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Antibacterial Schiff Bases of Oxalyl-hydrazine/diamide Incorporating Pyrrolyl and Salicylyl Moieties and of Their Zinc(II) Complexes

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Schiff bases derived from oxaldiamide/oxalylhydrazine and pyrrol-2-carbaldehyde, or salicylaldehyde respectively, as well as their Zn(II) complexes have been prepared and tested as antibacterial agents. These Schiff bases function as tetradentate ligands, forming octahedral Zn(II) complexes. The ketonic form for the diamide derived Schiff base and the enolic form of the hydrazide derived Schiff base were the preferred tautomers for coordination of the metal ions. The title compounds and their Zn(II) derivatives were evaluated for antibacterial activity against several bacterial strains which easily develop resistance to classical antibiotics, such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Some of them showed promising biological activity in inhibiting the growth of such organisms.

Keywords: Schiff base; Oxaldiamide; Oxalylhydrazine; Antibacterials; Zinc complex

INTRODUCTION

Most antibiotics used in clinical practice at the present time share a common mechanism of action, acting as inhibitors of the bacterial cell wall biosynthesis or affecting protein synthesis on ribosomes and not intervening in more fundamental metabolic processes of the pathogen.[1–5] Considering the constant emergence of antibiotic resistance to the clinically used compounds, it is of critical importance to develop novel antibiotic classes, that eventually would target the lipoid layer of the organisms and other aspects of the pathogen life cycle. One such possible class is constituted by the metal complexes with biological activity.[6]

Previous investigations[7–10] in our group have dealt with the interesting and varied ligational behavior of hydrazine and hydrazones towards transition metal ions. Due to their properties as potential ligands, certain acylhydrazines and their transition metals have been well-studied,[11–15] but the coordination behavior of some oxamide and oxaloyldihydrazide derived Schiff bases has been much less explored. The present work, therefore, was undertaken in order to determine the ligational behavior of some novel oxamide and oxalyldihydrazide derived pyrrolyl and salicylyl Schiff bases (Fig. 1) towards Zn(II) ions, as well as their biological activity in inhibiting the growth of some pathogenic bacteria. The present studies would thus bring more insight into the metallo-organic chemistry and biological activity of these Schiff bases, L^1–L^4, shown below.

MATERIALS AND METHODS

All chemicals and solvents used were of Analar grade. Zinc(II) salt was used as the chloride. Pyrrol-2-carboxaldehyde, salicylaldehyde, oxamide and oxaloyldihydrazide were obtained from the Merk Chemical Company. IR, ^{1}H NMR and ^{13}C NMR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer and on a Brucker 250 MHz spectrometer. UV–Visible spectra were obtained on a Hitachi U-2000 double-beam

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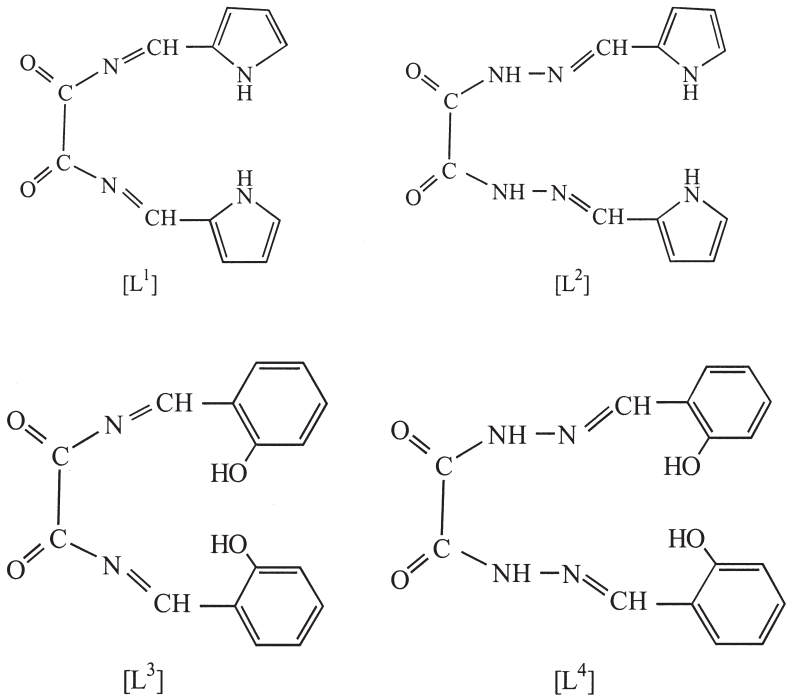

