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SYNTHESIS, CHARACTERIZATION, CYTOTOXIC AND ANTIOXIDANT STUDIES OF MIXED LIGAND SCHIFF BASE COMPLEXES DERIVED FROM P- NITROANILINE AND 2, 4-DINITROANILINE

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ABSTRACT: Four isatin mixed ligand complexes of the type ML_1L_2 , where $M = Co(II), Ni(II), Cu(II)$ and $Zn(II)$ ($L_1 =$ Schiff base formed by the condensation of isatin and p-nitroaniline and $L_2 =$ Schiff base formed by the condensation of isatin and 2,4-dinitroaniline) are synthesized. Mixed ligand complexes are different from routine metal complexes that they have a minimum of two special kinds of ligands linked to the one metal ion in a complex. Ethanol is used as a solvent for the synthesis of ligands and their mixed ligand complexes. All the mixed ligand complexes have been characterized by various physicochemical techniques such as Elemental analysis, IR, UV-Visible, conductivity measurements, magnetic moment measurements, thermogravimetric analysis, etc. Tetrahedral geometry is assigned for all the mixed ligand complexes. Here both the ligands are bidentate and potent donors are carbonyl oxygen and azomethine nitrogen atoms. The ligands and the mixed ligand complexes are screened for cytotoxicity and antioxidant properties. The mixed ligand metal complexes show higher antioxidant and cytotoxic activities as compared to the ligands.

INTRODUCTION: Schiff bases are commonly used to synthesize new mixed ligand complexes. The unique properties like chelating structure, electron donor nature, simply tunable electronic and steric properties have proved that Schiff bases are greatly flexible in nature. The prepared mixed ligand complexes are different from routine metal complexes that they have minimum two special kinds of ligands linked to the one metal ion in a complex¹.

Due to the occurrence of different ligands in a same complex definitely one can see better properties for mixed ligand complexes². This makes the synthesis of mixed ligand complexes interesting with varying properties.

Synthesis, characterization and applications of mixed ligands complexes have been extensively studied and published in recent years³⁻⁶. In continuation of our work on the synthesis and characterization of isatin schiff bases complexes⁷⁻⁸, the present paper deals with the synthesis and characterization of four mixed ligand complexes derived from the Schiff base, obtained by the condensation of isatin and 4-nitroaniline (L_1) and Schiff base formed by the condensation of isatin and 2, 4-dinitroaniline (L_2) using transition metal ions such as $Co(II), Ni(II), Cu(II)$ and $Zn(II)$.

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All the Schiff base ligands and their mixed ligand complexes have been analyzed by various physico-chemical methods such as elemental analysis, IR, UV-Visible, conductivity measurements, magnetic moment measurements, thermo gravimetric analysis. Tetrahedral geometry is assigned for all the mixed ligand complexes. The Schiff base ligands and the mixed ligand complexes were screened for cytotoxicity and antioxidant properties.

EXPERIMENTAL:

Materials: The chlorides of copper (II), cobalt(II), nickel(II) and zinc(II) are used as such. Other commercially available reagents are employed without any further purification, and they are isatin, p-nitroaniline, and 2,4-dinitroaniline purchased from Sigma-Aldrich. Ethyl alcohol is used as a solvent for the preparation of the Schiff base ligands and their respective mixed ligand-metal complexes.

Analysis and Physical Measurements: Sigma-Aldrich reagents are used for synthesizing all the ligands and complexes. All the glassware used for the preparation were cleaned with the chromic mixture, distilled water and then dried in an oven at 110 °C. With the help of CHN Analyzer Elementar Vario micro select, CHN elements are determined. IR spectral details were obtained in Shimadzu IR spectrophotometer with KBr pellets in the range of 400-4000 cm^{-1} . UV-visible data were recorded in UV-visible spectrophotometer (Perkin Elmer) using DMSO as a solvent. Using calibrate $\text{Hg}[\text{Co}(\text{CNS})_4]$ and Gouy balance magnetic moment values are recorded at room temperature molar conductance measurements are carried out in Elico Conductometer in DMF. Thermal analysis of the mixed ligand complexes was carried out using Perkin Elmer Diamond Thermal Analyzer in an inert atmosphere of nitrogen by recording the change in weight of the complexes. Melting points are determined in electrothermal capillary apparatus, and they are reported as uncorrupted values^{8,9}.

