RESEARCH ARTICLE

Evaluation of the Effectiveness of the Copper (II) Complex with a New Ligand derived from Benzothiazole and Anthranilic Acid as Anticancer and Antioxidant

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ABSTRACT

Four steps were used to convert 2-mercaptobenzothiazole into the new ligand (2-((2-((4-(1-((4'-(benzothiazol-2-ylamino)-[1,1'-biphenyl]-4-yl)imino) ethyl) phenyl)imino)-1,2diphenylethylidene) amino)benzoic acid (LH) type of schiff bases: The first step included preparing compound (A) N-(benzothiazol-2-yl)-[1, 1'-biphenyl]-4, 4'-diamine by the reaction 2-mercapto-benzothiazole with benzidine. The second step was prepared the compound(B) 2 OXO-1, 2-diphenylethylidene**)** amino) benzoic -((2- acid by the reacting anthranilic acid with benzil As for the third step, it included the reaction of the product of the firest step with 4-aminoacitophenon and the formation compound (C). The fourth step was the preparation ligand (LH) by reacting compound(B) with compound (C). Fourier-transform infrared spectroscopy (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), UV-vis, melting points, molar conductivity, CHN, atomic absorption, magnetic sensitivity, and other measurements were used to determine the structure of the ligand (LH) and its complex with copper (II). The MTT method was used to evaluate the activity of the ligand (LH) and its complex with copper (II) *in-vitro* as an anticancer (human breast cancer (MCF7). Nd (MTT) assay was used to evaluate the ligand schiff base *in-vitro* anticancer activity of a Cu(II) complex against human breast cancer MCF7.

Keywords: Heterocyclic schiff bases, Transition metal complexes, Antimicrobial, Anticancer, Metallodrugs, Breast cancer.

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INTRODUCTION

Cancer is one of the top five causes of death worldwide, and its incidence and mortality are quickly growing because it encompasses a diverse collection of disorders.[1,2] Chemotherapy is the most widely used nonsurgical method of treating cancer, and its constituent drugs can be given singly or in various combinations. Sometimes chemotherapy is used in conjunction with or after other treatments (*e.g.,* surgery and radiation). Despite the benefits of chemotherapy, the non-specificity of the medication has been linked to several early (*e.g.* nausea, vomiting, diarrhea, hair loss, appetite loss, fatigue, fever, mouth sores, pain, constipation, ease of bruising and bleeding) and late (e.g. lung and heart problems, infertility, acute and chronic kidney failure, and peripheral neuropathy)[3] side effects. Researchers were drawn to benzothiazole derivatives because of their wide range of biological activity Researchers have been drawn to schiff base because of its wide spectrum of pharmacological actions, which include antibacterial and antioxidant properties The activity of benzothiazoles against MCF-7 breast cancer cell lines is well-recognized. The epidermal growth factor receptor (EGFR)[4] is well-known for its high levels of expression, malignancies of the breast, colon, and bladder. Several researches has shown that the benzothiazole moiety and its derivatives can create the uncommon and important lead chemical.[5] Anticancer techniques such as tyrosine kinase inhibition, topoisomerase inhibition, and induction of death by reactive oxygen species (ROS) activation have all been discovered to be successful.[6] As a result, novel benzothiazole design and development can be used to treat a wide range of cancer to name a few he azomethine group,[7] which was formed *via* the condensation of primary amines and carbonyl compounds, is found in Schiff bases. The azomethine group in the Schiff base is usually responsible for a variety of therapeutic effects.[8] Schiff base contains physiologically significant locations. Active compounds with an intermolecular bonding connection and the balance of proton transport[9] complexes of metals. The Schiff base has a wide range of applications, including clinical, pharmaceutical, biochemical,

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agricultural, and other fields are also involved in numerous other fields.

