



**SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL ACTIVITY AND DNA CLEAVAGE STUDY OF (E)-3-(((3-HYDROXYPYRIDIN-2-YL) IMINO) METHYL) QUINOLIN-2-OL SCHIFF BASE METAL COMPLEXES**

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**Abstract:** A series of novel (E)-3-(((3-hydroxypyridin-2-yl)imino)methyl)quinolin-2-ol based metal complexes of Copper (II), Cobalt (II), Nickel (II), Zinc (II) and Manganese (II) have been synthesized. The ligand was synthesized by the condensation of 2-Hydroxyquinoline-3-carbaldehyde and 2-aminopyridin-3-ol in alcoholic medium and the metal complexes were synthesized by 1:1 metal to ligand ratio. The ligand and metal complexes were characterized by different analytical techniques such as FT-IR, UV-visible, Mass spectrometry, SEM, EDX, TGA and magnetic moment measurements. The ligand and all the metal complexes were tested for their antimicrobial activity and DNA cleavage studies. The antimicrobial screening results suggested that most of the metal complexes showed better activity compared to the free Schiff base ligand. In the DNA cleavage studies pUC18 DNA is used for cleavage experiment, complete cleavage of DNA occurred with the Nickel and Manganese complexes and Partial cleavage of DNA occurred with Zinc and copper complexes.

**Keywords:** 2-Hydroxyquinoline-3-carbaldehyde, 2-aminopyridin-3-ol, Schiff base, Thermo gram, antimicrobial activity, pUC18 DNA and DNA cleavage studies.

### **I. Introduction:**

Schiff bases are important class of compounds in coordination chemistry <sup>I</sup>. These are derived from the condensation reactions of aldehydes and amines; they form stable complexes with different metal ions <sup>II</sup>. Schiff bases and their metal complexes have been shown to be promising leads for both synthetic and structural research due to their relatively simple synthesis and structural diversity. They have been widely investigated, due to their incredible chemical properties and applications in various areas <sup>III</sup>. It is believed that the biological activity is related to the hydrogen bonding through the imine group of Schiff bases with the active centers of the cell constituents <sup>IV</sup>. Schiff base containing compounds show flexibility with natural biological substances due to the presence of imine group and this property is exploited for transformation

and racemisation reaction in the biological systems <sup>V</sup>. Further, the metal complexes prepared from Schiff base ligands have found to be oxygen carriers <sup>VI</sup>. Metal complexes synthesized from Schiff bases have application in the frontier research because of its DNA binding and cleavage properties <sup>VII</sup>. Schiff base metal complexes are extensively studied because of their versatility in the field of pharmaceutical industries, their biological activities - antitumor, antifungal, antiviral, anticonvulsant, anti-inflammatory and antimicrobial <sup>VIII</sup>.

Quinoline derivatives are important heterocyclics in medicinal chemistry due to their broad of biological activities including spectrum antimicrobial <sup>IX</sup>, anti-proliferative <sup>X</sup>, antimycobacterial <sup>XI</sup>, antimalarial <sup>XII</sup>, antitumor <sup>XIII</sup>, anti-inflammatory <sup>XIV</sup>, antioxidant <sup>XV</sup>, anti-HIV<sup>XVI</sup>, insecticidal <sup>XVII</sup>, antidyslipidemic and anticonvulsant <sup>XVIII</sup> activities. The properties described in the foregoing paragraphs, prompted us to carry out the research work on synthesis, characterization antimicrobial activity and DNA cleavage study of new Schiff base ligand (E)-3-(((3-hydroxypyridin-2-yl)imino)methyl)quinolin-2-ol and their metal complexes.

