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SYNTHESIS, CHARACTERIZATION AND APPLICATION OF COPPER (II) COMPLEX WITH HETEROCYCLIC BASE IN DFT ANALYSIS, DNA STUDIES, CYTOTOXICITY AND MOLECULAR DOCKING STUDIES

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Abstract

The synthesized new commercial ligand copper (II) complex [Cu (4-methyl-1,10-phen) (5,6-epoxy-1,10-phen) NO_3]NO_3·H_2O, confirmed by IR, elemental analysis, EPR and UV–Vis studies. This Cu (II) ion adopts a fashioned by two N atoms from the 4-methyl-1,10-phenligand and another two N atoms of the 5,6-epoxy-1,10-phen ligands and one more NO_3 atom. The nitrogen connected with the central metal atom. The Copper(II) metal complex are consist by energy holes of frontier orbital (HOMO-LUMO) considered with B3LYP /6-31G/LANL2DZ level of theory in the gaseous phase. Theoretical value can be calculated molecular orbitals (HOMO-LUMO) and their own energies, implying charge transport inside the complex. Moreover, the metal complex interacted with CT-DNA are confirmed about by UV–Vis absorption spectrum, EB displacement assay and CV studies. the pBR322 DNA cleavage with copper(II) metal complex have been analyzed by the gel electrophoresis method. The potent cytotoxic effects were against human cell line (HepG2) and The copper (II) metal complex has been discovered to have antimicrobial effects. Copper (II) metal Complex was bind to the DNA and intercalative mode and molecular docking analysis was supported out.

Keywords: Six-coordinated Copper(II); Epoxy-phenanthroline; DFT analysis; DNA binding; DNA cleavage; Cytotoxicity.

Introduction

In present century, transition metal based coordination compounds have become quite significant in medicinal chemistry [1–4]. Generally, different metal complexes have been enhanced from variety of transition metals due to greater DNA interaction and biological activities. The metal complex provides broad potential in medicinal chemistry and drug fabrication [5, 6]. The copper complexes in particularly higher potential interest in the improvement of chemotherapeutic agents [7]. Transition metal based compounds that are sufficient for

cleaving nucleic acids and binding, which is significant attention due to their various usage in nucleic acid, like foot-printing analysis and also as a supposed anticancer medicine. The binding experiment of metal complex with DNA have expected considerable responsiveness due to their prominence in chemotherapy, utilization of novel classes of pharmaceutical field and molecular sector [8,9]. The transition metal complex containing multi-dentate aromatic ligands and specifically N-containing ligands such as heterocyclic substrate with DNA interaction. The Copper is exhibits significant role in human being body and plays a very important role in biological manners undergoing electron transportation reactions. Here, exhibited that the Cu (II) complexes shows superior DNA binding ability in presence of ligands because of that ligands containing hetero atom like that {N,O,S}electron Donor soluble. [10]. Generally, the1,10-phenanthroline derivative ligands widely used in coordination chemistry, because of it has act for more ever best classic chelating ligand in to another [11-14]. The 5,6-double binding in 1,10-phenandroline has susceptible affected easily, since for the reason that simply form epoxies derivatives. [15,16]. Up on the above-examined results, so that we are involved in develop additional and more effectual chemo agents. In extension of our before work [17–21]. We have synthesized a new novel Cu (II) metal complex and characterize via different spectroscopic analysis such as FT-IR, UV-Vis and EPR analysis. Furthermore, the binding activity of complex with CT-DNA has estimated in UV-Visible spectrometer, CV studies, fluorescence, and which has performed as cleavage properties towards pBR322 DNA carried out by agarose gel electrophoresis.

2. Experimental

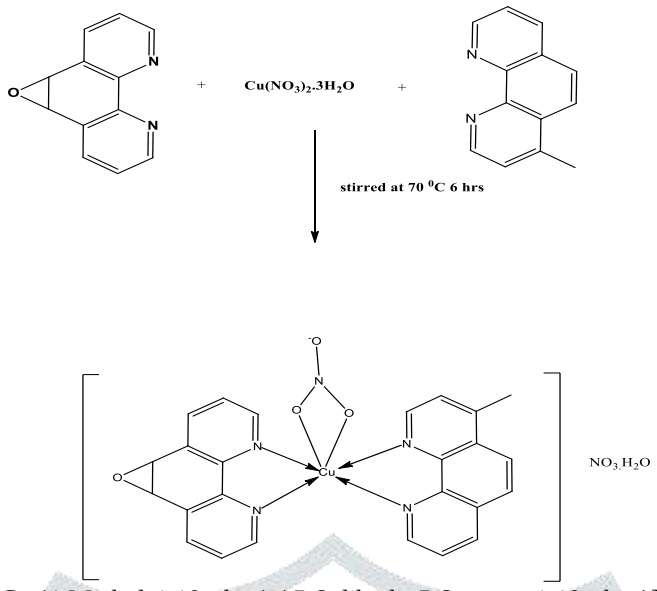
2.1. Materials

The commercial ligand 4-methyl-1,10-phenanthroline, was purchased from sigma Aldrich. 5,6-dihydro5,6-epoxy1,10-phenanthroline with Cu (II) nitrate tri hydrate were bought from TCI chemicals, Calf thymus DNA and super coiled pBR322 DNA were purchased from Genie, Bangalore, stored at 4°C. Ethidium Bromide and (Tris-HCl) were received since Himedia, India. Tris- HCl /NaCl buffer dissolved in DD water, along with the pH range were maintained to 7.2 in HCl / NaOH solution.

