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Synthesis, characterization, antibacterial activity and DNA cleavage studies of Schiff base Co(II) transition metal complexes

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ABSTRACT

Two Schiff base ligands L^1 *and* L^2 *were obtained by the condensation of o-phenylenediamine with p-methylbenzaldehyde and p-methoxybenzaldehyde respectively. Their complexes with Co(II) were prepared and characterized by elemental analyses, molar conductance, magnetic susceptibility, IR, UV-Vis spectra, NMR, Mass spectral studies, thermal behaviour and Powder X-ray diffraction studies have also been carried out. The IR data demonstrate the bidentate coordination of* L^1 *and* L^2*. The XRD data show that Co(II) complexes with* L^1 *and* L^2 *have the crystallite sizes of 70 and 72 nm respectively. The DNA cleavage activities of the Schiff base and its complexes were monitored by agarose gel electrophoresis method in the presence of hydrogen peroxide and the antibacterial activities of the ligand and complexes have also been carried out.*

Key words: Schiff base complex, transition metal, spectral characterization, XRD, DNA cleavage, antibacterial activity.

INTRODUCTION

Schiff bases have been playing an important part in the development of coordination chemistry. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous scientific areas. They play an important role in both synthetic and structural research, because of their preparative accessibility and structural diversity. Metal complexes of Schiff base derived from the reaction of o-phenylenediamine with aliphatic and aromatic amines represent a series of compounds containing nitrogen, sulphur and oxygen donor atoms that has been widely studied [1]. Schiff base molecules afford potential sites for bio chemically active compounds that are related to intermolecular hydrogen bonding and proton transfer equilibria. Schiff bases of o-phenylenediamine and its complexes have a variety of applications including biological, clinical and analytical.

The Schiff base ligand is found to be dibasic with N_2 donor sites. The ^{1}H-NMR, ^{13}C-NMR and Mass spectra confirm the formation of N_2 bidentate Schiff base chelate ligands. All the metal complexes have been fully characterized with the help of elemental analysis, molar conductance, magnetic susceptibility and spectral studies. The analytical data helped to elucidate the structure of the metal complexes. The complexes exhibit electrolytic behavior in ethanol. The IR spectral data suggest the coordination of azomethine nitrogen with the central metal ion [2]. The magnetic data suggest an octahedral geometry for Co(II) metal complex The thermogravimetric analysis shows that Co(II) metal complexes posses two aqua molecules coordinated in an octahedral environment. The complexes were subjected to powder XRD patterns with PAN-analytical diffractometer with Cu-Kα radiation of wavelength 1.54060

Å operating at a voltage of 30 kV and a current of 40 mA. The nucleolytic cleavage activities of the complexes were assayed on pUC19 DNA using gel electrophoresis in the presence of H_2O_2 and the complexes show promising nuclease activity [3, 4]. The compounds were subjected to antimicrobial activity screening and Minimum Inhibitory Concentration (MIC) is determined. The complexes show significant growth inhibitory activity against the bacteria like *Bacillus cereus*, *Streptococcus pyogenes*, *Listeria monocytogens*, *Escherichia coli* and *Salmonella typhi* than the free ligands. The MIC of 31.25 µg/ml of complexes of L^1 and L^2 is noticeable.

MATERIALS AND METHODS

All the reagents were of AR grade and the solvents were purified by standard methods. IR spectra (4000 – 400cm^{-1}) taken on KBr disc using a Perkin Elmer Spectrum ONE- N017-1159 Spectrophotometer. Micro analysis of carbon, hydrogen, nitrogen and sulphur were obtained using elemental analyzer, magnetic moments were measured at room temperature on Vibrating Sample Magneto meter EG & G Model: 155 using Hg $[Co(CN)_4]$ as standard. Electrical conductances of the complexes were made on a systronic conductivity meter type 304 in DMSO with a dip type cell having platinum electrode. The UV- visible spectra were run on a Hitachi U-2800 spectrophotometer (200-1100 nm) in nujol mull. TGA-DTA analyses were obtained by using NETZCH STA-409C/CD thermal analyzer. The ^1H NMR, ^{13}C NMR spectra were recorded on JKM-ECS 400 in DMSO-d_6 solvent. The mass spectrum was recorded using WATERS-Q-T of premier- HAB213, electro spray ionization-MS.

