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# Synthesis, Characterization, Biological Activity and Molecular Modeling Studies of Cu(II) Complex with N,O- Chelating Schiff's Base Ligand Incorporating Azo and Sulfonamide Moieties

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### Abstract

The copper(II) azo-dye Schiff base complex [CuL(OAc)]2, was prepared and characterized on the basis of elemental analyses, spectral, magnetic, molar conductance and thermal analysis. Square-planar geometry has been assigned to the prepared complex. Dimeric complex is obtained with 2:2 molar ratio. The IR spectrum of the prepared complex was suggested that the Schiff base ligand (HL) behaves as a bi-dentate ligand through the azomethine nitrogen atom and phenolic oxygen atom. Thermal properties and decomposition kinetics of copper(II) complex was investigated. The interpretation mathematical analysis and evaluation of kinetic parameters (E,A,  $\Delta H$ ,  $\Delta S$  and  $\Delta G$ ) of all thermal decomposition stages have been evaluated using Coats–Redfern (CR), Horowitz–Metzger (HM) and Piloyan–Novikova (PN) equations. In molecular modeling the geometries of ligand HL and its copper(II) complex was fully optimized with respect to the energy using the 6-31G basis set. The pathogenic activities of the synthesized compounds were tested in vitro against the sensitive organisms *Staphylococcus aureus* (RCMB010027), *Staphylococcus epidermidis* (RCMB010024) as Gram positive bacteria, *Klebsiella pneumonia* (RCMB 010093), *Shigella Flexneri* (RCMB 0100542), as Gram negative bacteria and *Aspergillus fumigates* (RCMB 02564), *Aspergillus clavatus* (RCMB 02593) and *Candida albicans* (RCMB05035) as fungus strain, and the results are discussed.

**Keywords:** Azo-dye Schiff's base ligand; Copper complex; Electronic; IR; ESR; Molecular modeling

Newly synthesized ligand and its copper(II) complex have been screened against different bacterial and fungal growth. The proposed structure for HL is shown in Figure 1.

# Introduction

Medical inorganic chemistry has exploited the unique properties of metal ions for the design of new drugs [1]. Sulfonamides were the first drugs found to act selectively and could be used systematically as preventive and therapeutic agents against various diseases [2]. Sulfur ligands are wide spread among coordination compounds and are important components of biological transition metal complexes [3]. Research on Fe-S complexes has flourished as a result of the discovery that they are present in electron transfer and nitrogen fixing enzymes [3]. Metal complexes with sulfur containing unsaturated ligands are also of a great interest in inorganic and organometallic chemistry, especially due to their potential with novel electrical and magnetic properties [3]. Schiff bases continue to occupy an important position as ligands in metal coordination chemistry [4], even almost a century since their discovery. Schiff bases have also been shown to exhibit abroad range of biological activities, including antifungal, antibacterial, antimalarial, antiinflammatory, anticancer and antiviral properties [5-10]. The study of the reactivity of various types of hetero aromatic containing Schiff bases linked to metal complexes has received a great deal of attention during the past decades [3]. Some transition metal(II)-complexes of biologically active Schiff bases derived from condensation of 2-acetylfuran and 2-acetylthiophene with sulfaguanidine, sulphathiazole, sulphisoxazole and sulphadiazine in a 1:1 molar ratio using ethanol as the reaction medium were prepared [4]. Metal ion complexes of Schiff bases derived from o-vaniline with suflanilamide and sulfamerazine were studied [11]. In continuation to our interest to prepare azo-dye Schiff bases [12,13] the present paper aims chiefly to prepare azo-dye Schiff base HL. The behavior of this ligand toward copper (II) ion was studied. The characterization of the prepared compounds was performed using different physicochemical methods.