2.2. Synthesis of Cu (II) complex

The mixture of 4-methyl- 1,10-phenanthroline (388.46 mg, 2.00 mmol) and $Cu(NO_3)_2{\cdot}3H_2O$ (483.0 mg, 2.00 mmol) was dissolved in methanol- water (1:1 ratio) solution, after, that was taken into RB flask and using magnetic stirrer was increased 200 RPM at 10 minute. Then methanolic solution (10 mL) of (2 mmol) [5,6-dihydro5,6-epoxy1,10-phenanthroline (416.5 mg) was mixed with RB flask solution. the mixture of solution was stirring sustained for 6 h at 60 °C. Finally, dark green color solution appeared. the mixture filtered and then transferred into the 100 ml clean beaker. It has evaporated at room temperature. The dark green colored products obtained.

Yield: 0.78 g (61.5%). Analytical Calculation.$C_{25}H_{20}CuN_6O_8$ (%): Carbon, 50.38; Hydrogen, 3.38; Nitrogen, 14.10. Found (%): Carbon, 50.25; Hydrogen, 3.20; Nitrogen, 14.00. Infra-Red (K-Br, cm^{-1}): 3423br, 2922m, 1579w, 1522s, 1427m, 1386vs, 1380w, 1125s, 1072s, 670s, 651vs. UV-Visible spectra have (H_2O), λ/nm (ε/M^{-1} cm^{-1}): 272(11.541) and 301(5.333; л–π*), 675 (32; d → d).Conductance ΛM (Ω^{-1} cm^2 mol^{-1}) in water at room temperature. μeff = 1.79 BM at 298 K. $g_{\|}$ = 2.19, $g_{\perp}$ = 2.10, μeff = 1.62 BM at 298 K.



Scheme:1. [Cu (4-Methyl-1,10-phen) (5,6-dihydro5,6-epoxy-1,10-phen)](NO_3)(H_2O**)**

2.3. Characterization and DNA & Biological studies

A Bruker Spectrometer was used to record infrared spectra of solid nature copper (II) complex within the region of wave number is 4000–400 cm^{-1}, at RT. UV-Vis spectroscopy range of 200-800nm was recorded, EPR spectrum, emission, DNA studies and biological activities were analyzed. After that, cyclic voltammetry studies depending on the current vs potential are described in our earlier publications [22,23].

3. Results and discussion

3.1. FT-IR Analysis

The new copper (II) complex were one-spot synthesized good yield obtained from in this reaction Cu (NO_3)$_2$.3H_2O with 4-methyl-1, 10 -phenanthroline and 5,6-dihydro5,6-epoxy1,10-phenanthroline. The new synthesized complex most stables and soluble in all organic solvents. Moreover, The FT-IR is completely consistent with the chemical structure and functional groups. The Infra-Red spectra of the Cu (II) metal complex have a broad peaks appear at 3423 cm^{-1} accredited towards O–H stretch frequency. The C–O epoxide peak appeared at 1579 cm^{-1} [24]. The [v(C=N) and v(C=C)] at 1437cm^{-1} and 1522cm^{-1}in the phenanthroline ligands, correspondingly. The coordinated nitrate appeared at 1380 cm^{-1} [25-26], and then (M-O) and (M-N) bands appeared at 1072 and 1125 cm^{-1}as shown as (Fig 1).

