Taylor & Francis
healthsciences

Antibacterial Cobalt(II), Nickel(II) and Zinc(II) Complexes of Nicotinic Acid-derived Schiff-bases

ZAHID H. CHOHAN[a], ABDUL RAUF[a], SOBIA NOREEN[a], ANDREA SCOZZAFAVA[b] and CLAUDIU T. SUPURAN[b,*]

[a]*Department of Chemistry, Islamia University, Bahawalpur, Pakistan;* [b]*University of Florence, Polo Scientifico, Dipartimento di Chimica, Laboratorio di Chimica Bioinorganica, Via della Lastruccia 3, Rm 188, 50019-Sesto Fiorentino, Firenze, Italy*

Nicotinic acid derived Schiff bases and their transition metal [cobalt(II), nickel(II) and zinc(II)] complexes have been prepared and characterized by physical, spectral and analytical data. The Schiff bases act as deprotonated tridentate ligands for the complexation of the above mentioned metal ions. These complexes, possessing the general formula $[M(L)_2]$ [where $M = Co(II)$, $Ni(II)$ and $Zn(II)$ and $L = HL^1–HL^4$] showed an octahedral geometry of the metal ions. For determining the effect of metal ions upon chelation, the Schiff bases and their complexes have been screened for antibacterial activity against several pathogenic strains of *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The new metal derivatives reported here were more bactericidal against one or more bacterial species as compared to the uncomplexed Schiff bases.

INTRODUCTION

Emerging bacterial resistance to the currently available antibiotics has driven the search for novel prokaryotic targets as well as new molecules to inhibit their activity.[1] Among such novel derivatives, metal complexes of biologically active ligands may represent an interesting approach for designing new antibacterials, due to the dual possibility of both ligands plus metal ion interacting with different steps of the pathogen life cycle.[1,2]

A bulk of research has reported ligational aspects[3−7] and the biological role[8−13] of Schiff bases and their metal complexes. These studies have highlighted the fact that biologically active compounds become more carcinostatic or bacteriostatic upon chelation/or coordination[14−24] with metal ions. Previously we have extensively studied[25−29] the possibility of altering biological activity via coordination to metal ions. In continuation of this work we now report some novel biologically active Schiff bases (Figure 1), their metal complexes and biological activity as bactericidal agents.

MATERIAL AND METHODS

All chemicals and solvents used were of Analar grade. Metal(II) salts were used as chlorides. IR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer as KBr discs. UV-Visible spectra were obtained in DMF on a Hitachi U-2000 double-beam spectrophotometer. C, H and N analyses were carried out by Butterworth Laboratories Ltd. (Leatherhead, Surrey, UK). Conductance of the metal complexes was determined in DMF on a Hitachi YSI-32 model conductometer. Magnetic measurements were made on solid complexes using the Gouy method. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

Preparation of Schiff-bases $HL^1–HL^4$

Salicylaldehydes (1.2 g, 1.1 mL, 0.01 M) in ethanol (10 mL) were added to an ethanol solution (20 mL) of 2-aminonicotinic acid (2.8 g, 0.01 M). Then 2−3 drops of conc.H_2SO_4 were added and the mixture refluxed for 2 h. On cooling, a solid product was formed

*Corresponding author. Fax: +39-055-4573385. E-mail: claudiu.supuran@unifi.it
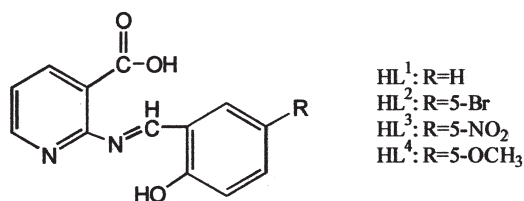
FIGURE 1   Structure of the Schiff bases.

which was filtered, washed with ethanol, then with ether and dried. Crystallization with hot ethanol gave the Schiff bases HL^1–HL^4.