FIGURE 1 Structure of the Schiff bases L^1–L^4 investigated in the present work.

spectrophotometer. C, H and N analyses were carried out by Butterworth Laboratories, Middlesex, UK. Conductances of the metal complexes were determined in DMF on a YSI-32 model conductometer. Magnetic measurements were done on solid complexes using the Gouy method. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

Preparation of the Schiff Bases L^1–L^4

N,N′-*Bis(2-pyrrolylmethylidene)oxamide* (L^1)

Pyrrol-2-carboxaldehyde (1.6 ml, 1.9 g, 0.02 mole) in absolute ethanol (20 ml) was added to a stirred hot ethanol solution (30 ml) of oxamide (1.8 g, 0.01 mole). Then 2–3 drops of conc. H_2SO_4 were added and the mixture was refluxed for 5 h. The reaction mixture was cooled and left for 24 h at room temperature. During this period yellow solid was formed, which was recrystallized from hot ethanol to give L^1 (1.6 g).

N,N′-*Bis(2-pyrrolylmethylidene)oxaloyldihydrazide* (L^2)

Pyrrole-2-carboxaldehyde (1.6 ml, 1.9 g, 0.02 mole) in absolute ethanol (20 ml) was added to a stirred hot ethanol solution (30 ml) of oxaloyldihydrazide (1.2 g, 0.01 mole). Then 2–3 drops of conc. H_2SO_4 were added and the mixture was refluxed for 8 h. The reaction mixture was then cooled and left for 24 h at room temperature. During this period, a light yellow solid was formed, which was recrystallized from hot ethanol to give the desired product (L^2) (1.8 g).

N,N′-*Bis(2-salicylylmethylidene)oxamide* (L^3)

Salicylaldehyde (0.8 ml, 2.4 g, 0.02 mole) in absolute ethanol (10 ml) was added to a stirred hot ethanol solution (30 ml) oxamide (1.8 g, 0.01 mole). Then 2–3 drops of conc. H_2SO_4 were added and the mixture was refluxed for 5 h. The reaction mixture was then cooled and left for 24 h at room temperature. During this period a discolored white solid was formed, which was recrystallized from hot ethanol to give L^3 (1.9 g).

N,N′-*Bis(2-salicylylmethylidene)oxaloyldihydrazide* (L^4)

Salicylaldehyde (0.8 ml, 2.4 g, 0.02 mole) in absolute ethanol (10 ml) was added to a stirred hot ethanol solution (30 ml) of oxaloyldihydrazide (1.2 g, 0.01 mole). Then 2–3 drops of conc. H_2SO_4 were added and the mixture was refluxed for 8 h. The reaction mixture was then cooled and left for 24 h at room temperature. During this period, a white solid was formed, which was recrystallized from hot ethanol to give the desired product (L^4) (2.2 g).

Preparation of the Zinc Complexes of Ligands L^1–L^4

An ethanol solution (20 ml) of the Zn(II) chloride salt (0.001 mole) was added to a stirred hot ethanol

TABLE I Physical, spectral and analytical data for the Schiff bases $\mathbf{L^1}$–$\mathbf{L^4}$ and their Zn(II) complexes **1**–**4**

