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Synthesis, structure and biological activity of nickel(II) complexes of 5-methyl 2-furfural thiosemicarbazone

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Abstract

5-Methyl 2-furfuraldehyde thiosemicarbazone (M5HFTSC) with nickel(II) leads to three types of complexes: $[Ni(M5HFTSC)_2X_2]$, $[Ni(M5FTSC)_2]$ and $[Ni(M5FTSC)_2]\cdot 2DMF$. In the first type the ligand remains in thione form, while in the two other, the anionic thiolato form is involved. The species $[Ni(M5HFTSC)_2X_2]$ has been characterized spectroscopically. The structures of $[Ni(M5FTSC)_2]\cdot 2DMF$ and $[Ni(M5FTSC)_2]$ have been solved using X-ray diffraction. Biological studies of $[Ni(M5HFTSC)_2Cl_2]$ have been carried out in vitro for antifungal activity on human pathogenic fungi, *Aspergillus fumigatus* and *Candida albicans,* and in vivo for toxicity on mice. The results are compared to those of the ligand, the metal salt and a similar copper complex $[Cu(M5HFTSC)Cl_2]$.

Keywords: Ni(II) complexes; Thiosemicarbazone complexes; Crystal structures; Spectroscopic studies; Biological activity

1. Introduction

The heterocyclic thiosemicarbazones and their metal complexes are among the most widely studied compounds for their potential therapeutic uses, such as antitumoral [1–5], fungicidal [6,7], bactericidal [8] or antiviral [3] activity.

We have previously described the complexes formed between various furan oximes [9] and semicarbazones with 3*d* metal dihalides [10]. The cytotoxic activity of some of the copper complexes has been characterized in our laboratory [11] as well as similar compounds [12,13].

We report here the synthesis and the characterization of complexes obtained by reaction of M5HFTSC with chlorides and bromides of Ni(II), where M5HFTSC is 5-methyl 2-furfuralehyde thiosemicarbazone. The crystal structures of the two complexes obtained, $[Ni(M5FTSC)_2]$ and $[Ni(M5FTSC)_2]\cdot 2DMF$ are discussed. Due to few studies concerning the biological activity of nickel complexes of thiosemicarbazones [14,15], the biological properties of $[Ni(M5HFTSC)_2Cl_2]$ were also studied and compared to $[Cu(M5HFTSC)Cl_2]$ which was described earlier [16]. The biological properties were tested in vivo on mice and in vitro on human pathogenic fungi, *Aspergillus fumigatus* and *Candida albicans.*

2. Experimental

2.1. Reactants

All reactants and solvents were of analytical grade. Thiosemicarbazide, 5-methylfurfural and nickel salts were purchased from Merck, Aldrich and Prolabo, respectively, and used without further treatment.

2.2. Measurements

Elemental analyses were carried out by the 'Service Central d'Analyses' (CNRS, Vernaison, France). Melting

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points were determined with a digital melting point apparatus using capillary technique. Conductance values were obtained with a Tacussel CD6NG conductometer at 25°C (298 K) from 10^{-3} M solutions of complexes in absolute EtOH. The solvent had a conductance of 10^{-8} S.

The IR spectra were recorded with a Shimadzu FTIR-8010M spectrometer between 400 and 4600 cm^{-1} (KBr disks) and with a Nicolet FTIR 20F in the range 50–400 cm^{-1} using polyethylene disks (Institut des Matériaux de Nantes, France). Electronic spectra were recorded with a Perkin-Elmer Lambda 19 spectrometer in ethanolic solutions (10^{-3} M). The ^{1}H NMR spectra were recorded on a Bruker Advance DRX 500 in DMSO-d_6 operating at 500 MHz. The chemical shifts, δ, are given in parts per million (relative to TMS) and coupling constants in Hertz.

