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Synthesis, Spectroscopic Characterization, and In Vitro Antimicrobial Screening of 16-Membered Tetraazamacrocyclic Schiff-Base Ligand and its Complexes with Co(II), Ni(II), Cu(II), and Zn(II) Ions

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Synthesis, Spectroscopic Characterization, and *In Vitro* Antimicrobial Screening of 16-Membered Tetraazamacrocyclic Schiff-Base Ligand and its Complexes with Co(II), Ni(II), Cu(II), and Zn(II) Ions

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A 16-membered tetraazamacrocyclic ligand has been synthesized by condensation reaction of 2-methyl acetoacetanilide with 1,8-diaminonaphthalene, and the metal complexes of the type $[MLCl_2]$ [M = Co(II), Ni(II), Cu(II), Zn(II)] were prepared by interaction of the ligand with metal salts. The ligand and its complexes were characterized by various spectroscopic studies. The mode of bonding and the overall geometry of these complexes have been deduced by elemental analysis, molar conductance values, Fourier-transform infrared (FT-IR), ¹H-nuclear magnetic resonance (NMR), fast-atom bombardment (FAB) mass, electron paramagnetic resonance (EPR), and ultraviolet-visible (UV-VIS) spectroscopy along with magnetic measurement studies. An octahedral geometry has been envisaged for all these complexes, while a distorted octahedral geometry has been noticed for the Cu(II) complex. The cyclic voltammograme of the Cu(II) complex exhibits a quasi-reversible one-electron transfer wave for the Cu(II)/Cu(I) couple. The low conductivity data of all the complexes suggest their nonionic nature. These complexes have also been screened against pathogenic bacteria and fungi in vitro as growth-inhibiting agents.

Keywords antimicrobial, octahedral geometry, tetraazamacrocycle, Schiff base

INTRODUCTION

Metal complexes containing synthetic macrocyclic ligands have attracted considerable attention due to their mimicry with more intricate biological system: metalloporhyrins (hemoglobin, myoglobin, cytochrome, chlorophylls),

corrins (vitamin B12), and antibiotics (valinomycin, nonactin). These studies have revealed the development of supramolecular chemistry and its enormous diversity.^[1-5] Structural factors, such as the cavity size, type and number of donor atoms, and stereochemical rigidity, have been shown to play significant roles in determining the binding features of macrocycles toward metal ions.^[6,7] Many of the more rational synthetic routes of Schiff-base macrocyclic ligands involve the use of a metal ion template to orient the reacting groups of linear substrates in the desired conformation prior to the ring closure.^[8] Functionalized pendant-arm macrocyclic complexes have been designed due to the fact that they can offer additional donor groups to maintain the coordination requirement of metals in the macrocycles, as well as mimic the structure and properties of certain metalloenzymes and metalloproteins.^[9] Macrocycles, particularly the ones containing aromatic moieties, are known to form charge-transfer complexes with a variety of guests. These macrocycles were used to study complexation of diverse guests to provide new insights into non-covalent binding interactions, chiefly cation π -interactions, which involve the stabilization of a positive charge by the face of an aromatic ring.^[10]

Acetoacetanilide, an important diketoanilide, has been reported to form a variety of Schiff base complexes with the different ligands,^[11–13] such as o-phenylenediamine, 4aminoantipyrine, and isonicotinic acid. Metal chelates of acetoacetanilide exhibit anticancer and antifungal activity. Copper(II) complexes formed by the series of macrocyclic ligands derived from diethylphthalate, o-phenylenediamine, and 2-methyl acetoacetanilide showed strong antifungal activities.^[14] Several macrocyclic complexes have been synthesized from 1,8-diaminonaphthalene and dicarbonyls via a template method.^[15-17] Tahir et al. recently reported 14- and 16-membered tetraazamacrocyclic Schiff-base ligands and their transition metal complexes formed by 2-methyl acetoacetanilide and diamines.^[18] In view of the already mentioned applications of acetoacetanilide complexes, we thought it worthwhile to synthesize a tetraazamacrocyclic Schiff-base ligand