### Materials and Methods:

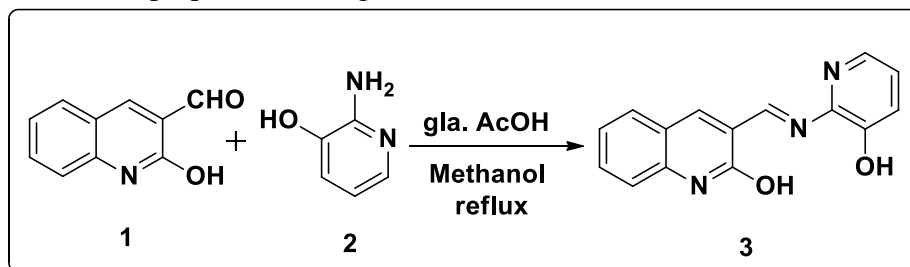
The purity of the compound was checked by TLC using precoated silica gel plates 60<sub>254</sub>(Merck). FTIR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethyl silane 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<sup>-1</sup>. A Gouy balance model 7550 using [Co(NCS)<sub>4</sub>] as standard is operated to examine the magnetic moment values of the metal complexes. The SEM/EDX images were obtained from a Hitachi SEM analyzer.

All the chemicals 2-Hydroxyquinoline-3-carbaldehyde, 2-aminopyridin-3-ol and metal chlorides were purchased from sigma Aldrich. The solvents methanol, DMSO and glacial acetic acid used were of AR grade, used without purification.

### EXPERIMENTAL:

**Synthesis of (E)-3-(((3-hydroxypyridin-2-yl)imino)methyl)quinolin-2-ol (ligand) (3):** Charged 5 mmol of 2-Hydroxyquinoline-3-carbaldehyde (**1**), 5 mmol of 2-aminopyridin-3-ol(**2**) to methanol (10 ml) in round bottom flask and added catalytic amount of glacial acetic acid. Then the reaction mixture was refluxed for 1 hr with continuous stirring. The completion of the reaction progress was checked by TLC (Methanol: Chloroform,1:9) and also observed formation of yellowish precipitate. After completion of the reaction, the precipitate was filtered, dried and recrystallized from ethanol. The yield obtained was pure (E)-3-(((3-hydroxypyridin-2-yl) imino) methyl) quinolin-2-ol (ligand) (**3**) showed in Scheme-1.

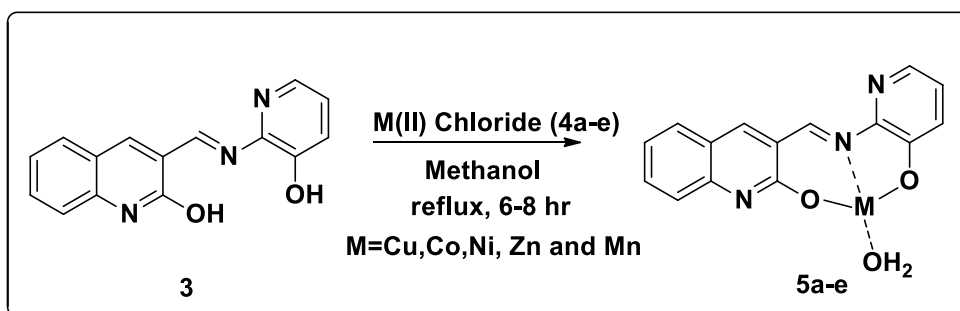
**Scheme-1:** preparation of ligand (3):



**Synthesis of metal complexes (5a-e):**

A methanolic solution of (E)-3-(((3-hydroxypyridin-2-yl)imino)methyl)quinolin-2-ol (ligand) (**3**) was taken in to round bottom flask and heated to 60°C then slowly added different Metal (II) chlorides (**4a-e**) (5 mmol) with a period of 5 min. The resulting mixture was refluxed for 6-8 hrs. and absence of ligand checked by TLC. After the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The obtained crude product was washed with methanol twice to yield amorphous metal complexes (**5a-e**).

**Scheme-2:** Synthesis of metal complexes (5a-e):



**Antimicrobial activity:**

**Antibacterial activity:** The ligand and metal complexes were screened for their *in vitro* antibacterial activity against *Bacillus faecalis*, *Staphylococcus aureus*, *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 Griseofulvin 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 100µg/ml in DMSO.

