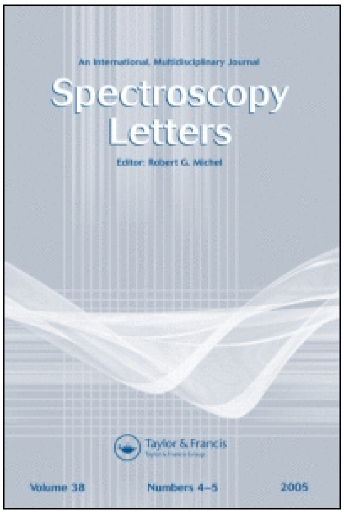

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Synthesis, Characterization and Antibacterial Activity of Some Transition Metal Complexes of 2-N-(isatinamino)-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene

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ABSTRACT Metal complexes of Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) with a Schiff base derived from isatin and 2-amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[b]thiophene were synthesised and characterised by elemental analysis, conductance measurements, magnetic susceptibility, UV-Vis, IR, ^{1}H NMR and EPR spectral studies. The spectral data revealed that the ligand acted as a neutral tridentate, coordinating to the metal ion through the azomethine nitrogen, ester carbonyl and carbonyl oxygen of the isatin moiety. The EPR spectral data indicated that metal-ligand bonds have considerable covalent character. The copper(II) complex was subjected to X-ray diffraction and cyclic voltammetric studies. The ligand and the metal complexes were screened for their antibacterial activity and it has been observed that the metal complexes are more potent bactericides than the ligand.

KEYWORDS 2-amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene, cyclic voltammetry, antibacterial activity, isatin, schiff base complexes, XRD

INTRODUCTION

Schiff bases and related metal complexes have experienced long standing applications in biology, medicine, catalysis and in photochemical properties.[1–3] Among the prodigious number and variety of Schiff bases, a potential group of heterocyclic Schiff bases containing the benzothiophene moiety has received comparatively less attention as ligands.[4] In this communication we report the synthesis and spectroscopic characterization of some bivalent transition metal complexes with a neutral tridentate Schiff base ligand viz. 2-N-(isatinamino)-3-carboxyethyl-4,5,6,7-tetrahydrobenzo-[*b*]thiophene (ISAT). The copper(II) complexes has been subjected to X-ray diffraction and cyclic voltammetric studies. Apart from the synthetic

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and structural aspects, it has been expected that linking of two biologically important compounds, isatin and benzothiophene derivatives through an azomethine functionality would exhibit pronounced biological activity. In view of this, the ligand and metal complexes have been screened for their antibacterial activity and the results have been discussed.

MATERIALS AND METHODS

Analytical grade chemicals purchased from Aldrich and Merck were used for synthesis. Elemental analyses were performed using Elementar Systeme, Vario EL III CHNS Analyser. The metal content of the complexes were analysed using Nulab GBC 902 atomic absorption spectrophotometer. Infrared spectra were recorded on a Shimadzu FTIR 8000 spectrophotometer and a Bruker DRX-300(300 MHz) FT NMR spectrometer was used for recording ^{1}H NMR spectra. The electronic spectra of the complexes were obtained from a Hitatchi 320 UV-Visible spectrophotometer. Far IR spectra were recorded on a polytec FIR 30 Fourier spectrometer using CsI discs. The EPR spectra of the copper(II) complex was recorded in the solid state and in DMSO at liquid nitrogen temperature using Varian E-112 EPR spectrometer. X-ray diffraction pattern of the same complex was obtained from a Siemens D 5005 model X-ray diffractometer and cyclic voltammetric studies were performed on a BAS CV-50 analyser.

Synthesis of the Ligand

2-Amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*]-thiophene was prepared by Gewald synthesis.[6] To a solution of cyclohexanone (10 m.mol) in ethanol (20 mL) was added ethylcyanoacetate (10 m.mol) and stirred well. Powdered sulphur (10 m.mol) was then added to it gradually with shaking. The reaction mixture was heated on a water-bath with an air condenser, maintaining the temperature in the range 55–60°C for a period of 3 h. Morpholine (10 mL) was added in small amounts during the initial half an hour. The resulting hot solution was filtered to remove the unreacted sulphur. It was then cooled, filtered and recrystallised to obtain the product.