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TABLE 1

		MIC and M	IBC results	s of complex	kes with po	sitive contro	ol ciproflox	acin		
		Gram-posit	ive bacteria	a	Gram-negative bacteria					
	S. pyogenes		S. aureus		P. aeruginosa		K. pneumoniae		E. coli	
Compounds	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
L	100	200	50	100	50	100	50	100	50	100
[CoLCl ₂]	25	50	25	50	25	50	25	100	25	10
[NiLCl ₂]	100	200	50	100	50	100	50	100	50	100
[CuLCl ₂]	25	25	25	50	25	50	25	50	25	25
[ZnLCl ₂]	50	100	50	100	25	50	50	100	50	50
Standard	6.25	12.5	6.25	12.5	6.25	12.5	6.25	12.5	6.25	12.5

MIC (μ g/mL) = minimum inhibitory concentration, i.e., the lowest concentration of the compound to inhibit the growth of bacteria completely; MBC (μ g/mL) = minimum bacterial concentration, i.e., the lowest concentration of the compound for killing the bacteria completely.

by [2 + 2] condensation of 2-methyl acetoacetanilide and 1,8diaminonaphthalene and its complexes. The biological activities of the synthesized complexes have also been examined against pathogenic bacterial strains, namely, Streptococcus pyogenes, Staphylococcus aureus (gram-positive), Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli (gramnegative), and some fungal strains, namely, Candida albicans, Aspergillus fumigates, Trichophyton mentagrophytes, and Penicillium marneffei.

EXPERIMENTAL

Materials and Methods

The metal salts $MCl_2 \cdot 6H_2O$ (M = Co(II), Ni(II)), CuCl₂·2H₂O, and ZnCl₂ (all Merck) were commercially available pure samples. The chemicals 2-methyl acetoacetanilide and 1,8-diaminonaphthalene (Acros) were used as received. Analytical-grade methanol was used as solvent.

Synthesis of Ligand

2,10-Dimethyl-4,12-di(N-amino)-2-methyl Phenyl 1,5,9,13-Tetraazacyclohexadecane 1,4,9,12 Tetraene -6,8:14,16-Bis(naphthalene)

A solution of 1,8-diaminonaphthalene (0.002 mol, 0.316 g) taken in 20 cm³ of methanol was slowly added to a methanolic solution ($\sim 20 \text{ cm}^3$) of 2-methyl acetoacetanilide (0.002 mol, 0.382 g) placed in a round-bottom flask. The reaction mixture was stirred overnight, followed by refluxing for 6 h. The reaction mixture was allowed to stand at room temperature, resulting in the isolation of microcrystalline product after couple of days. The product was washed several times with methanol and dried in vacuo.

Synthesis of the Complexes $[MLCl_2]$ [M = Co(II), Ni(II),Cu(II), and Zn(II)]

To a methanolic solution of hydrated metal chloride (0.001 mol) taken in round bottom flask was slowly added a methanolic solution ($\sim 20 \text{ cm}^3$) of ligand, (0.001 mol, 0.626 g). The reaction

