

Synthesis, Characterization, Antimicrobial and Anticancer Activities of 14-Membered Macrocyclic Schiff Base Metal Complexes

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New cationic 14-membered macrocyclic Schiff base metal complexes have been synthesized by condensation of benzalidene-curcuminy-4-iminoantipyrine and 2,6-diaminopyridine. Structural characterization of the compounds was done using elemental analysis, molar conductivity, magnetic susceptibility, Mass, SEM, XRD, ^1H NMR, UV-visible, IR and EPR spectra. X-ray diffraction patterns suggested that the size of Schiff base is reduced due to chelation by the metal ion. Different morphologies of synthesized compounds were identified by SEM images. Magnetic moment values, UV-visible and IR spectral studies confirms the square planar geometry of chelates. However $[\text{VOL}]\text{Cl}_2$ exists in octahedral geometry. Electron spin resonance spectra parameters of $[\text{CuL}]\text{Cl}_2$ and $[\text{VOL}]\text{Cl}_2$ complexes were well coinciding with proposed geometries. The *in vitro* biocidal activities of the compounds were done against some bacterial and fungal strains by disc diffusion method. Anticancer activity of Schiff base and copper complex were carried out by MTT method which reveals that the inhibition against the growth of breast cancer cell line culture for chelate is higher than Schiff base.

Keywords: Metal complexes, Schiff base, Curcumin, Biological activity, Cytotoxicity.

INTRODUCTION

Past three decades, attention in the chemistry of first row transition metal Schiff base chelates is very high because of their essential it in the field of catalysis like hydroformylation, carbonylation, oxidation, reduction, hydrolysis and epoxidation [1-7]. Schiff base complexes are also noted for their significant antifungal and antibacterial activities. Few transition metal chelates of pyrazolone derivatives are of large attention due to their biological activity. Amongst the derivatives of pyrazolone, 4-aminoantipyrine forms a wide number of Schiff bases with ketones/aldehydes and is recognized to be superior reagents in pharmacological, clinical, analytical and biological applications [8,9]. The biological activities of such Schiff bases are further improved by complexation with transition metal ions. Knoevenagel condensation between aldehyde and β -diketone act as dicarbonyls and fruitful source of macrocyclic polyaza ligand systems. Among the various β -diketones, curcumin is a versatile compound as their traditional consequence in medicinal field [10-17]. A search through literature reveals that more have been posted on the studies of Schiff bases [18-20]. But, there is no research articles accounted on the synthesis of macrocyclic Schiff base first row transition metal complexes using benzalidene-curcuminy-4-iminoantipyrine with 2,6-diaminopyridine [21-25]. Hence, the synthesis, characterization, biolo-

gical and cytotoxic activities of fully conjugated 14-membered macrocyclic pentaza transition metal Schiff base complexes derived by the condensation between benzalidene-curcuminy-4-iminoantipyrine and 2,6-diaminopyridine is reported.

EXPERIMENTAL

All Analar grade chemicals *viz.*, benzaldehyde, curcumin, 4-aminoantipyrine, 2,6-diaminopyridine and metal(II) chlorides were of procured from Merck, Germany. Elemental analyses (C, H and N) were carried out using Carlo Erba 1108, Heraeus. Deep Vision Model-601 conductivity meter were used to measure molar conductivities in DMSO (10^{-3} M) solutions. Magnetic moment values of complexes were determined by Gouy balance method. The IR spectra (Perkin-Elmer FT-IR 783), UV-visible, spectra (Shimadzu model UV-1601) and NMR spectra (Bruker Avance Dry 300 FT NMR Spectrometer in CDCl_3 with TMS as the internal standard) were recorded. X-band ESR spectra of $[\text{CuL}]\text{Cl}_2$ and $[\text{VOL}]\text{Cl}_2$ complexes in DMSO solution at 300 and 77 K were recorded on a JEOL 47 series ESR spectrometer. FAB-MS (VGZAB-HS Spectrometer) spectra were recorded at room temperature in 3-nitrobenzylalcohol as medium. SEM photograph was recorded under ultra high vacuum with Al K α excitation at 10 kV.

Synthesis of Schiff base: Benzalidene-curcuminy-4-iminoantipyrine (0.01 mol) and 2,6-diaminopyridine (0.01

mol) were mixed in 1:1 ratio and dissolved in 40 mL of ethanol containing 3 g of anhydrous K_2CO_3 . The resulting mixture was refluxed for about 24 h in a water bath and filtered. The red coloured pasty mass obtained after complete evaporation of solvent was stirred with 20 mL of water, boiled and cooled. The formed pale orange solid was separated by filtration and then recrystallized using methanol.

