Physicochemical studies of Cu(II) complex and antibacterial, anticancer activities bearing N, O-chelated Schiff base ligand

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Abstract

A new compound, Copper (II) has been synthesized and described in association with the schiff base ligand of thiazole derivatives. The structural composition of the novel substance was elucidated through the application of physicochemical approaches. The complex's analytical results validate the creation of 1:1 (M:L) complex and are consistent with the molecular formula proposed. The ligand and Cu(II) complex were investigated against two Gram-positive bacteria *Bacillus subtilis* (+ve) and *Staphylococcus aureus* (+ve), two Gram-negative bacteria *Escherichia coli* (-ve) and *Proteus vulgaris* (-ve). The antibacterial efficacy is arranged as follows: gentamicin, ampicillin > $[CuL(H_2O)Cl_2]2H_2O$ > L. Using cisplatin as a reference, the cytotoxicity of the Cu(II) complex and ligand against the human liver (Hep-G2) and breast MCF7 cancer cell lines was assessed. The complex of $[CuL(H_2O)Cl_2]2H_2O$ showed the maximum activity against the two cell lines.

Keywords: Complex, Copper, Antibacterial, Anticancer

Introduction

Hugo schiff recorded the first condensation reaction between primary amines and carbonyl-containing compounds, which resulted in the identification of Schiff bases, a class of chemical compounds that have been used extensively for almost a century and are still in use today **[1**, **2]**. Because of their high propensity for chelating with various metal ions, those incorporating heteroatoms like azomethine or (C=N) N, O, S groups and their resemblance to naturally occurring proteins and enzymes, Schiff base metal complexes that are produced are typically physiologically active. Thus, the significant contribution that these compounds have made to the field of coordination chemistry as well as their potential for usage in pharmaceutical and medical applications have motivated the amazing ongoing research activity in this class of molecules **[3]**. Many synthetic approaches and strategies have been developed over the course of more than a century of research in this field, with an emphasis on the industrial and catalytic applications of these Schiff base-containing compounds as well as their biological and medical significance **[4**, **5]**.

Practically speaking, the ability of metal-based drugs to penetrate pathogenic cell membranes and their tendency to attach to the genetic materials (DNA or RNA) of these pathogens are their primary characteristics **[6**, **7]**. Due to their bioactivity, Schiff base ligands and their metal complexes have garnered a lot of attention recently. Many studies have shown how beneficial these compounds are as anti-inflammatory, anti-cancer, antibacterial, antifungal, antioxidants and anti-hypertensive medications **[8-16]**. Recently, there has been a lot of interest in the interactions between metal complexes and nucleic acids due to the potential applications of these substances as physiologically active anticancer medications. One of the most important pharmacological targets for a large number of medications used in clinical practice is DNA. The transition metal complexes' ability to bind or cleave DNA suggests that they may have anti-cancer properties as novel therapeutic agents **[17-20]**. Moreover, Copper(II) complexes are widely recognized for their potent antibacterial, antiproliferative, nuclease, anti-inflammatory, and antimycobacterial characteristics **[21]**.

Here, we describe the simple synthesis, characterization, and bioactivities of a copper complex containing a ligand generated from 2-amino benzo thiazole, including antibacterial and anticancer properties.

Experimental

The supplemental file (Section S1) has comprehensive details on the materials, tools and techniques used for structural confirmation and application. (Section S2 and S3): procedure of antibacterial and anticancer activities **[22-24]**.

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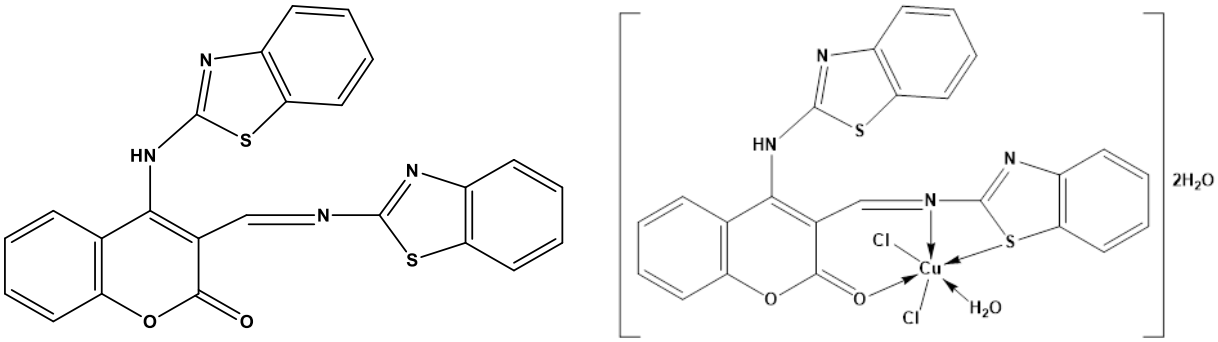
Synthesis of Compounds

