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Synthesis, Characterisation, Antimicrobial activity and DNA Cleavage of (*E*)-2-((Tetrazolo[1,5-A]Quinolin-4-ylmethylene)Amino)Phenol Schiff base Metal complexes

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Abstract : A series of novel (*E*)-2-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)phenol Cu(II), Co(II), Ni(II), Zn(II) and Mn (II) metal complexes have been synthesized 1:1 metal to ligand ratio, and these complexes were characterized by using analytical data such as FT-IR, UV-visible, Mass spectroscopy, SEM, EDX, TGA and magnetic moment measurements. The ligand and all the metal complexes were tested *in vitro* antimicrobial activity and DNA cleavage studies.
Keywords : Tetrazole, Quinoline, Schiff base, antimicrobial activity, DNA cleavage studies.

Introduction:

Tetrazole is a an interesting scaffold in heterocyclic due to their diverse medical application in various fields[1]. Losartan is a hypotensive, Cefamandol is a antimicrobial agent, TAK-456 used for treats many fungal infections, Tazanoplast & Planlukast are antihistaminic and Corazolum showed anticancer activity [2,3], these all compounds have tetrazole moiety as a core. In addition, quinoline derivatives possess wide varieties of biological activities including as antimicrobial[4], antiproliferative[5], antimycobacterial[6], antimalarial[7], antitumor[8], anti-inflammatory[9], antiparasitic[10], anti-HIV[11], insecticidal[12], antidyslipidemic and antioxidant[13]. Furthermore, many metal complexes derived from Schiff bases and are mostly coordinated with azomethine bonds. Recently, metal complexes were studied in vast due to their applications in various fields such as pharmacological, agrochemical and dye. Metal complexes are shows vast variety biological activities such as anticancer, antituberculosis, anti-HIV and antimicrobial etc. In view of the above findings and recent reports on metal complexes, we have inspired to carried out research work on synthesis and characterization of new Schiff base ligands and their metal of (*E*)-2-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)phenol and evaluated antimicrobial activity and DNA cleavage studies.

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Experimental:

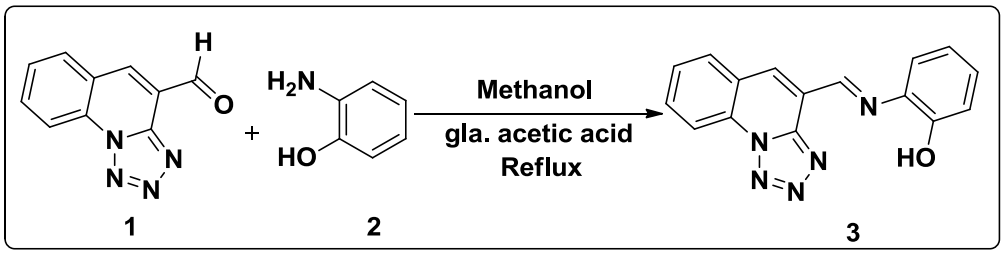
Materials:

All the chemicals were purchased from sigma Aldrich. The solvents and reagents used were of analytical grade.

Synthesis of (*E*)-2-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)phenol (ligand) (3):

5 mmol of Tetrazolo[1,5-a]quinoline-4-carbaldehyde solution**(1)**, 5 mmol of 2-aminophenol **(2)** in methanol was taken into round bottom flask and slowly added catalytic amount of glacial acetic acid to the reaction mixture, and refluxed with continuous stirring for 1 hr. The reaction completion was checked by TLC the formation of yellowish precipitate was observed, the precipitate filtered, dried and recrystallized from EtOH, yield obtained was 80% pure (*E*)-2-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)phenol **(3).**

