

# Unsymmetrical 1,1'-disubstituted Ferrocenes: Synthesis of Co(ii), Cu(ii), Ni(ii) and Zn(ii) Chelates of Ferrocenyl -1-thiadiazolo-1'-tetrazole, -1-thiadiazolo-1'-triazole and -1-tetrazolo-1'-triazole with Antimicrobial Properties

ZAHID H. CHOCHAN<sup>a</sup>, ANDREA SCOZZAFAVA<sup>b</sup> and CLAUDIU T. SUPURAN<sup>b,\*</sup>

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

(Received 24 April 2002)

Condensation reactions of 1,1''-diacetylferrocene with different heteroaromatic amines such as, 2-amino-1,3,4-thiadiazole, 5-aminotetrazole and 3-amino-1,2,4-triazole to form unsymmetrically 1,1'-disubstituted ferrocenes have been studied. The obtained compounds have been further investigated for their liganding and biological properties upon chelation with Co(II), Cu(II), Ni(II) and Zn(II) metal ions. The synthesized compounds have been characterized by physical, spectral and analytical data and have been screened against pathogenic bacterial strains e.g., *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, showing moderate activity as antibacterials *in vitro*.

**Keywords:** Asymmetric 1,1'-disubstituted ferrocenes; Metal(II) chelates; Antibacterials

## INTRODUCTION

At the present time, most the antibiotics used in clinical practice 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.<sup>1–5</sup> Even worse for the host is that bacteria have developed strategies for neutralizing plasma-derived protease inhibitors, assuring in this way an efficient attack of the invaded organism, whereas other critical processes, such as colonization and evasion of host immune defenses, acquisition of nutrients for growth and proliferation,

facilitation of dissemination, or tissue damage during infection are under evolutionary pressure by the indiscriminate use of classical antibacterials.<sup>1–5</sup> As a consequence, drug resistance to the presently available classes of antibacterials has become a dramatic medical problem worldwide.<sup>1–5</sup> The process of chelation via metal complexes and its correlation with biological activity constitutes one emerging possibility for the design of novel antibiotics.<sup>4</sup> In the past few years a number of studies have highlighted the use of ferrocene derivatives for the design of biologically active compounds.<sup>6–10</sup> The substituent chemistry and versatility of the Fe<sup>II</sup>–Fe<sup>III</sup> redox couple in ferrocene-containing compounds has led to its recognition as a useful synthon<sup>11–16</sup> in organic and bio-organic chemistry.<sup>17–20</sup> The application of ferrocene-containing systems in medicinal chemistry has not been much investigated. Some reports have only indicated<sup>21–23</sup> that if the aromatic group in penicillin and cephalosporin antibiotics is replaced by the ferrocenyl moiety it significantly increases the bactericidal properties. This is achieved only by coupling ferrocene with heterocyclic-based ring systems. These considerations also attracted our attention<sup>24–26</sup> for combining both the chemistry of ferrocene and several heterocyclic moieties in an attempt to design and study a new area of organometallic-based antibacterial compounds and their further antibacterial enhancement upon chelation with different metal ions.

\*Corresponding author. Fax: +39-055-4573385. E-mail: claudiu.supuran@unifi.it

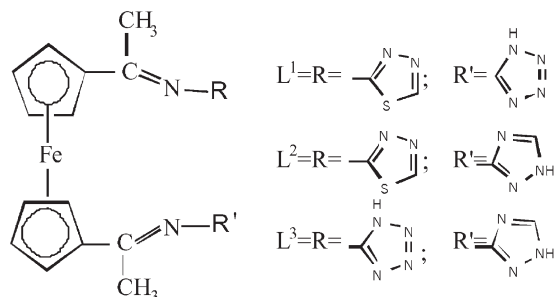


FIGURE 1 Structure of the ligands synthesized in the present work.

Acetylferrocene is a typical acylferrocene that undergoes an easy derivatisation with aromatic/heterocyclic amines. In an attempt to investigate such transformations of 1,1'-diacetylferrocene, we report here novel unsymmetrically 1,1'-disubstituted ferrocene derivatives (Figure 1) and their use as ligands for the preparation of Co(II), Cu(II), Ni(II) and Zn(II) complexes. These were also screened for their antibacterial properties against the pathogenic bacterial species, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* and the results are reported here.

