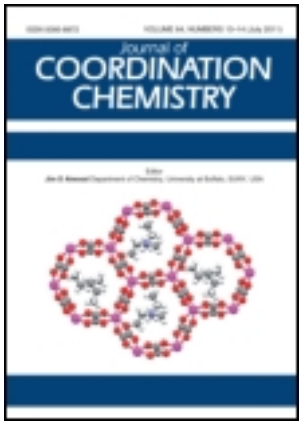

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Metal-based antibacterial agents: synthesis, characterization, and in vitro biological evaluation of cefixime-derived Schiff bases and their complexes with Zn(II), Cu(II), Ni(II), and Co(II)

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Metal-based antibacterial agents: synthesis, characterization, and *in vitro* biological evaluation of cefixime-derived Schiff bases and their complexes with Zn(II), Cu(II), Ni(II), and Co(II)

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The zinc(II), copper(II), nickel(II), and cobalt(II) complexes of Schiff bases, obtained by the condensation of cefixime with furyl-2-carboxaldehyde, thiophene-2-carboxaldehyde, salicylaldehyde, pyrrol-2-carboxaldehyde, and 3-hydroxynaphthalene-2-carboxaldehyde, were synthesized and characterized by their elemental analyses, molar conductances, magnetic moments, IR, and electronic spectral measurements. Analytical data and electrical conductivity measurements indicated the formation of M : L (1 : 2) complexes, $[M(L)_2(H_2O)_2]$ or $[M(L)_2(H_2O)_2]Cl_2$ [where M = Zn(II), Cu(II), Ni(II), and Co(II)] in which ligands are bidentate *via* azomethine-N and deprotonated-O of salicyl and naphthyl, furanyl-O, thienyl-S, and deprotonated pyrrolyl-N. The magnetic moments and electronic spectral data suggest octahedral complexes. The synthesized ligands, along with their metal complexes, were screened for their antibacterial activity against different bacterial strains. The studies show the metal complexes to be more active against one or more species as compared to the uncomplexed ligands.

Keywords: Metal-based; Schiff bases; Cefixime; Antibacterial

1. Introduction

Cephalosporins are important in the treatment of bacterial infections, exhibiting broad antibacterial activities with little toxicity and are generally well tolerated [1]. Structural modifications of the cephem nucleus have produced a variety of antimicrobial agents with improved spectra of activity and β-lactamase stability [2]. The antibiotic cefixime belongs to the third generation cephalosporin. The third generation has somewhat increased activity against Gram-negative microorganisms than the first and second generation cephalosporins.

The metal chelates of different cephalosporins have been studied because of their biological activity [3–5]. However, a survey of the literature reveals that metal chelates with Schiff bases derived from cephalosporin have not been reported. In continuation of earlier work [6, 7], we report a series of antibacterial Schiff bases derived by the condensation of cefixime (a third generation cephalosporin) with different aldehydes (L_1–L_5; figure 1) and their metal chelates (**1–20**; figures 2–4). The Schiff bases and their

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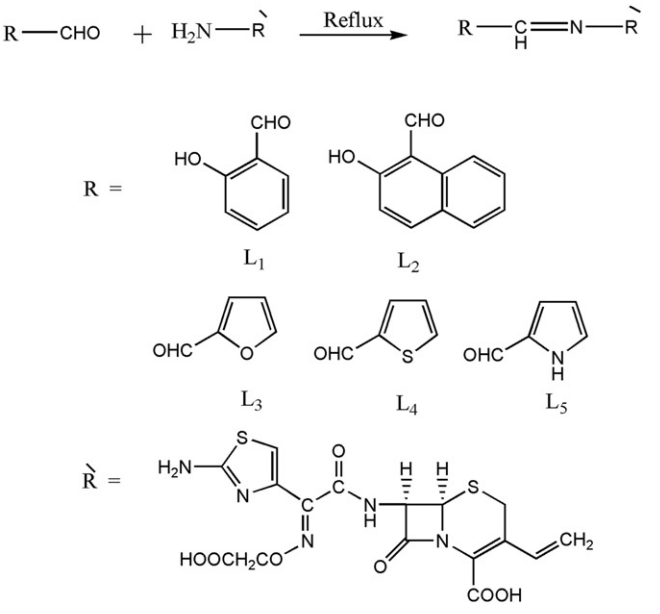

Figure 1. Proposed structure of Schiff-base ligands.

metal chelates were screened for antibacterial activity against *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, and *Klebsiella pneumoniae*. The Schiff bases showed increased antibacterial activity against certain strains and their activities were enhanced on chelation.

2. Experimental

2.1. *Materials and methods*

All chemicals, analytical grade, were purchased from Aldrich & Sigma and used as received. The solvents were redistilled by standard techniques before use. The metal contents of the complexes were determined by atomic absorption spectroscopy after decomposition with acid.

Elemental analyses were carried out on a Thermo Finnegan CHN MA 5200 elemental analyzer. FT-IR spectra were recorded with a Hitachi spectrometer using KBr disks. Magnetic moments were determined with a Gouy balance using $Hg[Co(NCS)_4]$ as the calibrant. Diamagnetic corrections were calculated from Pascal's constants [8]. Electronic absorption spectra of all the complexes were recorded on a Shimadzu spectrophotometer. Conductance measurements were done in DMSO (10^{-3} mol L^{-1}) using an electroconductivity bridge. ^1H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Avance DPX-400 spectrometer using TMS as internal standard and DMSO(d_6) as solvent. Electron impact mass spectra (EIMS) were recorded on a JEOL MS Route instrument.

2.2. *Preparation of Schiff bases (L_1–L_5)*

A stirred solution of cefixime (4.53 g, 10 mmol) in methanol (30 mL) was mixed with salicylaldehyde (1.3 g, 10 mmol) dissolved in methanol (25 mL). To this KOH (0.1% in methanol) was added to adjust the pH of the solution at 7–8 and the mixture was refluxed for ~30 min. A clear colored solution was obtained. The completion of reaction was monitored through TLC. After completion of the reaction, a few drops of dilute acetic acid were added to adjust the pH to 7. The volume was reduced to about one-third on a rotary evaporator and cooled to afford a solid product. The solid residue was filtered, washed with ethanol, then with ether, and dried. Crystallization from a mixture of ethanol–propanol (60 : 40) afforded the desired Schiff bases. The same method was applied for the preparation of all other ligands by using the corresponding aldehydes, working in the same conditions with their respective molar ratio.

2.2.1. 8-(2-Carboxymethoxyimino-2-{2-[(2-hydroxy-benzylidene)-amino]-thiazol-4-yl}-acetylamino)-7-oxo-4-vinyl-2-thia-bicyclo[4.2.0]oct-4-ene-5-carboxylic acid (L_1). Yield 85%; m.p. 154–156°C; (dark yellow), IR (KBr, cm^{-1}): 3435 (OH), 1610 (–HC = N), 1766 (C = O β-lactam), 1665 (C = O amide), 1595 (COO), 1320, 1480 (C–N); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.3–7.75 (m, 4H, –phenyl), 10.23 (s, 1H, –OH), 8.7 (s, 1H, HC = N), 11.0 (s, 1H, –COOH), 7.6 (s, 1H, thiozole), 9.1 (s, 1H, –NH–CO–), 6.1 (d, 1H, $J = 7.2$, β-lactam), 6.3 (d, 1H, $J = 7.4$, β-lactam), 2.1 (s, 2H, six-membered thiozole ring), 5.6 (t, 1H, vinyl), 4.47 (d, 2H, vinyl), 2.7 (s, 2H, –OCH_2–COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 176.31 (C_{13}–COOH), 170.45 (C_{15}, five-membered thiazole ring), 168.39 (C_{11}, –C = N), 163.62 (C_{17}, –CH = N), 163.43 (C_{10}, –HN–CO), 163.02 (C_2, β–lactam), 161.50 (C_7, –COOH), 157.82 (C_{19}, –OH–ph), 142.61 (C_5), 136.09 (C_8, C = CH_2), 132.24, 130.46, 121.25, 118.45, 115.82 (C_{18}, C_{20}–C_{23} phenyl), 58.12 (C_3, β-lactam ring), 57.33 (C_1, β-lactam); Anal. Calcd for $C_{23}H_{19}N_5O_8S_2$ (557.56) (%): C, 49.55; H, 3.41; N, 12.57. Found (%): C, 49.88; H, 3.42; N, 12.54. Mass spectrum (ESI) $[M]^+ = 557.10$. ^{1}H NMR of Zn(II) complex (DMSO-d_6, δ, ppm): 4.67 (d, 2H, CH_2), 7.48–7.87 (m, 4H, Ph), 8.32 (s, 1H, azomethine), 11.20 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 115.82, 118.45, 121.25, 130.46, 132.24, 157.82 (*Ph*OH), 164.42 (–*C*H = N), 176.34 (*C*OOH).