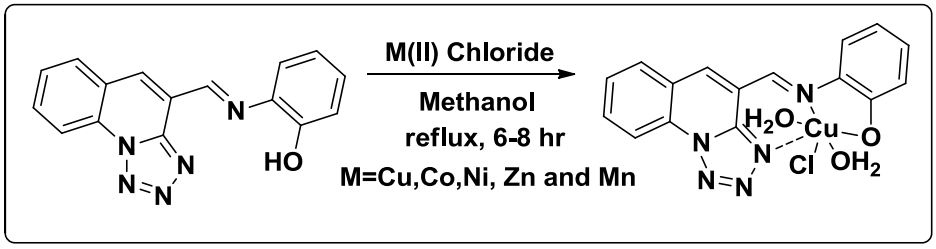
Scheme-1:



Synthesis of metal complexes:

5 mmol of Metal (II) (Cu, Co, Ni, Zn and Mn) chlorides solution was dissolved in methanol and then we added slowly to the 5 mmol methanolic solution of (*E*)-2-((Tetrazolo[1,5-a]quinolin-4-ylmethylene)amino)phenol (ligand) (3) . The resulting mixture solution was refluxed for 6-8 hr. The absence of ligand checked by TLC, the produsedsolution was cooled to room temperature and the solution is evaporated under reduced pressure. The crude product obtained is then washed with hot methanol to yield amorphous metal complexes **(4a-e)**.

Scheme-2:



Physical measurement:

The purity of the compound was checked by TLC using precoated silica gel plates 60_{254}(Merck). FTIR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a ESI mass spectrometer. Elemental analysis was determined by using a Perkin /elmer 240(USA) CHNS analyzer. The electronic spectra of ligand and its complexes were carried out in DMSO using a SHIMADZU UV-2600 spectrophotometer. Thermo gravimetric analysis of the metal complexes were carried on on a Shimadzu TGA-50H thermal analyzer in the temperature range of ambient temperature to 1200 °C with a heating rate of 10 °C min^{-1}. A Gouy balance model 7550 using $[Co(NCS)_4]$ as standard is operated to examine the magnetic moment values of the metal complexes. The SEM/EDX images were obtained from a Hitachi SEM analyser.

Antibacterial activity:

The ligand and metal complexes were screened for their *in vitro* antibacterial activity against *Bacillus faecalis, Staphylococcus aeureus, Klebsiella pneumonia* and *Escherichia coli* using ampicillin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The complexes were screened at the concentration of 500µg/ml in DMSO.

Antifungal activity:

The ligand and metal complexes were screened for their antifungal activity *in vitro* against *A. Niger* and *F. Oxysporum* using Grieseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The complexes were screened at the concentration of 500µg/ml in DMSO.

DNA cleavage studies:

The compounds were dissolved in DMSO then added separately to the pUC18 DNA sample and H_2O_2. The sample mixtures were incubated at 37ºC for 1 hour. The electrophoresis of the samples was done according to the following procedure. Weigh 0.25grams of agarose and dissolve it in 25 ml of 1x TAE buffer (121.1g Tris base, pH 8.0, 0.5 M EDTA, 57.1ml of Glacial acetic acid for 1 ltr) by boiling. When the gel attains approximately 55ºC, pour it into the gel cassette fitted with comb get solidified. Carefully remove the comb, place the gel in the electrophoresis chamber flooded with TAE buffer. Load DNA sample with bromophenol blue carefully into the wells, along with standard DNA marker and pass the constant 100 V of electricity till the dye front reaches to the end of gel. Remove the gel carefully stains with ETBR solution (10µg/ml) for 10-15 min. and observe the bands under UV transilluminator.

Results and Discussion

Physical characteristics of the complexes:

All the metal complexes were colored, insoluble in water and melt at high temperature, non-hygroscopic in nature.

Elemental analysis:

The percentage of the elements (C, H, N) present in the ligand and complexes were given in **Table-1** The experimental values were matches with the theoretical values and these results confirmed 1:1 metal to ligand ratio. The values shown in brackets are calculated.

