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Macrocyclic Schiff Base Complexes-Preparation, Characterisation and Biological Activity

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ABSTRACT

New macrocyclic Schiff base complexes of transition metals were synthesized using 1, 3-Dibenzoylbenzene and 1, 2-Diaminoethane/1,2-Diaminobenzene. The complexes MLX_2 [where $M=Zn(II)$, $Co(II)$, $Cu(II)$ and $Ni(II)$; L =condensation product of 1, 3-Dibenzoylbenzene and 1, 2-Diaminoethane/1, 2-Diaminobenzene; $X=Cl$, CH_3COO^-] were synthesized using template method. These complexes were characterized by elemental analyses, spectral analyses (IR, NMR), Magnetic moment measurements, ESR studies and electronic measurements. All the complexes were screened for gram positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*), gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and phytopathogenic fungi (*Candida albicans*, *Saccharomyces cerevisiae*). Minimum inhibitory concentration of the synthesized complexes was also measured and compared with standard antibacterial Ciprofloxacin and antifungal Amphotericin-B.

Keywords: Template synthesis, Gram positive bacteria, Gram negative bacteria, Phytopathogenic fungi, Minimum inhibitory concentration

INTRODUCTION

Template reactions have been widely used for the synthesis of macrocyclic complexes, in which transition metal ions are generally used as the template agent [1]. Synthesis of transition metal macrocyclic complexes of Schiff base ligands had gain a growing interest due to simplicity of their synthesis and wide applications in pharmacological field for the use as antimicrobial agents against pathogenic microorganisms [2,3]. Due to demand of new metal based antibacterial and antifungal compounds, coordination chemistry is becoming an emerging area of research. Due to lipophilic nature and penetration of complexes through the lipid membrane, transition metal complexes exhibited good antimicrobial activities. Moreover these complexes find their uses in many industries. Macrocyclic complexes are used as catalysts [4] and anti-corrosion agents [5]. Macrocyclic complexes are of great importance in many biological processes like oxygen transport and photosynthesis [6]. These complexes are widely used as anticancer [7,8] antifungal [9] anti-inflammatory [10] and antidiabetic [11] drugs. Because of similarity with biomolecules, the study of macrocyclic Schiff base complexes had reached to a significant era. We have incorporated metal ions onto cyclic/acyclic systems and synthesized biologically active macrocyclic Schiff base complexes of transition metals [12-15]. In continuation of the same work present complexes have been synthesized and their pharmacological effect has been explored.

MATERIALS AND METHODS

Synthesis of complexes

Template synthesis of metal complexes was carried out by mixing the methanolic solution of 1,3-Dibenzoylbenzene and 1,2-Diaminoethane/1,2-Diaminobenzene in the presence of metal salts. To the hot methanolic solutions of 1,2-Diaminoethane/1,2-Diaminobenzene (10 mmol), copper, nickel, cobalt, zinc salts (5 mmol) dissolved in same solvent were added and refluxed for half an hour. 1,3-Dibenzoylbenzene (10 mmol) was added to refluxing mixture. The reaction mixture was refluxed for 6-8 hrs and then concentrated to half of its volume by evaporation on water bath. Crystalline solids were obtained on standing the reaction mixture overnight. These crystalline solids were filtered and washed with methanol, acetone and diethyl ether and dried

in vacuo. The complexes were insoluble in water and common organic solvents but soluble in Dimethylsulphoxide (DMSO) and Dimethylformamide (DMF).

The purity of complexes was checked by TLC. These complexes were found thermally stable and decomposed only above 300°C temperature. The complexes were monomeric in nature as indicated by elemental analyses and molecular weight determination.

The molar conductance of these complexes determined in DMSO was found to be in the range of 5-15 ohm⁻¹ cm² mol⁻¹. The low value of molar conductance indicated that these complexes were non electrolytic. Tests for anions were negative in undecomposed complexes confirmed their absence outside the coordination sphere but in decomposed complexes these tests were positive indicating presence of anions inside the coordination sphere.

