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## Research Article

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME METAL COMPLEXES OF TRANSITION METAL IONS WITH COUMARIN SCHIFF BASES HAVING N AND O DONOR ATOM

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### ABSTRACT

The lipophilic nature of the ligands increases due to the introduction of halogen atoms. The presence of halogen atom (Cl, Br, I and F) also increases the bioactivity of those ligands. The core moiety gets enhanced in its bio-activity by the presence of such electronegative atoms. In the present study, some metal complexes of transition metal ions are synthesized using the Schiff base derived from 8-formyl-7-hydroxy-4-methylcoumarin and *p*-fluoroaniline.

#### Key Words:

Coumarin Schiff bases; Metal complexes;  
Fluorescence; Anti-tuberculosis; DNA  
cleavage; Anthelmintic

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## INTRODUCTION

Coumarin is a white crystalline compound having typical benzopyrone framework, occurs naturally in plants and it can also be chemically synthesized. Plant species of family Compositae, Rutaceae and Umbelliferae contain higher level of coumarin and it can be isolated using various extraction procedures [1]. Chemically coumarin can be synthesized by different methods [2-7]. The simple and common method used for synthesis of coumarin is Pechmann condensation, in which, different phenols are used. 7-Hydroxycoumarin (*Umbelliferone*), on its structural and biogenetic aspects is regarded as the parent coumarin among the structurally more complex coumarins [8]. Coumarin derivatives have the ability to express numerous pharmacological properties such as antimicrobial [9], antioxidant [10], antitubercular [11], antiplasmodial [12], anticancer [13], cytotoxic [14], anthelmintic [15], inhibition of platelet aggregation [16], antispermatogenic [17], anti HIV [18] and anti-inflammatory and anticoagulant [19] activities. A number of coumarins have been investigated for complexing ability [20]. Chelating ability

of coumarin derivatives have also been studied to suggest their use as chelating agents [21].

In recent years, many structural modifications have been made at various positions of the coumarin ring system to get more pharmaceutically active coumarin derivatives. In an aromatic ring, the presence and position of the electron withdrawing group may enhance its reactivity. The best pharmaceutical results can be expected by replacing a hydrogen atom of a molecule by halogen. Many of such derivatives are used as antibiotics, antineoplastic agents, CNS depressant, CNS stimulant and antipsychotic etc. Recently, K.N. Venugopala *et al.*, showed that, halogenated coumarin derivatives express anti-malarial activity [22]. These compounds act as inhibitors against various protein kinases [23]. Recent studies on halogen-bonding or X-bonding show increased affinity of ligand as potential anticancer drugs [24]. The presence of halogen atoms in a molecule enhances the lipophilic nature and is less soluble in water, which also improves the penetration through lipid membrane. Fluorine atom being less bulky among all the halogens (Cl, Br, I and F) has the ability to block metabolically active positions.

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In the light of all these observations, we have planned to synthesize and study the pharmacologically active new transition metal complexes with halogenated coumarin Schiff bases. In this part of research work, we have synthesized Co(II), Ni(II) and Cu(II) complexes of coumarin Schiff bases derived from 8-formyl-7-hydroxy-4-methylcoumarin and 3-chloro-8-formyl-7-hydroxy-4-methylcoumarin with 2,4-difluoroaniline and *o*-toluidine respectively. The synthesized compounds were characterized by spectral (IR, NMR, UV-visible, Mass, ESI-MS), thermal, fluorescence and molar conductivity studies. The bioassay of these synthesized compounds was also carried out.

## Experimental

### Reagents

All chemicals are of reagent grade and used without further purification.

### Physical measurements

Carbon, hydrogen and nitrogen were estimated using TRUSPEC CHN analyzer. The IR spectra of the Schiff base and their Co(II), Ni(II) and Cu(II) complexes were recorded on a HITACHI-270 IR spectrophotometer in the region 4000-400  $\text{cm}^{-1}$  using KBr disc. The electronic spectra of the complexes were recorded in HPLC grade DMF solvent on a VARIAN CARY 50-BIO UV-spectrophotometer in the region of 200 - 1100 nm. The  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectrum of Schiff base was recorded in  $\text{D}_6$ -DMSO on a BRUKER 400 MHz spectrometer at room temperature using TMS as an internal reference. The fluorescence studies of Schiff base and their metal complexes were carried out on HITACHI F-7000 Fluorescence Spectrophotometer. Mass spectrum of the Schiff base and electro spray mass spectra of metal complexes were recorded using QP 2010S and THERMO Finnegan LCQ Advantage max ion trap mass spectrometer respectively. Thermo gravimetric analyses data measured from a range of room temperature to 1000  $^\circ\text{C}$  at a heating rate of 10  $^\circ\text{C}/\text{min}$ . The data obtained by using a PERKIN-ELMER DIAMOND TG/DTA instrument. Molar conductivity measurements recorded on ELICO-CM-82 T Conductivity Bridge with a cell having cell constant 0.51 and magnetic moment was carried out using faraday balance for all the synthesized metal complexes.