Schiff base	M.p. (°C)	IR (cm^{-1})	Calc. (found) %			λ_{max} (cm^{-1})	Yield (%)
			C	H	N		
$\mathbf{L^1}$ $C_{12}H_{10}N_4O_2$ [242.0]	162	1710 (s, C = O), 1635 (s, HC = N)	59.5 (59.7)	4.1 (3.8)	23.1 (23.4)	–	52
$\mathbf{L^2}$ $C_{12}H_{12}N_6O_2$ [272.0]	177	1715 (s, C = O), 1635 (s, HC = N), 1530 (s, NH), 1020 (m, HN–N)	52.9 (53.1)	4.4 (4.1)	30.9 (30.6)	–	56
$\mathbf{L^3}$ $C_{16}H_{12}N_2O_4$ [296.0]	165	3315 (b, OH), 1715 (s, C = O), 1635 (s, HC = N)	64.9 (65.3)	4.1 (3.8)	9.5 (9.7)	–	62
$\mathbf{L^4}$ $C_{16}H_{14}N_4O_4$ [326.0]	168	3315 (b, OH), 1715 (s, C = O), 1635 (s, HC = N), 1530 (s, NH). 1020 (m, HN–N)	58.9 (59.3)	4.3 (4.5)	17.2 (17.0)	–	58
1 $[Zn(L^1)Cl_2]$ $C_{12}H_{10}ZnCl_2N_4O_2$ [378.3]	222–224	1710 (s, C = O), 1625 (s, HC = N), 465 (m, M–N), 355 (m, M–Cl)	38.1 (38.4)	2.6 (2.7)	14.8 (14.6)	28650 (CT)	70
2 $[Zn(L^2)Cl_2]$ $C_{12}H_{12}ZnCl_2N_6O_2$ [408.3]	230–232	3315 (b, OH), 1620 (s, HC = N), 1245 (C–O), 1035 m, N–N), 465 (m, M–N), 355 (m, M–Cl)	35.3 (35.5)	2.9 (3.1)	20.6 (20.4)	28645 (CT)	72
3 $[Zn(L^3)Cl_2]$ $C_{16}H_{10}ZnCl_2N_2O_4$ [430.3]	218–220	1710 (s, C = O), 1625 (s, HC = N), 515 (m, M–N), 465 (m, M–O), 355 (m, M–Cl)	44.6 (44.3)	2.3 (2.7)	6.5 (6.6)	28675 (CT)	75
4 $[Zn(L^4)Cl_2]$ $C_{16}H_{10}ZnCl_2N_4O_4$ [458.3]	225–228	3315 (b, OH), 1620 (s, HC = N), 1245 (C–O), 1035 (m, N–N), 515 (m, M–N), 465 (m, M–O), 355 (m, M–Cl)	41.9 (42.2)	2.2 (2.1)	12.2 (12.5)	28670 (CT)	72

s = sharp, m = medium, b = broad.

solution (20 ml) of the respective Schiff base (0.001 mole). The mixture was refluxed for 8 h. On cooling at room temperature, a solid product was precipitated. The product thus obtained was filtered off, washed with ethanol, then with ether and dried. Crystallization from aqueous ethanol (50%) gave the desired metal complexes.

Antibacterial Studies

Preparation of Discs and Agar Plates

The solution of the ligand/complex (30 μg) in DMF (0.01 ml) was applied on a paper disc, prepared from blotting paper (3 mm diameter), with the help of a micropipette. The discs were left in an incubator for 48 h at 37°C and then applied on the bacteria grown on agar plates. Minimal agar was used for the growth of specific bacterial species. For the preparation of agar plates for *Escherichia coli*, MacConkey agar (50 g), obtained from Merck Chemical Company, was suspended in freshly distilled water (1 l), allowed to soak for 15 min and then boiled on a water bath until the agar was completely dissolved. The mixture was autoclaved for 15 min at 120°C and then poured into previously washed and sterilized Petri dishes and stored at 40°C for inoculation.

Procedure of Inoculation and Application of Discs

Inoculation was done using a platinum wire loop, which was made red-hot in a flame, cooled and then used for the application of the bacterial strains having almost the same bacterial counts. Sterilized forceps were used for the application of the paper disc on previously inoculated agar plates. When the discs were applied, the plates were incubated at 37°C for 24 h. The zone of inhibition around the disc was then measured (in mm).

