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Mixed ligand complexes of Copper(II), Nickel(II) and Zinc(II) with salicylaldehyde tyrosine Schiff base and dimethylaminopyridine/ dimethylaminopyridine and Phenanthroline - Synthesis, Spectral characterization and Biological Studies.

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ABSTRACT

Mixed ligand complexes of Cu(II), Ni(II) and Zn(II) with salicylaldehyde-tyrosine Schiff base either in the presence of one or two dimethylaminopyridine (dmap) ligands or dimethylaminopyridine along with phenanthroline (phen) as coligands were synthesized and characterized by elemental and thermal analysis, IR, UV-Visible, NMR, ESR spectral studies and magnetic susceptibility studies. Photoluminescence studies indicated that the complexes exhibited luminescence. The complexes were subjected to anti microbial studies against the bacteria, *Staphylo cococcus aureus, Bacillus subtilis* and *E.Coli* and against the fungi, *Candida albicans*, *Trichoderma viride* and *Aspergillus niger*. MTT assay of cytotoxicity of the complexes against *HeLa* (Human cervical cell line) and *Vero* cell line(Normal kidney cells) indicated that the complexes exhibited excellent anticancer activity with very low IC_{50} values. DNA cleavage studies of copper complex showed groove binding of the complex to DNA.

Keywords: salicylaldehye-tyrosine Schiff base, dimethyl aminopyridine, phenanthroline, antimicrobial, anticancer, DNA cleavage studies.

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INTRODUCTION

Complexes of Schiff bases are the most studied chelating systems in coordination chemistry [1]. After the great success achieved with Cis-platin and other platinum complexes as anticancer drugs, extensive research activity followed on similar work with several transition metal complexes. Many complexes of Nickel(II) [2], copper(II) [3], zinc(II) [4], and manganese(II) [5] have been reported to possess significant anticancer properties. It is also well known that several established organic drugs exhibit enhanced activity when coordinated to metal [6]. First row transition metal complexes such as those of copper(II) and Zinc(II) are well known for their significance in biological systems and use as pharmacological agents. Due to the biological relevance, a large number of copper(II) complexes have been synthesized and are still being attempted and explored for the biological activities [7-9]. L-tyrosine-chlorambucil analogs are used as anticancer drugs for treatment of breast cancer [10]. Several complexes of 1,10-phenanthroline have significant anti-tumor, anti candidal, and anti microbial activities [11–13]. Catalytic activity of 4-(N,N-dimethylamino) pyridine(DMAP) has been well explored in organic synthesis[14] However, DMAP as a ligand has received less attention and there are only a very few reports on complexes of DMAP [15-17]. Hence we attempted to synthesize complexes of Cu(II), Ni(II) and Zn(II) with salicylaldehyde -tyrosine Schiff base (saltyrH_2) either in the presence of one or two dimethylaminopyridine (dmap) ligands or dimethylaminopyridine along with phenanthroline (phen) as coligands.

