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Synthesis, characterization and bioactivity of mixed-ligand Cu(II) complexes containing Schiff bases derived from *S*-benzyldithiocarbazate and saccharinate ligand and the X-ray crystal structure of the copper-saccharinate complex containing *S*-benzyl-β-*N*-(acetylpyrid-2-yl)methylenedithiocarbazate

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Abstract

Mixed-ligand complexes of general formula, [Cu(NNS)(sac)] (NNS′ = *S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate, NNS″ = *S*-benzyl-β-*N*-(2-benzoylpyrid-2-yl)methylenedithiocarbazate and NNS‴ = *S*-benzyl-β-*N*-(6-methylpyrid-2-yl)methylenedithiocarbazate, sac = the saccharinate anion) have been synthesized by reacting $[Cu(sac)_2(H_2O)_4]\cdot 2H_2O$ with the appropriate ligands in ethanol and characterized by various physico-chemical techniques. Magnetic and spectral evidence indicate that the complexes are four-coordinate in which the Schiff bases coordinate as NNS ligands and the sac- anion coordinates as a unidentate N-donor ligand. An X-ray crystallographic structural analysis of [Cu(NNS′)(sac)] shows that the complex has a distorted square-planar geometry with the Schiff base coordinated to the copper (II) ion as a uninegatively charged tridentate chelating agent via the pyridine nitrogen atom, the azomethine nitrogen atom and the thiolate sulphur atom while the fourth coordination position is occupied by the N-bonded saccharinate anion. The complexes have been evaluated for their biological activities against selected pathogens and cancer cell lines. They display weak activity against the pathogenic bacteria and fungi. The complexes were highly active against the leukemic cell line (HL-60) but only [Cu(NNS′)(sac)] was found to exhibit strong cytotoxicity against the ovarian cancer cell line (Caov-3). All complexes were inactive against the breast cancer cell line (MCF-7).

Keywords: Copper (II) complexes; Dithiocarbazate Schiff base; Saccharin complexes; *S*-benzyldithiocarbazate; Tridentate NNS Schiff bases

1. Introduction

Saccharin (1,2-benzisothiazoline-3-(2H)one 1,1-dioxide) was widely used as an artificial sweetener, especially in the 1970s' but was later banned as a food additive when preliminary studies indicated that high doses caused urinary bladder carcinoma [1] in mice. The ban was, however, lifted by the US FDA in 1991 when further studies disproved the earlier findings [2].

Because of the commercial importance of the saccharinate anion (Fig. 1) as a non-caloric sweetener and its ability to act as a polyfunctional ligand, many studies on its metal complexes, especially that of first row transition metals, have been carried out [3–12].

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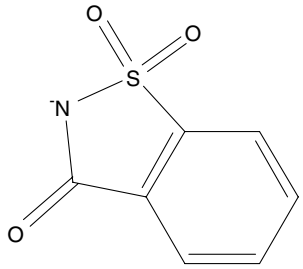

Fig. 1. The structure of the saccharinate anion.

A suggestion has been made that the importance of saccharin complexes lies in the potential use of saccharin as an antidote for metal poisoning [11,13]. Metal complexes of saccharin could also play a role in understanding human metabolic processes [6].

Since very little information has been reported on mixed-ligand complexes containing saccharin and tridentate sulfur–nitrogen chelating agents as co-ligands, we report herein the synthesis, characterization and bioactivity of mixed-ligand copper (II) complexes of three HNNS ligands formed between *S*-benzyldithiocarbazate with 2-acetylpyridine, 2-benzoylpyridine and 6-methyl pyridine-2-aldehyde (Fig. 2) with saccharinate anion as a co-ligand.

2. Experimental

All chemicals and solvents were of analytical grade and were used as received. The *S*-benzyldithiocarbazate (SBDTC), its Schiff bases (HNNS′, HNNS″ and HNNS‴ and $[Cu(sac)_2(H_2O)_4]\cdot 2H_2O$ were prepared by the following literature methods [6,14–16].