The amino derivative thus obtained was condensed with isatin in 1:1 molar ratio in ethanol medium to get the ligand viz. 2-N-(isatinamino)-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (ISAT). Isatin (10.0 mmol; 1.47 g) in ethanol (30 mL) was added slowly with constant stirring to a solution of the amine (10.0 mmol; 2.25 g) in ethanol (20 mL). The resulting mixture was refluxed on a water-bath for 3 h. The deep orange solution obtained was concentrated to about 25 mL and allowed to cool. Orange red crystals of the ligand formed were filtered, washed, dried and further purified by recrystallization from ethanol.

Synthesis of Metal Complexes

The metal complexes were prepared by a general procedure. Metal chlorides of Mn(II), Fe(II) and Co(II) (2.5 m.mol) and metal chlorides of Ni(II), Cu(II) and Zn(II) (5.0 m.mol) respectively were dissolved in ethanol (20 mL) and were added gradually to a magnetically stirred hot solution of the ligand (5.0 m.mol) dissolved in ethanol (30 mL) to prepare the respective complexes. The pH of the mixture was adjusted to ~6.5 and stirred further for 30 min. The solutions were refluxed on a water-bath to ensure the completion of the reaction. The complexes formed on concentrating and cooling the solutions were filtered, washed with ethanol and dried in vacuum over P_2O_5.

Antibacterial Experiments

The ligand and the complexes were screened for their antibacterial activity against *Salmonella typhi, Bacillus megaterium, Escherichia coli* and *Vibrio cholerea* at a concentration of 300 μg/mL in DMSO by the agar diffusion method.[5]

A hot nutrient agar solution (20 mL) was poured into sterilised petri dishes and allowed to attain room temperature. The seed layer medium was melted and cooled to about 45°C with gentle shaking. A previously grown subculture was added to the seed layer medium aseptically and mixed well. It was immediately raked into the petri dishes and allowed to attain room temperature. Wells were made with a sterile cork borer and to these wells, the drug solution (0.01 mL) was added. The plates were allowed to cool for 1 h to facilitate diffusion. Then the plates were incubated at 37°C for 48 h. The zone of inhibition around the well was measured at the end of the incubation period. Streptomycin was used as the standard antibacterial agent.

RESULTS AND DISCUSSION

Reaction of the Schiff base with the metal salts can be represented by the following general equations

$$MX_2 + ISAT \rightarrow [M(ISAT)\ X]X \quad (M = Cu(II), Ni(II) \text{ or } Zn(II); X = Cl)$$

$$MX_2 + 2\ ISAT \rightarrow [M(ISAT)_2]X_2 \quad (M = Mn(II), Fe(II), Co(II); X = Cl)$$

Analytical data indicated that the ligand reacted with Ni(II), Cu(II) and Zn(II) ions in the 1:1 metal-ligand ratio and with Mn(II), Fe(II) and Co(II) ions in 1:2 ratio. The analytical data and other details of the metal complexes are presented in Table 1. The complexes are stable at room temperature and possess good keeping qualities and they are soluble in DMSO, DMF *etc*.

Structure of the Ligand

It has been reported that aminothiophenes are unstable. But in this investigation 2-aminothiophene has been made stable by suitable substitution at position 3 and fusion with cyclohexane ring at position 4 and 5 by Gewald synthesis[6] to form 2-amino-3-carboxyethyl-4,5,6,7-tetrahydrobenzo[*b*] thiophene and its condensation product with isatin served as a prospective chelating agent for some transition metal ions. Apart from providing stability to aminothiophene, this approach has provided further scope for coordination and reactivity.

The UV spectrum of the ligand recorded in ethanol showed strong bands at 233 nm and 302 nm characteristic of the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the azomethine group.

The IR spectrum of the ligand exhibited an intense band at 1730 cm^{-1} which can be attributed to the >C=O stretching frequency of the ester group. Another intense band appearing at 1646 cm^{-1} is assignable to the >C=O group of isatin moiety[7]. A medium intensity band appearing at 1590 cm^{-1} is due to the >C=N- group. Another medium intensity band appearing at 3170 cm^{-1} can be assigned to the -NH- vibrations of the indole ring system. Bands obtained at 1525 cm^{-1}, 1420 cm^{-1} and 1355 cm^{-1} indicate the presence of substituted thiophene nucleus.[8]

The signals obtained in the ^1H NMR spectrum were in conformity with the UV and IR spectral data of the ligand. The ^1H NMR spectrum (in DMSO-d_6) of the ligand showed signals at 10.49 (s, 1H) −NH; 6.25–7.66 (m, 4H) Ar-H; 1.23 (m, 3H) $-CH_3$; 2.84 (m, 2H) $-CH_2$; 3.35 (s, 4H) $-CH_2$ ppm.