EXPERIMENTAL

The chemicals employed for the synthesis are of Analar grade and used without further purification. Copper sulphate, Nickel sulphate, Zinc sulphate, tyrosine, dimethylaminopyridine, 1,10-Phenanthroline and salicylaldehyde are pure chemicals from Merck and the genomic DNA was obtained from sigma Aldrich, Mumbai. Tyrosine(0.01m) is dissolved in an aqueous solution(20 ml) containing sodium hydroxide(0.01m) and methanolic solution of salicylaldehyde(0.01m) is added and the reaction mixture is refluxed for two hours at room temperature with constant stirring. To this, an aqueous solution of metal salts(Copper sulphate /Nickel sulphate/Zinc sulphate) (0.01m) and the co ligand DMAP(0.01m /0.02m) in 10 ml of methanol are simultaneously added and refluxed for three hours when the respective solids isolated out . Similarly for the phenanthroline complexes, after the addition of the metal salt, 0.01m of DMAP along with phenanthroline(0.01m) are added and refluxed for three hours. Green coloured copper and nickel complexes and white coloured zinc complexes that separated out from the mixture were washed with methanol and filtered several times ,then air dried. The metal content in the complexes was estimated by ICP-OES (Inductively coupled plasma - optical emission Spectroscopy). The nitrogen and sulphur content were estimated by Kjelhdhal's method and barium sulphate method respectively. TGA, thermogravimetric analysis were recorded in NETZSCH STA 449F3 thermal analyzer with a heating rate of 10^{o}/min. Magnetic susceptibility studies were carried out using Vibrating sample magnetometer Lakeshore VSM 7410. Photoluminescence spectra of complexes were recorded using a CARY ECLIPSE FLUORESCENCE SPECTROPHOTOMETER. UV-Visible absorption spectra of the complexes in DMSO were recorded using a SHIMADZU UV 1600 model spectrometer. The IR spectra of the complexes were recorded as KBr disc using SCHIMADZU Infra-red Spectrometer. The NMR spectra of the zinc complexes were recorded on a JOEL MODEL GSX (400 MHZ frequency). The EPR spectra of the copper and nickel complexes were recorded using JES-FA200 electron spin resonance spectrometer in the region from 1000-8000 gauss. The antibacterial and antifungal activities of the complexes were studied by agar disc diffusion method. The anti-cancer activities were studied by the MTT assay. The DNA cleavage studies was studied using genomic DNA by UV spectrophotometric method.

RESULTS AND DISCUSSION

The copper and nickel complexes were green in colour, whereas zinc complexes were white in colour. All the complexes were powdery and stable at room temperature. The electrical molar conductance of the complexes at a 10^{-3} M concentration were found to be 3.8, 3.1, 4.0, 4.2, 4.5, 5.2, 3.5, 4.7 and 5.3 Ohm^{-1} cm^2 mol^{-1}, indicating non-electrolytic nature. The elemental and thermal analysis data on the complexes are given in Table 1. The experimental values agree well with the theoretical values (given in parenthesis) confirming the proposed composition. The decomposition occurs in two or three steps, in which first step corresponds to rapid decomposition leading to the loss of coordinated water molecules between 70-300^{o}C. This continues slowly to give the corresponding metal oxides at around 600^{o}C and the values are consistent

