

## Synthesis, Characterization and Breast Anti-cancer Activity of Iron(II), Cobalt(II), Nickel(II), and Copper(II) Complexes with a Hexadentate Schiff Base Ligand Derived from 2,5-Dihydroxy-1,4-benzoquinone with 5-Amino-2-methylphenol

Riyam Baqer Ibrahim and Suad Taha Saad\*

Department of Chemistry, College of Science for Women, University of Babylon, Hilla 51002, Iraq

\* **Corresponding author:**

email: wsci.suaad.taha@uobabylon.edu.iq

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**Abstract:** The complexes of Fe(II), Co(II), Ni(II), and Cu(II) Schiff base ligand derived from 2,5-dihydroxy-1,4-benzoquinone and 5-amino-2-methylphenol were synthesized. The ligand was synthesized by the reaction between the mentioned ketone and amine in 1:2 molar ratio, respectively. The four metal complexes were synthesized by refluxing the ligand with the related metal(II) chloride salts. The synthesized compounds were characterized using FTIR spectroscopy, UV-visible, <sup>1</sup>H-NMR, conductivity, atomic absorption, magnetic susceptibility, and thermogravimetric analysis. According to the results, the chelation between metals and ligand occurs with the imine groups and the deprotonated hydroxyl groups of 2,5-dihydroxy-1,4-benzoquinone and 5-amino-2-methylphenol in the ligand. The conductivity test of the four complexes shows the non-electrolytic nature of them. The magnetic susceptibility values of Fe(II), Co(II), Ni(II), and Cu(II) complexes are 4.20, 4.11, 2.97, and 2.34 B.M, respectively. The thermogravimetric and atomic absorption analyses suggest the general chemical formula for the complexes is [M<sub>2</sub>(L)(H<sub>2</sub>O)<sub>6</sub>]. In addition, the ligand and one of its metal complexes (Co(II) complex) were examined against breast cancer cells, and they gave the IC<sub>50</sub> of 101.24 and 129.2 µg/mL, respectively. This result suggests that Co(II) complex is a better anti-cancer agent in comparison with the ligand.

**Keywords:** metal complexes; Schiff base; 2,5-dihydroxy-1,4-benzoquinone; 5-amino-2-methylphenol

### ■ INTRODUCTION

The German scientist Hugo Schiff gave the term "Schiff base" to a compound with the functional group –HC=N– where the nitrogen atom is attached to the organic structure instead of the hydrogen [1-2]. This group can be obtained by the reaction between amine with carbonyl compounds [3-4]. By this reaction, the carbonyl group in the ketone or the aldehyde is replaced by the imine group [5]. Many studies have revealed the considerable chemical and biological importance of the electron lone pair of nitrogen's imine group [6]. This group can be considered crucial for Schiff base exploitation in biology and various branches of chemistry and reactions [7-9]. For example, in the coordination chemistry, Schiff bases have the ability to act as ligands and chelate with

metals through the nitrogen in the imine group and an adjacent donor atom such as nitrogen, sulfur, and oxygen [10-13]. Schiff bases are the most common and favorable ligands thanks to stabilizing metal ions in various oxidation states [14]. This stability is due to the presence of the basic donor nitrogen atom of the azomethine group. Furthermore, Schiff bases are designed and synthesized widely because of the attachment with metal ions in different manners, their stability, and their biological effects [15-16].

In this work, a Schiff base ligand was derived from 2,5-dihydroxy-1,4-benzoquinone and 5-amino-2-methylphenol. Various Fe(II), Co(II), Ni(II), and Cu(II) complexes with this Schiff base ligand were synthesized, characterized, and tested against breast cancer-affected cells.

## ■ EXPERIMENTAL SECTION

### Materials

2,5-Dihydroxy-1,4-benzoquinone and 5-amino-2-methylphenol were purchased from Macklin biochemical. Metal(II) chlorides were supplied from Merck and C.D.H. ethanol, while hydrochloric acid was supplied from Thomas Baker for chemicals. All the chemicals were used with no further purification.