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### Materials and Methods

All the chemicals used were of AR grade, procured from Alfa/ Aesar and Aldrich. Solvents used were of analytical grade. IR spectra (KBr pellets) were recorded in the region 4000–400 cm<sup>-1</sup> on a FT-IR spectrum BX-II spectrophotometer. 1H NMR spectrum was recorded with a model Bruker Advance DPX-300 spectrometer operating at 300 MHz using DMSO-d6 as a solvent and TMS as an internal standard. EPR spectra of Cu(II) complex was recorded as polycrystalline sample and in the DMSO solution, at room temperature (RT) on E4-EPR spectrometer using the DPPH as the g-marker. Electronic spectra were recorded in DMSO solution on a Shimadzu UV mini-1240 spectrophotometer. Magnetic moment measurements (Gouy balance) were made at room temperature using CuSO<sub>4</sub>.5H<sub>2</sub>O as a calibrant. The thermal analyses (TGA and DTA) were carried out in dynamic nitrogen atmosphere (20 mL min<sup>-1</sup>) with a heating rate of 10°C min<sup>-1</sup>using Shimadzu TG-50H and DTA-50H thermal analyzers.

#### Preparation of ligand

The sulfanilamide azo-dye was prepared by the gradual addition of an aqueous solution of 0.01 mol of NaNO<sub>2</sub> to a concentrated HCl 1:1 solution of 0.01 mole of sulfanilamide with stirring and kept for about 20 min in an ice bath at -10°C. A solution of salicylaldehyde (0.01 mol) and sodium hydroxide (5 g) and doubly distilled deionized water (100 mL) was added drop wise to the resulting solution with stirring and the resulting mixture was reacted for 4 h at 0°C. The reaction mixture was acidified with hydrochloric acid. The crude material was recrystallized from ethanol and then dried. Then 0.01 mol p-toluidine was slowly added to a solution of 0.01 mol of the azo compound in 30 mL ethanol. After refluxing the reaction mixture for 2 h, the precipitate was cooled and collected by filtration. The formed solid product was separated by filtration, purified by crystallization from ethanol, washed several times with diethyl ether and dried in vacuum over anhydrous calcium chloride to give orange crystals, yield 90%. The product obtained give elemental analysis (Table 1) consistent with the proposed structure.

**Preparation of copper (II) complex:** HL ligand (0.01 mol) was added to 30 ml ethanol, then 10 ml ethanolic solution of (0.01 mol) of Cu(CH<sub>3</sub>COO)<sub>2</sub>.H<sub>2</sub>O was added with continuously stirring, after that the mixture was warmed at about ~60°C and then neutralized. Immediately, the Olive green precipitate was settle down and filtered off, washed several times by minimum amounts of hot ethanol and dried under vacuo over anhydrous CaCl<sub>2</sub>.

#### **Microbial analyses**

Antibacterial screening was performed by disc diffusion method [14] and ciprofloxacin was used as the standard. Antifungal screening was done by agar diffusion method and Greseofulvin was used as standard. The stains used were *Staphylococcus aureus* (RCMB010027), *Staphylococcus epidermidis* (RCMB010024), *Klebsiella pneumonia* (RCMB 010093), *Shigella flexneri* (RCMB 0100542), *Aspergillus fumigates* (RCMB 02564), *Aspergillus clavatus* (RCMB 02593) and *Candida albicans* (RCMB05035).

### Molecular modeling

We performed cluster calculations using DMOL3 program in Materials Studio package [15], which is designed for the realization of large scale density functional theory (DFT) calculations. DFT semicore pseudo pods calculations (dspp) were performed with the double numerical basis sets plus polarization functional (DNP). The DNP basis sets are of comparable quality to 6-31G Gaussian basis sets [16]. Delley et al. showed that the DNP basis sets are more accurate than Gaussian basis sets of the same size. The RPBE functional is so far the best exchange-correlation functional, based on the generalized gradient approximation (GGA), is employed to take account of the exchange and correlation effects of electrons. The geometric optimization is performed without any symmetry restriction.

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### **Results and Discussion**

Copper complex was prepared by reaction of copper salt with ligand. The molar conductivity at room temperature of  $10^{-3}$  M solutions of complex in DMSO was at  $16 \ ^{\Omega}-1 \ \text{cm}^2 \ \text{mol}^{-1}$  corresponding to non-electrolyte. The copper complex was sparingly soluble in water, ethanol, acetone and most of the organic solvents but completely soluble in DMSO and DMF. Higher melting point of the copper complex than the free ligand indicated the stability of the complex. The analytical data revealed that copper complex possessed 2:2 copper to ligand stoichiometry based on elemental analysis, the complex was assigned the composition as shown in Table 1.