2.2.2. 8-(2-Carboxymethoxyimino-2-{2-[(2-hydroxy-naphthalen-2-ylmethylene)-amino] thiazol-4-yl}-acetylamino)-7-oxo-4-vinyl-2-thia-bicyclo[4.2.0]oct-4-ene-5-carboxylic acid (L_2). Yield 80%; m.p. 153–155°C; (dark yellow); IR (KBr, cm^{-1}): 3445 (OH), 1610 (–HC=N), 1770 (C=O β-lactam), 1668 (C=O amide), 1595 (COO), 1315, 1485 (C–N); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.35–7.81 (m, 6H, *Naph*), 8.11 (s, 1H, azomethine), 9.83 (s, 1H, OH), 11.10 (s, 1H, COOH), 7.5 (s, 1H, thiozole), 9.2 (s, 1H, –NH–CO–), 6.3 (d, 1H, $J = 7.2$, β-lactam), 6.4 (d, 1H, $J = 7.8$, β-lactam), 2.2 (s, 2H, six-membered thiozole ring), 5.8 (t, 1H, vinyl group), 4.47 (d, 2H, vinyl), 2.9 (s, 2H, –OCH_2–COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 176.38 (C_{13}–COOH), 170.42 (C_{15}, five-membered thiazole ring), 168.45 (C_{11}, –C=N), 163.65 (C_{17}, –CH=N), 163.21 (C_{10}, –HN–CO), 163.02 (C_2, β-lactam), 161.50 (C_7, –COOH), 142.61 (C_5), 136.09 (C_8, C=CH_2), 111.4–152.8 (nephthyl), 58.7 (C_3, β-lactam ring), 57.01 (C_1, β-lactam). Anal. Calcd for $C_{27}H_{21}N_5O_8S_2$ (607.61) (%): C, 53.38; H, 3.46; N, 11.53. Found (%): C, 53.82; H, 3.40;

N, 11.34. Mass spectrum (ESI) $[M]^+ = 607.10$. ^{1}H NMR of Zn(II) complex (DMSO-d_6, δ, ppm): 4.63 (d, 2H, CH_2), 7.38–7.89 (m, 6H, *Naph*), 8.31 (s, 1H, azomethine), 11.23 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, δ, ppm): 111.8–153.85 (*Naph*O), 164.21 (–*C*H = N), 176.38 (*C*OOH).

2.2.3. 8-(2-Carboxymethoxyimino-2-{2-[(furan-2-ylmethylene)-amino]-thiazol-4-yl}-acetylamino)-7-oxo-4-vinyl-2-thia-bicyclo[4.2.0]oct-4-ene-5-carboxylic acid (L_3). Yield 80%; m.p. 155–158°C; (dark orange), IR (KBr, cm^{-1}): 3245 (OH), 1615 (–HC=N), 1768 (C=O β-lactam), 1667 (C=O amide), 1590 (COOH), 1310, 1255 (C–O); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.4 (d, 1H, $J = 1.81$ Hz, furanyl C_5–H), 6.35 (dd, 1H, $J = 3.62$, 1.81 Hz, furanyl C_4–H), 6.95 (d, 1H, $J = 3.62$ Hz, furanyl C_3–H), 7.5 (s, 1H, HC=N), 7.3 (s, 1H, thiozole), 9.3 (s, 1H, –NH–CO–), 6.2 (d, 1H, $J = 7.1$, β-lactam), 6.3 (d, 1H, $J = 7.4$, β-lactam), 11.15 (s, 1H, COOH), 2.2 (s, 2H, six-membered thiozole ring), 5.8 (t, 1H, vinyl group), 4.45 (d, 2H, vinyl), 2.9 (s, 2H, –OCH_2–COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 170.31 (C_{13}–COOH), 170.05 (C_{15}, five-membered thiazole ring), 168.32 (C_{11}, –C=N), 163.71 (C_{17}, –CH=N), 163.42 (C_{10}, –HN–CO), 163.05 (C_2, β-lactam), 161.25 (C_7, –COOH), 143.7 (C_{19}, furanyl), 141.56 (C_{22}, furanyl), 141.91 (C_5), 138.6 (C_8, C=CH_2), 112.7 (C_{21}, furanyl), 110.4 (C_{20}, furanyl), 58.39 (C_3, β-lactam ring), 57.71 (C_1, β-lactam); Anal. Calcd for $C_{21}H_{17}N_5O_8S_2$ (531.45) (%): C, 47.46; H, 3.20; N, 13.18. Found (%): C, 47.68; H, 3.40; N, 13.34. Mass spectrum (ESI) $[M]^+ = 531.08$. ^{1}H NMR of Zn(II) complex (DMSO-d_6, δ, ppm): 4.67 (d, 2H, CH_2), 6.38–7.45 (m, 3H, *furanyl*), 7.73 (s, 1H, azomethine), 11.21 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 110.8–143.80 (*furanyl*), 164.20 (–*C*H=N), 170.38 (*C*OOH).

2.2.4. 8-(2-Carboxymethoxyimino-2-{2-[(thiophene-2-ylmethylene)-amino]-thiazol-4-yl}-acetylamino)-7-oxo-4-vinyl-2-thia-bicyclo[4.2.0]oct-4-ene-5-carboxylic acid (L_4). Yield 78%; m.p. 170–172°C; (yellowish orange), IR (KBr, cm^{-1}): 3250 (OH), 1620 (–HC=N), 1765 (C=O β-lactam), 1670 (C=O amide), 1585 (COO), 755 (C–S); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.11 (d, 1H, $J = 4.78$ Hz, thienyl, C_5–H), 7.0 (dd, 1H, $J = 4.78$, 3.85 Hz, thienyl, C_4–H), 7.21 (d, 1H, $J = 3.85$ Hz, thienyl, C_3–H), 7.55 (s, 1H, HC=N), 7.7 (s, 1H, thiozole), 9.2 (s, 1H, –NH–CO–), 6.7 (d, 1H, $J = 7.3$, β-lactam), 6.7 (d, 1H, $J = 7.4$, β-lactam), 11.10 (1H, –COOH), 2.5 (s, 2H, six-membered thiozole ring), 5.9 (t, 1H, vinyl group), 4.45 (d, 2H, vinyl), 4.47 (s, 2H, –OCH_2–COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 170.21 (C_{13}–COOH), 170.12 (C_{15}, five-membered thiazole ring), 168.37 (C_{11}, –C=N), 163.70 (C_{17}, –CH=N), 163.53 (C_{10}, –HN–CO), 163.09 (C_2– β-lactam), 161.28 (C_7, –COOH), 144.6 (C_{19}, thienyl), 141.95 (C_5), 138.6 (C_8, C=CH_2), 127.80 (C_{22}, thienyl), 127.48 (C_{21}, thienyl), 126.4 (C_{20}, thienyl), 58.39 (C_3, β-lactam ring), 57.71 (C_1, β-lactam); Anal. Calcd for $C_{21}H_{17}N_5O_7S_3$ (547.56) (%): C, 46.07; H, 3.11; N, 12.80. Found (%): C, 47.65; H, 3.45; N, 12.34. Mass spectrum (ESI) $[M]^+ = 547.07$. ^{1}H NMR of Zn(II) complex (DMSO-d_6, δ, ppm): 4.57 (d, 2H, CH_2), 7.23–7.45 (m, 3H, *thienyl*), 7.85 (s, 1H, azomethine), 11.20 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 126.8–127.80 (*thienyl*), 164.25 (–*C*H=N), 170.58 (*C*OOH).