2.3. Preparation of ligand

The 5-methyl 2-furfuraldehyde thiosemicarbazone was obtained as previously described [2] from 5-methyl furfural and thiosemicarbazide (1:1 molar ratio) in absolute ethanol in the presence of pure acetic acid. The mixture was refluxed for 1 h and then cooled, filtered and recrystallized from a mixture of ethanol (75%) and water. Yellow microcrystalline products were obtained. [Analysis results for $C_7H_9N_3OS$. Found: C, 45.71; H, 4.95; N, 22.59. Calculated: C, 45.89; H, 4.95; N, 22.93%. M.P.=165°C and λ=0.82 S cm^2 mol^{-1}].

2.4. Preparation of complexes

2.4.1. [Ni(M5HFTSC)$_2$Cl$_2$]

The hexahydrated salt of nickel, $NiCl_2 \cdot 6H_2O$ (5×10^{-3} mol, 0.92 g), was dissolved in *n*-BuOH. This solution was heated until the solvent refluxed and then 10 ml of an equimolar *n*-BuOH solution of M5HFTSC was added slowly while stirring. The mixture was refluxed for 24 h and a green solid was removed by filtration, washed with MeOH and finally dried in vacuum over silica gel. [Analysis results for $C_{14}H_{18}C_{12}NiN_6O_2S_2$. Found: C, 33.6; H, 3.58; Cl, 14.83; Ni, 11.06. Calculated: C, 33.90; H, 3.66; Cl, 14.29; Ni, 11.83%. M.P. (decomposition)= 222°C and λ=31 S cm^2 mol^{-1}].

2.4.2. [Ni(M5FTSC)$_2$]

When [Ni(M5HFTSC)$_2$Cl$_2$] was dissolved in a mixture of 20 ml of EtOH and two drops of hydrochloric acid, dark-green crystals of formula [Ni(M5FTSC)$_2$] were isolated.

2.4.3. [Ni(M5HFTSC)$_2$Br$_2$]

It was obtained as a green solid in the same way as the chloro complex, but in EtOH solution and refluxing for only 5 h. [Analysis results for $C_{14}H_{18}Br_2NiN_6O_2S_2$. Found: C, 28.89; H, 3.17; Br, 27.32; Ni, 10.24. Calculated: C, 28.75; H, 3.10; Br, 27.32; Ni, 10.03%. M.P. (decomposition)=236°C and λ=39 S cm^2 mol^{-1}].

2.4.4. [Ni(M5FTSC)$_2$]·2DMF

When [Ni(M5HFTSC)$_2$Br$_2$] was dissolved in dimethylformamide (DMF), a dark-green crystalline product of formula [Ni(M5FTSC)$_2$]·2DMF was isolated after several days.

2.5. Crystal data collection and processing

Crystals of [Ni(M5FTSC)$_2$]·2DMF are triclinic with space group *P*-1, while those of [Ni(M5FTSC)$_2$] are trigonal with space group *R*-3.

The crystal and instrumental parameters used in the unit-cell determination and data collection for both compounds are summarized in Table 1. X-ray diffraction data were collected at 293 K on an Enraf Nonius MACH3 four-circles diffractometer ($\lambda_{Mo\ K\alpha}$=0.71073 Å) equipped with a graphite monochromator (IMMO, UMR, CNRS, 6501 Angers). The structures were solved by direct methods (SIR) using MolEN package programs [17] and F was refined by the full-matrix least-squares techniques.

For [Ni(M5FTSC)$_2$]·2DMF all non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were located by a Fourier difference synthesis and the missing atoms were calculated from the HYDRO program [17].

In the case of [Ni(M5FTSC)$_2$], the small size of crystal of the complex did not allow us to obtain enough data to specify the hydrogen atoms coordinates and non hydrogen atoms were refined isotropically and the DIFABS program [17] was used for absorption corrections.

2.6. Biological data

2.6.1. Materials and methods

The metal salt, the ligand and its complexes with copper [Cu(M5HFTSC)Cl$_2$] and with nickel [Ni(M5HFTSC)$_2$Cl$_2$] were stored dry at room temperature and dissolved in dimethyl sulfoxide (DMSO) just before their use.