2.1. General method of synthesis of the complexes

$[Cu(sac)_2(H_2O)_4]\cdot 2H_2O$ [6] (0.536 g, 0.001 mol) dissolved in boiling water (25 ml) was mixed with a solution of the appropriate Schiff base (0.001 mol) in ethanol (40 ml), and the resulting mixture was heated on a water bath for 30 min. On standing overnight, the mixture yielded crystalline complexes which were filtered, washed with ethanol and dried in a desiccator over silica gel for 24 h. Yield: (ca. 75%). Crystals of [Cu(NNS′)(sac)] (where NNS′ = *S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate) suitable for X-ray diffraction analysis were obtained from an acetonitrile solution.

2.2. Physical measurements

Microanalyses for carbon, hydrogen, nitrogen and sulphur were carried out using a LECO CHNS-932 instrument. The IR spectra as KBr pellets were recorded using a Perkin–Elmer FT IR 1750X spectrophotometer (4000–400 cm^{-1}). The molar conductance of 10^{-3} M solutions of the metal complexes in DMSO were measured at 29 °C using a Jenway 4310 conductivity meter and a dip-type cell with a platinized electrode. Magnetic susceptibilities at room temperature were measured using a Sherwood Scientific MSB-AUTO magnetic susceptibility balance. The UV–Vis spectra were run on a Shimadzu UV-2501 PC Recording Spectrophotometer (900–200 nm).

2.3. X-ray structure determination of [Cu(S-benzyl-β-N-(2-acetylpyrid-2-yl)methylenedithiocarbazate)(sac)]

Beautiful green-brown crystals of the metal complex were formed after the acetonitrile solution was allowed to slowly evaporate for a few weeks. A selected crystal was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cyrosystems CYROSTREAM unit. Diffraction data were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromated Mo Kα radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package [17]. The structures were solved using the direct-methods program [18] to locate all non-hydrogen atoms. Subsequent full-matrix least-squares refinement on *F* was carried out using CRYSTALS Program Suite [19]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of refinement. A five-term Chebychev polynomial weighting scheme

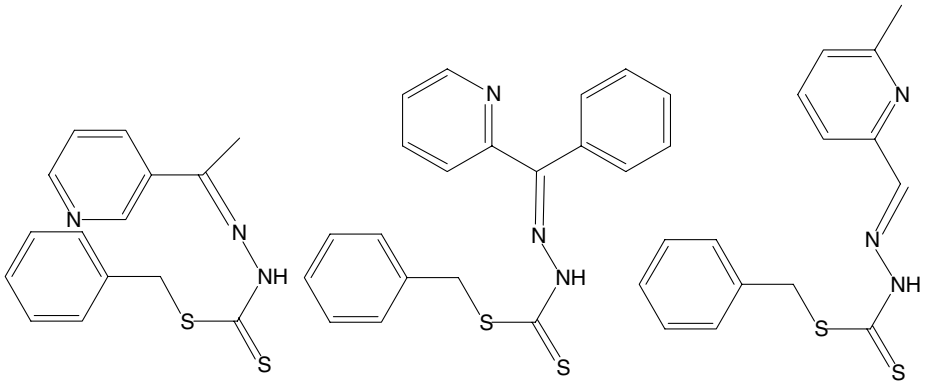

Fig. 2. Structure of HNNS′, HNNS″ and HNNS‴ ligands, respectively (in thione form).

was applied. Refinement converged satisfactorily to give $R = 0.0301$ and $R_w = 0.0360$ with residual electron density minimum and maximum of −0.49 and 0.44 e Å^{-3}. Further crystallographic and refinement details are shown in Table 3.