Table-1: Elemental analysis of Ligand and metal complexes

Compound	**Molecular Formula (weight)**	**Color**	**Anal. (%) (found (%))**			
			C	**H**	**N**	**M**
Ligand	$C_{16}H_{11}N_5O$ (289)	Yellowish	66.43 (66.40)	3.83 (3.81)	24.21 (24.16)	-
Cu(II)complex	$C_{16}H_{14}ClCuN_5O_3$ (423)	Blackish	49.62 (49.55)	2.60 (2.56)	18.08 (18.10)	16.41 (16.43)
Co(II)complex	$C_{16}H_{14}ClCoN_5O_3$ (418)	Brownish	45.90 (45.88)	3.37 (3.30)	16.73 (16.79)	14.08 (14.04)
Ni(II)complex	$C_{16}H_{14}ClNiN_5O_3$ (418)	Brownish	50.25 (50.21)	2.64 (2.61)	18.31 (18.29)	15.35 (15.39)
Zn(II)complex	$C_{16}H_{14}ClN_5O_3Zn$ (425)	Brownish	45.20 (45.25)	3.32 (3.24)	16.47 (16.42)	15.38 (15.33)
Mn(II)complex	$C_{16}H_{14}ClMnN_5O_3$ (414)	Brownish	46.34 (46.28)	3.40 (3.33)	16.89 (16.82)	13.25 (13.18)

Mass spectra:

The mass spectrum of the ligand and their metal complexes exhibits the molecular ion peak at (m/z), which is in agreement with its formula weight. The mass spectral values of the metal complexes were given in Table.

Table-2: Mass values of the Ligand and metal complexes.

Compound	Calculated mass	Obtained mass
Ligand	289	288 $[M-1]^+$
Cu(II) complex	423	424 $[M+1]^+$
Co(II) complex	418	419 $[M+1]^+$
Ni(II) complex	418	418 $[M]^+$
Zn(II) complex	425	426 $[M+1]^+$
Mn(II) complex	414	414 $[M]^+$

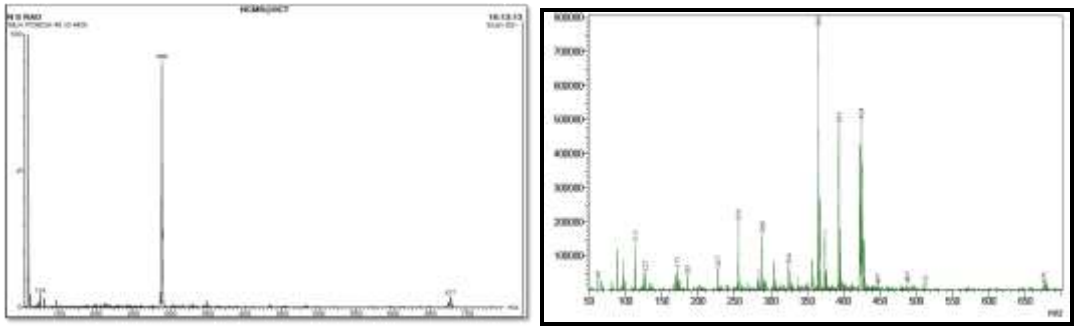


Figure-1: Mass spectrum of Lignad & Cu(II) complex.

NMR spectrum of ligand:

The ^{1}H-NMR spectra of the ligand shows a singlet at δ 9.38 ppm was assigned to azomethine proton integrated for one proton and another singlet at δ 8.64 ppm corresponds to quinoline singlet it is also integrated for one proton. A signal at δ 7.68 ppm was assigned to hydroxyl proton and reaming all proton showed in aromatic region.