with the theoretical data. The Electronic spectral data on the complexes are given in Table 2. The Copper complexes show a high intense band around 360 and 390 nm corresponding to $\pi \rightarrow \pi^*$ transfer of aromatic rings and n-π^* electronic transition of imine [18]. The Cu(II) complexes also exhibit a low intense band in the region 630-649 nm corresponding to $^2E_g \rightarrow {}^2T_{2g}$ d-d transition which suggests octahedral geometry for Cu(II) complexes and the broadness of the band may be due to jahn teller distortion[19]. The Nickel(II) complexes show pure ligand transition around 360 and 393-417nm and two d-d transitions. The first one in the range 430nm are high intense and so perhaps mixed with ligand transitions and the second one around 480nm [20]. These may be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$respectively. The Zn(II) complexes show two bands around 360 and 413 nm due to ligand transition and these complexes do not show any band corresponding to d-d transition due to the d^{10} configuration of Zn(II)ion. The IR spectral data are given in Table 3. The presence of bands in the region 3604-3850cm^{-1} in the complexes confirms the presence of coordinated water molecules which are absent in the phenanthroline substituted complexes. The presence of broad band in the region 3348-3474 cm^{-1} is characteristic of hydroxyl group in tyrosine. The absence of band in the region 1700-1800 cm^{-1} and the presence of intense band in the region 1524-1537cm^{-1} ($U_{C=N}$) confirms the formation of Schiff base in the complexes. The bands in the range 1620-1630cm^{-1} and 1365-1385cm^{-1} are due to $U_{COO(asy)}$ and $U_{COO(sym)}$ of the tyrosine residue [21]. The band in the region1446-1452cm^{-1} corresponds to aromatic ring stretching vibration. The presence of band in the region 1224-1285cm^{-1} due to U_{C-O} stretching confirms the presence of phenolic C-O. The presence of band in the region 812-879cm^{-1} indicates the coordination of aminopyridine group. The appearance of bands in the region 531-551cm^{-1} and 436-461cm^{-1} confirms M-N and M-O coordination in the complexes[19]. The Electron spin resonance spectra of the copper complexes show one intense broad signal at room temperature without any hyperfine splitting. The g values for the complexes are 2.081, 2.076 and 2.099 for [Cu(saltyr)(dmap)$(H_2O)_2$] [Cu(saltyr)$(dmap)_2(H_2O)$]and [Cu(saltyr)(dmap)(phen)] respectively which is higher than free electron value charateristic of distorted octahedral geometry with spin orbit coupling [22]. The Nickel complex, [Ni(saltyr)(dmap)(phen)] gives a broad single signal corresponding to g value of 2.0036 while the other complexes of nickel, [Ni(saltyr)(dmap)$(H_2O)_2$] and[Ni(saltyr)$(dmap)_2(H_2O)$] show split signal with little variation at g values 1.998, and 2.214 respectively may be due to lower symmetry. The ^1H NMR spectra of the Zinc complexes, [Zn(saltyr)(dmap)$(H_2O)_2$] [Zn(saltyr)$(dmap)_2(H_2O)$] and [Zn(saltyr)(dmap)(phen)] are furnished in Table 4. All the three complexes show OH proton of tyrosine around 9.2 ppm. The aromatic protons of the tyrosine ring appear in the region 7.54 – 8.17 ppm and are present in all the complexes. The Phenanthroline complex alone, [Zn(saltyr)(dmap)(phen)] shows aromatic protons of the phenanthroline ring at 8.821, 8.722 and 8.142 ppm. The aromatic protons of the salicylaldehyde portion of the schiff base appear in the region 6.8 – 7.62 ppm. The aromatic protons of the dimethylamino pyridine appears in the range 6.66 – 6.8 ppm. The imine CH proton appears in the range 6.28-6.55 ppm. The CH and CH_2 protons of the aminoacid tyrosine appear in the range 6.2 to 6.4 and around 3.8 respectively. The methyl protons of dimethylaminopyridine group of the DMAP ligand appear around 2.9 in all the complexes and the intensity ratios agree with presence of two DMAP ligands in [Zn(saltyr)$(dmap)_2(H_2O)$] and one DMAP ligand in [Zn(saltyr)(dmap)$(H_2O)_2$] and [Zn(saltyr)(dmap)(phen)]. The Copper and Nickel complexes show increase in mass in the presence of magnetic field while the zinc complexes showed a decrease in mass. This indicates Zinc complexes are diamagnetic in nature. The VSM plots (magnetic moment in emu Vs field in gauss) of Copper and nickel complexes show hysteresis loop indicating ferromagnetism. The copper and nickel complexes containing dimethylamino pyridine and phenanthroline ligands show excitation wavelength in the range 390-400 nm and the fluorescence spectra of the copper and nickel complexes thus obtained, showed high intense emission at 543nm and low intense signal around 420, 446, 460, 485 and 528nm. The zinc complexes do not show any emission peak, when excited at 400nm. However [Zn(saltyr)(dmap)$(H_2O)_2$], [Zn(saltyr)$(dmap)_2.H_2O$] and [Zn(saltyr)(dmap)(phen)] complexes show fluorescence when excited with 450, 475, and 410nm respectively. Zinc complexes[Zn(saltyr)(dmap)$(H_2O)_2$], and [Zn(saltyr)$(dmap)_2.H_2O$], show two emission peaks around 485 and 527 nm, while the phenanthroline complex clearly shows six emmision peaks at 421, 440, 460, 487.5, 533.3 and 543.97nm.

