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Synthesis, characterization, coordination and antibacterial properties of novel asymmetric 1,1′-disubstituted ferrocene-derived Schiff-base ligands and their Co(II), Cu(II) Ni(II) and Zn(II) complexes

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Some new asymmetric 1,1′-disubstituted ferrocene-derived Schiff-bases have been prepared and used as ligands in the preparation of their Co(II), Cu(II), Ni(II) and Zn(II) metal chelates. These synthesized ligands and their metal chelates have been characterized by their physical, analytical and spectral data. These have also been used for screening against pathogenic bacterial species, e.g. *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella pneumonae* and have been found to be a novel class of organometallic-based antibacterials. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: asymmetric 1,1′-disubstituted ferrocenes; Schiff-bases; metal(II) chelates; antibacterials

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INTRODUCTION

Different reports[1–6] have indicated the use of platinum and gold complexes[7,8] of 1,1′-bis(diphenylphosphino)ferrocene against various tumors. The enhanced antibiotic activity of penicillin and cephalosporine obtained by replacing the aromatic group with the ferrocenyl moiety[9–11] has also attracted the attention of many researchers for use of organometallics in biological sciences. The synthesis of such ferrocene-derived compounds thus allows the opening up of a potential area of research in designing and synthesizing multifunctional drugs. Keeping in view the same interest, we have previously synthesized a new class of symmetric 1,1′-disubstituted ferrocene-derived Schiff bases and have reported[12] their coordination and antibacterial properties. Paralleling the same factors, we now wish to report another class of asymmetric 1,1′-disubstituted ferrocene-derived Schiff-bases and their use as ligands in the preparation of their Co(II), Cu(II), Ni(II) and Zn(II) metal chelates and their further application as a class of organometallic-based antibacterial agents.

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EXPERIMENTAL

Material and methods

All solvents used were Analar grade. 1,1′-Diacetylferrocene, 2-aminopyrazine, 2-aminopyridine, 2-aminothiazole and 2-hydroxyaniline were obtained from Merck. All metals were used as chlorides. IR, ^{1}H NMR and ^{13}C NMR spectra were recorded on Perkin Elmer 283B and 300 MHz Varian XL-300 instruments. UV–visible spectra were obtained on a Baush and Lomb Spectronic 1001. Conductance of the metal complexes was determined in DMF using a YSI-32 model conductometer. Magnetic measurements were done on solid complexes using the Gouy method. Microanalyses were carried out by Butterworth Laboratories Ltd, UK. Melting points were re-

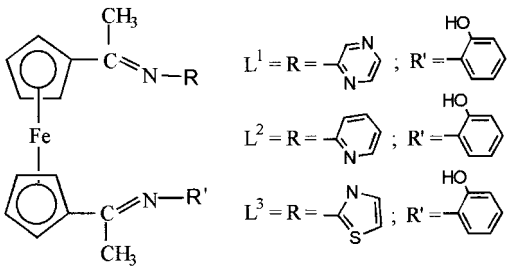

Figure 1 Structure of the asymmetric 1,1′-disubstituted ferrocene-derived Schiff-bases.

corded on a Gallenkamp apparatus and are uncorrected.

Antibacterial studies were carried out with the help of the Microbiology Department, Qaid-e-Azam Medical College, Bahawalpur, Pakistan. These studies were done on wild pathogenic bacterial species collected from urine and blood samples of infected patients admitted to the Bahawal Victoria Hospital, Bahawalpur.

Synthesis of ligands (HL^1, HL^2 and HL^3)

For the preparation of ligand HL^1, solutions of 2-aminopyrazine (0.47 g, 5 mmol) in dichloromethane (20 cm^3) and 2-aminophenol (0.5 g, 5 mmol) in dichlormethane (20 cm^3) were firstly mixed together and then added into a magnetically stirred solution of 1,1′-diacetylferrocene (2.7 g, 10 mmol) in dichloromethane (20 cm^3). The mixture was refluxed for 10 h under a slow stream of N_2. After cooling to room temperature the solvent was evaporated to give a dark-orange solid. TLC of the crude solid showed mixture of three products, which were separated by column chromatography over silica gel using a glass column (4 × 100 cm^2). The first two bands were collected using dichloromethane/petroleum ether (b.p. 40–60 °C (80:20) as eluent. One compound was characterized as a symmetric 1,1′-disubstituted pyrazine-derived ferrocene (20%) and the other was characterized as a symmetric 1,1′-disubstituted phenol-derived ferrocene (16%). The last band was collected as the desired asymmetric 1,1′-disubstituted ferrocene-derived Schiff-base ligand HL^1 (58%) using dichloromethane as an eluent. After removal of the solvent an orange crystalline solid was obtained, which was recrystallized from dichloromethane (Fig. 1).