2.4. Bioactivity

2.4.1. Target microorganisms

Eight pathogenic microbials were used to test the biological potential of the complexes. They were *Methicillin resistant staphylococcus* (MRSA), *Bacillus subtilis* wild type (B29), *Subtilis mutant* (mutant defective DNA repair-B28), *Pseudomonas aeruginosa* (60690), *Candida albicans* (CA), *Aspergillus ochraceous* (398), *Saccaromyces ceciricaee* (20341) and *Candida lypolytica* (2075). The source of microbes and culture maintenance were as previously described [20].

2.4.2. Qualitative antimicrobial assay

Antimicrobial activity of each sample was qualitatively determined by a modified disc diffusion method [21] as previously detailed [22]. A lawn of microorganisms was prepared by pipetting and evenly spreading inoculum (10^{-4} cm^3, adjusted turbidometrically to 10^5–10^6 cfu cm^{-3} (cfu: colony forming units) on to agar set in Petri dishes, using Nutrient agar (NA) for the bacteria and potato dextrose agar (PDA) for fungi. Whatman No. 1 filter paper discs of 6 mm diameter were impregnated with stock solution of the compound (100 mg cm^{-3}) and dried under sterile conditions. The dried discs were then placed on the previously inoculated agar surface. The plates were inverted and incubated for 24 h at 30 °C for bacteria and 37 °C for fungi. Antimicrobial activity was indicated by the presence of clear inhibition zones around the discs. Commercially available streptomycin (Sigma, USA) was used for the antibacterial control while nystatin (Sigma, USA) was used as the antifungal control.

2.4.3. Quantitative antimicrobial assay

Compounds that showed positive (>15 mm) anti-microbial inhibition with the disc diffusion assay were subjected to the broth dilution method for the quantitative measurement of microbiostatic (inhibitory) activity as described by Hufford and Clark [23]. The lowest concentration that completely inhibited visible microbial growth was recorded as the minimum inhibitory concentration (MIC, μg cm^{-3}). Streptomycin and nystatin were used as positive controls for bacteria and fungi, respectively.

2.4.4. Cytotoxic assay

The HL-60 (Human T-lymphoblastic leukemia) and MCF-7 cell lines were obtained from the National Cancer Institute, USA. The cells were cultured in RPMI-1640 (Sigma) medium supplemented with 10% fetal calf serum. Cytotoxicity was determined using the microtitration of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Sigma, USA) as reported by Mosmann [20]. Controls that contained only cells were included for each sample. Cytotoxicity was expressed as CD_{50}, i.e. the concentration that reduced the absorbance of treated cells by 50% with reference to the control (untreated cells). Doxorubicin, Tamoxifen and Cisplatin were used as standard cytotoxins.

3. Results and discussion

The reaction of $[Cu(sac)_2(H_2O)_4]$ with the Schiff bases in boiling ethanol afforded crystalline complexes containing one Schiff base and one saccharinate ligand. The physicochemical properties of the complexes together with their analytical data are shown in Table 1. The analytical data support the proposed formulations for the complexes. The complexes are sparingly soluble in most organic solvents but dissolve readily in donor solvents such as DMSO and DMF. They appear to be stable in air.

3.1. Magnetic and conductivity data

The complexes exhibit room temperature magnetic moments in the 1.8–1.87 BM range (Table 1), which is normal for a $3d^9$ metal ion in a magnetically dilute environment [8]. Their molar conductance values in DMSO (Table 1) fall in the range of 9.31–27.4 ohm^{-1} cm^2 mol^{-1} indicating that, although some dissociation of these complexes seems to occur in this solvent, the conductance values are much lower than that expected for a 1:1 electrolyte [24]. The con-