RESULTS AND DISCUSSION

Chemistry

The Schiff bases (Fig. 1) were prepared by reacting an appropriate amount of pyrrol-2-carboxaldehyde and salicylaldehyde, respectively, in hot ethanol with oxamide and oxaloyldihydrazide in 2:1 molar ratios, respectively. The structures of these Schiff bases were assigned with the help of their IR, ^{1}H-NMR, ^{13}C-NMR spectra, and analytical data.

The metal complexes (Table I) of these Schiff bases were prepared by the stoichiometric reaction of Zn(II) chloride and the corresponding Schiff base in equimolar ratio (M : L = 1 : 1). The complexes are stable solids, which decompose above 200°C without melting and are insoluble in common organic solvents such as ethanol, methanol, chloroform or

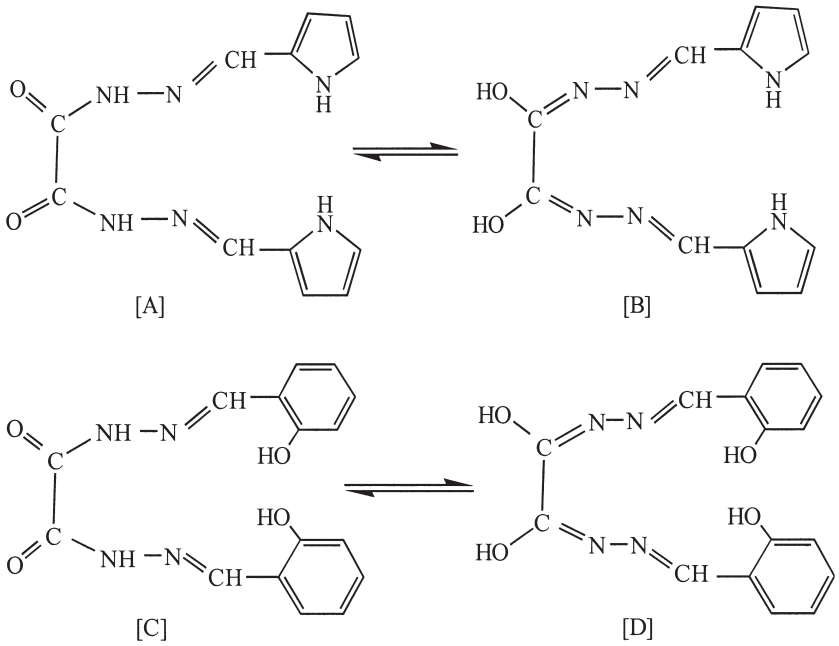

FIGURE 2 Keto–enol equilibria of ligands L^2 and L^4

acetone. DMSO and DMF, however, dissolved all the complexes. Molar conductance values of the soluble complexes in DMF showed low values ($18–20\,ohm^{-1}\,cm^2\,mol^{-1}$) indicating[16] that they are all non-electrolytic in nature.

Structural models of these Schiff bases in Fig. 1 show that in no case can these ligands exhibit bidentate, tridentate or hexadentate behavior. They are capable of exhibiting tetradentate behavior, as shown in Fig. 2. The Schiff bases L^2 and L^4 have a tendency to exhibit a dienol system (Fig. 2) in equilibrium. In its enol form, the ligands can function like the dienol showing donor sites by coordinating through two azomethine nitrogens (HC = N) and the two NH groups of the pyrrolyl and deprotonated OH of salicylyl moieties. The Schiff base ligands L^1 and L^3, however, do not exhibit any dienol or ketoenol equilibria.

The IR spectra of the Schiff bases and their Zn(II) complexes were recorded in KBr and are reported in Table I with some tentative assignments of the most characteristic bands. The Schiff bases displayed no bands at $\sim 3420\,cm^{-1}$ due to the characteristic $\nu(NH_2)$ stretching vibrations of the corresponding amides/hydrazides (starting material). Instead, a new band appeared at $\sim 1635\,cm^{-1}$, which has been assigned[17] as the azomethine (HC = N) vibration. Also presence of a band at $1020\,cm^{-1}$ due to the HN–N vibration in the spectra of the Schiff bases L^2 and L^4, however, suggested[18] that the hydrazine and aldehyde moieties of the starting reagents are no longer are present and condensation to the corresponding Schiff bases had occurred.