С	A	A	Æ	Т	М	P	М
MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
100	10	100	200	100	200	50	200
50	100	50	100	50	100	50	100
100	100	100	200	100	200	50	200
25	50	25	50	25	50	25	50
25	50	12.5	100	12.5	50	25	50
6.25	12.5	6.25	12.5	6.25	12.5	6.25	12.5
	MIC 100 50 100 25 25 6.25	CA MIC MFC 100 10 50 100 100 100 25 50 25 50 6.25 12.5	CA A MIC MFC MIC 100 10 100 50 100 50 100 100 25 25 50 25 25 50 12.5 6.25 12.5 6.25	CA AF MIC MFC MIC MFC 100 10 100 200 50 100 50 100 100 100 200 200 50 100 50 100 100 100 200 200 25 50 25 50 25 50 12.5 100 6.25 12.5 6.25 12.5	CA AF T MIC MFC MIC MFC MIC 100 10 100 200 100 50 100 50 100 50 100 100 200 100 25 50 25 50 25 25 50 12.5 100 12.5 6.25 12.5 6.25 12.5 6.25	$\begin{tabular}{ c c c c c c c } \hline CA & AF & TM \\ \hline \hline MIC & MFC & MIC & MFC & MIC & MFC \\ \hline 100 & 10 & 100 & 200 & 100 & 200 \\ 50 & 100 & 50 & 100 & 50 & 100 \\ 100 & 100 & 100 & 200 & 100 & 200 \\ 25 & 50 & 25 & 50 & 25 & 50 \\ 25 & 50 & 12.5 & 100 & 12.5 & 50 \\ 6.25 & 12.5 & 6.25 & 12.5 & 6.25 & 12.5 \\ \hline \end{tabular}$	CA AF TM P1 MIC MFC MIC MFC MIC MFC MIC MIC 100 10 100 200 100 200 55 50 25 50 25 50 25 50 25 50 25 6.25 12.5 6.25 12.5 6.25 12.5 6.25 12.5 6.25 12.5 6.25 12.5 6.25 12.5 </td

TABLE 2 MIC and MFC of complexes

CA, Candida albicans; AF, Aspergillus fumigates; TM, Trichophyton mentagrophytes; PM, Penicillium marneffei. MIC (μ g/mL) = minimum inhibitory concentration, i.e., the lowest concentration of the compound to inhibit the growth of fungus completely; MFC (μ g/mL) = minimum fungicidal concentration, i.e., the lowest concentration of the compound for killing the fungus completely.



[M = Co(II), Ni(II) n=6, Cu(II) n=2, Zn(II); X = Cl]

SCH. 1. Synthesis and proposed structure of macrocyclic ligand and its complexes.

mixture was stirred for 6 h, followed by refluxing for 4 h. Microcrystalline solid product was isolated on evaporation over a period of a few days. The product was washed several times with methanol and dried in vacuo.

Physical Measurements

The elemental analyses were obtained from the microanalytical laboratory of Central Drug Research Institute (CDRI), Lucknow, India. ¹H-Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker Avance 400 NMR spectrometer in DMSO-d₆. Fast-atom bombardment (FAB) mass spectra were recorded on a Joel SX-102 spectrometer. Electron paramagnetic resonance (EPR) spectra were recorded on an E-112 spectrometer from the Indian Institute of Technology, Chennai. The Fourier-transform infrared (FT-IR) spectra $(4000-200 \text{ cm}^{-1})$ of the complexes were recorded as KBr pellets on an Interspec 2020 FT-IR spectrometer. The electronic spectra in dimethyl sulfoxide (DMSO) were recorded on a Pye-Unicam-8800 spectrophotometer at room temperature. Metals and chlorides were determined volumetrically^[19] and gravimetrically,^[20] respectively. Magnetic susceptibility measurement was carried out on a Faraday balance at 25°C. The cyclic voltammogram was recorded on a CH-Instrument electrochemical analyzer using KCl as supporting electrolyte at room temperature. A three-cell electrode was used that contained a Pt microcylinder working electrode, Pt wire as auxiliary electrode, and Ag/AgCl as reference electrode. The molar conductance was measured for 10^{-3} M solutions in DMSO using a Systronic type 302 conductivity bridge thermostated at 25 \pm 0.01°C.