Based on the above spectral data a suitable structure has been assigned to the ligand (Figure 1). An insight into the bonding character of the ligand to the metal ions has been obtained from a careful comparison of the IR spectrum of the complexes and the ligand. The bands diagnostic of coordination have been noted and are presented in Table 2, along with their tentative assignments. The IR spectra of the complexes are closely similar among themselves. The carbonyl stretching frequency of the ester group at 1730 cm^{-1} has been lowered by *ca.* 60 cm^{-1} which suggests its coordination to the metal ion. This type of coordination by ester group has been reported by several investigators.[9,10] The carbonyl stretching frequency of the isatin moiety at 1646 cm^{-1} has been lowered by *ca.* 30 cm^{-1} in the spectra of complexes. This clearly indicates the coordination of the carbonyl group to the metal ion.[11] The vibrational characteristic of ν(C=N) (azomethine) group showed a negative shift by *ca.* 25 cm^{-1} in the complexes, indicating its involvement in bond formation. The possibility of coordination by the ring sulphur atom of thiophene moiety has been ruled out because vibrations occurring at 1525 cm^{-1}, 1420 cm^{-1} and 1355 cm^{-1} characteristic of substituted thiophene ring did not show any appreciable change in the spectra of metal complexes. Similarly, the vibrations characteristic of the -NH- group remained almost unaffected indicating the non- involvement of this group

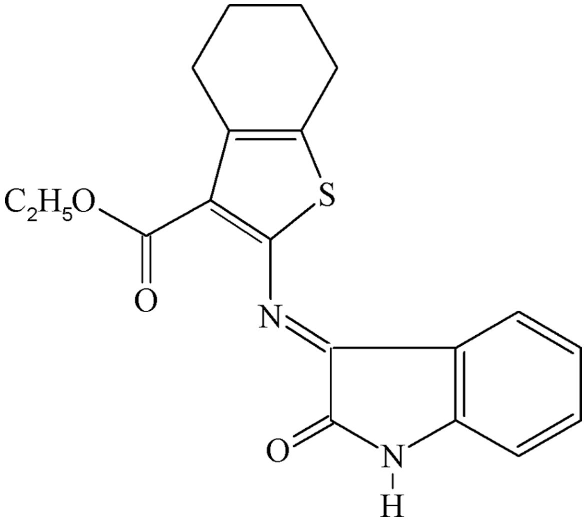

FIGURE 1 Structure of the ligand.

TABLE 1 **Analytical Data and Other Details of Ligand and its Metal Complexes**

Compound	Yield (%)	Metal (%)	Elemental analysis % calculated (found) C	 H	 N	 S	Molar conductance ($ohm^{-1} cm^2 mol^{-1}$) (DMF)	μ_{eff} (BM)
ISAT	88	–	64.40 (64.25)	5.08 (5.65)	7.90 (7.20)	9.03 (9.55)	–	–
$[Mn(ISAT)_2]Cl_2$	65	6.42 (6.58)	54.24 (54.68)	4.84 (4.31)	6.23 (6.71)	7.42 (7.67)	145.8	5.72
$[Fe(ISAT)_2]Cl_2$	67	6.44 (6.68)	54.34 (54.62)	4.85 (4.31)	6.49 (6.70)	7.34 (7.66)	138.5	5.24
$[Co(ISAT)_2]Cl_2$	68	7.25 (7.02)	54.85 (54.41)	4.64 (4.29)	6.32 (6.68)	7.92 (7.63)	142.2	4.86
[Ni(ISAT)Cl]Cl	72	12.64 (12.13)	47.84 (47.13)	3.42 (3.72)	5.18 (5.78)	6.26 (6.61)	80.1	D
[Cu(ISAT)Cl]Cl	76	13.25 (13.06)	46.84 (46.66)	3.87 (3.68)	5.94 (5.73)	6.32 (6.54)	82.4	1.95
[Zn(ISAT)Cl]Cl	62	13.92 (13.33)	46.28 (46.49)	3.34 (3.67)	5.92 (5.70)	6.24 (6.52)	85.3	D