Preparation of Metal(II) Complexes of Schiff Bases HL^1–HL^4

A warm ethanol solution (20 mL) of ligand (e.g. 0.9 g of HL^1, 0.002 M) was added to a magnetically stirred solution of metal(II) chloride hexahydrate (0.2 g, 0.001 M) in distilled water (25 mL). The mixture was refluxed for 1 h and cooled to room temperature. On cooling, the coloured precipitates which were formed were filtered, washed with ethanol, acetone and ether, and dried by suction. Crystallization from aqueous ethanol (30:70) gave the desired metal complex.

Antibacterial Studies

The synthesized metal complexes, in comparison to the uncomplexed Schiff-base ligands were screened for their antibacterial activity against pathogenic bacterial species, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The paper disc diffusion method[18–20] was adopted for determining the antibacterial activity.

RESULTS AND DISCUSSION

Chemistry

The Schiff bases (HL^1–HL^4) (Figure 1) were prepared by refluxing an appropriate amount of 2-aminonicotinic acid and the respective unsubstituted salicylaldehyde and its 5-bromo, 5-nitro or 5-methoxy substituted derivatives in hot ethanol in 1:1 molar ratio, respectively. The structures of these Schiff-bases were established with the aid of their IR, NMR, and microanalytical data (Tables I and II).

All metal complexes (**1**–**12**) (Table III) of these Schiff-bases were prepared by the stoichiometric reaction of the metals chlorides and the corresponding Schiff-bases, working in molar ratio metal salt:ligand of 1:2. The complexes are intensely coloured and amorphous solids, which decompose above 190°C. They are insoluble in common organic solvents such as ethanol, methanol, chloroform or

TABLE I   Physical, spectral and analytical data of the schiff bases

Schiff-base	IR (cm^{-1})	Calc (Found) %			M.P(°C)	Yield (%)
		C	H	N		
HL^1 $C_{13}H_{10}N_2O_3$ [242.0]	3420 (br, Ph–OH), 1680 (s, COOH), 1630 (s, HC = N), 1310 (s, CH = N of NA).	64.5 (64.9)	4.1 (4.5)	11.6 (11.5)	124	75
HL^2 $C_{13}H_9N_2O_3Br$ [320.9]	3425 (br, Ph–OH), 1685 (s, COOH), 1635 (s, HC = N), 1310 (s, CH = N of NA).	48.6 (48.8)	2.8 (3.2)	8.7 (8.8)	136	70
HL^3 $C_{13}H_9N_3O_5$ [287.0]	3425 (br, Ph–OH), 1685 (s, COOH), 1635 (s, HC = N), 1310 (s, CH = N of NA).	54.4 (54.8)	3.1 (3.5)	14.6 (14.3)	142	68
HL^4 $C_{14}H_{12}N_2O_4$ [272.0]	3425 (br, Ph–OH), 1685 (s, COOH), 1635 (s, HC = N), 1310 (s, CH = N of NA).	61.8 (62.1)	4.4 (4.2)	10.3 (10.5)	138	65

s = sharp, br = broad, NA = Nicotinic acid.

TABLE II ^{1}H NMR and ^{13}C NMR data of the Schiff bases and their Zn(II) complexes