2.2.5. 8-(2-Carboxymethoxyimino-2-{2-[(1H-pyrrol-2-ylmethylene)-amino]-thiazol-4-yl}-acetylamino)-7-oxo-4-vinyl-2-thia-bicyclo[4.2.0]oct-4-ene-5-carboxylic acid (L_5). Yield

78%; m.p. 170°C; IR (KBr, cm^{-1}): 3310 (NH), 3250 (OH), 1610 (–HC=N), 1765, (C=O β-lactam), 1660 (C=O amide), 1590 (COO), ^{1}H NMR (DMSO-d_6, δ, ppm): 6.43 (d, 1H, $J = 2.87$ Hz pyrrolyl, C_5–H), 6.2 (dd, 1H, $J = 3.95$, 2.87 Hz, pyrrolyl, C_4–H), 6.61 (d, 1H, $J = 3.95$ Hz, pyrrolyl, C_3–H), 9.7 (s, 1H, pyrrolyl, NH), 7.5 (s, 1H, HC=N), 7.3 (s, 1H, thiozole), 9.2 (s, 1H, –NH–CO–), 6.3 (d, 1H, $J = 7.4$, β-lactam), 6.5 (d, 1H, $J = 7.1$, β-lactam), 11.10 (s, 1H, COOH), 2.3 (s, 2H, six-membered thiozole ring), 5.9 (t, 1H, vinyl), 4.47 (d, 2H, vinyl), 2.6 (s, 2H, $-OCH_2$–COOH); ^{13}C NMR (DMSO-d_6, δ, ppm): 170.60 (C_{13}–COOH), 170.23 (C_{15}, five-membered thiazole ring), 168.31 (C_{11}, –C=N), 163.75 (C_{17}, –CH=N), 163.57 (C_{10}, –HN–CO), 163.17 (C_2, β-lactam), 161.22 (C_7, –COOH), 141.95 (C_5), 134.5 (C_{19}, pyrrolyl), 128.75 (C_8, C=CH_2), 118.70 (C_{22}, pyrrolyl), 108.4 (C_{21}, pyrrolyl), 126.4 (C_{20}, pyrrolyl), 59.2 (C_3, β-lactam ring), 54.4 (C_1, β-lactam); Anal. Calcd for $C_{21}H_{18}N_6O_7S_2$ (530.63) (%): C, 47.55; H, 3.40; N, 15.85. Found (%): C, 47.60; H, 3.45; N, 15.54. Mass spectrum (ESI) $[M]^+ = 530.08$. ^{1}H NMR of Zn(II) complex (DMSO-d_6, δ, ppm): 4.50 (d, 2H, CH_2), 6.23–6.65 (m, 3H, *pyrrolyl*), 7.90 (s, 1H, azomethine), 11.15 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6, δ, ppm): 108.8–118.85 (*pyrrolyl*), 164.35 (–*C*H=N), 170.60 (*C*OOH).

2.3. *Preparation of Schiff-base metal complexes (1–20)*

The Schiff base (L_1) (2.23 g, 2 mmol) dissolved in methanol (25 mL) was mixed with $CuCl_2 \cdot 2H_2O$ (0.171 g, 1 mmol) dissolved in methanol (25 mL). The reaction mixture was refluxed for 3–4 h. The volume was reduced to about one-third on a rotary evaporator and then cooled to room temperature. On cooling a solid product precipitated, was filtered off, washed with methanol, then with ether, and dried under vacuum. Crystallization from hot methanol gave the desired metal complex. The same method was used for the preparation of all other complexes by using their respective hydrated metal(II) chlorides.

2.4. *Antibacterial activity*

All the synthesized ligands (L_1–L_5) and their corresponding metal(II) complexes (**1–20**) were screened *in vitro* for their antibacterial activity against *E. coli*, *E. faecalis*, *S. aureus*, *P. aeruginosa*, *S. enteritidis*, and *K. pneumonia* bacterial strains using agar-well diffusion method, as described previously [9]. Two- to eight-hour-old bacterial inoculums containing approximately 104–106 colony forming units (CFU) mL^{-1} were used in these assays. Wells were dug in the media with a sterile metallic borer with centers at least 24 mm. Recommended concentration of the test sample in DMSO was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated at 37°C for 20 h. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug [10]. In order to clarify any role of DMSO in the biological screening, separate studies were carried out with DMSO alone, which showed no activity against any bacterial strains.

2.5. *Minimum inhibitory concentration*

The minimum inhibitory concentrations (MIC)s of selected compounds, which showed significant activity against selected bacterial strains, were determined using the disk diffusion method [11] by preparing disks containing 10, 25, 50, and 100 $\mu g\,mL^{-1}$ and applying the reported protocol. MIC was the lowest concentration of an antimicrobial compound at which the inhibition of growth occurred.

3. Results and discussion

L_1–L_5 were prepared by refluxing the appropriate amount of cefixime with the corresponding heteroaromatic (salicylaldehyde and 3-hydroxynaphthalene-2-carboxaldehyde) and heterocyclic (furyl-2-carboxaldehyde, thiophene-2-carboxaldehyde, and pyrrole-2-carboxaldehyde) systems, respectively, in methanol. The structures of synthesized Schiff-base ligands were established by IR, NMR, and microanalytical data. The air and moisture stable metal complexes (**1–20**) of these ligands were prepared by the stoichiometric reaction of the corresponding metal(II) chloride hydrate with the ligand in a molar ratio M : L of 1 : 2. The synthesized colored complexes were amorphous solids which decomposed without melting and were only soluble in DMSO. Karl–Fischer titrations indicated the presence of water in all these complexes. Molar conductance values (table 1) of the soluble complexes in DMSO (10^{-3} mol L^{-1} solution at 25°C) indicated that complexes with salicylaldehyde, 3-hydroxynaphthalene-2-carboxaldehyde, and pyrrole-2-carboxaldehyde have low values (20–25 $\Omega^{-1}\,cm^{-2}\,mol^{-1}$) indicating that they are non electrolytes, whereas complexes with furyl-2-carboxaldehyde and thiophene-2-carboxaldehyde have high values (120–125 $\Omega^{-1}\,cm^{-2}\,mol^{-1}$) indicating that they are electrolytic [12]. Elemental analyses of the Schiff bases (reported in experimental) and their complexes (table 2) are compatible with the structures shown in figure 1 and with that of formulae of the complexes, $[M(L)_2(H_2O)_2]$ where [M = Zn(II), Cu(II), Ni(II), or Co(II) and L = L_1, L_2, or L_5] and $[M(L)_2(H_2O)_2]Cl_2$ where [M = Zn(II), Cu(II), Ni(II), or Co(II) and L = L_3 or L_4]. The suggested structures of the ligands and their complexes are shown in figures 1–4.