TABLE 2 **Important IR Frequencies (in cm^{-1}) of Metal Complexes of ISAT**

Compound	ν(C=O) ester	ν(C=O)	ν(C=N)	ν(N-H) Indole ring	ν(M-N)	ν(M-O)	ν(M-Cl)
$[Mn(ISAT)_2]Cl_2$	1669 (s)	1620 (s)	1567 (m)	3172 (m)	410 (w)	515 (w)	–
$[Fe(ISAT)_2]Cl_2$	1670 (s)	1618 (s)	1568 (m)	3174 (m)	415 (w)	518 (w)	–
$[Co(ISAT)_2]Cl_2$	1672 (s)	1622 (s)	1565 (m)	3170 (m)	417 (w)	515 (w)	–
[Ni(ISAT)Cl]Cl	1668 (s)	1623 (s)	1567 (m)	3172 (m)	420 (w)	520 (w)	330 (w)
[Cu(ISAT)Cl]Cl	1670 (s)	1617 (s)	1565 (m)	3174 (m)	410 (w)	520 (w)	320 (w)
[Zn(ISAT)Cl]Cl	1672 (s)	1620 (s)	1562 (m)	3167 (m)	412 (w)	516 (w)	324 (w)

*s (strong), m (medium), w (weak).

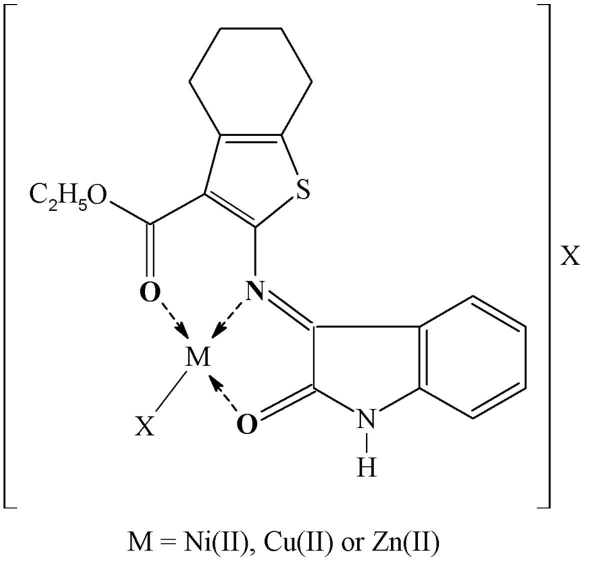

FIGURE 2 Structure of 1:1 metal complex.

in coordination. Far IR spectral data of the complexes provided evidence for bonding by nitrogen, oxygen and chlorine atoms, as these were not observed in the spectrum of the ligand. The non-ligand bands obtained in the range 515–525, 410–420 and 320–330 cm^{-1} can be assigned to ν(M-O), ν(M-N) and ν(M-Cl) vibrations respectively.[12] The ligand is thus bonded to the metal ion in a tridentate fashion through the carbonyl oxygen of the ester group, carbonyl group of the isatin moiety and azomethine nitrogen (Figure 2 & 3).

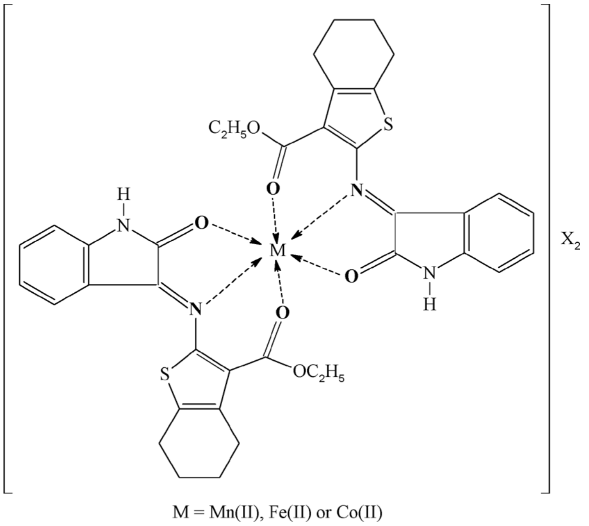

FIGURE 3 Structure of 1:2 metal complex.