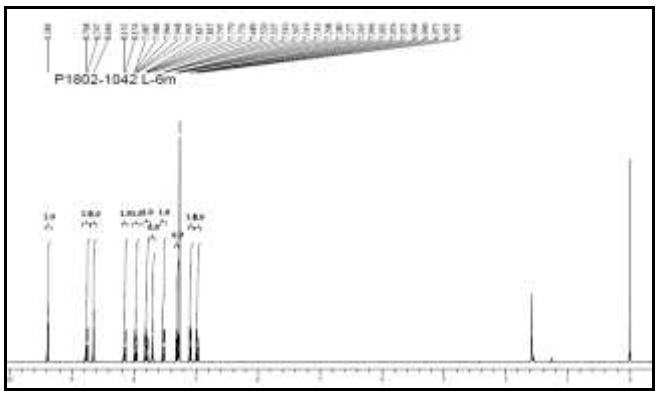
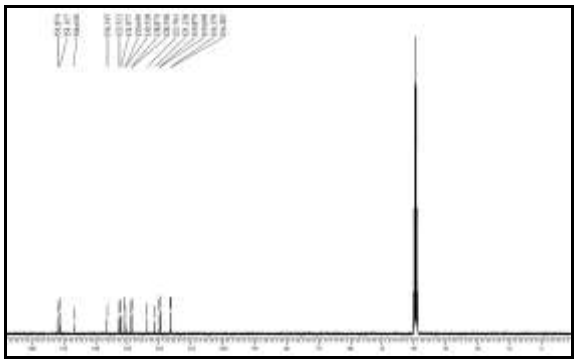


Figure-23: ^{1}H-NMR spectrum of ligand

In ^{13}C-NMR spectra of the ligand shows a signal at δ 151.8 ppm assigned to azomethine carbon and the entire reaming signal as follows δ 116.2, 116.3, 119.6, 119.8, 121.3, 123.7, 128.5, 128.8, 130.5, 130.6, 131.9, 132.5, 136.3, 146.6 and 151.1.

Figure-3: ^{13}C-NMR spectrum of ligand



UV- Vis Spectra and Magnetic moments:

The UV-Vis spectra of Schiff base ligand and its metal complexes were recorded in DMSO at room temperature. The absorption bands of a ligand observed at 258 and 383 nm, which corresponds to π- π*(- C=C) and n- π*(-C=N) transitions respectively. In addition, the copper complex was showed two bands in the regions of 443 nm and 630 nm which corresponds to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$, suggested that the complex is compatible with distorted octahedral geometry. The cobalt complex was showed two bands in the range 512 nm and 775-785 nm which corresponds to d-d transitions $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ and $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ suggested that the complex is compatible with octahedral geometry. Nickel complex showed two bands at 432 nm, 615-630 nm corresponds to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transitions which suggesting that the complex is compatible with octahedral geometry. The Zinc complex was showed broad band at 568 nm in the visible region was due to ligand to metal charge transfer, it suggesting that the geometry of the complex is octahedral. The Manganese complex was displayed broad band at 505 nm which corresponds to d-d transition of $^6A_{1g} \rightarrow {}^4A_{1g}(G)$, $^6A_{1g} \rightarrow {}^4T_{2g}(G)$ suggesting that the complex is compatible with octahedral geometry. The complexes Cu(II), Co(II), Ni(II) and Mn(II) were shows magnetic moment values at 1.88 B.M., 4.95 B.M., 3.26 B.M. and, 5.94 B.M. respectively, the values are also supported by the electronic spectral data also. The Zn(II) complex was not showed magnetic moment value due to it diamagnetic property.

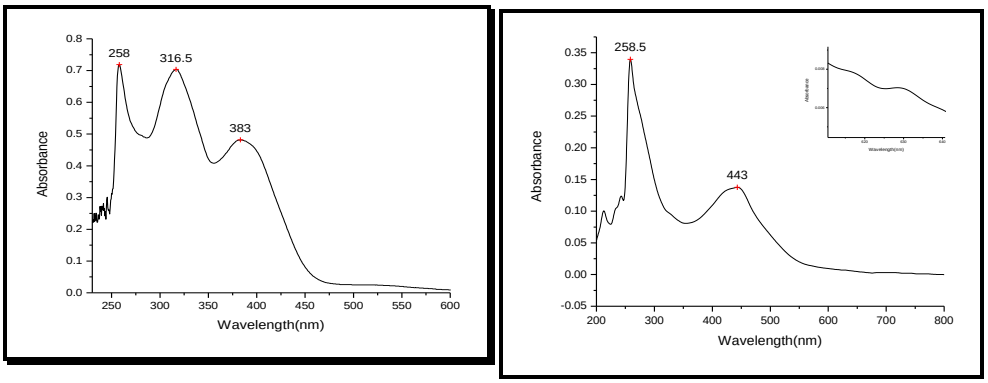


Figure-4: UV spectrums of ligand & Cu(II) complex

Table-3: UV spectrums values of the ligand & metal complexes.