### Synthesis

#### Synthesis of 7-hydroxy-4-methylcoumarin

A mixture of dry resorcinol (0.2 mol) and ethylacetoacetate (0.2 mol) was cooled to 0-5  $^\circ\text{C}$  and Conc. sulphuric acid (25 mL) was added gradually with constant shaking. The reaction mixture was then kept in a refrigerator for 24 h. and poured into crushed ice with stirring. The separated solid was filtered washed with water and recrystallized from ethanol as cream colored needles. Yield: 82%; Melting Point: 180-182  $^\circ\text{C}$ .

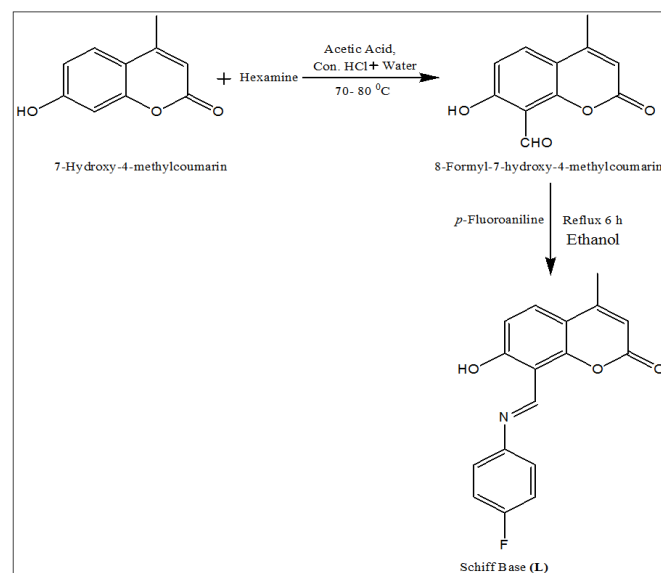
#### Synthesis of 8-formyl-7-hydroxy-4-methylcoumarin

A mixture of 0.03 mol of 7-hydroxy-4-methylcoumarin and 0.07 mol of hexamine in 50 ml of glacial acetic acid were heated for 4-5 h and then 75 mL of 20% hydrochloric acid was added, heating was continued for 20 min. The resulting mixture was cooled and extracted with ether. Pale yellow solid of 8-formyl-7-hydroxy-4-methylcoumarin was obtained after

evaporating the ether. Yield: 20.0 %; Melting Point: 176-178  $^\circ\text{C}$ .

### Synthesis of Schiff base L

The steps involved in the synthesis of Schiff base L is shown in Scheme-1. The reaction mixture of hot ethanolic solution of *p*-fluoroaniline with hot ethanolic solution of 8-formyl-7-hydroxy-4-methylcoumarin was refluxed for about 6 h with an addition of 1-2 drops of glacial acetic acid. The precipitate formed during refluxion was filtered, washed with cold ethanol and recrystallized with acetic acid.



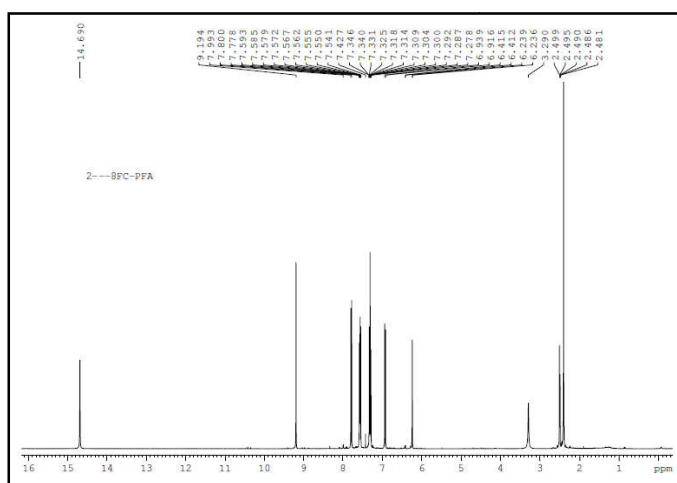
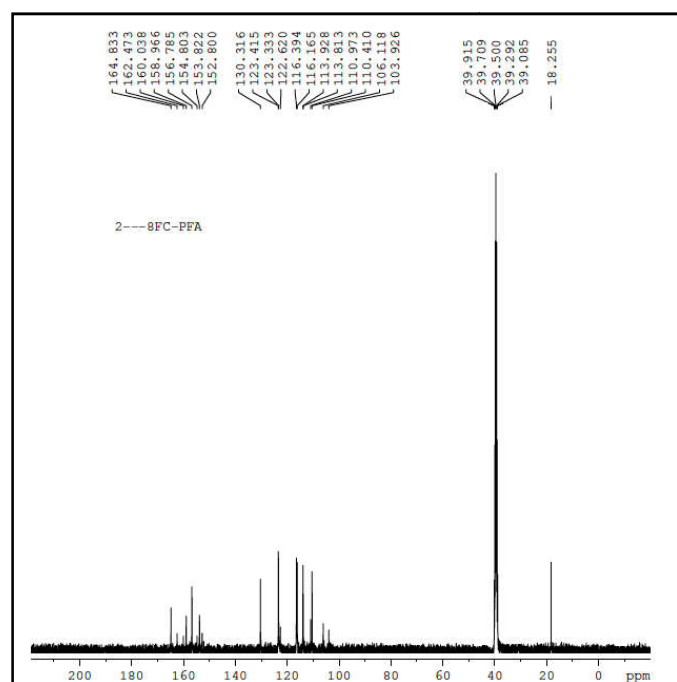
Scheme 1 Synthesis of Schiff base L.

