

Antibacterial Co(II), Cu(II), Ni(II) and Zn(II) Complexes of Thiadiazole Derived Furanyl, Thiophenyl and Pyrrolyl Schiff Bases

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2-Amino-1,3,4-thiadiazole undergoes a condensation reaction with furane-, thiophene- and pyrrole-2-carboxaldehyde to form tridentate NNO, NNS and NNN donor Schiff bases. These Schiff bases were further used to obtain complexes of the type $[M(L)_2]X$, where $M = Co(II), Cu(II), Ni(II)$ or $Zn(II)$, $L = L^1, L^2$ or L^3 and $X = Cl_2$. The new compounds described here have been characterized by their physical, spectral and analytical data, and have been screened for antibacterial activity against several bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The antibacterial potency of the Schiff bases increased upon chelation/complexation in comparison to the uncomplexed Schiff bases against the tested bacterial species thus, opening new approaches to find new ways in the fight against antibiotic-resistant strains.

Keywords: Antibacterial; Schiff bases; Metal complexes

INTRODUCTION

Thiazole and thiadiazole compounds are of considerable biological interest due to the fact that these five-membered heterocyclic rings are structurally similar to the imidazolyl moieties of the histidyl residue present in proteins.¹ As ligands, they also provide many potential binding sites for complexation of diverse metal ions (such as Cu(II); Co(II); Ni(II); or Zn(II) among others) with well established biological roles.^{2–8} Many recent studies have stressed the important role of metal ions in biological processes, and inorganic pharmacology has started

to be an important field with more than 25 inorganic compounds being used in therapy as diagnostic tools, antibacterial, antiviral and anticancer drugs.^{9–21} It has been suggested^{22,23} that the interaction between the metal ion from the ligand with cancer-associated viruses might represent an important route for designing new anticancer therapies.⁹ The inverse process, i.e., coordinating a metal ion from an important biomolecule, such as for instance a zinc finger protein, has recently been used to design novel antiviral therapies, targeted against human immunodeficiency (HIV) and human papilloma virus (HPV) infections.¹⁷ Palladium and platinum complexes of 6-mercaptapurine have already been shown to destroy²⁸ adenocarcinomas, whereas the complexes of dialkyldithiophosphate,²⁹ cisplatin and carboplatin are potent antineoplastic drugs used in chemotherapy.³⁰ Such metal complexes show best results in the treatment of testicular and ovarian carcinoma and are also effective against bladder tumors and head and neck tumors.³¹ It has also been demonstrated that chelation/complexation tends to enhance the biological activity of many compounds.^{32–35} In previous works we have explored the biological properties of thiazole-derived compounds and the effect of chelation on their bactericidal properties.^{36–39} Keeping in view the antibacterial,^{40,41} antiviral,⁴² antifungal,^{43,44} antitumor^{45,46} and antileukemia⁴⁷ properties of some thiadiazole derivatives, we report here some new Schiff bases, obtained by the condensation of 2-amino-1,3,4-thiadiazole with furane-, thiophene- and

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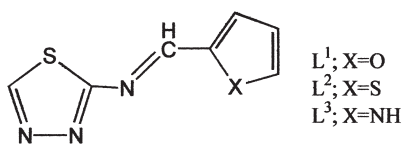


FIGURE 1 Structure of the Schiff bases.

pyrrole-2-carboxaldehyde to form tridentate NNO, NNS and NNN ligands, i.e., N-(2-furanylmethylene)-2-amino-1,3,4-thiadiazole (L^1), N-(2-thiophenylmethylene)-2-amino-1,3,4-thiadiazole (L^2) and N-(2-pyrrolylmethylene)-2-amino-1,3,4-thiadiazole (L^3). These newly prepared Schiff bases were then used to synthesize various metal complexes of the type $[M(L)_2]Cl_2$ where $M = Co(II), Cu(II), Ni(II)$ or $Zn(II)$ and $L = L^1, L^2$ or L^3 (Fig. 1). In order to evaluate the role of such metal ions on antibacterial activity, these Schiff bases and their metal(II) complexes were screened for antibacterial activity against pathogenic strains of *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, all of which ultimately develop increasing resistance to classical antibiotics.⁴⁸

MATERIALS AND METHODS

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

Preparation of Schiff Base (L^1)

Furan-2-aldehyde (0.97 g, 0.83 mL, 0.01 M) in ethanol (10 mL) was added to a hot ethanol solution (20 mL) of 2-amino-1,3,4-thiadiazole (1.0 g, 0.01 M). Then 2–3 drops of conc. H_2SO_4 were added and the mixture refluxed for 2 h. On cooling, a yellow solid was formed which was filtered, washed with ethanol, then with ether and dried. Crystallization in hot ethanol gave L^1 (1.0 g, 78%), M.p 121°C. The same method was applied for the preparation of other Schiff bases, L^2 (1.5 g, 82%), M.p 117°C and L^3 (1.6 g, 85%), M.p 128°C by using the corresponding reagents in the same molar ratio.