### Instrumentation

The infrared spectra were recorded by Fourier transform infrared spectrophotometer (FTIR 8400S, Shimadzu). The UV-visible spectrum was measured by using a UV-visible spectrophotometer (Peak Instruments C-7200) from Shimadzu. Bruker spectrometer instruments operating at 400 MHz were used to measure <sup>1</sup>H-NMR spectra. The metal content in all complexes was measured using Nova 350 spectrophotometer. The compound's decomposition was measured using the differential thermal gravimeter (DTG-160-FC-60A). Complexes conductivity was recorded by WTW SERIES, cond 722. The Sherwood Scientific auto balance magnetic susceptibility balance was used to measure magnetic susceptibility. Melting points were measured by melting point/SMP30 Stuart device.

### Procedure

#### **Synthesis of Schiff base ligand (L)**

The 2,5-dihydroxy-1,4-benzoquinone (1 g, 7.138 mmol) was mixed with 5-amino-2-methylphenol (1.758 g, 14.276 mmol) in ethanol (25 mL) as a reaction solvent. Hydrochloric acid (3 drops) was added and the mixture was refluxed for 6 h. The brown precipitate of the Schiff base ligand was filtrated, washed with water and ethanol, and then recrystallized from ethanol.

#### **Synthesis of Fe(II), Co(II), Ni(II) and Cu(II) complexes**

The four metal complexes were synthesized by dissolving the prepared ligand (0.5 g, 0.95 mmol) in ethanol (20 mL). This solution was mixed with the corresponding hydrated metal(II) chloride salts in 1:2 ligand:metal ratio. The reaction mixture was left to reflux for 12 h. Brown complexes precipitates were filtered and washed with water and ethanol.

### **Anti-cancer study**

The human breast cancer cell line (MCF-7) and the non-malignant breast epithelial cells (MCF10A) were supplied by the National Cell Bank of Iran (Pasteur Institute, Iran). The growth of these cells was carried out in Roswell Park Memorial Institute medium and Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 with 10% of fetal bovine serum and 100 U/mL penicillin and 100 µg/mL streptomycin. Cells were kept at 37 °C with humid air (5% CO<sub>2</sub>) and treated with trypsin/EDTA and phosphate buffer saline solution. The growth process was 3D colonies and a monolayer cell culture.

The cell viability was detected by [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. The cells were cultured and digested with trypsin adjusted to a density of  $1.4 \times 10^4$  cells/well and seeded to 96-well plates filled with 200 µL fresh medium per well for 24 h. Then, these cells were treated with the ligand and Co(II) complex in five concentrations (300–18 µg/mL). After 24 h the supernatant was separated and 200 µL/well of [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide solution and 0.5 mg/mL of phosphate buffer saline were added. The incubation for the plate was carried out at 37 °C for an extra 4 h. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide solution was then removed and added with DMSO (100 µL per well). The crystals were dissolved after the incubation of cells in a shaker at 37 °C. Cell viability was quantified by measuring absorbance at 570 nm.