The thiazole ligand (L) is made up of a combination of thiazole derivatives (5.49 mmol, 1.52 g) dissolved in hot pure ethanol and coumarin (5.49 mmol, 2 g) dissolved in hot pure ethanol for 10 minutes (alkaline medium). The mixture was refluxed and stirred for three hours, resulting yellow precipitate. The result was filtered, washed, and recrystallized and dried.

The (2 mmol; 0.910 g) from resulting ligand in 10 ml ethanol absolute was added to $CuCl_2.2H_2O$ (2 mmol; 0.498 g) in the same volume of ethanol. The mixed reactant was stirred and refluxed for 2 hrs. until dark green solid was precipitated. The result was filtered, washed, and recrystallized and dried **[25, 26]**.



Structures 1. Proposed structures of Compounds.

Results and discussion

Characterization of Compounds

Physicochemical properties

When exposed to air and moisture, Cu(II) complex maintains its hue. The complex's analytical results validate the creation of 1:1 (M:L) complex and are consistent with the molecular formulas proposed. The molar conductivity value in a 10^{-3} M DMF solution was 9.6 $\Omega^{-1}cm^2mol^{-1}$ of the complex. Their non electrolytic nature is shown by the values of complex **[27, 28]**.

IR spectra of Compounds

Cu(II) complex and ligand FTIR spectra are shown in table 2 and Figure 1, 2. A band at 1634 cm^{-1} in the ligand spectra is indicative of the stretching vibration of −C=N. During complexation, this band moves to a higher frequency for the complex (1667 cm^{-1}).

The redshift shows that the nitrogen atoms in azomethine have a role in the creation of complexes **[29, 30]**. Additionally, ligand had a band at 1723 cm^{-1} that was attributed to the stretching vibration of ν(C=O). The red shift of the ν(C=O) peak (1724 cm-1) during the formation of the metal complex confirmed the coordination of the carbonyl atom. The complex's bands which correspond to the stretching vibrations of the M–O and M–N bands present at 591 and 433 cm^{-1}, provided evidence in favor of this **[31-33]**. The coordinated H_2O molecule is the cause of the new band that appears in the compound at 984 cm^{-1}. Consistent with the elemental analysis. It was determined that the band at 3460 in Cu(II) complex, which was assigned to hydrated H_2O, portrayed the hydrated water molecules' stretching vibrations at υ(OH).

Table 1. Analytical data of the compounds.

Compds	Color Yield %	Molecular weight	Conductivity µs	M. P. °C	Found (cal.) %			
					C	H	N	M
Ligand	Yellow 94	454.52	-	142	63.41 (63.42)	3.14 (3.10)	12.32 (12.33)	-
Cu(II) complex	dark green 92	643.01	9.6	265	44.78 (44.83)	3.11 (3.14)	8.67 (8.71)	9.83 (9.88)

Table 2. FT-IR spectral values for Compounds.

Compds	ν (OH)	ν (C=O)	ν (CH)$_{arom}$	ν (C=N)	ν (H$_2$O)$_{Coord}$	ν (C-S)	ν (M–O)	ν (M–N)
Ligand	3200	1723	2832	1634	-	786	-	-
Cu(II) complex	3460	1724	2890	1667	984	794	591	433

