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Antimicrobial Activity of Azamacrocyclic Complexes of Cu (II), Ni (II), Zn (II) and Ag (I) with their Spectroscopic Approach

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Abstract- Microbial infections are now a day's more common than during the first half of the century. Although, a number of different classes of antibacterial and antifungal agents have been discovered during last two decades the use is limited due to development of microbial resistance. This situation highlights the need for development of novel, potent, and safe antimicrobial agents. Hence the synthesized aza-macrocyclic metal complexes by in situ one pot template condensation reactions were further confirmed by thermal analysis, UV–vis spectroscopy and molar conductivity measurements. The antimicrobial activity of the complexes has been screened in vitro against bacteria and fungi to access their inhibiting potential. The bioassays indicated that most of the synthesized metal complexes showed potential antibacterial and anti-fungal activity.

Index Terms- Antimicrobial assay, Azamacrocyclic complexes, Thermal studies

I. INTRODUCTION

There is an increasing demand for the development of compounds having improved properties and which can be used against several different diseases, such as the treatment of an infection caused by a microorganism. Concerning bacterial diseases, antibiotic research at the industrial level has been focused on the identification of more refined variants of already existing drugs. [1]. Despite the rapidity with which new chemotherapeutic agents are introduced, bacteria have shown a remarkable ability to develop resistance to these agents and the search for new drugs, such as metal complexes [2–7], is in progress.

There is also a pressing need for new antifungal agents because of the fast development of resistance of microorganisms to the state-of-the-art drugs currently used to treat different fungal infections. For this reason, the elaboration of new types of antifungal agents is presently a very real task. A promising field for this search is metal-based drugs [8–11]. Metal-based drugs have a different mode of action compared to the commonly used commercial polyene and azole antifungal drugs. Treatment of fungal cells with, for example, Cu (II) and Ag (I) complexes [2] resulted in a reduced amount of ergosterol in the cell membrane and a subsequent increase in its permeability.

It is now established that the nature of the metal ion, the type of the ligand and the topology of the complex moiety [12] are determinantal for the pharmacological efficacy [13-15] and medicinal relevance [16] of the metal complexes. Transition metal complexes of several functionalized or derivatized dicarboxylic acids have been successfully exploited as new generation metallo-pharmaceutical compounds [17-18].

An extensive literature has developed in recent years in the field of chelate compounds with special reference to their antimicrobial activities. Metal coordination complexes have been widely studied for their antimicrobial [19]. It is well known that various organic ligands possess strong antibacterial, herbicidal, insecticidal and fungicidal properties. It has also been reported that the activity of biometals is very often altered through the formation of chelates with different bioligands. It is suggested that the compounds having antimicrobial activity may act either by killing the microbe or by inhibiting multiplicity of the microbe or blocking their active site [20].

The family of complexes with aza-macrocyclic ligands has remained a focus of scientific attention for many decades [21]. In situ one pot template condensation reactions lie at the heart of the macrocyclic chemistry [22]. There is continued interest in synthesizing macrocyclic complexes because of their potential applications in fundamental and applied sciences [23, 24]. Synthetic macrocyclic complexes mimic some naturally occurring macrocycles because of their resemblance with many natural macrocycles like metalloproteins, porphyrins and cobalamine [25–27]. So biologically active macrocyclic complexes are used in the identification of diseased and normal tissues [28]. Transition metal macrocyclic complexes have received a great attention because of their biological activities, including antiviral, anticarcinogenic [27], antifertile [29], antibacterial and antifungal [30, 31].

Among the new substances exhibiting good antimicrobial activity, a large number of species are bearing either a biocation (Co (II), Ni(II), Cu(II), Fe(III), Cr(III), Mn(III) or Zn(II)) [32] or a metallic ion with a proven antimicrobial activity (Cd(II), Pd(II), Pt(II), Ag(I), Au (I)) [33-35].

Encouraged by these reports the present study for antibacterial and antifungal activities has been undertaken for the synthesized compound [36] with more spectroscopic techniques.

II. Experimental Section

Chemistry

Materials and Methods

All the reagents used in the preparation of macrocyclic Ligands and their metal complexes were of reagent grade(Merck).The solvents used for the synthesis of macrocyclic ligands and metal complexes were distilled before use. All other chemicals were of AR grade and used without further purification. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyser. The FT-IR spectra were recorded using KBr discs on FT-IR Jasco 4100 infrared spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker DRX 400 spectrometer at 400 MHz with TMS as the internal standard. The magnetic moments were measured out using gouy balance. Purity of the compound checked by TLC.