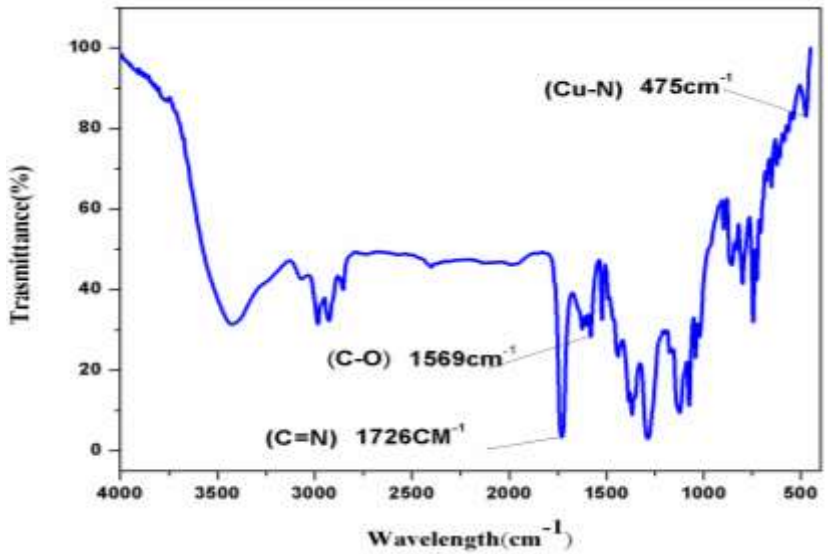


Figure 1. FT-IR-Spectrum of Cu (II) complex

3.2. EPR analysis

EPR spectroscopy can identify paramagnetic species such as copper (II). Particularly in this analysis was conducted at very low temperatures. The nature of the solid state Cu (II) metal complex evaluated by the EPR spectrum in liquid nitrogen atmosphere. The Cu (II) metal complex appeared at broad peak as shows as Figure 2 with a value for g = 2.08–2.13, specifying the anti-ferromagnetic communication meanwhile copper ions [27-28]. The g‖ values of EPR spectrum has been reported in previous paper [29-32]. Hence, copper (II) complex g‖ values are appeared the 2.10–2.19 with both Cu–O and Cu–N bonds [33]. The calculated parameter Value using following this equation G ¼ ($g_{\parallel}$ 2.0023) / ($g_{\perp}$ 2.0023) for the copper (II) metal complex values are lower than 4, this foretells that the substitute interaction meanwhile the metal middles I s slight [34].

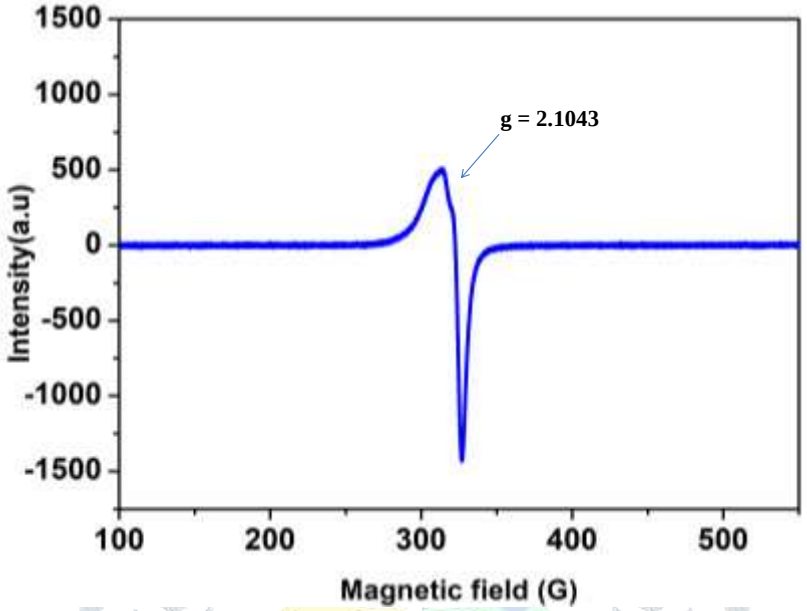


Figure 2. EPR spectrum of copper (II) complex

3.3. Electronic absorption spectral studies and interactions with DNA

Metal complexes' connections of DNA have been studied in order to create better chemotherapeutic agents. Moreover, the Transition metal copper (II) complex are especially attractive moieties for such studies because it has definite copper (II) metal complex and often have distinct electrochemical or photo-physical properties, which improve the binding agent's features. [35]. The complex shows two peaks an extreme charge transfer (CT) band at the range of 272 and 301 nm, it was consist to the π→π*and n→π* transition like the coordinated N, N-donor 1,10-phenanthroline unit with The d-d band was appeared at 675 nm for aqueous medium as shown in Fig. 3(A) [36-37]. However, the binding of copper(II) metal complex toward DNA helix have been studied using conformed by the absorption spectrum, which track variations in absorbance and wavelength shifts as shown in Fig.3(B).