3.1. *IR spectra*

IR spectra of the ligands showed the absence of bands at 1735 and 3420 cm^{-1} due to ν(C=O) and $\nu(NH_2)$ stretching vibrations and instead, a new band appeared at ~1620 cm^{-1} assigned [13] to azomethine ν(HC=N). This suggested that amino and aldehyde moieties of the starting reagents have been converted into the corresponding Schiff bases (figure 1). The bonding of the synthesized Schiff bases to metal ions was investigated by comparing FT-IR spectra of the complexes with those of the free ligands. Some important absorption bands and their assignments are given in table 3. The spectra of these complexes exhibited a broad band around 3445–3540 cm^{-1}, assigned to water, ν(OH), associated with the complexes. In addition to these modes, coordinated water exhibited $\delta r(H_2O)$ rocking at 850–890 cm^{-1} and $\delta w(H_2O)$ wagging at 540–550 cm^{-1} [13]. The spectra of all the ligands contained a band at 1610–1620 cm^{-1}, ν(C=N), which shifted to higher values (1615–1645 cm^{-1}) in the complexes suggesting

that the ligands coordinate to the metal ion through azomethine [14]. The absence of O–H and N–H stretching and bending vibrations, for salicyl-, naphthyl-, and pyrrolyl-, from the spectra of the complexes indicate the deprotonation of O–H and/or N–H, confirming formation of a bond to metal. A medium sharp band due to ν(C–O) and ν(C–S) is found at 1140–1150 and 760–750 cm^{-1}, respectively, in the spectra of the complexes which indicate the formation of a coordinate bond through these moieties [15]. The absorption due to lactam (C=O) and carboxylic groups did not change in spectra of the complexes, indicating that these groups are not involved in coordination. New absorption bands ν(M–N), ν(M–O), and ν(M–S) appeared at 510–520, 420–430, and 380–390 cm^{-1}, respectively, in the spectra of the complexes which indicate the coordination of the ligands through nitrogen, oxygen, and sulfur [16].

3.2. *^{1}H-NMR spectra*

^{1}H-NMR spectra of the Schiff bases (L_1–L_5) displayed the azomethine [17] proton (–CH=N) at δ 7.5–8.7 as a singlet. Multiplets at 6.9–7.75 ppm due to phenyl protons were also present with a hydroxyl proton as a singlet at δ 10.23 and 10.85. Similarly in ^{1}H-NMR spectra of L_2 six protons in naphthalene moiety C_{3-8}–H appear as a multiplet at δ 6.7–7.5 and the hydroxyl proton as a singlet at δ 9.83 due to its attachment with naphthalene. ^{1}H-NMR spectra of L_1–L_5 doublets from CO–CH and N–CH on the β-lactam ring and NH appear at 6.1–6.6 and 9.1–9.3 ppm, respectively [18]. In ^{1}H NMR spectrum of Schiff bases single peaks attributed to –CH_2–COOH appear at 2.9 and 11.10 ppm, respectively. In all the ligands, a singlet appeared at δ 2.3–2.6 due to 2H of the six-membered thiazole ring while a singlet also appeared at δ 7.5–7.7 due to 1H of the five-membered thiazole.

3.3. *^{13}C NMR spectra*

The ^{13}C NMR spectra of free ligands and their diamagnetic Zn(II) complexes were recorded in CD ^{13}C/DMSO-d_6 and reported along with possible assignments in the experimental section. Comparison of chemical shifts of the ligands with those of the complexes shows that the signal due to phenolic proton (L_1–L_2) and pyrrolyl-NH were absent in the complexes, suggesting coordination after deprotonation [19]. The azomethine proton (–CH=N–) undergoes a significant shift, indicating coordination of the azomethine nitrogen. More detailed information about the structure of the ligands was provided by ^{13}C NMR spectra. All the carbon atoms due to heteroatomic and/or aromatic groups were found in their expected region [20, 21]. In the spectra of diamagnetic Zn(II) chelates, these signals shifted downfield due to the increased conjugation and coordination to the metal ions. The number of protons and carbons calculated from the integration curves agreed with those obtained from the values of the CHN analysis.

3.4. *Magnetic and electronic absorption spectral studies*

The Co(II) complexes exhibited well-resolved bands around 17,560–17,650 cm^{-1} and a strong high-energy band at 21,767–21,790 cm^{-1} (table 1), which were assigned to

$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$, respectively, for a high-spin octahedral geometry. The magnetic susceptibility measurements (4.7–4.9 BM) for the solid Co(II) complexes are also indicative of three unpaired electrons per Co(II) ion consistent with their octahedral environment [22]. The electronic absorption spectrum of the Cu(II) complex showed a single low-intensity broad band at 15,256–15,320 cm^{-1}, typical for an octahedral configuration. The magnetic moment (1.7–1.9 BM) suggested one unpaired electron per Cu(II) consistent with their octahedral environment [23]. The spectrum of the Ni(II) complex showed d–d bands at 12,978–13,020, 16,565–16,630, and 24,385–24,440 cm^{-1}, assigned to the spin-allowed transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, respectively, consistent with octahedral configuration. The magnetic moment of 3.1–3.4 BM suggested two unpaired electrons per Ni(II) also consistent with octahedral geometry. The spectrum of the Zn(II) complex exhibited only a high-intensity band at 28,370–28,405 cm^{-1}, which was assigned to a ligand-to-metal charge transfer [24, 25].

3.5. *Thermogravimetric analysis*

Thermogravimetric analyses (TGA) for the complexes were carried out from room temperature to 700°C. Coordinated waters are usually eliminated at higher temperatures than those of hydration [26, 27], usually in the temperature range 100–350°C. The ligand together with the anions (Cl^-) in the complexes may decompose in more than two steps with the formation of intermediates [28, 29]; calculated and estimated mass losses are comparable.

The TGA curve of Schiff-base metal complexes from L_1, L_2, and L_5 have two stages of mass loss, at ≈135–223°C and at 223–595°C. At 82–109°C, the estimated mass loss of 5.47–5.67% may be due to the loss of two Cl atoms in complexes of L_3 and L_4. Weight loss in the range 102–227°C with estimated mass loss of 2.65–3.05% in all the complexes indicates the loss of two coordinated waters. From 210°C to 595°C, a sharp decrease in weight indicated the loss of one Schiff base from the complexes with estimated mass loss of 42.85–46.35% for all the complexes, respectively. The data are given in table 4.

In general, the stages of thermal decomposition of the metal complexes may be summarized by the following equations.

First decomposition step is represented as

$$[M(L)_2(2H_2O)]Cl_2 \xrightarrow{80-110^\circ C} [M(L)_2(2H_2O)] + Cl_2$$

$$[M(L)_2(2H_2O)] \underset{\text{Dehydration}}{\xrightarrow{102-227^\circ C}} [M(L)_2] + 2H_2O,$$

where M = Cu, Ni, Co, and Zn.

In the second step of decomposition, the loss of ligand occurs

$$[M(L)_2] \underset{\text{final decomp.}}{\xrightarrow{227-595^\circ C}} ML + L.$$

The molecular masses determined mass spectrometrically (table 1) also confirmed the ML_2 composition. Based upon experimental evidence thus obtained, the complexes were characterized as six coordinates with the two positions occupied by water. The

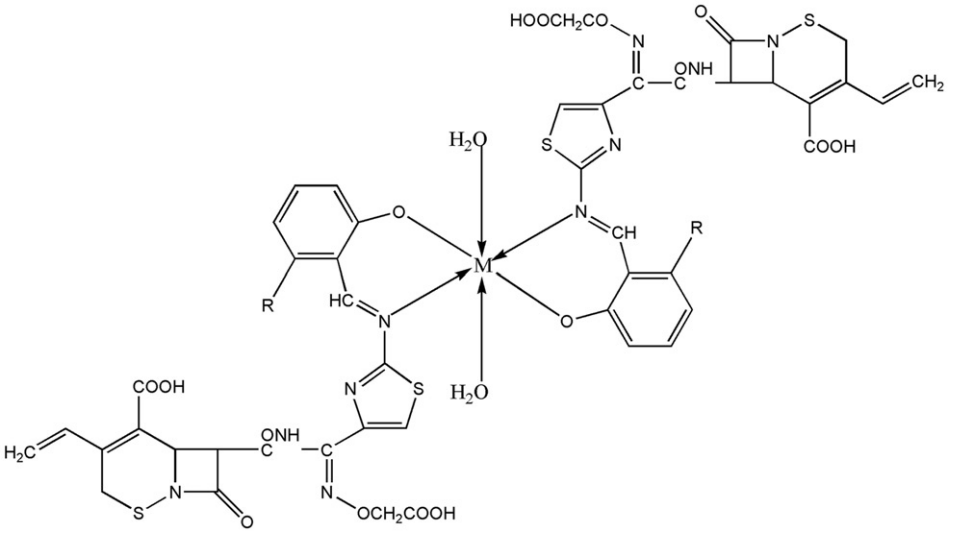

Figure 2. Proposed structure of metal complexes of L_1 and L_2, where R = H and phenyl; M = Zn(II), Cu(II), Ni(II), and Co(II).