Chemistry

Preparation of the Macrocyclic ligand and its metal complexes (a-d)

The macrocyclic ligand and its metal complexes (**a-d)** were synthesized by the template condensation of 2, 3, 5, 6-tetra methyl, 1, 4-diaminobenzene in MeOH, a solution of 36% formaldehyde in MeOH was added. After stirring for 10 min a solution of 1, 4-diaminobutane in MeOH was added. Finally a solution of metallic salt and 2, 4-pentanedione in MeOH was added and the resulting mixture was refluxed for ca. 7 hrs. The brown solid product was filtered off, washed with MeOH and dried over fused $CaCl_2$ in desiccators. The product was recrystallized from hot MeOH [36].

Pharmocology

Materials and methods for the antimicrobial activity

Streptomycin was used as positive controls against bacteria. ketoconazole (Himedia, Mumbai) were used as positive controls against fungi.

Tested microbes

The following gram positive bacteria were used for the experiments; *staphylococcus aureus*(*MTCC 7443), Staphylococcus aureus (MRSA) (MTCC 84), Enterobacter aerogenes(MTCC 111), Micrococcus luteus(MTCC 1538).* The gram negative bacteria included *Klebsiella pneumoniae(MTCC 109), Salmonella typhimurium(MTCC 2488), Salmonella paratyphi-B(MTCC 733), Proteus vulgaris(MTCC 321).* In addition, fungi *Candida albicans*(*MTCC 227*), *Botyritis cinerea*(*MTCC 2880*), *Candida krusei*(*MTCC 231*), *Malassesia pachydermatis*, were also used for the experiments. All cultures were obtained from the Department of Microbiology, Manasagangotri, Mysore.

Preparation of inoculums

Bacterial inoculums were prepared by growing cells in Mueller Hinton Broth (MHA) (Himedia) for 24 h at 37^{o}C. These cell suspensions were diluted with sterile MHB to provide initial cell counts of about 104 CFU/ml. The filamentous fungi were grown on sabouraud dextrose agar (SDA) slants at 28^{o}C for 10 days and the spores were collected using sterile doubled distilled water and homogenized.

Disc diffusion assay

Antibacterial activity was carried out using a disc diffusion method [37] Petri plates were prepared with 20 ml of sterile Mueller Hinton Agar (MHA) (Himedia, Mumbai). The test cultures were swabbed on the top of the solidified media and allowed to dry for 10 mins. The tests were conducted at 1000 µg/disc. The loaded discs were placed on the surface of the medium and left for 30 min at room temperature for compound diffusion. Negative control was prepared using respective solvent. Streptomycin (10 µg/disc) was used as positive control. The plates were incubated for 24 h at 37^{o}C for bacteria and 48 h at 27^{o}C for fungi. Zone of inhibition was recorded in millimeters and the experiment was repeated twice.

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration studies of synthesized compounds were performed according to the standard reference method for bacteria [38] and filamentous fungi [39]. Required concentrations (1000 µg/ml, 500µg/ml, 250 µg/ml, 125 µg/ml, 62.5 µg/ml, 31.25 µg/ml and 15.62 µg/ml) of the compound was dissolved in DMSO (2%), and diluted to give serial two-fold dilutions that were added to each medium in 96 well plates. An inoculum of 100 ml from each well was inoculated. The anti-fungal agent's ketoconazole, fluconazole for fungi and streptomycin, ciprofloxacin for bacteria were included in the assays as positive controls. For fungi, the plates were incubated for 48-72 h at 28^{o}C and for bacteria the plates were incubated for 24 h at 37^{o}C. The MIC for fungi was defined as the lowest extract concentration, showing no visible fungal growth after incubation time. 5 ml of tested broth was placed on the sterile MHA plates for bacteria and incubated at respective temperatures. The MIC for bacteria was determined as the lowest concentration of the compound inhibiting the visual growth of the test cultures on the agar plate.

III. Result and Discussion

Azamacrocyclic complexes of Cu (II), Ni (II), Zn (II) and Ag (I) has been prepared and characterized by elemental analysis, IR and magnetic moment. The synthesized complex was also subjected for Xanthine Oxidase and Antioxidant activity as previously reported by our group [36]. Further in this paper we have reported antifungal and antibacterial activity of the synthesized compounds with more spectroscopic approach like electronic spectra and thermal analysis.

Molar conductivity of metal chelates

The metal complexes were dissolved in DMSO and molar conductivities of 10^{-3} M of their solutions at room temperature were measured. The complexes showed molar conductance (12–18 Ω^{-1} cm^2 mol^{-1}). It was concluded from the results that complexes were non-electrolytic in nature **[**40]. The molar conductance value suggested that the anions were inside the coordination sphere and bonded to the metal ion, therefore, these complexes may be formulated as [MLX_2].

