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Spectral and magnetic properties and bio-activity of copper(II) clofibriates
Part I. Crystal and molecular structure of *trans*-Cu(clofibriate)$_2$(nicotinamide)$_2$

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Abstract

New copper(II) clofibriate (clof) Cu(clof)$_2$ and its compounds of composition Cu(clof)$_2$L$_2$ (where L = nicotinamide (na) or ronicol (ron)) and Cu(clof)$_2$–caffeine are reported. The characterizations were based on elemental analysis, electronic and EPR spectra, and magnetic susceptibility measurements over the temperature range 4.5–300 K. The crystal and molecular structure of Cu(clof)$_2$(na)$_2$ has been determined. The copper(II) atom is bonded in a *trans* square-planar arrangement by two N atoms of two nicotinamide molecules and one carboxylate oxygen atom from each of two clofibriate anions. The remaining two carboxylate oxygen atoms of the anions at the axial positions completed a tetragonal-bipyramidal geometry. On the basis of spectral and magnetic properties structures of the compounds were proposed. The antimicrobial effects have been tested on various strains of bacteria, yeasts and filamentous fungi.

Keywords: Crystal structures; Biological activity; Copper complexes; Clofibriate complexes

1. Introduction

Copper ions play a vital role in a number of widely differing biological processes, and their interaction with drugs administered for therapeutic reasons is of considerable interest. Propionic acid and some of its derivatives also play an important role in biological processes, and a number of copper(II) propionates have been investigated [1]. Clofibric acid {2-(4-chlorophenoxy)-2-methylpropionic acid} is a derivative of propionic acid for which only Cu(clof)$_2$(2-ampy) (2-ampy = 2-aminopyridine) has been prepared and studied by X-ray analysis [2]. In this paper we investigate the preparation of caffeine (caf), nicotinamide (na) and ronicol {3-pyridylcarbinol} (ron) compounds of copper(II) clofibriate. The complexes were characterized by elemental analysis, electronic and EPR spectra, and magnetic susceptibility measurements over the temperature range 4.5–300 K. The crystal and molecular structure of Cu(clof)$_2$(na)$_2$ was determined. The X-ray data are compared and discussed with those found in familiar Cu(RCOO)$_2$(LN)$_2$ compounds with the CuO_4N_2 chromophore [3].

Bioactivity of the complexes was tested on *Staphylococcus aureus*, *Escherichia coli*, *Candida parapsilosis*, *Candida albicans*, *Rhizopus oryzae*, *Botrytis cinerea*, *Alternaria alternata* and *Microsporum gypseum*.

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2. Experimental

2.1. Preparative

Sodium clofibriate solution was prepared from an aqueous solution of 0.40 g NaOH (0.01 mol) by addition of 2.15 g (0.01 mol) of clofibric acid followed by boiling. The partially evaporated solution was filtered hot and the filtrate left at room temperature (r.t.). White sodium clofibriate slowly precipitated, was isolated and dried at r.t. The anhydrous salt of copper(II) clofibriate was prepared by reaction of an aqueous solution of sodium clofibriate (2.37 g, 0.01 mol, pH adjusted to 4.5–5.0, using the free acid) with an aqueous solution of copper(II) sulfate in the molar ratio 2:1. The solution was left to crystallize at r.t. The green–blue precipitate was collected, washed with cold water and dried at r.t. *Anal.* Found: C, 49.1; H, 4.2, Cu, 12.9. *Anal.* Calc. for $Cu(clof)_2$: C, 48.94; H, 4.40; Cu, 12.94%.

The caffeine complex was prepared by adding the ligand (caf, 1.94 g, 0.01 mol) to copper(II) clofibriate (0.01 mol) in hot methanol with a small amount of the free acid. The mixture was stirred, filtered and left to cool and stand at r.t. A green product precipitated, was collected and recrystallized from methanol to give air-stable green microcrystals. *Anal.* Found: C, 50.0; H, 4.35; Cu, 9.25; N, 8.2. *Anal.* Calc. for $Cu(clof)_2(caf)$: C, 49.10; H, 4.4; Cu, 9.28; N, 8.18%.