TABLE I Spectral and Analytical Data of the Schiff bases

Schiff base	IR (cm^{-1})	1H NMR (DMSO- d_6) (ppm)	^{13}C NMR (DMSO- d_6) (ppm)	Calc (Found)%		
				C	H	N
L^1	1640 (s, HC = N), 1620 (s, C = N).	7.3 (s, 1H, CH = N), 7.5–7.6 (m, 1H, furanyl), 7.7–7.8 (m, 1H, furanyl), 7.9–8.0 (m, 1H, furanyl), 8.7 (s, 1H, thiadiazole)	117.2, 121.8, 122.4, 131.3 (furanyl), 165.2 (HC = N), 146.4, 152.3 (thiadiazole)	46.9 (47.2)	2.8 (2.9)	23.5 (23.2)
L^2 $C_7H_5N_3S_2$	1640 (s, HC = N), 1620 (s, C = N).	7.3 (s, 1H, CH = N), 7.6–7.7 (m, 1H, thiophenyl), 7.8–7.9 (m, 1H, thiophenyl), 8.0–8.1 (m, 1H, thiophenyl), 8.8 (s, 1H, thiadiazole)	118.2, 120.8, 122.6, 131.9 (thiophenyl), 165.2 (HC = N), 146.5, 152.4 (thiadiazole)	43.1 (43.5)	2.6 (2.3)	21.5 (21.2)
L^3 $C_7H_6N_4S$	1640 (s, HC = N), 1620 (s, C = N).	7.3 (s, 1H, CH = N), 7.7–7.8 (m, 1H, pyrrolyl), 7.8–7.9 (m, 1H, pyrrolyl), 8.1–8.2 (m, 1H, pyrrolyl), 8.8 (s, 1H, thiadiazole)	118.4, 120.8, 122.7, 131.9 (pyrrolyl), 165.5 (HC = N), 146.6, 152.4 (thiadiazole)	47.2 (47.0)	3.4 (3.9)	31.4 (31.6)

TABLE II Physical and Analytical Data of the Metal(II) Chelates

No	Metal chelate/Mol. Formula	Yield (%)	M.p. (°C) (decomp. m.p.)	B.M. (μ_{eff})	Calc (Found) %		
					C	H	N
1	[Co(L ¹) ₂]Cl ₂ [487.9] C ₁₄ H ₁₀ CoCl ₂ N ₆ O ₂ S ₂	59	222–224	4.1	34.4 (34.6)	2.0 (2.1)	17.2 (17.0)
2	[Cu(L ¹) ₂]Cl ₂ [492.5] C ₁₄ H ₁₀ CuCl ₂ N ₆ O ₂ S ₂	56	220–222	1.3	34.1 (34.0)	2.0 (2.4)	17.1 (17.3)
3	[Ni(L ¹) ₂]Cl ₂ [487.7] C ₁₄ H ₁₀ NiCl ₂ N ₆ O ₂ S ₂	58	221–223	3.2	34.4 (34.5)	2.1 (2.6)	17.2 (17.1)
4	[Zn(L ¹) ₂]Cl ₂ [494.4] C ₁₄ H ₁₀ ZnCl ₂ N ₆ O ₂ S ₂	60	225–227	Dia	34.0 (34.2)	2.0 (2.3)	17.0 (16.8)
5	[Co(L ²) ₂]Cl ₂ [520.0] C ₁₄ H ₁₀ CoCl ₂ N ₆ S ₄	58	218–220	4.6	32.3 (32.5)	1.9 (1.5)	16.2 (16.3)
6	[Cu(L ²) ₂]Cl ₂ [524.6] C ₁₄ H ₁₀ CuCl ₂ N ₆ S ₄	57	218–220	1.5	32.0 (32.3)	1.9 (1.6)	16.0 (16.4)
7	[Ni(L ²) ₂]Cl ₂ [519.8] C ₁₄ H ₁₀ NiCl ₂ N ₆ S ₄	58	212–214	3.4	32.3 (32.1)	1.9 (1.7)	16.2 (16.5)
8	[Zn(L ²) ₂]Cl ₂ [526.5] C ₁₄ H ₁₀ ZnCl ₂ N ₆ S ₄	60	226–228	Dia	31.9 (32.1)	1.9 (1.6)	15.9 (15.6)
9	[Co(L ³) ₂]Cl ₂ [485.9] C ₁₄ H ₁₂ CoCl ₂ N ₈ S ₂	59	220–222	4.4	34.6 (34.5)	2.5 (2.4)	23.0 (23.2)
10	[Cu(L ³) ₂]Cl ₂ [490.5] C ₁₄ H ₁₂ CuCl ₂ N ₈ S ₂	58	215–218	1.4	34.2 (34.5)	2.4 (2.1)	22.8 (22.9)
11	[Ni(L ³) ₂]Cl ₂ [485.7] C ₁₄ H ₁₂ NiCl ₂ N ₈ S ₂	60	222–224	3.3	34.6 (34.8)	2.5 (2.9)	23.1 (23.4)
12	[Zn(L ³) ₂]Cl ₂ [492.4] C ₁₄ H ₁₂ ZnCl ₂ N ₈ S ₂	61	218–220	Dia	34.1 (34.5)	2.4 (2.3)	22.7 (22.6)