Table 1
Analytical data and physical properties of the Cu(II) complexes

Compound[a]	Colour	M.p. (°C)	Λ[b]	μ[c]	Analytical data[d] (%)				
					C	H	N	S	Cu
[Cu(NNS′)(sac)]	brown-green	212	27.41	1.87	48.11 (48.29)	3.30 (3.50)	10.37 (10.24)	17.41 (17.58)	11.35 (11.61)
[Cu(NNS″)(sac)]	dark green	230	9.31	1.80	52.42 (53.32)	3.31 (3.31)	10.22 (9.21)	14.94 (15.82)	10.41 (10.45)
[Cu(NNS‴)(sac)]	green	146	13.41	1.84	47.64 (48.30)	3.75 (3.50)	10.61 (10.24)	17.27 (17.58)	11.77 (11.61)

[a] NNS′ = *S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate, NNS″ = *S*-benzyl-β-*N*-(2-benzoylpyrid-2-yl)methylenedithiocarbazate and NNS‴ = *S*-benzyl-β-*N*-(6-methylpyrid-2-yl)methylenedithiocarbazate.
[b] Molar conductance (ohm^{-1} cm^2 mol^{-1}) of ca. 10^{-3} M solutions in DMSO.
[c] Magnetic moments at 298 K.
[d] Calculated values are given in parentheses.

ductivity data, therefore, support that both the saccharinate anion and the Schiff base are coordinated to the central copper (II) ion as uninegatively charged ligands [25].

3.2. Electronic and infrared spectra

The IR spectra of the ligands exhibit the ν(C=N), ν(N–N) and ν(CSS) bands at ca. 1580, 1050–1100 and 800–900 cm^{-1} (Table 2), respectively, which are shifted in the spectra of the metal complexes indicating coordination of the ligands to the copper (II) ions via the pyridyl nitrogen, the azomethine nitrogen and the thiolate sulphur atom. The coordination of the azomethine nitrogen to the metal is indicated by the shift of the ν(C=N) band and the ν(N=N) band to higher frequencies (Table 2). Generally, evidence of coordination of thiosemicarbazone and dithiocarbazate ligands to metal ions via the azomethine nitrogen has been based on the shifting of the azomethine C=N band of the free ligand from higher to lower wavenumbers in the spectra of the metal complexes [26]. However, shifting of this band to both higher and lower frequencies has been reported [27]. The ν(N=N) bands of all the free ligands were shifted to higher wavenumbers on complexation as a result of a reduction in the repulsion between the lone pairs of electrons on the nitrogen atoms due to coordination via the azomethine nitrogen atom [28]. The lowering of the ν(CSS) band in the spectra of the copper (II) complexes as compared to the frequencies for the free ligands indicates coordination through one of the sulphur atoms. The pyridine ring deformation mode at ca. 600 cm^{-1} in the spectra of the free ligands is shifted to higher wavenumbers in the spectra of the complexes indicating coordination of the pyridine ring nitrogen atom to the copper (II) ion. The spectra of the complexes do not exhibit the ν(NH) bands of the free ligands supporting the fact that deprotonation of the ligands occurs during their coordination to the copper (II) ion. In addition to showing the characteristic bands due to the Schiff bases, the IR spectra of the present copper (II) complexes also show the $\nu(SO_2)_{sym}$, $\nu(SO_2)_{assym}$ and ν(C=O) bands for the saccharinate ion at ca. 1150, 1290 and 1640 cm^{-1}, respectively [11,29–31]. An X-ray crystallographic structural analysis of [Cu(*S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate)(sac)] agrees with the interpretation of the above IR spectral data.

The electronic spectra of the copper (II) complexes (Table 2) exhibit intra-ligand bands attributable to $n \rightarrow \pi^*$ transition in the range 328–354 nm, $S \rightarrow Cu(II)$ charge transfer band in the 422–400 nm and a d–d band in the 700–640 nm range. The presence of the $S \rightarrow Cu(II)$

Table 3
Crystallographic data and structure refinement details for [Cu(NNS′)(sac)]