In Vitro Antimicrobial Activity: Determination of Minimum Inhibitory Concentration

Antimicrobial activities of the compounds were tested using the bacterial and fungal cultures by disc diffusion in agar medium. Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. The nutrient broth, which contained logarithmic serially twofold diluted amounts of test compound and controls, was inoculated with approximately 5×10^5 CFU/mL of actively dividing bacterial cells. The cultures

 TABLE 3

 Elemental analyses, m/z value, color, yield, molar conductance, and melting point of complexes

					Fo	Molar conductivity			
Complexes	<i>m/z</i> found (calcd.)	Color	Yield (%)	Μ	Cl	С	Н	N	$(ohm^{-1} cm^2 mol^{-1})/m.p. (^{\circ}C)$
C ₄₂ H ₃₈ N ₆	627.52	White	52	_		80.26	6.21	12.00	
L	(626.80)			_		(80.48)	(6.11)	(12.40)	
C ₄₂ H ₃₈ N ₆ CoCl ₂	757.20	Black	40	7.45	9.15	66.30	5.01	11.23	13/>300
[CoLCl ₂]	(756.63)			(7.78)	(9.37)	(66.67)	(5.06)	(11.01)	
C42H38N6NiCl2	757.32	Pale	46	7.28	9.10	66.23	5.01	11.02	30/>300
[NiLCl ₂]	(756.39)	Green		(7.75)	(9.37)	(66.69)	(5.06)	(11.11)	
C ₄₂ H ₃₈ N ₆ CuCl ₂	762.19	Dark	50	8.20	9.22	66.29	5.00	11.18	34/>300
[CuLCl ₂]	(761.24)	Green		(8.34)	(9.31)	(66.26)	(5.03)	(11.03)	
C42H38N6ZnCl2	763.99	Pinkish	42	8.12	9.10	66.19	5.45	11.68	17/>300
[ZnLCl ₂]	(762.57)			(8.99)	(9.29)	(66.15)	(5.02)	(11.02)	

ik vibrational frequencies (cm ⁻¹) of complexes						
Compounds	$\nu(C = N)$	ν(N-H)	ν(M-N)	ν (M-Cl)	Phenyl ring vibrations	
L	1640	3126		_	1422, 1025, 726	
[CoLCl ₂]	1627	3123	433	255	1455, 1013, 757	
[NiLCl ₂]	1612	3108	426	261	1401,1006, 763	
[CuLCl ₂]	1629	3118	406	290	1457, 1007, 748	
[ZnLCl ₂]	1629	3130	418	274	1440, 1008, 752	

TABLE 4IR vibrational frequencies (cm⁻¹) of complexes

were incubated for 24 h at 37°C and the growth was monitored visually and spectrophotometrically. Fungal cultures were incubated for 48 h at 35°C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of bacteria and fungus was regarded as the minimum inhibitory concentration (MIC). The values of MICs are given in Tables 1 and 2.

RESULTS AND DISCUSSION

The 16-membered tetraaza Schiff-base macrocyclic ligand, L, has been synthesized by [2 + 2] condensation reaction between 2-methyl acetoacetanilide and 1,8-diaminonaphthalene (Scheme 1). The complexes of the type $[MLCl_2]$ [M = Co(II),Ni(II), Cu(II), and Zn(II)] were synthesized by reaction of ligand L and metal salts in 1:1 molar ratio in methanolic medium. The purity of the ligand and complexes was checked by thin-layer chromatography (TLC) run in 1:1 benzene-methanol. However, in spite of all possible efforts a single crystal for both ligand and complexes could not be successfully isolated. All the complexes were stable to atmosphere and soluble in DMSO. The formation of ligand framework and macrocyclic complexes was deduced on the basis of results of elemental analyses, molecular ion peak in mass spectra (Table 3), characteristic bands in FT-IR, and resonance signals in the ¹H-NMR. The overall geometry of the complexes was inferred from the observed values of magnetic moments and the position of the bands in electronic spectra. The EPR spectrum of the Cu(II) complex exhibits a distorted octahedral geometry. The molar conductance data of the 10^{-3} M solutions of the complexes measured in DMSO indicate the non-electrolytic nature of all the complexes.



FIG. 1. IR spectrum of Zn(II) complex.