**DNA cleavage studies:**

The compounds were dissolved in DMSO then added separately to the pUC18 DNA sample and H<sub>2</sub>O<sub>2</sub>. The sample mixtures were incubated at 37°C 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 55°C, 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 (10 $\mu$ g/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 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:**

Entry	M. F. (M.Wt.)	Anal. (%) (found (%))			
		C	H	N	M
Ligand	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> (265)	67.92 (67.88)	4.18 (4.23)	15.84 (15.91)	-
5a	C <sub>15</sub> H <sub>11</sub> CuN <sub>3</sub> O <sub>3</sub> (345)	52.25 (52.30)	3.22 (3.18)	12.19 (12.22)	18.43 (18.40)
5b	C <sub>15</sub> H <sub>11</sub> CoN <sub>3</sub> O <sub>3</sub> (340)	52.96 (52.90)	3.26 (3.18)	12.35 (12.22)	17.32 (17.40)
5c	C <sub>15</sub> H <sub>11</sub> NiN <sub>3</sub> O <sub>3</sub> (339)	52.84 (52.80)	3.55 (3.48)	12.32 (12.27)	17.21 (18.28)
5d	C <sub>15</sub> H <sub>11</sub> ZnN <sub>3</sub> O <sub>3</sub> (346)	51.97 (51.87)	3.20 (3.26)	12.12 (12.07)	18.86 (18.81)
5e	C <sub>15</sub> H <sub>11</sub> MnN <sub>3</sub> O <sub>3</sub> (336)	53.43 (53.38)	3.59 (3.48)	12.46 (12.42)	16.29 (16.30)

## 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-2.

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

Compound	Calculated mass	Obtained mass
Ligand	265	266 [M+1] <sup>+</sup>
Cu(II) complex	345	346 [M+1] <sup>+</sup>
Co(II) complex	340	341 [M+1] <sup>+</sup>
Ni(II) complex	339	339 [M] <sup>+</sup>
Zn(II) complex	346	347 [M+1] <sup>+</sup>
Mn(II) complex	336	338 [M+2] <sup>+</sup>

**NMR spectrum of ligand:**

The  $^1\text{H}$ -NMR spectra of the ligand showed a singlet at  $\delta$  9.22 ppm integrated for one proton are corresponding to azomethine proton. A singlet at  $\delta$  12.09 ppm integrated for assigned to hydroxy group proton and reaming all protons showed in the aromatic region.

In  $^{13}\text{C}$ -NMR spectra of the ligand shows a signal at  $\delta$  159.8 ppm assigned to azomethine carbon and the entire reaming signal as follows  $\delta$  111.7, 119.2, 122.0, 124.1, 124.8, 125.2, 127.5, 129.2, 129.8, 132.7, 143.3, 145.4 and 149.2.

**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 256 and 321 nm, which corresponds to  $\pi$ -  $\pi^*$ (- C=C) and n-  $\pi^*$ (-C=N) transitions respectively. In addition, the copper complex displayed absorption band at 451 nm respectively. This transition may be corresponding to the d-d transitions of  $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$ , suggesting that the complex compatible with square planar geometry, square planar complexes are expected to give three bands however, these bands usually overlap giving one absorption band. The cobalt complex was showed two bands in the range 495 nm and 640-650 nm which corresponds to d-d transitions  $^4\text{A}_2(\text{F}) \rightarrow ^4\text{T}_1(\text{P})$  and  $^4\text{A}_2(\text{F}) \rightarrow ^4\text{T}_1(\text{F})$  suggested that the complex is compatible with Tetrahedral geometry. Nickel complex displayed medium intensity band at 455 nm suggesting that the complex is compatible with square planar geometry. The Zinc complex was showed broad band at 455 nm in the visible region was due to ligand to metal charge transfer, it suggesting that the geometry of the complex is Tetrahedral. The Manganese complex was displayed broad bands at 386 and 476 nm which corresponds to d-d transition of  $^6\text{A}_{1g} \rightarrow ^4\text{T}_2(\text{G})$  and  $^6\text{A}_{1g} \rightarrow ^4\text{T}_1(\text{G})$  suggesting that the complex is compatible with Tetrahedral geometry. The complexes Cu(II), Co(II), Mn(II) were shows magnetic moment values at 1.80 B.M., 4.29 B.M and 5.85 B.M. respectively, the values are also supported by the electronic spectral data. The Ni(II) and Zn(II) complex were not showed any magnetic moment value due to its diamagnetic property.