Mass spectral studies

The FAB mass spectra of Cu (II), Ni (II), Zn (II) and Ag (I) macrocyclic complexes have been recorded. All the spectra

exhibit parent peaks due to molecular ions (M^+). The proposed molecular formula of these complexes was confirmed by comparing their molecular formula weights with m/z values. The molecular ion (M^+) peaks obtained for various complexes are as follows: (1) m/z = 1203(Cu (II) complex), (2) m/z = 951(Ni (II) complex), (3) m/z = 964 (Zn (II) complex) (4) m/z = 1155 (Ag (II) complex). This data is in good agreement with the proposed molecular formula for these complexes i.e. [M ($C_{40}H_{72}N_{10}$) X]. Where M = Cu (II), Ni (II), Zn (II) and Ag (I), and X = SO_4^{2-}, Cl^-, NO_3^-. This confirms the formation of the macrocyclic frame. In addition to the peaks due to the molecular ions, the spectra exhibit peaks assignable to various fragments arising from the thermal cleavage of the complexes. The peak intensity gives an idea of the stability of the fragments.

Magnetic susceptibility and electronic spectral studies

The electronic absorption spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The electronic spectral measurements were used for assigning the stereochemistry of metal ions in the complexes based on the positions and number of d–d transition peaks. The electronic absorption spectra of Cu (II), Ni (II) Zn (II) and Ag (I) complexes in DMSO were recorded at room temperature and the characteristic electronic absorption bands are listed in **Table 1**.

Table 1: Electronic absorption bands and magnetic values of Cu (II), Ni (II) Zn (II) and Ag (I) complexes

complexes	Electronic absorption bands and their assignments (nm)			Magnetic moment μ_{eff} BM
	π-π^*	n-π^*	d-d transition	
a	304	415	675	1.83
b	309	402	610	3.16
c	301	428	----	----
d	310	412	----	----

Copper (II) complex

The electronic spectrum of the mononuclear copper(II) complex recorded at room temperature, in DMSO solution, shows broad band absorption in the range 680-670 nm, 657-645 nm and 518-510 nm, which may be assign to $^2B_{1g} \rightarrow {}^2A_{1g}$, ($dx^2$-$y^2 \rightarrow dz^2$)($\nu_1$), $^2B_{1g} \rightarrow {}^2B_{2g}$, ($dx^2$- $y^2 \rightarrow$ dzy) (ν_2), and $^2B_{1g} \rightarrow {}^2E_g$, ($dx^2$- $y^2 \rightarrow$ dzy, dyz)(ν_3) transition and it is in conformity with octahedral geometry **[**41**]**. The broadness of the band which are similar in energy give rise to only one broad absorption band, and the broadness of the band is due to dynamic Jahn-Teller distortion. These data suggest that the Cu (II) complex have distorted octahedral geometry [42].

An indication of the most probable geometric configuration of the synthesized metal complexes is their magnetic moment values. So, it has been further confirmed by the magnetic moment measurements, room temperature values lie at 1.83 B.M corresponding to the presence of one unpaired electron and it supports a distorted octahedral geometry **[**43**]**.

Nickel (II) complex

The magnetic moment of the Ni (II) complex at room temperature lie at 3.16 B.M. These values are in tune with high spin configuration and show the presence of an octahedral environment around the Ni (II) ion. The electronic spectra of the Ni(II) complexes exhibit three absorption bands, in the range of 615-605 nm, 430-424 nm and 419-405 nm these bands may be assign to three spin allowed transition: $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)(\upsilon_1)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)(\upsilon_2)$, and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)(\upsilon_3)$, respectively **[**44**]**. This value is indicative to the octahedral geometry.

Zinc (II) and Silver (I) complex

The Zn (II) and Silver (I) complexes are diamagnetic. Due to the d^{10} electronic configuration electronic spectra of complexes did not show any d–d transition, but only charge transfer absorption is observed at 385-380 nm. By analogy with those described for the complexes containing N_4 donor of macrocyclic ligand and according to the empirical formula and molar conductance of this complex, an octahedral geometry is proposed for this complexes [45].

