub><sup>-</sup> (4)], [M(L)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] [M= Cu<sup>2+</sup> (2), Mn<sup>2+</sup> (5)], [M(L)(OAc)(H<sub>2</sub>O)] [M= Co<sup>2+</sup> (6), Pd<sup>2+</sup> (8)], [Ni(L)(OAc)] (7) were synthesized with 2-(5H-dibenzo [a,d][7] annulen-5-ylacetyl)-N-(4-chlorophenyl) hydrazinecarbothioamide (HL). All the metal complexes have been characterized by different physico-chemical techniques like molar conductivity, magnetic susceptibility measurements, electronic and infrared spectral studies, elemental and thermal analysis. The toxicity of newly synthesized compounds was evaluated using the Daphnia magna bioassay.*

**Keywords:** hydrazinecarbothioamide, copper(II), manganese(II), cobalt(II), nickel(II) and palladium(II) complexes, spectral studies, toxicity

The tricyclic framework of 5H-dibenzo[a,d][7]annulene constitutes an integral part of the structure of molecules that are known to be effective for the treatment of depressive disorders [1, 2]. Analogs of 5H-dibenzo[a,d][7]annulene, such as Protriptyline and Demexiptyline, are well known tricyclic antidepressants [3]. Dibenzo[a,d][7]annulene derivatives exhibit antidiabetic, antiparasitic, metalloprotease inhibitors, antihypertensive, orexygenic and antimicrobial activity [4, 5].

The hydrazinecarbothioamide derivatives were found to exhibit antimicrobial, antifungal, tuberculostatic, cytostatic, anticonvulsant, antiviral, and antioxidant and anti-inflammatory, antihypertensive activities [6-9]. In last years a wide variety of heterocyclic systems and hydrazinecarbothioamides have been explored for developing the new antimicrobial agents [4, 5]. Such pharmacological activities are due to the strong chelating ability of this ligand with biologically important metal ions [10-13].

In the present paper, we report the synthesis and structural characterization of new mononuclear Cu(II), Mn(II), Co(II), Ni(II) and Pd(II) complexes with 2-(5H-dibenzo [a,d][7] annulen-5-ylacetyl)-N-(4-chlorophenyl) hydrazinecarbothioamide. The toxicity of ligand and metal complexes was assessed on *Daphnia magna* Straus (Daphniidae). The method, along other bioassays is an alternative to rats or mice in the prescreening of chemical toxicity [14, 15].

## Experimental part

### Materials and methods

All reactants and solvents were obtained commercially with the highest purity and were used without further purification.

C, H and N analyses were performed with the Carlo-Erba LA-118 microdosimeter and the AAS-1N Carl-Zeiss-Jena spectrometer was used for the determination of Cu(II), Ni(II) and Co(II).

Infrared spectra (4000-400 cm<sup>-1</sup>) were recorded on a Bruker Vertex 70 spectrophotometer, using KBr pellets. Diffuse reflectance spectra were recorded on a Jasco V-670 spectrophotometer, using MgO dilution matrices. The molar conductance of the complexes in dimethylformamide solutions (10<sup>-3</sup> M), at room temperature, were measured using a Consort type C-533 conductivity instrument. Magnetic susceptibility measurements were performed at room temperature in the polycrystalline state on a Faraday magnetic balance (home-made). The complexes were studied by thermogravimetry (TG) in static air atmosphere, with a sample heating rate of 10 °C/min using a STA 6000 Perkin Elmer.

*D. magna* bioassay was performed using the method described by Socea *et al.* with some modifications [9, 16]. The determination was performed in 4 mL 12-tissue culture wells (Greiner Bio-One), using 10 daphnids/well and each sample was tested in duplicate. The assay was performed using concentrations ranging from 0.3 to 50.0 µM. The

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concentration range was different for each compound due to the low solubility in the 1% DMSO in artificial medium used as solvent. The daphnids were considered dead if they did not move their appendages for 30 s. The survivors were counted after 24 and 48 h of incubation at 25°C, 75% RH, in the absence of light, using a climatic room chamber (Sanyo MLR351H, Sanyo). The control samples used were the solvent and the ligand **HL**. The median lethal concentration (LC50) was determined by interpolation on lethality curve constructed using the least square method. The 95% confidence interval (CI95%) for LC50 and goodness of fit were also calculated using GraphPad Prism version 5.01 software (GraphPad Software, USA).