## ■ RESULTS AND DISCUSSION

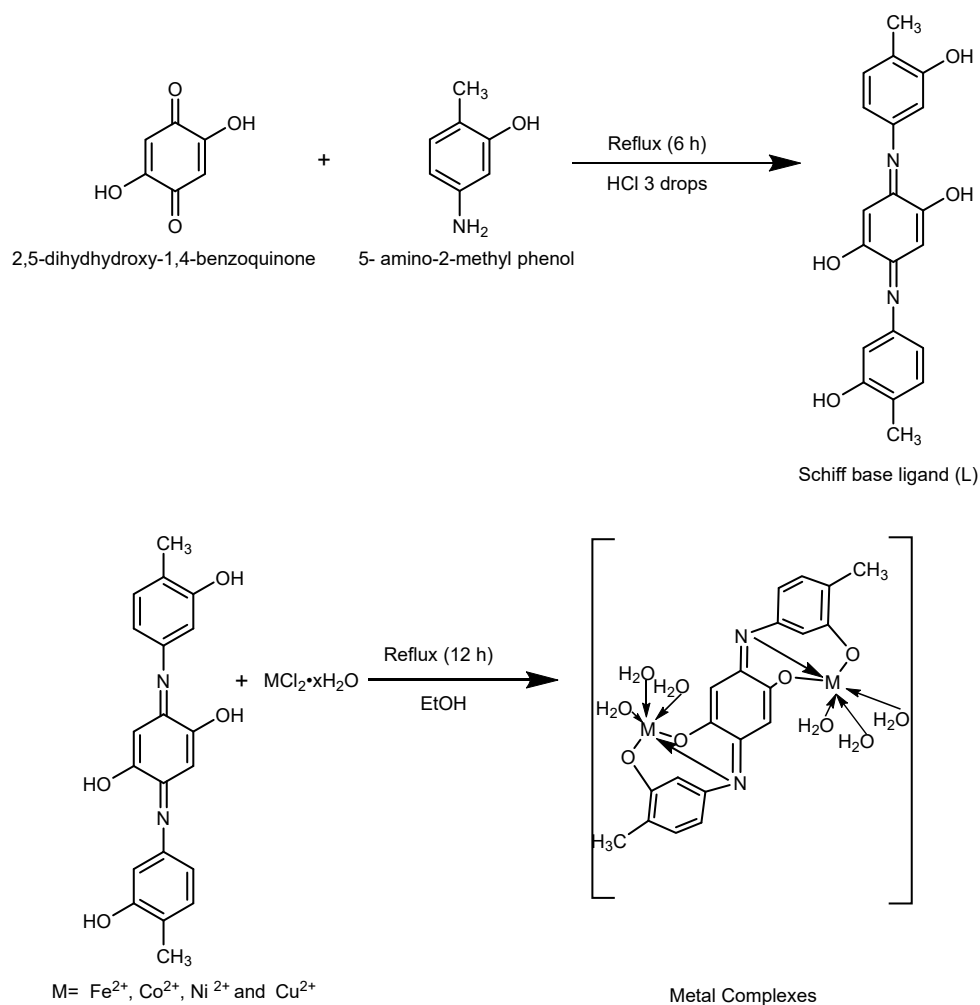
### **Ligand and Metal Complexes Synthesis**

The typical procedure for making the Schiff base ligand involves the condensation of the ketone (2,5-dihydroxy-1,4-benzoquinone) and the amine (5-amino-2-methylphenol) in a 1:2 molar ratio, respectively. In this reaction, the two carbonyl groups in the 2,5-dihydroxy-1,4-benzoquinone structure will be replaced by the new imine groups. HCl was used as a catalyst to fasten the reaction time and ensure the complete conversion of the carbonyl groups to imine groups. The

created brown ligand was then used to form complexes with Fe(II), Co(II), Ni(II), and Cu(II) in also 1:2 (L:M) molar ratio. The use of this molar ratio ensures the coordination of two similar metal ions with the separated three coordination sites. Scheme 1 shows steps to ligand synthesis and its metal complexes, while Table 1 shows some properties of them.

### <sup>1</sup>H-NMR of the Ligand

<sup>1</sup>H-NMR spectroscopy was used to determine the presence of protons in the Schiff base ligand using DMSO-*d*<sub>6</sub> as a solvent which can be detected at 2.50 ppm as a single signal. The main signals for the protons of L have been detected. Each -CH<sub>3</sub> and -OH proton signals emerged at about 1.0 and 9.5 ppm, respectively. Several



**Scheme 1.** Schiff base ligand synthesis with its Fe(II), Co(II), Ni(II), and Cu(II) complexes

**Table 1.** Some properties of the ligand and the metal complexes

Complexes and ligand	Color	Melting point (°C)	Molecular weight (g/mol)	Yield (%)	Metal content (%)	
					Theoretical value	Experimental value
Ligand	Brown	205–207	350.00	78	-	-
[Fe <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	Brown	344	567.03	77	6.08	6.50
[Co <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	Brown	284–286	572.20	52	6.30	6.80
[Ni <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	Brown	233–235	571.72	75	6.30	7.20
[Cu <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	Brown	293–295	585.44	44	6.60	7.30

signals between 6 and 9 ppm are related to the aromatic protons [17-20].