Preparation of the Schiff Base Ligand (L₁): Procedure available in the literature is used to

synthesize Schiff base ligand (L₁). 1.47g (0.01M) of isatin in 50 ml of ethanol is mixed with 1.38g (0.01) of p-nitroaniline taken in 50 ml ethanol. The mixture was refluxed for 2-3 h. The reaction mixture was concentrated and cooled. On cooling, orange colored Schiff base (L₁) ligand precipitates. The precipitate is filtered washed with ethyl alcohol and recrystallized. Schiff base ligand purity is monitored by using ethyl acetate and petroleum ether as eluents, and column chromatography was used for separation. The molecular formula of Schiff base ligand C₁₄H₉O₃N₃ [L₁].

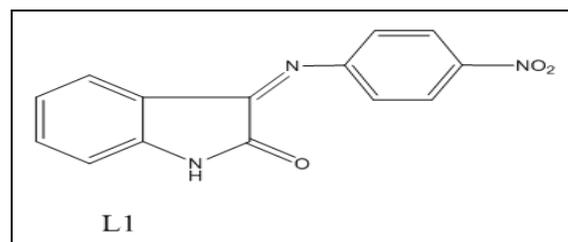


FIG. 1: STRUCTURE OF L₁

Preparation of the Schiff Base Ligand (L₂): The ethanolic solution of isatin (0.01M, 1.47g) in 50 ml is mixed with 50 ml ethanolic solution of 2, 4-dinitroaniline (0.01M, 1.83g) and refluxed for about 2-3h. The mixture was concentrated and allowed to cool.

On cooling, Schiff base ligand (L₂) precipitates, and the precipitate is filtered off, washed with ethanol and recrystallized. Schiff base ligand purity is monitored by using ethyl acetate and petroleum ether as eluents, and column chromatography was used for separation. The molecular formula of Schiff base ligand C₁₄H₈O₅N₄ [L₂]. The analytical and physical data of both the ligands (L₁&L₂) presented in **Table 1**.

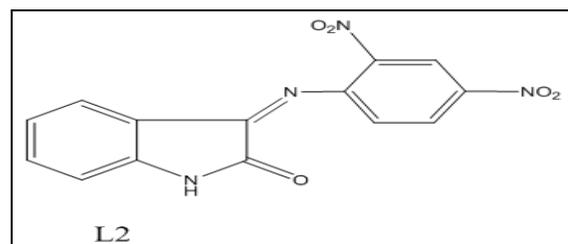


FIG. 2: STRUCTURE OF L₂

TABLE 1: THE ANALYTICAL AND PHYSICAL DATA OF THE LIGANDS

Ligand	MP °C	Colour	Yield	Mol. Wt	% found (calculated)		
					C	H	N
L ₁	108	Bright yellow	82.64%	267	61.66(62.9)	3.383(3.37)	15.92(15.73)
L ₂	114	Light yellow	65.44%	312	53.38(53.84)	3.033(2.56)	17.77(17.94)

Synthesis of Mixed-Ligand Complexes: Mixed ligand metal complexes are synthesized with salts of respective metal chlorides (0.01M in 50 ml of ethanol) added to 100 ml ethanolic solution of L₁ and L₂ (0.01M each) respectively and are refluxed for 4-5 h at 80-90°C and then concentrated to small

volume metal complexes precipitates on cooling. Mixed ligand complexes precipitates are, filtered and washed with ethanol and using fused calcium chloride complexes are dried. Stored in airtight containers.

