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Copper(II) complexes with 2-pyridineformamide-derived thiosemicarbazones: Spectral studies and toxicity against *Artemia salina*

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ABSTRACT

The copper(II) complexes [Cu(H2Am4DH)Cl_2] (**1**), [Cu(H2Am4Me)Cl_2] (**2**), [Cu(H2Am4Et)Cl_2] (**3**) and [Cu(2Am4Ph)Cl] (**4**) with 2-pyridineformamide thiosemicarbazone (H2Am4DH) and its *N*(4)-methyl (H2Am4Me), *N*(4)-ethyl (H2Am4Et) and *N*(4)-phenyl (H2Am4Ph) derivatives were studied by means of infrared and EPR spectral techniques. The crystal structure of **4** was determined. The studied compounds proved to be toxic to *Artemia salina*, suggesting that they could present cytotoxic activity against solid tumors. Among the free thiosemicarbazones H2Am4Ph presented higher toxicity than all other compounds, which showed comparable effects. In the case of complexes **2** and **3** toxicity is probably attributable to the complex as an entity or to a synergistic effect involving the thiosemicarbazone and copper. H2Am4Ph and complexes **2** and **3** revealed to be the most promising compounds as potential antineoplasic agents.

1. Introduction

Thiosemicarbazones and their metal complexes represent an interesting class of compounds with a wide range of pharmacological applications [1,2]. Due to their chelating ability thiosemicarbazones play an important role in Inorganic Medicinal Chemistry. α(*N*)-heterocyclic thiosemicarbazones derived from 2-formyl-, 2-acetyl-, and 2-benzoylpyridine have been extensively investigated, as well as the effects of metal coordination in their mechanism of action [1–4].

In recent years some structural and spectral studies on 2-pyridineformamide-derived thiosemicarbazones have been undertaken [5–11] but to our knowledge their pharmacological profile has not so far been investigated. Our group recently started the study of the pharmacological properties of this class of compounds. We demonstrated that 2-pyridineformamide thiosemicarbazones as well as their organotin complexes are active as antimicrobials against the growth of *Candida albicans* and *Salmonella typhimurium* and are highly active against malignant glioblastoma [12]. We also demonstrated that iron(III) complexes with this class of thiosemicarbazones are toxic to *Artemia salina*, indicating that they could present antineoplasic activity [13].

Copper(II) complexes with a variety of ligands such as aminoacids [14], peptides [15], quinoxalines [16], mono- and *bis*(thiosemicarbazones) [17,18] proved to be effective as cytotoxic agents in cell cultures as well as *in vivo*. Therefore in the present work, copper(II) complexes with 2-pyridineformamide thiosemicarbazone (H2Am4DH) and its *N*(4)-methyl (H2Am4Me), *N*(4)-ethyl (H2Am4Et) and *N*(4)-phenyl derivatives (Fig. 1) were obtained. The toxicity of the complexes against *A. salina* was assayed as a pre-screening of antitumoral action.

2. Experimental

2.1. Apparatus

Partial elemental analyses were performed on a PerkinElmer CHN 2400 analyzer. Infrared spectra were recorded on a PerkinElmer FT-IR Spectrum GX spectrometer using CsI pellets; an YSI model 31 conductivity bridge was employed for molar conductivity measurements. Magnetic susceptibility measurements were carried out on a Johnson Matthey MSB/AUTO balance. Electron paramagnetic resonance (EPR) spectra were obtained on a Bruker ESP300E equipment with modulation frequency of 100 kHz and modulation amplitude of 0.4–1 mT, where appropriate. Ambient temperature spectra of the samples in the solid state and as DMF solutions (1 mg mL^{-1}) were obtained in glass capillaries of 1.2 mm internal diameter. Frozen DMF solution spectra were acquired at liquid N_2 temperature (77 K) in 3 mm internal diameter

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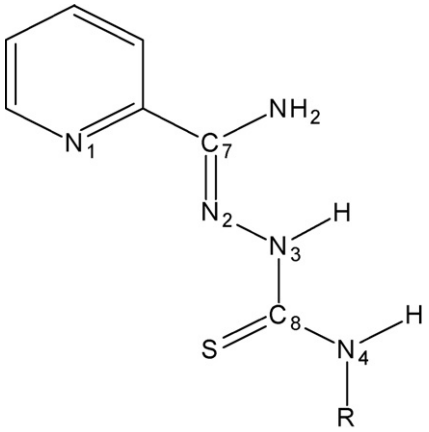

Fig. 1. General structure of 2-pyridineformamide-derived thiosemicarbazones: R = H (H2Am4DH); R = CH_3 (H2Am4Me); R = CH_2CH_3 (H2Am4Et); R = C_6H_5 (H2Am4Ph).

Teflon® tubes. Spectral simulations were performed using EasySpin [19].

2.2. Synthesis of the copper(II) complexes with 2-pyridinoformamide thiosemicarbazone (H2Am4DH) and its N(4)-methyl (H2Am4Me) and N(4)-ethyl (H2Am4Et) and N(4)-phenyl derivatives (H2Am4Ph)

The thiosemicarbazones were obtained as reported in literature [5]. The copper(II) complexes with H2Am4DH and H2Am4Me had already been obtained by other authors [10,11] but were prepared again in the present work to be studied for their EPR spectral properties and their pharmacological profile. The copper(II) complexes with H2Am4Et and H2Am4Ph were obtained by mixing the desired thiosemicarbazone with $CuCl_2{\cdot}2H_2O$ in ethanol at room temperature in 1:1 metal-to-ligand molar ratio. The solids which precipitated were filtered off and washed with diethyl ether.