Synthesis of metal complexes: The corresponding $M(II)Cl_2$ ($M = Cu, Ni, Co, VO, Zn$) (0.005 mol) and Schiff base (0.005 mol) in ethanol was magnetically stirred for about 12 h. Then the solvent was reduced to one-third by using water bath, the precipitated complex was filtered, washed and recrystallized from hot ethanol.

Antimicrobial assay: In a usual procedure [26], Schiff base and its complexes were tested against two Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and three Gram-negative (*Escherichia coli*, *Salmonella typhi* and *Klebsiella pneumoniae*) bacterial and *Aspergillus flavus*, *Aspergillus niger*, *Rhizoctonia bataicola*, *Candida albicans* and *Rhizopus stolonifer* fungal strains by disc diffusion method. Chloramphenicol and nystatin were used as standard for bacteria and fungi.

Anticancer effects of Schiff base and $[CuL]Cl_2$ complex: From National Centre for Cell Science (NCCS), Pune, India, the human breast cancer cell line (MCF-7) was acquired and full-grown in Eagles minimum essential medium containing 10 % fetal bovine serum (FBS). Cells were sustained at 37 °C, 100 % relative humidity, 95 % air and 5 % CO_2 . Cell culture was maintained as per standard procedure [27]. Anticancer MTT assay of investigated ligand and $[CuL]Cl_2$ were determined by utilizing the breast cancer cell culture.

RESULTS AND DISCUSSION

The physical properties of compounds and their elemental analysis data are given in Table-1. It corresponds well with the general formula $[ML]Cl_2$, where, $M = Ni(II), Co(II), Cu(II), Zn(II)$ and $VO(II)$; $L =$ Schiff base. Magnetic moment values of the complexes are consistent with square planar geometry except $[VOL]Cl_2$, which shows octahedral geometry. Electrolytic nature of the metal complexes (1:2 ratio) was confirmed by their higher conductance values. It is suggested that Cl^- ion present out side the coordination sphere and behave as 1:2 electrolytes.

Mass spectra: Schiff base ($C_{55}H_{49}N_9O_4$) shows a molecular ion peak at m/z 899 $[M^+]$ for its monomeric formulation. The molecular ion peak of $[CuC_{55}H_{49}N_9O_4]Cl_2$ complex was observed at m/z 1033 $[M^+]$, which indicates that the stoichiometric compo-

sition of complex is $[CuL]Cl_2$. This is further supported by elemental analysis data.

XRD studies: The XRD patterns of Schiff base, $[CuL]Cl_2$, $[NiL]Cl_2$ and $[ZnL]Cl_2$ chelates are given in Fig. 1.

Schiff base (Fig. 1a) shows the peaks at 10.320°, 12.417°, 14.625°, 15.528°, 21.654°, 24.642°, 29.261°, 31.208°, 31.876°, 33.190° and 42.002° which suggests that the compound is high-quality polycrystalline in nature. It exhibits 100 % intensity peak at 21.654°. All the peaks were observed in the XRD patterns of the chosen metal complexes and they also showed some additional peaks due to chelation. Highest intensity peak of $[CuL]Cl_2$ complex (Fig. 1b) is observed at 36.133° which is lower intensity than the ligand. $[NiL]Cl_2$ and $[ZnL]Cl_2$ complexes (Fig. 1c & d) shows their strongest diffraction peaks at 29.552° and 25.013°, respectively with reduced intensity than the Schiff base. All the peaks are fairly sharpened in the complexes which indicate that the quantum confinement of Schiff base by the metal ion [28]. X-ray diffraction pattern of metal chelates insists reduced size in chelate than ligand owing to the increasing values of full width half maximum (FWHM). The crystallite sizes were calculated for prominent peaks for the prepared Schiff base metal complexes using Debye-Scherrer's formula [29]. An average crystallite sizes of 84, 55.6, 50 and 17 nm have obtained for Schiff base, $[CuL]Cl_2$, $[NiL]Cl_2$ and $[ZnL]Cl_2$ complexes, respectively.