Antibacterial activity and MIC values

The antibacterial screening of the compounds was carried out against the Gram positive bacteria (*Bacillus cereus*, *Streptococcus pyogenes* and *Listeria monocytogens)* and Gram negative bacteria (*Escherichia coli* and *Salmonella typhi)* on the free ligand and metal complexes by cup plate method using the nutrient agar as medium. In a typical procedure, molten nutrient agar kept at 115°C –120°C was poured into a Petri dish and allowed to solidify. The small wells (10 mm diameter with 1cm distance) were made in the agar medium by carefully using a sterile cork and these were completely filled with test solutions. The plates were incubated for 24 hours at 37 °C. The diameters of the zones of inhibition for all the test compounds were measured and the results were compared with that of standard *Tetracycline* at the same condition. The antibacterial activities were done at 15.62, 31.25, 62.5 and 125 µg/ml concentration in DMSO solvent by using three G +ve and two G –ve bacteria by the MIC method.

DNA cleavage studies

The pUC19 DNA at pH 7.5 in Tris- HCL buffered solution was used to form agarose electrophoresis. Oxidative cleavage of DNA was examined by keeping the concentration of the 30 µM of complex and 2 µL of pUC19 DNA and made up the volume to 16 µL with 5mM Tris-HCL/ 5mM NaCl buffer solution. The resulting solution was incubated at 37^{0}C for 2 h and electrophoresed for 2 h at 50V in Tris-acetate-EDTA (TAE) buffer using 1% agarose gel containing 1.0 µg/ml ethidiumbromide and photographed under UV light. All the experiments were performed at room temperature.

Synthesis of Schiff base L^1, L^2

A solution of o-phenylenediamine (0.01mole) and p-methylbenzaldehyde / p-methoxy benzaldehyde / (0.02mole) in 1:2 molar ratio in ethanol was mixed with constant stirring. The resulting mixture was refluxed for five hours in a water bath. The concentrated solution was filtered out, washed with ethanol and recrystallized using a solution of chloroform and ethanol mixture, its purity was checked by TLC.

- o-phenylenediamine + p-methylbenzaldehyde $\longrightarrow L^1$ (Fig-1)
- o-phenylenediamine + p-methoxy benzaldehyde $\longrightarrow L^2$ (Fig-2)

Synthesis of metal complexes (ML^1, ML^2)

A hot ethanolic solution of Schiff base (L^1/ L^2) with 1, 1’-binaphthyl-2, 2’-diol (BINOL) and an ethanolic solution of metal acetate solution were mixed in 1:1:1 molar ratio. The mixture was refluxed for about 2-4 h in water bath. The mixture was cooled in ice. The resulting precipitate was then filtered, washed with ethanol and recrystallized using a solution of chloroform and ethanol mixture, its purity was checked by TLC [5, 6].

RESULTS AND DISCUSSION

Micro analysis

Co(II) complexes are stable at room temperature, insoluble in water but soluble in DMF and DMSO. The physical properties and analytical data of the ligands and their complexes are given in Table 1. Elemental analysis data of the complexes are in good agreement with theoretical values. The analytical data (Table 1) indicate the molecular formula of the complexes as [Co L^1 (BINOL) $(H_2O)_2$], [Co L^2 (BINOL) $(H_2O)_2$] and [Co L^3 $(H_2O)_2$]. The Co(II) complexes have lower molar conductance values indicating that the L^1 and L^2 complexes are non-electrolytes [7, 8].

Electronic Spectra

The electronic absorption spectra of free Schiff base ligands (L^1 and L^2) and their Co(II) complexes were recorded in ethanol solution (10^{-3} M) in the range 200–1000 nm at room temperature Table 2. Schiff base ligands show two bands at 241 -243 nm and 305-378 nm corresponding to $\pi \rightarrow \pi^*$ transition of aromatic benzene moiety and $n \rightarrow \pi^*$ transition of azomethine C=N bond respectively [9].