The template synthesis of complexes derived from 1,3-Dibenzoylbenzene and 1,2-Diaminoethane/1,2-Diaminobenzene in the presence of copper, nickel, zinc and cobalt metal ions may be represented by the following Table 1 and Schemes 1 and 2.

Biological activity

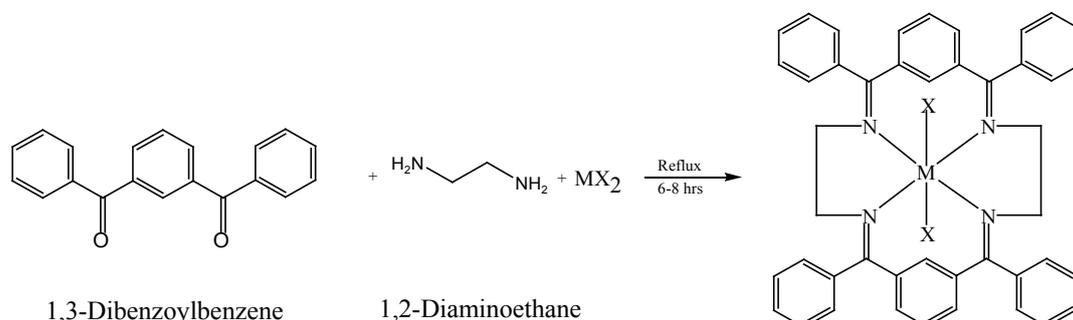
Clinical strains of human pathogenic bacteria such as *Escherichia coli* (MTCC1652), *Pseudomonas aeruginosa* (MTCC741), *Bacillus subtilis* (MTCC121) *Staphylococcus aureus* (MTCC96) and phytopathogenic fungi *Saccharomyces cerevisiae* (MTCC170), *Candida albicans* (MTCC3017) were procured from Microbial Type Culture Collection IMTECH, Chandigarh. Bacterial strains were sub cultured on Nutrient Agar (NA) and fungi on Malt Extract Agar (MEA) medium and were incubated aerobically at 37°C.

Antimicrobial activity

The antimicrobial activity of the complexes was determined against above mentioned four bacterial strains and two yeast strains using the agar well diffusion method [16]. Density of all the microbial cultures were adjusted to 0.5 McFarland standards, which were visually comparable to a microbial suspension of approximately 1.5 × 10⁸ cfu/ml. 20 ml of the Nutrient agar medium (for bacteria) and Malt extract agar medium (for yeast) were poured into each Petri plate. One hundred microlitre (100 µl) inocula of the test microorganisms was spread in each plate and kept for 15 min for adsorption. Solutions of each complex were prepared by dissolving the complex in 20% DMSO. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume of the solution of each complex. All the plates were incubated at 37°C for 24 h. Antimicrobial activity of each complex was evaluated by measuring the zone of growth inhibition against the test organisms with

Table 1: Physical and analytical data of macrocyclic Schiff base complexes derived from 1, 3-Dibenzoylbenzene and 1,2-Diaminoethane/1,2-Diaminobenzene