#### Synthesis of 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(4-chlorophenyl)hydrazinecarbothioamide (**HL**)

The ligand was synthesized by nucleophilic addition of 2-(5H-dibenzo[a,d][7]annulen-5-yl)acetohydrazide to 4-chlorophenylisothiocyanates, in absolute ethanol, at reflux [5]. The 2-(5H-dibenzo[a,d][7]annulen-5-yl) acetohydrazide was prepared starting from dibenzosuberone, according to the literature method (scheme 1) [4, 5].

Hydrazinecarbothioamide was present as two conformational isomers, 5'-axial and 5'-equatorial in about 3:1 ratio, interconvertible by middle ring inversion, confirmed by <sup>1</sup>H-NMR spectra.

#### General Procedure for the preparation of the metal complexes

To a solution of 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(4-chlorophenyl)hydrazinecarbothioamide (0.433 g, 1 mmol) in DMSO/methanol (1:2, v/v, 15 mL) was added a solution of the corresponding metal salt in methanol (10 mL). The molar ratio used was 1:2 (M:L) for the copper(II) complexes and 1:1 (M:L) for the manganese(II), cobalt(II), nickel(II) and palladium(II) complexes. The following metal salts were used: Cu(CH<sub>3</sub>COO)<sub>2</sub>·H<sub>2</sub>O for complex **1**, Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O for complex **2**, CuCl<sub>2</sub>·2H<sub>2</sub>O for complex **3**, Cu(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O for complex **4**, Mn(CH<sub>3</sub>COO)<sub>2</sub>·2H<sub>2</sub>O for complex **5**, Co(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O for complex **6**, Ni(CH<sub>3</sub>COO)<sub>2</sub>·4H<sub>2</sub>O for complex **7** and Pd(CH<sub>3</sub>COO)<sub>2</sub> for complex **8**. The mixture was stirred for 6 h at 50 °C. The precipitate obtained was filtered, washed with methanol followed by ether and dried in vacuo.

[Cu(L)(CH<sub>3</sub>COO)(H<sub>2</sub>O)] (**1**) Brown solid. Yield: 71%; m.p. >220 °C; FW: 573 g/mol; Anal. Calc. for C<sub>26</sub>H<sub>24</sub>CuN<sub>3</sub>O<sub>4</sub>SCl: C, 54.45; H, 4.18; N, 7.32; S, 5.58; Cu, 11.08%. Found: C, 54.73; H, 3.96; N, 7.05; S, 5.39; Cu, 10.87%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1631, ν(N-H) -

, 3258, ν(C=S) 1278, ν(CH<sub>3</sub>COO) 1649; ν(CH<sub>3</sub>COO) 1320. The complex is soluble in pyridine and is partially soluble in ethanol, methanol, acetonitrile, acetone, DMF and DMSO.

[Cu(L)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] (**2**) Green solid. Yield: 84%; m.p. >220 °C; FW: 964.5 g/mol; Anal. Calc. for C<sub>52</sub>H<sub>48</sub>Cu<sub>2</sub>N<sub>6</sub>O<sub>8</sub>SCl<sub>2</sub>: C, 59.70; H, 4.35; N, 8.70; S, 6.63; Cu, 6.58%. Found: C, 59.91; H, 4.12; N, 8.32; S, 6.48; Cu, 6.29%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1626, ν(N-H) -, 3258, ν(C=S) 1277. The complex is soluble in pyridine and is partially soluble in ethanol, methanol, acetonitrile, acetone, DMF and DMSO.