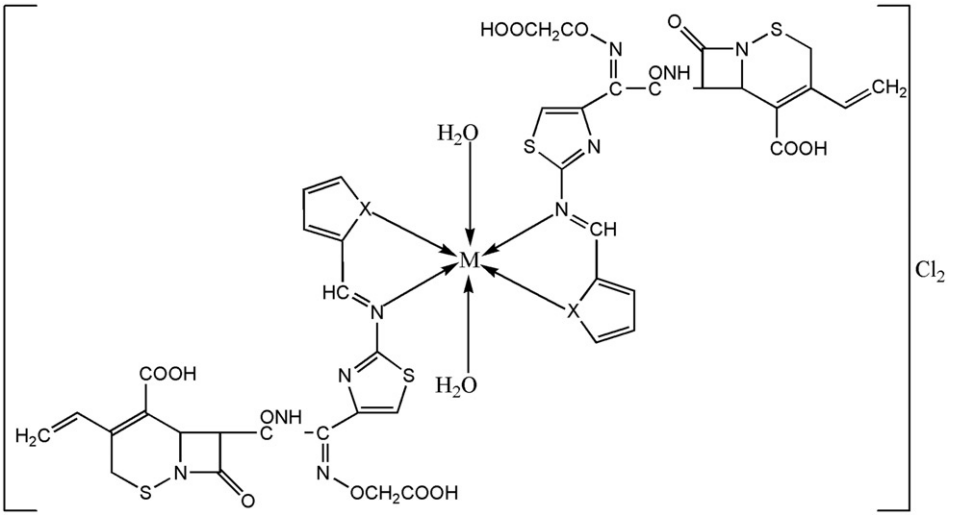

Figure 3. Proposed structure of metal complexes of L_3 and L_4, where X = O and S; M = Zn(II), Cu(II), Ni(II), and Co(II).

hydrated complexes have significant importance in the enzymatic systems, as the substrates can bind to metal by substituting the coordinated water. The proposed structures of the complexes under investigation, on the basis of above experimental evidence, are shown in figures 2–4. Unsuccessful attempts to isolate crystals suitable for X-ray analysis prevented further structure elucidation.

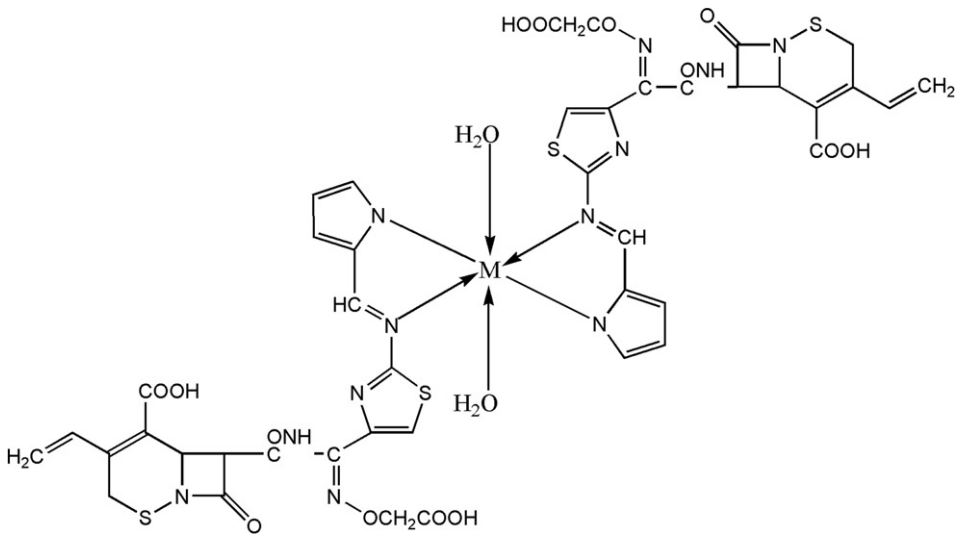

Figure 4. Proposed structure of metal complexes of L_5, where M = Zn(II), Cu(II), Ni(II), and Co(II).

Table 1. Physical and spectral data of the metal(II) complexes (**1–20**).

Metal chelates		Molar conductance ($\Omega^{-1}cm^{-2}mol^{-1}$)	μ (BM)	λ_{max} ($cm^{-1}mol^{-1}$)
1	(M^+: 1210 *m/e*)	20	Dia	–
2	(M^+: 1211 *m/e*)	24	1.8	15,256
3	(M^+: 1206 *m/e*)	22	3.2	12,978; 16,570; 24,390
4	(M^+: 1206 *m/e*)	20	4.7	17,560; 21,780
5	(M^+: 1310 *m/e*)	25	Dia	–
6	(M^+: 1311 *m/e*)	20	1.7	15,320
7	(M^+: 1306 *m/e*)	21	3.4	13,020; 16,565; 24,385
8	(M^+: 1306 *m/e*)	24	4.9	17,620; 21,767
9	(M^+: 1231 *m/e*)	120	Dia	–
10	(M^+: 1232 *m/e*)	124	1.9	15,280
11	(M^+: 1227 *m/e*)	122	3.1	13,010; 16,630; 24,430
12	(M^+: 1227 *m/e*)	125	4.9	17,650; 21,780
13	(M^+: 1263 *m/e*)	123	Dia	–
14	(M^+: 1264 *m/e*)	124	1.8	15,275
15	(M^+: 1259 *m/e*)	121	3.3	12.980; 16,590; 24,440
16	(M^+: 1259 *m/e*)	125	4.8	17,590; 21,790
17	(M^+: 1156 *m/e*)	20	Dia	–
18	(M^+: 1157 *m/e*)	23	1.7	15,310
19	(M^+: 1152 *m/e*)	22	3.2	12,980; 16,610; 24,425
20	(M^+: 1152 *m/e*)	25	4.7	17,625; 21,785

3.6. *Biological activity*

All compounds were tested against *E. coli*, *E. faecalis*, *S. aureus*, *P. aeruginosa*, *S. enteritidis*, and *K. pneumonia* bacterial strains (table 5) according to literature protocol [10]. The ligands were active against one or more bacterial strains. Cobalt(II), copper(II), nickel(II), and zinc(II) metal complexes of these synthesized ligands (L_1–L_5)

Table 2. Physical and analytical data of the metal(II) complexes (**1–20**).