Thermal studies

The TG and DTA studies of the complexes have been recorded in the nitrogen atmosphere at the constant heating rate of 10°C/minute. Thermal study on the complexes in controlled nitrogen atmosphere was carried out to understand the stages and temperature range of decomposition. The most probable decomposition pattern of the complexes is proposed on the basis of the careful examination of TG and DTA curves. The thermo analytical data are summarized in **Table 2** and **figure 1**. The TG of the complexes shows that they are thermally quite stable but to varying degree. The complexes show gradual loss in weight due to decomposition by fragmentation with increasing temperature. The thermogram of TGA of macrocyclic complexes exhibits decomposition between 230°C and 480°C which may be due to the removal of the coordinated chloride, sulphate, nitrate ions or organic part of the compounds [46]. Since the decomposition started above 230°C, the presence of any solvent/water molecules may be ruled out. Further horizontal constant curve may be due to the presence of metal oxides residue in the remaining part.

The TG curve and DTG peak temperature of all these complexes indicate that the decomposition of the complexes takes place in two identical stages. The weight loss in the range 230-370°C in TG curves of complexes is termed the first stage of thermal degradation. In this case, the present weight loss is in the range 57.10-70.15%, which may be attributed to the decomposition of organic moiety. The second step decomposition occurs in the range 370-485°C, which gave the loss of 13.10-31.8% be attributed to the decomposition of inorganic ligand bonding with the metal ion. The experimental values were in full agreement with the percent weight calculated on the basis of stiochiometry proposed for the complexes. The complexes are present in the form of its respective metal oxides above 480 °C [47, 48].

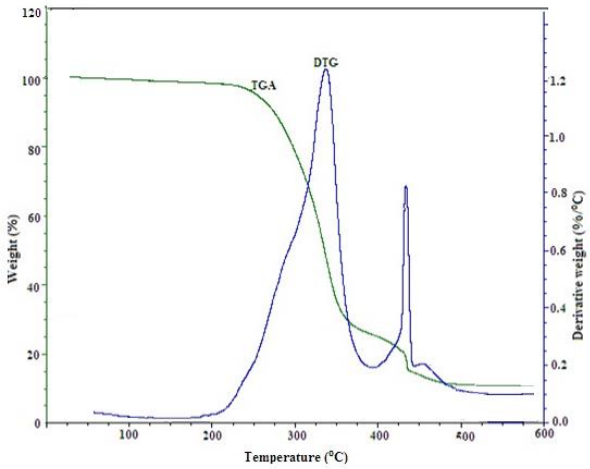

Figure 1: Stepwise Thermal Degradation curve for complex c.

Table 2: Stepwise Thermal Degradation Data obtained from TGA Curves and their Composition.

Complex	Process	Temp. range (°C)	Degradation Products	% Weight loss		No. of Moles	% Residue		Nature
				Calcd	Expt		Calcd	Expt	
a	I II	235-375 380-460	ligand SO_4	57.50 31.90	56.60 30.10	1 4	13.22	12.10	CuO
b	I II	230-370 370-440	Ligand Cl	72.81 14.92	70.08 13.10	1 4	15.71	11.85	NiO
c	I II	240-365 370-440	Ligand Cl	71.8 14.7	70.05 14.2	1 4	16.87	15.54	ZnO
d	I II	255 370 385-480	Ligand NO_3	59.87 21.43	57.25 20.10	1 4	21.43	20.50	AgO

Pharmocology

The antimicrobial activities of synthesized complex compounds were screened against eight bacteria and four fungi using in vitro disc diffusion method. The results revealed that most of the synthesized complex compounds exhibited antimicrobial activities against Staphylococcus aureus, Staphylococcus aureus (MRSA), Enterobacter aerogenes, Micrococcus luteus, Klebsiella pneumoniae, Salmonella typhimurium, Salmonella paratyphi-B, Proteus vulgaris, Candida albicans, Botyritis cinerea, Malassesia pachydermatis, and Candida krusei organisms. The results are summarized in Table **3** and **4**.

Compounds **a, c** and **d** showed good activity more than standard drug against S. aureus. Compound **d** with silver has metal ion showed potent activity against both Gram-positive and Gram-negative bacteria among all synthesized compounds compared with the standard. Compound **a** with copper metal shown good activity against S. aureus, M. luteus, P. vulgaris and S. typhimurium. Compound **c** with nickel metal has shown good activity against S. aureus, E. erogenes, M. luteus, P. vulgaris and S. typhimurium whereas compound **b** has shown poor activity against both Gram-positive and Gram-negative bacteria.

Compound **d** showed significant antifungal activity against all the tested fungi compared with standard drug. Compound **a** has shown potent activity against B. cinerea C.

Krusei, M. pachydermatis. Similarly compound **c** showed more activity against C. albicans and C. krusei compared to standard drug. In contrast, compounds **b** with exhibited lowest activity.