Morphological studies: The SEM images of the complexes were viewed at different magnifications (Fig. 2). They have clear and well defined grains with different shapes. SEM images of Schiff base (Fig. 2a) exhibits its smooth fine spherical shape morphology with highly agglomerated grains, $[CuL]Cl_2$ complex (Fig. 2b) images have well dispersed rough surface with cracks and $[NiL]Cl_2$ complex (Fig. 2c) shows spherical flower shaped grains images. $[ZnL]Cl_2$ complex (Fig. 2d) resembles of rod shaped crystal with linearly arranged grains. Thus, the SEM results revealed that the metal complexes have modified size and shape [30]. The smaller grain sizes of chelates were found in XRD pattern which suggested that they are nano sized polycrystalline structure. This is further supported by UV-visible spectra of Schiff base and its metal complexes and they have leads to enhancing antibacterial activity for complexes than Schiff base ligand.

Infrared spectral studies: Schiff base shows two strong bands at 1630 and 1600 cm^{-1} regions are attributable to azomethine ($-C=N$) groups. In complexes, this peak is observed at lower frequency regions at 1590-1580 cm^{-1} , which indicates the coordination of $-C=N$ group with metal ion. Free Schiff base demonstrates its unique nature of 2,6-diaminopyridine ring vibration at 1022

TABLE-1
COLOUR, MELTING POINT, ELEMENTAL ANALYSIS, MOLAR CONDUCTANCE AND
MAGNETIC MOMENT VALUES OF SCHIFF BASE AND ITS METAL-COMPLEXES

Compound	Color	m.p. (°C)	Elemental analysis (%): Found (calcd.)						$\Lambda_m \times 10^{-2}$ ($\Omega^{-1} cm^2 mol^{-1}$)	μ_{eff} (BM)
			M	C	H	N	O	Cl		
L	Pale orange	328	–	73.35 (73.41)	5.40 (5.45)	13.97 (14.02)	7.09 (7.12)	–	–	–
$[CuL]Cl_2$	Pale green	377	6.12 (6.15)	63.82 (63.86)	4.72 (4.74)	12.14 (12.19)	6.16 (6.19)	6.82 (6.86)	86.4	1.78
$[CoL]Cl_2$	Pale pink	382	5.71 (5.73)	64.12 (64.15)	4.73 (4.76)	12.23 (12.25)	6.20 (6.22)	6.86 (6.89)	75.8	1.73
$[NiL]Cl_2$	Red	381	5.68 (5.71)	64.13 (64.16)	4.73 (4.76)	12.21 (12.25)	6.18 (6.22)	6.85 (6.89)	87.4	–
$[VOL]Cl_2$	Brown	365	4.87 (4.91)	63.62 (63.65)	4.70 (4.73)	12.10 (12.15)	7.70 (7.72)	6.81 (6.84)	97.8	1.83
$[ZnL]Cl_2$	Brown	379	6.28 (6.32)	63.73 (63.75)	4.69 (4.73)	12.13 (12.17)	6.14 (6.18)	6.83 (6.85)	73.2	–