A similar method was used for the preparation of the ligands HL^2 and HL^3.

Synthesis of metal complexes

To a magnetically stirred and warmed (40 °C) solution of the ligand (1.0 mmol) in ethanol (30 cm^3) was added a solution of the respective metal(II) chloride (1.0 mmol) in ethanol (20 cm^3). The mixture was refluxed for 2.5 h. During this time, a complex was precipitated which, upon cooling, was filtered, washed several times with ethanol and diethyl ether and then dried over anhydrous $CaCl_2$. All other complexes were prepared similarly using the same method.

ANTIBACTERIAL STUDIES

Preparation of disc

The ligand/complex (30 μg) in DMF (0.01 cm^3)

Table 1 Physical, spectral and analytical data of the ligands

Ligand/mol. formula	M.p. (°C)	IR (cm^{-1})	Calc. (Found) (%) C	H	N	Yield (%)
HL^1 $C_{24}H_{22}FeN_4O$ [437.84]	176	3435 (OH), 1625 (C═N), 1570, 1520, 1170, 950	65.8 (66.1)	5.0 (5.2)	12.8 (13.1)	60
HL^2 $C_{25}H_{23}FeN_3O$ [436.84]	162	3435 (OH), 1620 (C═N), 1575, 1525, 1175, 1065, 955	68.7 (68.8)	5.3 (5.0)	9.6 (9.3)	58
HL^3 $C_{23}H_{21}FeN_3OS$ [442.87]	188	3430 (OH), 1625 (C═N), 1580, 1525, 1325, 1170, 955	62.3 (62.6)	4.7 (4.5)	9.5 (9.2)	55

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Table 2 Physical, analytical and spectral data of the metal complexes

Complex/mol. formula	m.p. (°C)	IR (cm^{-1})	$\lambda_{max}(cm^{-1})$	μ_{eff} (B.M.)	Calc. (Found) (%) C	H	N
1 $[Co(L^1)(Cl_2)]$ [566.67]	222–224	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 370 (M—N), 305 (M—Cl)	7545, 17255, 20530, 22415	3.9	50.8 (51.1)	3.7 (3.4)	9.9 (9.8)
2 $[Cu(L^1)]Cl$ [535.83]	218–220	1585 (C═N, heteroaromatic), 1635 (C═N), 1280 (C—O), 465 (M—O), 370 (M—N)	15170, 19605, 22415, 30345	1.7	53.7 (53.6)	3.9 (3.5)	10.5 (10.3)
3 $[Ni(L^1)(Cl_2)]$ [566.43]	228–230	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 460 (M—O), 372 (M—N), 305 (M—Cl)	10210, 15565, 22415, 26245	3.2	50.8 (50.9)	3.7 (3.5)	9.9 (9.7)
4 $[Zn(L^1)(Cl_2)]$ [573.12]	225–227	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 372 (M—N), 305 (M—Cl)	22415, 28255	diamagnetic	50.3 (50.5)	3.7 (3.8)	9.8 (9.9)
5 $[Co(L^2)(Cl_2)]$ [565.67]	220–222	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 462 (M—O), 372 (M—N), 305 (M—Cl)	7615, 17290, 20765, 22415	4.2	53.0 (53.3)	3.9 (4.3)	7.4 (7.3)
6 $[Cu(L^2)]Cl$ [534.83]	212–214	1585 (C═N, heteroaromatic), 1635 (C═N), 1280 (C—O), 465 (M—O), 370 (M—N),	15190, 19585, 22415, 30425	1.9	56.1 (56.4)	4.1 (4.3)	7.9 (8.2)
7 $[Ni(L^2)(Cl_2)]$ [565.43]	220–222	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 460 (M—O), 372 (M—N), 305 (M—Cl)	10865, 15715, 22415, 26550	2.9	53.1 (53.0)	3.9 (3.7)	7.4 (7.6)
8 $[Zn(L^2)(Cl_2)]$ [572.12]	228–230	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 372 (M—N), 305 (M—Cl)	22415, 29115	diamagnetic	52.4 (52.3)	3.8 (3.6)	7.3 (7.5)
9 $[Co(L^3)(Cl_2)]$ [571.70]	225–227	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 372 (M—N), 305 (M—Cl)	7585, 17275, 22415, 20680	4.0	48.3 (48.7)	3.5 (3.3)	7.3 (7.2)
10 $[Cu(L^3)]Cl$ [5540.86]	220–222	1585 (C═N, heteroaromatic), 1635 (C═N), 1280 (C—O), 460 (M—O), 370 (M—N),	15185, 19600, 22415, 30390	1.8	51.0 (51.4)	3.7 (3.5)	7.8 (7.6)
11 $[Ni(L^3)(Cl_2)]$ [5571.46]	228–230	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 372 (M—N), 305 (M—Cl)	10615, 15610, 22415, 26345	3.1	48.3 (48.8)	3.5 (3.5)	7.3 (7.4)
12 $[Zn(L^3)(Cl_2)]$ [578.15]	224–226	1585 (C═N, heteroaromatic), 1630 (C═N), 1280 (C—O), 465 (M—O), 372 (M—N), 305 (M—Cl)	22415, 28870	diamagnetic	47.7 (47.5)	3.5 (3.2)	7.3 (7.5)