Table 1: Elemental and thermal analysis data

Complexes	%N (theo) exp	% Metal (theo) exp	TGA Data % Cu/Ni/ZnO (theo) exp
[Cu(saltyr)(dmap)$(H_2O)_2$]	(8.3)8.0	(12.6)12.1	(15.7) 16.4
[Cu(saltyr)$(dmap)_2(H_2O)$]	(11.3)10.8	(10.4)9.8	(13.1) 12.1

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[Cu(saltyr)(dmap)(phen)]	(10.8)10.1	(9.7)9.6	(12.3) 13.3
[Ni(saltyr)(dmap)(H_2O)$_2$]	(8.4)7.9	(11.8)11.0	(15.0) 14.9
[Ni(saltyr)(dmap)$_2$(H_2O)]	(11.6)11.3	(9.7)9.1	(12.4)12.1
[Ni(saltyr)(dmap)(phen)]	(10.9)10.3	(9.1)8.3	(11.6) 12.5
[Zn(saltyr)(dmap)(H_2O)$_2$]	(8.3)8.1	(12.9)12.2	(16.1) 15.8
[Zn(saltyr)(dmap)$_2$(H_2O)]	(11.5)11.1	(10.6)10.0	(13.3) 12.0
[Zn(saltyr)(dmap)(phen)]	(10.8)10.3	(10.0)9.1	(12.5) 12.3

Table 2: UV-Visible spectral data

Complexes	Ligand transfer transition	d-d transitions
[Cu(saltyr)(dmap)(H_2O)$_2$]	363,393	630
[Cu(saltyr)(dmap)$_2$(H_2O)]	362,397	633
[Cu(saltyr)(dmap)(phen)]	364, 391	649
[Ni(saltyr)(dmap)(H_2O)$_2$]	361, 414	430, 481
[Ni(saltyr)(dmap)$_2$(H_2O)]	363, 417	433, 482
[Ni(saltyr)(dmap)(phen)]	361, 393	428, 480
[Zn(saltyr)(dmap)(H_2O)$_2$]	362,413	-
[Zn(saltyr)(dmap)$_2$(H_2O)]	360,414	-
[Zn(saltyr)(dmap)(phen)]	365, 412	-

Table 3: IR spectral data on the complexes

Complexes	υ_{O-H} H_2O	υ_{O-H} Tyrosine	υ_{COO} (asy)	$\upsilon_{C=N}$	$\upsilon_{COO(sym)}$	υ_{C-O} (phenolic)	υ_{M-N}	υ_{M-O}
[Cu(saltyr)(dmap)(H_2O)$_2$]	3743 3847	3436	1624	1529	1385	1242	542	436
[Cu(saltyr)(dmap)$_2$(H_2O)]	3615 3741 3851	3431	1627	1524	1373	1231	534	459
[Cu(saltyr)(dmap)(phen)]	-	3431	1623	1530	1376	1285	551	460
[Ni(saltyr)(dmap)(H_2O)$_2$]	3627 3739 3850	3348	1629	1531	1372	1224	536	450
[Ni(saltyr)(dmap)$_2$(H_2O)]	3604 3741 3847	3383	1620	1537	1373	1227	531	441
[Ni(saltyr)(dmap)(phen)]	-	3387	1625	1527	1365	1242	534	449
[Zn(saltyr)(dmap)(H_2O)$_2$]	3738 3845	3336	1624	1534	1383	1244	537	448
[Zn(saltyr)(dmap)$_2$(H_2O)]	3737 3827	3474	1623	1529	1377	1230	527	461
[Zn(saltyr)(dmap)(phen)]	-	3379	1630	1533	1371	1245	532	452

Table 4: NMR spectral data on the complexes

Complexes	OH (tyr)	aromatic protons (phen)	aromatic protons (tyr)	aromatic protons (sal)	Aromatic protons (dmap)	CH (imine)	CH amino acid	CH_2 amino acid	CH_3 (dmap)
[Zn(saltyr)(dmap)(H_2O)$_2$]	9.185	-	8.092 7.537	7.115 6.796 6.781	6.761 6.746 6.682	6.551	6.364	3.75	2.9
[Zn(saltyr)(dmap)$_2$.H_2O]	9.198	-	8.168	7.620	6.788	6.519	6.321	3.8	