No.	Metal chelates (mol. wt.)	Color	m.p. (°C)	Yield (%)	Calculated (Found) %			
					C	H	N	M
1	$[Zn(L_1)_2(H_2O)_2]$ [1211.39] $C_{46}H_{40}N_{10}O_{18}S_4Zn$	Pale yellow	230	70	45.57 (45.50)	3.30 (3.70)	11.56 (11.20)	5.23 (5.40)
2	$[Cu(L_1)_2(H_2O)_2]$ [1211.54] $C_{46}H_{40}N_{10}O_{18}S_4Cu$	Dark green	235	75	45.56 (45.62)	3.30 (3.60)	11.56 (11.31)	5.24 (5.25)
3	$[Ni(L_1)_2(H_2O)_2]$ [1206.69] $C_{46}H_{40}N_{10}O_{18}S_4Ni$	Light green	232	72	45.74 (45.79)	3.31 (3.72)	11.60 (11.10)	4.86 (4.80)
4	$[Co(L_1)_2(H_2O)_2]$ [1206.93] $C_{46}H_{40}N_{10}O_{18}S_4Co$	Pink	237	73	45.74 (45.89)	3.31 (3.75)	11.60 (11.32)	4.88 (4.81)
5	$[Zn(L_2)_2(H_2O)_2]$ [1311.39] $C_{54}H_{44}N_{10}O_{18}S_4Zn$	Pale yellow	245	69	49.41 (49.01)	3.36 (3.53)	10.68 (10.47)	4.83 (4.90)
6	$[Cu(L_2)_2(H_2O)_2]$ [1311.54] $C_{54}H_{44}N_{10}O_{18}S_4Cu$	Green	242	73	49.41 (49.12)	3.35 (3.69)	10.67 (10.68)	4.84 (4.73)
7	$[Ni(L_2)_2(H_2O)_2]$ [1306.69] $C_{54}H_{44}N_{10}O_{18}S_4Ni$	Light green	240	75	49.59 (49.32)	3.37 (3.59)	10.71 (10.67)	4.49 (4.52)
8	$[Co(L_2)_2(H_2O)_2]$ [1306.93] $C_{54}H_{44}N_{10}O_{18}S_4Co$	Pink	248	72	49.58 (49.16)	3.37 (3.68)	1.71 (10.68)	4.51 (4.61)
9	$[Zn(L_3)_2(H_2O)_2]Cl_2$ [1232.39] $C_{42}H_{38}N_{10}O_{18}S_4Cl_2Zn$	Off white	236	71	40.90 (41.01)	3.08 (3.20)	11.36 (11.15)	5.14 (5.09)
10	$[Cu(L_3)_2(H_2O)_2]Cl_2$ [1232.54] $C_{42}H_{38}N_{10}O_{18}S_4Cl_2Cu$	Dark green	232	75	40.89 (40.99)	3.08 (3.35)	11.36 (11.18)	5.16 (5.21)
11	$[Ni(L_3)_2(H_2O)_2]Cl_2$ [1227.69] $C_{42}H_{38}N_{10}O_{18}S_4Cl_2Ni$	Sea green	238	72	41.05 (41.01)	3.10 (3.13)	11.40 (11.19)	4.78 (4.85)
12	$[Co(L_3)_2(H_2O)_2]Cl_2$ [1227.93] $C_{42}H_{38}N_{10}O_{18}S_4Cl_2Co$	Pink	240	70	41.04 (41.17)	3.09 (3.31)	11.40 (11.20)	4.80 (4.75)
13	$[Zn(L_4)_2(H_2O)_2]Cl_2$ [1264.39] $C_{42}H_{38}N_{10}O_{16}S_6Cl_2Zn$	Pale yellow	260	73	39.86 (39.72)	3.01 (3.21)	11.07 (11.59)	5.01 (4.99)
14	$[Cu(L_4)_2(H_2O)_2]Cl_2$ [1264.54] $C_{42}H_{38}N_{10}O_{16}S_6Cl_2Cu$	Dark green	255	71	39.86 (39.79)	3.01 (3.17)	11.07 (11.47)	5.02 (5.08)
15	$[Ni(L_4)_2(H_2O)_2]Cl_2$ [1259.69] $C_{42}H_{38}N_{10}O_{16}S_6Cl_2Ni$	Light green	256	74	40.01 (40.03)	3.02 (3.12)	11.11 (11.48)	4.66 (4.57)
16	$[Co(L_4)_2(H_2O)_2]Cl_2$ [1259.93] $C_{42}H_{38}N_{10}O_{16}S_6Cl_2Co$	Brown	255	73	40.00 (40.05)	3.02 (3.21)	11.11 (10.83)	4.68 (4.69)

(*Continued*)

Table 2. Continued.

No.	Metal chelates (mol. wt.)	Color	m.p. (°C)	Yield (%)	Calculated (Found) %			
					C	H	N	M
17	$[Zn(L_5)_2(H_2O)_2]$ [1157.39] $C_{42}H_{38}N_{12}O_{16}S_4Zn$	Off white	245	75	43.55 (43.65)	3.28 (3.45)	14.52 (14.18)	5.48 (5.42)
18	$[Cu(L_5)_2(H_2O)_2]$ [1157.54] $C_{42}H_{38}N_{12}O_{16}S_4Cu$	Greenish brown	243	72	43.54 (43.62)	3.28 (3.50)	14.51 (14.07)	5.49 (5.45)
19	$[Ni(L_5)_2(H_2O)_2]$ [1152.69] $C_{42}H_{38}N_{12}O_{16}S_4Ni$	Green	250	74	43.72 (43.79)	3.30 (3.41)	14.57 (14.20)	5.09 (5.12)
20	$[Co(L_5)_2(H_2O)_2]$ [1152.93] $C_{42}H_{38}N_{12}O_{16}S_4Co$	Dark pink	248	75	43.71 (43.89)	3.30 (3.53)	14.57 (14.61)	5.11 (5.08)

Table 3. Observed IR frequencies (cm^{-1}) and assignments.

Metal chelates	ν(OH)	ν(C=N)	ν(CO)lact	ν(COO)	ν(MN)	ν(MO)	ν(MS)
1	3540	1630	1775	1590	510	419	–
2	3500	1625	1770	1595	512	420	–
3	3520	1635	1770	1590	520	425	–
4	3510	1625	1775	1595	511	430	–
5	3535	1630	1780	1592	514	430	–
6	3445	1630	1770	1591	519	427	–
7	3525	1625	1775	1592	516	426	–
8	3505	1635	1780	1595	520	428	–
9	3530	1640	1780	1591	513	420	–
10	3505	1630	1775	1593	512	426	–
11	3530	1635	1770	1589	518	430	–
12	3520	1640	1770	1590	510	430	–
13	3530	1645	1780	1582	517	421	390
14	3495	1640	1770	1580	515	423	380
15	3525	1635	1775	1582	516	426	385
16	3515	1640	1780	1584	520	420	390
17	3535	1620	1770	1588	515	430	–
18	3500	1615	1770	1587	513	427	–
19	3530	1610	1775	1590	518	423	–
20	3510	1620	1775	1585	513	421	–

Table 4. Thermal analyses (TGA and DTA) results of cef-binary chelates.

Complexes	Temperature range (°C)	Mass loss % Found (Calcd)	Assignment
1	155–220	2.81 (2.97)	Loss of $2H_2O$
	220–590	45.65 (45.98)	Loss of (L_1) + metallic residue
2	150–215	2.85 (2.97)	Loss of $2H_2O$
	215–592	45.58 (45.99)	Loss of (L_1) + metallic residue
3	150–210	2.87 (2.98)	Loss of $2H_2O$
	210–585	46.03 (46.16)	Loss of (L_1) + metallic residue
4	157–220	2.86 (2.98)	Loss of $2H_2O$
	220–595	46.05 (46.18)	Loss of (L_1) + metallic residue
5	150–223	2.65 (2.74)	Loss of $2H_2O$
	223–584	46.11 (46.28)	Loss of (L_2) + metallic residue
6	156–210	2.67 (2.73)	Loss of $2H_2O$
	210–590	46.15 (46.27)	Loss of (L_2) + metallic residue
7	150–225	2.71 (2.75)	Loss of $2H_2O$
	225–590	46.35 (46.47)	Loss of (L_2) + metallic residue
8	157–210	2.67 (2.74)	Loss of $2H_2O$
	210–593	46.35 (46.46)	Loss of (L_2) + metallic residue
9	82–109	5.57 (5.67)	Loss of $2Cl_2$
	109–227	2.67 (2.73)	Loss of $2H_2O$
	227–559	42.95 (43.10)	Loss of (L_3) + metallic residue
10	82–109	5.47 (5.65)	Loss of $2Cl_2$
	109–225	2.65(2.74)	Loss of $2H_2O$
	225–558	42.85 (43.09)	Loss of (L_3) + metallic residue
11	80–110	5.67 (5.70)	Loss of $2Cl_2$
	110–225	2.87(2.93)	Loss of $2H_2O$
	225–590	43.15 (43.24)	Loss of (L_3) + metallic residue
12	83–110	5.67 (5.70)	Loss of $2Cl_2$
	110–220	2.85 (2.93)	Loss of $2H_2O$
	220–593	43.17 (43.25)	Loss of (L_3) + metallic residue