### FTIR Spectra

The FTIR spectra (Fig. 1) of the ligand and the metal complexes show the characteristic bands that related to the significant groups in ligand structure and how they changed upon the complex formation. For example, the formation of the imine group was seen as a new band at  $1570\text{ cm}^{-1}$  in the free ligand. The formation of this group was also supported by the absence of both bands of the amino group in 5-amino-2-methylphenol and the carbonyl group in 2,5-dihydroxy-1,4-benzoquinone which appeared at  $3385$ ,  $3319$ , and  $1647\text{ cm}^{-1}$ , respectively.

The  $\nu(\text{O-H})$  stretching frequency was seen around  $3387$  and  $3323\text{ cm}^{-1}$  as single bands in the free ligand spectra also. When the metal complexes formed, the characteristic bands were changed and shifted which confirmed the complexes' formation. The imine group frequency is shifted to higher frequencies of  $1627$ ,  $1600$ ,  $1602$ , and  $1600\text{ cm}^{-1}$  in  $[\text{Fe}_2\text{L}(\text{H}_2\text{O})_6]$ ,  $[\text{Co}_2\text{L}(\text{H}_2\text{O})_6]$ ,  $[\text{Ni}_2\text{L}(\text{H}_2\text{O})_6]$  and  $[\text{Cu}_2\text{L}(\text{H}_2\text{O})_6]$ , respectively. This shift confirms the metal coordination with the ligand imine groups. This linkage was also confirmed by the new bands in the range  $559\text{--}599\text{ cm}^{-1}$  which refers to M-N bond in these metal complexes.

The hydroxyl groups at the phenyl ring in the ligand structure are deprotonated and coordinated with the metal ions through the free oxygen atoms. This was confirmed by the absence of hydroxyl group bands at  $3387$  and  $3323\text{ cm}^{-1}$ . The FTIR spectra of the complexes also show broad bands in the region  $3600\text{--}3200\text{ cm}^{-1}$ , which refers to water molecules. The coordination with deprotonated hydroxyl groups and water molecules was confirmed by the appearance of new bands related to  $\nu(\text{M-O})$  bonds in the range  $518\text{--}545\text{ cm}^{-1}$  in the metal complexes. Table 2 gives a summary of the FTIR characteristic bands of all compounds.

### Conductance Measurements and Magnetic Susceptibility

As a solvent, ethanol was used to test the conductivity of the produced complexes at a concentration of  $1 \times 10^{-3}\text{ M}$ . According to the results, all complexes are classified as non-electrolytes, as shown in Table 3 [21].

On the other hand, the magnetic susceptibility measurements were carried out at  $298\text{ K}$ . It is obvious from the magnetic susceptibility values in Table 3. The Fe(II) complex is in a high spin electronic configuration and its  $\mu_{\text{eff}}$  value ( $4.2\text{ B.M}$ ) agrees with the presence of four unpaired electrons in  $d$ -orbitals and this also confirms