## MATERIALS AND METHODS

All solvents used were Analar grade. 1,1'-Diacetylferrocene, 2-amino-1,3,4-thiadiazole, 5-amino-tetrazole and 3-amino-1,2,4-triazole were from Merck. All metals were used as chlorides. IR and 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. Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

## Synthesis of Ligand (L<sup>1</sup>)

For the preparation of ligand (L<sup>1</sup>), solutions of 2-amino-1,3,4-thiadiazole (10 g, 0.01 M) in hot ethanol (20 cm<sup>3</sup>) and 5-amino-tetrazole (1.0 g, 0.01 M) were simultaneously added to a magnetically stirred solution of 1,1'-diacetylferrocene (2.7 g, 0.01 M) in ethanol (20 cm<sup>3</sup>). The mixture was refluxed for 8 h. After allowing to cool at room temperature the solvent was evaporated to give a dark orange solid product. TLC on the obtained solid showed a mixture of three products, which were successfully separated by column chromatography over a silica gel using a glass column (4 × 100 cm<sup>2</sup>). The first two bands were collected using dichloromethane: ethanol (95: 5) as eluent. One compound was characterized as the symmetrical 1,1'-disubstituted thiadiazole-derived ferrocene (16%) and the other one was characterized as a symmetrical 1,1'-disubstituted tetrazole-derived ferrocene (20%). The last band was collected as the desired, unsymmetrical 1,1'-disubstituted ferrocene-derived ligand (L<sup>1</sup>) (58%). After removal of the solvent, an orange crystalline solid was obtained which was recrystallized from hot dichloromethane. A similar method was used for the preparation of the other ligands (L<sup>2</sup> and L<sup>3</sup>).

## Synthesis of the Metal(II) Complexes

To a magnetically stirred and warmed (40°C) solution of the ligand (1.0 mmol) in ethanol (30 cm<sup>3</sup>) was added the solution of the corresponding metal(II) chloride (1.0 mmol) in ethanol (20 cm<sup>3</sup>). The mixture was refluxed for 2 h. During this time, a complex was precipitated which upon cooling was filtered, washed several times with ethanol, then with diethyl ether and dried over anhydrous CaCl<sub>2</sub>. All other complexes were prepared similarly by the same method.

## RESULTS AND DISCUSSION

The ligands are all soluble in methanol and ethanol. All metal complexes on the other hand dissolved

TABLE I Physical, spectral and analytical data of the ligands

Ligand/Mol. formula	M.P. (°C)	IR (cm <sup>-1</sup> )	Calc (Found) %			Yield (%)
			C	H	N	
L <sup>1</sup> C <sub>13</sub> H <sub>10</sub> FeN <sub>6</sub> S [337.8]	173	1620 (CH <sub>3</sub> C = N), 1570 (C = N), 1515, 1170, 955	46.2 (46.5)	3.0 (3.2)	24.9 (24.6)	60
L <sup>2</sup> C <sub>14</sub> H <sub>11</sub> FeN <sub>5</sub> S [336.8]	168	1620 (CH <sub>3</sub> C = N), 1575 (C = N), 1525, 1175, 1065, 955	49.9 (50.2)	3.3 (3.4)	20.8 (20.9)	61
L <sup>3</sup> C <sub>13</sub> H <sub>11</sub> FeN <sub>7</sub> [320.8]	188	1620 (CH <sub>3</sub> C = N), 1575 (C = N), 1520, 1325, 1170, 955	48.6 (48.5)	3.4 (3.8)	30.5 (30.2)	61

only in DMF and DMSO. All of them are amorphous solid. Molar conductance values of the Co(II), Ni(II) and Zn(II) complexes ( $12\text{--}14\ \Omega\ \text{cm}^2\ \text{mol}^{-1}$ ) in DMF showed them to be non-electrolytes and the Cu(II) complexes ( $92\text{--}95\ \Omega\ \text{cm}^2\ \text{mol}^{-1}$ ) to be electrolytes in nature.<sup>28</sup>