Preparation of Cobalt (II) Complex of L¹

A warm ethanol solution (20 mL) of L¹ (0.002 M) was added to a magnetically stirred solution of cobalt(II) chloride hexahydrate (0.001 M) in distilled water (25 mL). The mixture was refluxed for 1 h and cooled thereafter to room temperature. On cooling, a pink precipitate was formed which was filtered, washed with ethanol, acetone and ether, and dried by suction. Crystallization in aqueous ethanol (70:30) gave the desired metal complex (**1**) (0.5 g, 68%). All other metal derivatives were obtained from the corresponding ligands and metal salts, following the same method.

Antibacterial Studies

The synthesized metal complexes, as well as the uncomplexed Schiff bases were screened for their antibacterial activity against pathogenic bacterial strains of *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The paper disc diffusion method^{49,50} was adopted for determining the antibacterial activity.

RESULTS AND DISCUSSION

Chemistry

The Schiff bases (L¹–L³) (Fig. 1) were prepared by refluxing an appropriate amount of 2-amino-1,3,4-thiadiazole with the corresponding furan-, thiophene- and pyrrole-2-carboxaldehyde in ethanol in 1:1 molar ratio. The structures of these Schiff bases were established with the help of their IR, NMR, and microanalytical data (Table I). All metal complexes (**1**–**12**) (Table II) of these Schiff bases were air stable and prepared by the stoichiometric reaction of the corresponding metal(II) chloride with the Schiff base ligand, in molar ratio M:L of 1:2. These complexes are intensely colored and amorphous solids, which decompose without melting. They are insoluble in common organic solvents such as ethanol, methanol, chloroform or acetone being only soluble in DMSO and DMF. Molar conductance values of the soluble complexes in DMF show low values (12–21 ohm⁻¹·cm²·mol⁻¹) indicating⁵¹ that they are all non-electrolytic in nature.

IR spectra of the Schiff bases reported here showed the absence of bands at 1735 and 3420 cm⁻¹ due to carbonyl ν (C=O) and ν (NH₂) stretching vibrations (present in the starting materials) and the appear-

TABLE III IR and UV-Visible Spectral Data of the Metal(II) Chelates

No	IR (cm ⁻¹)	λ_{max} (cm ⁻¹)
1	1625 (HC = N), 1610 (C = N), 525 (M-N), 455 (M-O)	30110, 17610, 8670
2	1630 (HC = N), 1605 (C = N), 525 (M-N), 455 (M-O)	30555, 22250
3	1630 (HC = N), 1600 (C = N), 530 (M-N), 460 (M-O)	29115, 15845, 9715
4	1630 (HC = N), 1610 (C = N), 530 (M-N), 460 (M-O)	28550
5	1625 (HC = N), 1610 (C = N), 525 (M-N), 525 (M-N)	30475, 18215, 8715
6	1630 (HC = N), 1605 (C = N), 530 (M-N), 530 (M-N)	30645, 22355
7	1625 (HC = N), 1610 (C = N), 525 (M-N), 530 (M-N)	28440, 16255, 10115
8	1625 (HC = N), 1610 (C = N), 530 (M-N), 525 (M-N)	28610
9	1630 (HC = N), 1605 (C = N), 525 (M-N), 360 (M-S)	30365, 17815, 8885
10	1630 (HC = N), 1605 (C = N), 525 (M-N), 365 (M-S)	30625, 22315
11	1625 (HC = N), 1610 (C = N), 525 (M-N), 365 (M-S)	28635, 16150, 9875
12	1630 (HC = N), 1605 (C = N), 525 (M-N), 365 (M-S)	28585