Table 1
Crystal data and structure refinement for $Cu(clof)_2(na)_2$

Empirical formula	$C_{16}H_{16}ClCu_{0.5}N_2O_4$
Formula weight	367.53
Temperature (K)	293(2) K
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	13.961(3)
b (Å)	10.518(2)
c (Å)	11.857(2)
β (°)	108.16(3)
Volume (Å^3)	1654.4(6)
Z	4
D_{calc} (Mg m^{-3})	1.476
Absorption coefficient (mm^{-1})	2.878
$F(000)$	758
Crystal size (mm)	$0.15 \times 0.15 \times 0.10$
2θ Range for data collection (°)	6.1–58.2
Index ranges	$-18 \le h \le 18$, $-14 \le k \le 7$, $-16 \le l \le 16$
Reflections collected/unique	11 004/3871 [$R_{int} = 0.0303$]
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	3623/0/278
Goodness-of-fit on F^2	1.096
Final R indices [$I > 2\sigma(I)$]	$R = 0.0461$, $wR_2 = 0.1153$
R indices (all data)	$R = 0.0489$, $wR_2 = 0.1192$
Largest difference peak and hole (e Å^{-3})	0.588 and −0.612

Blue compounds of composition $Cu(clof)_2(LN)_2$ (L = nicotinamide or ronicol (3-pyridylcarbinol)) were prepared by adding LN in excess to a methanol solution of $Cu(clof)_2$ and boiling. The reaction mixture was filtered off and left to stand at r.t.

The blue impure products were recrystallized from methanol to give air-stable crystals. *Anal.* Found: C, 51.8; H, 4.4; Cu, 8.7; N, 7.7. *Anal.* Calc. for $Cu(clof)_2(na)_2$: C, 52.28; H, 4.39; Cu, 8.64; N, 7.62%.

Anal. Found: C, 57.5; H, 4.6; Cu 9.0; N, 4.0. *Anal.* Calc. for $Cu(clof)_2(ron)_2$: C, 57.60; H, 4.55; Cu 8.96; N, 3.95%.

2.2. Spectroscopic studies

Electronic spectra in the region 10–28 kK were measured with a Perkin–Elmer 450 spectrophotometer using a Nujol suspension. EPR spectra of microcrystalline samples were run on a Varian model E4 spectrometer at r.t.

2.3. Magnetic susceptibilities

Measurements were made in the range 4.5–300 K for $Cu(clof)_2(na)_2$ and 79–300 K for all remaining compounds by the Gouy method using mercury tetrathiocyanatocobaltate(II) as a calibrant [4]. The molar susceptibilities were corrected for diamagnetism using Pascal's constant [5] and t.i.p. (N_α) of 60×10^{-6} cm^3 mol^{-1} per copper atom. The effective magnetic moments were calculated from the expression

$$\mu_{eff} = 2.83\ (\chi_M^{corr} \times T)^{0.5}$$

2.4. Crystallography

Data collection and cell refinement were carried out using Kuma KM4 diffractometer software [6]. Intensity data were corrected for Lorenz and polarization factors. The structure was solved by the heavy atom method with SHELXS-86 [7], and subsequent Fourier synthesis using SHELXL-97 [8], anisotropic thermal parameters were refined for all non-hydrogen atoms. Geometrical analysis was performed using SHELXL-97 [8]. The structure was drawn using ORTEP [9]. The final parameters after refinement are summarized in Table 1. Selected inter-atomic distances and bond angles are given in Table 2.

2.5. Bio-tests

The antimicrobial action of the compounds under investigation was evaluated by a microdilution method [10] using G^+ bacteria *S. aureus* (CCM 3824). The effects of these compounds on the yeasts *C. parapsilosis* and *C. albicans* (isolated from human patients) were

Table 2
Selected bond lengths (Å) and angles (°) for $Cu(clof)_2(na)_2$ [a]

Cu–O(1)	1.994(2	Cu–N(1)	1.995(2)
Cu–O(2)	2.614(2)	O(1)–C(1)	1.280(2)
O(2)–C(1)	1.246(2)	N(1)–C(15)	1.348(3)
N(1)–C(11)	1.345(2)		
O(1)–Cu–O(1) # 1	180.0	O(1)–Cu–N(1)	88.30(6)
O(1)–Cu–N(1) # 1	91.70(6)	N(1)–Cu–N(1) #	180.0
C(15)–N(1)–Cu	121.0(2)	C(11)–N(1)–Cu	120.1(2)
O(2)–C(1)–O(1)	122.5(2)	C(11)–N(1)–C(15)	118.8(2)

[a] Symmetry transformations used to generate equivalent atoms: # 1 $-x, -y, -z+1$.

determined by the macrodilution method in L-shaped tubes [11]. The cultures of the bacteria and yeasts were incubated under vigorous shaking.