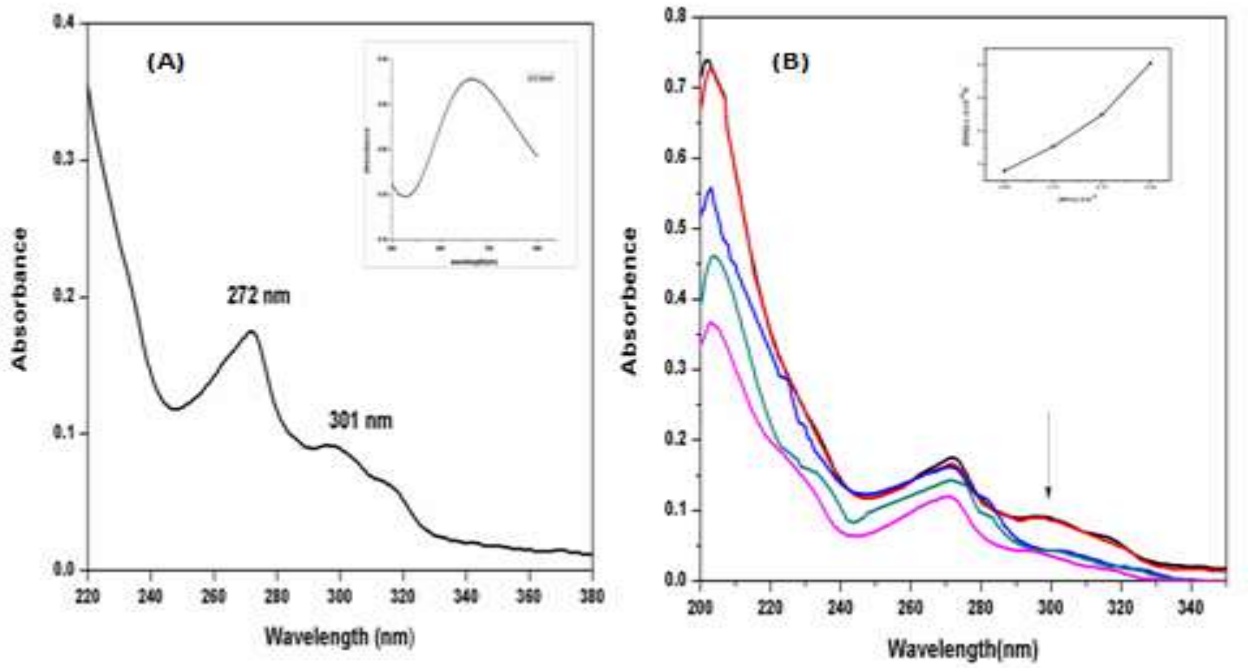


Figure 3. The absorption spectrum of Cu (II) complex and DNA Binding

Moreover, the electronic absorption spectrum of Cu (II) complex by the absence and presence in the CT-DNA since amount of increasing concentration of CT-DNA result in hypochromisum was seen and red shift was noted which confirmed by non-covalent intercalative binding involving complex along with CT-DNA. while the DNA double helix retains several hydrogen-bonding site, Especially, the methyl group of the 4-methyl-1,10 phenanthroline connected with the hydrogen bonds to the DNA helical chain, the hypochromism peak was identified in the absorption spectrum. All so the related hypochromism has been noted for Cu (II) complex manner C–H and methyl group into incomplete intercalation binding DNA base pair [38-39].

The ability of binding constant, K_b of 1.4 (± 0.4) × $10^5 M^{-1}$was calculated coming from the plot of [DNA]/(ε_a – ε_f)versus [DNA] . It could be attributable to the complex's most number of planar 1,10-phenanthroline ligands and large number of Cu (II) complex substituent's, which work together to reduce the complex's overall binding ability to DNA. This demonstrated that binuclear Cu (II) complex having strongly bind to CT-DNA [40].

3.4. Fluorescence analysis

The complexes' comparative binding to CT-DNA has been used in the emission analyses. The intensity concentration to ethidium bromide (EB) emission was used often a spectral investigation. Which fluorescence spectra of the metal complex were analyzed using in DMSO Figure.4. The copper (II) complex was excited 550nm, which metal complex display the emission spectra was noted in the intensity spectral range of 550-650 nm. Particularly, copper (II) complex of the florescence emission maximum at 650 nm. The metal complexes make the energy transfer from the excited state metal ions causing decreases of the PL intensity. For this reason, the PL intensity of copper (II) complex is decreased. Moreover, the copper (II) complex appearance a values are reduced in PL concentrations associated to the ligand usually due to the delocalization of π electrons inside the system [41-42].

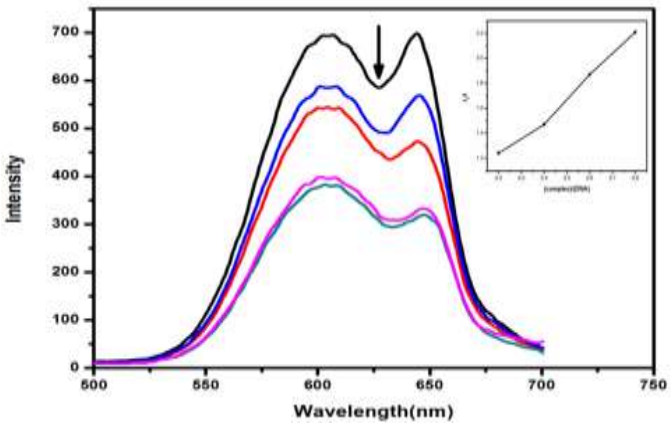


Figure 4. Emission spectrum of Cu (II) complex

The k_q values are obtained for the copper (II) complex among copper chelates were 2.76 X $10^4 M^{-1}$ for respectively. Such a reduced Emission behavior of EB bound to DNA produce in means of the interface Cu (II) complex with DNA [43-44].

3.5. Cyclic voltammetry studies

The metal complex was analyzed by the cyclic voltammetry to using DMSO solvent. In this study was evaluated by the intercommunication among complex and DNA deliver a valuable supplement to the before make use of analysis such seeing that UV-Vis and fluorescence investigates. The typical CV of 0.01 mM solution of complex [Cu(4-Methyl-1,10-phen)(5,6-dihydro5,6-epoxy-1,10-phen)]$(NO_3)(H_2O)$ without and with DNA on using GC electrode in DMSO solution as shown in (Fig. 5).