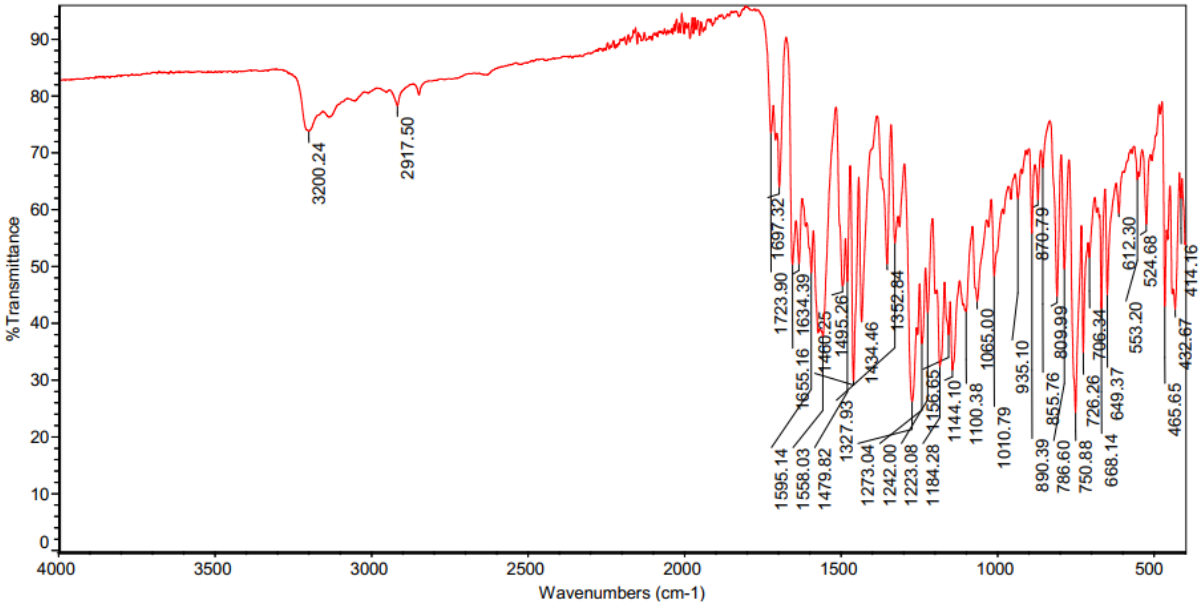


Fig (1) IR spectra of ligand

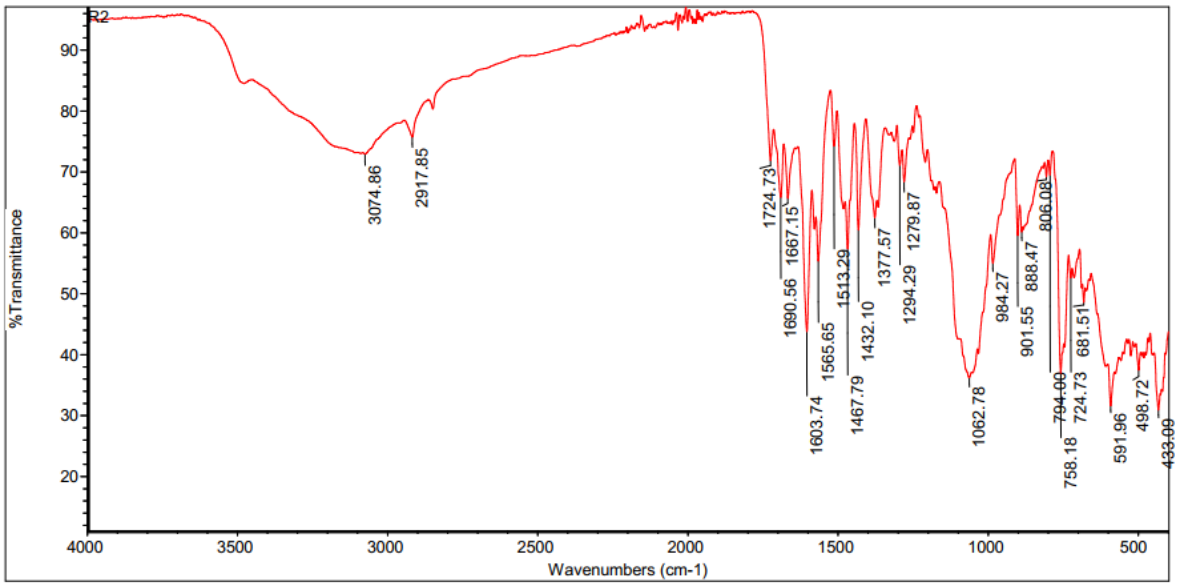


Fig (2) IR spectra of Cu(II) complex

Electronic spectra

The ligand and Cu(II) complex's UV–Vis spectra were recorded at room temperature in DMSO, with a wavelength range of 200 and 800 nm Figure 3. There are two absorption bands visible in the ligand's absorption spectra. The initial high intensity band seen at λ_{max} = 263 nm may be caused by the aromatic rings' π⟶π* transition.