A comparison of the infrared spectra of the Schiff bases and their Zn(II) complexes indicates[18] that the Schiff bases are coordinated to the metal ion in two ways, thus indicating L^1–L^4 to act tetradentately. The band due to $\nu(C = O)$ was absent in the spectra of complexes of the Schiff bases L^2 and L^4 suggesting[19] enolization during complexation. This is supported by the evidence of the presence of a band due to ν(OH) in the spectra of these complexes at $3315\,cm^{-1}$. The band due to $\nu(C = O)$ at $1710\,cm^{-1}$ remained unchanged in the spectra of the Schiff bases L^1 and L^3. These facts suggested that the Schiff bases L^2 and L^4 remained in the keto form in solid state as uncomplexed ligand but in solution the keto and enol forms are in equilibrium[20], as shown in Fig. 2. The amide band was split, shifted to higher frequency and reduced in intensity as compared with the complexes. The shift ($15\,cm^{-1}$) to higher frequency of the ν(N–N) band at $\sim 1035\,cm^{-1}$ and its splitting indicates coordination of the azomethine nitrogen. Furthermore, comparison of the uncomplexed ligand with the complexed ones showed a low frequency shift ($10–15\,cm^{-1}$) of the band due to azomethine (HC = N) linkage at $1635\,cm^{-1}$ that indicates the involvement of the azomethine nitrogen in coordination. The absence of the OH band at ~ 3315 due to the salicylyl moiety in Schiff bases L^3 and L^4 and appearance of a new band instead at $1245\,cm^{-1}$ indicated deprotonation and coordination through oxygen. Furthermore, the appearance of a weak, low frequency new band at 445 and $515\,cm^{-1}$ was assigned[21,22] to metal-nitrogen ν(M–O) and ν(M–N) vibrations. These bands were only observable in the spectra of the metal complexes and not

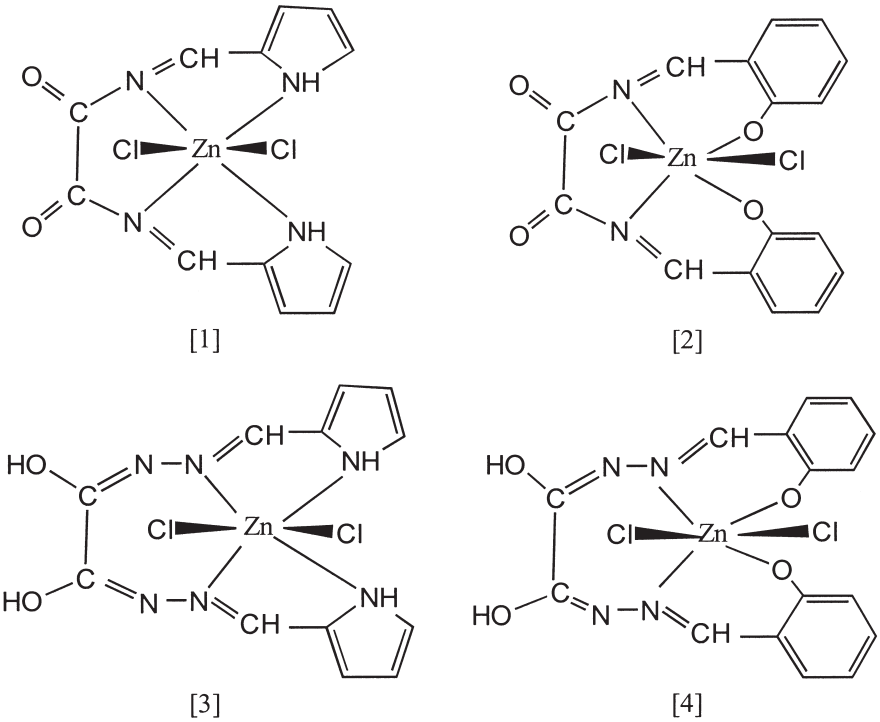

FIGURE 3 Proposed structures of the Zn(II) complexes prepared in this study.

in the spectra of their Schiff bases, which in turn, confirmed the participation of the heteroatom (NH) and deprotonated (OH) in the coordination. Also, a weak band at 355 cm^{-1} was found only in the spectra of the Zn(II) complexes due to the ν(M–Cl) mode which suggested[23,24] coordination of the metal ion with chloride anions, giving thus a clue to their octahedral geometry proposed below (structures 1–4 in Fig. 3).