### NMR spectral study

The synthesized Schiff base has been characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra to elucidate the differently positioned proton and carbon atoms respectively. The  $^1\text{H}$  NMR spectrum of the Schiff base (L) is shown in Fig. 1

$^1\text{H}$  NMR spectrum (Fig. 1) of Schiff base (L) exhibited two singlets around 14.69 ppm and 6.23 ppm which were attributed to phenolic -OH and C3-H proton of coumarin moiety respectively. Two doublets appeared at 7.79 ppm and 6.93 ppm was attributed to C4-H and C5-H of coumarin moiety respectively. These protons were coupled with the each other with a coupling constant of 8.8 Hz. The presence of azomethine proton as a singlet at 9.19 ppm confirms the formation of Schiff base. Methyl protons were resonated at 2.48 ppm as a singlet and rest of the protons were resonated in the expected region.

In the  $^{13}\text{C}$  NMR spectrum of Schiff base L, signals at 164.833, 158.996 and 18.25 ppm are due to C=O, C=N and  $-\text{CH}_3$  respectively. The doublet (appears as two independent peaks) at 162.473 and 160.038 ppm was assigned to the fluorocarbon atom with  $^1J_{\text{C-F}}$  243.5 Hz. The two bond coupling constant of fluorine with the *o*-carbon, was found as  $^2J_{\text{C-F}} = 22.9$  Hz and the corresponding peak was appeared as a doublet at 116.394-116.165 ppm. However, a weak three bond coupling was observed between fluorine and *m*-carbon atom at  $^3J_{\text{C-F}}$  8.2 Hz. The respective peak was observed at 123.412-123.333 and the remaining carbon atoms resonated in the aromatic region. The  $^{13}\text{C}$  NMR spectrum of the ligand is reproduced in Fig. 2.

Fig 1 <sup>1</sup>H NMR Spectra of the of the Schiff base LFig 2 <sup>13</sup>C NMR Spectra of the of the Schiff base L

### Mass Spectral Study

The mass spectrum analysis confirmed the formation of Schiff base L by exhibiting a molecular ion peak at  $m/z$  297; corresponding to its molecular weight. A fragment peak observed at  $m/z$  280 is due to the cleavage of  $-OH$  group. The mass spectrum of the Schiff base L is depicted in Fig. 3.

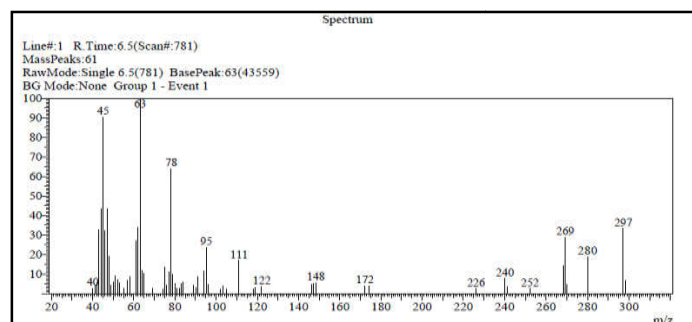
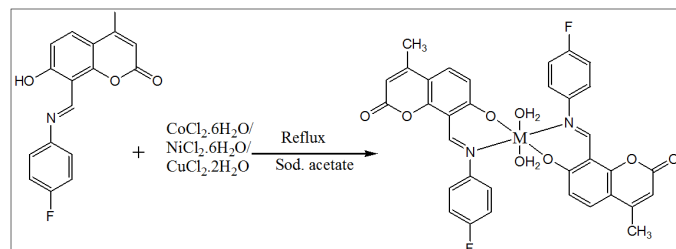


Fig 3 Mass Spectrum of Schiff Base (L)

## Synthesis of Metal Complexes

### General procedure for the synthesis of metal complexes

An alcoholic solution of Schiff base L (2 mmol) was refluxed with  $CoCl_2 \cdot 6H_2O$ / $NiCl_2 \cdot 6H_2O$ / $CuCl_2 \cdot 2H_2O$  (1 mmol) on water bath for 1h. Then, sodium acetate (1mmol) was added to the reaction mixture and reflux was continued for 3 h. The separated metal complex was filtered, washed thoroughly with water, ethanol and ether and then dried in vacuum over fused  $CaCl_2$ .