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				7.13 7.115 7.1	6.773 6.738 6.721 6.685 6.673	6.502	(t)		2.95
[Zn(sal-yr)(dmap)(phen)]	9.354	8.821 8.722 8.142	7.900 7.809	7.023 6.911	6.800 6.667	6.274	6.201	3.892	2.991

ANTIBACTERIAL STUDIES

The Complexes were screened for antibacterial activity against three different bacteria namely *Staphylococcus aureus, Bacillus subtilis & E.Coli* and compared against standard ampicillin by the Agar disc diffusion method[23] and the data are given in Table 5. As the concentration increases, the diameter of the inhibitory zone also increases, indicating that the complexes are active. The Table clearly shows that all the complexes are active even at lower concentration. copper complexes follows a certain trend that, when the substituents changed from one dmap ligand to two dmap and then to phenanthroline, the activity increases. All the nickel complexes show only very moderate activity against all bacteria, whereas Zinc complexes, [Zn(saltyr)(dmap)$_2$(H_2O)] shows highest activity for all the bacteria, compared to other two analogues.

Table 5: Antibacterial studies

Complexes	Bacteria	Inhibition Zone(mm) Concentration(µg/ml)			Standard (1mg/ml)
		1000	750	500	
[Cu(saltyr)(dmap)(H_2O)$_2$]	*Staphylococcus aureus*	9	8	7	28
	Bacillus subtilis	7	6	5	15
	E. coli	12	11	10	20
[Cu(saltyr)(dmap)$_2$(H_2O)]	*Staphylococcus aureus*	9	8	7	21
	Bacillus subtilis	7	6	5	12
	E. coli	15	11	10	21
[Cu(saltyr)(dmap)(phen)]	*Staphylococcus aureus*	20	19	16	18
	Bacillus subtilis	19	16	15	17
	E. coli	20	19	18	20
[Ni(saltyr)(dmap)(H_2O)$_2$]	*Staphylococcus aureus*	8	7	6	22
	Bacillus subtilis	8	7	8	18
	E. coli	13	8	8	23
[Ni(saltyr)(dmap)$_2$(H_2O)]	*Staphylococcus aureus*	9	8	8	18
	Bacillus subtilis	8	7	7	24
	E. coli	8	8	7	21
[Ni(saltyr)(dmap)(phen)]	*Staphylococcus aureus*	8	7	7	19
	Bacillus subtilis	8	8	6	18
	E. coli	7	7	7	22
[Zn(saltyr)(dmap)(H_2O)$_2$]	*Staphylococcus aureus*	8	7	7	17
	Bacillus subtilis	8	8	7	18
	E. coli	12	10	9	23
[Zn(saltyr)(dmap)$_2$(H_2O)]	*Staphylococcus aureus*	9	7	7	20
	Bacillus subtilis	13	12	10	20
	E. coli	17	17	12	20

[Zn(saltyr)(dmap)(phen)]	*Staphylococcus aureus*	8	8	7	22
	Bacillus subtilis	8	7	7	18
	E. coli	16	10	8	22

ANTIFUNGAL STUDIES

The antifungal activities of the complexes were carried out using three different fungi namely *Trichoderma viride, Rhizopus microspores & penicillium chrysogenum* and compared against standard *amphotericin* by the Agar disc diffusion method[23] and the data are given in Table 6. As the concentration increases, the diameter of the inhibitory zone also increases, indicating that the complexes are active. The copper complexes seem to show better activity towards fungi compared to nickel and zinc analogues. Otherwise all the complexes are only moderately active except [Cu(saltyr)(dmap)(H_2O)$_2$] against *Trichoderma viride* and *Rhizopus microspores* and [Cu(saltyr)(dmap)(phen)] against *trichoderma viride* and *penicillium chrysogenum*. All nickel complexes and [Zn(saltyr)(dmap)$_2$(H_2O)] are inactive against *penicillium chrysogenum*, even at 1000µg while [Ni(saltyr)(dmap)(H_2O)$_2$] and [Cu(saltyr)(dmap)(H_2O)$_2$] complexes are inactive against *trichoderma viride* even at 1000 µg. Otherwise both nickel and zinc complexes are very moderately active.