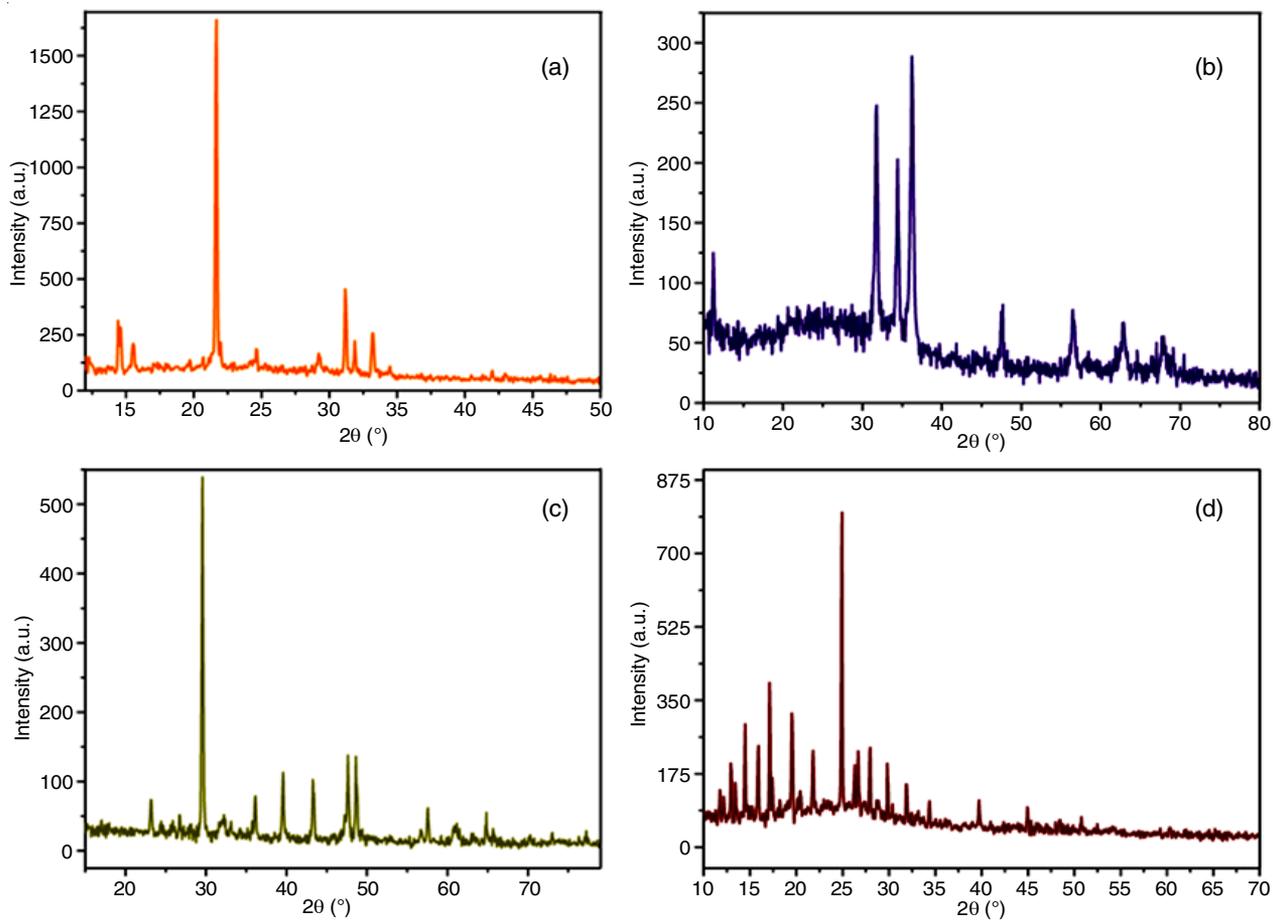


Fig. 1. Powder XRD pattern of Schiff base (a), $[\text{CuL}]\text{Cl}_2$ (b), $[\text{NiL}]\text{Cl}_2$ (c) and $[\text{ZnL}]\text{Cl}_2$ (d) complexes