Empirical formula	$C_{22}H_{18}CuN_4O_3S_3$
Formula weight	546.15
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	$P\bar{1}$
Unit cell dimensions	
a (Å)	8.4795(2)
b (Å)	9.5364(2)
c (Å)	15.5272(4)
α (°)	97.56(9)
β (°)	92.93(1)
γ (°)	115.373(1)
Volume (A^3)	1116.50(5)
Z	2
Absorption coefficient (mm^{-1})	1.293
F(000)	558.00
Crystal size (mm)	$0.08 \times 0.12 \times 0.18$
Reflections collected/unique [R_{int}]	9001/5068 [0.0002]
Maximum and minimum transmission	0.90, 0.86
Data/restraints/parameters	4070/0/298
Goodness-of-fit on F^2	1.063
Final R indices [$I > 3D_i$]	$R = 0.0301$, $R_w = 0.0360$
Largest differential peak and hole (e $Å^{-3}$)	0.44 and −0.49

Table 2
Selected IR bands and electronic spectral data for the ligands and their copper (II)-saccharinate complexes

Compound[a]	IR bands								Electronic spectra[b]
	νNH	νCN	νNN	νCSS	$\nu_s SO_2$	$\nu_{as} SO_2$	νCO	ν(py)	$\lambda_{max}(\log\varepsilon)$ nm(L mol^{-1} cm^{-1})
HNNS′	3175w	1579m	1063s	890w				622m	339(4.4)
HNNS″	3024w 2916w	1582m	1040s	848m				600m	354(4.5)
HNNS‴	3080w 2910w	1584m	1052s	838w				608m	342(4.6)
[Cu(NNS′)(sac)(H_2O)]		1592m	1074m	816w	1154s	1294s	1674s	630m	640(2.7), 398(4.1) 328(4.6)
[Cu(NNS″)(sac)(H_2O)]		1592m	1090m	816m	1156s	1306s	1648s	607m	651(2.4), 422(3.9) 340(4.2)
[Cu(NNS‴)(sac)(H_2O)]		1592m	1057w	789m	1146s	1288vs	1641s	612m	700(2.5) 342(4.2)

[a] NNS′ = *S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate, NNS″ = *S*-benzyl-β-*N*-(2-benzoylpyrid-2-yl)methylenedithiocarbazate and NNS‴ = *S*-benzyl-β-*N*-(6-methylpyrid-2-yl)methylenedithiocarbazate.
[b] $\log\varepsilon$ (L mol^{-1} cm^{-1}) are given in parentheses.

LMCT band at ca. 420 nm in all these spectra is indicative of the coordination of the Schiff base to the copper (II) ion via the thiolate sulphur atom [32]. Such LMCT bands are common in the electronic spectra of copper (II) complexes of related tridentate NNS thiosemicarbazone ligands [33]. The presence of a d–d band in the 690–640 nm range agrees well with the position of the d–d band in the electronic spectra of other square-planar copper (II) complexes that contain the CuN_3S chromophore, some structures of which have been established by X-ray diffraction [2,10,22,34,35].

4. The structure of the [Cu(*S*-benzyl-β-*N*-(2-acetylpyrid-2-yl)methylenedithiocarbazate)(sac)] complex

The thermal ellipsoid drawing of the [Cu(NNS′)(sac)] molecule with the atom numbering scheme is shown in Fig. 3. The bond lengths and bond angles are given in Table 4. The complex crystallizes as a monomeric species. As implied by the physicochemical results, the copper (II) ion is of distorted four-coordinate geometry with the donor atoms of the Schiff base being the pyridine nitrogen atom, the azomethine nitrogen atom and the mercapto-sulphur atom. The nitrogen of the saccharinate anion occupies the fourth coordination position. The Schiff base is coordinated to the copper (II) ion in its iminothiolate form. Tautomerism of the dithiocarbazate ligand to its iminothiolate form is expected to convert the C=S bond to a single C–S bond, but the length of the C–S bond in the present complex falls between a C–S single bond and C=S double bond, indicating extensive delocalization over the C–N–N–C–S chain. This is also evident in the interatomic bond distances, C(7)–N(8) [1.295(2) Å], N(8)–N(9)[1.389(2) Å], and C(10)–N(9) [1.301(3) Å]. The C(10)–S(11) bond [1.739(19) Å] retains its partial double bond character with the length between that of a C–S single bond [1.82 Å] and a C=S double bond [1.62 Å]. It is longer than that found in