Scheme 2 Synthesis of Metal Complexes

### Pharmacology

#### Anti-Tuberculosis Activity

The anti-tuberculosis activity of the newly synthesized compounds was assessed against *M. tuberculosis* ATCC 27294 using microplate Alamar Blue assay (MABA). This methodology is non-toxic, utilizes a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200 mL of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimize the evaporation of medium in the test wells during incubation. The 96 wells plate received 100 mL of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 mg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this time, 25 mL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 were added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

#### Anthelmintic Activity

The assay was executed on adult Indian earthworm, *Pheretima posthuma* due to its anatomical and physiological similarity with the intestinal roundworm parasite of human beings [25]. The anthelmintic assay was studied as per the method given in the literature [26] with minor modifications. The earthworms, *P. posthuma* collected from moist soil, washed with normal saline (0.5%) for about 30 s to remove all faecal matter, were used for the anthelmintic study. The earthworms of 2-4 cm in length were used for all the experimental protocol. All the synthesized compounds were subjected to study anthelmintic activity against the earthworms at 2 and 10  $\mu\text{g/ml}$  concentrations. DMSO in distilled water was used as control and Albendazole as a reference drug. The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was recorded by placing the earthworms in warm water (50 °C) and observed for stimulated movement, if the worm was alive.

### DNA Cleavage Activity

For the gel electrophoresis experiments, solutions of the complexes in DMSO (1 mg/mL) were prepared and these test samples (100  $\mu$ M) were added to the pBR322 plasmid DNA and incubated for 2 h at 37  $^{\circ}$ C. Agarose gel was prepared in TAE buffer (4.84 g Tris base, pH 8.0, 0.5 MEDTA/l pH 7.3), the solidified gel obtained at 55  $^{\circ}$ C was placed in an electrophoresis chamber flooded with TAE buffer. Then, each of the incubated complex-DNA mixtures (mixed with bromophenol blue dye at a 1:1 ratio) was loaded on the gel along with the standard DNA marker, and the electrophoresis was carried out under the TAE buffer system at 100 V for 2 h. At the end of electrophoresis, the gel was carefully stained with EtBr (ethidium bromide) solution (10  $\mu$ g/mL) for 10–15 min and visualized under UV light using a Bio-Rad Geldoc gel imaging system.

### Antimicrobial Activity

Microbial strains *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus fumigatus* and *Candida albicans* were used in the present study. MIC was determined by the micro dilution method using a 96 well plate according to the NCCLS (National Committee on Clinical Laboratory Standards). First, 100  $\mu$ L of Mueller-Hinton broth (for bacterial strains) or Sabouraud dextrose broth (for fungal strains) was placed in each well. The stock solutions of the extracts were diluted and transferred into the first well and serial dilutions were performed; so that, concentrations in the range of 100–0.781  $\mu$ g/mL were obtained. The inoculums were adjusted to contain approximately  $10^5$  CFU/mL of bacteria and  $10^4$  CFU/mL of fungi. One hundred micro litres of the inoculums were added to all the wells and the plates were incubated at 37  $^{\circ}$ C for 24 h for bacteria and at 30  $^{\circ}$ C for 48 h for fungi. Antimicrobial activity was detected by adding 20  $\mu$ L of 0.5% TTC aqueous solution. The MIC value taken was the lowest concentration of the extract that inhibited any visible bacterial or fungal growth, as indicated by TTC staining after incubation. Flucanazole and Gentamycin were used as the reference antibiotic controls.

## RESULTS AND DISCUSSION

All the synthesized Co(II), Ni(II) and Cu(II) metal complexes are stable, soluble in DMSO, whereas insoluble in water and common organic solvents such as methanol, ethanol, chloroform, ethyl acetate and acetone. The analytical data showed that, the metal complexes having the stoichiometry of the type  $[M(L)_2(H_2O)_2]$ . Here,  $[M = Co(II), Ni(II) \text{ and } Cu(II)]$  where 'L' stands for a deprotonated ligand. The molar conductivity of the metal complexes 1–4 at  $10^{-3}$ M concentrations were carried out using DMSO solvent at room temperature. The results obtained are given in the Table- 1, which indicate that all the synthesized bivalent metal complexes have conductivity values in the range agreeable for the non-electrolytic nature suggesting that these complexes are non-electrolytic in nature. Several attempts were made to grow the single crystal of the metal complexes. However, those attempts were failed due to insolubility of the complexes in common organic solvents.