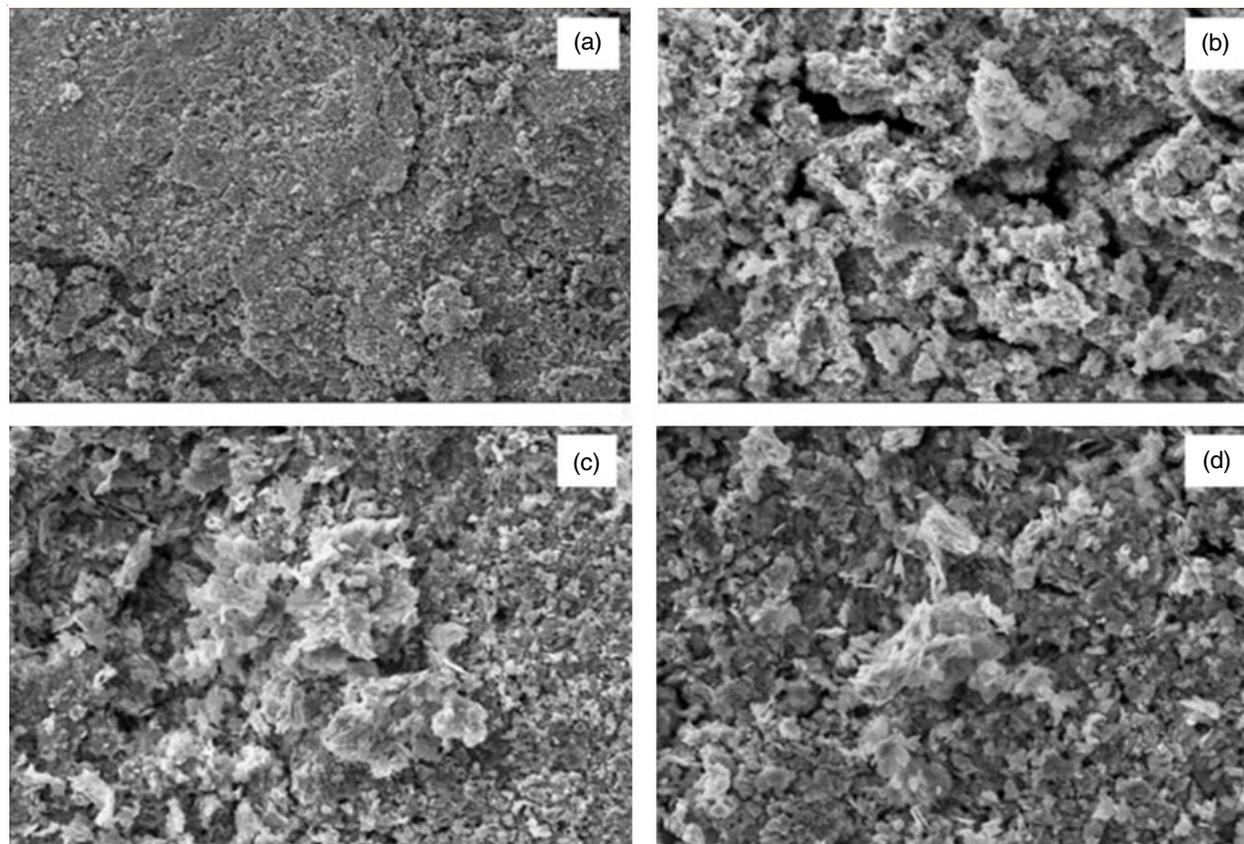


Fig. 2. SEM images for Schiff base (a), $[\text{CuL}]\text{Cl}_2$ (b), $[\text{NiL}]\text{Cl}_2$ (c) and $[\text{ZnL}]\text{Cl}_2$ (d) complexes

and 696 cm^{-1} regions, which are not shifted in all the metal complexes except $[\text{VOL}]\text{Cl}_2$, also it confirmed that the presence of pyridine nitrogen atom and are not involved in chelation [31,32]. In $[\text{VOL}]\text{Cl}_2$ complex, these two peaks are shifted to shorter frequency at 1012 and 682 cm^{-1} region attesting the involvement of pyridine nitrogen atom in coordination. All the metal complexes also show a new peak around at 500 cm^{-1} region due to the development of M-N bonds. Both Schiff base and metal complexes exhibited their typical absorption bands of -C-H aromatic group in the region of $3100\text{--}2850\text{ cm}^{-1}$. In addition to this $[\text{VOL}]\text{Cl}_2$ complex shows a new band at 980 cm^{-1} for characteristic V=O frequency [33].

^1H NMR Spectral studies: In ^1H NMR spectra of Schiff base and $[\text{ZnL}]\text{Cl}_2$ complexes in CDCl_3 solution were shown in Fig. 3. The following signals are exhibited by the Schiff base: phenolic -OH group at 11.28δ , phenyl as multiplet at $7.86\text{--}7.50\delta$, -N- CH_3 at 3.19δ , =C- CH_3 at $2.16\text{--}2.86\delta$, -CH- group at 6.2δ and -O CH_3 group at $5.47\text{--}5.55\delta$. In zinc complex, all the peaks were slightly shifted to downfield region due to metal-coordination [34].