All the complexes exhibit three bands at 12,650 – 13,100 cm^{-1} (υ_1), 15,185 – 16,450 cm^{-1} (υ_2) and 21,420 – 21,760 cm^{-1} (υ_3) which correspond to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ respectively. The observed magnetic moment values 4.66 BM and 4.56 BM indicate that the Co(II) complexes are paramagnetic having of three unpaired electrons in an octahedral environment [10].

Infrared Spectra

The Schiff base ligands L^1 and L^2 show υ(C=N) azomethine bands observed at 1643 and 1619 cm^{-1}. On complexation, this band was shifted to 1617 and 1611 cm^{-1} regions due to the coordination of azomethine nitrogen [11] to the Co(II) ion Table-3. Furthermore, the presence of coordinated water molecules is confirmed by the bands at 3450 and 3408 cm^{-1} in CoL^1 and CoL^2 complexes may respectively attributed to O-H stretching vibrations. In all these complexes two new bands appear at in the range 461 - 492 cm^{-1} and 536 - 545 cm^{-1} respectively the existence of υ(M-N) and υ(M-O) bonds.

^{1}H-NMR spectrum of Schiff base

^{1}H-NMR spectral data of the Schiff base (L^1) was recorded in $CDCl_3$ (Fig-3), shows peaks at 7.58-6.97 and 2.38-2.32 ppm due to aromatic protons and CH_3 group respectively Table-4. The formation of Schiff base (L^2) was further confirmed [12] by the ^{1}H-NMR spectra. ^{1}H-NMR spectra of the ligand were taken in DMSO-d_6 solvent (Fig-4). The aromatic region gives a set of multiples in the range 6.8–7.6 ppm for the Schiff base ligand, while the azomethine protons were observed in the range 8.4-8.6 ppm. The methoxy group protons show a peak at 3.6-3.8 ppm. The total number of protons present in the Schiff base exhibited signals their respective in their expected region. It was also observed that DMSO did not show any coordinating effect on all the ligands [13].

^{13}C-NMR spectrum of Schiff base

^{13}C- NMR spectral data of the Schiff base (L^1) was recorded in $CDCl_3$ (Fig-5), shows peaks at 121.8 – 141.3 and 21.1 -21.5 ppm due to aromatic carbons [14] and CH_3 groups respectively. The formation of Schiff base ligand (L^2) was confirmed by the ^{13}C-NMR spectra. ^{13}C-NMR spectra of the ligand were taken in DMSO-d_6 solvent (Fig-6). The aromatic region shows a set of multiples in the range 114.13-162.8 ppm for the Schiff base ligand, while the azomethine carbons were observed in the range 161.8 ppm. All the total number of carbons present in the Schiff base exhibited signals their expected regions. It was also observed that DMSO did not show any coordinating effect on all the ligands.

Mass spectral fragmentation of the Schiff base

The mass spectrum of Schiff base (L^1) shows a base peak m/e+ at 313 which is due to the observed molecular weight of the prepared Schiff base (Fig-7). This proves the condensation of aldehyde and amine to form the Schiff base [15]. The mass spectra of the ligand recorded at room temperature were used to ascertain [16] the stoichiometric composition. The Ligand (L^2) shows a molecular ion peak at m/z 345, which corresponds to [L+H] peak as the calculated m/z being 344 (Fig-18).

Thermal studies

The TGA curve of the cobalt complex [Co L^1 (BINOL) $(H_2O)_2$] shows that it is stable up to 115°C. A weight loss is observed [17] around 128-135°C corresponding to the elimination of two coordinated water molecules. In the complexes [Co L^2 (BINOL) $(H_2O)_2$] this loss of coordinated water is observed at 125-140 °C respectively [18].