The efficiency of prepared derivatives on filamentous fungi *R. oryzae* (obtained from the Collection of Microorganisms of the Slovak Technical University; *B. cinerea* (CCMF-16); *A. alternata* (CCMF-128) and *M. gypseum* (isolated from human patients), were tested by macrodilution technique on solidified broth medium during static culturing [11].

Chromatographically pure compounds were dissolved in dimethyl sulfoxide, its final concentration never exceeded 1.0 vol% in either control or treated samples. Concentration of solutions, 1.25–5 mmol l^{-1} for bacteria and yeasts and 1.25–10 mmol l^{-1} for filamentous fungi, was used in experiments.

The antimicrobial activity was characterized by the IC_{50} values (concentration of a derivative which in comparison to the control inhibits the growth of microorganisms to 50%) and MIC values (minimal inhibitory concentration of a derivative which inhibits microbial growth by 100%). The IC_{50} and MIC values were read from toxicity curves.

MIC experiments on subculture dishes were used to assess the minimal microbicidal concentration (MMC). Subcultures were prepared separately in Petri dishes containing competent agar medium and incubated at 30°C for 48 h (bacteria, yeasts) and at 25°C for 96 h (filamentous fungi). The MMC values were taken as the lowest concentration that showed no visible growth of microbial colonies in the subculture dishes.

The effect of $Cu(clof)_2(caf)$ on energy requiring processes in *P. aeruginosa* was determined by the incorporation of [^{14}C] precursors into the nucleic acids and proteins. The microorganism *P. aeruginosa* 9/93 was isolated from a patient suffering from nosocomial infection. The bacterial suspension (0.4 ml, $A_{600} = 0.5$) was inoculated into 10 ml of the synthetic medium and was incubated under conditions of intensive aeration at 37°C up to the logarithmic phase of growth ($A_{600} =$ 0.20). 100 μl of $Cu(clof)_2(caf)$, dissolved in dimethyl sulfoxide (final concentration ranging 0–5 mmol l^{-1}) was added to 1 ml of cell suspension ($A_{600} = 0.20$), and the cells were preincubated for 10 min with intensive aeration at 37°C. 5 μl of [^{14}C] precursors were then added to the tubes. The specific radioactivity of stock solutions was [8-^{14}C]adenine 0.25 Ci per 10 μg ml^{-1}, l-[U-^{14}C]leucine 0.1 Ci per 80 μg ml^{-1}. The incubation with [^{14}C] precursors lasted for 1 h. The tubes were transferred to an ice-bath and their contents were precipitated with 1 ml of 10% ice-cold TCA. The precipitates were filtered through membrane filters (Sartorius 0.45 μm) and the radioactivity was assayed (Scintillation counter Rack-Beta, LKB).

3. Results and discussion

The electronic spectrum of $Cu(clof)_2$ shows a broad symmetrical band at about 14 kK due to d–d transitions and a shoulder at about 24.5 kK due to charge transfer transition. The electronic spectrum of $Cu(clof)_2(caf)$ shows a band at 14.5 kK, which was identified as a d–d transition of the copper(II), and a shoulder at 27.0 kK. The shoulder is characteristic of the dimeric system of copper(II) acetate with an antiferromagnetic interaction [12]. The solid-state spectra of $Cu(clof)_2(na)_2$ and $Cu(clof)_2(ron)_2$ exhibit a broad ligand field band, maximum at about 15.4 kK, and a shoulder at about 13.0 kK for the former and 15.8 kK for the latter. These types of d-d spectrum are typical of a tetragonal arrangement around copper(II) corresponding to electron transfer from the one-electron orbital state $d_{x^2-y^2}$ [13].

The EPR spectrum of $Cu(clof)_2$ is of the isotropic type with $g_{iso} = 2.09$. The EPR spectrum of $Cu(clof)_2(na)_2$ is of the axial type with $g_\perp = 2.04$, $g_\parallel = 2.30$ and $g_{av} = 2.13$. This points to a structure having a value of effective spin $S = 1/2$ and a ground state $d_{x^2-y^2}$. All the compounds thus seem to possess an octahedral stereochemistry with differing degrees of tetragonal distortions about the copper(II) atom.