Further for proficient molecules MIC values were determined by broth dilution method against selected strains and the MIC values of active compounds (**a-d)** against bacteria and fungi are given in Table **5** and **6**. Significant MIC values were observed against Gram positive and Gram negative bacteria. In particular, it is noticeable that compound **a** and **d** has exhibited good MIC result against tested bacteria and fungi. Finally we can conclude that compound **d** with silver has metal ion showed potent activity against both Gram-positive and Gram-negative bacteria among all synthesized compounds compared with the standard.

Table 3: In-vitro antibacterial activity of complex compounds (a-d)

Compounds	Zone of inhibition in mm							
	Gram positive bacteria				Gram negative bacteria			
	S. aureus	S. aureus (MRSA)	E. erogenes	M. luteus	K. pneumonia	P. vulgaris	S. typhimurium	S. Paratyphi-B
a	22	17	18	20	16	19	23	12
b	11	9	9	10	11	12	11	10
c	21	11	20	21	15	17	24	13
d	23	20	25	21	22	17	13	24
Streptomycin	24	21	26	23	23	19	25	25

Table 4: In-vitro antifungal activity of complex compounds (a-d)

	Zone of inhibition in mm			
Compounds	B. cinerea	C. albicans	C. krusei	M. pachydermatis
a	12	14	16	22
b	9	11	8	9
c	11	22	15	13
d	13	22	17	21
Ketoconazole	14	23	18	24

Table 5: MIC (µg /ml) of complex compounds (a-d) against tested bacteria

Compounds	Minimum inhibitory concentration (µg / ml)							
	Gram positive bacteria				Gram negative bacteria			
	S. aureus	S. aureus (MRSA)	E. aerogens	M. luteus	K. pneumonia	P. vulgaris	S. typhimurium	S. Paratyphi-B
a	15.62	125	62.5	62.5	550	125	31.25	500
b	31.25	62.5	250	31.25	250	62.5	31.25	250
c	31.25	250	500	250	250	250	125	250
d	15.62	31.25	62.5	15.62	125	31.25	62.5	500
Streptomycin	6.25	>100	25	6.25	6.25	ni	30	6.25
Ciprofloxacin	<0.78	>100	>100	<0.78	<0.78	6.25	>100	<0.78

ni = no inhibition

Table 6: MIC (µg /ml) of complex compounds (a-d) against tested fungi

Compounds	Minimum inhibitory concentration (µg / ml)			
	B. cinerea	C. albicans	C. krusei	M. pachydermatis
a	15.62	62.5	250	125
b	250	125	125	125
c	62.5	125	250	250
d	15.62	15.62	62.5	125
Fluconazole	ni	>100	12.5	12.5
Ketoconazole	25	25	15	15

ni = no inhibition.

IV. Conclusion

The synthesized complexes have been characterized by utilizing the various physico-chemical methods. The molar conductance of all the complexes in DMSO shows that they are non-electrolytes. Non-electrolytic nature of the studied complexes showing the anions is coordinated to the central metal ion. The magnetic and electronic spectral studies support an octahedral geometry for all the metal complexes. Thermal studies suggested that metal complexes show two or three steps thermal degradation. Mass spectrum of the complex confirms the proposed structure. The proposed geometries of the studied complexes are given in Figure **2**.

The antimicrobial activities of synthesized complex compounds were screened against eight bacteria and four fungi using in vitro disc diffusion method. The results revealed that most of the synthesized complex compounds exhibited antimicrobial activities. Compounds **a, c** and **d** showed good activity more than standard drug against S. aureus. Compound **d** with silver has metal ion showed potent activity against both Gram-positive and Gram-negative bacteria among all synthesized compounds compared with the standard.

From the present study, we infer that, aza macrocyclic metal complexes could lead to the development of newer therapeutics as antimicrobial agent.

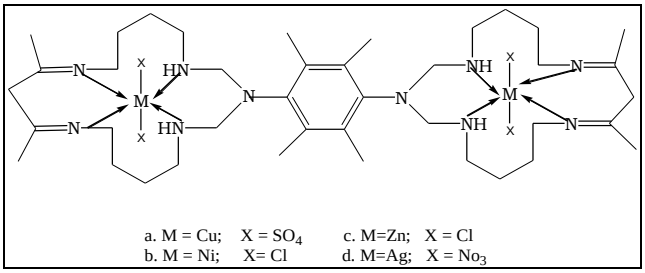

Figure 2: Structure of complex based on spectroscopic analysis.

Conflict Of Interest

The authors declare that they have no conflicts of interest with respect to the content of the manuscript.

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