TABLE 2: MIXED LIGAND COMPLEXES ANALYTICAL AND PHYSICAL INFORMATION

Complex	Mol. Wt	Formula	Analysis of elements calculated (found) (%)			Yield (%)	Colour	MP °C
			C	H	N			
[CoL ₁ L ₂]	638	CoC ₂₈ H ₁₇ N ₇ O ₈	52.66 (54.33)	2.66 (3.89)	15.36 (17.45)	67.08	Yellow	>300
[NiL ₁ L ₂]	637	NiC ₂₈ H ₁₇ N ₇ O ₈	52.69 (53.01)	2.66 (1.98)	15.36 (17.02)	45.09	Brown	>320
[CuL ₁ L ₂]	642	CuC ₂₈ H ₁₇ N ₇ O ₈	52.24 (55.00)	2.64 (2.00)	15.25 (14.96)	52.5	Brown	>300
[ZnL ₁ L ₂]	644	ZnC ₂₈ H ₁₇ N ₇ O ₈	52.14 (54.09)	2.63 (2.09)	15.20 (14.02)	35.29	Pale yellow	>300

RESULTS AND DISCUSSION: All the Four newly synthesized complexes have high decomposition temperatures and are colored complexes are stable towards air and are amorphous solids in nature The complexes have the common formula [ML₁L₂] where M = Co(II), Ni(II), Cu(II) and Zn(II). All the complexes show solubility in solvents like DMF and DMSO. And are insoluble in water. And our efforts are failed in determining molecular weights. The analytical and physical data of the mixed ligand metal complexes are as shown in **Table 2**.

Molar Conductance Measurements: The observed molar conductance data values in 10⁻³M DMF are in the range of 10-18 ohm⁻¹ cm²mol⁻¹, indicating the non-electrolyte nature of complexes and presented in **Table 3**. But the slightly higher

conductivity values the complexes may be attributed to the partial solvolysis of the complexes in DMF^{10, 11, 12, 13, 14}.

Infrared Spectra: Mixed ligand complexes distinguishing vibration frequencies are recognized by comparing with the spectra of Schiff base ligand. Almost assignments of infrared bands on mixed ligand complexes are done purely on the reported information available in the literature on almost same systems^{8, 9, 10}. There are four possible donor sites in the complexes, and these are the two oxygen atoms and the two azomethine nitrogen atoms from each of the two isatin molecules of the ligands, L₁ and L₂. The IR spectrum of both the ligands (L₁ and L₂) and their mixed complexes are characterized mainly by the strong bands, and their stretching frequencies are depicted in **Table 3**.

TABLE 3: SELECTED FT IR FREQUENCIES (cm⁻¹) OF THE LIGAND AND THE MIXED COMPLEXES

Ligand/complex	ν _{N-H}	ν _{C=N}	ν _{C=O}	ν _{M-N}	ν _{M-O}
L ₁	3450	1622	1747	-	-
L ₂	3400	1623	1729	-	-
[NiL ₁ L ₂]	3420	1618	1719	610	499
[CoL ₁ L ₂]	3430	1615	1721	615	485
[ZnL ₁ L ₂]	3400	1614	1708	613	492
[CuL ₁ L ₂]	3410	1610	1711	617	488

The IR spectrum of both the ligands have characterized the bands around 1622 cm⁻¹, 1747 cm⁻¹ and 3450 cm⁻¹ corresponds to azomethine group (C=N), carbonyl (C=O) and NH(aromatic) of the isatin ring. The lower shift of wave numbers is observed in the IR spectra for mixed ligand complexes by 10-15 cm⁻¹ for azomethine group. Carbonyl oxygen and N-H group. The lower shift in stretching frequency of both azomethine group and carbonyl oxygen in the spectra of metal complexes indicating that the involvement of

carbonyl oxygen atom in coordination to the central metal ion^{7, 8, 9, 10, 11}. The change in the distribution of electrons and molecular environment around the ligand due to the introduction of metal ion causes a minor shift in the stretching frequencies of all the mixed ligand-metal complexes. In the far infrared region, one would expect the metal-ligand vibrations due to metal-nitrogen, metal-oxygen stretching vibrations. However, in the complexes, it is not easy to do the categoric assignments of these bands, as various skeletal vibrations of the ligands

interfere and the definite assignments are rather difficult. The appearance of new bands around 485 cm^{-1} and 617 cm^{-1} assignable to $\nu_{\text{M-N}}$ and $\nu_{\text{M-O}}$ respectively. Selected FT IR frequencies (cm^{-1}) of the ligand and mixed complexes are presented in **Table 3**.