MATERIALS AND METHODS

The chemicals used in this study were all pure and imported by companies Sigma-Aldrich, Merck, MSDS and BDH, the UV spectra have been recorded in the range of (200–1000) nm using (Shimadzu UV-165 pcs spectrophotometer). ^{1}H-NMR spectra were recorded on the fourier transform varian spectrometer, operating at 300 MHz with tetramethyl silane as a standard internal reference in DMSO-d6 solvent. FTIR Spectra in the range (400–4000 cm^{-1}) were recorded by using FTIR 8400S Shimadzu Spectrophotometer (Japan). Melting points of all compounds were recorded using Stewart's melting point. Room temperature was used to compute the (FESEM) images of the ligand" and its' metal estimations were recorded on the conductivity coefficient scale with ethanol arrangement (10-3M) using (31A) computerized conductivity coefficient scale at room temperature.

Cell lines, Cell Culture and in-vitro Cytotoxicity Assay

MCF-7 and AGS cell lines (Pasteur Institute, Iran) were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS; Gibco) and 1% penicillin-streptomycin and were incubated at 37°C in a humidified atmosphere with 5% (v/v) CO_2. Cytotoxicity evolution of the samples was performed by MTT reagent-based colorimetric assay. Briefly, 10^4 cells/well were seeded into 96 well plates in 2 mL DMEM + 10% FBS medium and then incubated for 24 hours. Then, the samples' desired concentrations were produced (100 µL) and added to the wells. After 48 hours treatment of the cells, the medium was removed and replaced with 100 µL of 0.5 mg/mL MTT (3-(4,5-dimethylthiazolyl)-2,5-diphenyltetrazolium bromide; Sigma Aldrich) solution. After four 4 incubation, the supernatant was removed and then the formed formazan crystals were dissolved by 100 µL of DMSO (by 20 minutes shaking). Then, the plates were read at 570 nm using a microplate reader (DNM-9602G). The absorption is correlated to the number of viable cells in the medium. The cell viability was presented as the percentage viability of the treated cells compared to the untreated cells. All experiments were presented in triplicate

Preparation of the Ligand

The Ligand was Prepared in Four Steps

Step 1: Preparation (N-benzothiazole-2-yl)-1,1-biphenyl]-4,4-diamine (compound–A) compound (A) was prepared from the reaction 1.67 g, 0.01 mol of the compound 2-mercaptobenzothiazole dissolved in 25 mL of absolute ethanol as a solvent in a circular flask 100 mL, to which a solution was added consisting of dissolving 1.84 g, 0.01 mole of benzidine dissolved in 25 mL of absolute ethanol with continuous stirring and by the process of refluxing for a period of 6 hours, the reaction continued to escalate until the blackening of the lead acetate leaf stopped, which indicates the end of the reaction. The solution was cooled at room temperature and filtered. After that, the precipitate was collected and recrystallized using absolute hot ethanol to get rid of the remnants of the unreacted materials. The precipitate was left to dry, then collected and weighed for use in the second step. It gave a product of 70% and a melting point/degree (192–190°C).

Step 2: Preparation of compound 2-((2-oxo-2,1-diphenylethylidene) amino) benzoic acid (compound-B) Compound (B) was prepared by dissolving (2.1 g, 0.01 mol) of benzil in 25 mL absolute ethanol by continuous stirring and adding (5–6) drops of glacial acetic acid, then adding a solution to it. 1.37 g 0.01 mol) of anthranilic acid in 15 mL absolute ethanol. The mixture was refluxed for 8 hours, a precipitate was observed, cooled, filtered, dried, recrystallized from ethanol and collected for use in the subsequent step.

Step 3: Preparation of the compound N-(4/-((4-aminophenyl (ethylidene) amino)-[1,1/-diphenyl [4-yl)benzothiazole-2-amine (compound–C): Compound (C) was prepared by dissolving (1.59 g, 0.005 mol) (of compound (A) in 25 mL of absolute ethanol by continuous stirring and adding to it a solution of (1.35 g, 0.005 mol) from 4-aminoacetophenone dissolved in 15 mL) Absolute ethanol, and 6 to 5 drops of glacial acetic acid were added to a solution of 4-aminoacetophenone. The mixture was stirred for 8 hours, and the mixture was cooled, where it was observed that a precipitate was filtered and dried. It was recrystallized from absolute ethanol, and then the precipitate was collected, giving a yield of 60%, (m.p: 100–98°C).