### IR spectra

In the absence of a powerful technique such as X-ray crystallography, IR spectra have proven to be the most suitable technique to give enough information to elucidate the nature of bonding of the ligand to the copper ion. The IR spectra of the free ligand and copper(II) complex was carried out in the range 4000–400 cm<sup>-1</sup> (Figure 2 and Table 2).

The IR spectra of the complex shows a sharp band at 1612 cm<sup>-1</sup>, attributed to  $\nu$ (-C=N-), which is shifted to lower frequency on going from the free ligand (at 1625 cm<sup>-1</sup>) to the complex. This is indicative of the coordination of the imine nitrogen to the metal. Deprotonation of



Ligand or complex (Molecular weight)	Colour	m.p.°C	Elemental Analyses (Found) calculated % AO				
			C%	Н%	N%	Cu%	mol <sup>-1</sup>
HL (394.45)	Orange	132-134	(60.12) 60.90	(4.28) 4.60	(13.93) 14.20	-	-
[Cu(L)(OAc)] <sub>2</sub> (1032.06)	Olive green	>250	(51.15) 51.21	(3.87) 3.91	(10.27) 10.86	(11.09) 12.31	16

Table 1: Elemental analysis and some physical measurements to ligand HL and its copper complexes.

all phenolic functions is confirmed by the lack of -OH stretching bands in the IR at 3400 cm<sup>-1</sup> for copper complex [17]. The band at 1212 cm<sup>-1</sup> for [HL] is ascribed to the phenolic C-O stretching vibrations. This band is shifted to lower frequencies due to O-metal coordination. The v(NH)mode of the sulfonamide group/amino group in the uncoordinated Schiff base remains unchanged in the spectrum of this complex. This suggests that the sulfonamide nitrogen or amino group is not taking part in coordination. The bands, in this ligand, due to vasym (-SO<sub>2</sub>) and vsym (-SO<sub>2</sub>) appear at 855 and 640 cm<sup>-1</sup>, respectively. These remain almost unchanged in the spectrum of complex, indicating that sulfonamide oxygens are not participating in coordination. In the free ligand, the sharp band observed at 1496 cm<sup>-1</sup> is due to v(-N=N-) stretching frequency of azo-dye. In copper(II) complex, this band remains quite unchanged confirming the noninvolvement of the azo-dye nitrogen in complex formation [17]. The IR spectrum of copper(II) complex exhibits two bands at 1590 and 1435 cm<sup>-1</sup> which are characteristic for vasym (-COO-) and vsym (-COO-) of the symmetrical group COO- present in bridging complexes [18]. For copper(II) complex two new bands appear in their IR spectrum at 434 cm<sup>-1</sup> and 454 cm<sup>-1</sup> respectively which are absent from the IR spectrum

Assignments	Ligand (HL)	Copper(II) complex
v(OH)	3386br	-
vas(NH <sub>2</sub> )	3476br	3400br
vs(NH <sub>2</sub> )	3350br	3350br
vas(NH)	3271br	3273br
vs(NH)	3199br	3197br
ρ(NH)	1567m	1560m
v(C=N)	1625m	1612m
v(C-O)	1212m	1200m
vas(SO2)	1325w	1325w
vs(SO2)	1095m	1095m
v(N=N)	1496s	1494m
vas(COO)-	-	1590m
vs(COO)-	-	1435m
vpr(H <sub>2</sub> O)	-	788m
vpw(H <sub>2</sub> O)	-	624s
v(M–N)	-	434m
v(M–O)	-	454m

Table 2: Important IR bands (cm<sup>-1</sup>) of HL ligand and its copper complex.

of the free ligand, these can be assigned to vM-N and vM-O bands, respectively.

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### 1H NMR spectra

The <sup>1</sup>H NMR spectrum of ligand (Figure 3) is assigned as follows (HL): <sup>1</sup>H NMR (300 MHz, DMSO-d6) d (ppm):  $\delta$  3.6 ppm (singlet, 2H, H2N-SO2),  $\delta$  7.9 ppm (multiplet, 4H,-ph-),  $\delta$  8.28 ppm (singlet, <sup>1</sup>H, -CH=N-),  $\delta$  12.78 ppm (singlet, <sup>1</sup>H, -OH).