IR Spectra

The binding mode of the ligand to metal ion in macrocyclic complexes was studied by comparing the IR spectrum of free ligand with the spectra of macrocyclic complexes. The main bands and their assignments are listed in Table 4. The IR spectrum of the ligand shows a new strong-intensity band at 1640 cm^{-1} , which may reasonably be assigned^[21] to the imine function in the macrocyclic framework. However, no band has been observed characteristic of either free primary amine or carbonyl function supportive of the formation of proposed macrocyclic skeleton. A significant negative shift (15–20 cm⁻¹) in ν (C = N) stretching mode has been observed for the complexes as compared to free ligand, suggesting^[22] the involvement of imine nitrogen of the (C = N) group in coordination with metal ions (Figure 1). The bands characteristic of aromatic ring vibrations appeared in the 1457–1440, 1155–1008, and 750–748 cm^{-1} regions in all the complexes. A broad medium-intensity band in the spectra of ligand and its complexes in the 3130–3108 cm^{-1} region may reasonably be assigned to the -NH stretching mode of anilide group^[12] on the macrocyclic skeleton, characteristic of a free secondary amino group similar to that observed in the IR spectrum of 2-methyl acetoacetanilide. A weak absorption band in the region 2920–2925 cm⁻¹ may be assigned to the CH₃ stretching vibration. The formation of macrocyclic complexes has been further confirmed by appearance of a medium-intensity band in the 418–406 cm^{-1} region, which may reasonably be ascribed to ν (M-N) vibration.^[23] However, a band in the 290–255 cm⁻¹ region may be assigned to the ν (M-Cl) mode.^[24]

¹H-NMR Spectra

The ¹H-NMR spectra of macrocyclic ligand and its Zn(II) complex recorded in DMSO-d₆ show a sharp singlet at 2.35 and 2.11 ppm, respectively, which may be assigned to the methyl protons (-CH₃; 12H).^[25] However, a singlet at 8.04 ppm may be attributed to the pendant secondary amino protons (C-NH-C; 2H).^[26] The proton resonance peaks expected for various aromatic moieties on the macrocyclic framework were observed as multiplets in the region 6.61–7.09 ppm. However, the resonance signals obtained for the Zn(II) complex show a downfield shift as compared to the ligand, indicating the coordination of the ligand to the Zn(II) ion.



FIG. 2. EPR spectrum of Cu(II) complex.

EPR Spectrum

The EPR spectrum of the polycrystalline Cu(II) complex was recorded at room temperature. The spectrum exhibits a single broad signal. The analysis of spectrum gives $g_{\parallel} = 2.15$ and g = 2.05 (Figure 2). The observed g_{\parallel} and g values for the

copper(II) complex are less than 2.3, which is in agreement with the covalent character of the M–L bond. The relationship $g_{\parallel} > g > 2.0023$ calculated for the Cu(II) complex suggests that the unpaired electron is present in the dx^2-y^2 orbital and the spectral features are characteristic of axial symmetry with tetragonal elongation.^[27]

 $G = (g_{\parallel} - 2)/(g - 2)$, which measures the exchange interaction between the metal centers in polycrystalline solid, has been calculated. According to Hathaway and Billing,^[28] if G >4 the exchange interaction is negligible but G < 4 indicates considerable exchange interaction in the solid complex. The calculated G value for the complex is 1.83 (G < 4), which indicates considerable exchange interaction present between the Cu(II) centers.

Mass Spectra

The mass spectrum of the ligand exhibits a molecular ion peak $[L]^+$ at m/z = 627.52. The mass spectra of all the synthesized macrocyclic complexes exhibit molecular ion peaks $[M]^+$, m/z at 757, 757, 762, and 763 a.m.u., corresponding to their molecular formulas $[CoLCl_2]$, $[NiLCl_2]$, $[CuLCl_2]$, and $[ZnLCl_2]$, respectively (Table 3). The proposed molecular formula of these complexes were confirmed by comparing their molecular formula weights with m/z values. The mass spectrum of macrocyclic Co(II) complex shows a series of peaks at m/z



FIG. 3. Mass spectrum of Co(II) complex.