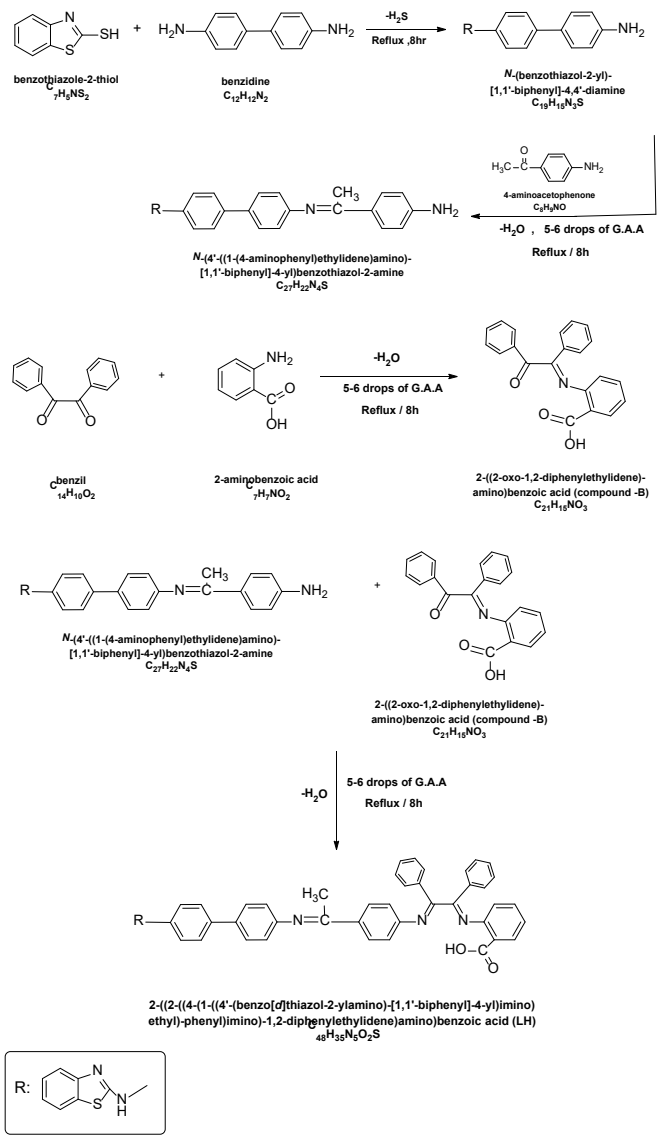
Step 4: Preparation of the ligand 2-((2-(4-(1-((4'-(benz othiazole -2-yl amino))))-[1,1'-diphenyl]-4-yl) amino (ethyl (phenyl) amino)-2,1-diphenyl ethylidene (amino) benzoic acid (LH). The LH was prepared by dissolving (1.65 g, 0.005 mol) of compound (B) in 25 mL of absolute ethanol by continuous stirring and adding to it a solution of (2.17 g, 0.005 mol) of compound (C) dissolved in 15 mL of Absolute ethanol, and 6 to 5 drops of glacial acetic acid were added to the solution of compound (B). The mixture was ascended for 8 hours, by cooling the mixture, where it was observed that a precipitate was filtered and dried. It was recrystallized from absolute ethanol, and then the precipitate was collected (Table 1), giving a product of (79%), (m.p: 100–98°C) (Scheme 1).