2.6.2. Antifungal tests

The broth microdilution test was performed by following the guidelines of the approved reference method for yeasts (NCCLS document M27-A) [18]. An antifungal susceptibility test was performed with *Candida albicans* (ATCC 663.90) and *Aspergillus fumigatus* (CBS 113.26) using RPMI-1640 medium (Sigma) with 2 mM L-glutamine, buffered at pH 7.0 with 0.165 M morpholine propane-sulfonic acid (MOPS) and then sterilized by filtration. The fungal suspensions were prepared in RPMI-1640 culture medium and spectrophotometrically adjusted at 630 nm to give final inocula concentrations of about 5×10^3 to 2.5×10^4 cells ml^{-1}. The broth microdilution tests were performed using sterile 96-well flat-shaped microtitre plates. Each well was inoculated with 195 μl of

Table 1
Crystallographic data for $[Ni(M5FTSC)_2]\cdot 2DMF$ and $[Ni(M5FTSC)_2]$

	Compound	
	$[Ni(M5FTSC)_2]\cdot 2DMF$	$[Ni(M5FTSC)_2]$
Formula	$C_{20}H_{30}N_8NiO_4S_2$	$C_{14}H_{16}N_6$ Ni O_2 S_2
Molecular weight	569.35	423.14
Crystal system	Triclinic	Trigonal
Space group	*P*-1	*R*-3
a/Å	7.828(1)	14.60(1)
b/Å	8.4779(6)	14.60(1)
c/Å	10.610(1)	21.90(1)
α/°	72.950(6)	90
β/°	79.19(1)	90
γ/°	82.243(9)	120
V/Å^3	658.8(1)	4047(9)
Z	1	9
Color	Dark-green	Dark-green
Crystal size (mm)	0.29×0.29×0.11	0.14×0.14×0.09
D_c/g cm^{-3}	1.43	1.47
F (000)	298	1836
μ (mm^{-1})	0.936	1.326
Scan mode	$\omega/2\theta$	$\omega/2\theta$
hkl limits	−9.9/−10.10/−13.0	0.13/−11.0/−19.19
θ_{min}, θ_{max}	2.5, 25.97	2.5, 18.79
Number of data measured	2730	809
Number of data with $I > 3\sigma(I)$	1873	252
Weighting scheme	$4F_o^2/((\sigma(F_o^2))^2 + 0.0064F_o^4)$	$4F_o^2/((\sigma(F_o^2))^2 + 0.0064F_o^4)$
Number of variables	176	50
R	0.037	0.056
R_w	0.058	0.066

the corresponding fungal working suspension. Serial two-fold drug dilutions were made in DMSO, 40 times the strength of the final drug concentration (0.75–10 mg ml^{-1}) and were dispensed in triplicate into the wells of three rows at a volume of 5 μl. Final concentrations for the drugs were from 1.95 to 250 mg ml^{-1}. The growth control wells contained 195 μl of fungal working suspension and 5 μl of drug-free DMSO. The positive control was made with amphotericin B. The microplates were incubated at 37°C for 48 h (*C. albicans*) and 72 h (*A. fumigatus*) and spectrophotometric readings of each well were performed at 630 nm with a Dynatech Laboratories MRX_{TC} automatic plate reader. The spectrophotometric MIC (minimum inhibitory concentration) endpoint was calculated from the turbidimetric data as the lowest drug concentration giving rise to an inhibition of growth equal to or greater than 80% of that of the drug-free control (MIC_{80}).

2.6.3. Toxicity tests

Male Swiss mice from Debré (France) weighing from 20 to 25 g were used because of their regular weight gain and the absence of oestral cycle with changes in sexual hormonal status, which could lead to some errors in in vivo experiments.

Animals have free access to both water and standard diet containing 0.8% Ca, 0.7% P and 3 IU g^{-1} vitamin D. They were placed at room temperature (20±2°C) and exposed to a 12-h light/dark cycle. After intraperitoneal injection with various doses of studied species, the animals were kept under the same conditions and were kept under observation for 7 days.