13	83–110	5.47 (5.53)	Loss of $2Cl_2$
	110–227	2.75 (2.84)	Loss of $2H_2O$
	227–595	43.25 (43.27)	Loss of (L_4) + metallic residue
14	75–105	5.51 (5.54)	Loss of $2Cl_2$
	105–225	2.76 (2.83)	Loss of $2H_2O$
	225–587	43.08 (43.25)	Loss of (L_4) + metallic residue
15	70–102	5.52 (5.55)	Loss of $2Cl_2$
	102–217	2.81 (2.87)	Loss of $2H_2O$
	217–590	43.33 (43.41)	Loss of (L_4) + metallic residue
16	77–105	5.48 (5.56)	Loss of $2Cl_2$
	105–210	2.79 (2.86)	Loss of $2H_2O$
	210–593	43.15 (43.40)	Loss of (L_4) + metallic residue
17	135–220	3.02 (3.11)	Loss of $2H_2O$
	220–574	45.75 (45.80)	Loss of (L_5) + metallic residue
18	138–223	3.02 (3.10)	Loss of $2H_2O$
	223–587	45.68 (45.79)	Loss of (L_5) + metallic residue
19	135–219	3.05 (3.13)	Loss of $2H_2O$
	219–585	45.85 (46.00)	Loss of (L_5) + metallic residue
20	137–211	3.05 (3.12)	Loss of $2H_2O$
	211–590	45.78 (45.99)	Loss of (L_5) + metallic residue

Table 5. Antibacterial activity of cefixime Schiff base and their metal complexes (zone of inhibition in mm) ($400\,\mu g\,mL^{-1}$).

No.	Compounds	(a)	(b)	(c)	(d)	(e)	(f)
1	Cefixime	35	21	40	9	44	25
2	L_1	37	23	42	10	46	26
3	L_2	37	25	43	7	46	23
4	L_3	39	23	42	10	47	26
5	L_4	36	23	44	11	48	27
6	L_5	36	25	42	10	46	26
7	$[Zn(L_1)_2(H_2O)_2]$	50	36	55	17	60	40
8	$[Cu(L_1)_2(H_2O)_2]$	46	32	50	15	57	38
9	$[Ni(L_1)_2(H_2O)_2]$	40	25	44	11	48	26
10	$[Co(L_1)_2(H_2O)_2]$	42	29	48	13	51	33
11	$[Zn(L_2)_2(H_2O)_2]$	50	38	55	15	61	38
12	$[Cu(L_2)_2(H_2O)_2]$	46	34	50	12	58	37
13	$[Ni(L_2)_2(H_2O)_2]$	39	28	45	10	48	25
14	$[Co(L_2)_2(H_2O)_2]$	42	30	48	11	51	30
15	$[Zn(L_3)_2(H_2O)_2]Cl_2$	52	36	54	16	61	40
16	$[Cu(L_3)_2(H_2O)_2]Cl_2$	48	32	52	15	58	38
17	$[Ni(L_3)_2(H_2O)_2]Cl_2$	41	25	44	11	49	28
18	$[Co(L_3)_2(H_2O)_2]Cl_2$	44	27	47	13	52	33
19	$[Zn(L_4)_2(H_2O)_2]Cl_2$	49	35	57	17	62	41
20	$[Cu(L_4)_2(H_2O)_2]Cl_2$	44	33	52	15	60	39
21	$[Ni(L_4)_2(H_2O)_2]Cl_2$	39	26	45	11	49	28
22	$[Co(L_4)_2(H_2O)_2]Cl_2$	40	28	49	13	53	34
23	$[Zn(L_5)_2(H_2O)_2]$	50	37	54	16	62	40
24	$[Cu(L_5)_2(H_2O)_2]$	45	33	50	15	58	38
25	$[Ni(L_5)_2(H_2O)_2]$	39	26	44	11	48	29
26	$[Co(L_5)_2(H_2O)_2]$	41	29	47	13	52	33

(a) = *Escherichia coli*, (b) = *Enterococcus faecalis*, (c) = *Staphylococcus aureus*, (d) = *Pseudomonas aeruginosa*, (e) = *Salmonella enteritidis*, (f) = *Klebsiella pneumoniae*.

Table 6. MICs ($\mu g\,mL^{-1}$) of the cefixime Schiff-base ligands and their metal complexes (10, 25, 50, $100\,\mu g\,mL^{-1}$).

No.	Compounds	(a)	(b)	(c)	(d)	(e)	(f)
1	Cefixime	15	>100	12.5	>100	<10	50
2	L_1	14	>100	12.2	>100	<10	48
3	L_2	14	100	12.1	>100	<10	55
4	L_3	13	>100	12.1	>100	<10	48
5	L_4	14.5	>100	12	>100	<10	47
6	L_5	14.5	100	12.2	>100	<10	48
7	$[Zn(L_1)_2(H_2O)_2]$	<10	75	<10	90	<10	20
8	$[Cu(L_1)_2(H_2O)_2]$	10.5	85	10.2	100	<10	25
9	$[Ni(L_1)_2(H_2O)_2]$	13.5	100	12>	100	<10	48
10	$[Co(L_1)_2(H_2O)_2]$	12	95	10.5	>100	<10	35
11	$[Zn(L_2)_2(H_2O)_2]$	<10	70	<10	100	<10	24
12	$[Cu(L_2)_2(H_2O)_2]$	10.5	80	10.2	>100	<10	25
13	$[Ni(L_2)_2(H_2O)_2]$	13	95	11.5	>100	<10	50
14	$[Co(L_2)_2(H_2O)_2]$	12	97	10.5	>100	<10	40
15	$[Zn(L_3)_2(H_2O)_2]Cl_2$	<10	75	<10	95	<10	20
16	$[Cu(L_3)_2(H_2O)_2]Cl_2$	10	87	10	100	<10	25
17	$[Ni(L_3)_2(H_2O)_2]Cl_2$	13.5	100	12	>100	<10	44
18	$[Co(L_3)_2(H_2O)_2]Cl_2$	11.5	93	10.5	>100	<10	35
19	$[Zn(L_4)_2(H_2O)_2]Cl_2$	<10	75	<10	90	<10	21
20	$[Cu(L_4)_2(H_2O)_2]Cl_2$	11.5	87	10	100	<10	25
21	$[Ni(L_4)_2(H_2O)_2]Cl_2$	13	100	11.5	>100	<10	44
22	$[Co(L_4)_2(H_2O)_2]Cl_2$	13.5	95	10.4	>100	<10	36
23	$[Zn(L_5)_2(H_2O)_2]$	<10	72	<10	95	<10	20
24	$[Cu(L_5)_2(H_2O)_2]$	11	90	10.2	100	<10	25
25	$[Ni(L_5)_2(H_2O)_2]$	13	100	12	>100	<10	46
26	$[Co(L_5)_2(H_2O)_2]$	12.5	95	10.6	>100	<10	35

(a) = *Escherichia coli*, (b) = *Enterococcus faecalis*, (c) = *Staphylococcus aureus*, (d) = *Pseudomonas aeruginosa*, (e) = *Salmonella enteritidis*, (f) = *Klebsiella pneumoniae*.