Synthesis if the Cu(Ii) Complex

Complex of Cu(II) with LH were prepared according to the following method: A solution (0.74 g, 1 mmol) of LH dissolved in 10 mL of absolute ethanol was added to (0.085 g , 0.5 mmol) of the $CuCl_2.2H_2O$ solution in 5 mL of distilled water, the mixture refluxed with stirring for 2 hours, a precipitate was observed, the solution cooled, filtered and dried, and crystallized from absolute ethanol, where colored and pure precipitate of the metal ion complex were obtained.

RESULTS AND DISCUSSION

The new LH 2-((2-((4-(1-((4'-(benzothiazol-2-ylamino)-[1,1'-biphenyl]-4-yl) amino) ethyl) phenyl)amino)-1,2-diphenylethylidene) amino) benzoic acid was synthesized from the 2-mercapto benzothiazole, in the four steps. The Cu(II)



Scheme 1: Synthesis of the LH.

complex have been prepared from reaction the ligand (LH) with $CuCl_2.2H_2O$ in ethanol solvent.

^{1}H-NMR Spectrum of the LH

DMSO-d_6 was used as a solvent and TMS as a standard internal reference for the measurement of the nuclear magnetic resonance (NMR) spectrum of the prepared ligand at room temperature the spectrum of the ligand showed a single signal at (S, 3H, δ = 2.66 ppm) belonging to the protons of the methyl group (CH_3 -N = C) related to the azomethine group,[10] while the multiple signals at (M, 4H, δ 77.6, 7.93 ppm) belong to the protons of the benzothiazole ring,[11] as well as the other multiple signals at (M, 8H, δ = 7.38–7.69 ppm) belong to the protons of the two phenyl-benzidine rings[12] and the phenyl anthranilic acid ring.[13] The spectrum also gave multiple signals at (M, 12H, δ = 7.24-7.82 ppm) belonging to the protons of the other phenyl rings within the ligand structure.[14] The signal at (S, 1H, δ = 10.25 ppm) refers to the proton of the secondary amine group (-NH),[15] and the signal at (S, 1H, δ = 12.77 ppm), which counts the proton of the hydroxyl group (-OH) of the carboxylic acid (Figure 1).

Infra-red Spectra

Infra-red Spectrum of the Synthesized LH

The infrared spectrum was measured in order to identify the functional groups in the free LH, where the (FTIR) spectrum of the free LH has shown many bands, the most important those are bands at the wave number (3363 and 3255 cm^{-1}), which belong to the two hydroxyl groups υ (O-H). and the minor amine υ (N-H), respectively.[16] A band has appeared in the spectrum of the LH, which is an important one whose appearance indicates the formation of the LH is the azomethine group υ(C=N) belonging to the Schiff base,[17] that appeared at 1674 cm^{-1}, while the band of the carbonyl group presents in the reactants before the reaction disappears. The bands at (1697 and 1658 cm^{-1}) belong to the carbonyl group υ (C=O) carboxylic acid and the azomethine group υ (C=N) benzothiazole ring. Other bands have appeared at 3047 cm^{-1} and 2962 and 2893 cm^{-1} which belong to the υ(C-H) aromatic and aliphatic groups, respectively, the υ (C = C) aromatic group gave bands at 1596, 1527 cm^{-1}. As for the group υ(C-S) benzothiazole ring, a band has appeared in the spectrum of the ligand at 1010 cm^{-1}.

Infrared Spectrum of Cu(II) Complex

By following up on the complex spectrum prepared for the LH and comparing it with the free LH spectrum (Table 2 and Figure 2), some bands' displacement, the disappearance of bands, and the appearance of new bands were observed. The disappearance of the absorption band of the hydroxyl group of carboxylic acid after losing its proton as a result of coordination

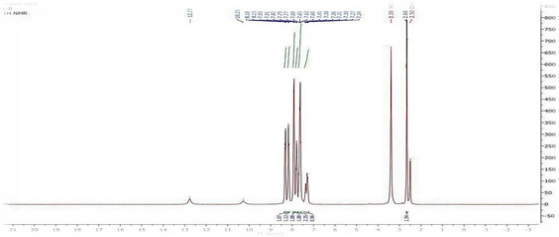


Figure 1: The ^{1}H-NMR spectrum of the ligand (LH).