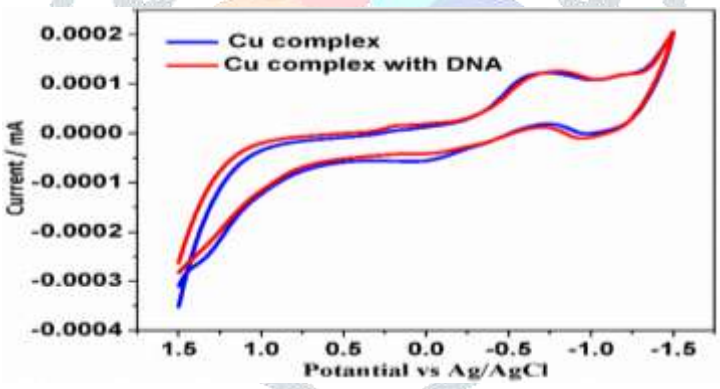


Figure 5. CV analysis of the optimized Cu (II) Complex in addition of DNA and free DNA

The cyclic voltammetric (CV) analysis were achieved to understand the electrochemical activity of metal complex was conformed in -0.500 V potential window on a scan speed of 50 mV s^{-1} with pulse amplitude 50 mV (Fig. 5) indicates the copper complex in DMSO solutions (1x 10^{-1}M) are given the anodic and cathodic CV peaks from CV study well resolved anodic and cathodic potentials were observed in copper (II) complex. However, a cathodic peak was obtained at –0.80 V reduction of copper(II) to copper(I). the overturn scanning process, no significant oxidation peak was appearing, found that the progression be irreversible. while addition of CT–DNA into the Cu (II) complex, the reduction peak displayed at –0.71 V. it optimized that synthesized Cu (II) complex is decreases the current at positive peak potential. In adding of CT–DNA into the metal complex are not shows reduction peak and the obtained the existing intensity decrease is attributed to the diffusion of an equilibrium mix up of free and DNA-bound Cu(II) complex. The positive shift of reduction potential shows that the captured the Cu (II) complex with the CT–DNA bases [45].

3.6. Nuclease activity

In order to investigate, DNA cleavage studies is a significant tool to identification of prepared transition metal complex with DNA recognition [46]. Variants in complex DNA cleavage efficiency gains could come since a result of complex binding affinities into the DNA [47]. Loosening the superconducting circular shape of pBR322 DNA if spherical and linear shapes controls DNA splitting. Once spherical plasmid DNA was separated via gel electrophoresis process, the tightly coiled form migrates the quickly (Form I). When a strand splits, the super coils relax to create a slowly moving open circular shape (Form II). DNA cleavage was confirmed by observing coming from super-spiral DNA (Form I) to nick DNA (Form II). The copper (II) metal complex activity had calculated by the adaptation of DNA from Form I to Form II. The DNA cleavage dependents on the concentration of complex are Fig. 6 shows the clear indicate that results into gel electrophoresis departures of plasmid pBR322 DNA prompted through growing the various concentration by the Cu (II) metal complex during the deficiency of neutral pH = 7.2 (Tris $–H^+Cl^-/Na^+Cl^-$ buffer solution) at room temperature.

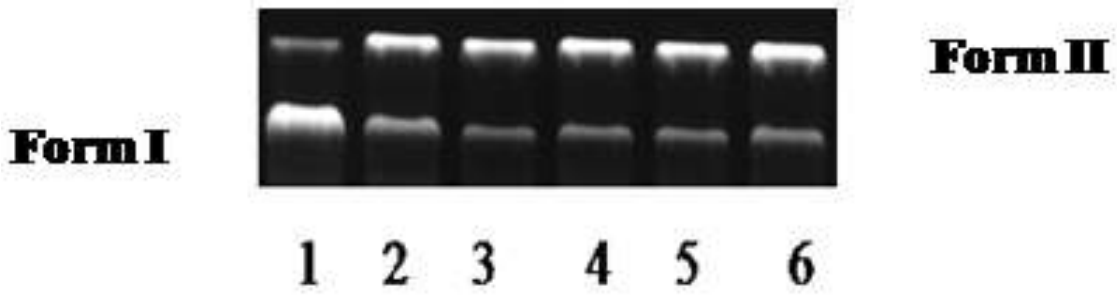


Figure 6. DNA cleavage of Cu(II) complex

The various amount of adding the Cu(II) metal complex strength, to Form(I) decrease step by step and Form(II) gradually increase, The Cu (II) Complex Super Spiral pBR322 ability by splitting plasmid DNA Form (I) keen on nick circular Form (II) was identified. At 15 μM and 20 μM (Lane 4 to 5) increments the form (I) on the premises almost completely disappeared. As a result, the Cu (II) metal complex be cleaved DNA capably without any reducing agent.

3.7. Molecular docking studies

To conform the interface of commercially obtained ligand to Cu(II) metal complex with CT-DNA, it has very attractive tools of the molecular docking method to optimize an internal into the behavioral process, by inserting a molecule primarily non-covalently to the ligand connecting of the targeted delivery territory of the DNA [48], Furthermore, the critical role including both molecular gratitude of nucleic acid and the cogent design of new chemotherapeutic drugs. the current copper(II) metal complex through arrangement d(CGCGAATTCGCG)2 dodecahedra were achieved in start with guess the selected binding place near the chosen location of satirically suitable copper (II) complex intimate the DNA channel. the external edge of the DNA connections without distracting the double helical structure are keen on the intercalative method under attack DNA, Vander Waals contact and hydrophobic connections with DNA molecules calm the AT rich region and copper(II) metal complex, that also define groove stability (Fig. 7) [49]. Meanwhile, the minimum energy docked poses confirmed by complex had not changed, and the total energy content designated was zero.