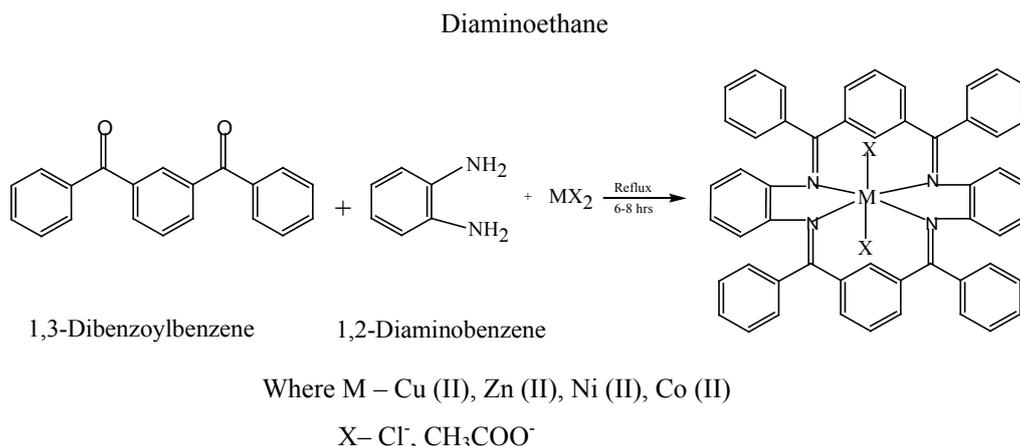
Sr. No.	Complexes	Colour	Yield (%)	Found (Calculated) %				Molecular Mass
				M	C	H	N	
1.	[Co(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	Yellow	71	7.24 (7.39)	72.37 (72.28)	5.18 (5.27)	7.01 (7.03)	796.9
2.	[Co(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	Black	72	6.43 (6.60)	74.32 (75.26)	4.92 (4.70)	6.25 (6.27)	892.9
3.	[Ni(C ₄₄ H ₃₆ N ₄)Cl ₂]	White	64	7.71 (7.83)	70.32 (70.43)	4.91 (4.80)	7.34 (7.47)	749.7
4.	[Ni(C ₅₂ H ₃₆ N ₄)Cl ₂]	White	68	6.81 (6.94)	73.86 (73.79)	4.20 (4.26)	6.48 (6.62)	845.7
5.	[Cu(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	Blue	62	7.71 (7.92)	71.98 (71.86)	5.13 (5.24)	6.87 (6.99)	801.5
6.	[Cu(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	Black	68	7.26 (7.07)	71.42 (74.87)	4.51 (4.68)	6.19 (6.24)	897.5
7.	[Zn(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	White	64	8.05 (8.14)	71.56 (71.70)	5.38 (5.22)	6.66 (6.97)	803.4
8.	[Zn(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	Yellow green	69	7.42 (7.27)	74.64 (74.71)	4.42 (4.67)	6.02 (6.23)	899.4



Where M – Cu (II), Zn (II), Ni (II), Co (II)

X– Cl⁻, CH₃COO⁻

Scheme 1: Synthesis of transition metal complexes derived from 1,3-Dibenzoylbenzene and 1,2-Diaminoethane



Scheme 2: Synthesis of transition metal complexes derived from 1,3-Dibenzoylbenzene and 1,2-Diaminobenzene

a zone reader (Hi Antibiotic zone scale). Ciprofloxacin and Amphotericin-B were used as a positive control. This procedure was performed in three replicate plates for each organism.

Determination of minimum inhibitory concentration (MIC)

Minimum inhibitory concentration of the complexes for each test organism has been determined by following the modified agar well diffusion method [17]. A twofold serial dilution of each complex has been prepared. Each complex has been dissolved in 20% DMSO to achieve a concentration of 100 mg/ml followed by dilution in sterile distilled water (1:1) to achieve a decreasing concentration range of 50 mg/ml to 0.39 mg/ml. A 100 μ l volume of each dilution has introduced into wells (in triplicate) in the agar plates already seeded with 100 μ l of standardized inoculum (10^6 cfu/ml) of the test microbial strain. All test plates are incubated aerobically at 37°C for 24 hrs and observed for the inhibition zones. Zone of inhibition (>8 mm) has been observed in each plate. Concentration of the complex that completely inhibited the growth of the microorganism has been taken as minimum inhibitory concentration.

RESULTS AND DISCUSSION

Purification of materials

Solvents

The solvents used in present research like ethanol, methanol (AR, Merck), petroleum ether, diethyl ether, dimethylsulphoxide (GR, Merck), dimethylformamide (GR, Merck), acetone and chloroform were used as received.

Reagents

1,3-Dibenzoylbenzene, 1,2-Diaminobenzene, 1,2-Diaminoethane, copper acetate, zinc acetate, nickel chloride and cobalt acetate were supplied by Aldrich and was used as such without any further purification.