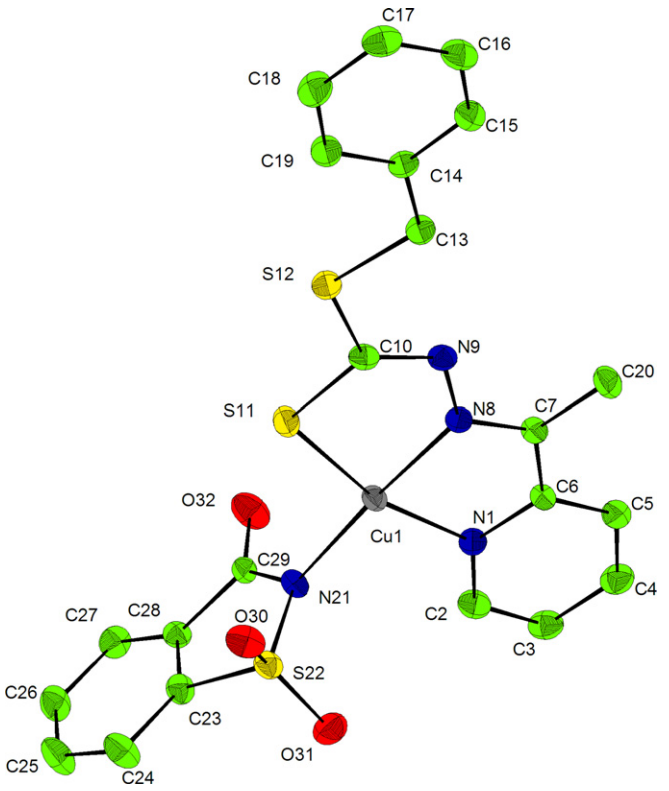

Fig. 3. ORTEP diagram of $C_{22}H_{18}CuN_4O_3S_3$ (with 50% probability displacement ellipsoids) with atomic numbering scheme.

Table 4
Selected bond lengths (Å) and bond angles for [Cu(NNS′)(sac)]

Bond lengths		Bond angles	
Cu(1)–N(1)	2.016(16)	N(1)–Cu(1)–N(1)	165.22(5)
Cu(1)–N(8)	1.958(16)	N(21)–Cu(1)–S(11)	97.51(5)
Cu(1)–S(11)	2.243(5)	N(8)–Cu(1)–S(11)	85.02(5)
Cu(1)–N(21)	1.966(16)	N(21)–Cu(1)–N(1)	96.99(7)
C(7)–N(8)	1.295(2)	N(8)–Cu(I)–N(1)	80.68(7)
N(8)–N(9)	1.389(2)	N(8)–Cu(1)–N(21)	175.76(7)
C(10)–N(9)	1.301(3)		
C(10)–S(11)	1.739(19)		