Electronic Spectra and Magnetic Susceptibility

The UV spectral bands of the ligand recorded in DMSO were only marginally red shifted in the spectra of the metal complexes which vividly show that no structural alteration of the ligand occurred on metal chelation. The electronic spectrum of manganese(II) complex showed weak absorption bands around 14250 cm^{-1}, 17000 cm^{-1} and 19500 cm^{-1} assignable to ${}^6A_{1g} \rightarrow {}^4T_{1g}$, ${}^6A_{1g} \rightarrow {}^4T_{2g}$ and ${}^6A_{1g} \rightarrow {}^4E_g$, ${}^4A_{1g}$ transitions respectively, and these transitions are compatible with a distorted octahedral geometry around the metal ion. The magnetic moment value (5.72 B.M) obtained also indicates a high-spin octahedral environment around the metal ion.[13] The spectrum of iron(II) complex showed a weak absorption band at 11100 cm^{-1} which is due to ${}^5T_{2g} \rightarrow {}^5E_g$ transition and is indicative of a high-spin (5.24 B.M) octahedral geometry for iron(II) complex.[14] The cobalt(II) complex showed distinct low energy bands at 7300 cm^{-1}, 17250 cm^{-1} and a strong high energy band at 20500 cm^{-1} corresponding to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions respectively, suggesting an octahedral environment around the metal ion. The magnetic moment (4.86 B.M) obtained for the complex is again consistent with that of an octahedral geometry.[15] Two bands obtained around 18850 cm^{-1} and 13500 cm^{-1} corresponding to ${}^1A_{1g} \rightarrow {}^1A_{2g}$ and ${}^1A_{1g} \rightarrow {}^1B_{1g}$ transitions, along with the diamagnetic nature of the complex suggest a square planar geometry for the nickel(II) complex.[16] The visible spectral band observed around 13690 cm^{-1} can be attributed to ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transition, which is in agreement with a square planar geometry for the copper(II) complex.[17] The magnetic moment value (1.95 B.M) obtained for the copper(II) complex supported this geometry. It also indicates the absence of any metal–metal interaction in the complex at room temperature. A coordination number of four has been presumed for the zinc(II) complex, which is adequately supported by analytical data and conductance measurements. It has been reported that a tetrahedral geometry is the most preferred structure for four coordinated zinc(II) complex.[18]

The X-band EPR spectrum of the copper(II) complex was recorded in solid state at room temperature and in DMSO at liquid nitrogen temperature using DPPH as the g marker. The spectrum obtained for the complex at a microwave frequency 9.425 GHz with a field strength of 3200 G is characteristic of copper(II) ion in axial ligand field symmetry. The spectrum showed a well resolved $g_{||}$ and a broadened $g_{\perp}$ region and the Hamiltonian parameters were calculated ($g_{||} = 2.260$; $g_{\perp} = 2.082$; $A_{||} = 160 \times 10^4$). It has been reported that g values of the copper(II) complex can be used as a measure of the covalent character of the metal–ligand bond. If the value is more than 2.3 the metal–ligand bond is essentially ionic and the value less than 2.3 is indicative of covalent character[19]. The trend $g_{||} > g_{\perp} > g_e$ observed in this complex indicates that the unpaired electron is most likely in the $d_{x^2-y^2}$ orbital. The covalence parameter α^2 has been calculated using the Kievelson and Neiman equation.[20]

$$\begin{aligned}\alpha^2_{Cu} &= -(A_{||})/0.036 + (g_{||} - 2.002)\\ &\quad + 3/7(g_{\perp} - 2.002) + 0.04\end{aligned}$$

The value obtained (0.76), indicates considerable covalent character to the metal–ligand bond.[21] On the basis of the above spectral data and physicochemical studies the structure shown in Figure 2 and 3 may be assigned to the 1:1 and 1:2 complexes respectively.

Cyclic Voltammetry

Electrochemical behaviour of the ligand and the copper(II) complex, [Cu(ISAT)Cl]Cl were examined by means of cyclic voltammetry. The measurements were carried out using 2 mM solution at room temperature in the potential range -1.5 V to $+1.5$ V with a scan rate 100 mV/sec. In the voltammometer, glassy carbon was employed as the working electrode, Ag/AgCl as the reference electrode and platinum wire as the auxiliary electrode. The working media consisted of DMSO and Bu_4NPF_6 as supporting electrolyte. The solution was degassed with argon prior to use and kept under an argon atmosphere throughout the experiment.