### IR Spectra

IR frequencies of the ligands and their complexes are reported in Tables I and II. The IR spectrum of the ligands is almost identical in the region  $670\text{--}1550\ \text{cm}^{-1}$  to those of the metal complexes. The ligands ( $L^1\text{--}L^3$ ) showed the absence of bands at  $\sim 1735$  and  $3420\ \text{cm}^{-1}$  due to characteristic carbonyl  $\nu(\text{C}=\text{O})$  and  $\nu(\text{NH}_2)$  stretching vibrations of the respective starting materials. Instead the appearance of a new band in the spectra of the complexes at  $1620\ \text{cm}^{-1}$  assigned to the  $\nu(\text{CH}_3\text{C}=\text{N})$  linkage suggested<sup>29,30</sup> the formation of the proposed ligands. The shifting of this band to the higher frequency side ( $10\text{--}15\ \text{cm}^{-1}$ ) furthermore provided evidence in support of the involvement of the nitrogen in coordination to the metal atom. Also a characteristic band at  $1570\ \text{cm}^{-1}$  due to heteroaromatic ring  $\nu(\text{C}=\text{N})$  in the spectra of the ligands moved to higher frequency ( $10\text{--}15\ \text{cm}^{-1}$ ) in the spectra of the metal complexes suggesting coordination of the heteroaromatic ring nitrogen of the ligands to the metal atom. Moreover, in the far infrared region the band at  $\sim 385\text{--}390\ \text{cm}^{-1}$  attributed to  $\nu(\text{M}\text{--}\text{N})$  was observed for all the complexes (Table II), which was not found in the spectra of the free ligands. It however, suggested<sup>31</sup> coordination of the heteroaromatic ring nitrogen  $\nu(\text{C}=\text{N})$  and the nitrogen of  $\nu(\text{CH}_3\text{C}=\text{N})$  group to the metal atom. A weak band at  $310\ \text{cm}^{-1}$  due to the  $\nu(\text{M}\text{--}\text{Cl})$  mode was also observed only in the spectra of the Co(II), Ni(II) and Zn(II) complexes strongly suggesting<sup>32,33</sup> an octahedral geometry for the complexes (Figure 2A). This band however, was not found in the spectra of the Cu(II) complexes thus suggesting a four coordinated square-planar geometry for the Cu(II) complexes (Figure 2B).

### <sup>1</sup>H NMR and <sup>13</sup>C NMR Spectra

The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the free ligands and their metal(II) chelates were done in DMSO-*d*<sub>6</sub>. The <sup>1</sup>H NMR spectral data are reported along with the possible assignments in Table III. The ligands display signals at  $\delta$  2.3–2.5, 4.1–5.1, 8.7–8.8, 8.9–9.1 and 12.8–12.9 ppm due to  $-\text{CH}_3$ , ferrocenyl, heteroaromatic (thiadiazole, triazole and tetrazole) protons. The protons due to heteroaromatic groups were found as to be in their expected region.<sup>34,35</sup> The conclusions drawn from these studies lend further support to the mode of