### Mass spectra

The mass spectrum of Schiff base ligand (Figure 4a) shows the molecular ion peak at m/z 394 corresponding to  $[C_{20}H_{18}N_4O_3S]$  ion. The peaks at m/z=367, 314, 194, 167, 92, 64 and 58 are due to different fragments. The intensities of remaining peaks are in accordance with their abundances.

On the other hand, the mass spectrum of Cu(II) complex (Figure 4b) give [M+] 1032 for [CuL(OAc)]<sub>2</sub>. This peak represents the dimer mass of the parent complex. For [CuL(OAc)]<sub>2</sub>, which have the formula  $[Cu_2C_{44}H_{40}N_8O_{10}S_2]$ , six additional lines appear at the positions: m/ z=984, 833, 797, 638, 516, and 393. These lines correspond to the fragments  $[C_{44}H_{38}Cu_2N_7O8S_2]$ ,  $[C_{37}H_{31}Cu_2N_5O_8S]$ ,  $[C_{34}H_31Cu_2N5O_8S]$ ,  $[C_{24}H_{23}Cu_2N_4O_7S]$ ,  $[C_{22}H_20CuN_4O_5S]$ , and  $[C_{20}H_{17}N_4O_3S]$ , respectively. So it is reasonable to conclude from the assignment of the fragments of the copper complex that this compound exists in a dimeric form.

Electronic spectrum and magnetic properties: The UV-vis spectrum of the ligand (Figure 5a) show three bands in the range 222,









285 and 379 nm which can be assigned to  $\pi$ - $\pi$ <sup>\*</sup> transitions within the aromatic rings,  $\pi$ - $\pi$ <sup>\*</sup> transitions within C=N and intramolecular charge transfer (CT) transition with the whole molecule.

The electronic spectral data of the free ligand and Cu(II) complex (Figure 5b), in the range 200–400 and 200–700 nm, respectively, in DMF solvent as well as their magnetic susceptibility ( $\mu$  eff) and molar conductance values are displayed in Table 1. Electronic spectrum of the free ligand in DMF solution displayed two absorption bands at 35,211 and 26,455 cm<sup>-1</sup>, the first band could be attributed to the  $\pi$ - $\pi$ <sup>\*</sup> transition of the azomethine group (K-band), and the second band might arises from the n- $\pi$ <sup>\*</sup> transitions resulting from nitrogen and oxygen atoms (R-band). These bands exhibit more or less shift in complexes [18].

## **EPR** spectra

EPR studies of Copper(II) complex (Figure 6) was carried out on the X-band at 9.1 GHz under the magnetic field strength 3000 G. The spectrum was recorded in DMSO at room temperature. The trend  $g||>g^{\perp}>2.0024$  indicated that the copper the one unpaired electron is localized in  $dx^2-y^2$  orbital of the Cu(II) ion and the spectral figures are characteristic for the axial symmetry tetragonal geometry. The parameter G, determined as  $G=(g||-2)/(g^{\perp}-2)$ , which measures the exchange interaction between the copper centers in a polycrystalline solid, has been calculated. According to Alaghaz [17,18] if G>4, the



exchange interaction is negligible, but G<4 indicates considerable exchange interaction in the solid complex. The Cu(II) complex reported in this paper gave the "G" values which are greater than 4 indicating the exchange interaction is absent in solid complex.

### Thermal analysis

Recently, there has been increasing interest in determining the ratedependent parameters of solid-state non-isothermal decomposition reactions by analysis of TG curves. Thermo gravimetric (TG) and differential thermo gravimetric (DTG) analyses were carried out for Cu(II) complex in ambient conditions. The correlations between the different decomposition steps of the complex with the corresponding weight losses are discussed in terms of the proposed formula of the complex.