The EPR spectrum of $Cu(clof)_2(caf)$ showed an absorption band typical of an axially symmetric dimeric species [14]. The powder of the compound shows absorption features at both low (H_{Z1}) and high (H_{Z2}) fields, and an asymmetric absorption near 4500 G (H_{T2}). One is missing, because $|D| > h\nu$ at the X-band frequency. The spectrum can be interpreted using a spin Hamiltonian for axial symmetry

$$H = g_\parallel \beta H_Z S_Z + g_\perp (H_X S_X + H_Y S_Y) + D(S_Z^2 + 2/3)$$

with $S = 1$ for the thermally accessible triplet state and the other symbols have their usual meaning. The values obtained for the spin Hamiltonian parameters are: $g_\perp = 2.06$; $g_\parallel = 2.32$, $g_{av} = 2.15$; $|D| = 0.382$ cm^{-1}. The $|D|$ value is large compared to the magnetic quantities (~ 3.00 G), but small compared to the vibration fre-

Table 3
Magnetic data for $Cu(clof)_2$ (**1**) and $Cu(clof)_2(ron)_2$ (**2**)

	1		**2**	
T (K) [a]	$\chi_M^{corr} \times 10^5$ (cm^3 mol^{-1})	μ_{eff} (BM)	$\chi_M^{corr} \times 10^5$ (cm^3 mol^{-1})	μ_{eff} (BM)
79	314	1.41	493	1.77
115	254	1.53	336	1.76
157	230	1.70	275	1.86
190	204	1.76	228	1.86
247	174	1.85	182	1.90
273	160	1.87	164	1.89
299	143	1.85	147	1.88

[a] Selected from 20 experimental points; (1) $M_r = 490.83$; diamagnetic correction $+Na \times 10^{-6}$ cm^3 mol^{-1}; $\Delta = 253$; (2) $M_r = 709.03$; $\Delta = 384$.

quencies. The values are comparable to those found in dimeric copper(II) carboxylates [1].

The magnetic susceptibility results for polycrystalline samples of $Cu(clof)_2$, $Cu(clof)_2(ron)_2$, between 79 and 300 K, and $Cu(clof)_2(na)_2$ between 4.5 and 300 K, obey the Curie–Weiss law

$$\chi_M^{corr} = C/(T - \Theta)$$

where the Curie constant $C = Ng^2\beta^2S(S+1)/3K$ and $S = 1/2$. The temperature variation of magnetic susceptibility and magnetic moments for $Cu(clof)_2$ and $Cu(clof)_2(ron)_2$ are given in Table 3. The values of the magnetic moment at 299 K of 1.85 and 1.8 BM, respectively, are well over the 1.73 BM for one unpaired electron, indicating spin–orbital contributions which are somewhat larger in $Cu(clof)_2(ron)_2$ than in $Cu(clof)_2$. As can be seen, the magnetic moments are dependent on temperature in both compounds, decreasing as the temperature drops. The change is greater for $Cu(clof)_2$ than for $Cu(clof)_2(ron)_2$. The best values of

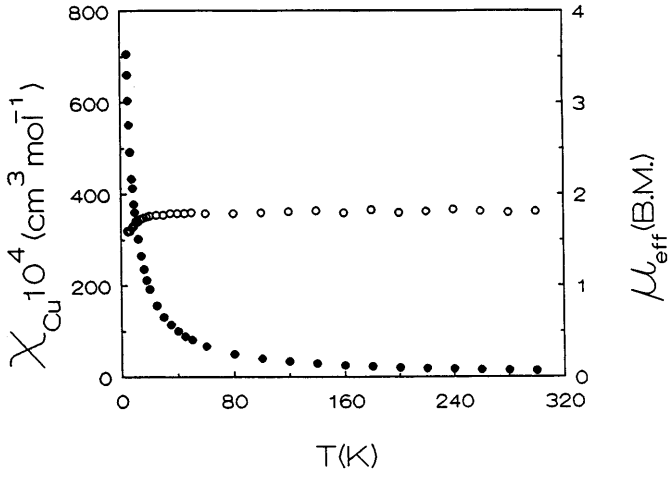

Fig. 1. Magnetic susceptibility (●) and magnetic moment (○) versus temperature for $Cu(clof)_2(na)_2$.