Figure 7. Molecular docking image of the prepared Cu (II) complex

The lesser the comparative binding energy, then the additional binding attraction is meanwhile of the DNA species. The molecular docking result of metal complex efficiently binding with the DNA receptor and shows excellent FEB value –5.15 kcal mol^{-1}, respectively. The prepared complex is showed the maximum negative comparative binding energy, which is strongly binds to the DNA compare then the metal complex. It is confirmed that the strong binding interactions through symmetrical oxygen bonding interactions as given in the **Table 1** [50**].**

Table 1. Molecular docking binding energy of the complex.

Rank	Lowest Binding Energy (kcal/mol)
1	-5.15
2	-5.03
3	-4.73
4	-4.52
5	-4.4
6	-4.33
7	-4.29
8	-4.25
9	-4.23
10	-4.21

As a result, we can reach the conclusion that spectroscopic techniques and molecular docked models supplement each other, substantiating our spectroscopic findings and providing additional proof of complex formation binding.

3.8. Computational details

The structures of studied complex have been cautiously optimized use the B3LYP/6-31G/LANL2DZ rule of theory. Since, the Highly Occupied Molecular Orbital (HOMO) was primarily dispersed on the coordinated with non-coordinated nitrate oxygen atom to the metal atom in complex, particularly; LUMO has a primarily concentrated just like above metal center. The HOMO-LUMO energy cavity (HLG) for the Cu (II) metal complex is 1.5453 eV. HLG is a precarious parameter in defining molecular electron conduction property since it is calculating the e^- conductivity. HOMO and LUMO energy gap recommend the electron transfer relations between the copper complex molecules as shown in Fig. 8 [51].

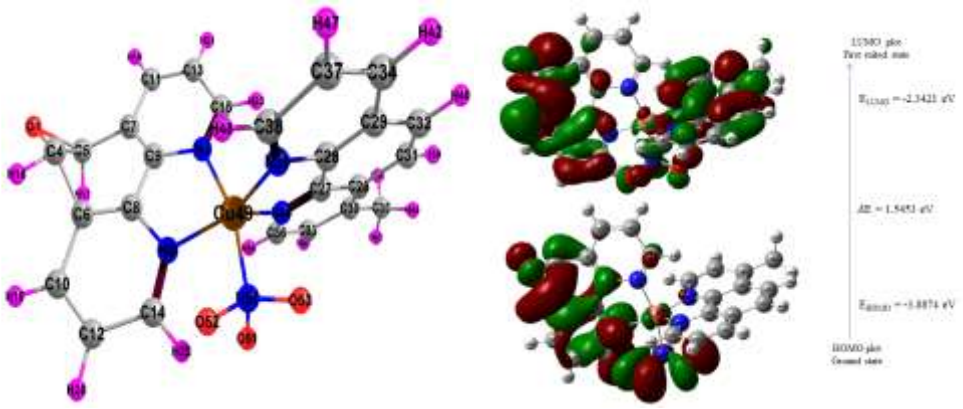


Figure 8. Theoretical geometries of optimized Cu(II) complex

Table 2. (A) parameter values of synthesized Cu (II) complex

Parameter	Values
PDB ID	423D
Binding Energy (kcal/mol)	-5.15
Inhibition constant, ki (µm)	168.75
RMSD (Å)	49.900
Intermolecular Energy (kcal/mol)	-7.24
Vdw + Hbond + desolv Energy (kcal/mol)	-6.10
Electrostatic Energy (kcal/mol)	-1.13
Final Total Internal Energy (kcal/mol)	-3.18
Torsional Free Energy (kcal/mol)	+2.09
Unbound System's Energy (kcal/mol)	-3.18

Table 2. (B) parameter values of synthesized Cu (II) complex

Parameter	Values
HOMO(eV)	-3.8874
LUMO(eV)	-2.3421
Ionization potential	3.8874
Electron affinity	2.3421
Energy gap(eV)	1.5453
Electronegativity	3.1148
Chemical potential	-3.1148
Chemical hardness	0.7727
Chemical softness	0.6471
Electrophilicity index	6.2781