TABLE IV NMR spectra of the Zn(II) complexes **4**, **8**, **12**

Complex	¹ H NMR (DMSO-d ₆) (ppm)	¹³ C NMR (DMSO-d ₆) (ppm)
4	7.5 (s, 1H, CH = N), 7.6–7.7 (m, 1H, furanyl), 7.8–7.9 (m, 1H, furanyl), 8.1–8.2 (m, 1H, furanyl), 8.9 (s, 1H, thiadiazole)	117.6, 121.9, 122.5, 131.5 (furanyl), 165.8 (HC = N), 146.6, 152.7 (thiadiazole)
8	7.5 (s, 1H, CH = N), 7.7–7.8 (m, 1H, thiophenyl), 7.9–8.0 (m, 1H, thiophenyl), 8.2–8.4 (m, 1H, thiophenyl), 8.9 (s, 1H, thiadiazole)	118.4, 120.9, 122.8, 132.1 (thiophenyl), 165.4 (HC = N), 146.7, 152.8 (thiadiazole)
12	7.6 (s, 1H, CH = N), 7.8–7.9 (m, 1H, pyrrolyl), 7.9–8.0 (m, 1H, pyrrolyl), 8.2–8.4 (m, 1H, pyrrolyl), 8.9 (s, 1H, thiadiazole)	118.5, 120.9, 122.9, 132.2 (pyrrolyl), 165.7 (HC = N), 146.7, 152.6 (thiadiazole)

ance of a strong new band at $\sim 1640\text{ cm}^{-1}$ assigned as azomethine $\nu(\text{HC} = \text{N})$ vibration.⁵² The comparison of the infrared spectra of the Schiff bases with their metal chelates indicated that the Schiff bases were principally tridentately coordinated to the metal ions. The band appearing at 1640 cm^{-1} due to the azomethine vibration is shifted to lower frequency by $\sim 10\text{--}15\text{ cm}^{-1}$ indicating⁵³ participation of the azomethine nitrogen in complexation. The band at 1620 cm^{-1} assigned to the thiadiazole ring $\nu(\text{C} = \text{N})$ vibrations is also shifted to lower frequency by $\sim 10\text{ cm}^{-1}$ which is indicative of the involvement of the thiadiazole ring nitrogen in chelation. Further evidence of the coordination of these Schiff bases with the metal ions, was shown by the appearance of weak low frequency new bands at $525\text{--}530$ and $455\text{--}460$ and $360\text{--}365\text{ cm}^{-1}$ (Table III). These were, in turn, assigned⁵⁴ to metal-nitrogen $\nu(\text{M-N})$ (in pyrrolyl compounds) metal-oxygen $\nu(\text{M-O})$ (in furanyl compounds) or metal-sulfur $\nu(\text{M-S})$ (in thiophenyl compounds), vibrations, respectively. These new bands were observable only in the spectra of the metal complexes and not in the spectra of the uncomplexed Schiff bases and thus confirm the participation of these heteroatoms (N, O or S) in the coordination.

The NMR spectral data of these Schiff bases as well as some of their Zn(II) complexes in DMSO-d₆ are listed in Tables I and IV. The Schiff bases exhibited signals due to all the expected protons in their expected region and have been identified from the scans, which corresponded to the total number of protons deduced from their proposed structures. These were compared with the reported⁵⁵ signals of known structurally related compounds and give further support for the composition of these new Schiff bases as well as their complexes suggested by their IR and elemental analyses data. Comparison of the chemical shifts of the uncomplexed Schiff bases with those of the corresponding zinc complexes show that some of the resonances are shifted upon complexation. In each case, the protons assigned due to heteroaromatic (HC = N) ring and azomethine (HC = N) were found at around $\delta 7.3\text{--}8.8$ ppm in the spectra of the Schiff bases. These protons undergo downfield shift in the zinc complexes indicating participation of these groups in coordination of the metal ions. The same shifts were observed in the ¹³C NMR spectral data of the Schiff bases versus their zinc complexes.