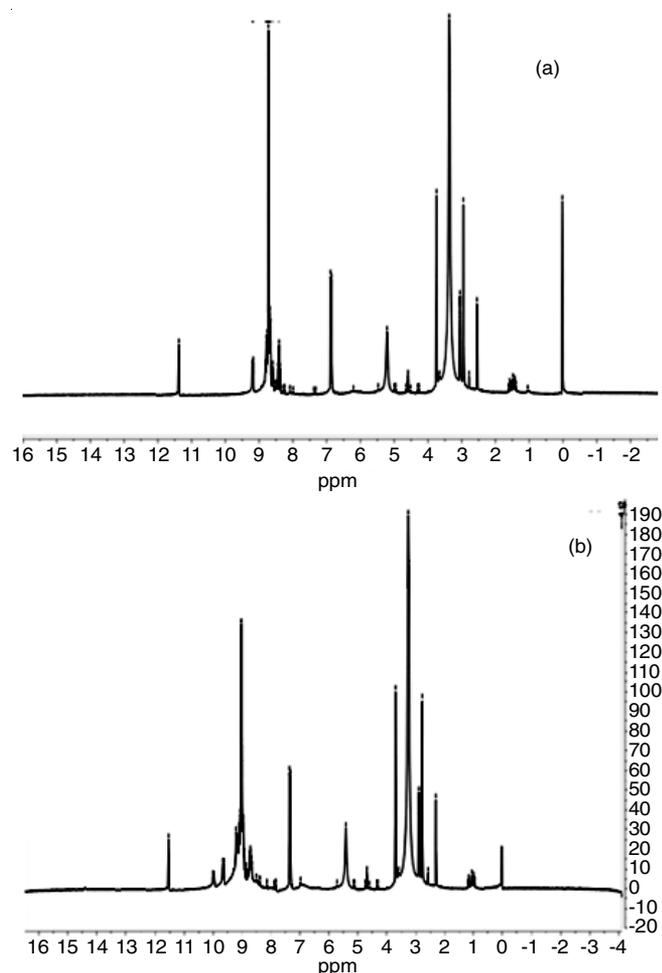


Fig. 3. ^1H NMR spectra of (a) Schiff base and (b) $[\text{ZnL}]\text{Cl}_2$ complex in CDCl_3 solution

Electronic spectral studies: The UV-visible spectra of Schiff base and its $[\text{NiL}]\text{Cl}_2$, $[\text{CoL}]\text{Cl}_2$, $[\text{CuL}]\text{Cl}_2$ and $[\text{VOL}]\text{Cl}_2$ complexes were recorded in MeCN solution at 300 K. Ligand shows two peaks at 32051 and 23866 cm^{-1} due to intra-ligand charge transfer (INCT) transition. $[\text{CuL}]\text{Cl}_2$ shows a band at 19881 cm^{-1} and other strong broad band at 12578 cm^{-1} , which are assignable

to $^2\text{B}_{2g} \rightarrow ^2\text{B}_{1g}$ and $^2\text{B}_{2g} \rightarrow ^2\text{A}_{1g}$ transitions which were appeared at 31847 and 24937 cm^{-1} region. In addition, the two INCT bands revealed that the complex has square planar geometry [35]. $[\text{NiL}]\text{Cl}_2$ shows three bands at 30960 , 22728 and 15601 cm^{-1} region. The foremost two bands are due to INCT bands and left one appeared at 15601 cm^{-1} region is due to $^1\text{A}_{1g} \rightarrow ^1\text{B}_{1g}$ transition and the calculated zero magnetic moment (diamagnetic) confirms square planar geometry of $[\text{NiL}]\text{Cl}_2$ chelate [36]. $[\text{CoL}]\text{Cl}_2$ shows three peaks at 31152 , 23980 and 15898 cm^{-1} region. First two peaks in lower regions are assignable to INCT transitions and another one is a $d\text{-}d$ band ($^1\text{A}_{1g} \rightarrow ^1\text{T}_{1g}$) which reveals $[\text{CoL}]\text{Cl}_2$ complex is square planar structure [37]. $[\text{VOL}]\text{Cl}_2$ exhibits two INCT bands (30960 and 24096 cm^{-1}) and two $d\text{-}d$ transitions at 16207 ($^2\text{B}_{2g} \rightarrow ^2\text{B}_{1g}$) and 11669 cm^{-1} ($^2\text{B}_{2g} \rightarrow ^2\text{E}_g$) which are supporting the octahedral geometry due to presence of axial oxygen atom.

EPR spectral studies: X-Band ESR spectra of $[\text{CuL}]\text{Cl}_2$ complex was recorded in dimethyl sulphoxide at 300 and 77 K which are shown in Fig. 4. The observed order of ESR parameters for $[\text{CuL}]\text{Cl}_2$ complex, A_{\perp} ($68 \times 10^4\text{ cm}^{-1}$) $<$ A_{\parallel} ($158 \times 10^4\text{ cm}^{-1}$) and $2 < g_{\perp}$ (2.08) $<$ g_{\parallel} (2.37) is coincide well with other related systems and akin to axially symmetric square planar geometry [38].