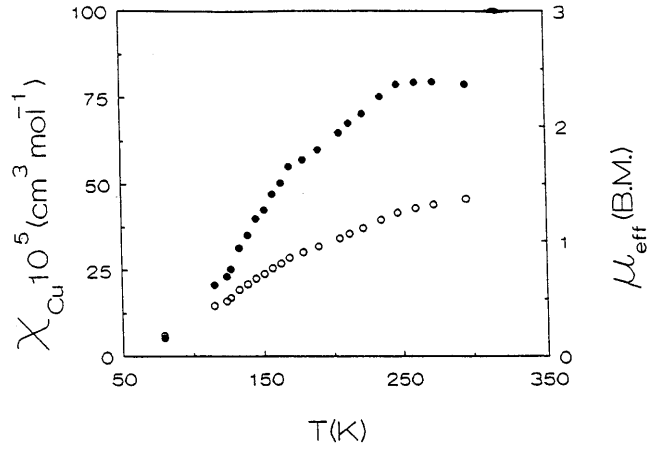

Fig. 2. Magnetic susceptibility (●) and magnetic moment (○) versus temperature for $Cu(clof)_2(caf)$.

the Curie (C) constant of 0.64(1) cm^3 mol^{-1} and Weiss (Θ) constant of $-127(5)$ K for the former differ from the values of 0.487(5) cm^3 mol^{-1} and $-23.6(6)$ K, respectively observed for the latter. The negative Weiss constants indicate an antiferromagnetic interaction in both derivatives, being much greater in the former than the latter.

The temperature variation of magnetic susceptibility and magnetic moment for $Cu(clof)_2(na)_2$ are shown in Fig. 1. For this derivative the magnetic moment of 1.81 BM at 300 K drops to 1.60 BM at 4.5 K. The best values of the C and Θ are 0.411(5) cm^3 mol^{-1} and $-1.4(1)$ K, respectively. The very small negative values of the Weiss constant indicate a very weak antiferromagnetic interaction. The molar susceptibility of $Cu(clof)_2(caf)$ and magnetic moment temperature dependence are shown in Fig. 2. The temperature variable magnetic susceptibility data can be described by the equation:

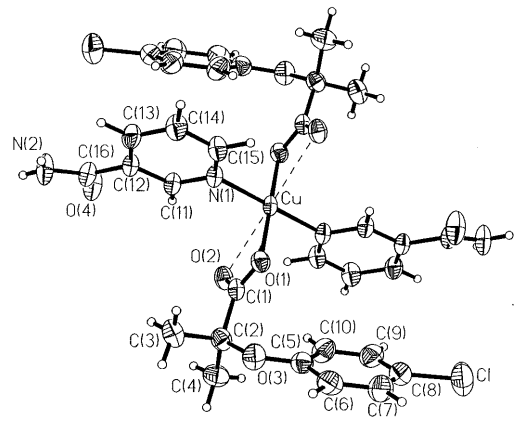

Fig. 3. Perspective view of complex $[Cu(clof)_2(na)_2]$, with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