No	^{1}H NMR (DMSO-d$_6$) ppm	^{13}C NMR (DMSO-d$_6$) ppm
HL^1	6.8 (s, 1H, CH = N), 6.9–7.1 (m, 1H, Ph), 7.2–7.3 (m, 1H, Ph), 7.4–7.5 (m, 1H, Ph), 7.6–7.7 (m, 1H, Ph), 7.9–8.1 (m, 1H, Py), 8.2–8.3 (m, 1H, Py), 8.4–8.5 (m, 1H, Py), 10.2 (s, 1H, OH), 11.3 (s, 1H, COOH).	115.6, 126.4, 127.3, 130.5, 148.6, 159.7 (Ph), 150.8 (C = N), 140.3, 149.2, 149.7, 155.6, 158.9 (Py), 179.8 (COO)
HL^2	6.8 (s, 1H, CH = N), 7.2–7.3 (m, 1H, Ph), 7.4–7.5 (m, 1H, Ph), 7.6–7.7 (m, 1H, Ph), 7.8–7.9 (m, 1H, Ph), 7.9–8.1 (m, 1H, Py), 8.2–8.3 (m, 1H, Py), 8.4–8.5 (m, 1H, Py), 10.2 (s, 1H, OH), 11.3 (s, 1H, COOH).	116.2, 126.6, 127.8, 130.7, 149.5, 159.7 (Ph), 150.8 (C = N), 140.3, 149.2, 149.7, 155.6, 158.9 (Py), 179.8 (COO)
HL^3	6.8 (s, 1H, CH = N), 7.1–7.2 (m, 1H, Ph), 7.3–7.4 (m, 1H, Ph), 7.5–7.6 (m, 1H, Ph), 7.7–7.8 (m, 1H, Ph), 7.9–8.1 (m, 1H, Py), 8.2–8.3 (m, 1H, Py), 8.4–8.5 (m, 1H, Py), 10.2 (s, 1H, OH), 11.3 (s, 1H, COOH).	116.4, 126.5, 127.9, 130.8, 149.6, 159.7 (Ph), 150.8 (C = N), 140.3, 149.2, 149.7, 155.6, 158.9 (Py), 179.8 (COO)
HL^4	3.1 (s, 3H, OCH$_3$), 6.8 (s, 1H, CH = N), 7.2–7.3 (m, 1H, Ph), 7.4–7.5 (m, 1H, Ph), 7.6–7.7 (m, 1H, Ph), 7.8–7.9 (m, 1H, Ph), 8.0–8.1 (m, 1H, Py), 8.2–8.3 (m, 1H, Py), 8.4–8.5 (m, 1H, Py), 10.2 (s, 1H, OH), 11.3 (s, 1H, COOH).	116.7, 126.6, 127.8, 130.8, 149.7, 159.8 (Ph), 150.8 (C = N), 140.3, 149.2, 149.7, 155.6, 158.9 (Py), 179.8 (COO)
3	6.9 (s, 1H, CH = N), 7.0–7.1 (m, 1H, Ph), 7.3–7.4 (m, 1H, Ph), 7.5–7.6 (m, 1H, Ph), 7.6–7.7 (m, 1H, Ph), 8.0–8.1 (m, 1H, Py), 8.2–8.3 (m, 1H, Py), 8.5–8.6 (m, 1H, Py), 11.3 (s, 1H, COOH).	115.7, 126.6, 127.4, 130.5, 148.7, 159.7 (Ph), 150.9 (C = N), 140.3, 149.2, 149.7, 155.6, 159.7 (Py), 179.8 (COO)
6	6.9 (s, 1H, CH = N), 7.1–7.2 (m, 1H, Ph), 7.3–7.4 (m, 1H, Ph), 7.5–7.6 (m, 1H, Ph), 7.7–7.9 (m, 1H, Ph), 7.9–8.1 (m, 1H, Py), 8.3–8.4 (m, 1H, Py), 8.6–8.7 (m, 1H, Py), 11.4 (s, 1H, COOH).	115.7, 126.5, 127.4, 130.5, 148.8, 159.7 (Ph), 150.9 (C = N), 140.3, 149.2, 149.7, 155.6, 159.6 (Py), 179.8 (COO)
9	6.9 (s, 1H, CH = N), 7.1–7.2 (m, 1H, Ph), 7.3–7.4 (m, 1H, Ph), 7.6–7.7 (m, 1H, Ph), 7.8–7.9 (m, 1H, Ph), 8.0–8.1 (m, 1H, Py), 8.4–8.5 (m, 1H, Py), 8.6–8.7 (m, 1H, Py), 11.4 (s, 1H, COOH).	115.7, 126.6, 127.4, 130.5, 148.8, 159.7 (Ph), 151.1 (C = N), 140.3, 149.2, 149.7, 155.6, 159.7 (Py), 179.8 (COO)
12	3.2 (s, 3H, OCH$_3$), 7.1 (s, 1H, CH = N), 7.3–7.4 (m, 1H, Ph), 7.5–7.6 (m, 1H, Ph), 7.7–7.8 (m, 1H, Ph), 7.9–8.0 (m, 1H, Ph), 8.1–8.2 (m, 1H, Py), 8.3–8.4 (m, 1H, Py), 8.5–8.6 (m, 1H, Py), 11.4 (s, 1H, COOH).	116.7, 126.6, 127.8, 130.8, 149.7, 159.8 (Ph), 150.8 (C = N), 140.3, 149.2, 149.7, 155.6, 158.9 (Py), 179.8 (COO)