Table 1: Some physical properties of the prepared LH and its complex with Cu(II)

Compound	*Color*	*m.p (°C)*	*Yield (%)*	*M. Wt g/mol*	*Calc. (Found)%*				
					C	*H*	*N*	*S*	*M*
Ligand (LH) $C_{48}H_{35}N_5O_2S$	yellow	100–102	79	744.9	77.29 (77.01)	4.73 (4.64)	9.39 (9.46)	4.40 (4.31)	_
$[Cu(L)_2]. H_2O$	green	165–167	65	1572	73.38 (73.12)	4.49 (4.41)	8.91 (8.98)	4.08 (3.98)	4.04 (3.93)

Table 2: The infrared spectrum bands of the prepared ligand and its complex with copper (II)

Compounds	*υ(O-H)*	*υ(N-H) 2°amine*	*υ(C-H) aromatic*	*υ(C-H) aliphatic*	*υ(C=O) Carboxylic acid*	*υ(C=N) Imine*	*υ(C=N) Benzoxazole ring*	*υ(C=C) aromatic*	*υ(M–N) υ(M–O)*
Ligand (LH)	3363	3255	3047	2962 2893	1697	1674	1658	1596 1527	—
$[Cu(L)_2] . H_2O$	-	3255	3062	2962	1697	1662	1652	1596 1527	524 470

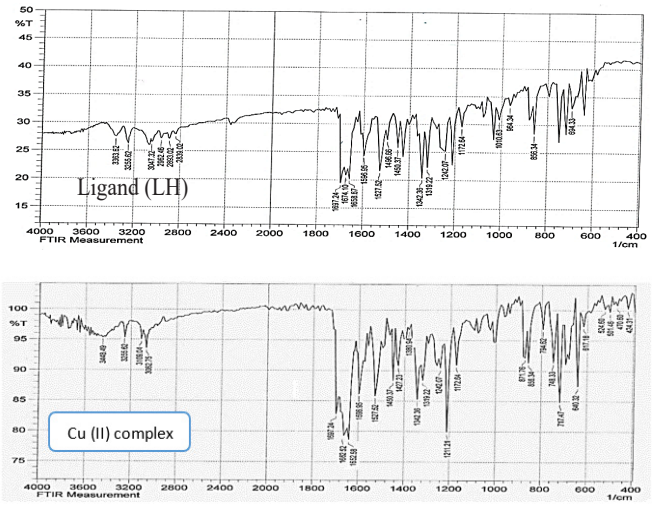


Figure 2: The FT-IR spectra of the ligand (LH) and its complex with Cu(II).

with metal ion and appearance of a band at 470 cm^{-1} belonging to the υ(M-O) group. The azomethine group υ(C=N) belonging to the Schiff base, which appeared at 1674 cm^{-1} in the spectrum of the free ligand shifted towards lower frequencies compared to the spectra of the complex, as it gave a shift of 12 cm^{-1} after coordination and appeared at 1662 cm^{-1}.[18] A new band appeared at (524 cm^{-1}), this band belongs to the υ(M-N) group, as a result of the coordination of the ligand with the metal ions through the nitrogen atoms of the azomethine group.[19] The appearance of broad groups at (3448 cm^{-1}) belonging to the hydroxyl group of the water of crystallization molecules in the complex spectrum.