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

Compound	Wavelength (nm)
Ligand	256 and 321
Cu(II) complex	264, 451
Co(II) complex	280,323,495 and 640-650
Ni(II) complex	258, 322 and 455
Zn(II) complex	262, 316 and 455
Mn(II) complex	260, 320,386 and 476

**Infrared spectroscopy:**

A strong band at  $1651\text{ cm}^{-1}$  in the IR spectra assigned to the Azomethine nitrogen( $\nu\text{C}=\text{N}$ ) of the ligand <sup>xix</sup>, which was shifted to lower frequency region  $1637\text{ cm}^{-1}$ ,  $1635\text{ cm}^{-1}$ ,  $1639\text{ cm}^{-1}$ ,  $1631\text{ cm}^{-1}$  and  $1631\text{ cm}^{-1}$  after formation of Cu(II), Co(II) Ni(II), Zn(II) and Mn(II) metal complexes respectively <sup>xx</sup>. This confirms the coordination of azomethine nitrogen to the metal ion. A peak showed in the spectrum in between  $3345\text{--}3442\text{ cm}^{-1}$  indicates the presence of water molecule and the presence of oxygen and nitrogen in the coordination sphere is further confirmed by the presence of (M–N) and (M–O) bands in the range of  $448\text{--}593\text{ cm}^{-1}$ . The FTIR results showed that the Schiff base ligand act as tridentate chelating ligand.

**Table-4: FTIR data (cm<sup>-1</sup>) of Ligand and metal complexes:**

Entry	Complex	$\nu\text{H}_2\text{O}$	$\nu\text{C}=\text{N}$	$\nu\text{M}-\text{O}$	$\nu\text{M}-\text{N}$
1	Ligand	3166 (-OH)	1651	-	-
2	Cu(II) complex	3442	1637	515	458
3	Co(II) complex	3345	1635	572	467
4	Ni(II) complex	3350	1639	593	487
5	Zn(II) complex	3371	1631	559	448
6	Mn(II) complex	3378	1631	552	465

**Thermogravimetric analysis (TGA):**

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

**EDX and SEM 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 in Figure-7, it is observed that the experimental atom percentage is close to the expected (theoretical) values. In EDX spectrum-1 the ligand shows characteristic 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 and Cu characteristics signals, it clearly confirm the formation of C<sub>15</sub>H<sub>11</sub>CuN<sub>3</sub>O<sub>3</sub> complex.

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-8. 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.

**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 standard drug.

**Table-5: Antimicrobial zone of inhibition for ligand and metal complexes:**

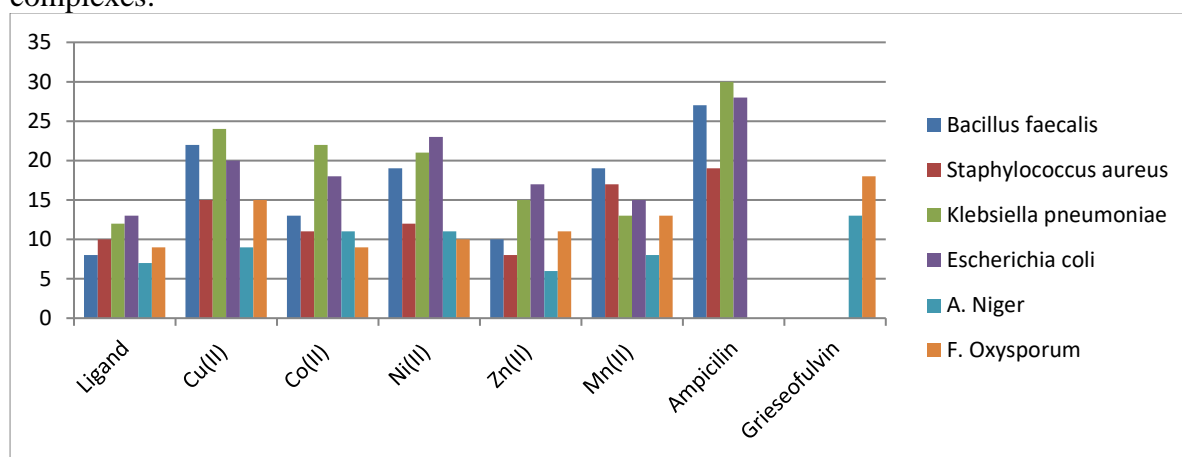
Compound	<i>Bacillus faecalis</i>	<i>Staphylococcus aureus</i>	<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>A. Niger</i>	<i>F. Oxysporum</i>
Ligand	08	10	12	13	07	09
Cu(II)	22	15	24	20	09	15
Co(II)	13	11	22	18	11	09
Ni(II)	19	12	21	23	11	10
Zn(II)	10	08	15	17	06	11
Mn(II)	19	17	13	15	08	13