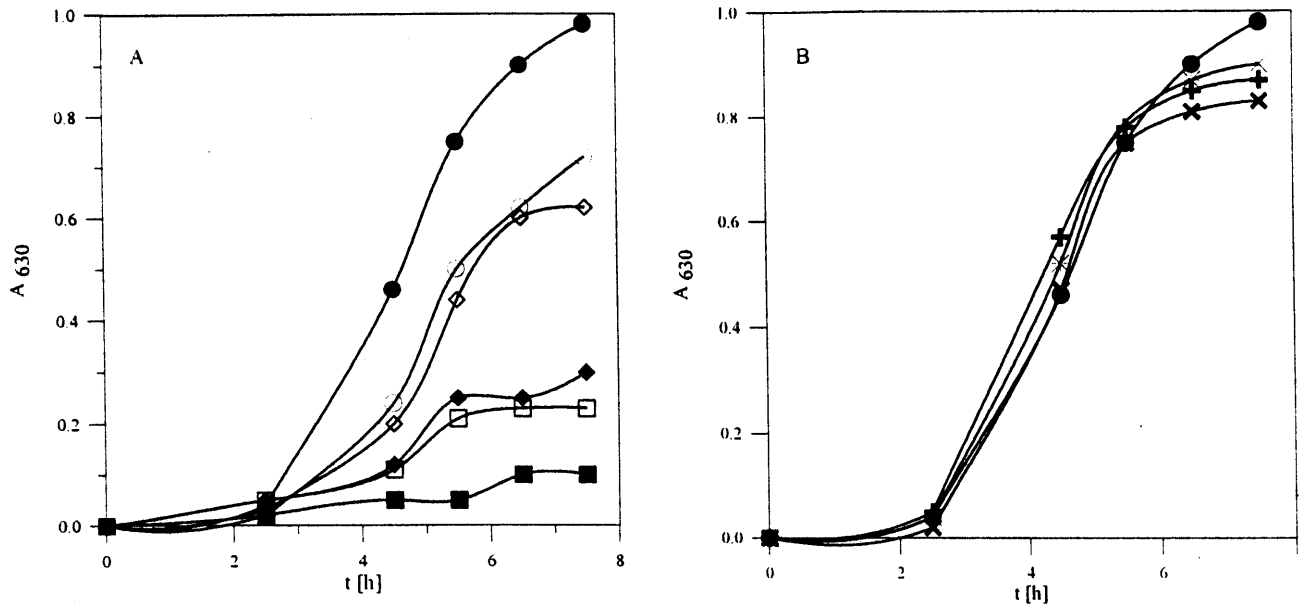

Fig. 4. Growth of *S. aureus* in the presence of copper(II) compounds and the ligands in concentration of 5 mmol l^{-1}. A: ○, Hclof; ■, $Cu(clof)_2$; ◆, $Cu(clof)_2(ron)_2$; □, $Cu(clof)_2(caf)$; ◇, $Cu(clof)_2(nia)_2$. B: +, ron; ×, caf; *, nia; ●, control (1% DMSO).

$$\chi_M^{corr} = Ng^2\beta^2/3kT(1/(1 + 1/3\, e^{-2J/kT}))$$

where χ_M^{corr} was also corrected for t.i.p. of 60×10^{-6} $cm^3\ mol^{-1}$ per copper(II) atom, and the other symbols have their usual meaning. The spectroscopic splitting factor $g_{av} = 2.15$ was obtained from the EPR spectrum and used in the least-squares fitting procedure to give a best-fit for $-2J$ of 334 ± 10 cm^{-1} between the thermally accessible singlet state ($S = 0$) and triplet state ($S = 1$). This is similar to values found in related copper(II) carboxylates [1]. From the above it may reasonably be supposed that the caffeine compound has a dimeric structure $Cu_2(clof)_4(caf)_2$ with a distorted square-pyramid around each copper(II) atom. Each of these is coordinated to four oxygen atoms of the clofibriate anions (in plane) in a *syn–syn* fashion, together with a nitrogen atom of caffeine at the apex.

On the basis of the spectral and magnetic data, a tetragonal bipyramidal geometry is deduced for remaining compounds. It is suggested that in $Cu(clof)_2$ the clofibriate anions use both carboxylate oxygen atoms