### FTIR studies of Schiff base ligand and its metal complexes

The IR spectrum of Schiff base (L) was recorded, a characteristic band of high intensity was observed at 1621  $\text{cm}^{-1}$  and is ascribed to  $\nu(C=N)$  vibrations [27]. The broad band at 3426  $\text{cm}^{-1}$  is attributed to  $\nu(O-H)$  and another strong band at 1724  $\text{cm}^{-1}$  is assigned to  $\nu(C=O)$ , lactonyl carbon of the coumarin moiety of L [28]. The infrared spectrum of Schiff base L is reproduced in Fig. 4.

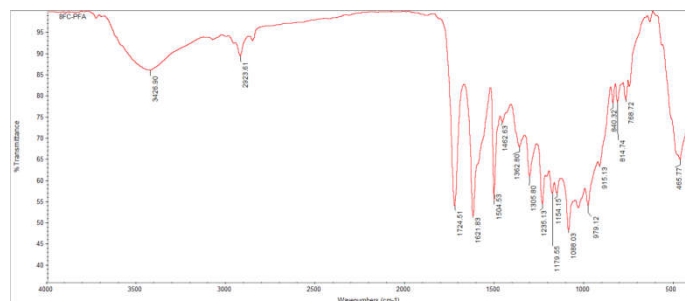


Fig 4 IR Spectrum of Schiff Base L

The binding of Schiff base to the metal ion in the complexes was studied by recording the IR spectra of the synthesized metal complexes and compared with that of Schiff base. The lowered values of azomethine group confirm the formation of complexes. The respective bands observed in the complexes of Co(II) Ni(II) and Cu(II) at 1598, 1592 and 1591  $\text{cm}^{-1}$  are the shifted values of  $\nu(C=N)$  from the ligand. The absence of  $\nu(O-H)$  band in the spectrum of metal complexes reveals that the coordination via deprotonation and the formation of M-O bond. The bands observed at 1327 and 1719  $\text{cm}^{-1}$  are assigned to phenolic  $\nu(C-O)$  and lactonyl  $\nu(C=O)$  respectively. The representative IR spectrum of Co(II) complex has been depicted in Fig. 5.

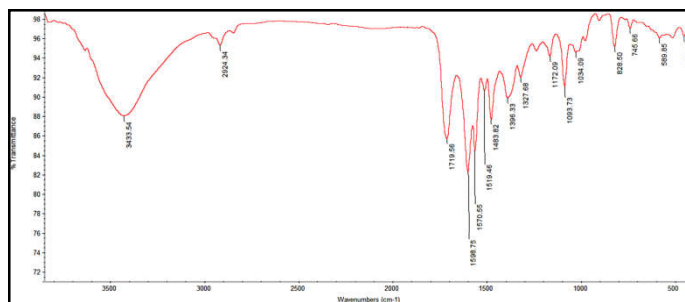


Fig 5 IR Spectrum of the Co(II) Complex

The lower shifts in azomethine frequency of all the synthesized metal complexes indicate that, the chelation takes place through nitrogen atom of azomethine group. The negligible shifts in the position of  $\nu(C=O)$  suggest that, the lactone carbonyl oxygen is not involved in coordination. A strong band observed in the region 1327  $\text{cm}^{-1}$  is assigned to  $\nu(C-O)$ , these observations are in good agreement to the formation of  $\nu(M-O)$  bond. A broad band in the region 3443  $\text{cm}^{-1}$  supports the presence of coordinated water molecules. The bands in the region 458 and 589  $\text{cm}^{-1}$  are metal sensitive and are ascribed to  $\nu(M-N)$  and  $\nu(M-O)$  respectively.



**Table 1** Elemental Analyses of Schiff Base and its Metal Complexes Along with Molar Conductance Data

Compound Name	Empirical Formula	Yield %	M%		C%		H%		N%		Molar Cond. (Ohm <sup>-1</sup> cm <sup>2</sup> mole <sup>-1</sup> )	$\mu_{\text{eff}}$ (BM)
			Obsd.	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.	Obsd.	Calcd.		
Schiff Base	C <sub>17</sub> H <sub>12</sub> NO <sub>3</sub>	80%	-	-	68.68	68.65	4.07	4.09	4.71	4.68	-	-
Co(II)L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	Co(C <sub>17</sub> H <sub>12</sub> NO <sub>3</sub> ) <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	59%	8.57	8.54	59.40	59.43	3.81	3.79	4.07	4.04	22.10	4.56
Ni(II)L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	Ni(C <sub>17</sub> H <sub>12</sub> NO <sub>3</sub> ) <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	63%	8.16	8.14	59.42	59.45	3.81	3.83	4.08	4.11	12.45	3.16
Cu(II)L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	Cu(C <sub>17</sub> H <sub>12</sub> NO <sub>3</sub> ) <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	56%	9.18	9.15	59.00	59.05	4.07	4.09	4.05	4.08	27.40	1.78