The NMR spectra of the free ligands and their metal complexes were recorded in DMSO-d_6. The diagnostic features of the free ligands and their complexes are shown in Table II. The heteroaromatic and aromatic proton signals of the Schiff bases appeared at δ 4.3–5.9 and 6.5–7.9 ppm and the C = NH proton signals at δ 7.3 ppm as expected[25,26]. In the complexes, these proton signals appeared downfield, mainly due to increased conjugation during coordination of the metal ion[27]. ^{13}C NMR spectra of the free Schiff bases as well as their complexes (Table II), showed similar features[25]. Pyrrolyl and salicylyl carbons, on comparison with similarly reported[28,29] compounds, were found in the ranges of 104.5–122.8 and 124.8–142.9 ppm, whereas the azomethine carbon signals were at 152.6–153.3 ppm. The presence of the C = O signal at 187.6–188.0 ppm in the spectra of the ligand L^1 and L^3 and their complexes confirmed that these ligands retained their ketonic form in the ligand as well as the complexes. The absence of this signal in the spectra of the complexes of the ligand L^2 and L^4 and the appearance of a new signal at 155.2 ppm supported the view that L^2 and L^4 behaved in an enolized form. Furthermore the presence of bands at 153.2 and 153.3 ppm were assigned to C–O confirmed deprotonation of hydroxyl group of salicylyl moiety in the ligands L^2 and L^4 during coordination.

The electronic spectra of the complexes are consistent with an octahedral environment around the zinc(II) ion. The diamagnetic zinc(II) complexes did not show any d–d bands and their spectra are dominated only by charge transfer bands. The charge transfer band at 28,645–28,675 cm^{-1} was assigned[30,31] due to a $^2E_g \rightarrow {}^2T_{2g}$ transition.

On the basis of the above observations, it is tentatively suggested that Zn(II) complexes showed an octahedral geometry (Fig. 3, A–D) in which the ligands act tetradentately, with two chlorides also coordinated to the metal ion.

Antibacterial Studies

The title Schiff bases and their Zn(II) chelates were evaluated for antibacterial activity against the standard bacterial strains of *E. coli* (a), *Staphylococcus aureus* (b) and *Pseudomonas aeruginosa* (c) (Table III). The compounds were tested at a concentration of 30 μg/0.01 ml in DMF solution using the paper disc diffusion method[32,33]. The inhibition zones were the clear zones around the discs, which were measured in mm. All the Schiff bases described here were found to be biologically active and their Zn(II) complexes showed significantly enhanced

TABLE II NMR spectral data for the Schiff bases $\mathbf{L^1}$–$\mathbf{L^4}$ and their Zn(II) complexes **1**–**4**