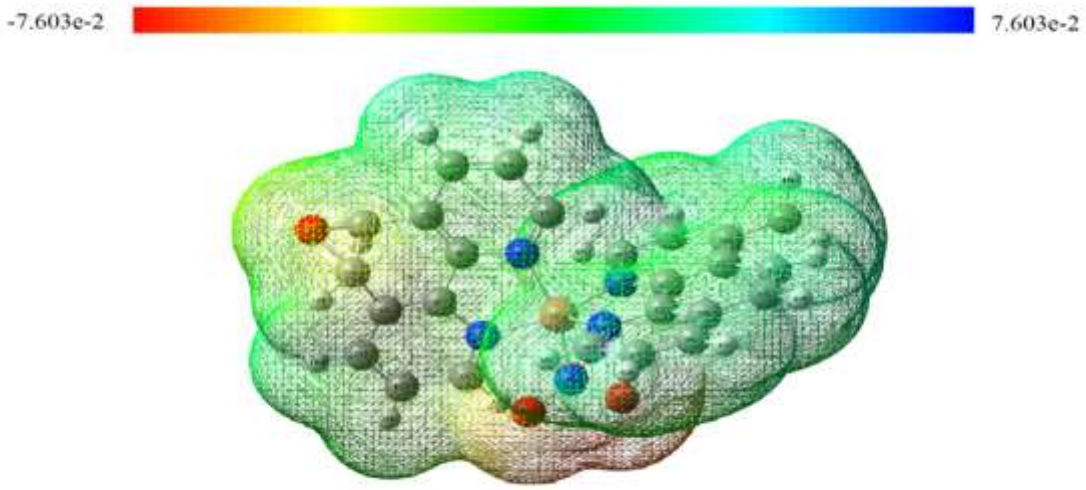


Figure 9. DFT based conformational structure of Cu (II) complex

3.9. Cytotoxic activity

The MTT assay is used to investigate the anti-cancer activity of copper metal complexes that could be used as chemotherapeutic agents. The metal complex's capability on A 549 cells has been tested for 24 hours with or without various concentrations (6.25-100 g/mL) As a positive control, cells incubated with various concentrations of doxorubicin were used. MTT assay was performed after the incubation period to estimate the percentage of cell death. The Cu (II) metal complex cells were incubated here triplicate for each concentration. Fig. 10. Has clearly shown there is an obvious reduce in the amount of live cells into cells incubate inside complex it was concentration-dependent method. Capability of cells incubated with no any other compound was consider into 100% and all so the percentage of be alive cells incubated within compounds be given because relative to the control. Moreover, the IC50 value by the Cu (II) complex also doxorubicin was 39.76 µg /ml (R2= 0.985) likewise. Especially, the morphology assessment also shown this the spreading of the cells be significant introverted and the cells display morphological modify such while cell contraction and cell detachment (Fig. 10,11).

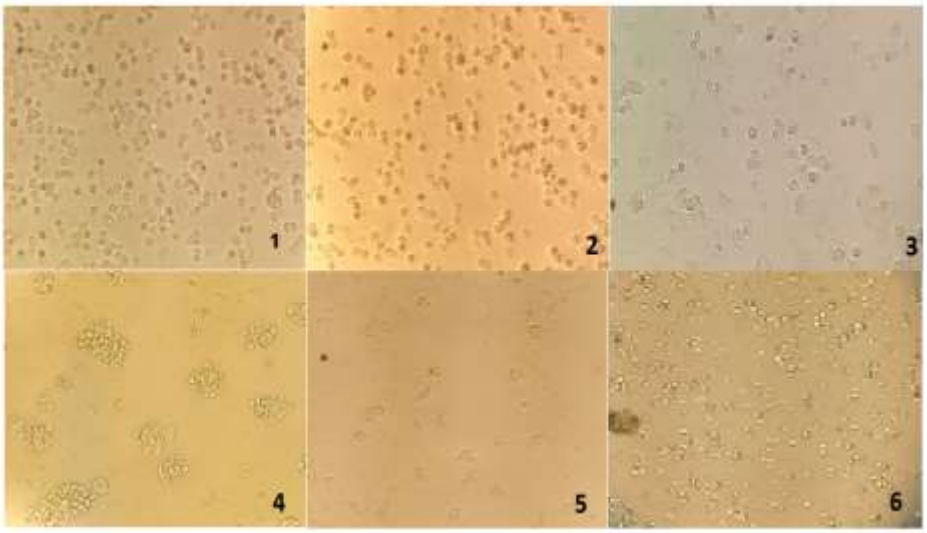


Figure 10. Morphological changes behind treat with HepG2 cell after an incubation interlude of 48 h. (6) Normal HepG2 cell, (1,2,3,4 and 5) treat HepG2 cells after 48 h

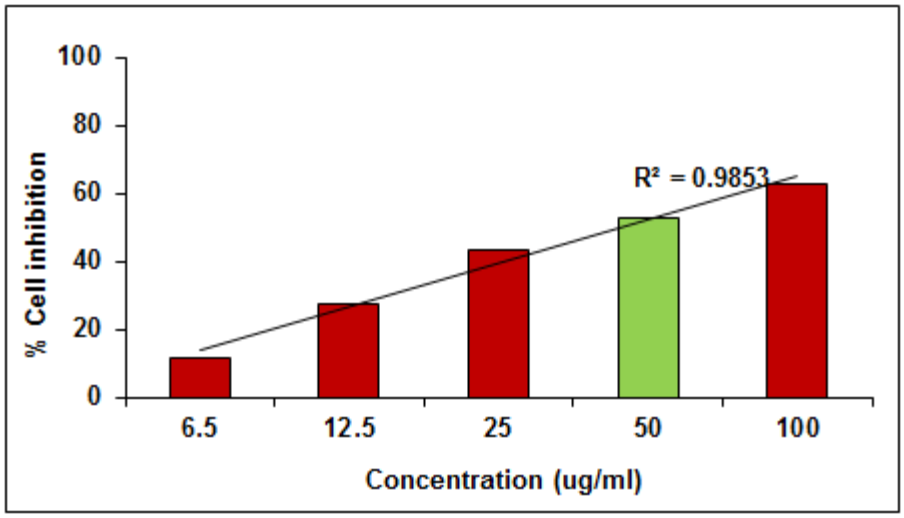


Figure 11. IC_{50} values for the complex [Cu(epoxy-phen)(4-methyl- phen)(NO_3)](NO_3) H_2O beside HepG2 cell lines.