The second bands at 376 nm are caused by charge transfer and the n⟶π* transition of the azomethine group (C=N). The electronic spectra of the complex, which exhibits bands that were shifted to 271 and 383 nm for the π-π* and n-π* transitions, in compared to those of the free ligand, proved that the azomethine nitrogen was coordinated to the metal ions **[34**, **35]**.

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ESI-MS spectra

MS is being utilized more and more to clarify the complicated molecular structure of Cu (II) and ligand. Figures 4 and S1 display the complexes' ESI-MS spectra, while Scheme 1 displays the suggested fragmentation patterns for the Cu (II) complex. The mass spectra of Cu (II) complex and ligand show molecular peaks at m/z 455.17 amu and 644.21 amu, respectively. The hypothesized chemical formulae for the ligand and Cu(II) complexes agree well with these findings.

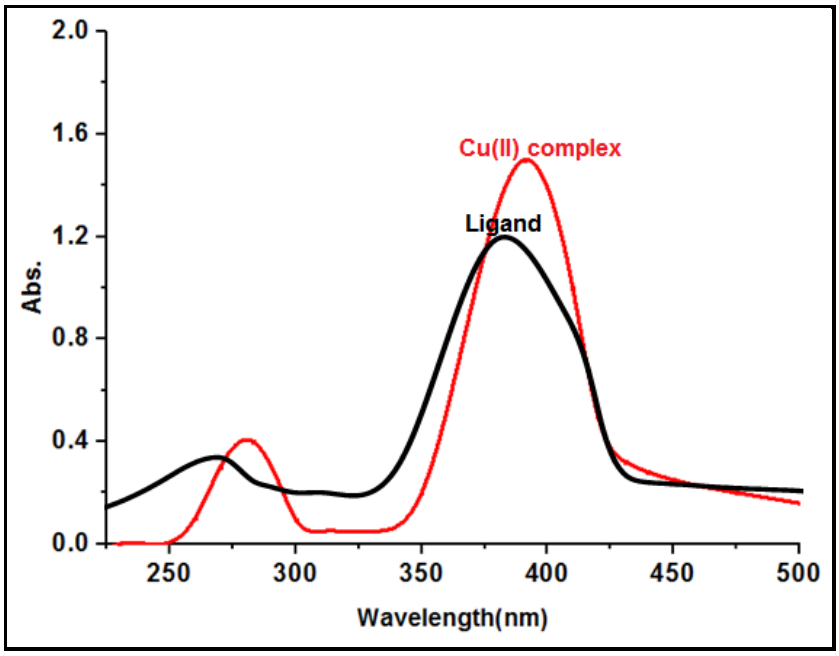


Fig (3) Electronic spectra of the Compounds

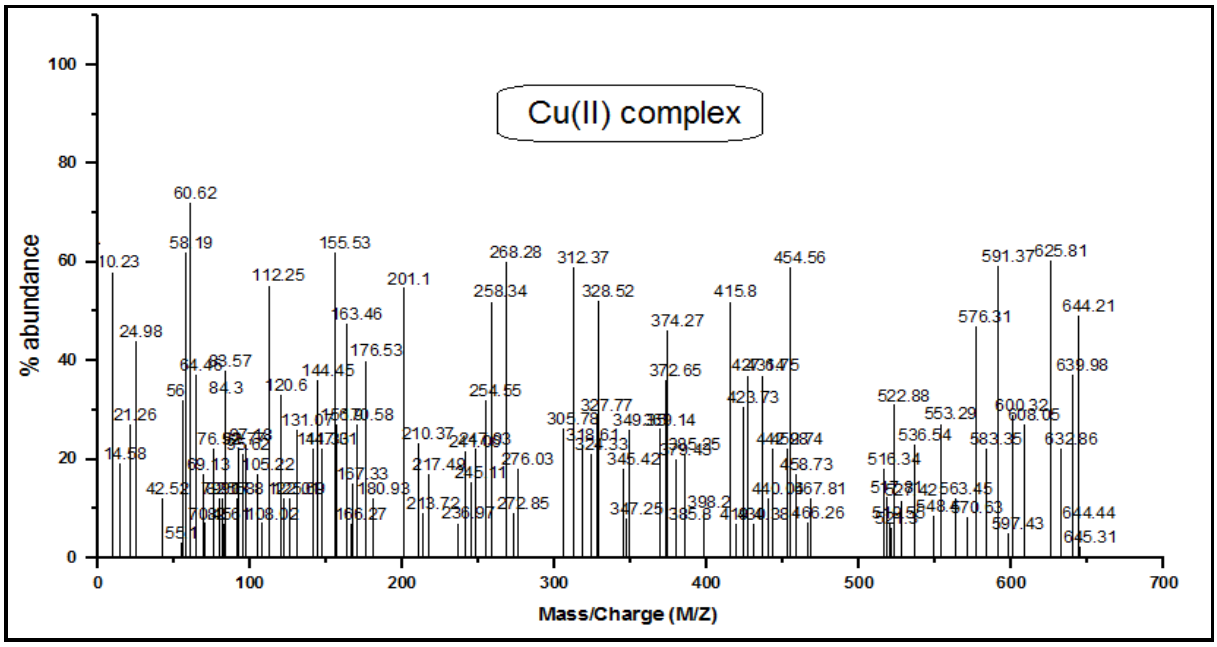
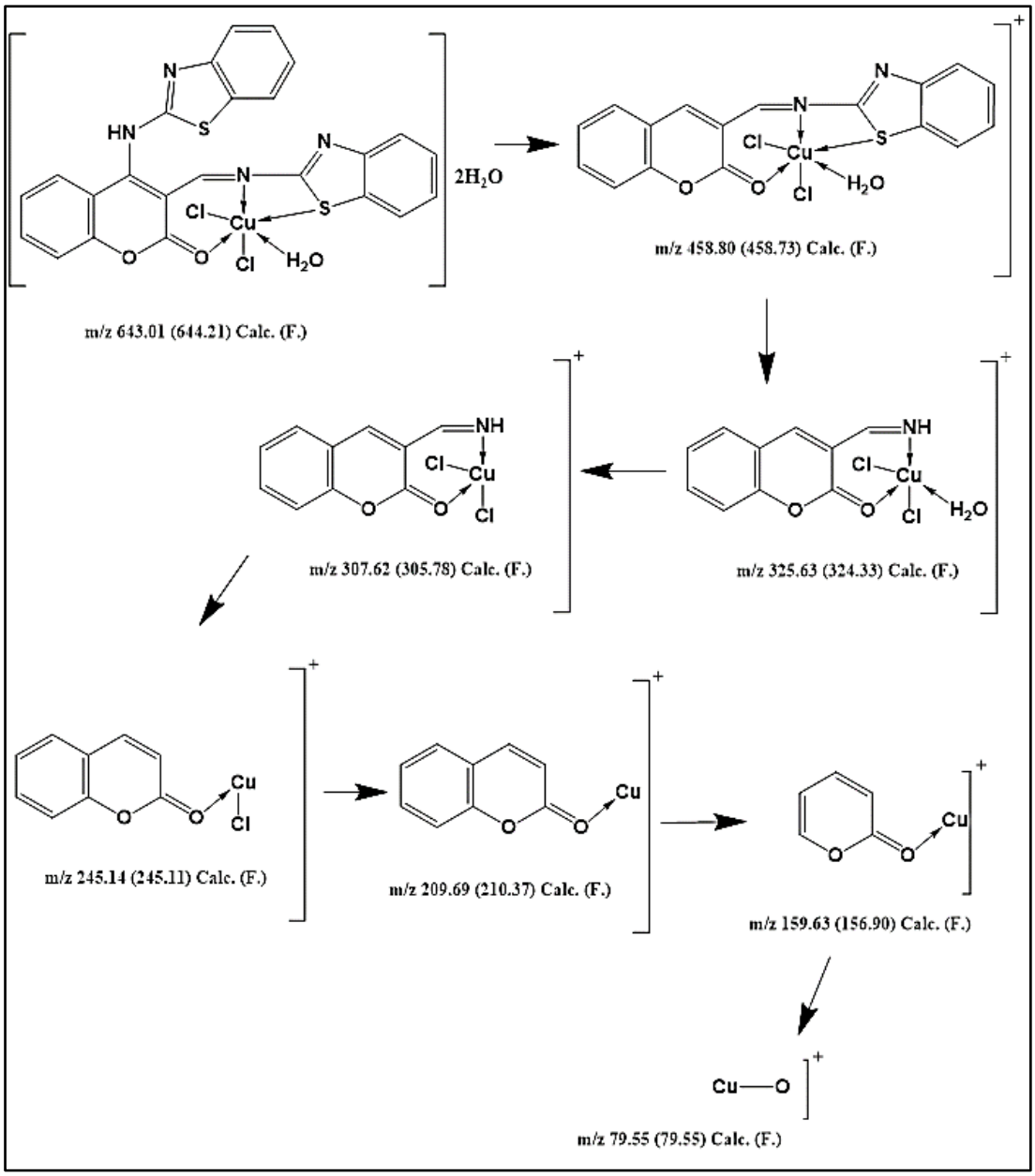