Powder X-ray diffraction studies

The XRD pattern of Co(II) complexes show well defined crystalline peaks indicating that the samples are crystalline in nature (Fig-9). The above complexes have specific'd' values which can be used for its characterization. The crystallite size of the complexes d_{XRD} could be estimated from XRD patterns [19] by the Scherrer's formula $d_{XRD} = 0.9\lambda/\beta\ (\text{Cos}\theta)$, where λ is the wavelength, β is the full width at half maxima and θ is the diffraction angle. The XRD shows that Co(II) complexes have the average crystallite size of 70 and 72 nm respectively, suggesting the complexes to be nanocrystalline [20].

DNA cleavage studies

Gel electrophoresis experiments were performed using pUC19 DNA with ligands and their complexes in the presence and absence of H_2O_2. Complexes exhibit cleavage ability at low concentration (40 µM). The ligand exhibits no significant activity in the presence of oxidant. The activity was much higher for the complexes in presence of H_2O_2. When the calf-thymus DNA is subjected [21] to electrophoresis, relatively fast migration will be observed for the intact super coil form (Form I). If scission occurs on one strand (nicking), the super coil will relax to generate a slower moving open circular form (Form II). If both strands are cleaved, a linear form (Form III) that migrates between Forms I and II will be generated. The complexes show more activity in the presence of oxidant which may be due to the reaction of hydroxyl radical with DNA. These hydroxyl free radicals participate in the oxidation of the dexoyribose moiety followed by hydroxyl cleavage of sugar phosphate backbone [22]. The results of DNA cleavage studies have been shown in (Fig-10). All metal complexes were able to convert DNA (Form I) into open circular (Form II). The L^1 Co(II) complex was found to be highly active in cleaving DNA in the presence of hydrogen peroxide. The H_2O_2 is coordinated to the cobalt ion of the complex, affording a peroxo - cobalt species. This coordinated peroxide ion attacks the DNA phosphate bond via a nucleophilic mechanism and hydrolyzes the P–O bond [23].

$$\boxed{[DNA + ML^1 + H_2O_2] > [DNA + L^2 + H_2O_2] > [DNA + L^1 + H_2O_2] > [DNA + ML^2 + H_2O_2]}$$

Antibacterial activity

The antibacterial activity of the Co(II) complexes were studied against five pathogenic bacteria strains. The results of the antibacterial activity studies for the complexes and standard antibiotic *tetracycline* were evaluated by Muller Hinton agar diffusion method and serial dilution sensitivity test against [24] both Gram-positive and Gram-negative bacteria. DMSO solvent was also used as control. As it could be seen from these tables, both Gram positive and Gram negative bacteria were affected by these antibacterial agents and *L.monocytogens* was the most sensitive microorganism of the studied complexes (Fig-11). On the other hand, *E.coli*, *S. typhi*, *B.cereus*, and *S.pyogenes* were, to some extent, more resistant to these compounds. It is previously reported that the presence of electronegative and electron donating groups on the sulphur part of the Schiff base increases the antibacterial activity of their metal complexes.

The MIC was calculated as the highest dilution showing complete inhibition of the tested strains and reported in (Table- 5 & 6). These Schiff base and complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which further restricts the growth of the microorganisms. The ML^2 complex has good activity when compared to Schiff base and other metal complexes [25].

Table-1: Physical and analytical data of Schiff bases and their metal complexes

Ligand /complex	**M.F (M.Wt.)**	**Yield %**	**Found (Calcd.) %**				**Λ_m Scm^2 Mol^{-1}**
			C	**H**	**N**	**Co**	
$C_{22}H_{20}N_2$ (L^1)	312.42	72	84.58 (84.52)	6.45 (6.40)	8.97 (8.94)	-	-
$C_{22}H_{20}N_2O_2$ (L^2)	344.41	75	76.72 (76.70)	5.85 (5.82)	8.13 (8.10)	-	-
[Co L^1 (BINOL) $(H_2O)_2$]	691.69	76	72.93 (72.90)	5.25 (5.21)	4.05 (4.00)	8.52 (8.48)	44.10
[Co L^2 (BINOL) $(H_2O)_2$]	723.69	80	69.71 (69.67)	5.02 (4.98)	3.97 (3.92)	8.14 (8.12)	46.30