2.2.1. Dichloro(2-pyridineformamidethiosemicarbazone)copper(II) [Cu(H2Am4DH)Cl_2] (**1**) and dichloro(N(4)-methyl-2-pyridineformamidethiosemicarbazone)copper(II) [Cu(H2Am4Me)Cl_2] 1.5H_2O (**2**)

These complexes have been prepared by other authors [10,11].

2.2.2. Chloro(N(4)-ethyl-2-pyridineformamidethiosemicarbazone)copper(II) chloride [Cu(H2Am4Et)Cl_2] (**3**)

Green solid. *Anal*. Calc. for $CuC_9H_{13}SCl_2N_5$: C, 30.22; H, 3.66; N, 19.58. Found: C, 29.87; H, 2.99; N, 19.26%; FW: 357.75 g mol^{-1}. IR (CsI/Nujol, cm^{-1}): ν(C=N)+ ν(C=C) 1643, ν(C=S) 843, ρ(py) 648, ν(Cu–N) 482, ν(Cu–S) 347, ν(Cu–Cl) 315, ν(Cu–N_{py}) 224. Molar conductivity (1×10^{-3} mol L^{-1} DMF): 55.1 Ω^{-1} cm^2 mol^{-1}. Effective magnetic moment = 1.79 (BM). Yield: 95%.

2.2.3. Chloro(N(4)-phenyl-2-pyridineformamidethiosemicarbazonato)copper(II) [Cu(2Am4Ph)Cl] (**4**)

Green solid. *Anal*. Calc. for $CuC_{13}H_{13}SClN_5$: C, 42.28; H, 3.27; N, 18.96. Found: C, 41.91; H, 2.97; N, 18.84%; FW: 369.33 g mol^{-1}. IR (CsI/Nujol, cm^{-1}): ν(C=N)+ ν(C=C) 1591, ν(C=S) 811, ρ(py) 624, ν(Cu–N) 468, ν(Cu–S) 342, ν(Cu–Cl) 318, ν(Cu–N_{py}) 246. Molar conductivity (1×10^{-3} mol L^{-1} DMF): 10.0 Ω^{-1} cm^2 mol^{-1}. Effective magnetic moment = 1.84 (BM). Yield: 95%.

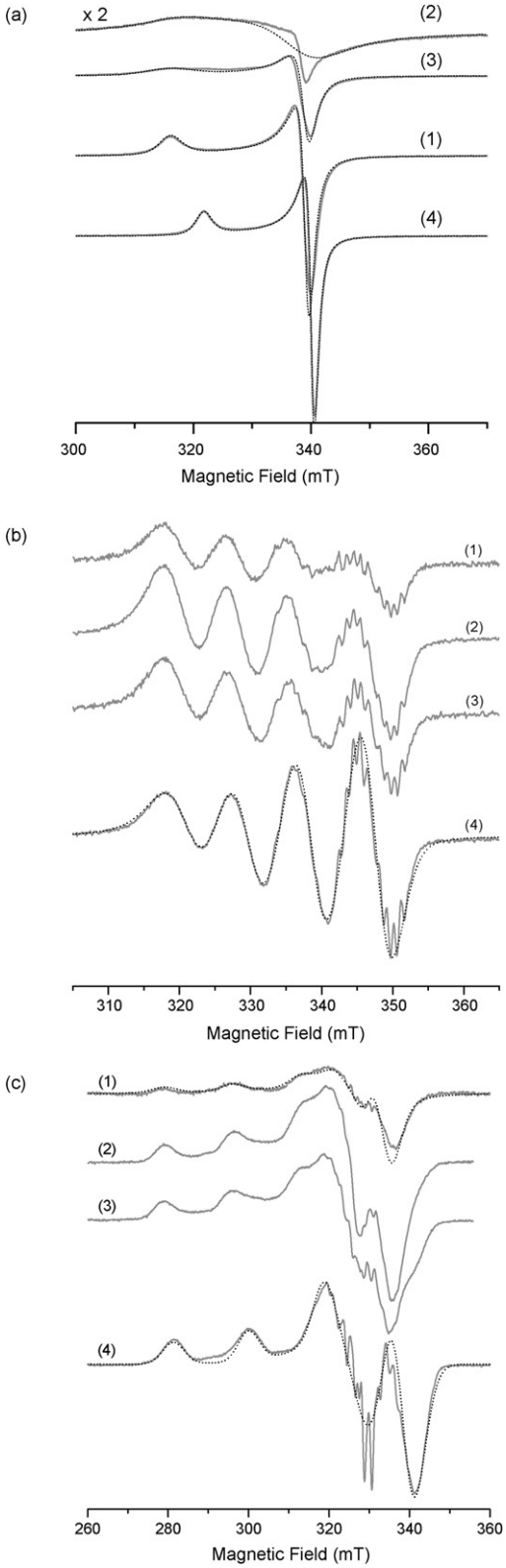

Fig. 2. (a) Ambient temperature EPR spectra of polycrystalline compounds **1**–**4** (gray) and simulations (dotted lines) using EasySpin (S = 1/2, axial symmetry). Only the main components of (**2**) is presented in the simulation. (b) Ambient temperature EPR spectra of compounds **1**–**4** (2 mg/mL) in DMF and the simulation of **4**, without the nitrogen superhyperfine structure, using EasySpin (function garlic, with $g_{||} = 2.165$, $g_{\perp} = 2.038$; for ^{63}Cu $A_{||} = 180 \times 10^{-4}$ cm^{-1}, $A_{\perp} = 30 \times 10^{-4}$ cm^{-1}; correlation time 7.0×10^{-11} s, lorentzian line width 1.5 mT and gaussian line width 4.5 mT). (c) EPR spectra of compounds **1**–**4** (2 mg/mL) in DMF at 77 K, and the simulations of **1** and **4**, without the nitrogen superhyperfine structure, using EasySpin (function pepper, parameters in Table 1).