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Table 3 ^{1}H NMR and ^{13}C NMR data of ligands and metal(II) complexes

No.	^{1}H NMR (DMSO-d_6) (ppm)	^{13}C NMR (DMSO-d_6) (ppm)
HL^{1}	2.4 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.2–4.4 (m, 2H, ferrocenyl), 4.5–4.7 (m, 2H, ferrocenyl), 6.5 (s, 1H, CH=N), 6.8–7.0 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.3–8.4 (m, 1H, pyrazine), 8.5–8.6 (m, 2H, pyrazine), 9.6 (s, 1H, OH)	22.7 (CH_3), 68.7, 69.5, 83.7 (ferrocenyl), 142.7 (C=N), 145.8, 147.7, 149.6, 153.8 (pyrazine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 185.2 (C—OH)
HL^{2}	2.3 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.5 (m, 2H, ferrocenyl), 4.2–4.4 (m, 2H, ferrocenyl), 4.5–4.7 (m, 2H, ferrocenyl), 6.5 (s, 1H, CH=N), 6.8–7.0 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.1–8.3 (m, 1H, pyridine), 8.3–8.4 (m, 1H, pyridine), 8.5–8.7 (m, 1H, pyridine), 8.8–8.9 (m, 1H, pyridine), 9.6 (s, 1H, OH)	22.6 (CH_3), 68.6, 69.5, 83.5 (ferrocenyl), 142.4 (C=N), 140.8, 143.7, 146.5, 148.7, 149.5 (pyridine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 185.2 (C—OH)
HL^{3}	2.4 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.2–4.4 (m, 2H, ferrocenyl), 4.5–4.7 (m, 2H, ferrocenyl), 6.5 (s, 1H, CH=N), 6.8–7.0 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.6–8.8 (m, 1H, thiazole), 8.8–8.9 (d, 1H, thiazole), 9.6 (s, 1H, OH)	22.8 (CH_3), 68.7, 69.5, 83.6 (ferrocenyl), 142.8 (C=N), 118.7, 143.8, 152.7 (thiazole), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 185.3 (C—OH)
1	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.3–7.5 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.3–8.4 (m, 1H, pyrazine), 8.6–8.8 (m, 2H, pyrazine)	22.7 (CH_3), 68.7, 69.5, 83.7 (ferrocenyl), 142.9 (C=N), 145.8, 147.7, 149.6, 153.8 (pyrazine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
2	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.8–8.0 (m, 1H, aromatic), 8.3–8.4 (m, 1H, pyrazine), 8.6–8.8 (m, 2H, pyrazine)	22.7 (CH_3), 68.7, 69.5, 83.7 (ferrocenyl), 142.9 (C=N), 145.8, 147.7, 149.6, 153.8 (pyrazine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
3	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.8–8.0 (m, 1H, aromatic), 8.3–8.4 (m, 1H, pyrazine), 8.6–8.8 (m, 2H, pyrazine)	22.7 (CH_3), 68.7, 69.5, 83.7 (ferrocenyl), 142.9 (C=N), 145.8, 147.7, 149.6, 153.8 (pyrazine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
4	2.6 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.3–8.4 (m, 1H, pyrazine), 8.6–8.8 (m, 2H, pyrazine)	22.7 (CH_3), 68.7, 69.5, 83.7 (ferrocenyl), 142.9 (C=N), 145.8, 147.7, 149.6, 153.8 (pyrazine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
5	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.1–8.3 (m, 1H, pyridine), 8.3–8.4 (m, 1H, pyridine), 8.6–8.8 (m, 1H, pyridine)	22.6 (CH_3), 68.6, 69.5, 83.5 (ferrocenyl), 142.9 (C=N), 140.8, 143.7, 146.5, 148.7, 149.5 (pyridine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)