Table-2: UV-Vis spectra of Schiff base and its complexes

Ligand / Complex	**Absorbance nm**	**υ/ cm^{-1}**	**Assignment**	**Geometry**	**Magnetic moment (BM)**
L^1	241 378	41,150 26,455	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-	-
L^2	243 305	41,152 32,786	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-	-
[Co L^1 (BINOL) $(H_2O)_2$]	790 626 460	12,650 15,960 21,760	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	Octahedral	4.66
[Co L^2 (BINOL) $(H_2O)_2$]	763 608 467	13,100 16,450 21,420	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$	Octahedral	4.56

Table-3: IR Spectral data of ligands and its metal complexes (cm^{-1})

Ligand / Complex	**υO-H$_2$**	**υC=N**	**υM-N**	**υM-O**
L^1	-	1643.28	-	-
L^2	-	1619.52	-	-
[Co L^1 (BINOL) $(H_2O)_2$]	3450.14	1617.88	545.12	492.22
[Co L^2 (BINOL) $(H_2O)_2$]	3408.48	1611.31	536.75	461.38

Table-4: ^{1}H-NMR Spectral data of ligand and its metal complexes (δ ppm) in d$_6$-DMSO

Ligand	**^{1}H-NMR Spectra**	**^{13}C-NMR spectra**
L^1	8.32 (2H,s, CH=N), 6.97-7.58(12H,m, Ar-H), 2.32-2.38(6H,-CH$_3$)	21.1 -21.1(2C,-CH$_3$), 121.8,124.6,130.2,134.5,141.3 (18C, Ar-C), 161.5 (2C, CH=N)
L^2	8.60 (2H,s,CH=N), 6.8–7.6(12H,m, Ar-H), 3.80(6H,-OCH$_3$)	54.68-55.60(2C,-OCH$_3$), 114.7,121.5,123.8,127.8,129.6,131.4,162.8 (18C, Ar-C), 161.8(2C, CH=N)

Table-5: Determination of MIC for antibacterial activity

Micro organisms	L^1				ML^1				L^2				ML^2			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
Bacillus cereus	-	+	+	+	-	-	+	+	-	+	+	+	-	-	+	+
Streptococcus pyogenes	-	-	+	+	-	-	+	+	-	+	+	+	-	-	+	+
Listeria monocytogens	-	-	+	+	-	+	+	+	-	+	+	+	-	-	+	+
Escherichia coli	-	-	+	+	-	-	+	+	-	-	+	+	-	-	-	+
Salmonella typhi	-	-	+	+	-	+	+	+	-	-	+	+	-	-	+	+

a= 125 µg/ml, b= 62.5 µg/ml, c= 31.25 µg/ml, d= 1562 µg/ml: M= Co(II) ion
Minus (-) indicates the absence of growth, Plus (+) indicates presence of growth

Table-6: Antibacterial activities MIC values

Micro organisms	MIC values (µg/ml)			
	L^1	ML^1	L^2	ML^2
Bacillus cereus	125	62.5	125	62.5
Streptococcus pyogenes	62.5	62.5	125	62.5
Listeria monocytogens	62.5	125	125	62.5
Escherichia coli	62.5	62.5	62.5	31.5
Salmonella typhi	62.5	125	62.5	62.5

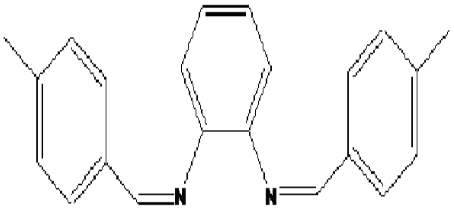

Fig-1: Schiff base free ligand (L^1)

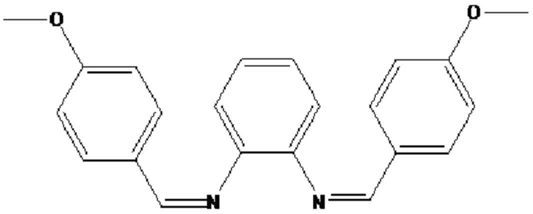

Fig-2: Schiff base free ligand (L^2)