### Solution Electronic Absorption Spectra and Magnetic Studies

The information regarding stereochemistry of the metal ions can be obtained with the help of UV Visible spectra. The electronic spectra of all the synthesized compounds are recorded in DMF. The Schiff base (L) exhibited two absorption bands around 258 and 327 nm. The peaks below 350 nm correspond to the ligand centred transitions i.e. intraligand  $\pi-\pi^*$  and  $n-\pi^*$  of aromatic ring and non-bonding electrons present on the nitrogen atom of azomethine group in the Schiff base [30, 31].

Electronic spectra of the synthesized metal complexes are recorded in DMF. The electronic spectrum of Co(II) complex exhibited the absorption bands in the region 563 and 980 nm corresponding to  ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$  ( $\nu_1$ ) and  ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$  ( $\nu_3$ ) transitions respectively. Observed magnetic moment of Co(II) complex was 4.56 BM, both the above facts are in good agreement with the octahedral geometry for the synthesized Co(II) complex.

In case of Ni(II) complex, three bands were observed in the region 986, 672 and 366 nm are due to the  ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$  ( $\nu_1$ ),  ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$  ( $\nu_2$ ) and  ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$  ( $\nu_3$ ) transitions respectively, this observation supports octahedral geometry around Ni(II) ion. The magnetic moment value of 3.16 BM also is in good agreement for octahedral geometry for Ni(II) complex.

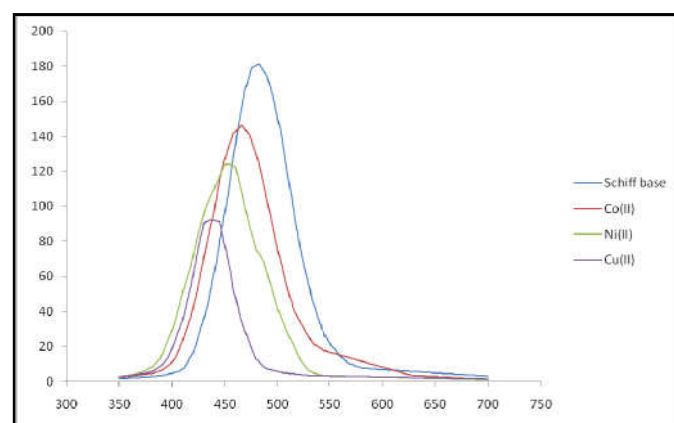
Two absorption bands were observed in the spectrum of Cu(II) complex at 689 and 388 nm. A low intense band at 680 nm is assigned to  ${}^2E_g \rightarrow {}^2T_{2g}$  transition which supports the distorted octahedral geometry to the metal ion. The other band at 386 nm is due to symmetry forbidden ligand  $\rightarrow$  metal charge transfer. The obtained magnetic moment value of 1.78 BM also suggests the octahedral environment around the metal ion. The electronic spectral data is depicted in Table- 2.

**Table 2** Electronic Spectral Data

Compound	$\lambda_{\text{max}}$ in cm <sup>-1</sup> (nm)	Band Assigned	Geometry
Co.L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	10,204 (980)	${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ ( $\nu_1$ )	Octahedral
	17662 (563)	${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ ( $\nu_3$ )	
Ni.L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	10142 (986)	${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ ( $\nu_1$ )	Octahedral
	14881 (672)	${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ( $\nu_2$ )	
	26595 (366)	${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ( $\nu_3$ )	
Cu.L <sub>2</sub> .(H <sub>2</sub> O) <sub>2</sub>	15384 (650)	${}^2T_{2g} \leftarrow {}^2E_{2g}$	Distorted Octahedral
	25773 (388)	L $\rightarrow$ M	

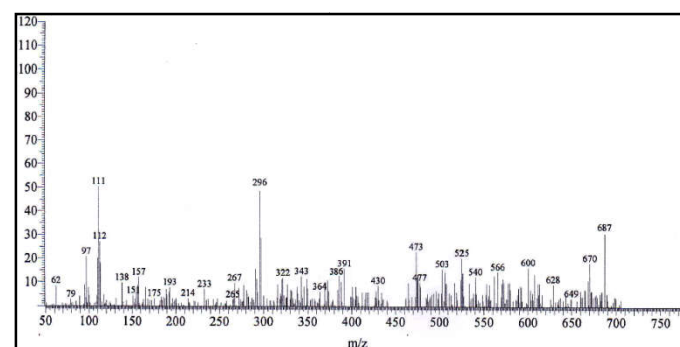
Fluorescence study of Schiff base L and its metal complexes  
Fluorescence is a spectrochemical method of analysis where molecules of an analyte get excited by irradiation at a certain wavelength and emit the radiation of a different wavelength.