TABLE II Physical, analytical and spectral data of the metal complexes

Complex/Mol. formula	M.P (°C)	IR (cm <sup>-1</sup> )	$\lambda_{\text{max}}$ (cm <sup>-1</sup> )	B.M. ( $\mu\text{e}it$ )	Calc (Found) %C H N
(1) [Co(L <sup>1</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>10</sub> FeCoCl <sub>2</sub> N <sub>6</sub> S] <sub>4</sub> [467.7]	195–197	1635 (CH <sub>3</sub> C=N), 1585 (C=N), 390 (M–N), 310 (M–Cl)	8,715, 17,665, 29,985.	4.7	33.4 2.1 18.0(33.8)(2.3)(17.8)
(2) [Co(L <sup>2</sup> )Cl <sub>2</sub> ][C <sub>14</sub> H <sub>11</sub> FeCoCl <sub>2</sub> N <sub>5</sub> S] <sub>4</sub> [466.7]	202–204	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N), 310 (M–Cl)	8,790, 17,425, 30,110	4.8	36.0 2.4 15.0(36.5)(2.2)(15.1)
(3) [Co(L <sup>3</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>11</sub> FeCoCl <sub>2</sub> N <sub>7</sub> ] <sub>4</sub> [450.7]	205–207	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N), 310 (M–Cl)	8,7410 17,590, 29,995.	4.6	36.6 2.4 21.7(36.4)(2.2)(21.9)
(4) [Cu(L <sup>1</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>10</sub> FeCuCl <sub>2</sub> N <sub>6</sub> S] <sub>4</sub> [472.3]	208–210	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N).	15,165, 19,470, 30, 235.	1.4	33.0 2.1 17.8(33.2)(2.4)(17.5)
(5) [Cu(L <sup>2</sup> )Cl <sub>2</sub> ][C <sub>14</sub> H <sub>11</sub> FeCuCl <sub>2</sub> N <sub>5</sub> S] <sub>4</sub> [471.3]	206–208	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N).	15,215, 19,595, 30,310	1.5	35.6 2.3 14.8(35.9)(2.7)(14.5)
(6) [Cu(L <sup>3</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>11</sub> FeCuCl <sub>2</sub> N <sub>7</sub> ] <sub>4</sub> [455.3]	210–212	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N).	15,185, 19,555, 30,285.	1.5	34.3 2.4 21.7(34.0)(2.7)(21.5)
(7) [Ni(L <sup>1</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>10</sub> FeNiCl <sub>2</sub> N <sub>6</sub> S] <sub>4</sub> [467.9]	202–204	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N), 310 (M–Cl)	10,255, 16,245, 29,345.	3.3	33.7 2.1 17.9(33.9)(2.5)(17.6)
(8) [Ni(L <sup>2</sup> )Cl <sub>2</sub> ][C <sub>14</sub> H <sub>11</sub> FeNiCl <sub>2</sub> N <sub>5</sub> S] <sub>4</sub> [466.9]	206–28	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N), 310 (M–Cl)	10,380, 16,305, 29,365.	3.6	36.0 2.4 15.0(35.7)(2.2)(15.4)
(9) [Ni(L <sup>3</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>11</sub> FeNiCl <sub>2</sub> N <sub>7</sub> ] <sub>4</sub> [450.9]	212–214	1640 (CH <sub>3</sub> C=N), 1585 (s, C=N), 385 (M–N), 310 (M–Cl)	28,220	3.4	34.6 2.4 21.7(34.3)(2.6)(21.5)
(10) [Zn(L <sup>1</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>10</sub> FeZnCl <sub>2</sub> N <sub>6</sub> S] <sub>4</sub> [474.1]	197–198	1635 (CH <sub>3</sub> C=N), 1585 (C=N), 390 (M–N), 310 (M–Cl)	28,285	Dia	32.9 2.1 17.7(32.5)(2.3)(17.9)
(11) [Zn(L <sup>2</sup> )Cl <sub>2</sub> ][C <sub>14</sub> H <sub>11</sub> FeZnCl <sub>2</sub> N <sub>5</sub> S] <sub>4</sub> [461.1]	205–207	1640 (CH <sub>3</sub> C=N), 1580 (C=N), 385 (M–N), 310 (M–Cl)	28, 285	Dia	36.4 2.4 15.2(36.9)(2.2)(15.1)
(12) [Zn(L <sup>3</sup> )Cl <sub>2</sub> ][C <sub>13</sub> H <sub>11</sub> FeZnCl <sub>2</sub> N <sub>7</sub> ] <sub>4</sub> [457.1]	212–214	1640 (CH <sub>3</sub> C=N), 1585 (C=N), 385 (M–N), 310 (M–Cl)	28,255	Dia	34.1 2.4 21.4(34.3)(2.6)(21.5)

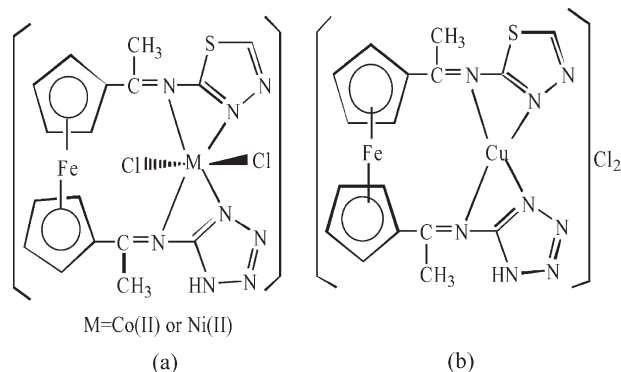


FIGURE 2 Proposed structure of the metal(II) chelates prepared in this study.