Fig (4) Mass spectra of Cu(II) complexes



Scheme 1: Mass fragmentation of [CuL(H_2O)Cl_2]2H_2O complex

Thermogravimetric analysis

Thermogravimetric measurements were used to examine the behavior thermals of the compound's combination during a temperature range of 25 to 800 °C. The outcomes are displayed in Figure 5 and Table 3. The total gel time (TG) of the ligand was shown to be partially decomposed at temperatures between 98 and 425 °C, and fully decomposed at temperatures over 425 °C. Three weight-loss events are visible on the Cu(II) complex's TG curves. The loss of two hydrated H2O and one coordinated H_2O occurs during the first breakdown stage, which occurs between 25 and 200 °C, this is read as a weight loss of (Found/Calc. %); 8.35 (8.39).

The breakdown of the $C_{17}H_{10}C_{l2}N_2OS$ moiety takes place in the second step, which is between 200 and 398 °C, the anticipated weight loss range for this phase is (Found/Calc. %; 56.25 (56.18)). The projected mass reduction for the third stage, which occurs between 398 and 600 °C, is 22.97 (23.06) (Found/Calc.%), is thought to represent the full breakdown of the $C_7H_4N_2S$ moiety, leaving CuO as the final residue.

Antibacterial bioassay

It has been discovered that some pharmaceutical medications are more efficient against Gram-positive bacteria than Gram-negative bacteria. In this study, the antibacterial activity of the ligand and

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Cu(II) complex was assessed using the agar diffusion technique against Gram-ve bacteria *P. vulgaris* and *E. coli* as well as Gram +ve bacteria *S. aureus* and *B. subtilis*. Table S1 and Figure 6 present a list of the measured bactericidal activity of Cu (II) and ligand **[36]**. When the ligand chelated with Cu (II) to form complexes, we saw an increase in the ligand's activity against several bacterial strains. The partial sharing of the metal ion's positive charge with the donor (N and O) atoms of the ligand, which results in electron delocalization throughout the entire chelate ring system, accounts for the complexes' increased antibacterial activity. Considering that the complex's geometrical shape, the kind of donor atoms, the metal ion, the complex ion's overall charge and the ligands' chelating action all influence the biological activity of metal compounds **[37]**.