3. Results and discussion

3.1. X-ray crystallography

For comparison, the bond distances and angles of both crystals are shown in Table 2. Fig. 1 shows a view of the molecule of $[Ni(M5FTSC)_2]\cdot 2DMF$, with numbering scheme.

3.1.1. Crystal structure of [Ni(M5FTSC)$_2$]·2DMF

The centrosymmetric structure consists of the neutral molecules $Ni(M5FTSC)_2$ with two molecules of dimethylformamide, and the metal at the center of symmetry. The coordination results in a square planar configuration, which involves the thiolato sulfur atoms and the imine nitrogen atom N3 of the two ligands in trans configuration.

In the complex, the monodeprotonated bidentate ligand shows a *cis* configuration for the donor nitrogen N3 and sulfur S atoms. In the free ligand, however, these centers present a *trans*-configuration, indicating that the complexation is obtained after a 180° rotation around the C1–N2 bond [16].

The deprotonation of the ligand on the level of N2

Table 2
Bond lengths (Å) and angles (°) for $[Ni(M5FTSC)_2]\cdot 2DMF$ and $[Ni(M5FTSC)_2]$

	$[Ni(M5FTSC)_2]\cdot 2DMF$	$[Ni(M5FTSC)_2]$
Bond lengths		
Ni–S	2.162(1)	2.164(5)
Ni–N3	1.912(2)	1.88(2)
S–C1	1.734(3)	1.72(2)
O1–C3	1.375(4)	1.39(2)
O1–C6	1.355(4)	1.38(3)
O2–C8	1.229(4)	
N1–C1	1.334(4)	1.39(2)
N2–N3	1.397(3)	1.42(2)
N2–C1	1.307(4)	1.27(3)
N3–C2	1.297(4)	1.31(3)
C2–C3	1.422(4)	1.45(3)
C3–C4	1.360(4)	1.29(3)
C4–C5	1.417(5)	1.36(3)
C5–C6	1.333(5)	1.36(3)
C6–C7	1.496(5)	1.45(3)
C8–N4	1.307(5)	
C9–N4	1.446(5)	
C10–N4	1.425(6)	
Bond angles		
S–Ni–N3	85.15(8)	93.9(4)
Ni–S–C1	96.5(1)	95.0(6)
C3–O1–C6	107.0(2)	109(1)
N3–N2–C1	111.8(2)	109(1)
Ni–N3–N2	120.9(2)	122(1)
Ni– N3–C2	125.0(2)	125(1)
N2–N3–C2	114.1(2)	111(1)
S–C1–N1	117.2(2)	116(1)
S–C1–N2	122.5(2)	127(1)
N1–C1–N2	120.3(2)	116(1)
N3–C2–C3	128.8(3)	126(1)
O1–C3–C2	113.4(3)	111(1)
O1–C3–C4	109.2(3)	105(1)
C2–C3–C4	137.4(3)	142(1)
C3–C4–C5	106.1(3)	111(1)
C4–C5–C6	107.5(3)	108(2)
O1–C6–C5	110.2(3)	104(1)
O1–C6–C7	116.5(3)	120(1)
C5–C6–C7	133.2(3)	135(2)
O2–C8–N4	126.8(4)	
C8–N4–C9	121.4(3)	
C8–N4–C10	121.3(3)	
C9–N4–C10	117.2(3)	

causes a negative charge delocalized over the thiosemicarbazone moiety. This is explained by the difference noted on the level of the bond distances in the deprotonated ligand of nickel complex which is for S1–C1 = 1.734(3) Å (thiolato form); C1–N2 = 1.307(4) Å and C2–N3 = 1.297(4) Å, and the bond distances in the case of non-deprotonated free ligand, for S1–C1 = 1.684(1) Å (thione form); C1–N2 = 1.341(2) Å and C2–N3 = 1.282(2) Å [16].