Electronic Spectra

When observing the electronic spectrum of LH, shows three absorption peaks at 207 nm (48309 cm^{-1}), 258 nm (38760 cm^{-1}) and 322 nm (31056 cm^{-1}), the first two peaks return to (π-π*) transitions and the last peak return to the (n-π*) of the azomethane group (C=N) and carbonyl (C=O) (20). Copper complex spectrum show several absorption peaks centered at 226 nm (44248 cm^{-1}), 299 nm (33448 cm^{-1}), 346 nm, (28902 cm^{-1}),

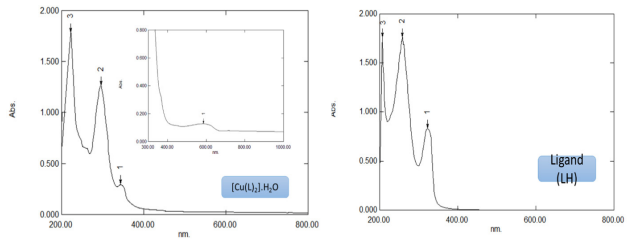


Figure 3: The electronic spectra of the synthesized ligand (LH) and its complex with Cu(II)

all peaks belong to the ligand field spectrum, and the broad absorption peak at 568 nm (17606 cm^{-1}) due to $^2B_1g \rightarrow {}^2Eg$ transition, a wide peak appeared due to the presence of Jean teller deformations giving the complex a distorted octahedral (Figure 3).[21] Measurements of the magnetic sensitivity of the copper complex (II), Table 3 showed that the value of the magnetic moment is (1.72 B.M), indicating the presence of one single electron. The hybridization of the copper complex with the sp^3d^2 complex has a distorted octahedral geometry.

Molar Conductance Measurements

Molar conductivity was measured by using absolute ethanol in a concentration of 10^{-3} M at room temperature. The prepared complex showed molar conductivity values at 15.2 $ohm^{-1} cm^2.mol^{-1}$, these values indicate that this complex has no ionic properties.[22]

Scanning Electron Microscopy (FESEM)

The scanning electron microscopy technology is one of the most important techniques that can be used to obtain information about the surface properties (morphology),[23] the shape and size of particles, the crystal structure of particles and the gatherings that occur to the particles for each of the ligand and its complexes. The analysis of the images of the scanning electron microscope for the LH (Figure 4) has shown that it is in the form of tetrahedral particles and the average particle size is 150.3 nm, copper (II) complex was shown as small, heterogeneous micro-objects, and the average particle size was 93 nm.

Table 3: The electronic transitions, magnetic moment, and expected geometry of the ligand (LH) and its complex with Cu(II)

Compounds	*λ (nm)*	*υ⁻ (Cm^{-1})*	*Transitions*	*μeff (B.M)*	*Geometry*
Ligand (LH)	207 258 322	48309 38760 31056	π-π* π-π* n-π*	—	—
$[Cu (L)_2]. H_2O$	226 299 346 586	44248 33445 28902 17065	Ligand field Ligand field Ligand field $^2B_1g \rightarrow {}^2Eg$	1.72 (Para.)	Octahedral sp^3d^2 distorted

DPPH Scavenging Activity

The 1,1-diphenyl-2-picrylhydrazal (DPPH) radical accepts an electron or hydrogen radical to produce a stable diamagnetic molecule with pale yellow colour.[24] Scavenging activities grew in tandem with the expansion of the population utilized sample concentration The ability of produced compounds to scavenge free radicals was tested using standard compound: ascorbic acid Each compound's IC_{50} was computed and ascorbic acid as a control. DPPH yielded the Cu (II)-Complex with IC_{50} values of 88.3333, 1250 g/mL, the Cu (II)-Complex has a stronger antioxidant. Overall, the antioxidant activity of the complexes against free radicals, including DPPH, revealed that they are more effective than free ligands at scavenging free radicals. Furthermore, ascorbic acid, the most common antioxidant, has substantially stronger scavenging activity than complexes. The low IC_{50} values suggest that The remaining chemicals with medium to low activity had their concentrations recorded substances that can DPPH (purple) can be converted to its non-radical form DPPH by contributing electrons/hydrogen atoms (Yellow) (Table 4 and, Figures 5 and 6).[25]