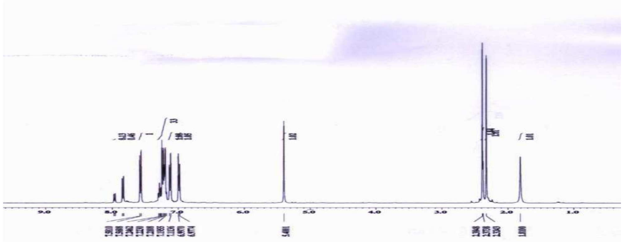

Fig-3: ^{1}H-NMR spectrum of the free Schiff base (L^1)

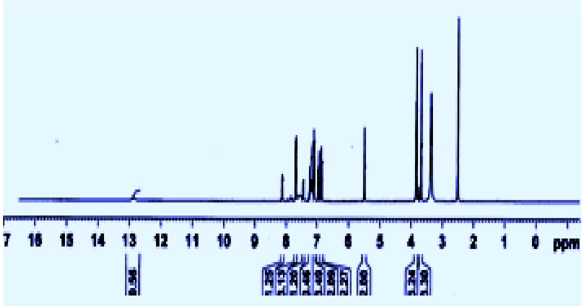

Fig-4: ^{1}H-NMR spectrum of the free Schiff base (L^2)

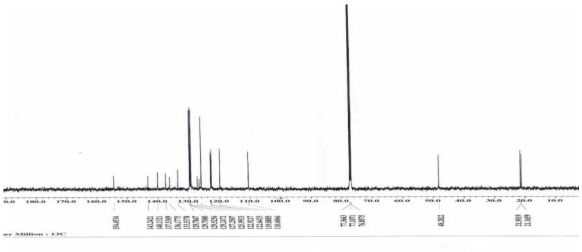

Fig-5: ^{13}C-NMR spectrum of the free Schiff base (L^1)

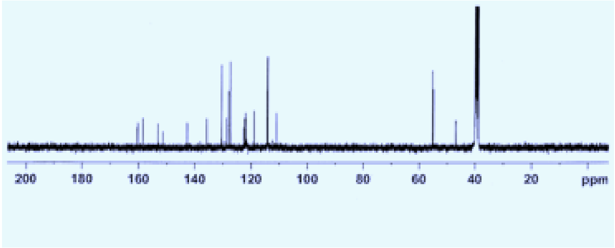

Fig-6: ^{13}C-NMR spectrum of the free Schiff base (L^2)

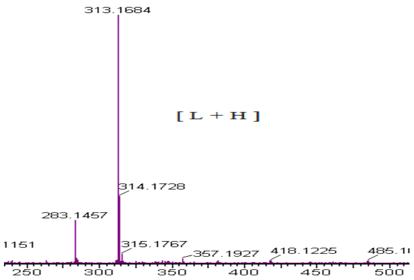

Fig-7: Mass spectra of the Schiff base (L^1)

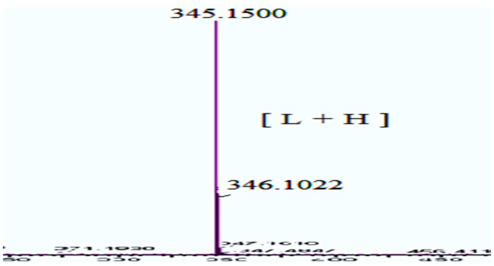

Fig-8: Mass spectra of the Schiff base (L^2)