In this investigation, we have studied the fluorescent nature of the Schiff base L and its metal complexes with same concentration of 10<sup>-5</sup> M in DMSO solution at room temperature. It is observed that, the emission band at 482 nm of Schiff base got disappeared upon complexation due to the interaction of phenolic oxygen and metal ion. The synthesised metal complexes i.e. Co(II), Ni(II) and Cu(II) exhibited the emission bands at 466, 452 and 437 nm respectively. The weak intensity bands of metal complexes are due to decrease in electron density on ligand [51, 52]. The decreased fluorescence intensities of synthesized metal complexes were compared with Schiff base L is in the order Co(II) > Ni(II) > Cu(II) and is shown in Fig. 6.

**Fig 6** Emission Spectra of Schiff base and its Metal Complexes

### ESI-MS Study

The ESI-MS study of Co(II) (1), Ni(II) (2) and Cu(II) (3) complexes showed a M+1 peak at  $m/z$  687, 688 and 691 respectively, which are equivalent of their molecular weight, these facts support the formation of respective metal complexes of type  $ML_2(H_2O)_2$  and a base peak at  $m/z$  296 is due to the formation of deprotonated ligand. The representative  $Co(C_{18}H_{14}NO_3)_2 \cdot 2H_2O$  is shown in Figure-7.

**Fig 7** ESI-MS Spectrum of Co(II) Complex

### Thermal studies of the metal complexes

As a function of temperature, thermal behaviour of the synthesized Co(II), Ni(II) and Cu(II) complexes of Schiff base L were studied. The decomposition took place in two steps. It shows that, thermal features of all the metal complexes were almost same. Here, the representative TG/DTA spectrum (Fig. 8) of  $\text{Cu}(\text{C}_{18}\text{H}_{13}\text{ClNO}_3)_2 \cdot 2\text{H}_2\text{O}$  is discussed. First decomposition occurred in the region 180- 220 °C centred at 198 °C is due to loss of coordinated water molecules. Decomposition in the regions 350- 540 °C centred at 475 °C corresponding to loss of organic moieties. Finally metal oxide was formed above 650 °C.

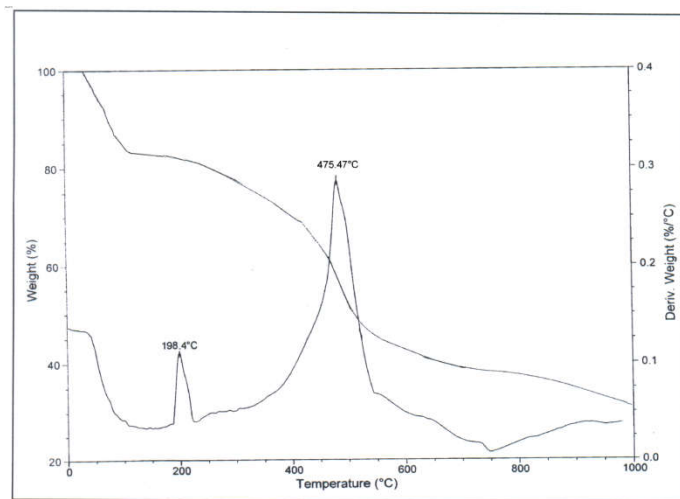


Fig 8 TG/DTA spectrum of  $\text{Cu}(\text{C}_{18}\text{H}_{13}\text{ClNO}_3)_2 \cdot 2\text{H}_2\text{O}$

### Anti-tuberculosis Activity Study

The synthesized metal complexes were screened for their anti-tuberculosis against *M. Tuberculosis* using Microplate Alamar Blue Assay (MABA). The results reveal that, the metal complexes exhibited a better activity than Schiff base L with different MIC values as shown in Table- 3. This study concludes that the Cu(II) complex showed the prominent activity with the MIC of 12.5 ( $\mu\text{g}/\text{mL}$ ) when compared to other metal complexes.

Table 3 Results of anti-tuberculosis Activity

Compound	MIC Values
Schiff base L	50
1	25
2	25
3	12.5
Sreptomycin Std.	6.25

### Antimicrobial Activity

The activity ensures that, the synthesized metal complexes exhibit the higher lethal effect compared to their parent ligand. Among the synthesized metal complexes, Cu(II) complex showed the prominent antibacterial and antifungal activity against all the strains. The results are tabulated in Table- 4 and 5. By this it can be suspected that, the presence of metal ions may possibly increase the activity.