Assays for Cell Viability and Cytotoxicity

Chemotherapy is the most common treatment for metastatic cancer.[26] The MTT test was used to measure the viability of cells. At a concentration of 500 g mL, the LH inhibited liver cancer (MCF-7) the greatest (97.127%), but normal cells

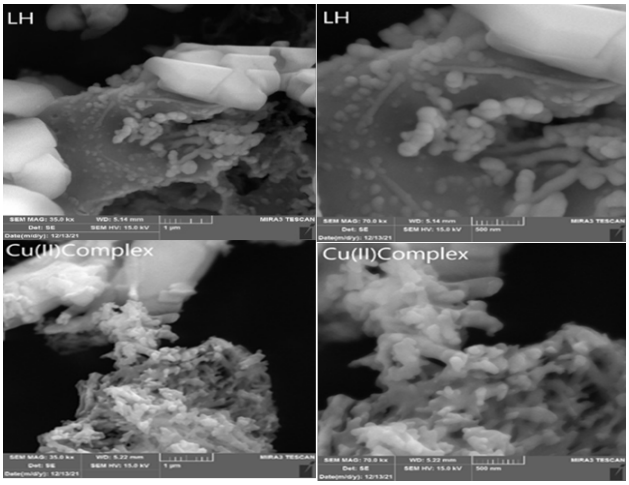


Figure 4: The (FESEM) images of each of the ligand (LH) and its complex with Cu(II).

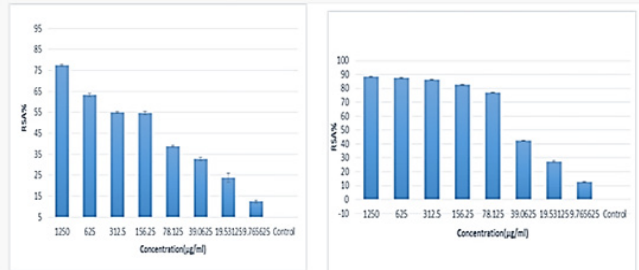


Figure 5: Percentage of inhibition, compared to ascorbic acid with ligand (LH) and its metal complexes

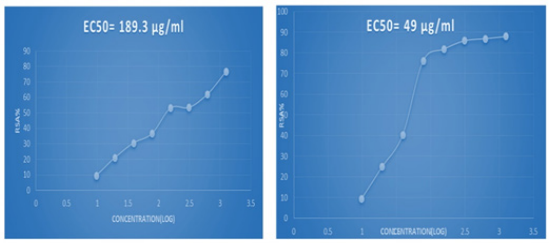


Figure 6: IC_{50} values of DPPH scavenging activity of ligand, complexes and ascorbic acid

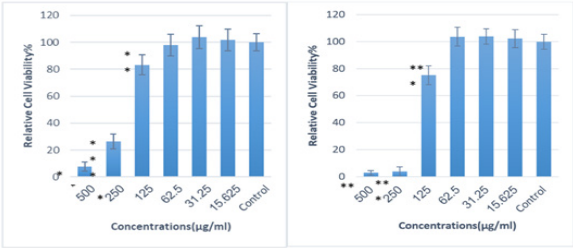


Figure 7: Comparison at viability and inhibition for the ligand in cancer and normal cells.

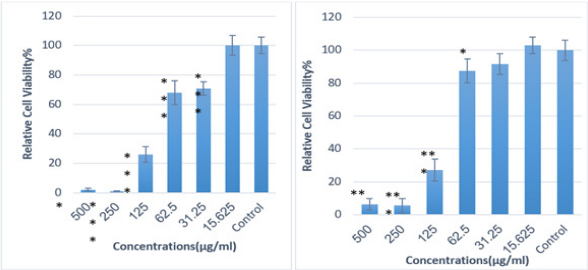


Figure 8: Comparison at viability and inhibition for the Cu (II)-complex in cancer and normal cells.