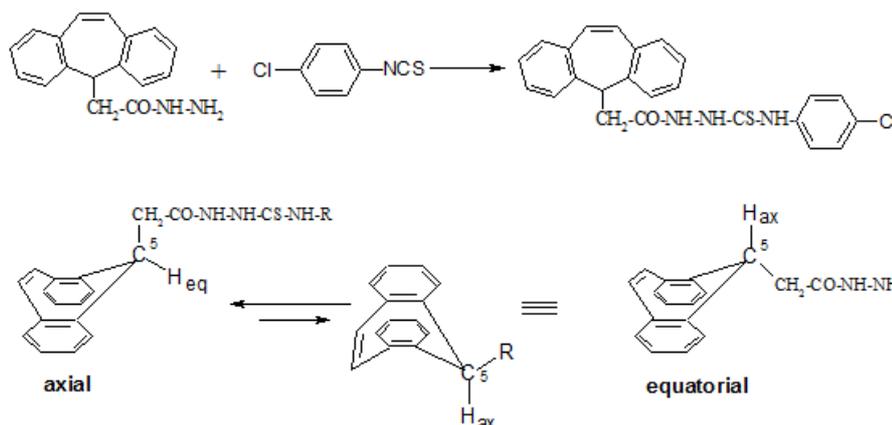
[Cu(L)(Cl)(H<sub>2</sub>O)] (**3**) Brown solid. Yield: 86%; m.p. >220 °C; FW: 549.5 g/mol; Anal. Calc. for C<sub>26</sub>H<sub>24</sub>CuN<sub>3</sub>O<sub>2</sub>SCl: C, 52.41; H, 3.82; N, 7.64; S, 5.82; Cu, 11.55%. Found: C, 52.70; H, 3.56; N, 7.38; S, 5.57; Cu, 11.28%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1620, ν(N-H) -, 3258, ν(C=S) 1278. The complex is soluble in pyridine and is partially soluble in ethanol, methanol, acetonitrile, acetone, DMF and DMSO.

[Cu(L)(ClO<sub>4</sub>)(H<sub>2</sub>O)] (**4**) Brown solid. Yield: 74%; m.p. >220 °C; FW: 613.5 g/mol; Anal. Calc. for C<sub>26</sub>H<sub>24</sub>CuN<sub>3</sub>O<sub>5</sub>SCl<sub>2</sub>: C, 46.94; H, 3.42; N, 6.84; S, 5.21; Cu, 10.35%. Found: C, 46.65; H, 3.17; N, 6.53; S, 4.86; Cu, 10.07%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1629, ν(N-H) -, 3260, ν(C=S) 1276, ν<sub>3</sub>(ClO<sub>4</sub><sup>-</sup>) 1121; ν<sub>4</sub>(ClO<sub>4</sub><sup>-</sup>) 1107. The complex is soluble in pyridine and is partially soluble in ethanol, methanol, acetonitrile, acetone, DMF and DMSO.

[Mn(L)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] (**5**) Brown solid. Yield: 73%; m.p. >220 °C; FW: 955.9 g/mol; Anal. Calc. for C<sub>48</sub>H<sub>42</sub>MnN<sub>6</sub>O<sub>8</sub>SCl<sub>2</sub>: C, 60.25; H, 4.39; N, 8.78; S, 6.69; Mn, 5.74%. Found: C, 60.49; H, 4.18; N, 8.46; S, 6.48; Mn, 5.39%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1625, ν(N-H) -, 3258, ν(C=S) 1274. The complex is soluble in pyridine, DMF and DMSO, and is partially soluble in ethanol, methanol, acetonitrile, acetone.

[Co(L)(CH<sub>3</sub>COO)(H<sub>2</sub>O)] (**6**) Green solid. Yield: 82%; m.p. >220 °C; FW: 568.4 g/mol; Anal. Calc. for C<sub>26</sub>H<sub>24</sub>CoN<sub>3</sub>O<sub>4</sub>SCl: C, 54.89; H, 4.22; N, 7.38; S, 5.62; Co, 10.36%. Found: C, 55.12; H, 4.03; N, 7.11; S, 5.39; Co, 10.09%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1640, ν(N-H) -, 3258, ν(C=S) 1274, ν(CH<sub>3</sub>COO) 1555; ν(CH<sub>3</sub>COO) 1318. The complex is soluble in pyridine, DMF and DMSO, and is partially soluble in ethanol, methanol, acetonitrile, acetone.