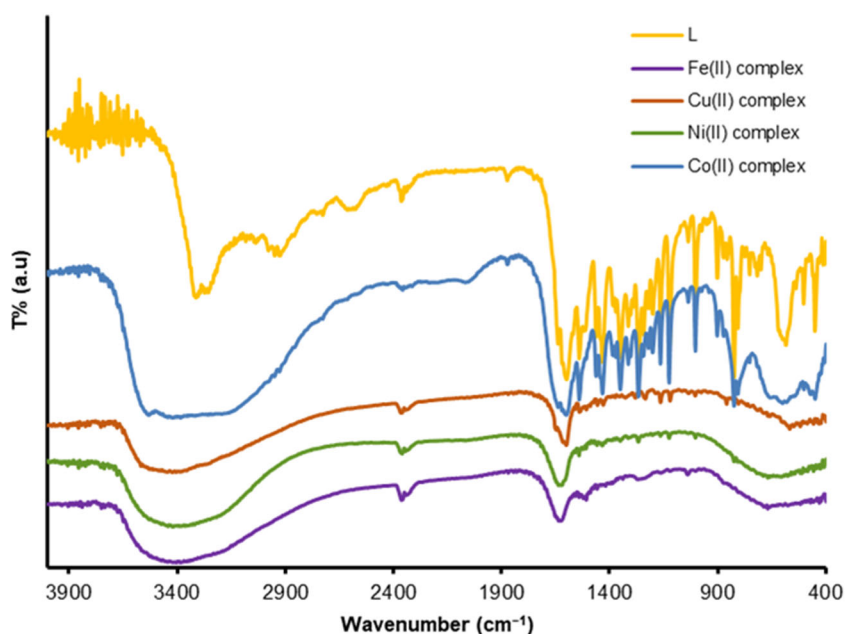


Fig 1. FT-IR spectra of L and the metal complexes

**Table 2.** A summary of the characteristic bands in the FTIR spectrum in  $\text{cm}^{-1}$  of L and metal complexes

Compound	$\nu(\text{H}_2\text{O})$	$\nu(\text{OH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$
Ligand	-	3387–3323	1570	-	-
$[\text{Fe}_2\text{L}(\text{H}_2\text{O})_6]$	3600–3200	-	1627	597	518
$[\text{Co}_2\text{L}(\text{H}_2\text{O})_6]$	3600–3200	-	1600	599	545
$[\text{Ni}_2\text{L}(\text{H}_2\text{O})_6]$	3600–3200	-	1602	559	522
$[\text{Cu}_2\text{L}(\text{H}_2\text{O})_6]$	3600–3200	-	1600	567	518

**Table 3.** The value of molar conductivity of metal complexes at  $10^{-3}$  M concentration in ethanol

Compound	Molar conductivity ( $\text{Ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$ )	$\mu_{\text{eff}}$ (B.M)	Suggested complex shape
$[\text{Fe}_2\text{L}(\text{H}_2\text{O})_6]$	7.70	4.20	Octahedral
$[\text{Co}_2\text{L}(\text{H}_2\text{O})_6]$	7.80	4.11	Octahedral
$[\text{Ni}_2\text{L}(\text{H}_2\text{O})_6]$	8.90	2.97	Octahedral
$[\text{Cu}_2\text{L}(\text{H}_2\text{O})_6]$	8.16	2.34	Octahedral

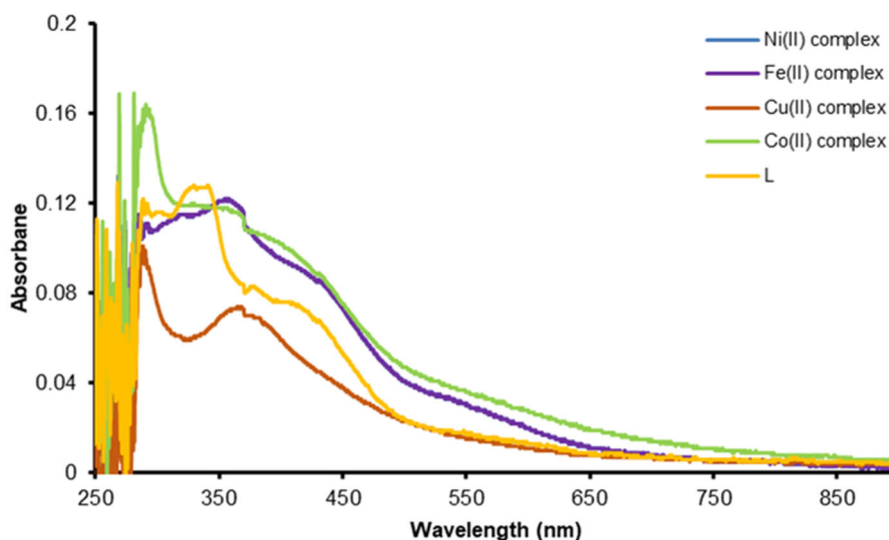
the octahedral shape of Fe(II) complex [22].

Co(II) complex is also paramagnetic with a magnetic susceptibility value of 4.11 B.M. Therefore, Co(II) is present with a high spin  $d^7$  electronic configuration and this agrees with the three unpaired electrons in the  $d$ -orbitals of Co(II) and the octahedral shape [23-24].

Ni(II) complex has a  $\mu_{\text{eff}}$  value (2.97 B.M), which shows that it has a paramagnetic property due to the two unpaired electrons in  $d$ -orbitals and its shape is also octahedral [25-26]. For the Cu(II) complex its  $\mu_{\text{eff}}$  is 2.34 B.M also suggests the paramagnetic characteristics of this ion and agrees with the octahedral structure of the Cu(II) complex and the presence of one electron [8].