In the CV profile obtained for the ligand, a broad irreversible single electron response was identified at -0.63 V, which is due to the reduction of the ligand and no oxidative response has been found. The single electron reversible couple identified at $E_{pa} = 0.054$ V and $E_{pc} = -0.012$ V in the voltammogram of the complex is assigned to the metal-centred Cu(II)/Cu(I) couple. At slower scan rate the peak separation (ΔE_p) is close to 59 mV, which indicates that the number of electron transferred is one (n = 1). It was also noted that the ratio of the anodic to cathodic peak current (ip_a/ip_c) approaches to one at this scan rate. From the above voltammetric data the electron transfer process can be schematically represented as follows

$$[Cu^{II}(ISAT)Cl]^+ + 1e \rightarrow [Cu^I(ISAT)Cl]^+ + Cl^-.$$

X-ray Diffraction

The indexing of the X-ray diffraction powder photograph obtained for the copper(II) complex indicated that it has an orthorhombic crystal lattice. The diffractogram recorded reflections with 2θ values ranging from 15° to 56°. The maximum recorded was at 16.1496°, which corresponds to 5.4838 Å d-spacing. The 2θ values from the various peaks obtained and other data related to the diffraction pattern are presented in Table 3. The pattern was indexed by trial and error method.[22,23] The Bragg angles and the set of interplanar spacing obtained by measuring the X-ray diffraction pattern of the complex were related to the unit cell parameters and Miller indices assigned to the individual reflections with the help of expressions involving $\sin^2\theta$. The relation between $\sin^2\theta$, the Miller indices and the unit cell dimensions is less cumbersome than the relationship between interplanar spacing and the Miller indices. A careful comparison of the calculated and observed $\sin^2\theta$ values of the complex reveal that they are in good agreement. The unit cell dimensions for the orthorhombic system were calculated using the relation, $\sin^2\theta_{hkl} = A\ h^2 + B\ k^2 + C\ l^2$, where $A = \lambda^2/4a^2$, $B = \lambda^2/4b^2$ and $C = \lambda^2/4c^2$ are the lattice constants. The lattice constants for the complex [Cu(ISAT)Cl]Cl has been calculated $A = 0.019731$, $B = 0.023635$ and $C = 0.013586$ and the unit cell dimensions are a = 6.6087 Å, b = 5.0087 Å and c = 3.9899 Å.

Antibacterial Activity

The in vitro antibacterial screening of the ligand and the complexes have been carried out against

TABLE 3 X-Ray Diffraction Data of [Cu(ISAT)Cl]Cl

Peak No.	Relative intensity	Observed 2θ	Observed $\mathrm{Sin}^2\theta$	hkl	Observed dÅ	Calculated dÅ
1	100	16.1496	0.0197	100	5.4838	5.4838
2	37.33	17.6165	0.0234	010	5.0303	5.0300
3	64.44	23.9935	0.0432	110	3.7058	3.7058
4	18.96	37.1813	0.1016	210	2.4162	2.6518
5	62.24	22.2629	0.0372	011	3.9898	3.9897
6	26.84	39.6861	0.1152	211	2.2692	2.2692
7	66.57	31.5903	0.0740	102	2.8298	2.8297
8	48.14	32.4317	0.0779	012	2.7583	2.7583
9	5.60	56.9521	0.2273	222	1.6156	1.6155
10	13.89	44.7371	0.1448	013	2.0241	2.0240

TABLE 4 Antibacterial Activity of the Ligand (ISAT) and its Divalent Metal Complexes

	Zone of inhibition (mm)			
Compound	*E.Coli*	*S.typhi*	*B.megaterium*	*V.cholerae*
ISAT	16	14	17	18
$[Mn(ISAT)_2]Cl_2$	24	22	21	20
$[Fe(ISAT)_2]Cl_2$	26	18	24	25
$[Co(ISAT)_2]Cl_2$	22	23	20	28
[Ni(ISAT)Cl]Cl	28	22	24	32
[Cu(ISAT)Cl]Cl	30	26	32	34
[Zn(ISAT)Cl]Cl	17	22	26	24
Standard	38	38	38	38

Salmonella typhi, Bacillus megaterium, Escherichia coli and *Vibrio cholerea* using a nutrient agar medium by the agar diffusion method.[5,24] The complexes have been found to be more toxic against the bacteria than the ligand, as noted from their respective zones of inhibition presented in Table 4. The increased toxicity of the complexes compared to that of the free ligand may be explained in terms of chelation theory.[25] However, it may be noted that chelation is not the only criterion for antibacterial activity, but it is an intricate blend of several contributing factors such as nature of the metal ion, nature of the ligand, coordinating sites, geometry of the complex, concentration, hydrophilic nature, lipophilic nature and presence of co-ligands.[26] Certainly, steric and pharmacokinetic factors also play important roles in deciding the antibacterial activity of metal complexes.

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