TABLE III Physical and analytical data of the metal(II) complexes **1**–**12**

No	Metal chelate/Mol. Formula	Yield (%)	M.p (°C) (decomp)	B.M. (μ_{eff})	Calc. (Found)%		
					C	H	N
1	[Co(L^1)$_2$] [540.9] C$_{26}$H$_{18}$CoN$_4$O$_6$	69	190–192	3.9	57.7 (57.9)	3.3 (3.1)	10.4 (10.6)
2	[Ni(L^1)$_2$] [540.7] C$_{26}$H$_{18}$NiN$_4$O$_6$	65	206–208	3.2	57.7 (58.0)	3.3 (3.7)	10.4 (10.2)
3	[Zn(L^1)$_2$][547.4]C$_{26}$H$_{18}$ZnN$_4$O$_6$	68	212–214	Dia	57.0 (57.3)	3.3 (3.5)	10.2 (10.5)
4	[Co(L^2)$_2$] [698.7] C$_{26}$H$_{16}$CoBr$_2$N$_4$O$_6$	68	208–210	4.1	44.7 (44.9)	2.3 (2.6)	8.0 (8.1)
5	[Ni(L^2)$_2$] [698.5] C$_{26}$H$_{16}$NiBr$_2$N$_4$O$_6$	67	213–215	3.3	44.7 (44.5)	2.3 (2.0)	8.0 (8.2)
6	[Zn(L^2)$_2$] [705.2] C$_{26}$H$_{16}$ZnBr$_2$N$_4$O$_6$	65	220–222	Dia	44.2 (44.3)	2.3 (2.5)	7.9 (8.2)
7	[Co(L^3)$_2$] [630.9] C$_{26}$H$_{16}$CoN$_6$O$_{10}$	69	192–194	4.0	49.5 (49.2)	2.5 (2.7)	13.3 (13.6)
8	[Ni(L^3)$_2$] [630.7] C$_{26}$H$_{16}$NiN$_6$O$_{10}$	65	207–209	3.4	49.5 (49.9)	2.5 (2.9)	13.3 (13.2)
9	[Zn(L^3)$_2$] [637.4] C$_{26}$H$_{16}$ZnN$_6$O$_{10}$	68	215–217	Dia	49.0 (49.2)	2.5 (2.2)	13.2 (13.5)
10	[Co(L^4)$_2$][600.9]C$_{28}$H$_{22}$CoN$_4$O$_8$	69	189–191	4.2	56.0 (56.4)	3.7 (3.6)	9.3 (9.5)
11	[Ni(L^4)$_2$] [600.7] C$_{28}$H$_{22}$NiN$_4$O$_8$	65	207–209	3.3	56.0 (56.2)	3.7 (3.9)	9.3 (9.0)
12	[Zn(L^4)$_2$] [607.4] C$_{28}$H$_{22}$ZnN$_4$O$_8$	68	211–213	Dia	54.3 (54.8)	3.6 (3.8)	9.2 (9.4)

acetone but only soluble in DMSO and DMF. Their solubility nature and elemental analysis data suggest that they are monomers (Table III). Molar conductance values of the soluble complexes in DMF show low values, in the range of 14–20 ohm^{-1} cm^2 mol^{-1}, indicating that they are all non-electrolytic in nature.[30,31]