[Ni(L)(CH<sub>3</sub>COO)] (**7**) Brown solid. Yield: 77%; m.p. >220 °C; FW: 550.19 g/mol; Anal. Calc. for C<sub>26</sub>H<sub>22</sub>NiN<sub>3</sub>O<sub>3</sub>SCl: C, 54.91; H, 4.22; N, 7.39; S, 5.63; Ni, 10.32%. Found: C, 55.23; H, 4.01; N, 7.10; S, 5.29; Ni, 10.06%. Main IR peaks (KBr, cm<sup>-1</sup>): ν(C=N) 1621, ν(N-H) -, 3261, ν(C=S) 1277, ν(CH<sub>3</sub>COO) 1457; ν(CH<sub>3</sub>COO) 1381. The complex is soluble in pyridine, DMF and DMSO, and is partially soluble in ethanol, methanol, acetonitrile, acetone.



Scheme 1. Synthesis of the ligand 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(4-chlorophenyl)hydrazinecarbothioamide (**HL**)

Scheme 2. Isomeric forms of 2-(5H-dibenzo[a,d][7]annulen-5-ylacetyl)-N-(4-chlorophenyl)hydrazinecarbothioamide

$[Pd(L)(CH_3COO)(H_2O)]$  (**8**) Brown solid. Yield: 73%; m.p.  $>220$  °C; FW: 615.9 g/mol; Anal. Calc. for  $C_{26}H_{26}PdN_3O_4S$ : C, 50.65; H, 3.89; N, 6.81; S, 5.19; Pd, 17.27%. Found: C, 50.89; H, 3.51; N, 6.57; S, 5.04; Pd, 16.97%. Main IR peaks (KBr,  $cm^{-1}$ ):  $\nu$  (C=N) 1628,  $\nu$  (N-H), 3259,  $\nu$  (C=S) 1276,  $\nu_{as}$  ( $CH_3COO^-$ ) 1562;  $\nu_s$  ( $CH_3COO^-$ ) 1317. The complex is soluble in pyridine, DMF and DMSO, and is partially soluble in ethanol, methanol, acetonitrile, acetone.

## Results and discussions

All complexes were synthesized by direct reaction of the inorganic salt solutions with the ligand solution. The obtained complexes are microcrystalline solids which are stable in air and decompose above 250°C. The synthesis of the complexes is reproducible and the hydrazine carbothioamide coordinates as a mononegative bidentate ligand.

The molar conductance values of the soluble complexes in DMF ( $6-37 \Omega^{-1} cm^2 mol^{-1}$ ) showed that all complexes are non-electrolytes [17]. The elemental analyses data of the metal complexes are in agreement with the proposed structures of the complexes (scheme 3).

The structures of the compounds synthesized were elucidated by IR, UV-Vis spectrometry and thermal analyses.

The IR spectra of the complexes are compared with that of the free ligand to determine the changes that might occur during complex formation.

The ligand **HL** having three vibrational frequency from 3321 to 3147  $cm^{-1}$  which are assigned to the stretching vibration of the NH groups, a strong band at 1682  $cm^{-1}$  corresponding to  $\nu$ (C=O) stretching vibration [18, 19]. In all IR spectra of complexes the  $\nu$ (C=O) mode of ligand is not observed, but the presence of a new band at 1620-1640  $cm^{-1}$ , due to the  $\nu$ (N<sup>1</sup>=C) of N<sup>1</sup>=C-O group, indicates the enolisation of C=O group followed by deprotonation and complexation with metal ions. This is further supported by the presence of band at 1277  $cm^{-1}$  corresponding to  $\nu$ (C=S) stretching vibrations in free ligand which have not

presented considerable change in the complexes and ruling out the possibility of bonding through the C=S group [20].

So, IR spectral data suggests that the ligand **HL** act as mononegative bidentate ligand and coordinate through deprotonated enolic carbonyl oxygen (=C-O) and hydrazinic N<sup>2</sup>H nitrogen atoms and form a five-membered chelate ring.