Compound	Wavelength (nm)
Ligand	258, 316, 383
Cu(II) complex	258, 443, 630
Co(II) complex	258, 347, 512, 775-785
Ni(II) complex	258, 298, 432, 615-630
Zn(II) complex	260, 352, 568
Mn(II) complex	260, 324, 505

Infrared spectroscopy:

A strong band at 1612 cm^{-1} in the IR spectra assigned to the Azomethine nitrogen of the ligand, which was shifted to another frequency in the corresponding metal complexes. The frequencies of Cu(II), Co(II)

Ni(II), Zn(II) and Mn(II) complexes were observed at 1584, 1583, 1591, 1589 and 1585 cm^{-1} respectively. Corresponding to this confirms the coordination of azomethine nitrogen to the metal ion. The broad peak around 3350-3500 cm^{-1} indicates the presence of water molecules and the presence of oxygen and nitrogen in the coordination sphere is further confirmed by the presence of (M–Cl), (M–N) and (M–O) bands at 300-600 cm^{-1} regions. The FTIR results show that all Schiff base ligand act as tridentate chelating ligand.

Table-4: FTIR data (cm^{-1}) of Ligand and metal complexes:

Entry	Complex	υH_2O	υC=N	υM-O	υM-N	υM-Cl
1	Ligand	3400	1612	-	-	-
2	$[Cu(L^2)(H_2O)_2Cl]$	3404	1584	568	446	302
3	$[Co(L^2)(H_2O)_2Cl]$	3352	1583	578	484	362
4	$[Ni(L_2)(H_2O)_2Cl]$	3455	1591	540	459	376
5	$[Zn(L^2)(H_2O)_2Cl]$	3500	1589	582	465	335
6	$[Mn(L^2)(H_2O)_2Cl]$	3434	1585	578	447	305

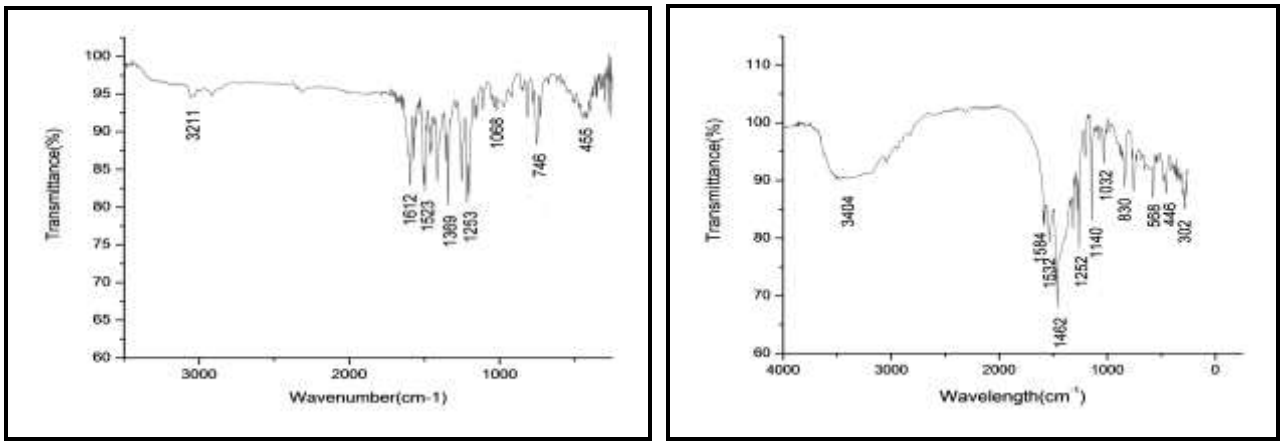


Figure-5: FT-IR spectrums of ligand & Cu(II) complex

Thermal Gravimetric analysis:

All the metal complexes shown significant weight loss in between 150-200°C suggested that presence of coordinated water molecule. The complexes show weight loss in between 400-800°C due to removal of organic moiety. The thermo gram above this temperature gave a straight line indicating the formation of metal oxide

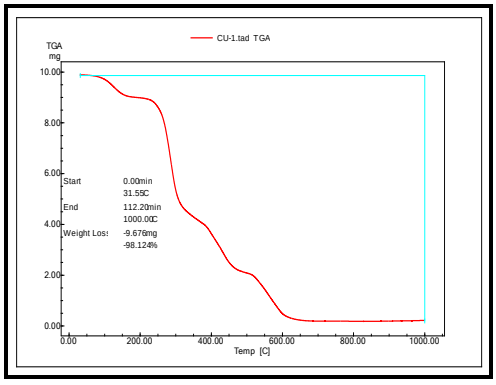


Figure-6: TG curve of the Cu(II) complex

SEM and EDX studies:

The ligand and metal complexes composition were obtained from Energy Dispersive X-ray (EDX) analysis. The analysis of ligand and Cu(II) complex represented Figure-8, it is observed that the experimental atom percentage is close to the expected (theoretical) values.. In EDX spectrum-1 the ligand shows three characteristics signals which corresponds to C (carbon), O (Oxygen) and N (nitrogen) it indicate the ligand present without any impurity, in spectrum-2 the Cu(II) complex shows C, O, N with Zn and Cl characteristics signals, it clearly confirm the formation of $[Cu(L)(H_2O)_2Cl]$ complex.

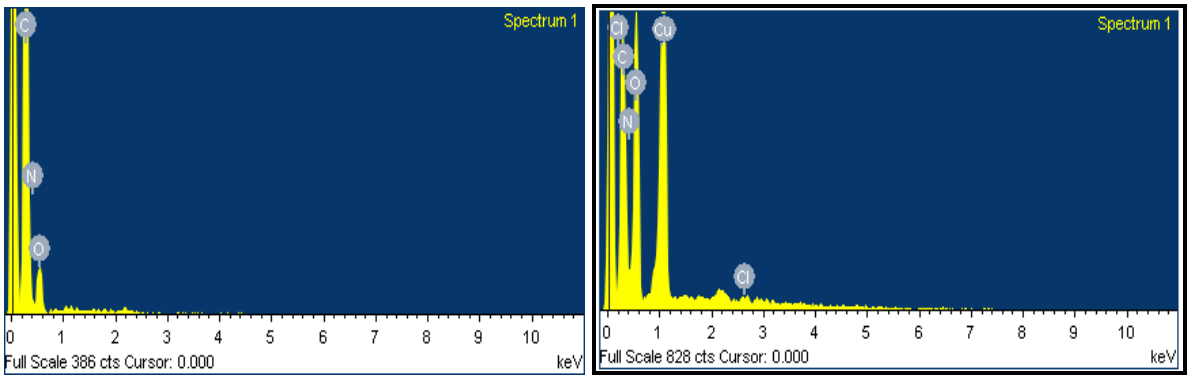


Figure-7: EDX images of the ligand and Cu (II) complexes

The SEM (Scanning Electron Microscope) is used to evaluate the morphology and particle size of the compounds. The SEM photographs of Ligand and Cu(II) complex were shown in Figure 9.The SEM micrographs show the agglomerate particles of the complexes. In case of Ligand and Cu(II) complex, some agglomerates appear to have tiny needles, while the other agglomerates appear to be of spherical plates like morphologies.