NMR spectra

Multiplets in the ¹HNMR spectrum of zinc complexes in the region δ 7.5-8.3 may be assigned to protons of aromatic ring of 1,3-Dibenzoylbenzene. A peak at δ 2.6 in the ¹HNMR spectrum of zinc complexes may be due to (8H) protons of 1,2-Diaminoethane moiety. Absence of broad peak at δ 2.0 due to N-H of 1,2-Diaminoethane and at δ 4 due to phenylenediamine confirms the formation of C=N by condensation of carbonyl group of 1,3-Dibenzoylbenzene and NH₂ of 1,2-Diaminoethane/1,2-Diaminobenzene (Figure 1).

Infrared spectra

Absence of strong absorption peak at 1655 cm⁻¹ due to carbonyl group of 1,3-Dibenzoylbenzene and medium intensity peaks at 3230/3200 and 3260/3250 cm⁻¹ due to NH₂ group of 1,2-Diaminoethane/1,2-Diaminobenzene indicated condensation of carbonyl and diamine to form imine (C=N) [18]. A band appeared near 1563-1595 cm⁻¹ confirmed the presence of C=N group [19]. The lower value of this peak might be due to drifting of lone pair electron density of azomethine nitrogen of (C=N) group towards metal atom [20]. While ν (C-H) stretching vibrations near 3015-3040 cm⁻¹ and 3295-3362 cm⁻¹ might be due to aromatic rings of 1,3-Dibenzoylbenzene moiety in the complex. Bands in the range 2937-2949 and 2855-2887 were due to C-H stretching vibrations of aliphatic part of the complexes.

Medium intensity band near 1651 cm⁻¹ might be due to stretching vibrations of (C=C) aromatic. Bands near 721-783 cm⁻¹ were assigned to out of plane banding vibrations due to ν (C-H) of aromatic rings [21]. Band near 1261-1268 cm⁻¹ might be assigned (C-N) stretching. Band near 1654-1678 cm⁻¹ and at 1126-1266 cm⁻¹ might be assigned to ν (COO)_{as} asymmetric stretching and ν (COO)_s symmetric stretching respectively of acetate ion. The difference between asymmetric and symmetric vibrations showed unidentate

coordination of acetate ion with central metal ion as the difference in the two vibrations was more than 144 [22]. Band at 415-475 cm^{-1} in far infrared spectra corresponded to ν (M-N) vibrations of metal complexes [23]. This indicated coordination of azomethine nitrogen to the central metal ion (Figure 2 and Table 2).

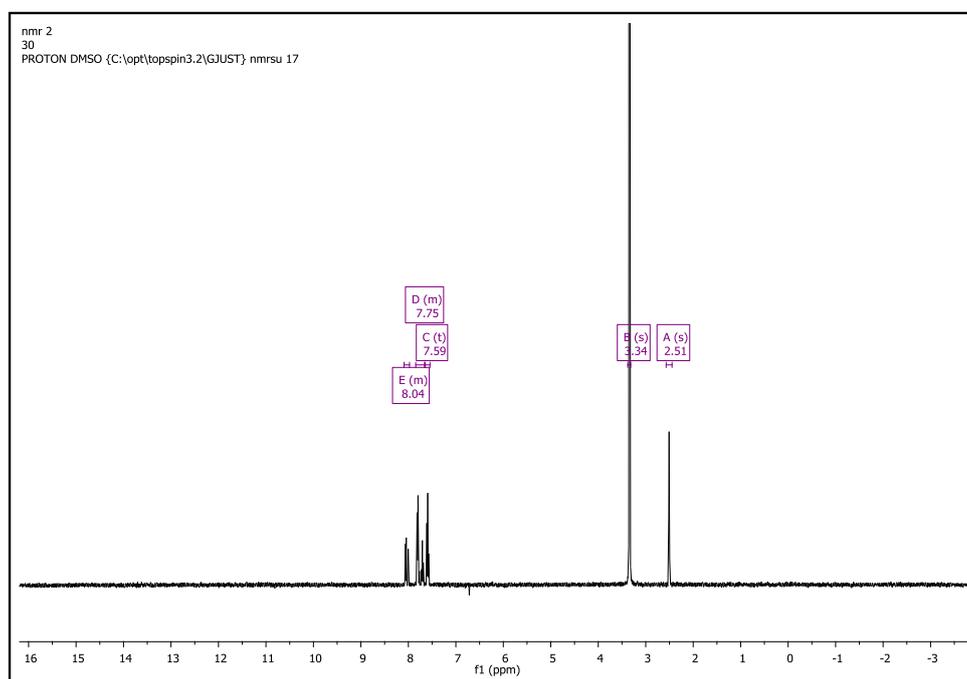


Figure 1: NMR spectrum of complex derived from zinc acetate: 1,3-Dibenzoylbenzene and 1,2-Diaminobenzene