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Table 3 continued

No.	^{1}H NMR (DMSO-d_6) (ppm)	^{13}C NMR (DMSO-d_6) (ppm)
6	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.1–8.3 (m, 1H, pyridine), 8.3–8.4 (m, 1H, pyridine), 8.6–8.8 (m, 1H, pyridine)	22.6 (CH_3), 68.6, 69.5, 83.5 (ferrocenyl), 142.8 (C=N), 140.8, 143.7, 146.5, 148.7, 149.5 (pyridine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
7	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.1–8.3 (m, 1H, pyridine), 8.3–8.4 (m, 1H, pyridine), 8.6–8.8 (m, 1H, pyridine)	22.6 (CH_3), 68.6, 69.5, 83.5 (ferrocenyl), 142.8 (C=N), 140.8, 143.7, 146.5, 148.7, 149.5 (pyridine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
8	2.5 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 7.7–7.9 (m, 1H, aromatic), 8.1–8.3 (m, 1H, pyridine), 8.3–8.4 (m, 1H, pyridine), 8.6–8.8 (m, 1H, pyridine)	22.6 (CH_3), 68.6, 69.5, 83.5 (ferrocenyl), 142.9 (C=N), 140.8, 143.7, 146.5, 148.7, 149.5 (pyridine), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.2 (C—O)
9	2.6 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 8.5–8.7 (m, 1H, thiazole), 8.9–9.1 (m, 1H, thiazole)	22.8 (CH_3), 68.7, 69.5, 83.6 (ferrocenyl), 142.8 (C=N), 118.7, 143.8, 152.7 (thiazole), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.3 (C—O)
10	2.6 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 8.5–8.7 (m, 1H, thiazole), 8.9–9.1 (m, 1H, thiazole)	22.8 (CH_3), 68.7, 69.5, 83.6 (ferrocenyl), 142.9 (C=N), 118.7, 143.8, 152.7 (thiazole), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.3 (C—O)
11	2.6 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.8 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 8.5–8.7 (m, 1H, thiazole), 8.9–9.1 (m, 1H, thiazole)	22.8 (CH_3), 68.7, 69.5, 83.6 (ferrocenyl), 142.9 (C=N), 118.7, 143.8, 152.7 (thiazole), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.3 (C—O)
12	2.6 (s, 6H, CH_3), 4.1–4.3 (m, 2H, ferrocenyl), 4.4–4.6 (m, 2H, ferrocenyl), 4.7–4.9 (m, 2H, ferrocenyl), 5.0–5.2 (m, 2H, ferrocenyl), 6.7 (s, 1H, CH=N), 6.9–7.1 (m, 1H, aromatic), 7.2–7.4 (m, 1H, aromatic), 7.5–7.6 (m, 1H, aromatic), 8.5–8.7 (m, 1H, thiazole), 8.9–9.1 (m, 1H, thiazole)	22.8 (CH_3), 68.7, 69.5, 83.6 (ferrocenyl), 142.9 (C=N), 118.7, 143.8, 152.7 (thiazole), 115.8, 117.2, 121.3, 128.6, 146.7 (aromatic), 154.3 (C—O)

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was applied to 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 to the bacteria grown on the agar plates.

Preparation of 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). It was 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 37 °C for inoculation.

Inoculation procedure

Inoculation was done with the help of a platinum wire loop which was made red hot in a flame, cooled and then used for the application of bacterial strains.

Application of discs

Sterilized forceps were used for the application of paper discs to the already inoculated agar plates. The discs were then incubated at 37 °C for 24 h. The diameter of the zone of inhibition was measured around the disc.