The complex  $[\rm Cu(L)(OAc)]_2$  with the molecular formula  $[\rm C_{44}\rm H_{40}\rm Cu_2\rm N_8\rm O_{10}\rm S_2]$  is thermally decomposed in two successive decomposition steps (Figure 7). The first estimated mass loss of 38.00% (calculated mass loss=38.08%) within the temperature range 545–595K may be attributed to the loss of ( $\rm C_{20}\rm H_{17}\rm N_4O_3\rm S)$  fragment. The DTG curve gives an exothermic peak at 555K (the maximum peak temperature). The second step occurs within the temperature

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range 660-857K with the estimated mass loss 46.44% (calculated mass loss=46.46%) which corresponds to the loss of  $C_{24}H_{23}N_4O_5S$  fragment leaving 2CuO as residue. The DTG curve gives an exothermic peak at 778K (the maximum peak temperature). Total estimated mass loss is 84.44% (calculated mass loss=48.54%).

The thermodynamic activation parameters of decomposition processes of dehydrated complex namely activation energy (E), enthalpy ( $\Delta$ H), entropy ( $\Delta$ S) and free energy of decomposition ( $\Delta$ G) (Table 3), were evaluated by employing the Horowitz-Metzger [19] (HM), Coats-Redfern [20] (CR), and Piloyan-Novikova [21] (PN) methods and were helpful in assigning the strength of the complex. According to the kinetic data obtained from the TG curves, all the complexes have negative entropy which indicates that the complex is formed spontaneously. The negative value of entropy also indicates a more ordered activated state that may be possible through the chemisorption of oxygen and other decomposition products. The negative values of the entropies of activation are compensated by the values of the enthalpies of activation, leading to almost the same values for the free energy of activation [22].

On the basis of above discussion following structure (Figure 8) can be proposed for the synthesized complex.

### Anti pathogenic activities

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The anti pathogenic screening data of compounds are summarized in Tables 4 and 5. The in vitro anti pathogenic screening of the compounds and observed findings indicate that the ligand shows considerable anti pathogenic behavior and coordination provokes its therapeutic action [23]. These observed findings can be explained by the basic Overtone's Concept and Chelation Theory [24,25]. The theory states that the polarity of the copper ion is reduced on complexation due to the partial sharing of its positive charge with donor groups.

Consequently, the positive charge is delocalized over the whole ring, which causes the improved lipophilicity of the compound through cell membrane of the pathogen.

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### **DNA cleavage studies**

The DNA cleavage activities of the azo-dye Schiff base ligand HL and its copper (II) complex at a 50 lM concentration were studied using CT DNA (30 µM) in H<sub>2</sub>O<sub>2</sub> (500 µM) in 50 mMTris-HCl buffer (pH 7.1) and upon irradiation with UV light (Figure 10) of 280 nm. The reaction is modulated by metallo complexes bound hydroxyl radical or a peroxo species generated from the co-reactant H<sub>2</sub>O<sub>2</sub>. In the control experiment using DNA alone (lane 1), no significant cleavage of DNA was observed even on longer exposure time. It is evident from Figure 9, that the Cu(II) complex cleaves DNA more efficiently in the presence of an oxidant than the ligand. This may be attributed to the formation of hydroxyl free radicals, which can be produced by metal ions reacting with H<sub>2</sub>O<sub>2</sub> to produce the diffusible hydroxyl radical or molecular oxygen, which may damage DNA through Fenton type chemistry.





Using Co	ats-Redfern equation					
Stage	Decomposition range (°C)	A(S-1)	Ea(kJ/mol)	ΔH(kJ/mol)	ΔS (kJ/mol K)	ΔG (kJ/mol)
1 <sup>st</sup>	468	3.00×10 <sup>9</sup>	43.35	53.28	-0.031	163
2 <sup>nd</sup>	574	5.48×10 <sup>11</sup>	72.87	73.42	-0.076	182
3 <sup>rd</sup>	798	2.86×10 <sup>6</sup>	113.76	104.96	-0.097	195
UsingHor	owitz-Metzger equation					
1 <sup>st</sup>	468	2.99×10 <sup>9</sup>	43.33	114.48	-0.032	164
2 <sup>nd</sup>	574	5.49×10 <sup>11</sup>	72.26	72.98	-0.076	181
3 <sup>rd</sup>	798	2.88×10 <sup>6</sup>	114.48	105.04	-0.097	193
UsingPilo	yan–Novikova equation					
1 <sup>st</sup>	468	3.05×10 <sup>9</sup>	42.78	54.16	-0.028	165
2 <sup>nd</sup>	574	5.47×10 <sup>11</sup>	71.98	73.48	-0.076	183
3rd	798	2.89×10 <sup>6</sup>	114.33	105.07	-0.098	194
Using Co	ats-Redfern equation					
Stage	Decomposition range (°C)	A(S-1)	Ea(kJ/mol)	ΔH(kJ/mol)	ΔS (kJ/mol K)	ΔG (kJ/mol)
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3 <sup>rd</sup>	798	2.89×10 <sup>6</sup>	114.33	105.07	-0.098	194