Table 3. Thermal values of the compounds

Compound	TAG(A)/ºC	Wt. loss Found (Calc.) %	Leaving species
Ligand	98-425	83.26 (83.15)	decomposition of the partial of organic ligand
Residue	> 425	16.74 (16.84)	complete decomposition of the organic ligand
Cu(II) complex	25-200	8.35 (8.39)	$2H_2O_{hyd} + H_2O_{coor.}$
	200-398	56.25 (56.18)	$C_{17}H_{10}Cl_2N_2OS$
	398-600	22.97 (23.06)	$C_7H_4N_2S$
Residue	>600	12.42 (12.37)	CuO

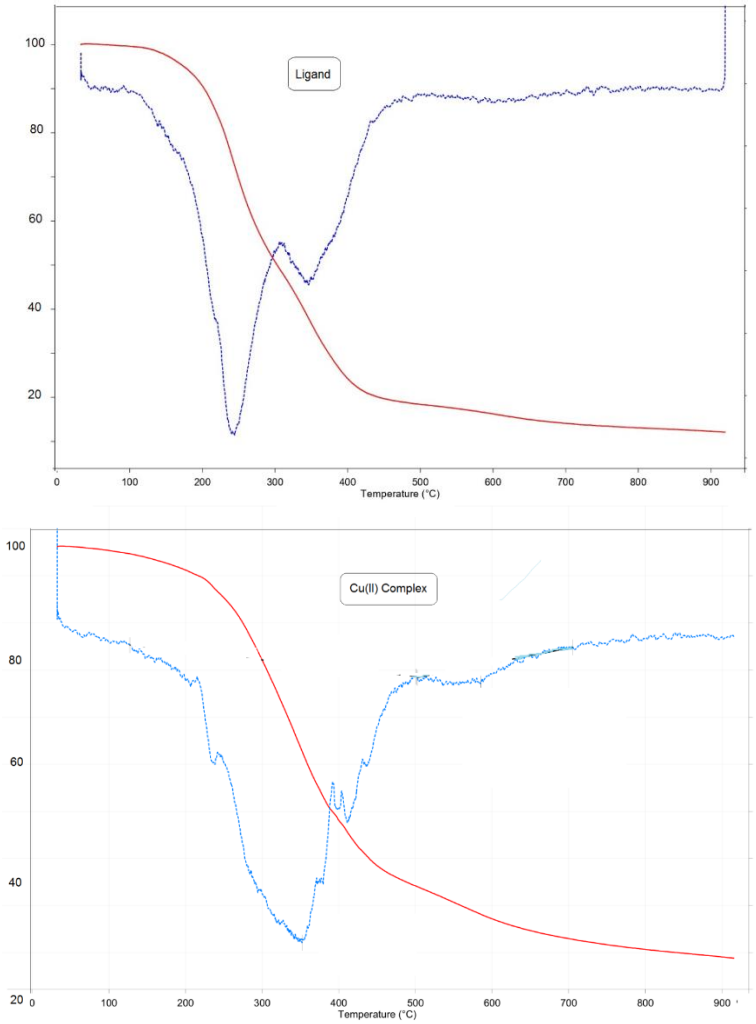

Fig (5) TGA/ DTG diagram of the compounds

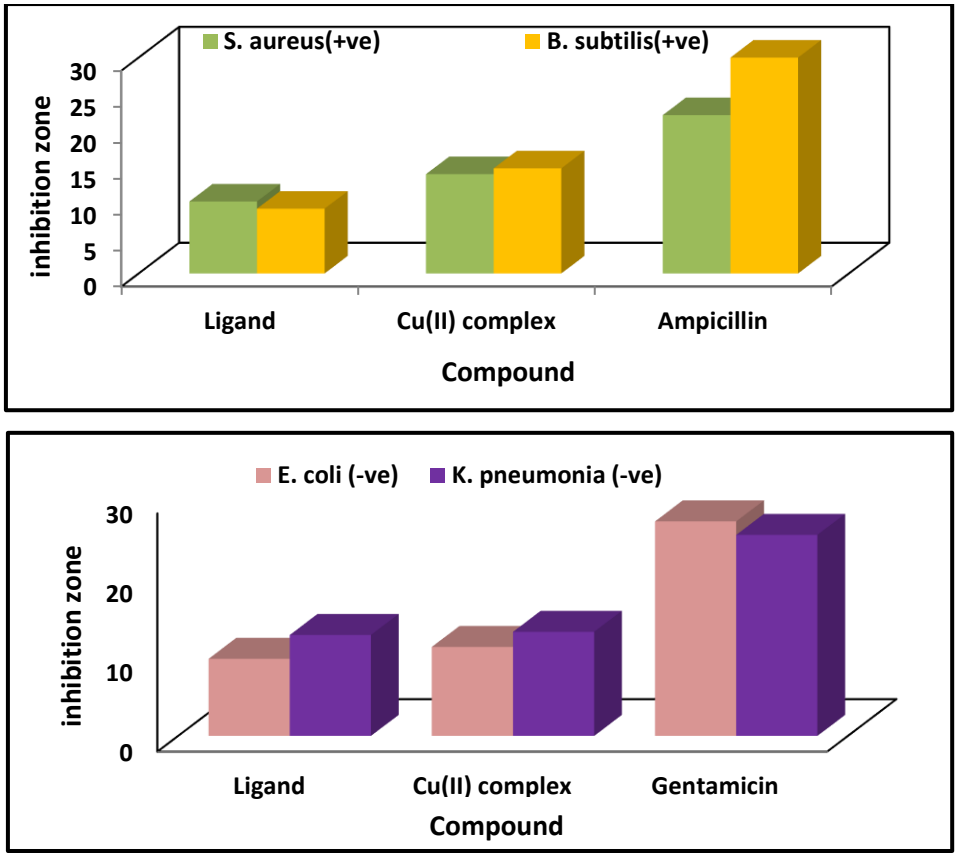

Fig (6) The antibacterial activity of Cu(II) complex and ligand at a concentration of 10 mg ml^{-1} in relation to gentamycin and ampicillin as standard medications.

Cytotoxicity

The in vitro cytotoxicity of the compounds against human MCF7 breast and Hep-G2 liver cancer cell lines was evaluated using the MTT test. Based on optical density, the MTT assay quantifies mitochondrial dehydrogenase activity, a marker of cell viability. Non-linear regression techniques were employed to evaluate the absorbance values in order to obtain the IC50 values for the compounds under investigation in both cancer cell lines **[24, 38, 39]**.