Fig. 4. X-band ESR spectra of $[\text{CuL}]\text{Cl}_2$ at (a) 300 and (b) 77 K in MeCN solution

This conclusion is also sustained by exchange interaction parameter ($G = 4.6$). The in-plane σ -bonding ($\alpha^2 = 0.842$), in-plane π -bonding ($\beta^2 = 1.06$) and out-of-plane π -bonding ($\gamma^2 = 0.79$) values indicates that there is no extensive interaction between in-plane π -bonding and out of-plane π -bonding and γ^2 is more significant [39]. This is also supported by orbital reduction factors K_{\parallel} (0.89) $>$ K_{\perp} (0.84) values. ESR spectra of $[\text{VOL}]\text{Cl}_2$ complex is given in Fig. 5 at 77 and 300 K.

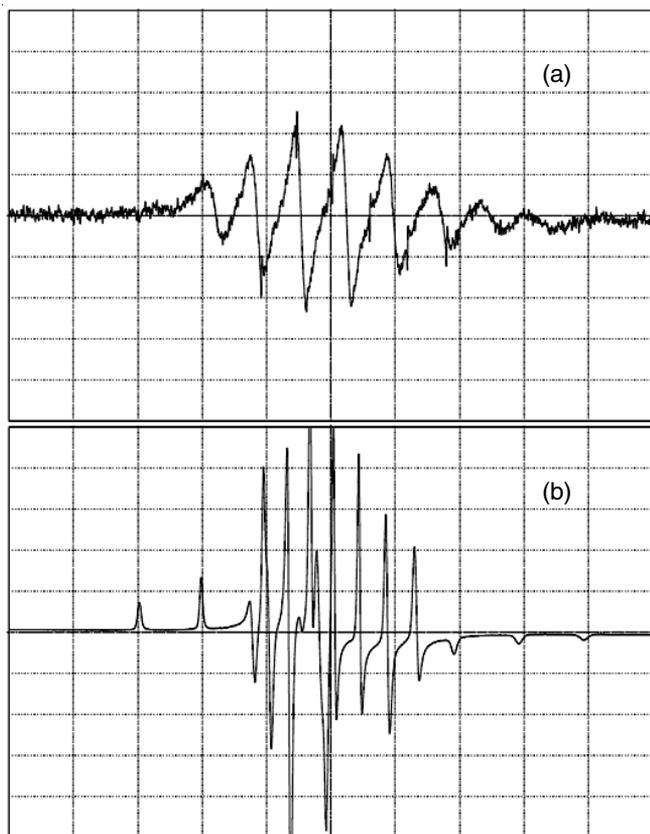


Fig. 5. X-band ESR spectra of the [VOL]Cl₂ complex at (a) 300 and (b) 77 K in DMSO solution

The spin hamiltonian parameters of [VOL]Cl₂ complex [A_{\perp} ($74 \times 10^{-4} \text{ cm}^{-1}$) < A_{\parallel} ($181 \times 10^{-4} \text{ cm}^{-1}$) and g_{\perp} (1.94) < g_{\parallel} (1.98)] show that the chelate is octahedral geometry. The bonding parameters ($\alpha^2 = 0.91$, $\beta^2 = 0.74$ and $\gamma^2 = 0.88$) values implied that in-plane π -bonding coefficient (β^2) is significant than the in-plane σ -bonding (α^2) and out of-plane π -bonding (γ^2).

in vitro Antimicrobial studies: The antimicrobial activities of the complexes are shown in Tables 2 and 3. Chloramphenicol and DMF are used as standard and solvent for antibacterial activities, respectively. For fungal screening studies, nystatin is used as standard drug. The observed data demonstrated that the complexes have greater activity than Schiff base.

Anticancer effects of Schiff base and [CuL]Cl₂ complex: The anticancer activities of Schiff base and [CuL]Cl₂ complex against the growth breast cancer (human) cell line (MCF-7) are reported in Table-4. The % cell inhibition and IC₅₀ values were found out and mentioned in Table-4 indicates that copper complex have higher sensitivity towards the breast cancer lines than the Schiff base ligand.

Biological screening studies revealed that higher biological activities of metal complexes than ligand is due to higher lipophilicity and greater penetration power of metal ion [40-43]. It also increases the interaction of metal chelates with cell wall of microbes which disturbs the respiratory process of the cell and blocks the production of proteins that retards the growth of organisms [44-47].