binding discussed above. The protons due to the ferrocenyl moiety were also found in the same region as expected and reported<sup>24–27</sup> earlier. In the spectra of their diamagnetic Zn(II) complexes (10–12) these protons shifted downfield due to the increased conjugation and coordination to the metal atoms. The number of protons calculated from the integration curves, and those obtained from the values of the expected CHN analyses agree with each other. In the <sup>13</sup>C NMR spectra, the ligand displays signals at  $\delta$  22.6–22.8, 68.6–83.7, 142.4–142.7 and 152.7–158.9 ppm assigned respectively to, –CH<sub>3</sub>, ferrocenyl, CH<sub>3</sub>C = N, and heteroaromatic carbons. These signals appear downfield in comparison with the corresponding signals of the ligand indicating<sup>36</sup> coordination and complexation with the central metal atom. It was observed

that DMSO did not have any coordinating effect either on the spectra of the ligands or on its metal complexes.

### Electronic Spectra and Magnetic Moments

The nature of the ligand field around the metal ion and the geometry of the metal complexes have been deduced from the electronic spectra and magnetic moment data (Table II). The room temperature magnetic moment of the solid cobalt(II) complexes was found to be in the range of 4.6–4.8 B.M., indicative<sup>37</sup> of three unpaired electrons per Co(II) ion in an octahedral environment. The magnetic moment of the Cu(II) complexes was found to be in the range of 1.4–1.5 B.M., consistent<sup>38</sup> with square-planar geometry. The nickel(II) complexes showed  $\mu_{\text{eff}}$  values of 3.3–3.6 B.M., corresponding<sup>37</sup> to two unpaired electrons per Ni(II) ion for their six-coordinated configuration. The electronic spectra of the Co(II) complexes showed three bands observed at 8,715–8,790, 17,425–17,665 and 29,985–30,110 cm<sup>-1</sup> which may be assigned to  ${}^4T_{1g} \rightarrow {}^4T_{2g}(F)$ ,  ${}^4T_{1g} \rightarrow {}^3A_{2g}(F)$  and  ${}^4T_{1g} \rightarrow {}^4T_{1g}(P)$  transitions respectively and are suggestive<sup>39</sup> of the octahedral geometry around the cobalt ions. The electronic spectra of the Cu(II) complexes showed two low-energy weak bands at 15,165–15,215 and 19,470–19,595 cm<sup>-1</sup> and a strong high-energy band at 30,235–30,310 cm<sup>-1</sup>. The low-energy bands in this region are typically expected for its square-planar configuration and may be assigned to  ${}^2B_{1g} \rightarrow {}^2A_{1g}$  and  ${}^2B_{1g} \rightarrow {}^2E_g$  transitions, respectively. The strong

TABLE III <sup>1</sup>H NMR and <sup>13</sup>C NMR data of the ligands and Zn(II) complexes (10–12)