Table 5
Comparison of bond lengths in some copper (II)-saccharinate complexes

Compound[a]	Cu–N_{sac}	Cu–S	Cu–N_{py}	Cu–N_{azo}	Cu–O_{sac}	Ref.
$[Cu(pytsc)(sac)(H_2O)]\cdot 0.5H_2O$	1.974(8)	2.264(3)	2.020(8)	1.956(8)		[10]
[Cu(pysme)(sac)(MeOH)]	1.967(2)	2.295(9)	2.062(2)	1.958(2)		[35]
$[Cu(6mpsme)(sac)(H_2O)]$	2.004(2)	2.304(8)	2.113(2)	1.973(2)		[34]
$[Cu(sac)(NH_3)_4]$					2.113(8)	[37]
$[Cu(sac)(NH_3)_4]\cdot sac\cdot H_2O$	2.328(2)				2.715(2)	[37]
	2.309(2)				2.705(3)	[37]
$[Cu(sac)_2(mpy)_2]$	2.335(15)		1.9667(13)			[8]
[Cu(NNS′)(sac)]	1.966(16)	2.243(5)	2.016(16)	1.958(16)		this work
$[Cu(sac)(PPh_3)_2]\cdot CH_2Cl_2$	1.933(2)				2.130(2)	[37]
$[Cu(sac)(PPh_3)_2]\cdot \frac{3}{4}CHCl_3$	1.965(5)					[37]
trans-$[Cu(sac)_2(NH_3)_4]$	2.508(12)		2.07(12)			[37]
			2.042(12)			
$[Cu(sac)_2(H_2O)_4]\cdot 2H_2O$	2.061(2)					[2]

[a] pytsc = pyridine-2-aldehydethiosemicarbazone, pysme = pyridine-2-aldehyde SMDTC, 6mpsme = 6-methylpyridine-2-aldehyde SMDTC, mpy = 2-pyridylmethanol.

the free methylpyruvate Schiff base of SMDTC [1.652(6) Å] [25] and pyridine-2-carboxaldehydethiosemicarbazone [1.698(3) Å] [28]. The Cu–S [2.243(5) Å], Cu–$N_{azomethine}$ [1.958(16) Å} and Cu–N_{py} [2.016(16) Å] bond lengths compare well with other copper (II)-saccharinate complexes regardless of the geometry around the central Cu(II) ion, as shown in Table 5.

An examination of the bond angle data in Table 4 shows that the [Cu(NNS′)(sac)] complex does not have ideal square-planar geometry. The angles N(21)–Cu(1)–S(11), N(8)–Cu(1)–S(11), N(21)–Cu(1)–N(1) and N(8)–Cu(1)–N(1) deviate substantially from that expected for an ideal square-planar structure. This distortion could be due to the restricted bite size of the deprotonated tridentate Schiff base ligand.

5. Biological activities

5.1. Antimicrobial activities

These copper (II) complexes have been assayed against several selected pathogens to evaluate their antibacterial and antifungal properties. The results collected in Table 6 indicate that the complexes are weakly active against all the bacteria and fungi chosen (inhibitory zones < 15 mm). The values are lower than those found for both SBDTC and SMDTC [28,36]. The [Cu(NNS‴)(sac)(H_2O)] complex is completely inactive against the bacteria and fungi assayed whereas the [Cu(NNS″)(sac)] complex is completely inactive towards the bacterial strains and weakly active against the fungal strains. This is in contrast with the antimicrobial activities of the complexes of SMDTC that have been shown to exhibit moderate to strong activities against the bacteria and fungi assayed [34]. It appears that the coordination of the saccharinate anion to the copper (II) in the complexes of the present tridentate Schiff base ligands diminishes the antibacterial and antifungal activities of the Schiff bases which were previously found to be active against several bacteria and fungi [34].