### Electronic Spectra

The UV-vis spectra (Fig. 2) of the ligand and the metal complexes were recorded in ethanol in the range 200–1000 nm. Table 4. shows the UV-Vis. peaks and the related transitions. The ligand spectra show three peaks at 344, 421, and 594 nm, which are related to  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$ , respectively. These peaks were shifted when the metal complexes are formed, which suggests the M-L coordination and the MLCT [27]. In Fe(II) complex, peaks appear at 365, 438, and 573 nm. In  $[\text{Co}_2\text{L}(\text{H}_2\text{O})_6]$ , peaks are shifted to 369, 411, and 578 nm. For  $[\text{Ni}_2\text{L}(\text{H}_2\text{O})_6]$ , they are also shifted to 367, 436, and 562 nm. While a broad peak at 389 nm is assigned to two

**Fig 2.** UV-vis spectra of L and the metal complexes

**Table 4.** Transition types in the UV-Vis spectra with their  $\lambda_{\max}$  for the ligand and the metal complexes

Compound	$\lambda_{\max}$ (nm)	Type of transition
Ligand	344, 421, 594	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$
[Fe <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	365, 438, 573	MLCT
[Co <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	369, 411, 578	MLCT
[Ni <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	367, 436, 562	MLCT
[Cu <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	290, 389	intraligand transition ${}^2B_{1g} \rightarrow {}^2E_g$ ${}^2B_{1g} \rightarrow {}^2A_{1g}$

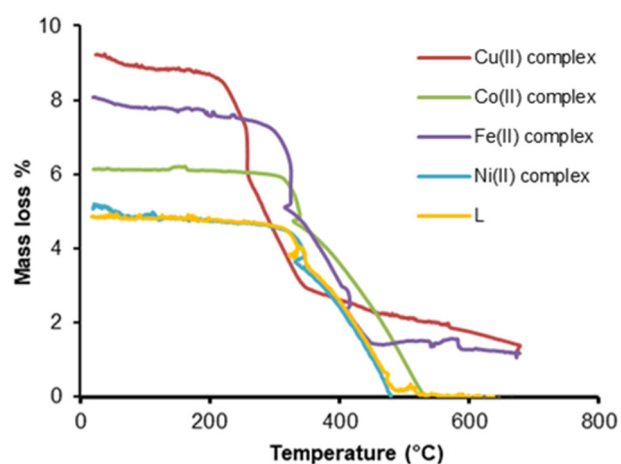
transitions  ${}^2B_{1g} \rightarrow {}^2E_g$  and  ${}^2B_{1g} \rightarrow {}^2A_{1g}$ , respectively, in [Cu<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>], and that at 290 nm related to intraligand transition.

### Thermal Analysis

Fig. 3 shows the thermal analysis curves for the ligand and the four metal complexes. This analysis was carried out under air with a temperature range 0–800 °C. Table 5 gives a summary of the decomposition temperature range and the mass loss and the proposed formed fragments from all the studied compounds. The ligand decomposed in two steps in the temperature range 27.77–429.57 °C. The first step starts at 27.77–331.88 °C includes the loss of the –OH and –CH<sub>3</sub> groups. At the same time, the second step shows the loss of C=N, –OH, –CH<sub>3</sub>, and –C<sub>5</sub>H<sub>6</sub> at 331.88–429.57 °C.

Fe(II) complex decomposition curve shows three steps of decomposition. The first one shows the loss of 2H<sub>2</sub>O in 6.86% loss percentage in the temperature range