Table 3: Kinetic parameters of [Cu(L)(OAc)],

Compd. (no)	Gram-positi	ve	Gram-negative		
	S.aureus	S.epidermidis	K.pneumonia	S.flexneri	
Cont. DMSO	0	0	0	0	
St.	29.2 ± 0.14	26.5 ± 0.18	27.4 ± 0.15	25.7 ± 0.24	
(MIC)	(0.06)	0.48)	(0.24)	(0.48)	
HL	11.7 ± 0.58	13.9 ± 0.44	12.2 ± 0.16	0	
(MIC)	(125)	(62.5)	(125)		
CuL2	16.3 ± 0.56	16.8 ± 0.67	21.3 ± 0.76	16.7 ± 0.67	
(MIC)	(7.81)	(7.81)	(31.25)	(31.25)	

Table 4: Antibacterial activity data of the compounds.

Ligand/complex (MIC)	A. fumigatus	A. clavatus	C.albicans
Cont. DMSO	0.0	0.0	0.0
St.	23.7 ± 0.10 (0.97)	21.9 ± 0.12 (1.95)	26.4 ± 0.20 (0.48)
HL	11.0 ± 0.63 (125)	12.1 ± 0.43 (62.5)	0
(1)[CuL(OAc)] <sub>2</sub> .H <sub>2</sub> O	16.7 ± 0.23 (15.63)	13.9 ± 0.54 (15.63)	12.2 ± 0.36 (7.81)



**Figure 9:** Gel electrophoresis diagram of the metal complexes. Lane 1: control DNA; lane 2: DNA + HL +  $H_2O_2$ ; lane 3: DNA + Cu(II) complex + $H_2O_2$ .



This hydroxyl radical participates in the oxidation of the deoxy ribose moiety, followed by hydrolytic cleavage of sugar–phosphate backbone [26]. Further, the presence of a smear in the gel diagram indicates the presence of radical cleavage.

### Molecular modeling

In case of a zo-dye Schiff's base ligand (Figure 10) it is noticed that the HOMO or bitals (-8.68466 eV) are located on the substituent of the



phenyl group while the LUMO orbitals (-0.72565 eV) on the phenyl group. Computed dipole moment is 5.356 Debye. N=N bond lengths are 1.37 Å, N-C 1.39, 1.36 Å, S=O 1.68 Å, C=N 1.31 Å and C-O 1.91 Å.

In the Cu(II) complex (Figure 11) with ligand the hydroxyl (OH), acetate (OAc) and azomethine (CH=N-) ligand occupying the equatorial position bound trans fashion in a distorted tetragonal geometry. The bond lengths and angles are close to those reported in literature [17]. The copper atom lies on the mean plane of the two chelating nitrogen and two chelating oxygen atom. The two phenyl groups on the ligand are exactly parallel to each other. The chelating part of the ligand adopts a distorted pentagonal arrangement with the metal centre as one of the apices. Attempts to optimize the copper(II) was not successful.

## Conclusion

Our proposed structure of azo-dye Schiff base ligand on the basis of the IR, <sup>1</sup>H NMR, mass, UV–vis. spectra has potential binding sites towards the copper ion and act as bidentate chelate by coordinating through hydroxyl oxygen and azomethine nitrogen. Spectral characterizations of the new complex showed that Cu(II) form four coordinate square-planar complex with 2:2 (copper:ligand) stoichiometry. The proposed structure of complex was geometrically optimized and their structural parameters were calculated on the basis of using DMOL3 program were performed in Materials Studio package program and the calculated data were correlated with the current experimental data. The complex can effectively cleave plasmid DNA in the presence of  $H_2O_2$  as an oxidant. The mycological studies reveal that the compounds act as anti pathogenic agents and anti pathogenic behavior provokes on coordination.

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