The room temperature magnetic moment of the solid cobalt(II) complexes was found to lie in the range of $4.1\text{--}4.6$ B.M, indicative⁵⁶ of three unpaired electrons per Co(II) ion in an octahedral environment. The Cu(II) complexes showed μ_{eff} values in the range of $1.3\text{--}1.5$ B.M indicative of one unpaired electron per Cu(II) ion suggesting⁵⁷ that these complexes had structures within the range consistent

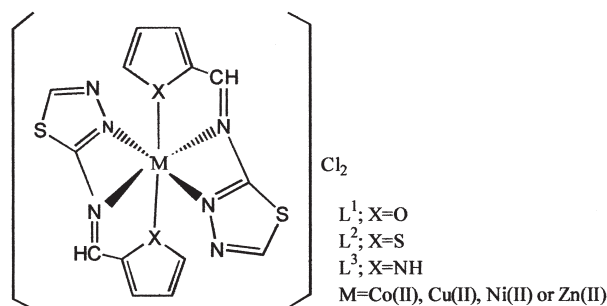


FIGURE 2 Proposed structure of the metal(II) complex 1–12.

to spin-free distorted octahedral geometry. Similarly, the Ni(II) complexes showed μ_{eff} values in the range of 3.2–3.4 B.M, corresponding⁵⁷ to two unpaired electrons per Ni(II) ion for their ideal six-coordinated configuration. The Zn(II) complexes were all found to be diamagnetic.

The electronic spectra of the Co(II) chelates showed three bands observed at 8670–8885, 17610–18215 and 30110–30475 cm^{-1} which may be assigned to ${}^4T_{1g} \rightarrow {}^4T_{2g}(\text{F})$, ${}^4T_{1g} \rightarrow {}^3A_{2g}(\text{F})$ and ${}^4T_{1g} \rightarrow {}^4T_{1g}(\text{P})$ transitions, respectively, and are suggestive^{58,59} of their octahedral geometry around the cobalt ions. The Cu(II) complexes showed three absorption bands between 10 Dq band for a distorted octahedral geometry corresponding^{60,61} to the transitions ${}^2E_g \rightarrow {}^2T_{2g}$. The bands at 22250–22355 and 30555–30645 cm^{-1} may be due to intra-ligand charge transfer transitions. The Ni(II) complexes exhibited three spin-allowed bands at 9715–10115, 15845–16255 and 28440–29115 cm^{-1} assignable^{62,63} respectively, to the transitions ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{2g}(\text{F})(\nu_1)$, ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{1g}(\text{F})(\nu_2)$ and ${}^3A_{2g}(\text{F}) \rightarrow {}^3T_{2g}(\text{P})(\nu_3)$ which are characteristic of Ni(II) in octahedral geometry (Fig. 2). The diamagnetic zinc(II) complexes did not show any d–d bands and their spectra are dominated only by charge transfer bands. The charge transfer band at 28550–28610 cm^{-1} was assigned⁶⁴ as due to ${}^2E_g \rightarrow {}^2T_{2g}$ transitions possibly in an octahedral environment.

Antibacterial Properties

The title Schiff bases and their metal chelates were evaluated for antibacterial activity against bacterial strains of (a) *Escherichia coli*, (b) *Staphylococcus aureus* and (c) *Pseudomonas aeruginosa* (Table V). The compounds were tested at a concentration of 30 $\mu\text{g}/0.01\text{ mL}$ in DMF solution using the paper disc diffusion method. The diameter of the susceptibility zones was measured in mm. The measured susceptibility zones were the clear zones around the discs killing the bacteria. All the Schiff bases and their complexes individually exhibited varying degrees of inhibitory effects on the growth of the tested bacterial species. The antibacterial results

TABLE V Antibacterial Activity Data of the Schiff bases and their Metal(II) chelates 1–12

Schiff base/chelate	Microbial species		
	a	b	c
L ¹	++	++	+
L ²	++	+	++
L ³	++	++	+++
1	+++	++++	++
2	++++	++	++++
3	++++	+++	+++
4	++++	+++	+++
5	+++	+++	+++
6	++++	+++	+++
7	+++	+++	++
8	+++	+++	+++
9	+++	+++	+++
10	++++	++++	++
11	++	+++	++++
12	+++	+++	+++

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

evidently show that the activity of the Schiff bases became more pronounced and significant when coordinated to these metal ions. On the basis of these observations, it is claimed that chelation dominantly affects the biological behavior of the compounds that are potent against some bacterial strains. It is however, suspected that factors such as solubility, dipole moment and cell permeability mechanisms are certainly influenced by the presence of the metal ions which, in turn, affect the mechanisms of permeation through the lipid layer of the organisms thus killing them more effectively and efficiently.

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