Table 6: Antifungal studies

Complexes	Fungi	Inhibition Zone(mm) Concentration(µg/ml)			Standard (1mg/ml)
		1000	750	500	
[Cu(saltyr)(dmap)(H_2O)$_2$]	*Trichoderma viride*	9	8	7	9
	Rhizopus microsporus	8	7	6	10
	Penicilliumchrysogenum	7	6	-	15
[Cu(saltyr)(dmap)$_2$(H_2O)]	*Trichoderma viride*	7	7	7	11
	Rhizopus microsporus	9	8	7	20
	Penicillium chrysogenum	9	8	6	24
[Cu(saltyr)(dmap)(phen)]	*Trichoderma viride*	10	8	7	11
	Rhizopus microsporus	7	6	5	16
	Penicilliumchrysogenum	17	16	11	17
[Ni(saltyr)(dmap)(H_2O)$_2$]	*Trichoderma viride*	-	-	-	10
	Rhizopus microsporus	11	9	7	21
	Penicillium chrysogenum	-	-	-	20
[Ni(saltyr)(dmap)$_2$(H_2O)]	*Trichoderma viride*	12	10	9	20
	Rhizopus microsporus	11	10	8	19
	Penicilliumchrysogenum	-	-	-	19
[Ni(saltyr)(dmap)(phen)]	*Trichoderma viride*	8	7	5	18
	Rhizopus microsporus	11	10	9	15
	Penicillium chrysogenum	-	-	-	16
[Zn(saltyr)(dmap)(H_2O)$_2$]	*Trichoderma viride*	-	-	-	16
	Rhizopus microsporus	9	8	7	20
	Penicillium chrysogenum	6	5	-	19
[Zn(saltyr)(dmap)$_2$(H_2O)]	*Trichoderma viride*	8	7	6	16
	Rhizopus microsporus	8	7	5	16
	Penicillium chrysogenum	-	-	-	19
[Zn(saltyr)(dmap)(phen)]	*Trichoderma viride*	15	13	11	25
	Rhizopus microsporus	10	9	7	20
	Penicillium chrysogenum	7	6	5	20

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ANTI CANCER STUDIES

The anticancer activities of the complexes were studied by MTT assay[24] on *Hela-29*(human cervical cell line). In parallel, the invitro cytotoxicity was studied on *Vero* cell line(monkey kidney cell line). The observation of the data suggests that, the complexes possess excellent anticancer activities with very low IC50 values as given in Table 7. The complexes, [Cu(saltyr)(dmap)(H_2O)$_2$] and [Ni(saltyr)(dmap)(phen)] require only 7.8µg to destroy more than fifty percent of the cancer cells. The IC_{50} values of normal cell line are very high greater than 1000µg which indicate that the complexes are not at all harmful to normal cell.

Table 7: Anticancer activity and destruction of normal cells by the complexes

Complex	IC_{50} in HeLa Cell line(µg)	% cell death of normal cells at this conc.
[Cu(saltyr)(dmap)(H_2O)$_2$]	7.8	1.59
[Cu(saltyr)(dmap)$_2$(H_2O)]	31.2	23.8
[Cu(saltyr)(dmap)(phen)]	62.5	19.05
[Ni(saltyr)(dmap)(H_2O)$_2$]	15.6	2.82
[Ni(saltyr)(dmap)$_2$(H_2O)]	125	9.86
[Ni(saltyr)(dmap)(phen)]	7.8	1.41
[Zn(saltyr)(dmap)(H_2O)$_2$]	31.2	13.24
[Zn(saltyr)(dmap)$_2$(H_2O)]	15.6	2.95
[Zn(saltyr)(dmap)(phen)]	15.6	4.42