RESULTS AND DISCUSSION

The ligands are all soluble in dichloromethane, methanol and ethanol. All the metal complexes dissolve only in DMF and DMSO. All of them are amorphous solids. Molar conductance values of metal complexes (13.5–15.2 $\Omega\ cm^2\ mol^{-1}$) in DMF solution show all the complexes to be non-electrolytic[13] in nature (Table 1).

IR spectra

The important IR frequencies of the ligands and their complexes, along with their assignments, are reported in Tables 1 and 2. The following observations were made from the comparison of the IR spectra of the ligands and their metal complexes.

(a) The IR spectra of the ligands are almost identical to those of the metal complexes in the region 670–1550 cm^{-1}.
(b) All the ligands showed the absence of bands at about 1735 and 3420 cm^{-1} due to the characteristic carbonyl ν(C═O) and $\nu(NH_2)$ stretching vibrations of the respective starting materials. Instead, the appearance of new bands in the spectra of the complexes at 1620–1625 cm^{-1} due to the azomethine linkage ν(C═N) clearly suggested[14,15] the formation of the proposed Schiff-base ligands (HL^1–HL^3). The shifting of this azomethine band to the higher frequency side (10–15 cm^{-1}) furthermore provided evidence in support of the involvement of azomethine nitrogen in coordination to the metal atom.
(c) Some characteristic bands due to pyrazine, pyridine and thiazole ring vibrations in the spectra of the ligand moved to the slightly higher frequency side (5–10 cm^{-1}) in the spectra of their metal complexes, which suggested that coordination of the ligands took place through the pyrazine, pyridine and thiazole ring nitrogen atoms to the metal atom.
(d) A broad band at 3435 cm^{-1} was observed in the spectra of all the ligands due to ν(OH) stretching vibrations. This band disappeared in the spectra of all the complexes; instead a new band appeared at 1280 cm^{-1} due to the ν(C—O) frequency, which strongly supports the observation that during complexation the deprotonation of the hydroxyl group occurred.
(e) Moreover, in the far infrared region the bands at ~370 and ~465 cm^{-1} attributed to ν(M—N) and ν(M—O) were observed for all the complexes (Table 2); these were not found in the spectra of the free ligands. However, this suggests[16] that the hetero-aromatic ring nitrogen, azomethine nitrogen and deprotonated oxygen of the phenol moiety are all involved in the complexation.
(f) Also, a weak band at 305 cm^{-1} was found in the spectra of the Co(II), Ni(II) and Zn(II) complexes due to the ν(M—Cl) mode. This was, however, not observable in the spectra of the Cu(II) complexes. This observation strongly suggests[17,18] a square-planar ge-

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ometry for the Cu(II) complexes (Fig. 2A) and an octahedral geometry for the complexes of Co(II), Ni(II) and Zn(II) (Fig. 2B).

^{1}H NMR and ^{13}C NMR spectra

The ^{1}H NMR and ^{13}C NMR spectra of the free ligands and their metal(II) chelates were taken in DMSO-d_6. The ^{1}H NMR spectral data are reported along with possible assignments in Table 3. The ligand displays signals at δ 2.3–2.4, 4.1–4.7, 6.5, 6.8–7.9, 8.3–8.9 and 9.6 ppm due to —CH_3, —ferrocenyl, —CH=N, aromatic, heteroaromatic and —OH protons. The protons due to aromatic and heteroaromatic groups (pyrazine, pyridine and thiazole rings) were found in their expected regions.[19] The conclusions drawn from these studies lend further support to the mode of bonding discussed above. The presence of the phenolic (OH) protons at δ 9.6 ppm that vanished in the spectra of the metal complexes suggested deprotonation and subsequent participation in complexation. The protons due to the ferrocenyl moiety were also found in the same region as expected and reported[12,20] earlier. In the spectra of their metal complexes these protons shifted downfield due to increased conjugation and coordination to the metal atoms. The signals due to azomethine protons also shifted downfield compared with the corresponding ligand signals, indicating coordination of the ligand via the azomethine nitrogen. The number of protons of various groups, calculated from the integrations, and those calculated for the expected CHN analyses agree. In the ^{13}C NMR spectra, the ligand displays signals at δ 22.6–22.8, 68.6–83.7, 142.4–142.7, 142.4–153.7, 115.8–146.7 and 185.2 ppm downfield from TMS and assigned respectively to, —CH_3, ferrocenyl, C=N, heteroaromatic, aromatic and C—O carbon atoms. These signals appear downfield in comparison[19] with the corresponding signals of the ligand, indicating coordination and complexation with the central metal atom. It was observed that DMSO did not have any coordinating effect on either the spectra of the ligands or on their complexes.