Ampicillin	27	19	30	28	---	---
Griseofulvin	---	---	---	---	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>Mn>Ni>Co>Zn for *Bacillus faecalis*, Mn>Cu>Ni>Co>Zn for *Staphylococcus aureus*, Cu>Co>Ni>Zn>Mn for *Klebsiella pneumoniae* and Ni>Cu>Co>Zn>Mn for *Escherichia coli*.

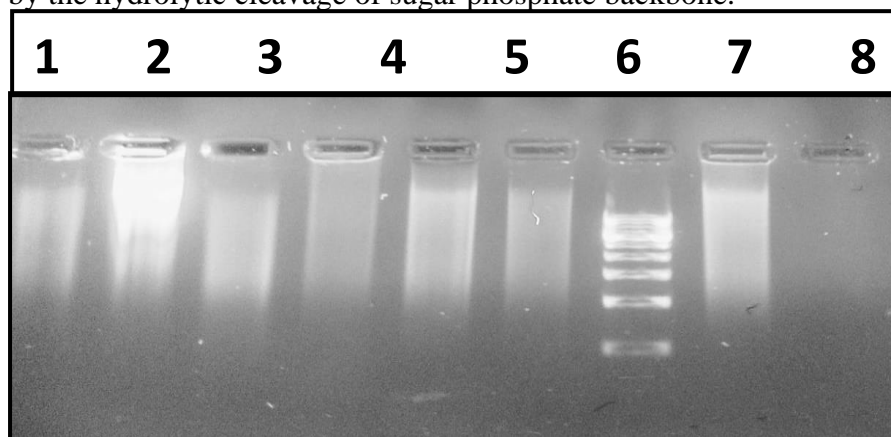
Order of the antifungal activity of complexes were shown as follows as Ni>Co>Cu>Mn>Zn for *Aspergillus Niger* and Cu>Mn>Zn>Ni>Co for *Fusarium Oxysporum*.

**Figure-9:** Graphical representation of antimicrobial activity of the Ligand and their metal complexes:



**DNA cleavage study:**

The agarose gel electrophoresis method was used to study the DNA cleavage activity of the Schiff base and their 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<sub>2</sub>O<sub>2</sub> the complete cleavage of DNA occurred with the Nickel and Manganese complexes. Zinc and copper complexes were showed partial cleavage and no cleavage observed in Ligand and Cobalt complex. The metal complexes were catalyzed by the production of hydroxyl radicals from H<sub>2</sub>O<sub>2</sub> these hydroxyl radicals participate in the oxidation of deoxyribose moiety followed by the hydrolytic cleavage of sugar phosphate backbone.



**Figure-10:** DNA cleavage of ligand and their metal complexes.

Lane-1: Control DNA+DMSO; Lane-2: Control DNA; Lane-3: DNA+Cu(II) complex+H<sub>2</sub>O<sub>2</sub>; Lane-4: DNA+ Ni(II) complex+H<sub>2</sub>O<sub>2</sub>; Lane-5: DNA+Co(II) complex+H<sub>2</sub>O; Lane-6: DNA+Zn(II) complex+H<sub>2</sub>O<sub>2</sub>; Lane-7: DNA+Marker; Lane-8: DNA+L1+H<sub>2</sub>O<sub>2</sub>; Lane-9: DNA+Mn(II) complex+H<sub>2</sub>O<sub>2</sub>;

### CONCLUSION:

A series of novel (E)-3-(((3-hydroxypyridin-2-yl)imino)methyl)quinolin-2-ol based Cu(II), Co(II), Ni(II), Zn(II) and Mn(II) metal complexes have been synthesized 1:1 metal to ligand ratio. All the synthesized compounds were analyzed by different analytical techniques. All the synthesized compounds were tested for their antimicrobial activity and DNA cleavage studies the results suggested that most of the metal complexes showed better activity than the ligand. We wish this study may help in the development of Organometallic chemistry.

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