The acetato complexes **1**, **6**, **8** have two strong bands at 1649, 1555, 1562 and 1320, 1318, 1330  $cm^{-1}$  respectively, corresponding to  $\nu_{as}$  ( $COO^-$ ) and  $\nu_s$  ( $COO^-$ ) with a difference between frequencies of 237-329  $cm^{-1}$ . This difference confirms the monodentate nature of the coordinated acetate group [21]. The presence of  $\nu_s$  ( $COO^-$ ) and  $\nu_{as}$  ( $COO^-$ ) absorption bands at 1457 and 1381  $cm^{-1}$ , in the IR spectra of complexes **7** suggests that the bidentate behaviour of acetate group [22].

The perchlorate complex **4** shows a band at 1121  $cm^{-1}$  assignable to  $\nu_3$ (ClO<sub>4</sub><sup>-</sup>) and a strong band at 1107  $cm^{-1}$  assignable to  $\nu_4$ (ClO<sub>4</sub><sup>-</sup>). The splitting of this band in two components indicates the presence of a monodentate perchlorate group [23]. All the complexes (except **7**) exhibit  $\nu$ (OH) and  $\gamma$ (H<sub>2</sub>O) bands in the 3435-3468 and 1158-1161  $cm^{-1}$  regions, which are indicative of coordinated water [24].

The geometry of the metal complexes has been deduced from the electronic spectra of the complexes. In the electronic spectra of the complexes the bands of ligand are shifted to lower energies (fig. 1).

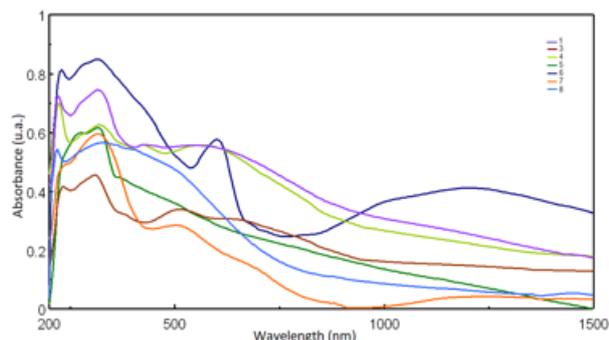
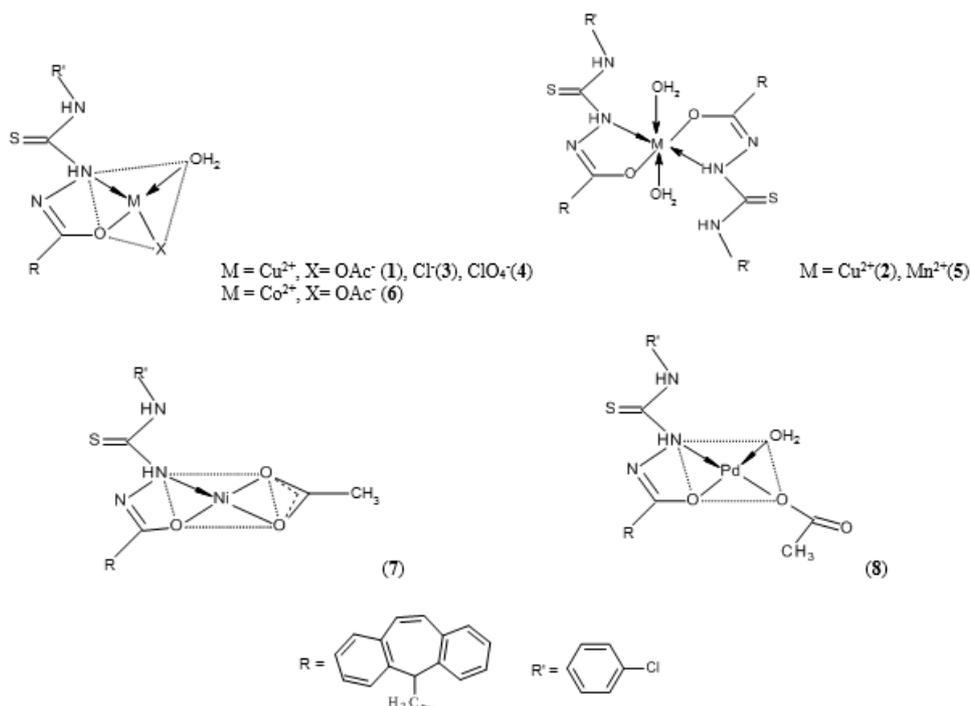