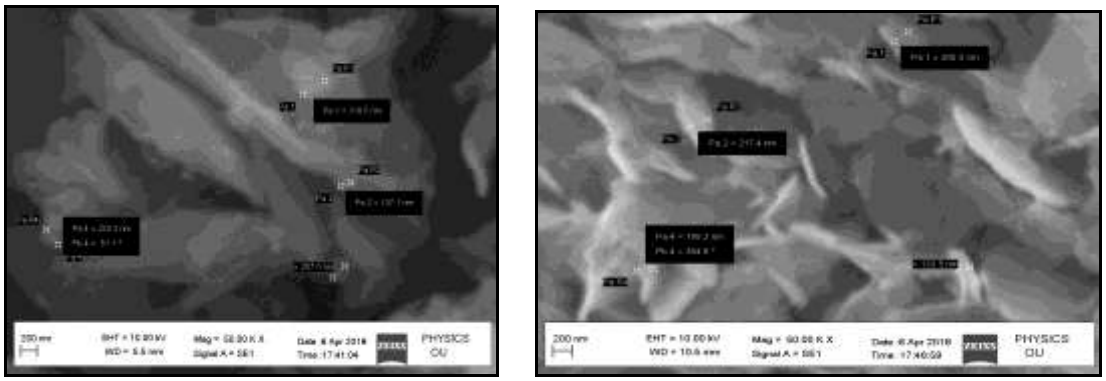


Figure-8: SEM images of the ligand and Cu(II) complexes

Antimicrobial activity:

The antimicrobial activity zone of inhibition of the Schiff base ligand and its metal complexes values are tabulated in the below Table-4. It is observed that all the metal complexes have shown greater activity than free ligand. This is explained on the basis of chelation theory and overtones concept. The complexes have shown good activity against all microorganisms compared with slandered drug.

Table-4: Antibacterial zone of inhibition for ligand and metal complexes

Compound	*Bacillus faecalis*	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Escherichia coli*	*A. Niger*	*F. Oxysporum*
Ligand	11	08	10	12	06	08
Cu(II)	24	13	21	23	09	14
Co(II)	13	13	26	12	07	08
Ni(II)	19	16	16	19	08	07
Zn(II)	10	08	08	13	07	10
Mn(II)	08	10	14	18	11	11
Ampicillin	33	20	35	33	---	---
Grieseofulvin	---	---	---	---	13	18

The antimicrobial screening results suggested that most of the metal complexes showed better activity compared to their Schiff-base. Order of the antibacterial activity of complexes were shown as follows as Cu>Ni>Co>Zn>Mn for *Bacillus faecalis*, Ni>Cu>Co>Mn>Zn for *Staphylococcus aureus*, Co>Cu>Ni>Mn>Zn for *Klebsiella pneumoniae* and Cu>Ni>Mn>Zn >Co for *Escherichia coli*.

Order of the antifungal activity of complexes were shown as follows as Mn>Cu>Ni>Zn>Co for *Aspergillus Niger* and Cu>Mn>Zn>Co>Ni for *Fusarium Oxysporum*.