Electronic Spectra and Magnetic Moment Measurements: In UV-Visible region, the electronic spectra of complexes are measured using DMSO solvent. The ultraviolet spectrum of both the ligands (L_1 and L_2) showed absorption bands at 38759 cm^{-1} , and 3703 cm^{-1} which has been given to $\pi - \pi^*$ transitions, and the band at 32786 cm^{-1} and 33112 cm^{-1} has been given to $n - \pi^*$ transitions respectively. These transitions will remain to appear at almost the same wavelength in the complexes. Indicating the coordination of ligand with metal ions^{15, 16, 17}. Co(II) complex magnetic moment is found to be 4.46 BM and shows bands at 6263 cm^{-1} 9342 cm^{-1} and assigned transitions are to $^4A_2 - ^4T_1(\text{F})$ and $^4A_2 - ^4T_1(\text{P})$. Thus, the tetrahedral geometry has been suggested¹².

The geometry of any mixed ligand complex can be predicted using the d-d transitions in the electronic spectroscopy above 25000 cm^{-1} . However, the Zn(II) complexes due to the completely filled d^{10} configuration, do not exhibit d-d transition and shows absorption band at 26901 cm^{-1} a charge transfer transition is assigned. Nevertheless, tetrahedral geometry may be proposed by comparing spectrum and configuration of Zinc (II) ion. Magnetic moment value of Ni(II) the complex is found to be 4.36 B.M. The electronic spectra of

the Ni(II) complex show the bands at 10480 cm^{-1} and 15483 cm^{-1} and assigned transitions are $^3T_1(\text{F}) - ^3A_2(\text{F})$ and $^3T_1(\text{F}) - ^3T_1(\text{P})$. Tetrahedral geometry may be assigned for the complex¹³.

The value of the magnetic moment of Cu(II) the complex is 1.98 B.M. The electronic spectra of the Cu(II) complex shows the band at 24092 cm^{-1} and is given $^2E - ^2T_2$ transition. Thus, the tetrahedral geometry has been suggested¹⁵. Electronic spectral data of the complexes are presented in **Table 5**.

TABLE 4: MOLAR CONDUCTANCE AND MAGNETIC MOMENT OF THE COMPLEXES

Complex	Molar conductance ($\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$)	Magnetic moment (BM)
[CoL ₁ L ₂]	16.8	4.46
[NiL ₁ L ₂]	14.4	4.36
[CuL ₁ L ₂]	13.0	1.98
[ZnL ₁ L ₂]	12.5	Diamagnetic

TABLE 5: ELECTRONIC SPECTRAL DATA OF THE COMPLEXES

Complex	ν cm^{-1}	Band Assignment	Suggested structure
[CoL ₁ L ₂]	6263	$^4A_2 - ^4T_1(\text{F})$	Tetrahedral
	9342	$^4A_2 - ^4T_1(\text{P})$	
[ZnL ₁ L ₂]	26901	Charge transfer	Tetrahedral
[NiL ₁ L ₂]	10480	$^3T_1(\text{F}) - ^3A_2(\text{F})$	Tetrahedral
	15483	$^3T_1(\text{F}) - ^3T_1(\text{P})$	
[CuL ₁ L ₂]	24092	$^2E - ^2T_2$	Tetrahedral

Thermo-gravimetric Studies (TGA): Mixed ligand complexes are subjected to thermo-gravimetric analysis at a rate of 20 $^{\circ}\text{C}/\text{min}$ up to 600 $^{\circ}\text{C}$ in the nitrogen atmosphere. Thermo-gravimetry relates weight change with temperature. It gives us information about the thermal stability of complexes.