Fig. 1. Electronic spectra of the metal complexes **1-8**



Scheme 3. Proposed structures of the metal complexes **1-8**

Except for complex **2**, all the copper(II) complexes show absorption band in the area 16120-18340  $\text{cm}^{-1}$  which was attributed to the d-d transitions:  ${}^2B_2 \rightarrow {}^2B_1$  and  ${}^2B_2 \rightarrow {}^2A_1$ , suggesting a pseudo-tetrahedral geometry for the metal center. For complex **2**, the electronic spectrum show an absorption bands at 17850 and 13510  $\text{cm}^{-1}$  that were assigned to the d-d transitions:  ${}^2B_{1g} \rightarrow {}^2E_g$  and  ${}^2B_{1g} \rightarrow {}^2B_{2g}$ , respectively. These transitions indicate an axial distorted octahedral geometry of the copper(II) ion [25, 26]. The magnetic moment values (1.64-1.98 BM) for the copper(II) complexes corresponds to one unpaired electrons per metal ion.

The observed value of 5.92 BM for the Mn(II) complex is consistent with the high spin

octahedrally coordinated  $\text{Mn}^{2+}$  ion ( ${}^6A_{1g}$  ground state) with five unpaired electrons. The electronic spectrum of this complex exhibits peaks at 19.100 and 27.027, assigned to the  ${}^6A_{1g} \rightarrow {}^4T_{1g}(G)$  and  ${}^4T_{2g}(G)$  transitions, respectively [27].

The electronic spectrum of the cobalt(II) complex **6** show an intense band attributable to  ${}^4A_2(F) \rightarrow {}^4T_1(P)$  transition at 16.670  $\text{cm}^{-1}$  indicating a tetrahedral geometry for the complex. The magnetic susceptibility value and the deep green color for complex **6** is more consistent with tetrahedral stereochemistry [28].

For complex **7**, the electronic spectrum showed a two band association for square-planar geometry. The magnetic moment value (3.54 B.M) corresponding to two unpaired electrons per nickel (II) centres for square-planar configuration [29].

The electronic spectrum of complex **8** showed a square-planar geometry for the palladium ion. The very intense band at about 22.200  $\text{cm}^{-1}$  are assignable to a combination of metal-ligand charge transfer and d-d bands [30].

The thermogravimetric analysis tool is the most essential for supporting the presence of solvent molecules in attachment with the complex molecule.

Thermal analyses data reveal that compounds **1-6** and **8** are hydrated, having a weight loss

between 100 and 211 $^{\circ}\text{C}$  which corresponds to one molecule (**1, 3, 4, 6, 8**) or two molecules (**2, 5**) of water respectively directly bonded to the metal center. The second weight loss steps correspond to the release of small coordinated anions: OAc, Cl,  $\text{ClO}_4^-$ . The other weight loss refers to the decomposition of the ligand (fig. 2).

In the first 24 h, no significant lethality was observed for any compound. The ligand **HL** toxicity was predicted using Lazar software (lazy structure-activity relationships), a modular framework for predictive toxicology used widely in the risk assessment of new synthesized compounds [31]. The predicted LC50 for *Daphnia magna* was 123  $\mu\text{M}$  with a CI95% of 1.68 - 8990  $\mu\text{M}$ . Experimental data at 48h, showed that **HL** induced at highest concentrations a lethality between 20 and 40% and an estimated value of LC50 higher than 3800  $\mu\text{M}$ . Given the low solubility of the compound, no concentration above 50  $\mu\text{M}$  could be tested. Along with the experimental results, the predicted values indicate a low toxicity of the compound. Even if the predicted values are different from the obtained data, the predicted CI95% includes our results. After 48 h, only complexes **3-5**, induced a lethality equal or higher than 50%. For these compounds LC50 values were calculated and presented in table 1. All compounds induced on *Daphnia magna* mortalities between 0 and 30%. These results show a higher toxicity of two  $\text{Cu}^{2+}$  and one  $\text{Mn}^{2+}$  complexes compared to the effect of ligand **HL**. In our previous work [29], we tested a series of complexes along with their precursor salts on *Daphnia magna* and demonstrated that the ligand lowered their toxicity. The  $\text{Cu}^{2+}$  salts had high toxicity with a LC50