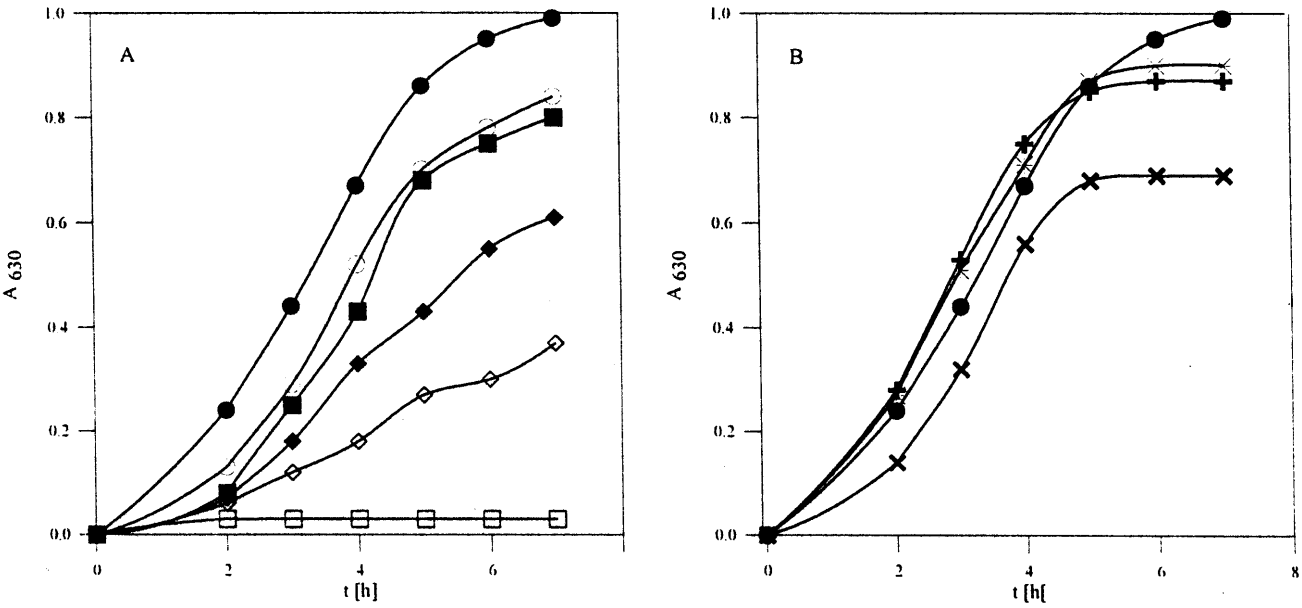

Fig. 5. Growth of *E. coli* in the presence of copper(II) compounds and the ligands in concentration of 5 mmol l^{-1}. A: ○, Hclof; ■, $Cu(clof)_2$; ◆, $Cu(clof)_2(ron)_2$; □, $Cu(clof)_2(caf)$; ◇, $Cu(clof)_2(nia)_2$. B: + ron; × caf; *, nia; ●, control (1% DMSO).

Table 4
Antifungal activity of copper(II) compounds and free by the numerical values of IC_{50} (mmol l^{-1}) and MIC (mmol l^{-1})

Compound	Filamentous fungi								Yeasts			
	R. oryzae		*B. cinerea*		*A. alternata*		*M. gypseum*		*C. parapsilosis*		*C. albicans*	
	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC
Hclof	>10	>10	6	>10	7	>10	3.3	5 [b]	>5	>5	>5	>5
ron	>10	>10	>10	>10	>10	>10	>10	>10	>5	>5	>5	>5
caf	10	>10	6.2	>10	10	>10	<2.5	≤2.5 [b]	>5	>5	>5	>5
na	>10	≥10	>10	>10	>10	>10	>10	>10	>5	>5	>5	>5
$Cu(clof)_2$	>10	>10	>10	>10	>10	>10	<2.5	≤2.5 [b]	2.5	>5	4	>5
$Cu(clof)_2(ron)_2$	5	>10	4	>10	4	>10	1.4	≤5 [b]	3.5	>5	>5	>5
$Cu(clof)_2(caf)$	2.5	5 [a]	3	10 [a]	3	>10 [a]	<2.5	≤2.5 [b]	2.5	>5	1.5	5 [a]
$Cu(clof)_2(na)_2$	<1.25	<1.25 [a]	<2.5 [a]	>10	<2.5 [a]	>10 [a]	2.5	≤5 [b]	2.7	>5	2.2	5 [a]

[a] Microstatical effect.
[b] Microbicidal effect.

for bonding to the copper(II) atoms in the polymeric structure. In the ron adduct in addition to the clofibriate anions both a pyridine ring atom and a carbinol oxygen atom act as donors to copper(II), as in the derivative $Cu(niflumate)_2(ron)_2$ for which the X-ray structure is known [15]. In this example the ron groups are ambidentate, linking the copper(II) atoms into infinite chains.

The $Cu(clof)_2(na)_2$ was also studied by the X-ray method and its crystal structure is shown in Fig. 3. As can be see the copper(II) atom is bonded in a *trans* square-planar arrangement to the nitrogen atoms of two nicotinamide molecules (Cu–N(1) = 1.995(2) Å) and one carboxylate oxygen atom from each of two clofibriate anions (Cu–O(1) = 1.994(2) Å. The remaining two carboxylate oxygen atoms which are weakly bonded to the copper (Cu–O(2) = 2.614(2) Å) and the direction of the Cu–O(2) bonds lie at 60.1° from the normal to the CuO_2N_2 plane completed a tetragonal-bipyramidal coordination. The copper(II) atom lies on a crystallographic center of symmetry.

Bond distances and angles are listed in Table 2. The in-plane O(1)–Cu–N(1) angles are 88.30(6) and 91.70(6)° and out-off-plane O(2)–Cu–N(1) angles are 92.30(6) and 87.70(6)°, but because of the small bite of the carboxylate group the angle between the short Cu–O(1) bond the long Cu–O(2) bond is only 55.49(5)°. The oxygen atom which is most strongly bonded to the copper(II) atom has a C(1)–O(1) bond distance of 1.280(2) Å which is longer, than the other C(1)–O(2) bond, 1.246(5) Å, of the carboxylate unit.