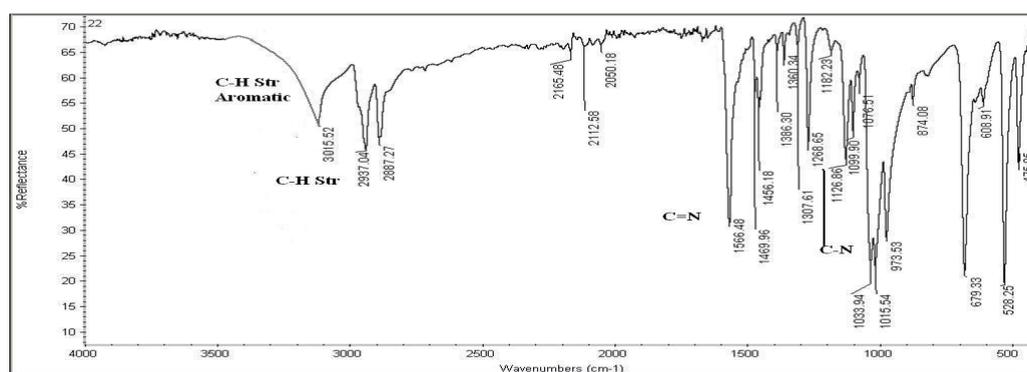


Figure 2: Infrared spectrum of complex derived from copper acetate: 1,3-Dibenzoylbenzene and 1,2-Diaminoethane

Table 2: Infrared spectral characteristics of complexes derived from 1,3-Dibenzoylbenzene and 1,2-Diaminoethane/1,2-Diaminobenzene

Sr. No.	Complexes	ν (C-H)	ν (C=N)	ν (C-N)	ν (COO) _{as}	ν (COO) _s	ν (M-N)
1.	[Co(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	3027, 2932, 2874	1569	1236	1628	1272	474
2.	[Co(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	3017	1574	1244	1651	1273	462
3.	[Ni(C ₄₄ H ₃₆ N ₄)Cl ₂]	2965, 2875,	1572	1238	-	-	487
4.	[Ni(C ₅₂ H ₃₆ N ₄)Cl ₂]	3043.3	1575.3	1263.6	-	-	489
5.	[Cu(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	3015, 2937, 2887	1566	1268	1654	1126	475
6.	[Cu(C ₅₂ H ₃₄ N ₄)Cl ₂](OAc) ₂	3034	1572	1254	1671	1249	464
7.	[Zn(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	3041, 2940, 2884	1571	1244	1652	1266	459
8.	[Zn(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	3031	1564	1244	1651	1268	444

Magnetic measurements and electronic spectral studies

Copper (II) complexes

The effective magnetic moment of copper (II) complexes measured at room temperature was 1.79-1.80 B.M. This value agreed well with distorted octahedral geometry of d^9 system. The expected value of one electron octahedral complexes was 1.75 B.M. The higher value of magnetic moment of these complexes might be due to spin orbital coupling and spin orbit coupling.

Electronic spectra of copper (II) complexes showed a band at 17800-20650 cm^{-1} and a weak low energy shoulder at ~ 14750 -16650 cm^{-1} these bands could be assigned if tetragonal distortion of octahedral symmetry was assumed [24]. Due to tetragonal distortion the d orbital splitting should be $x^2-y^2 > z^2 > xy > xz > yz$. So the electronic transition involved in the band formation were ${}^2B_{1g} \rightarrow {}^2B_{2g}$ ($xy \rightarrow x^2-y^2$) and ${}^2B_{1g} \rightarrow {}^2E_g$ ($xz, yz \rightarrow x^2-y^2$) and the low energy shoulder assigned ${}^2B_{1g} \rightarrow {}^2A_{1g}$ ($z^2 \rightarrow x^2-y^2$) transition [24].