IR spectra of the Schiff bases (HL^1–HL^4) showed the absence of bands at ~1735 and 3315 cm^{-1} due to the carbonyl ν(C = O) and ν(NH$_2$) stretching vibrations and, instead, a strong new band appeared at ~1630 cm^{-1} assigned to the azomethine ν(HC = N) linkage, showing[32] that amino and aldehyde moieties of the starting reagents are absent and have been converted into their Schiff-base compounds. The comparison of the IR spectra of the Schiff-bases and their metal chelates indicated that the ligands are principally coordinated to the metal ions in three ways, thus acting as tridentate ligands. The band appearing at 1630 cm^{-1} due to the azomethine is shifted to lower frequency by ~10–15 cm^{-1} in these complexes, indicating participation of the azomethine nitrogen in interaction with the metal ion. The band at 1315 cm^{-1}, assigned to the nitrogen of the pyridine ring ν(C = N), is also shifted to lower frequency by ~10 cm^{-1} which was indicative of the involvement of the pyridine ring nitrogen in the coordination. A broad band, appear-

ing at 3415 cm^{-1} and assigned to ν(OH) in the Schiff-bases, was no longer found in the spectra of the metal complexes and instead, appearance of a new band at ~1380 cm^{-1} indicated deprotonation and coordination of the hydroxyl oxygen to the metal atom. Further conclusive evidence of the coordination of these Schiff-base compounds with the metal ions, was shown by the appearance of weak low frequency new bands at 525–530 and 455–460 cm^1 (Table IV). These were assigned[33] to the metal-nitrogen ν(M–N) and metal-oxygen ν(M–O) vibrations, respectively. These new bands were only observable in the spectra of the metal complexes and not in the spectra of the uncomplexed Schiff-bases, thus confirming participation of the groups (O or N) in the coordination.

^{1}H NMR spectra of the Schiff bases and their Zn(II) complexes were taken in DMSO-d$_6$ (Table II). By comparing the chemical shifts of the uncomplexed Schiff bases with those of their corresponding Zn(II) complexes, it was found that some of the resonance signals such as heteroaromatic (HC = N) and azomethine (HC = N) signals, experienced down-field shifts by 0.9–1.0 ppm upon coordination.[34] Furthermore, a signal corresponding to the hydroxyl proton disappeared in the spectra of metal complexes indicating[35] deprotonation of the hydroxyl group upon coordination. On the other hand, a new

TABLE IV IR and UV-visible spectral data of the metal(II) complexes **1**–**12**

| No.	IR (cm^{-1})	λ_{max} (cm^{-1})
1	1620 (HC = N), 1380 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	30235, 17475, 8780
2	1625 (HC = N), 1382 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	29940, 15850, 9960
3	1620 (HC = N), 1380 (M–O), 1305 (Py), 530 (M–N), 460 (M–O).	28850
4	1625 (HC = N), 1385 (M–O), 1305 (Py), 530 (M–N), 455 (M–O).	30270, 17615, 8810
5	1620 (HC = N), 1380 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	29985, 16155, 10165
6	1625 (HC = N), 1385 (M–O), 1305 (Py), 530 (M–N), 460 (M–O).	28975
7	1620 (HC = N), 1380 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	30255, 17515, 8790
8	1625 (HC = N), 1382 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	29965, 15965, 9985
9	1620 (HC = N), 1380 (M–O), 1305 (Py), 530 (M–N), 460 (M–O).	28885
10	1625 (HC = N), 1385 (M–O), 1305 (Py), 530 (M–N), 455 (M–O).	30260, 17775, 8805
11	1620 (HC = N), 1380 (M–O), 1305 (Py), 525 (M–N), 455 (M–O).	29955, 15910, 9965
12	1625 (HC = N), 1385 (M–O), 1305 (Py), 530 (M–N), 460 (M–O).	28965
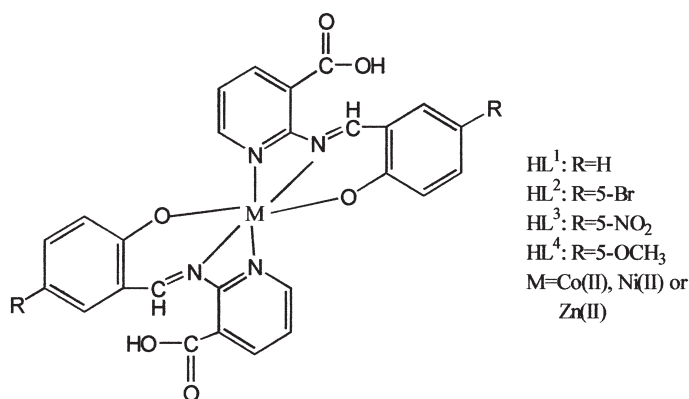
FIGURE 2 Proposed structure of the metal complex.