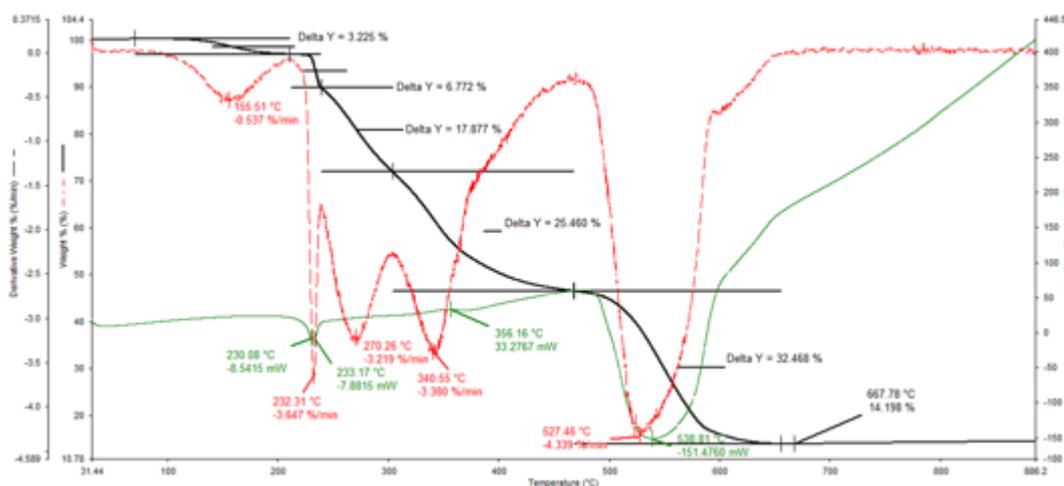


Fig. 2. Thermogravimetric analysis of complex **1**

Compound	LC50 at 48h ( $\mu\text{M}$ )	CI95% of LC50 ( $\mu\text{M}$ )	Goodness of fit (r2)
HL	ND, >50	ND	ND
<b>1</b>	ND, >35	ND	ND
<b>2</b>	ND, >35	ND	ND
<b>3</b>	32.04	13.25 - 77.46	0.8611
<b>4</b>	34.05	25.81 - 44.93	0.9643
<b>5</b>	24.6	14.81 to 40.87	0.9229
<b>6</b>	ND, >35	ND	ND
<b>7</b>	ND, >25	ND	ND
<b>8</b>	ND, >35	ND	ND

ND-Not determined due to the results obtained.

Table 1  
DAPHNIA MAGNA BIOASSAY RESULTS

ranging from 0.3 to 5  $\mu\text{M}$ . In the present paper, complexes **1**, **2**, **5** and **7**, induced no toxicity above 30% at 48 h, showing the capability of the ligand to significantly lower the toxicity of the metal ions.

## Conclusions

The coordination ability of the 2-(5H-dibenzo [a,d][7]annulen-5-ylacetyl)-N-(4-chlorophenyl) hydrazinecarbothioamide (**HL**) has been proved in complexation reactions with Cu(II), Mn(II), Co(II), Ni(II), Pd(II) ions.

The physico-chemical analyses (molar conductivity, magnetic susceptibility measurements, IR, UV-Vis., elemental and thermal analysis) confirmed the composition and the structures of the newly obtained complexes. In all the complexes, the ligand **HL** acted as ON bidentate donor forming mononuclear complexes. A pseudo-tetrahedral and octahedral geometry for Cu<sup>2+</sup>, octahedral for Mn<sup>2+</sup>, tetrahedral geometry for Co<sup>2+</sup> and a square-planar arrangement for Ni<sup>2+</sup> and Pd<sup>2+</sup> complexes were proposed, respectively.

The newly synthesized complexes are far less toxic for *Daphnia magna* than the metal ions and the ligand showed a good ability to lower the toxicity of Cu(II), Mn(II), Co(II), Ni(II), Pd(II) ions. These metal complexes with lower toxicity represents promising candidates for future investigation regarding their biological effects.

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