5.2. Cytotoxic activities

The measure of cytoxicity used in this work, CD_{50}, is the concentration required to reduce growth of cancer cells by 50%. CD_{50} values <5.0 μg cm^{-3} indicate that the complex is strongly active; CD_{50} values of 5.0–10.0 μg cm^{-3} indicate that the complex is moderately active, values of 10.0–25.0 μg cm^{-3} indicate that the complex is weakly active and values above 25 μg cm^{-3} indicate that the complex is inactive. The complexes, [Cu(NNS″)(sac)] and [Cu(NNS‴)(sac)] exhibit marked activity against the HL-60 cell line (Human Myeloid leukemic cells) with CD_{50}(μg cm^{-3}) values of 0.25 and 0.5, respectively, whereas the complex [Cu(NNS′)(sac)] is inactive. *S*-benzyldithiocarbazate from which the Schiff bases are derived [34] and the simple $CuCl_2 \cdot 2H_2O$ salt are both inactive. Since complexes with bulkier ligands are expected to be thermodynamically less stable, it is possible that the saccharinate ligand from [Cu(NNS″)(sac)] and [Cu(NNS‴)(sac)] are more easily displaced in solution making available a site through which coordination can occur with a suitable donor atom in the cancer cells. All of the Cu(II) complexes reported herein are inactive against the MCF-7 cell line (human breast carcinoma with positive estrogen receptor). The values for the standards, Doxorubicin, Tamoxifen and cisplatin are 0.8, 1.8 and 1.00 μg cm^{-3}, respectively (see Table 7).

Table 7
Cytotoxic activities of the copper (II)-saccharinate complexes

Compound[a]	HL-60	MCF-7	Caov-3
[Cu(NNS′)(sac)]	–	–	0.40
[Cu(NNS″)(sac)]	0.25	–	40.0
[Cu(NNS‴)(sac)]	0.50	–	13.5
Doxorubicin (standard)	0.80		
Tamoxifen (standard)		1.80	
Cisplatin (standard)			1.00

HL-60 = Human Myeloid Leukemic Cells, MCF-7 = Human Breast Carcinoma Cells with Positive Estrogen Receptor, Caov-3 = Human Ovarian Papillary Adenocarcinoma Cancer Cells, – ,inactive.

[a] CD_{50} < 5.0 μg cm^{-3} – strongly active, CD_{50} 5.0 < 10.0 μg cm^{-3} – moderately active, CD_{50} 10.0 < 25.0 μg cm^{-3} – weakly active, CD_{50} > 25.0 μg cm^{-3} – not active. CD_{50} (μg cm^{-3}) = Cytotoxic dose at 50%, i.e. the concentration to reduce growth of cancer cells by 50%.

6. Conclusion

The reaction of $[Cu(sac)_2(H_2O)_4] \cdot 2H_2O$ with the tridentate Schiff bases derived from *S*-benzyldithiocarbazate and heterocyclic ketones in a methanol–water mixture produces crystalline green complexes in high yields which are mixed-

Table 6
Qualitative antimicrobial assay results[a] (diameter in mm)

Compound	MRSA	B29	60690	S-T	C.A	398	20341
[Cu(NNS′)(sac)]	12	13	14	12	12	11	12
[Cu(NNS″)(sac)]	–	–	–	–	8	7	7
[Cu(NNS‴)(sac)]	–	–	–	–	–	–	–
Streptomycin (antibacterial control)	31	30	30	30			
Nystatin (antifungal control)					21	25	24

Methicillin resistant staphylococcus (MRSA); *Bacillus subtilis* wild type (B29), *P. aeruginosa* (60690); *S. typhimurium* (S-T), *C. albicans* (C.A), *A. ochraceous* (398), *S. ceciricaee* (20341).

[a] Diameter of 15 mm and above is considered active; –, inactive.

ligand binary copper (II) complexes containing the saccharinate anion and the tridentate NNS^- Schiff bases. An X-ray crystal structure determination of [Cu(NNS′)(sac)] shows that it has a distorted square-planar geometry. In view of the similarity of the IR and electronic spectra of the [Cu(NNS″)(sac)] and [Cu(NNS‴)(sac)] complexes with that of the [Cu(NNS′)(sac)], it is proposed that the former complexes also have a distorted square-planar geometry.

Of the three mixed-ligand complexes, the ones with methyl and phenyl groups in the ligands exhibit marked anticancer activity against the leukemic HL-60 cell lines, the activities being higher than the standard anticancer drug, Doxorubicin. The high selectivity towards this cell line is of particular interest and is worthy of further investigation.

7. Supplementary data

Crytallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 262373 A copy of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, Cb2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.ac.uk).

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