HL^1: R=H
HL^2: R=5-Br
HL^3: R=5-NO$_2$
HL^4: R=5-OCH$_3$
M=Co(II), Ni(II) or Zn(II)

chemical shift (probably due to the formation of the M−O bond) appeared in the ^{13}C NMR spectra of the metal complexes which was absent in the ^{13}C NMR spectra of the ligands, giving a clue for deprotonation of the hydroxyl group in the Schiff bases and the involvement of the oxygen in coordination.

The room temperature magnetic moment of the solid cobalt(II) complexes was found at 3.9–4.2 B.M, indicative of three unpaired electrons per Co(II) ion in an octahedral environment.[36] The Ni(II) complexes showed μ_{eff} values 3.2–3.4 B.M, corresponding to two unpaired electrons per Ni(II) ion for their ideal six-coordinated configuration.[37] The Zn(II) complexes were all diamagnetic. The electronic spectra of the Co(II) chelates showed three bands at 8780–8810, 17475–17775 and 30235–30270 cm^{-1} which may be assigned to $^4T_{1g} \rightarrow^4 T_{2g}(F)$, $^4T_{1g} \rightarrow^3 A_{2g}(F)$ and $^4T_{1g} \rightarrow^4 T_{1g}(P)$ transitions, respectively, and suggested[38,39] octahedral geometry around the cobalt ions. The Ni(II) complexes exhibited three bands at 9960–10165, 15850–16155 and 29940–29985 cm^{-1} assignable[40−42] respectively, to the transitions $^3A_{2g}(F) \rightarrow^3 T_{2g}(F)(\nu_1)$, $^3A_{2g}(F) \rightarrow^3 T_{1g}(F)\times (\nu_2)$ and $^3A_{2g}(F) \rightarrow^3 T_{2g}(P)(\nu_3)$ which are characteristic for Ni(II) in octahedral geometry. The diamagnetic zinc(II) complexes did not show any d−d bands and their spectra were dominated only by the charge transfer bands. These charge transfer bands (28850–28975 cm^{-1}) are probably due to $^2E_g \rightarrow^2 T_{2g}$ transition.[41,42]

On the basis of the above observations, it is tentatively suggested that that Co(II), Ni(II) and Zn(II) complexes show an octahedral geometry (Figure 2) in which the Schiff bases act as tridentate ligand.

Antibacterial Activity

The title Schiff bases and their metal chelates were evaluated for antibacterial activity against the following bacterial species: (*a*) *Escherichia coli*, (*b*) *Staphylococcus aureus* and (*c*) *Pseudomonas aeruginosa*.

The compounds were tested at a concentration of 30 µg/0.01 mL in DMF solution using the paper disc diffusion method. The susceptibility zones were measured in diameter (mm) and the results are shown in Table V. The susceptibility zones measured were the clear zones around the discs killing the bacteria.