TABLE 5Antibacterial activity of the complexes

	Diameter of zone of inhibition								
	Gram-posit	ive bacteria	Gram-negative bacteria						
Compounds	S. pyogenes	S. aureus	P. aeruginosa	K. pneumoniae	E. coli				
L	10.2 ± 0.3	11.9 ± 0.5	19.9 ± 0.3	11.2 ± 0.2	15.2 ± 0.4				
[CoLCl ₂]	14.2 ± 0.3	12.9 ± 0.5	21.9 ± 0.3	13.2 ± 0.2	19.2 ± 0.4				
[NiLCl ₂]	11.5 ± 0.7	9.1 ± 0.3	17.2 ± 0.5	11.1 ± 0	15.2 ± 0.9				
[CuLCl ₂]	16.1 ± 0.3	17.8 ± 0.8	20.2 ± 0.3	14.1 ± 0.2	20.5 ± 0.3				
$[ZnLCl_2]$	13.1 ± 0.3	11.1 ± 0.5	14.3 ± 0.6	10.3 ± 0.6	17.8 ± 0.4				
Standard	23.0 ± 0.2	22.0 ± 0.2	32.0 ± 0.3	19.0 ± 0.2	27.0 ± 0.2				
DMSO	—	—	—	—	—				

Positive control (standard), ciprofloxacin, and negative control (DMSO) measured by the halo zone test (unit, mm).

722, 698, 626, 597, 514, 464, 442, 376, 350, 337, 274, 228, 195, 174, and 156 a.m.u., corresponding to various fragments (Figure 3).

Electronic Spectra and Magnetic Data

The electronic spectrum of the Co(II) complex showed three bands at 9,090 cm⁻¹ 16,750 cm⁻¹, and 21,508 cm⁻¹, which correspond^[29] to ${}^{4}T_{1}g(F) \rightarrow {}^{4}T_{2}g(F)$, ${}^{4}T_{1}g(F) \rightarrow {}^{4}A_{2}g(F)$, and ${}^{4}T_{1}g(F) \rightarrow {}^{4}T_{1}g(P)$ transitions, respectively, consistent with the octahedral geometry around the cobalt(II) ion. The magnetic moment value of 4.57 B.M. further supports the electronic data.

The absorption spectrum of Ni(II) complex showed three spin-allowed transitions ${}^{3}A_{2}g(F) \rightarrow {}^{3}T_{1}g(P)$, ${}^{3}A_{2}g(F) \rightarrow {}^{3}T_{1}g(F)$, and ${}^{3}A_{2}g(F) \rightarrow {}^{3}T_{2}g(F)$ appearing at 11,250 cm⁻¹, 13,460 cm⁻¹, and 24,450 cm⁻¹, respectively, characteristic of the octahedral nickel(II) complex.^[30] The geometry has been further confirmed by the observed value of magnetic moment of 3.12 B.M.

A broad band centered at $19,000 \text{ cm}^{-1}$ has been recorded along with a shoulder at $16,120 \text{ cm}^{-1}$ in the electronic spectra

of the Cu(II) complex and may reasonably be assigned to the ${}^{2}B_{1}g \rightarrow {}^{2}Eg$ and ${}^{2}B_{1}g \rightarrow {}^{2}B_{2}g$ transitions, respectively, characteristic of distorted octahedral geometry^[31] around the Cu(II) ion. The magnetic moment value of 1.85 B.M. further compliments the electronic spectral results.

Electrochemical Studies

The electrochemical redox behavior of the Cu(II) complex has been studied with Ag/AgCl as reference electrode in the potential range -1.0 to 1.0V at 0.05 VS⁻¹ scan rate at room temperature using KCl as solid electrolyte. The cyclic voltammogram exhibited one quasireversible redox wave Cu^{II}/Cu^I attributed to one electron transfer process with $E_{pc} = 0.35$ V and $E_{pa} = -0.30$ V, and I_{pa}/I_{pc} ratio 1.4. For this couple, the differences between cathodic and anodic peak potential ΔE_p and formal peak potential $E_{1/2}$ are 50 mV and 0.325V, respectively.