The metal and the thiosemicarbazone moiety of the two ligands are in the same plane, while the furanic ring is slightly out of the plane, with an angle of 7.13(1)°. The bond distance of Ni–S = 2.162(1) Å is compared to Ni–S = 2.134(2) Å [19] and 2.140 (2) Å [20], which are typical values for square planar nickel species. The calculation distance Ni–N = 1.912(2) Å is within the range found in the literature, e.g. Ni–N = 1.857(5) Å [21] and Ni–N = 1.854(5) Å [20].

The dimethylformamide molecules lie in the cavities between the complexes (Fig. 2) and they control the packing by hydrogen bonds between the nitrogen of the amino group N1 and the dimethylformamide oxygen atom N1–H02 . . . O2 = 2.35(4) Å and N1–H01 . . . O2 = 2.13(3) Å. The angle for hydrogen bond N1–H02 . . . O2 is 161(1)° and for N1–H01 . . . O2 it is 155(1)°.

3.1.2. Crystal structure of [Ni(M5FTSC)$_2$]

This structure is solved with little data because of the small size of the crystal (Table 1). The bond distances, angles and the geometry of $Ni(M5FTSC)_2$ molecules in the crystal $[Ni(M5FTSC)_2]$ are similar to those of the $[Ni(M5FTSC)_2]\cdot 2DMF$ crystal, as mentioned above in Table 2.

The molecular arrangement in the unit-cell, shows that the atoms Ni and S are again according to (001) plane, with an interspacing of about 7.30(1) Å. The rest of the atoms of the complex are within the interspace.

3.2. Spectroscopic study

As all thiosemicarbazones, our ligand can exhibit thione-thiol tautomerism, since it contains a thioamide –NH–C=S functional group [21]. There is no IR band at 2500–2600 cm^{-1} in the spectrum of the free ligand, and this indicates the absence of S–H grouping in the free ligand. However, there are bands in the regions of 855 and 3150 cm^{-1}, characteristic of ν(C=S) and ν(N–H), respectively, indicating that the ligand remains as the thione tautomer. This is supported by the ^1H NMR spectrum which does not show any peak at 4 ppm attributable to the S–H proton, but it shows a singular peak at 11.3 ppm relative to the NH next to C=S.

The bands appearing around 1345 and 785 cm^{-1} in the spectrum of the ligand are either weakened or shifted to higher wave numbers in all the complexes [22,23], and this shift can be assigned to ν(C=S) vibration. On the other hand, the bands in the region 3440–3270 cm^{-1} attributed to symmetrical and asymmetrical stretching mode $\nu(NH_2)$ in the spectra of the ligand, undergo appreciable change in the spectra of the complexes. This is due to the coordination of sulfur from the $C{=}S(NH_2)$ group as reported earlier [24]. This coordination is confirmed by the presence of a new band at 380–395 cm^{-1} [5,25] which is assigned to ν(M–S) for all the complexes.

In ligand spectra, the strong band observed at 1600 cm^{-1} corresponds to ν(C=N) vibration band [24]. This band shifts to a higher region [22,24] in the spectra of nickel complexes and this indicates the coordination of nitrogen of the azomethine group to the central metal atoms in these complexes. The presence of a new band in