All the Schiff bases and their complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The antibacterial results show that the activity of the Schiff-base compounds became more pronounced when coordinated to the metal ions. It is suggested that in the chelated complex, the positive charge of the metal is partially shared with the donor atoms present in the ligands and there is π-electron delocalization over the whole chelate ring. This in turn increases the lipophilic character of the metal chelate and favours its penetration through the lipid

TABLE V Antibacterial activity data of the schiff-bases and their metal(II) complexes reported in the paper

Schiff-base/ Complex	Microbial species		
	a	b	c
HL^1	++	+	++
HL^2	++	++	+
HL^3	++	++	++
HL^4	+	++	−
1	+++	+++	+++
2	++++	+++	+++
3	+++	+++	+++
4	++++	+++	+++
5	+++	+++	++++
6	+++	++++	++
7	+++	++++	+++
8	++++	+++	++++
9	+++	++++	+++
10	++++	+++	++
11	++++	+++	+++
12	+++	++++	+++

a = *Escherichia coli*, b = *Staphylococcus aureus*, c = *Pseudomonas aeruginosa* Inhibition zone diameter mm (% inhibition): +, 6−10 (27−45 %); ++, 10−14 (45−64%); +++, 14−18 (64−82%); ++++, 18−22 (82−100%). Percent inhibition values are relative to inhibition zone (22 mm) of standard antibacterials (sulfadiazine, sulfathiazole), considered as 100% inhibition, tested under the same conditions as the new compounds reported here.

layer of the bacterial wall. Apart from this, other factors such as solubility, conductivity and dipole moment influenced by the presence of metal ions may also be among the possible reasons for the increased bactericidal activity of the metal complexes as compared to the ligand Schiff base.