TABLE 6: THERMAL DATA OF THE MIXED LIGAND COMPLEXES

Complex	Temperature ($^{\circ}\text{C}$)	% Weight loss Calculated(found)	Species lost	Residue found
[ZnL ₁ L ₂]	310-330	89.9(84.5)	$L_1 + L_2$	ZnO
[CuL ₁ L ₂]	300 - 330	90.2(86.5)	$L_1 + L_2$	CuO
[NiL ₁ L ₂]	305-315	90.9(93.8)	$L_1 + L_2$	NiO
[CoL ₁ L ₂]	290-310	90.7(94.1)	$L_1 + L_2$	Co_2O_3

Weight variation with an increase in temperature graphs can be obtained. The thermal decomposition all the four mixed ligand complexes take place in one stage with a temperature range^{18, 19, 20}. The decomposition is noticed in the temperature vary from 290-330 $^{\circ}\text{C}$. It is due to the elimination of two ligand molecule ($L_1 + L_2$) and finally left with the corresponding metal oxide. Thermogravimetric studies of mixed ligand complexes are shown in **Table 6**.

Anticancer and Antioxidant Properties:

Reagents: Dimethyl sulfoxide (DMSO), Dulbecco's modified Eagle medium (DMEM), fetal bovine serum (FBS), Rosewell park memorial institute (RPMI), penicillin, streptomycin, amphotericin B and 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide (MTT) reagents were purchased from Sigma Aldrich and used without any further purification.

Cytotoxicity Assay: *In-vitro* cancer cells such as cervical cancer (HeLa), breast cancer (MDA MB-231), colon cancer (HCT-15) & Prostate cancer (PC-3) cells and non-cancer cells such as human embryonic kidney cells (HEK-293) and peripheral blood mononuclear cells (PBMCs) were purchased from National Centre for Cell Science (NCCS), Pune, India and maintained in the CO₂ incubator as per the standard protocol. The test was used to test the ligands and mixed ligand complexes using MTT assay¹⁶. Briefly, 1×10^6 cells/ml were treated with ligands and complexes dissolved in DMSO for 48 h, and MTT assay was performed as described^{24, 25}. The dose decreases 50% of the inhibition of the cells (IC₅₀) was calculated using the GraphPad prism from the dose-response curve. Statistical analysis was performed by one way ANOVA test from the five independent experiments and treatments were performed by octuplets.

Antioxidant Test: The antioxidant potential was determined by using the DPPH free radical scavenging assay²⁵. Briefly, 1 ml of the different

concentrations of complex ranging from 0 to 100 μ M was added to 1 ml of 0.004% of DPPH solution and incubated at room temperature for 35 min under dark. Absorbance values are recorded at 500nm after 30 min by considering ascorbic acid as positive reference antioxidant activity. Then the percentage activity calculations are carried out^{24, 25}.

RESULTS AND DISCUSSION: The cytotoxicity of the two ligands and their mixed complexes exhibited dose-dependent cytotoxicity in the cancer cells. Among them, the copper and nickel complexes were active at the lower dose levels compared to the ligands other complex and metal complexes **Table 7**. Notably, the cytotoxicity was more two increase than their ligands and selective to the cancer cells. However, when compared to the standard reference drug cisplatin, copper, and nickel complex were more active was observed. Similarly, the antioxidant activity of copper and nickel complex was found to be active antioxidant activity than other complex^{26, 27}.