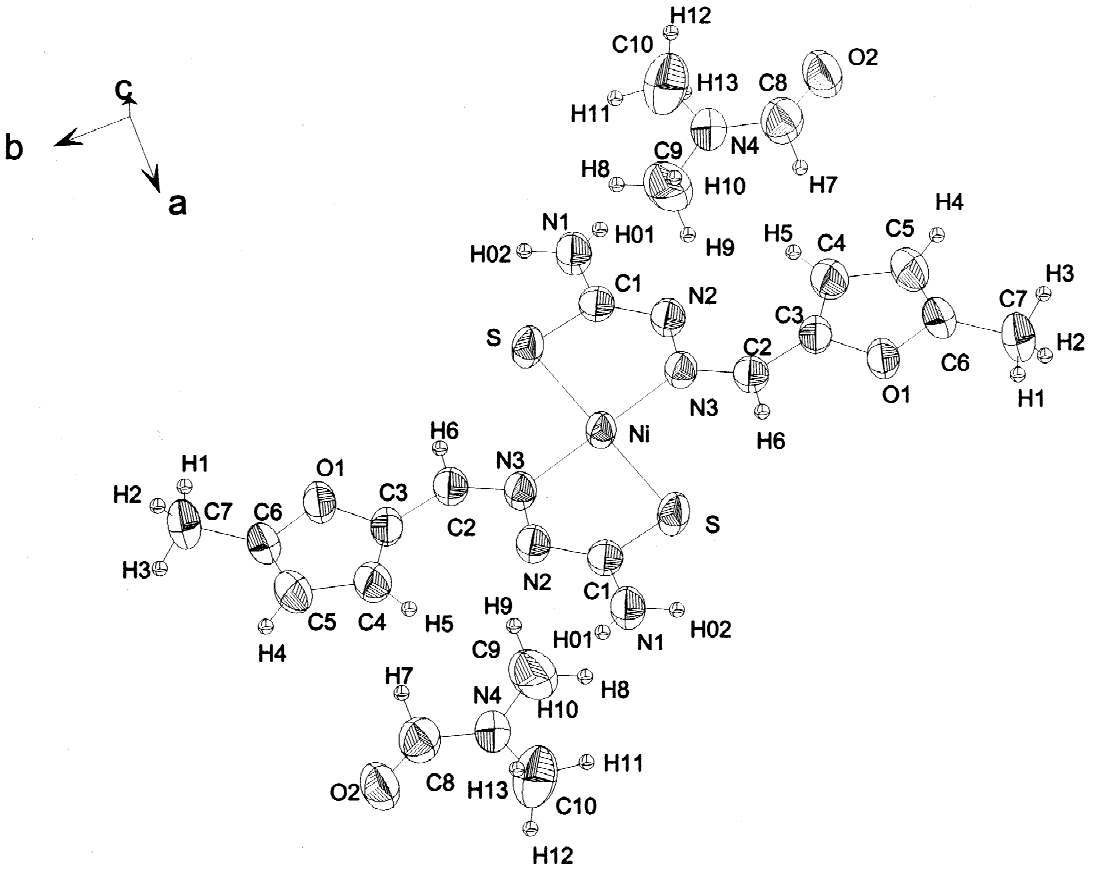

Fig. 1. Perspective view of complex and atom numbering of [Ni(M5FTSC)$_2$]·2DMF.

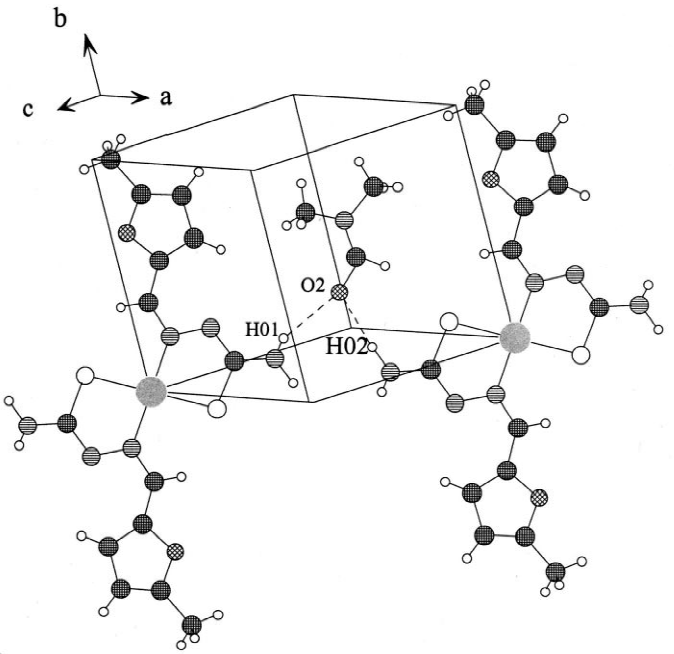

Fig. 2. Hydrogen bonding in [Ni(M5FTSC)$_2$]·2DMF X-ray structure.

the region 440–450 cm^{-1} due to ν(Ni–N) is another indication of the involvement of nitrogen of the azomethine group in coordination [5,25]. In the spectra of $[Ni(M5HFTSC)_2Cl_2]$ and $[Ni(M5HFTSC)_2Br_2]$ several bands were observed in the region 220–280 cm^{-1}, corresponding to nickel–chloride and nickel–bromide stretching vibrations [7,10].