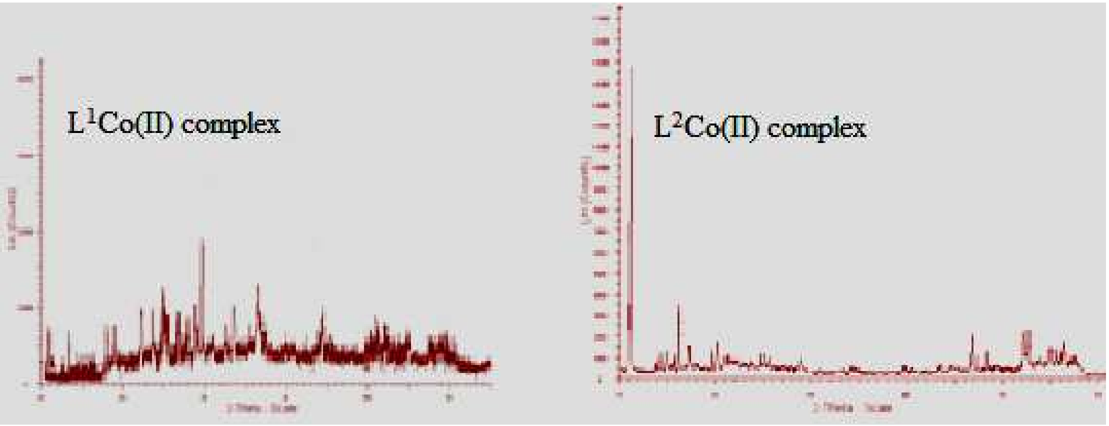

Fig-9: XRD pattern of Co(II) complexes

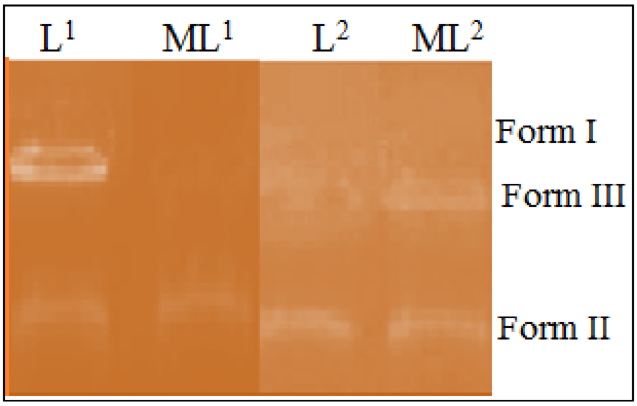

Fig-10: DNA cleavage Schiff base metal complexes

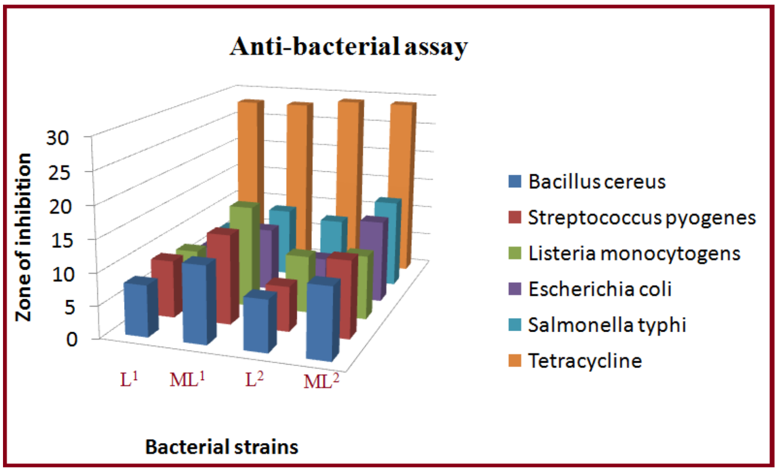

Fig-11: Antibacterial activity

CONCLUSION

In this paper we have reported the synthesis of Schiff base ligands from o-phenylenediamine and p-methylbenzaldehyde / p-methoxybenzaldehyde and their Co(II) complexes have been synthesized using the Schiff base ligands. The ligands and complex were characterized by spectral and analytical data. The electronic spectral data indicates that all the Co(II) complexes are paramagnetic with octahedral geometry. The pUC19 DNA cleavage studies explain the total cleavage of pUC19 DNA by Co(II) complexes in the presence of H_2O_2. The antibacterial studies carried out with the complexes confirm that they are good antibacterial agents. Their MIC values being 125 µg / litre.

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