TABLE 7: CYTOTOXIC STUDIES OF THE COMPLEX IN CANCER AND NORMAL CELL LINES

Cell lines	Type	IC ₅₀ (μ M)						
		L ₁	L ₂	CuL ₁ L ₂	ZnL ₁ L ₂	CoL ₁ L ₂	NiL ₁ L ₂	Cisplatin
HEK-293	Normal human embryonic kidney cells	89.2 \pm 2.43	71.2 \pm 1.23	96.3 \pm 5.2	89.2 \pm 3.3	83.2 \pm 4.5	74.5 \pm 3.8	36.8 \pm 3.4
PBMCs	Normal peripheral blood mononuclear cells	93.2 \pm 3.74	76.4 \pm 2.33	92.4 \pm 4.2	91.2 \pm 5.3	97.3 \pm 2.3	82.4 \pm 4.5	46.7 \pm 2.6
HeLa	Cervical cancer cells	63.4 \pm 2.23	62.3 \pm 3.73	43.4 \pm 2.3	56.8 \pm 4.2	37.3 \pm 3.2	33.4 \pm 4.3	78.9 \pm 3.5
MDA MB-231	Breast cancer cells	74.3 \pm 3.21	62.8 \pm 3.27	13.5 \pm 3.2	28.8 \pm 3.7	21.8 \pm 2.3	22.3 \pm 1.5	38.5 \pm 2.7
HCT-15	Colon cancer cells	68.5 \pm 2.73	62.3 \pm 3.82	16.8 \pm 1.7	32.4 \pm 2.3	24.7 \pm 3.8	18.4 \pm 2.3	35.3 \pm 2.6
PC-3	Prostate cancer cells	78.3 \pm 3.23	72.3 \pm 4.22	19.3 \pm 2.3	28.8 \pm 3.7	21.7 \pm 3.7	21.4 \pm 2.8	45.4 \pm 3.4

TABLE 8: ANTIOXIDANT POTENTIAL ACTIVITY OF COMPLEXES

Ligand/Complex	DPPH Scavenging activity (IC ₅₀ in μ M)
L ₁	>200
L ₂	153.0 \pm 2.45
CuL ₁ L ₂	68.7 \pm 4.22
ZnL ₁ L ₂	167.0 \pm 2.45
CoL ₁ L ₂	92.4 \pm 3.23
NiL ₁ L ₂	76.3 \pm 2.45
Ascorbic acid	71.6 \pm 3.12

CONCLUSION: In the present study, synthesis and characterization of four mixed ligand complexes obtained by reacting isatin and 4-nitroaniline and isatin with 2,4-dinitro aniline with respective metal chlorides in ethanol medium was carried out. Both the ligands being bidentate and

potent donors were found be carbonyl oxygen and azomethine nitrogen atoms. Tetrahedral geometry was proposed for all the mixed complexes and the probable structure is shown in **Fig. 3**.

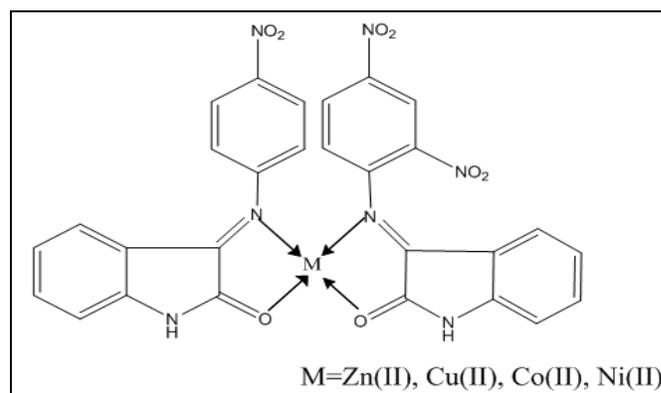


FIG. 3: PROPOSED STRUCTURE FOR THE COMPLEXES IS (TETRAHEDRAL GEOMETRY)

The metal complexes of Cu, Co, Ni and Zn showed significantly potent cytotoxicity against breast, colon and prostate cancer cell lines. DPPH scavenging activity of Cu, Co and Ni complexes are found to be higher than the standard ascorbic acid. Cytotoxic and antioxidant activities of metal complexes were found to be higher compared to the ligands.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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