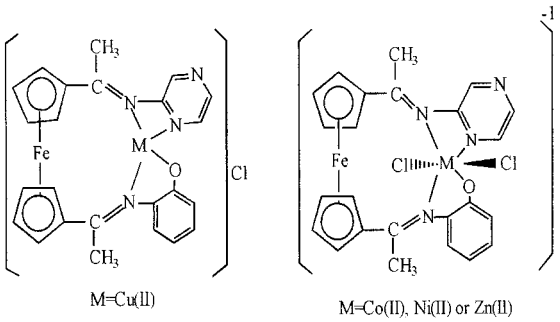

Figure 2 Proposed structure for the metal(II) chelate of the Schiff-base ligand HL[1].

Electronic spectra and magnetic moments

The electronic spectra of the Cu(II) complexes

Table 4 Antibacterial activity data[a]

Ligand/complex	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumonae*
HL[1]	++	++	++	+++
HL[2]	++	+	–	++
HL[3]	++	+	++	++
1	+++	+++	+++	++++
2	++	++	++	++
3	+++	++	++	+++
4	+++	++	++	++
5	+++	+++	+++	+++
6	++	++	++	++
7	+++	+++	++	++
8	++	++	++	+++
9	++++	++	++	+++
10	++	+++	++	++
11	+++	++	++	+++
12	++	+++	+++	+++

[a] 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 the most active compound with 100% inhibition.

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(Table 2) showed two low-energy weak bands at 15170–15190 and 19585–19605 cm^{-1} and a strong high-energy band at 30345–30425 cm^{-1}. The low-energy bands in this position typically are expected for its square-planar configuration and may be assigned to the $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions respectively.[21,22] The strong high-energy band, in turn, is assigned to metal → ligand charge transfer. Also, the magnetic moment values (1.7–1.9 B.M.) (Table 2) for Cu(II) complexes were found to be consistent with the proposed square-planar structure of the Cu(II) complexes (Fig. 2A).

The Co(II) complexes exhibited well-resolved low-energy bands at 7545–7615 and 17255–17290 cm^{-1} and a strong high-energy band at 20530–20765 cm^{-1} assigned to the transitions $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ for high-spin octahedral geometry.[23,24] The magnetic susceptibility measurements (3.9–4.2 B.M.) for the Co(II) solid complexes are also indicative of three unpaired electrons per Co(II) ion, suggesting[25] consistency for their octahedral environment (Fig. 2B).

The electronic spectra of the Ni(II) complexes showed *d–d* bands in the region 26245–26550, 15565–15715 and 10210–10865 cm^{-1}. These are assigned[25] to the transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)$ respectively, consistent for their well-defined octahedral configurations. The magnetic measurements (2.9–3.2 B.M.) showed two unpaired electrons per Ni(II) ion, suggesting[26] also an octahedral geometry for the Ni(II) complexes (Fig. 2B). The electronic spectra of the Zn(II) complexes exhibited only a high-intensity band at 28255–29115 cm^{-1} assigned[23] to ligand–metal charge transfer. Furthermore, a broad band centered at 22415 cm^{-1} observed for every complex was assigned to the transition $^1A_{1g} \rightarrow {}^1E_{1g}$ in the iron atom of the ferrocenyl group, which indicated[24] that there is no magnetic interaction between the Cu(II), Co(II), Ni(II) and Zn(II) ions and the diamagnetic Fe(II) ion of the ferrocenyl group.

Antibacterial properties

Antibacterial properties of the ligands and their metal complexes were studied against the bacterial species *E. coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Klebsiella pneumonae*. These were tested at a concentration of 30 μg/0.01 ml in DMF solution using a paper disc diffusion method devised and reported earlier.[27,28] The results of these studies, reproduced in Table 4, indicated that both the Schiff-base ligands and their metal complexes showed variable activity against one or more bacterial strains. In comparison with the ligands, the metal complexes were found to be more biologically active. These studies, however, provided useful information about the biological activity of ferrocene-containing compounds and the knowledge that this activity could become more pronounced when more potent compounds are coupled with ferrocene molecules.

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