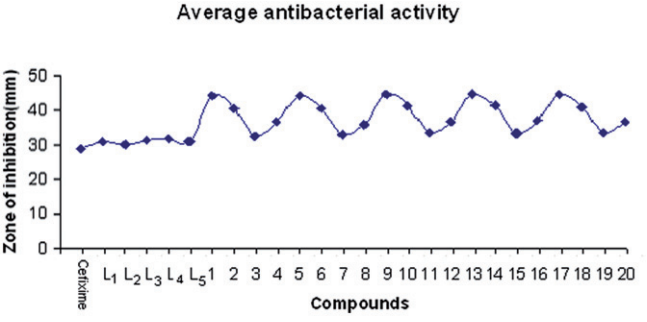

Figure 5. Average antibacterial activity.

were also screened against the same bacterial strains. The potency of the uncoordinated ligands was enhanced on coordination with metal.

3.7. *Minimum inhibitory concentration*

The MIC was determined using the disk diffusion method [11]. MIC was the lowest concentration of a substance at which the inhibition of growth occurred. The MIC of

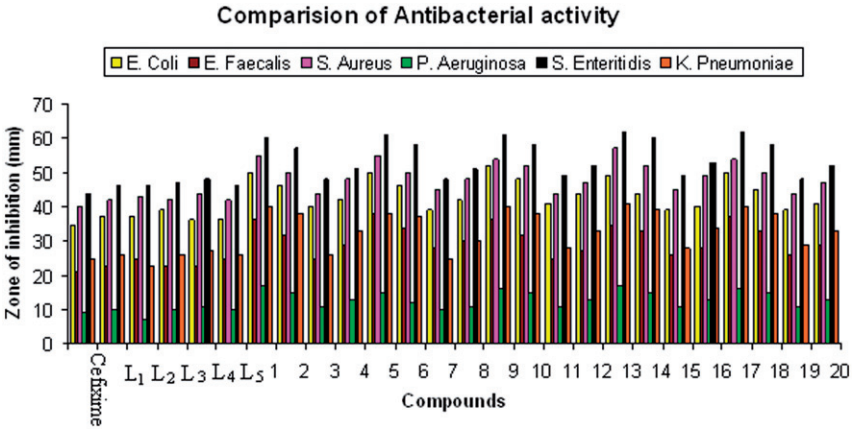

Figure 6. Comparison of antibacterial activity.

these compounds varied from 10 to 100 μg mL^{-1}. The results (table 6) indicated that these compounds are most active by inhibiting the growth of the tested organisms at 10 mg mL^{-1}. Some of the compounds showed good antibacterial activity against some bacterial species (figures 5 and 6). This enhancement in the activity is rationalized on the basis of the structures of (L_1–L_5) by possessing an additional azomethine (C=N) linkage important in elucidating the mechanism of transamination and resamination reactions in biological system [30]. It has also been suggested that ligands with nitrogen and oxygen donors might inhibit enzyme production, because the enzymes which require these groups for their activity appear to be more susceptible to deactivation by the metal ions upon chelation.

4. Conclusion

The synthesized cefixime-derived Schiff bases showed antibacterial properties with metal complexes more active against all bacterial strains. These observations, in line with other studies, suggest that the metal-based drugs possess potential as therapeutics.

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References

[1] N.X. Chin, J.W. Gu, W. Fang, H.C. Neu. *Antimicrob. Agents Chemother.*, **35**, 259 (1991).
[2] K.P. Fu, B.D. Foleno, S.C. Lafredo, J.M. Lococo, D.M. Isaacson. *Antimicrob. Agents Chemother.*, **27**, 301 (1993).
[3] J.R. Anacona, J. Estacio. *Transition Met. Chem.*, **31**, 227 (2006).
[4] J.R. Anacona, C.C. Gil. *Transition Met. Chem.*, **30**, 605 (2005).
[5] J.R. Anacona, P. Alvarez. *Transition Met. Chem.*, **27**, 856 (2002).
[6] M.S. Iqbal, I.H. Bukhari, M. Arif. *Appl. Oraganomet. Chem.*, **19**, 864 (2005).
[7] I.H. Bukhari, M. Arif, I. Akbar, A.H. Khan. *Pak. J. Biol. Sci.*, **8**, 614 (2005).
[8] A. Earnshaw. *Introduction to Magnetochemistry*, 3rd Edn, p. 6, Academic Press, New York (1968).
[9] Z.H. Chohan, M. Arif, M. Sarfraz. *Appl. Organomet. Chem.*, **21**, 294 (2007).
[10] J.L. McLaughlin, C.J. Chang, D.L. Smith. In *Studies in Natural Products Chemistry, Bench–Top, Bioassay for the Discovery of Bioactive Natural Products: An Update, Structure and Chemistry (Part-B)*, Atta-ur-Rahman (Ed.), p. 283, Elsevier Science, Amsterdam (1991).
[11] Atta-ur-Rahman, M.I. Choudhary, W.J. Thomsen. *Bioassay Techniques for Drug Development*, Harwood Academics, Netherlands (2001).
[12] W.J. Geary. *Coord. Chem. Rev.*, **7**, 81 (1971).
[13] K. Nakamoto. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, John Wiley, New York (1978).
[14] G.H. Rist, J.S. Hydes, T. Vanngard. *Proc. Natl. Acad. Sci., U.S.A.*, **67**, 79 (1970).
[15] L.J. Bellamy. *The Infrared Spectra of Complex Molecules*, John Wiley, New York (1971).
[16] J.R. Ferrero. *Low Frequency Vibrations of Inorganic and Coordination Compounds*, John Wiley, New York (1971).
[17] A.S. Burlov, E.N. Shepelenko, I.S. Vasil'chenko. *Russ. J. Coord. Chem.*, **32**, 879 (2006).
[18] J.R. Anacona, I. Rodriguez. *J. Coord. Chem.*, **57**, 1263 (2004).
[19] E. Canpolat, A. Yazici, M. Kaya. *J. Coord. Chem.*, **60**, 473 (2007).
[20] W.W. Simmons. *The Sadtler Handbook of Proton NMR Spectra*, Sadtler Research Laboratories Inc., Philadelphia (1978).
[21] Z.H. Chohan, C.T. Supuran. *J. Enzyme Inhib. Med. Chem.*, **23**, 240 (2008).
[22] Z.H. Chohan, H. Pervez, S. Kausar, C.T. Supuran. *Synth. React. Inorg. Met.-Org. Chem.*, **32**, 529 (2002).
[23] G.G. Mohameda, C.M. Sharaby. *Spectrochim. Acta, Part A*, **66**, 949 (2007).
[24] W.E. Estes, D.P. Gavel, W.B. Hatfield, D.J. Hodgson. *Inorg. Chem.*, **17**, 1415 (1978).
[25] C.J. Balhausen. *An Introduction to Ligand Field Spectra*, McGraw Hill, New York (1962).
[26] G.G. Mohamed, Z.H. Abd El-Wahab. *J. Therm. Anal. Calorim.*, **73**, 347 (2003).
[27] Y.M. Essa, H.M. Abdel-Fattah, A.A. Soliman. *J. Therm. Anal.*, **42**, 1175 (1994).
[28] N.T. Abdel-Ghani, O. Esherif. *Thermochim. Acta*, **156**, 69 (1989).
[29] M.A. Zayed, F.A. Nour El-Dien, G.G. Mohamed, N.E.A. El-Gamel. *Spectrochim. Acta, Part A*, **60**, 2843 (2004).
[30] Z.H. Chohan, M. Arif, A. Rashid. *J. Enzyme Inhib. Med. Chem.*, **6**, 785 (2008).