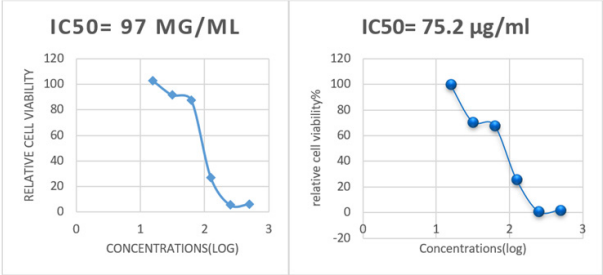


Figure 9: IC_{50} (µg\mL) values for ligand (LH) in MCF-7cell line and natural cell line.

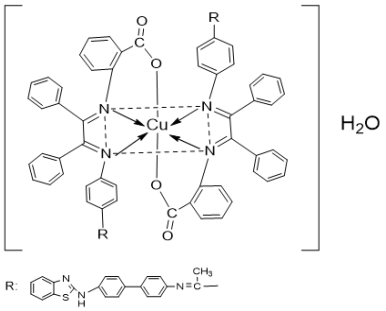


Figure 10: The proposed chemical structure formula of the complex

Table 4: Antioxidant activity from the analysis *in-vitro* for ligand (LH) and its metal complex

LH (A)			*Complex (II)Cu (B)*		
Conc. µg\mL	*Average*	*St. dev*	*Conc. µg\mL*	*Average*	*St. dev*
1250	77.478	0.533	1250	88.333	0.384
625	63.418	0.706	625	87.307	0.462
312.500	55	0.462	312.5	86.324	0.195
156.25	54.658	0.706	156.25	82.478	0.412
78.125	38.760	0.391	78.125	77.008	0.322
39.062	32.777	0.657	39.062	42.307	0.256
19.531	23.717	2.118	19.531	27.393	0.657

Table 5: The impact of the ligand (LH) of MCF-7cells in a (48 hours)-(MTT) test at (37°C) compared to a control cell line at the same dose.

Conc. µg\mL	*Visibility*	*Studev V.*	*Inhibition*
500	2.872372	1.713104	97.1276
250	3.760734	3.473334	96.2392
125	75.18508	6.908163	24.81492
62.5	85.7311	6.959154	14.2689
31.25	88.8469	5.848362	11.1531
15.625	90.3394	6.587793	9.6606

Table 6: The impact of the Cu (II)-complex of MCF-7cells in a (48hr.) - (MTT) test at (37°C) compared to a control cell line at the same dose

Conc. µg\mL	*Visibility*	*Studev V.*	*Inhibition*
500	2.872372	1.713104	97.1276
250	3.760734	3.473334	96.2392
125	75.18508	6.908163	24.81492
62.5	85.7311	6.959154	14.2689
31.25	88.8469	5.848362	11.1531
15.625	90.3394	6.587793	9.6606

showed no effect at varying concentrations (Table 5). The Cu(II)-complex showed the highest efficient suppression of (MCF-7) at a concentration of 250 g mL (98.24%) (Tables 5 and 6). The normal cellular cell (HEK) had no effect at the same concentration. "TABLE and "FIGURES indicate the effect of the ligand and Cu(II)-complex on (MCF-7) cells in a 48 hour MTT test at 37°C compared to ordinary cells of the same concentration (Figures 7-10).

CONCLUSION

Physical methods (melting point, molar conductivity, micro elemental analysis) were used to characterize the synthesized ligand and its complexes, as well as spectral methods (IR, UV-vis., ^{1}H-NMR) and FESEM techniques. The LH is coordinated with transitional metal ions through the azomethine group of the Schiff base, in addition to the oxygen atom of the hydroxyl group after proton loss. According to the above, complexes have octahedral geometry. The LH was effective as an antioxidant when tested. LH complexes lacked antioxidants. The cytotoxicity experiments were performed on LH and its Cu(II) complex using MCF-7 and normal cells (HEK).

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