Table 4 Antibacterial Studies of Schiff Base (L) and its Metal Complexes

Compound Name/No.	Conc. ( $\mu\text{g}/\text{mL}$ )	Zone of Inhibition (mm)			
		<i>E. coli</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>S. aureus</i>
Schiff base L	200	6	5	6	7
1	200	9	7	9	8
2	200	9	8	8	10
3	200	10	10	11	12
Gentamicin	200	14	13	14	15

Table 5 Antifungal Studies of Schiff Base (L) and its Metal Complexes

Compound Name/No.	Conc. ( $\mu\text{g}/\text{mL}$ )	Zone of Inhibition (mm)	
		<i>P. chrysogenum</i>	<i>A. niger</i>
Schiff base L	200	5	6
1	200	8	10
2	200	9	9
3	200	10	12
Flucanazole	200	13	16

### Anthelmintic Activity

Table- 6 shows the results of anthelmintic activity of all the synthesized compounds. From the results obtained it is clear that, the metal complexes are more active than their corresponding ligand. In particular, the Cu(II) complex exhibits the efficient activity compared to the other metal complexes against the standard drug Albendazole at 10 $\mu\text{g}/\text{mL}$  concentration.

Table 6 Anthelmintic Studies of Schiff Base (L) and its Metal Complexes

Compound	Concentration ( $\mu\text{g}/\text{mL}$ )	Time of Paralysis (Min)	Time of Death (Min)
Albendazole Std.	10	3.49 $\pm$ 0.06	7.26 $\pm$ 0.14
DMSO*	-	-	-
Schiff base (L)	2	20.16 $\pm$ 0.02	24.28 $\pm$ 0.12
	10	9.29 $\pm$ 0.22	14.30 $\pm$ 0.12
1	2	12.16 $\pm$ 0.15	19.60 $\pm$ 0.02
	10	7.51 $\pm$ 0.04	10.14 $\pm$ 0.03
2	2	16.21 $\pm$ 0.24	21.30 $\pm$ 0.08
	10	9.10 $\pm$ 0.01	15.60 $\pm$ 0.01
3	2	10.30 $\pm$ 0.03	16.41 $\pm$ 0.05
	10	5.48 $\pm$ 0.22	9.45 $\pm$ 0.01

### DNA Cleavage Activity

The DNA cleavage activity of Schiff base and its metal complexes were studied by agarose gel electrophoresis method using pBR322 Plasmid DNA. The cleavage activity of Schiff base and its complexes are reproduced in Fig. 9. Gel electrophoresis works on, migration of DNA under the influence of electric potential. In the present case, ligand along with the Co(II) and Ni(II) complexes shows the partial cleavage; whereas, the Ni(II) complex cleaves the DNA completely.

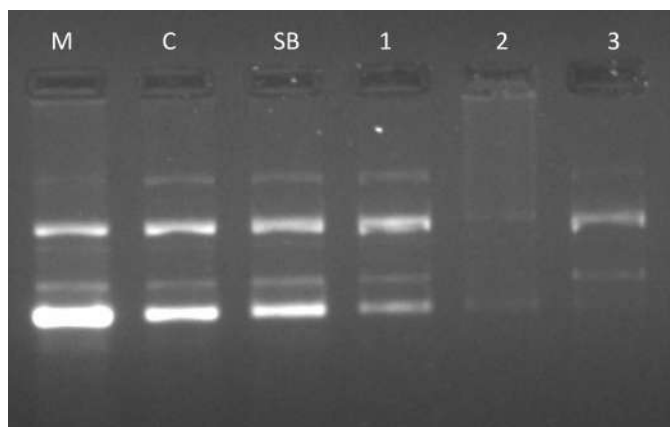


Fig 9 DNA Cleavage Activity of Schiff Base and its Metal Complexes

(‘M’-is standard DNA molecular weight marker, ‘C’-control DNA i.e. untreated pBR322 Plasmid DNA and lanes SB and 1-3 are pBR322 treated with different Schiff base and metal complexes respectively).

## CONCLUSION

The newly synthesized Schiff base acts as a bidentate ligand which is coordinated to metal ions through azomethine nitrogen and oxygen atoms via deprotonation. The elemental analyses confirmed that, the synthesized metal complexes have the stoichiometry of the type  $[M(L)_2(H_2O)_2]$  where,  $[M= Co(II), Ni(II) \text{ and } Cu(II)]$  and ‘L’ is a doubly deprotonated ligand. The molar conductivity study shows that, all the synthesized metal complexes have low conductivity values. These various spectro-analytical techniques performed help in assigning the following tentative structure for the synthesized metal complexes. The newly synthesized Schiff base and its metal complexes have been screened for their *in-vitro* antitubercular, cytotoxicity, antimicrobial and DNA cleavage activities. Among the tested compounds Cu(II) complex was proved to be a good antitubercular agent. Whereas, antimicrobial assays show the increased activity of Schiff Base upon coordination. The DNA cleavage activity of Schiff base and its metal complexes were studied by agarose gel electrophoresis method using pBR322 Plasmid DNA, in which the Ni(II) complex showed the effective cleavage than any other synthesized compounds.

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