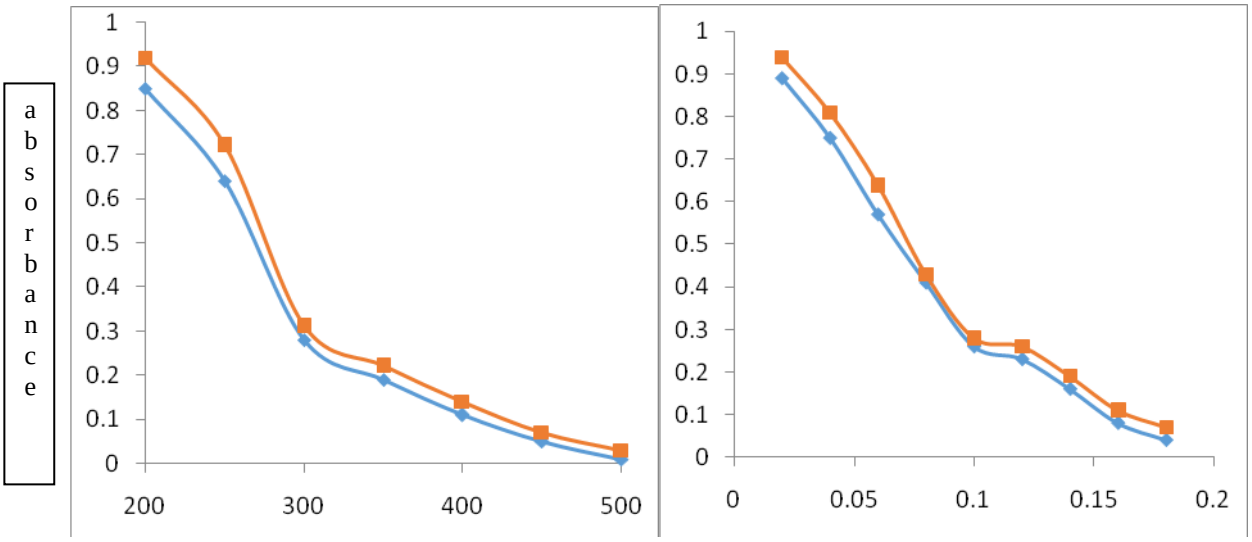

Figure 1 Absorption spectra of the [Cu(saltyr)(dmap)(H_2O)$_2$]Complex in the Cu(saltyr)(dmap)(H_2O)$_2$] absence and presence of DNA

Figure 2 Absorbance of DNA at different concentrations of complex, at 300K and 310 K

DNA BINDING STUDIES

The anticancer activity of complexes is generally attributed to DNA binding of the metal complexes followed by cleavage. The DNA cleavage study for one of the complexes with lowest IC_{50} value namely, [Cu(saltyr)(dmap)(H_2O)$_2$] is carried out a. by varying DNA concentration(DNA titration procedure) at different wavelengths and b.by studying the absorbance at 260 nm by varying the concentration of the complexes at

two different temperatures viz; 300 and 310K on genomic DNA. The results are presented in figures 1 and 2. It shows huge change in intensity of UV-visible spectral band of the complex in the region below 290 nm and a slight increase in intensity above 290 nm, due to presence of DNA. There is not much variation in the position of the absorption bands. The hyperchromism, without any change in the position of the absorption bands of the complex due to the presence of DNA rules out intercalative mode of binding, since intercalation leads to hypochromism in the spectral band[25]. The results suggest the possibility of groove binding of the complex to DNA[26].

CONCLUSIONS

Among the copper, nickel and zinc complexes of Tyrosine- schiff bases, copper complexes exhibited better antibacterial activity, especially the copper complex of phenanthroline exhibited superb activity. The anti cancer action of some of the complexes are also extraordinary. This opens up further scope for research in these type of complexes when the whole world is witnessing multi drug resistant syndrome. These complexes also exhibit luminescent properties which could be utilized in making sensors, emitters etc.

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