Biological Screening

Antibacterial activity of the compounds was tested in vitro against Escherichia coli, Staphylococcus aureus, Pseudomonas

TABLE 6

Antifungal activity of compounds, with positive control (greseofulvin) and negative control (DMSO), measured by the halo zone test (unit, mm)

	Diameter of zone of inhibition (mm)						
Compounds	СА	AF	TM	PM			
L	15.5 ± 0.4	14.3 ± 1.2	11.1 ± 0.4	10.2 ± 0.2			
[CoLCl ₂]	20.5 ± 0.4	18.3 ± 1.2	16.1 ± 0.4	13.2 ± 0.2			
[NiLCl ₂]	12.2 ± 0.3	11.5 ± 0.3	10.2 ± 1.2	8.9 ± 0.5			
[CuLCl ₂]	24.2 ± 0.3	$20.8 \pm 0 - 4$	17.9 ± 0.5	14.6 ± 0.9			
[ZnLCl ₂]	19.1 ± 0.5	17.5 ± 0.2	14.9 ± 0.7	11.1 ± 0.5			
Standard	30.0 ± 0.2	27.0 ± 0.2	24.0 ± 0.3	20.0 ± 0.5			
DMSO	_	_	_	_			

CA, Candida albicans; AF, Aspergillus fumigates; TM, Trichophyton mentagrophytes;

PM, Penicillium marneffei.

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aeruginosa, Streptococcus pyogenes, and *Klebsiella pneumoniae* bacterial strains by a disc diffusion method.^[32] Ciprofloxacin (30 μ g) was used as positive control, while the disc poured in DMSO was used as negative control. The susceptibility was assessed on the basis of diameter of zone of inhibition against gram-positive and gram-negative strains of bacteria. Inhibition zones were measured and compared with the controls. The bacterial zones of inhibition values are given in Table 5. The results of antibacterial study suggest the maximum inhibition capacity of the copper(II) complex.

Antifungal screening of the compounds was done *in vitro* on *Candida albicans, Aspergillus fumigatus, Penicillium marnef-fei, and Trichophyton mentagrophytes* by using an agar diffusion method. ^[33] The fungal activity of each compound was compared with greseofulvin as standard drug. Inhibition zones were measured and compared with the control. The fungal zones of inhibition values are given in Table 6. Maximum fungal growth inhibition was shown by the copper(II) complex and the minimum by nickel(II) complex.

The reason for the high antimicrobial activity of copper complex can be explained in terms of the effect of copper metal ion on the normal cell process. The complexation reaction reduces the polarity of the metal ion by the partial sharing of metal ion positive charge with donor groups and electron delocalization over the chelate ring.^[34] Thus, the lipophilic character of the central metal atom is enhanced, which results in a higher capability to penetrate the microorganisms through the lipid layer of the cell membrane.

CONCLUSION

A series of novel 16-membered Schiff-base macrocyclic ligands have been synthesized by condensation reaction between 2-methyl acetoacetanilide and 1,8-diaminonaphthalene, and its macrocyclic complexes were prepared by interaction of ligand with metal salts and have been characterized by various spectroscopic techniques. The ligand to metal stoichiometry and the nature of the bonding were ascertained on the basis of elemental analysis, position of molecular ion peaks in the mass spectra, and conductivity data. An octahedral geometry has been assigned for all the complexes on the basis of position of bands in electronic spectra and magnetic moment data, while a slight distortion in octahedral geometry has been observed in the Cu(II) complex on the basis of EPR data. All the macrocyclic complexes showed considerable antimicrobial activity and the relative order has been estimated as Cu(II) > Co(II) > Zn(II) > Ni(II).

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