Acknowledgement

References

[1] Supuran, C.T., Scozzafava, A. and Mastrolorenzo, A. (2001) *Exp. Opin. Ther. Patents* **11**, 221.
[2] Travis, J. and Potempa, J. (2000) *Biochim. Biophys. Acta* **14**, 35.
[3] Scozzafava, A. and Supuran, C.T. (2000) *J. Med. Chem.* **43**, 3677.
[4] Chohan, Z.H., Munawar, A. and Supuran, C.T. (2001) *Metal Based Drugs* **8**, 137.
[5] Chohan, Z.H., Farooq, M.A. and Supuran, C.T. (2001) *Metal Based Drugs* **8**, 171.
[6] Chohan, Z.H. and Praveen, M. (2000) *Appl. Organomet. Chem.* **14**, 376.
[7] Chohan, Z.H. and Praveen, M. (2000) *Synth. React. Inorg. Met-Org. Chem.* **30**, 175.
[8] Supuran, C.T. and Scozzafava, A. (2000) *Eur. J. Med. Chem.* **35**, 867.
[9] Brown, D.H., Smith, W.E., Teape, J.W. and Lewis, A.J. (1980) *J. Med. Chem.* **23**, 729.
[10] Crowe, A.J. (1988) In: Gielen, M., ed., *Metal Based Antitumor Drugs* (Freund, London), pp. 201–213.
[11] Clare, M.J. and Heeschele, J.D. (1973) *Bioinorg. Chem.* **2**, 187.
[12] Narayanan, V.L., Nasr, M. and Paull, K.D. (1990) In: Gielen, M., ed., *Tin-Based Antitumor Drugs*, NATO ASI Series, (Springer, Berlin) **Vol. H37**, pp. 38–46.
[13] Alzuet, G., Casanova, J., Borras, J., Garcia-Granda, S., Gutierrez-Rodriguez, A. and Supuran, C.T. (1998) *Inorg. Chim. Acta* **273**, 334.
[14] Gokhale, N., Padhye, S., Newton, C. and Pritchard, R. (2000) *Metal Based Drugs* **7**, 121.
[15] Bergamo, A., Gigliardi, R., Scarcia, V., Furlani, A., Alessio, E., Mestroni, G. and Perbillini, A. (1999) *J. Pharmacol. Exp. Ther.* **289**, 559.
[16] Perez, J.M., Montero, E.I., Quiroga, A.G., Fuertes, M.A., Alonso, C. and Navarro-Ranninger, C. (2001) *Metal Based Drugs* **8**, 29.
[17] Chohan, Z.H. (1999) *Metal Based Drugs* **6**, 75.
[18] Chohan, Z.H. and Kausar, S. (2000) *Metal Based Drugs* **7**, 17.
[19] Chohan, Z.H., Sherazi, S.K.A. and Iqbal, M.S. (1998) *Metal Based Drugs* **5**, 347.
[20] Chohan, Z.H. and Sherazi, S.K.A. (1999) *Synth. React. Inorg. Met-Org. Chem.* **29**, 105.
[21] Supuran, C.T., Mincione, F., Scozzafava, A., Briganti, F., Mincione, G., and Ilies, M.A. (1998) *Eur J. Med. Chem.* **33**, 247.
[22] Supuran, C.T., Scozzafava, A., Saramet, I. and Banciu, M.D. (1998) *J. Enz. Inhib.* **13**, 177.
[23] Scozzafava, A., Menabuoni, L., Mincione, F., Mincione, G. and Supuran, C.T. (2001) *Bioorg. Med. Chem. Lett.* **11**, 575.
[24] Walsh, C. (2001) *Science* **409**, 226.
[25] Chohan, Z.H. (2001) *Synth. React. Inorg. Met-Org. Chem.* **31**, 1.
[26] Chohan, Z.H., Praveen, M. and Ghaffar, A. (1998) *Synth. React. Inorg. Met-Org. Chem.* **28**, 1673.
[27] Chohan, Z.H. and Pervez, H. (1993) *Synth. React. Inorg. Met-Org. Chem.* **23**, 1061.
[28] Mahmood-ul-Hassan, E.D., Scozzafava, A., Chohan, Z.H. and Supuran, C.T. (2002) *J. Enz. Inhib.*, (In press).
[29] Chohan, Z.H., Farooq, M.A., Scozzafava, A. and Supuran, C.T. (2002) *J. Enz. Inhib.*, (In press).
[30] Geary, W.J. (1971) *Coord. Chem. Rev.* **7**, 81.
[31] Shallary, A.M., Moustafa, M.M. and Bekheit, M.M. (1979) *J. Inorg. Nucl. Chem.* **41**, 267.
[32] Bellamy, L.J. (1968) *The Infrared Spectra of Complex Molecules*, (Methuen, London), pp. 62–69.
[33] Nakamoto, K. (1978) *Inorganic and Raman Spectra of Coordination Compounds*, Wiley, New York, pp. 127–154.
[34] Williams, D.H. and Fleming, I. (1989) *Spectroscopic Methods in Organic Chemistry*, 4th Ed. (McGraw Hill, London), pp. 228–241.
[35] Hong-Yun, Z., Dong-Li, C., Pei-Kun, C., De-Ji, C., Guang-Xia, C. and Hong-Quan, Z. (1992) *Polyhedron* **11**, 2313.
[36] Earnshaw, A. (1968) *Introduction to Magnetochemistry* (Academic Press, New York), pp. 19–37.
[37] Meek, D.W., Drago, R.S. and Piper, T.S. (1962) *Inorg. Chem.* **1**, 285.
[38] Carlin, R.L. (1965) *Transition Metal Chemistry* (Marcel Decker, New York), pp. 42–49.
[39] Liehr, A.D. (1967) *J. Phys. Chem.* **67**, 1314.
[40] Balhausen, C.J. (1962) *An Introduction to Ligand Field* (McGraw Hill, New York), pp. 125–127.
[41] Lever, A.B.P. (1984) *Inorganic Electronic Spectroscopy* (Elsevier, Amsterdam), pp. 23–39.
[42] Figgis, B.N. (1976) *Introduction to Ligand Field* (Wiley, New York), pp. 321–333.