TABLE-2
ANTIBACTERIAL EFFECTS OF THE SCHIFF BASE AND ITS COMPLEXES

Compound	Minimum inhibitory concentration (mg/L)				
	<i>E. coli</i>	<i>S. aureus</i>	<i>K. pneumoniae</i>	<i>S. typhi</i>	<i>B. subtilis</i>
L	103	97	59	107	52
[CuL]Cl ₂	14	61	27	39	25
[CoL]Cl ₂	16	49	60	21	63
[NiL]Cl ₂	18	49	55	23	60
[(VO)L]Cl ₂	105	85	76	109	55
[ZnL]Cl ₂	20	56	31	37	25
Chloramphenicol (standard)	06	15	09	05	10

TABLE-3
ANTIFUNGAL SCREENING EFFECTS OF THE SCHIFF BASE AND ITS COMPLEXES

Compound	Minimum inhibitory concentration (mg/L)				
	<i>C. albicans</i>	<i>R. bataticola</i>	<i>A. flavus</i>	<i>A. niger</i>	<i>R. stolonifer</i>
L	58	59	62	61	57
[CuL]Cl ₂	16	17	18	19	20
[CoL]Cl ₂	18	18	19	17	22
[NiL]Cl ₂	19	20	22	20	21
[VOL]Cl ₂	17	21	15	16	17
[ZnL]Cl ₂	11	21	14	15	16
Nystatin (standard)	12	14	11	10	15

TABLE-4
ANTICANCER EFFECTS OF SCHIFF BASE AND ITS [CuL]Cl₂ CHELATE IN TERMS OF % CELL INHIBITION AT VARIOUS CONCENTRATIONS

L concentration (μM)	Cell inhibition (%)	IC ₅₀ (μM)	R ²	[CuL]Cl ₂ concentration (μM)	Cell inhibition (%)	IC ₅₀ (μM)	R ²
0.1	0.171821			0.1	-0.08591		
1	2.920962			1	6.701031		
10	9.450172	75.7	0.998	10	25.17182	47.98	0.9991
100	57.64605			100	62.45704		

Conclusion

A fully conjugated 14-membered macrocyclic pentaza Schiff base forms cationic solid complexes with copper(II), nickel(II), cobalt(II), vanadyl(II) and zinc(II) ions. The decreased crystalline size for complexes was observed in XRD data. SEM images of complexes confirmed that they have well known different morphologies. Elemental analysis and FAB mass spectral data of the complex confirms the stoichiometry composition of the metal chelates as $[ML]Cl_2$ type. IR, UV-visible spectral data and magnetic moment values of complexes suggested that square planar except $[VOL]Cl_2$ which shows octahedral geometry due to axial oxygen atom. The ESR spectra of $[CuL]Cl_2$ and $[VOL]Cl_2$ complexes in DMSO solution at 77 and 300 K indicated that the complexes are akin to square planar and octahedral geometry, respectively. Schiff base and $[CuL]Cl_2$ complex were tested against the growth of breast cancer (human) cell line (MCF-7) using MTT assay method. IC_{50} values for ligand and $[CuL]Cl_2$ were 75.7 and 47.98 μM , respectively. The % cell inhibition of Schiff base at 100 μM is 57.64605 and $[CuL]Cl_2$ at 100 μM is 62.45704. The minimum inhibitory concentration values of metal chelates for antimicrobial activities have lower than the Schiff base ligand. The proposed structure of metal complexes is shown in Fig. 6.

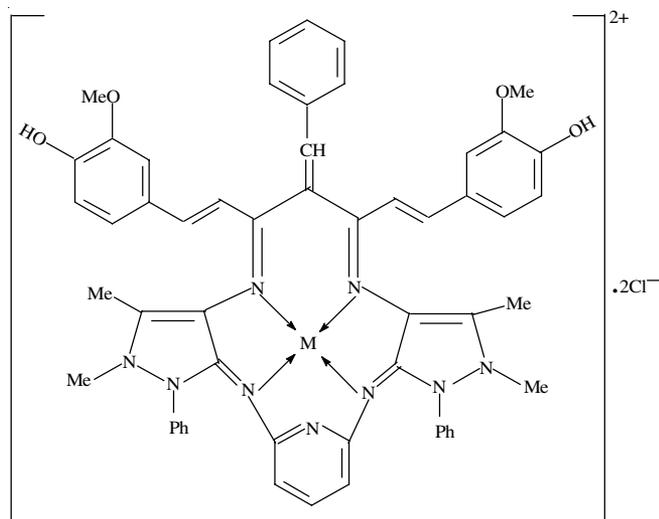


Fig. 6. Structure of metal complexes, where, M = Ni(II), Co(II), VO(II), Cu(II) and Zn(II)

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