Schiff base/complex	^{1}H NMR (DMSO-d_6) (ppm)	^{13}C NMR (DMSO-d_6) (ppm)
$\mathbf{L^1}$	4.3–4.5 (m, 1H, pyrrolyl), 4.8–5.0 (m,1H, pyrrolyl), 5.6–5.8 (m, 1H, pyrrolyl),7.3 (s, 1H, HC = N)	104.6, 112.6, 120.4, 122.5 (pyrrolyl), 152.6 (HC = N), 187.6 (C = O)
$\mathbf{L^2}$	4.6–4.8 (m, 1H, pyrrolyl), 5.1–5.2 (m, 1H, pyrrolyl), 5.7–5.9 (m, 1H, pyrrolyl),7.3 (s, 1H, HC = N), 10.8 (s, 1H, NH)	105.2, 112.7, 121.5, 122.8 (pyrrolyl), 152.7 (HC = N), 188.0 (C = O)
$\mathbf{L^3}$	6.5–6.7 (m, 1H, salicylyl), 6.8–7.0 (m, 1H, salicylyl), 7.4–7.6 (m, 1H, salicylyl), 7.7–7.9 (m, 1H, salicylyl), 7.3 (s, 1H, HC = N), 11.3 (s, 1H, OH)	142.8, 134.5, 128.6, 129.3, 126.6, 124.8 (salicylyl), 153.2 (HC = N), 187.6 (C = O)
$\mathbf{L^4}$	6.5–6.7 (m, 1H, salicylyl), 6.8–7.1 (m, 1H, salicylyl), 7.4–7.6 (m, 1H, salicylyl), 7.7–7.9 (m, 1H, salicylyl), 7.3 (s, 1H, HC = N), 10.8 (s, 1H, NH), 11.3 (s, 1H, OH)	142.9, 134.6, 128.6, 129.4, 126.7, 124.8 (salicylyl), 153.3 (HC = N)
1	4.4–4.6 (m, 1H, pyrrolyl), 4.8–5.0 (m, 1H, pyrrolyl), 5.7–5.9 (m, 1H, pyrrolyl), 7.5 (s, 1H, HC = N)	104.8, 112.7, 120.8, 122.8 (pyrrolyl), 153.2 (HC = N), 187.6 (C = O)
2	4.7–4.9 (m, 1H, pyrrolyl), 5.2–5.4 (m, 1H, pyrrolyl), 5.8–5.9 (m, 1H, pyrrolyl),7.7 (s, 1H, HC = N), 8.3 (s, 1H, NH)	155.2 (C–OH), 105.7, 112.9, 121.6, 122.8 (pyrrolyl), 153.1 (HC = N)
3	6.6–6.8 (m, 1H, salicylyl), 6.9–7.0 (m, 1H, salicylyl), 7.5–7.7 (m, 1H, salicylyl), 7.8–7.9 (m, 1H, salicylyl), 7.8 (s, 1H, HC = N), 11.3 (s, 1H, OH)	153.2, 134.7, 128.9, 129.6, 126.8, 124.8 (salicylyl), 153.8 (HC = N), 187.6 (C = O)
4	6.7–6.9 (m, 1H, salicylyl), 7.0–7.1 (m, 1H, salicylyl), 7.5–7.7 (m, 1H, salicylyl), 7.8–7.9 (m, 1H, salicylyl), 7.8 (s, 1H, HC = N), 8.3 (s, 1H, NH), 11.3 (s, 1H, OH)	155.2 (C–OH), 153.3, 134.7, 128.8, 129.5, 126.9, 124.8 (salicylyl), 153.8 (HC = N)

TABLE III Antibacterial activity of the Schiff bases $\mathbf{L^1}$–$\mathbf{L^4}$ and their Zn(II) Complexes **1**–**4**

	Microbial species		
Schiff base/complex	a	b	c
$\mathbf{L^1}$	++	++	+
$\mathbf{L^2}$	+	+	+
$\mathbf{L^3}$	++	+	+
$\mathbf{L^4}$	++	+	+
(**1**)	++++	++	+++
(**2**)	+++	+++	+++
(**3**)	+++	++	++++
(**4**)	+++	+++	+++

a = *E.coli*, b = *S.aureus*, c = *P.aeruginosa*. Inhibition zone diameter in 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) with 100% inhibition.

antibacterial activity against one or more bacterial species, in comparison to the parent ligand from which they were obtained. The metal complexes (**1**) and (**3**) significantly showed 100% inhibition against bacterial species (a) and (b), respectively. It is known that chelation tends to make the ligands act as more powerful and potent bactericidal agents, thus killing more of the bacteria than the parent Schiff bases do[34,35]. A possible explanation for this increased activity upon chelation is proposed here: it was suggested[33] 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 a π-electron delocalization over the whole chelate ring. This, in turn, increases the lipophilic character of the metal chelate and favors its permeation through the lipoid layers of the bacterial membranes. 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 increasing the biological activity of metal complexes as compared to the ligands from which they are derived.[36]

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