34.94–258.46 °C. The second step includes the loss of 4H<sub>2</sub>O, 4O and 2CH<sub>3</sub> in the temperature range 258.46–330.07 °C. While the third step shows the loss of 2C<sub>5</sub>H<sub>6</sub> and C=N in the temperature range 330.07–420.20 °C. The decomposition of the cobalt complex shows two steps of decomposition in the temperature range 40.68–572.17 °C. The first step shows the loss of 3H<sub>2</sub>O, 4O and CH<sub>3</sub> in the temperature range 40.68–383.31 °C with a mass loss of 25.5%, while the second shows the loss of C=N, 3H<sub>2</sub>O, 12H, 2C<sub>6</sub>H<sub>5</sub> at 383.31–487.57 °C with a loss of 46.6%. The decomposition of [Ni<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>] complex also goes in two steps. The first one shows the loss of 3H<sub>2</sub>O in the range 37.18–278.34 °C with a loss of 10.2%, while the second shows the loss of 3H<sub>2</sub>O, 4OH, 2CH<sub>3</sub>, 2(C=N), 6H and C<sub>6</sub>H<sub>5</sub> at 278.34–412.07 °C with a loss of 44.0%.

**Fig 3.** TGA curve of Schiff base ligand and the complexes**Table 5.** Thermal analysis results for the ligand, [Fe<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>], [Co<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>], [Ni<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>], and [Cu<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>]

Compound	Steps of degradation	Decomposition temperature (°C)	Mass loss (%)	Type of lost species
Ligand	1	27.33-331.88	13.8%	CH <sub>3</sub> , 2OH
	2	331.88-429.57	47.3%	C=N, OH, CH <sub>3</sub> , C <sub>5</sub> H <sub>6</sub>
[Fe <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	1	34.94-258.48	6.86%	2H <sub>2</sub> O
	2	258.48-330.07	31.3%	4H <sub>2</sub> O, 4O, 2CH <sub>3</sub>
	3	330.07-420.20	35.0 %	2C <sub>5</sub> H <sub>6</sub> , C=N
[Co <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	1	40.68-383.31	25.5%	3H <sub>2</sub> O, 4O, CH <sub>3</sub>
	2	383.31-487.57	46.6%	C=N, 3H <sub>2</sub> O, 12H, 2C <sub>6</sub> H <sub>5</sub>
[Ni <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	1	37.18-278.34	10.2%	3H <sub>2</sub> O
	2	278.34-412.07	44.0%	3H <sub>2</sub> O, 4OH, 2CH <sub>3</sub> , 2C=N, 6H, C <sub>6</sub> H <sub>5</sub>
[Cu <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	1	43.49-237.65	13.3%	3H <sub>2</sub> O
	2	237.65-261.27	19.5%	3H <sub>2</sub> O, 2O, 2CH <sub>3</sub>
	3	261.27-332.47	27.5%	C <sub>5</sub> H <sub>6</sub> , C=N, 2O, 6H

Copper complex decomposition in the temperature range 43.49–332.47 °C in three steps. The beginning starts at 43.49–237.65 °C with the loss of 3H<sub>2</sub>O and O in 13.3% loss percentage. The second occurs in the range 237.65–261.27 °C with the loss of 3H<sub>2</sub>O, 2O, and 2CH<sub>3</sub> in 19.5% loss percentage, while the third occurs in the range 261.27–332.47 °C with the loss of C<sub>6</sub>H<sub>5</sub>, C=N, O<sub>2</sub>, and 6H in 27.5% loss percentage.

### Anti-cancer Activity

The anti-cancer activity of the ligand and its Co(II) complex was tested against MCF-7 and MCF10A with the concentration range 18.75–300 µg/mL. The results are shown in Table 6. and Fig. 4 and 5. According to the results [Co<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>] shows a high anti-cancer effect in comparison with the ligand with IC<sub>50</sub> values of 101.24 and 129.2 µg/mL, respectively. This shows the increase of