There are over 20 examples [3] of the general formula $Cu(RCOO)_2(LN)_2$ in which bidendate RCOO ligands with two monodendate N donor ligands build up a tetragonal-bipyramidal coordination about the Cu(II) atom (CuO_4N_2) with a different degree of distortion. In this series is a relationship between Cu–L bond distances and metallocyclic rings. While Cu–N bond distance elongated with an increasing size of metallocyclic ring, in the sequence: 2.00 Å versus 54.2° (four-) < 2.02 Å versus 75.0° (five-) < 2.06 Å versus 89.3° (six-membered O–Cu–O metallocyclic ring). The difference between two Cu–O bond distances of the respective chelate, decrease in the same sequence: 0.76 Å (mean 1.97 and 2.73 Å) > 0.40 Å (1.94 and 2.34 Å) > 0.265 Å (2.01 and 2.275 Å).

Antibacterial activities of copper(II) compounds as well as of free ligands are shown in Figs. 4 and 5. As can be see in Figs. 4 and 5 the ligands (except caf) have almost no influence on the growth of the respective bacteria. Clofibrinic acid has an approximately 20% of inhibition (Figs. 4 and 5). An expressive increase of antimicrobial activity was attained for copper(II) clofibriates. The inhibition activity against the G^+ bacterium *S. aureus* (Fig. 4) increases in the order: na < ron < caf < Hclof < $Cu(clof)_2(na)_2$ < $Cu(clof)_2(ron)_2$ < $Cu(clof)_2$-(caf) < $Cu(clof)_2$; and against G^- bacteria *E. coli* in the order: na < ron < Hclof < $Cu(clof)_2$ < caf < $Cu(clof)_2$-$(ron)_2$ < $Cu(clof)_2(na)_2$ < $Cu(clof)_2(caf)$.

As can be seen, the binuclear $Cu(clof)_2(caf)$ is most active against both types of bacterium G^+ and G^-, while a polymeric $Cu(clof)_2$ is dominant against G^+ bacteria but not against G^- bacteria.

Antifungal activities of the compounds are summarized in Table 4. As can be seen, the inhibition activities increase in the sequences: Hclof = ron = na = Cu-$(clof)_2$ < caf < $Cu(clof)_2(ron)_2$ < $Cu(clof)_2(caf)$ < Cu-$(clof)_2(na)_2$ against *R. oryzae*; na = ron = $Cu(clof)_2$ < Hclof < caf < $Cu(clof)_2(ron)_2$ < $Cu(clof)_2(caf)$ < Cu-$(clof)_2(na)_2$ against *B. cinerea*; na = ron = $Cu(clof)_2$ < caf < Hclof < $Cu(clof)_2(ron)_2$ < $Cu(clof)_2(caf)$ < Cu-$(clof)_2(na)_2$ against *A. alternata*; na = ron = Hclof < $Cu(clof)_2(na)_2$ < caf < $Cu(clof)_2(caf)$ = $Cu(clof)_2$ < Cu-$(clof)_2(ron)_2$ against *M. gypseum*; and na = ron = caf = Hclof < $Cu(clof)_2(na)_2$ < $Cu(clof)_2(caf)$ < $Cu(clof)_2$ against *C. parapsilosis*.

In general, the inhibition activity of the $Cu(clof)_2(na)_2$ complex against fungi is most effective. The $Cu(clof)_2(caf)$ complex shows the highest inhibition activity against yeasts (*C. parapsilosis*, *C. albicans*).

The effect of $Cu(clof)_2(caf)$ on the synthesis of nucleic acids and proteins in growing cells of *P. aeruginosa* has also been studied. The values IC_{50} and R represent the first fundamental biochemical information about the bacterial activity of tested compound. In the case of $Cu(clof)_2(caf)$, the incorporation of [^{14}C]adenine (IC_{50}, adenine 0.38 mmol l^{-1}), was more inhibited which indicated that the synthesis of nucleic acids was more affected than the synthesis of proteins (IC_{50}, leucine 0.64 mmol l^{-1}). The R value ($R = IC_{50}$ adenine: IC_{50} leucine) of 0.59 is also typical for other biologically active substances interfering with cellular energy metabolism [16,17].

4. Supplementary material

Supplementary material including atomic coordinates ($\times 10^4$), anisotropic displacement parameters for non-hydrogen atoms (Å $\times 10^3$) has been deposited at the Cambridge Crystallographic Data Centre, CCDC 142025 for compound $Cu(clof)_2(na)_2$. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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