Nickel (II) complexes

The effective magnetic moment for nickel (II) complexes at room temperature was in the range of 2.90-3.20 B.M. This value showed octahedral high spin nature of nickel (II) complexes [25]. The expected value for octahedral two electron system was 2.83 B.M. This value was due to spin only moment. Observed higher value of these complexes showed orbital momentum contribution to spin moment of high spin octahedral nickel (II) complexes.

Electronic spectra of Nickel (II) complexes showed a band at 9650-10500 cm^{-1} with a low energy shoulder at ~ 11400 -12650 cm^{-1} . These bands were formed due to splitting of one band and transition involved for this band may be ${}^3B_{1g} \rightarrow {}^3E_g$ and ${}^3B_{1g} \rightarrow {}^3B_{2g}$ for D_{4h} symmetry. The other two bands were at 16700-17500 cm^{-1} (ν_2) and at 27250-28700 cm^{-1} (ν_3). These bands were assigned to ${}^3A_{2g} \rightarrow {}^3T_{1g}$ (F) and ${}^3A_{2g} \rightarrow {}^3T_{1g}$ (P) transition. The $\Pi \rightarrow \Pi^*$ transition, of (C=N) group resulted in observed high energy band at 35400 cm^{-1} . Effective magnetic moment and electronic spectra confirmed high spin nature and distorted octahedral symmetry of nickel (II) complexes.

Cobalt (II) complexes

At room temperature the effective magnetic moment of cobalt (II) complexes was in the range of 4.60-4.95 B.M. This value agreed with three electron octahedral system as the expected value was ~ 3.75 B.M [26]. The higher value of magnetic moment (μ_{eff}) for d^7 complexes was due to orbital angular momentum contribution and spin orbit coupling. This also confirmed high spin nature of cobalt (II) complexes.

Electronic spectra of cobalt (II) complexes exhibited three bands at 8160-9300 cm^{-1} (ν_1) 13150-15900 cm^{-1} (ν_2) and 18700-21200 cm^{-1} (ν_3) respectively. These bands also confirmed D_{4h} symmetry of high spin cobalt (II) complexes. The transition assigned to these bands were ${}^4T_{1g} \rightarrow {}^4T_{2g}$ (F), ${}^4T_{1g} \rightarrow {}^1A_{2g}$ (F) and ${}^4T_{1g} \rightarrow {}^4T_{2g}$ (P).

ESR

The ESR spectrum was recorded in solid state on X- band at a frequency of 9.1 GHz under the magnetic field of 2000 G. Tetracyanoethylene radical was used as g-marker. The ESR spectrum of copper (II) complexes of 1,3-Dibenzoylbenzene and 1,2-Diaminoethane at room temperature in solid state exhibited anisotropic peak with two unique g_{\parallel} and g_{\perp} . The values of g_{\parallel} and g_{\perp} were 2.14 and 2.04 respectively. At LNT in solid state these complexes had $g_{\parallel}=2.14$ and $g_{\perp}=2.05$ while at LNT in DMSO these complexes had $g_{\parallel}=2.46$ and $g_{\perp}=2.10$. This shifting of g value (g for free electron= 2.0023) was due to interaction between the spin and orbital motion. Transition metal complexes having d-shell more than half filled should have g value greater than 2.0023. The value of g for these complexes was found 2.007 (greater than 2.0023) indicating more than half filled d-shell in synthesized copper (II) complexes [27]. $g_{\parallel} > g_{\perp} > 2.0023$ indicated that the unpaired electron was localized in $d_{x^2-y^2}$ orbital of copper (II) ion. This again showed distortion in the copper (II) complex from O_h symmetry to D_{4h} symmetry.

The ESR spectrum of 1,3-Dibenzoylbenzene and phenylenediamine at LNT in solid state showed an isotropic peak with g_{iso} value 2.02. Shifting of g value (2.0023) indicated spin orbit coupling. A higher value of g might be due to mixing of spin orbital coupling of metal orbitals having unpaired electrons with filled ligand orbitals. Higher value of g also showed distorted octahedral symmetry of these copper (II) complexes.