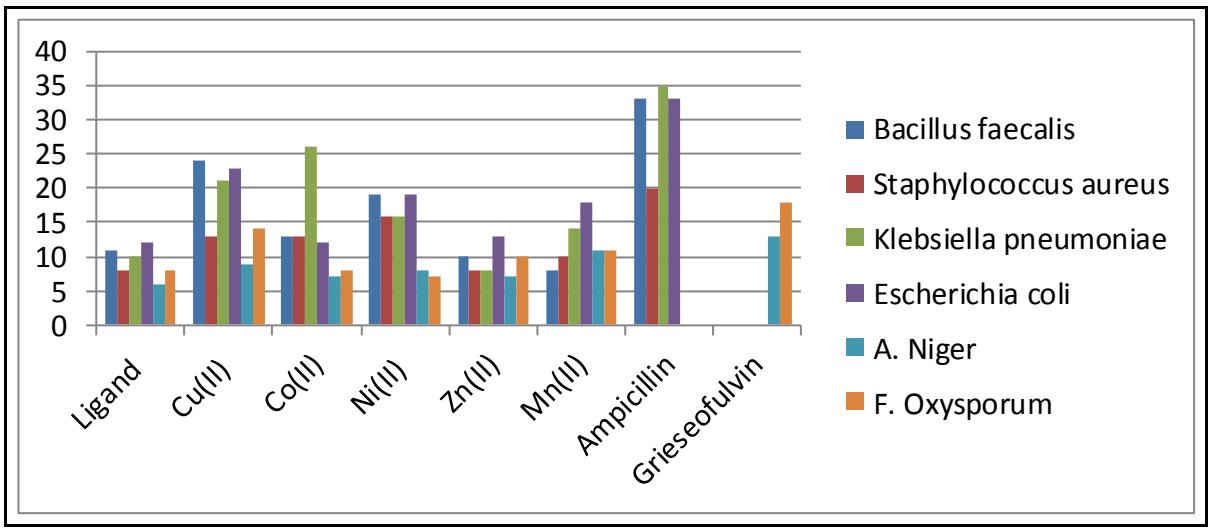


Figure-2: Graphical representation of Antimicrobial activity of the L^2 and their metal complexes:

DNA cleavage study:

The agarase gel electrophoresis method was used to study the DNA cleavage activity of the Schiff base and metal complexes. In the present work pUC18 DNA is used for cleavage experiment. All the metal complexes were interacted with pUC18 DNA in the presence of H_2O_2 the complete cleavage of DNA occurred with the Manganese and Copper complexes metal complexes and the Zinc, Cobalt and Nickel metal complexes of showed partial cleavage. The metal complexes were catalyzed by the production of hydroxyl radicals from H_2O_2 these hydroxyl radicals participate in the oxidation of deoxyribose moiety followed by the hydrolytic cleavage of sugar phosphate backbone.

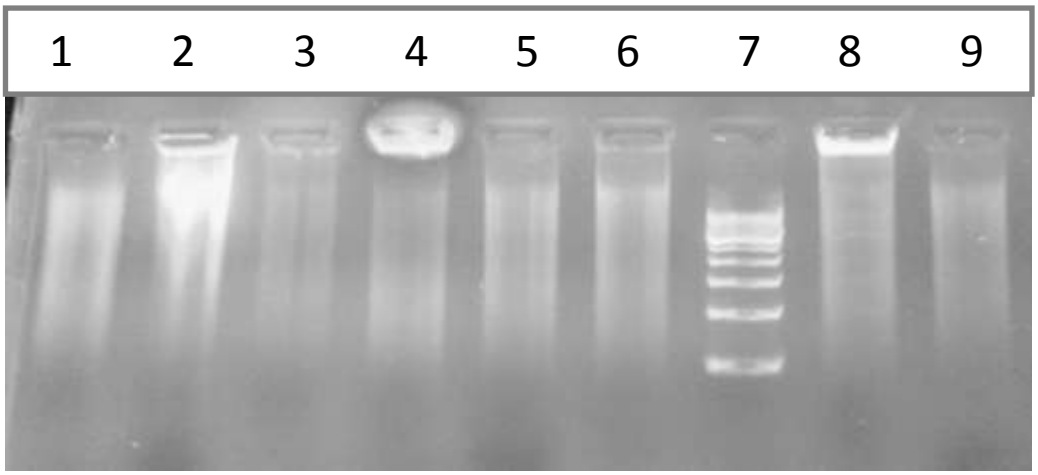


Figure-7: DNA cleavage of Ligand and their metal complexes:

Lane-1: Control DNA+DMSO; Lane-2: Control DNA; Lane-3: DNA+Mn(II) complex+H_2O_2; Lane-4: DNA+Cu(II) complex+H_2O_2; Lane-5: DNA+Zn(II) complex+H_2O;

Lane-6: DNA+Ni(II) complex+H_2O_2; Lane-7: DNA+Marker**;** Lane-8: DNA+L^2+H_2O_2; Lane-9: DNA+Co(II) complex+H_2O_2;

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