On the other hand their electronic spectra show three bands at 8165, 13985 and 29678 cm^{-1} for the chloride complex and at 7875, 13160 and 23950 cm^{-1} for the bromide complex. The use of König's relation [26] lead to relative values of 10 Dq: 8165 cm^{-1} (Cl^-) and 7875 cm^{-1} (Br^-). There are no significant differences between experimental and calculated values of ν_1, ν_2 and ν_3. These values are in good agreement with those of trans dihalogeno octahedral structures [27].

3.3. Biological test

In a previous study [28], it was found that the ligand furfural thiosemicarbazone was a very active fungicide against phytopathogenic fungi such as *Alternaria tenuis* and *Helminthosporium sativum* but the combined activity of the ligand with that of cobalt was lower than expected. In this study, fungitoxicity of $[Ni(M5HFTSC)_2Cl_2]$ and $[Cu(M5HFTSC)Cl_2]$ complexes has been evaluated against two important human pathogen fungi: the filamentous fungus *A. fumigatus* and the yeast *C. albicans* (Table 3). In contrast to the previous study, no antifungal activity for the ligand was found, however, it was observed that after complex formation with nickel and copper, the combined activities were not modified in comparison to the activities of free metals. Eventually, our study of toxicity on mice showed that coordination to nickel and copper did not diminish the toxicity of free metals. Nevertheless, a slight effect of copper complex on the growth of *C. albicans* can be noticed. It may be concluded that complexation of furfural thiosemicarbazone with nickel or copper had no effect on biological activities of the corresponding free metals.

Our results are in agreement with other authors who demonstrated no antifungal activity against *Aspergillus niger* and *Paecilomyces variotii* for derived salicylaldehyde thiosemicarbazones with copper(II) [29]. Other studies [7,30] reported that complexes of acetylpyridine ethylthiosemicarbazone with transition metals like iron(III), cobalt(II) and (III), nickel(II), copper(II), zinc(II), cadmium(II) or mercury(II) had little or no activities against previous fungi. Recently, de Souza et al. [31] showed that 2-acetylpyridine 3-hexamethylene-iminylthiosemicarbazone complexes of zinc(II) or tin(IV) have no activity against *A. niger* and only modest activity against *P. variotii*.

4. Supplementary materials

Crystallography data have been deposited with the CCDC (12 Union Road, Cambridge, CB2 1EZ, UK) and are available on request quoting the deposition numbers CCDC 152338 and 152339.

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Table 3
Biological activities of free metals and metal complexes

Compounds	Antifungal activity MIC_{80} values ($\mu g\ ml^{-1}$)[a]		Toxicity in mice LD_{50} ($\mu g\ kg^{-1}$)[b]
	A. fumigatus	*C. albicans*	
Amphotericin B[c]	8	1	ND
M5FTSC	125	>250	ND
$CuCl_2 \cdot 2H_2O$	8	250	23
$[CuCl_2(M5FTSC)]$	16	32	25
$NiCl_2 \cdot 6H_2O$	125	16	7.4×10^3
$[NiCl_2(M5FTSC)]$	>250	16	10^4

[a] MIC_{80}: The spectrophotometric MIC (minimum inhibitory concentration) endpoint was calculated from the turbidimetric data as the lowest drug concentration giving rise to an inhibition of growth equal to or greater than 80% of that of the drug-free control (MIC 80%).
[b] Dose leading to 50% dead mice 7 days after intraperitoneal injection (lethal dose).
[c] Positive control. ND, not determined.

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