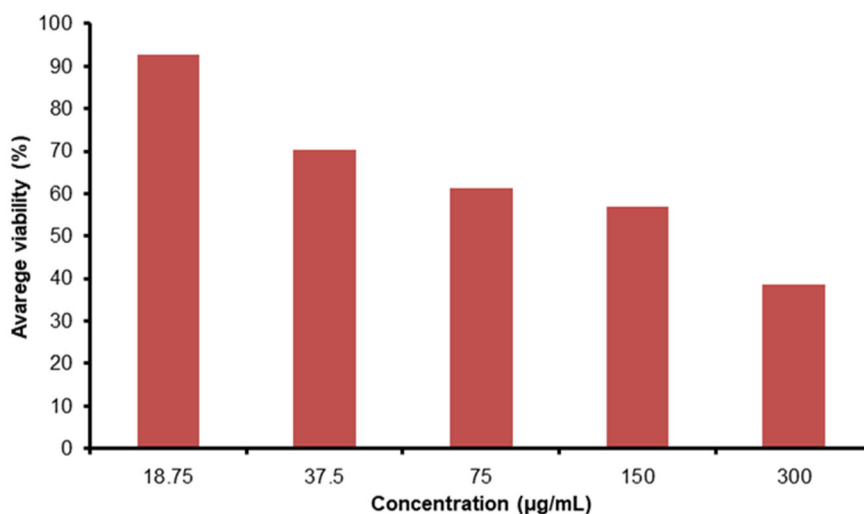


Fig 4. IC<sub>50</sub> for the ligand against a human breast cancer cell line

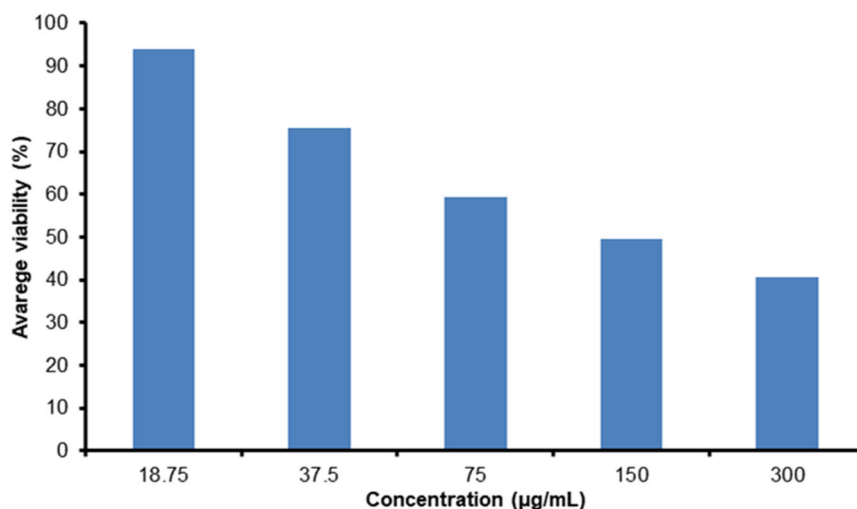


Fig 5. IC<sub>50</sub> for [Co<sub>2</sub>L(H<sub>2</sub>O)<sub>6</sub>] against a human breast cancer cell

Table 6. The effect of complexes and ligand to healthy cell and infected cells

Compound	IC <sub>50</sub> (µg/mL) healthy cell	IC <sub>50</sub> (µg/mL) infected cell
Ligand	166.25	129.20
[Co <sub>2</sub> L(H <sub>2</sub> O) <sub>6</sub> ]	153.39	101.24

the anti-cancer activity when the metal coordinates with the ligand. This activity can be attributed to the chelation theory. According to this theory, when the metal chelates with the ligand, its polarity will decrease due to the share of its positive charge with the electron-rich ligand. As a result, the lipophilicity of the metal and the resulting complex will increase and that leads to better penetration of the cell membrane, which consists of lipids [28-29].

## ■ CONCLUSION

The condensation reaction between 2,5-dihydroxy-1,4-benzoquinone and 5-amino-2-methylphenol in a 1:2 molar ratio produced a Schiff base ligand. By the ligand imine and phenol groups, it acts as a hexadentate ligand and coordinates with Fe(II), Co(II), Ni(II), and Cu(II). This coordination takes place with 1:2 molar ratio of ligand:metal. The produced compounds were characterized by FTIR, UV-vis, thermal analysis, conductivity, magnetic susceptibility, and atomic absorption. At the same time, the ligand was identified by <sup>1</sup>H-NMR and FTIR. All the complexes are non-electrolytes and the octahedral structure was suggested for them by the obtained results. The ligand and Co(II) complex were tested against breast cancer cells and the latest complex shows better anti-cancer activity with IC<sub>50</sub> values of 101.24 and 129.20 µg/mL for the ligand. This result encourages the test of the other prepared metal complexes against the same type of cancer cells or other types.

## ■ ACKNOWLEDGMENTS

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