No	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> ) (ppm)	<sup>13</sup> C NMR (DMSO-d <sub>6</sub> ) (ppm)
L <sup>1</sup>	2.4 (s, 6H, CH <sub>3</sub> ), 4.2–4.3 (m, 2H, ferrocenyl), 4.5–4.6 (m, 2H, ferrocenyl), 4.7–4.8 (m, 2H, ferrocenyl), 4.8–4.9 (m, 2H, ferrocenyl), 8.7 (s, 1H, thiadiazole), 12.8 (s, 1H, NH tetrazole).	22.6 (CH <sub>3</sub> ), 68.6, 69.6, 83.5(ferrocenyl), 142.4 (C = N), 152.8, 156.5 (thiadiazole), 158.9 (tetrazole).
L <sup>2</sup>	2.3 (s, 6H, CH <sub>3</sub> ), 4.1–4.2 (m, 2H, ferrocenyl), 4.4–4.5 (m, 2H, ferrocenyl), 4.6–4.7 (m, 2H, ferrocenyl), 4.8–4.9 (m, 2H, ferrocenyl), 8.8 (s, 1H, thiadiazole), 8.9 (s, 1H, NH triazole), 12.8 (s, 1H, NH triazole).	22.7 (CH <sub>3</sub> ), 68.6, 69.5, 83.5 (ferrocenyl), 142.5 (C = N), 152.7, 156.3 (thiadiazole), 153.4, 158.5 (triazole).
L <sup>3</sup>	2.5 (s, 6H, CH <sub>3</sub> ), 4.3–4.4 (m, 2H, ferrocenyl), 4.6–4.7 (m, 2H, ferrocenyl), 4.8–4.9 (m, 2H, ferrocenyl), 5.0–5.1 (m, 2H, ferrocenyl), 9.1 (s, 1H, triazole), 12.8 (s, 1H, triazole), 12.9 (s, 1H, NH tetrazole).	22.8 (CH <sub>3</sub> ), 68.7, 69.5, 83.6, 83.6 (ferrocenyl), 142.7 (C = N), 158.8 (tetrazole), 153.6, 158.8 (triazole).
10	2.5 (s, 6H, CH <sub>3</sub> ), 4.3–4.4 (m, 2H, ferrocenyl), 4.6–4.7 (m, 2H, ferrocenyl), 4.9–5.1 (m, 2H, ferrocenyl), 5.1–5.2 (m, 2H, ferrocenyl), 9.1 (s, 1H, thiadiazole), 12.9 (s, 1H, NH, tetrazole).	22.8 (CH <sub>3</sub> ), 68.9, 69.7, 83.8 (ferrocenyl), 143.1 (C = N), 152.8, 156.6 (thiadiazole), 158.9 (tetrazole).
11	2.5 (s, 6H, CH <sub>3</sub> ), 4.3–4.4 (m, 2H, ferrocenyl), 4.6–4.7 (m, 2H, ferrocenyl), 4.8–4.9 (m, 2H, ferrocenyl), 5.1–5.2 (m, 2H, ferrocenyl), 9.2 (s, 1H, thiadiazole), 9.4 (s, 1H, triazole), 12.9 (s, 1H, NH, triazole).	22.7 (CH <sub>3</sub> ), 68.8, 69.9, 83.6 (ferrocenyl), 143.2 (C = N), 152.9, 156.5 (thiadiazole), 153.6, 158.7 (triazole).
12	2.6 (s, 6H, CH <sub>3</sub> ), 4.5–4.6 (m, 2H, ferrocenyl), 4.7–4.8 (m, 2H, ferrocenyl), 5.1–5.2 (m, 2H, ferrocenyl), 5.3–5.4 (m, 2H, ferrocenyl), 9.5 (s, 1H, triazole), 12.8 (s, 1H, NH triazole), 12.9 (s, 1H, NH, triazole).	22.9 (CH <sub>3</sub> ), 69.1, 69.7, 83.7, 83.8 (ferrocenyl), 143.4 (C = N), 158.9 (tetrazole), 153.8, 158.9 (triazole).

TABLE IV Antibacterial activity data of the investigated ligands and complexes

Ligand/ Complex*	Microbial species		
	(a)	(b)	(c)
L <sup>1</sup>	++	+++	++
L <sup>2</sup>	++	++	+
L <sup>3</sup>	+	++	++
(1)	+++	++++	++++
(2)	++++	+++	+++
(3)	+++	+++	+++
(4)	++	++++	++++
(5)	+++	+++	+++
(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 the inhibition zone (22 mm) of the most active compound with 100% inhibition. \*At 3 mg/mL concentration of compound in the assay system.