3.10. Antimicrobial activity

The using disc diffusion method, Cu(II) metal complex confirmed in vitro used for anti-bacterial and anti-fungal activity against around of pathogenic bacteria also fungal species. Moreover, this Cu (II) metal complex have been discovered to have significant act against Gram-positive bacteria also Gram-negative bacteria, and the fungus. The anti-microbial activity findings are shortened after the solutions have been prepared by water. in table 3 [52]. We detected anti-microbial action against Gram-negative Bacteria Escherichia coli, Gram-positive Bacteria Staphylococcus epidermis is and Streptococcus facials fungi by activity of with experimental procedures utilizing Cu(II) complex. The metal Cu (II) complex to have excellent anti-microbial activity against the Gram-positive and Gram-negative bacteria. The Cu (II) metal complex takes place to be most successful anti-microbial activity heaving's against Gram-positive bacteria than Gram-negative bacteria. The Cu (II) metal complex most energetic next to the fungus Aspergillus Niger, Candida albicans and MucorSps than more the standard anti-fungal drug, Amphotericin-B. It is may be confirmed to estimated determined ours synthesized Cu (II) metal complex inhibits the growth of fungi and bacteria to a greatest extent all so shown by Fig. 12. And Table (3,4).

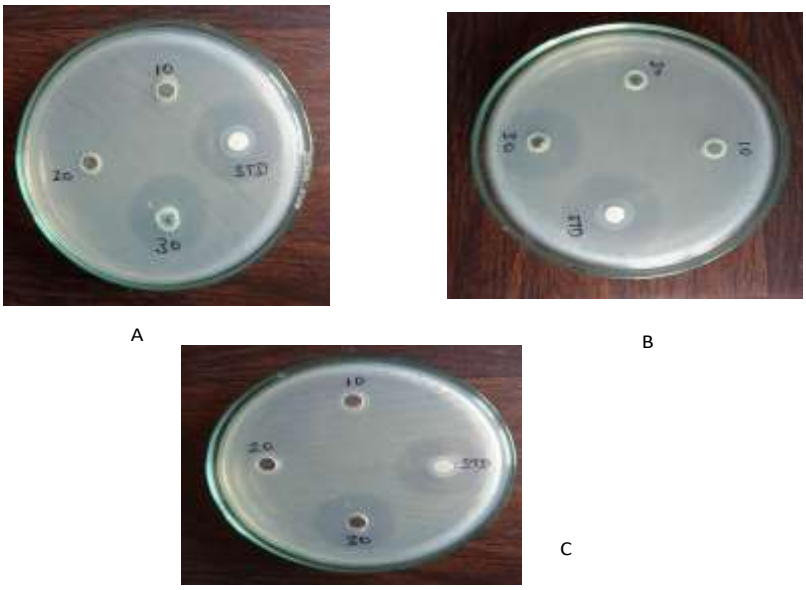


Figure 12. Cu (II) complex with inhibits growth fungi and bacteria of Anti-Microbial activity

Table 3. Pathogenic bacteria activity against Cu (II) complex

S. No	Pathogenic bacteria	Zone of inhibition (mm)			Standard (Chloramphenicol)
		10 ug	20 ug	30 ug	
1.	*Staphylococcus aureus*	06	08	13	18
2.	*E.Coli*	05	08	14	18

The experiment was conducted in triplicates (n=3)

Table 4. Pathogenic fungus activity against Cu (II) complex

S. No	Pathogenic fungus	Zone of inhibition (mm)			Standard (Chloramphenicol)
		10 ug	20 ug	30 ug	
1.	*Aspergillus fumicatus*	05	07	12	16

The experiment was conducted in triplicates (n=3)

Conclusion

We have synthesize and characterize to binuclear Cu (II) metal complex, along with N,N-electron donor ligands. respectively, the [Cu(epoxy)(4-methyl- phen)(NO_3)](NO_3)·H2O (epoxy = 5,6-dihydro-5,6-epoxy-1,10-phenanthroline; phen = 4-methyl 1,10-phenanthroline), the Cu (II) complex was clearly indicates intercalative binding mode properties with CT-DNA and all so clearly cleaved DNA into small fragments by using agarose gel electrophoresis. The weak intercalation binding mechanism of the complex through DNA has been proposed based taking place the above data and the complexity is that the plasmid DNA cleavage efficiently. The synthesized new metal complex having good anticancer activity and antimicrobial activity upon based on above the clear data. In this work, DFT studies into structural along with spectroscopic properties like (HOMO-LUMO) of Cu(II) complex have been displayed and consist experimental report. More ever Characterized by using elemental analysis, FT-IR and UV-Vis spectroscopy, EPR spectrum. According to the electronic spectrum, the communication between Cu (II) metal complex with DNA was confirmed by UV and Cyclic voltammetry, fluorescence spectroscopy and molecular docking studies.

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