Pharmacological effect of complexes

Minimum inhibitory concentrations of complex 5 $[\text{Cu}(\text{C}_{44}\text{H}_{36}\text{N}_4)(\text{OAc})_2]$, was extremely good against *Saccharomyces cerevisiae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Bacillus subtilis*. The MIC of this complex was found even less than standard antibiotic and antifungal drugs in use these days. Its MIC for *Saccharomyces cerevisiae*, *Pseudomonas aeruginosa* and *Escherichia coli* was 3.125 much less than standard while MIC for *Bacillus subtilis* (6.25) was same as for ciprofloxacin. The MIC for complex 8 $[\text{Zn}(\text{C}_{52}\text{H}_{36}\text{N}_4)(\text{OAc})_2]$, against *Candida albicans* was found equal to standard (Tables 3 and 4).

CONCLUSION

Conductance measurements, elemental analyses and magnetic susceptibilities, as well as IR, NMR and electronic spectral studies confirmed a distorted octahedral geometry for all these complexes. MIC of complexes shows that these complexes are very effective on tested microorganisms. These complexes may be used for the formulation of novel chemotherapeutic agents as the problem of antimicrobial resistance has increased enormously [28]. Because of the partial sharing of its positive charge with a donor group in the chelate ring system, polarity of the metal ion decreases. The lipophilic nature of the central metal ion increases due to chelation

Table 3: *In vitro* antimicrobial activity of synthetic macrocyclic complexes through agar well diffusion method

Compound No.	Diameter of growth of inhibition zone (mm) ^a					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>	<i>Saccharomyces cerevisiae</i>
[Co(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	-	12	-	-	-	-
[Co(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	-	-	-	-	10	-
[Ni(C ₄₄ H ₃₆ N ₄)Cl ₂]	-	-	-	10	-	-
[Ni(C ₅₂ H ₃₆ N ₄)Cl ₂]	-	-	10	-	-	-
[Cu(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	26	10	30	30	-	32
[Cu(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	20	-	-	-	20	-
[Zn(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	-	15	10	20	-	-
[Zn(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	25	-	25	-	22	-
Ciprofloxacin	24.0	26.6	25	22	-	-
Amphotericin-B	-	-	-	-	16.6	19.3

- No activity; Values, including diameter of the well (8mm), are means of three replicates

Table 4: MIC of synthetic macrocyclic complexes

Sr. No.	complexes	Diameter of growth of inhibition zone (mm) ^a					
		Gram positive bacteria		Gram negative bacteria		Fungi	
		<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>	<i>Saccharomyces cerevisiae</i>
1	[Co(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	Nt	Nt	Nt	Nt	Nt	Nt
2	[Co(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	Nt	Nt	Nt	Nt	Nt	Nt
3	[Ni(C ₄₄ H ₃₆ N ₄)Cl ₂]	Nt	Nt	Nt	Nt	Nt	Nt
4	[Ni(C ₅₂ H ₃₆ N ₄)Cl ₂]	Nt	Nt	Nt	Nt	Nt	Nt
5	[Cu(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	6.25	Nt	3.125	3.125	Nt	3.125
6	[Cu(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	25	Nt	Nt	Nt	25	Nt
7	[Zn(C ₄₄ H ₃₆ N ₄)(OAc) ₂]	Nt	Nt	Nt	25	Nt	Nt
8	[Zn(C ₅₂ H ₃₆ N ₄)(OAc) ₂]	12.5	Nt	12.5	Nt	12.5	Nt
9	Ciprofloxacin	6.25	6.25	6.25	12.5	-	-
10	Amphotericin-B	-	-	-	-	12.5	12.5

which favours its permeation through the lipid layer of the membrane [29]. So the metal complexes cross the bacterial membrane more effectively thereby activity of the complexes increases. Many other factors, such as dipole moment, conductivity, solubility and the influence of the metal ion may also be responsible for the remarkable antibacterial activities of these complexes.

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