high-energy band, in turn is assigned to a metal → ligand charge transfer. The Ni(II) complexes exhibited three spin-allowed bands at 10,255–10,380, 16,245–16,305, and 29,280–29,365 cm<sup>-1</sup> assignable<sup>40</sup> respectively, to the transitions <sup>3</sup>A<sub>2g</sub>(F) → <sup>3</sup>T<sub>2g</sub>(F)(ν<sub>1</sub>), <sup>3</sup>A<sub>2g</sub>(F) → <sup>3</sup>T<sub>1g</sub>(F)(ν<sub>2</sub>) and <sup>3</sup>A<sub>2g</sub>(F) → <sup>3</sup>T<sub>2g</sub>(P)(ν<sub>3</sub>) which were characteristic of their octahedral geometry. The electronic spectra of the Zn(II) complexes showed only a high intensity band at 28,220–28,285 cm<sup>-1</sup> due to ligand → metal charge transfer in a distorted octahedral environment.<sup>41</sup>

On the basis of the above observations, it is suggested that the Co(II), Ni(II) and Zn(II) complexes show an octahedral geometry and distorted octahedral geometry respectively and the Cu(II) complexes a square-planar geometry (Figure 2B) in which the two Schiff bases act as tridentate ligands and accommodate themselves around the metal ion in such a way that a stable chelate ring of the complex is formed, giving a stable structure to the complex.

### Antibacterial Properties

The title ligands and their metal(II) chelates were evaluated for antibacterial activity against pathogenic strains of (a) *Escherichia coli*, (b) *Pseudomonas aeruginosa* and (c) *Staphylococcus aureus*. The compounds were tested at a concentration of 30 μg/0.01 mL in DMF solution using the paper disc diffusion method.<sup>42–44</sup> The susceptibility zones were measured in diameter (mm) and the results are reproduced in Table IV. The susceptibility zones measured were the clear zones around the discs killing the bacteria.

All the ligands 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 ligands became more pronounced when coordinated to the metal. Our previous studies have suggested<sup>42–45</sup> that in the chelated complex, the positive charge of the metal ion is partially shared with the donor atoms and there is π-electron delocalization over the whole chelate ring. This increases the lipophilic character of the metal chelate and favors its penetration permeation through the lipid layers of the bacterial membranes. Apart from this, other factors such as solubility, conductivity and dipole moment, influenced by the presence of the metal ion, may also be possible reasons for increasing this activity of the ligands upon chelation.

### References

- [1] Travis, J. and Potempa, J. (2000) *Biochim. Biophys. Acta* **14**, 35–50.
- [2] Wright, G.D. (2000) *Chem. Biol.*, **7**, R127–R132.
- [3] Rice, S.A., Givskov, M., Steinberg, P. and Kjelleberg, S. (1999) *J. Mol. Microbiol. Biotechnol.*, **1**, 23–31.
- [4] Scozzafava, A. and Supuran, C.T. (2000) *J. Med. Chem.* **43**, 3677.
- [5] Smith, H.J., and Simons, C., eds, (2001) *Proteinase and Peptidase Inhibition: Recent Potential Targets for Drug Development* (Taylor and Francis, London).
- [6] Kobayashi, A., Kim, H., Sasaki, Y., Kato, R., Moriyama, S., Nishio, Y., Kajita, K., Sasaki, W. and Kobayashi, H. (1988) *Synth. Met.*, **27**, B339.
- [7] McCleverty, J. (1968) *Prog. Inorg. Chem.*, **10**, 49.
- [8] Clemenson, P.I. (1990) *Coord. Chem. Rev.* **106**, 171.
- [9] Browal, K.W. and Interrante, L.V. (1973) *J. Coord. Chem.*, **3**, 27.
- [10] Brossard, L., Ribault, M., Valade, L. and Cassoux, P. (1989) *J. Phys.* **50**, 152.
- [11] Gang, G., Feng, L., Jishan, X. and Yongxiang, M. (1988) *Polyhedron* **7**, 303.
- [12] Xiaoxian, Z., Youngmin, L., Fajun, N. and Yongxiang, M. (1992) *Polyhedron* **11**, 447.
- [13] Singh, S.P. and Singh, N.B. (1990) *Polyhedron* **9**, 557.
- [14] Praveen, M. and Chohan, Z.H. (1999) *Synth. React. Inorg. Met-Org. Chem.*, **29**, 355.
- [15] Chohan, Z.H. (1986) *Ind. J. Chem.*, **25B**, 1065.
- [16] Patil, S.R., Kantak, U.N. and Sen, D.N. (1963) *Inorg. Chim. Acta.* **68**, 1.
- [17] Green, M.L.H., Marder, S.R., Thompson, M.E., Bandy, J.A., Bloor, D., Kolinskt, P.V. and Jones, R.J. (1987) *Nature (Lond.)* **330**, 360.
- [18] Constable, A.C. (1991) *Angew. Chem. (Int. Ed. Engl.)* **30**, 407.
- [19] Longato, B., Pilloni, G., Valle, G. and Gorain, B. (1988) *Inorg. Chem.*, **27**, 956.
- [20] Beer, P.D., Nation, L.E., McWhinnie, S.W.L., Harman, M.E., Hursthouse, M.B., Ogden, M.I. and White, A.H. (1991) *J. Chem. Soc., Dalton Trans.*, 2485.
- [21] Edwards, E.I., Epton, R. and Marr, G. (1975) *J. Organomet. Chem.*, **85**, C-23.
- [22] Rockett, B.W. and Marr, G. (1976) *J. Organomet. Chem.*, **123**, 205.
- [23] Houlton, A., Dilworth, J.R., Roberts, R.M.G., Silver, J. and Drew, M.B. (1991) *Polyhedron* **9**, 2751.
- [24] Chohan, Z.H. and Praveen, M. (2001) *Appl. Organomet. Chem.*, **15**, 617–625.
- [25] Chohan, Z.H. and Praveen, M. (2000) *Appl. Organomet. Chem.*, **14**, 376–382.
- [26] Chohan, Z.H. (2002) *Appl. Organomet. Chem.*, **16**, 17–20.