Table S2 and Figure 7 display the cytotoxicity data for the ligand and Cu (II) combination against HepG-2 and MCF7 at doses of 7.812, 15.625, 31.25, 62.5, 125, 250, 500 and 1000 µg/ml. Using cisplatin as the standard reference, we compared the IC50 values for the ligand and Cu (II) complex and discovered that the activity followed this order: cisplatin > Cu(II) complex > Ligand in the presence of MCF7 and HepG-2.

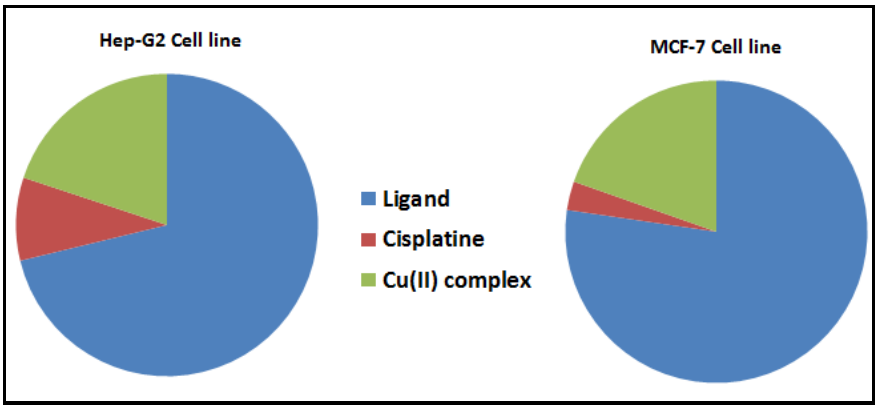

Fig (7) IC_{50} values of Cu (II) complex and ligand against Hep-G2 and MCF7 cancer cell lines in comparison to cisplatin.

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Conclusions

This work used a variety of spectroscopic and structural methods to completely describe and create novel Cu(II) complex. They assessed their biological activity against several bacterial strains, human MCF7 breast and Hep-G2 liver cell lines. It was discovered that Cu(II) complex exhibited greater efficacy against two cancer cell lines and against distinct strains of bacteria than it did against ligand. According to the results of thermal analysis, FTIR, molar conductivity and elemental analysis, the complex produced with a molar ratio of 1:1 M:L and the formula $[CuL(H_2O)Cl_2]2H_2O$.

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