- [27] Chohan, Z.H. and Praveen, M. (2000) *Synth. React. Inorg. Met-Inorg. Chem.*, **30**, 175–182.
- [28] Geary, W.J. (1971) *Coord. Chem. Rev.*, **7**, 81.
- [29] Yongxiang, M., Zhengzhi, Z., Yun, M. and Gang, Z. (1989) *Inorg. Chim. Acta.* **165**, 185.
- [30] Nakamoto, K. (1970) *Infrared Spectra of Inorganic and Coordination Compounds*, 2nd Ed. (Wiley Interscience, New York).
- [31] Agarwal, R.K. (1988) *J. Ind. Chem. Soc.* **65**, 448.
- [32] Bellamy, L.J. (1971) *The Infrared Spectra of Complex Molecules* (John Wiley, New York).
- [33] Ferrero, J.R. (1971) *Low-frequency Vibrations of Inorganic and Coordination Compounds* (John Wiley, New York).
- [34] Williams, D.H. and Fleming, I. (1989) *Spectroscopic Methods in Organic Chemistry* (McGraw-Hill, London).
- [35] Simmons, W.W. (1978) *The Sadtler Handbook of Proton NMR Spectra* (Sadtler Research Laboratories, Inc.).
- [36] Pasto, D.J. (1969) *Organic Structure Determination* (Prentice Hall International, London).
- [37] Lever, A.B.P. and Lewis, J. (1963) *J. Chem. Soc.*, 2552.
- [38] Carlin, R.L. (1965) *Transition Metal Chemistry*, 2nd Ed. (Marcel Decker, New York).
- [39] Estes, W.E., Govel, D.P., Halfield, W.B. and Hodgson, D.J. (1978) *Inorg. Chem.* **17**, 1415.
- [40] Balhausen, C.J. (1962) *An Introduction to Ligand Field* (McGraw Hill, New York).
- [41] Lever, A.B.P. (1984) *Inorganic Electronic Spectroscopy* (Elsevier, Amsterdam).
- [42] Chohan, Z.H., Munawar, A. and Supuran, C.T. (2001) *Metals-Based Drugs* **8**, 137.
- [43] Chohan, Z.H. and Supuran, C.T. (2001) *Main Group Metal Chem.* **24**, 399.
- [44] Chohan, Z.H., Pervez, H., Rauf, A. and Supuran, C.T. (2002) *Metal-Based Drugs* **8**, 42.
- [45] Hassan, M.U., Chohan, Z.H. and Supuran, C.T. (2002) *Main Group Metal Chem.* **25**, 291.