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RESEARCH ARTICLE

Synthesis, Characterization, and Anticancer Evaluation of Novel Nickel(II) and Copper(II) Complexes Derived from Isatin Thiosemicarbazones

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ABSTRACT

The complex of (2,2′-(7,7′-dimethyl-2,2′-dioxo-1,1′,2,2′-tetrahydro-3H,3′H-5,5′-biindole-3,3′-diylidene) dihydrazinecarbo thioamide), denoted as L, was prepared by the reaction of o-tolidine with chloral hydrate and hydroxylamine hydrochloride in the presence of sodium sulfate and a co-solvent, absolute ethanol. The novel complexes of Ni(II) and Cu(II) with the ligand, L, have been synthesized from a reaction of one mole of L with two moles of $NiCl_2$ and $CuCl_2$ to produce complexes with the general formula $[M_2LCl_2]$ [where M = Ni(II) or Cu(II)]. All three complexes are novel and have a square planar geometry. The metal ions in the two metal complexes coordinate with the ligand via nitrogen, oxygen, and sulfur centers. FT-IR spectroscopy, ^{1}H-NMR spectroscopy, UV-visible spectra and elemental analysis (CHNS) studies were employed for characterization. Existing anticancer agents often face limitations and challenges such as resistance and adverse side effects. This study aims to bridge this research gap by synthesizing and characterizing novel nickel(II) and copper(II) complexes as potential anticancer agents and evaluating their in vitro anticancer activity against the MCF-7 breast cancer cell line. Both compounds proved to be more potent against the MCF-7 cell line than widely used anticancer drug cisplatin. In assessing in vitro anti-proliferative activity against the MCF-7 cell line, $[Cu_2(L)Cl_2]$ exhibited notable cytotoxicity, with an IC_{50} of 8.43 μM (5.53 μg/mL), surpassing cisplatin (34.29 μM or 10.29 μg/mL). The IC_{50} for $[Ni_2(L)Cl_2]$ was 26.73 μM (17.45 μg/mL). These results highlight the potential of $[Cu_2(L)Cl_2]$ as a promising candidate for further investigation in cancer treatment.

Keywords: Anti-proliferative activity, Cu(II) and Ni(II) complexes, IC_{50}, Isatin moiety, Spectra

Introduction

Erdman and Laurent discovered isatins [1H-indol-2,3-dione] as indole, heterocyclic compounds in 1840.[1] Isatin derivatives, notably isatin-thiosemicarbazones, have piqued the interest of researchers due to their ease of preparation and variety of therapeutic activities that can regulate cell growth, differentiation, and death.[2,3] Isatin derivatives have been demonstrated to exhibit cytotoxic, antibacterial, antifungal, tuberculostatic, antiviral, anticonvulsive, antioxidant, and anticancer effects.[4–6] Isatin-thiosemicarbazone compounds are appealing targets for further research and development in the field of medicinal chemistry due to their versatility and broad spectrum of biological activity.[7,8] Some thiosemicarbazone derivatives' biological activity is connected to their ability to form chelates with transition metal ions via O, N, and S.[9–12] Their ability to engage in complexation with transition metals, coupled with the resultant redox activity, positions them as promising candidates in medicinal chemistry, particularly in the development of therapeutic agents with anticancer activites.[13,14] Thus, thiosemicarbazones and associated transition-metal-ion complexes, such

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as Cu(II) and Ni(II), have received considerable attention due to their wide therapeutic uses, which range from antiviral to anticancer activity.[15–17] They are attracted to molecules that are rich in electrons like proteins and DNA which results in mutagenesis and cancer.[18,19] Even though cisplatin and its derivatives, including carboplatin and oxaliplatin, are presently used as anticancer agents, they are associated with significant side effects such as neurotoxicity, hepatotoxicity, ototoxicity, and nephrotoxicity[20,21] also developing resistance.[22,23] The limitations of these anticancer drugs have prompted a considerable number of researchers to explore novel transition metal-based compounds with various ligands.

The purpose of this study is to present the synthesis and chemical characterisation of three novel isatin thiosemicarbazone derivatives with the empirical formulas, $C_{20}H_{18}N_8O_2S_2$ (L), $C_{20}H_{16}Cl_2N_8Ni_2O_2S_2$ [$Ni_2(L)Cl_2$] and $C_{20}H_{16}Cl_2Cu_2N_8O_2S_2$ [$Cu_2(L)Cl_2$]. The structures were confirmed using IR, ^{1}H NMR, and UV-visible spectroscopy. The two metal complexes were investigated for in vitro cytotoxic properties against the human breast cancer cell line (MCF-7). Through this investigation, the study aims to contribute to the advancement of cancer therapeutics by validating the anticancer potential of these metal complexes against MCF-7 cells.

Materials and methods

All chemicals are of reagent grade and are used as specified (Fluka), (Merk), (Alpha), or (B.D.H). The Shimadzu FT-IR. 8400 spectrometer was used to record infrared spectra in the (400–4000) cm^{-1} range. Elemental analysis was performed on the (LECO CHNS-932). The metal analyses were performed using a Perkin Elmer OPtema 7300DV ICP-OES Spectrometer. Complex ^{1}H-NMR spectra were acquired using a Bruker ultra shield 300 MHz with TMS as an internal reference at Mashhad University in Iran. The melting point was measured with the Melting Point-MPD-100Pixel Technology CO., Limited. The conductivity measurements were recorded using a SenzSiemen conductivity tester. Shimadzu's AE-UV1609 (UK) CO., LTD was used to capture electronic transition spectra in the (200–800) nm region. The Capricorn Company in Germany provided trypsin/EDTA, RPMI 1640, and fetal bovine serum. Santacruz Biotechnology Company in the United States provided the DMSO. Bio-World in Germany supplied the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT stain).

Cell lines

The Michigan Cancer Foundation-7 (MCF-7) cell line was obtained in 1970 from a 69-year-old White woman. MCF-7, alluding to the institute in Detroit where Herbert Soule and his colleagues created the cell line in 1973.

Preparation of the complexes

Synthesis of 2,2′-(7,7′-dimethyl-2,2′-dioxo-1,1′, 2,2′- tetrahydro-3H,3′H-5,5′-biindole-3,3′-diylidene)

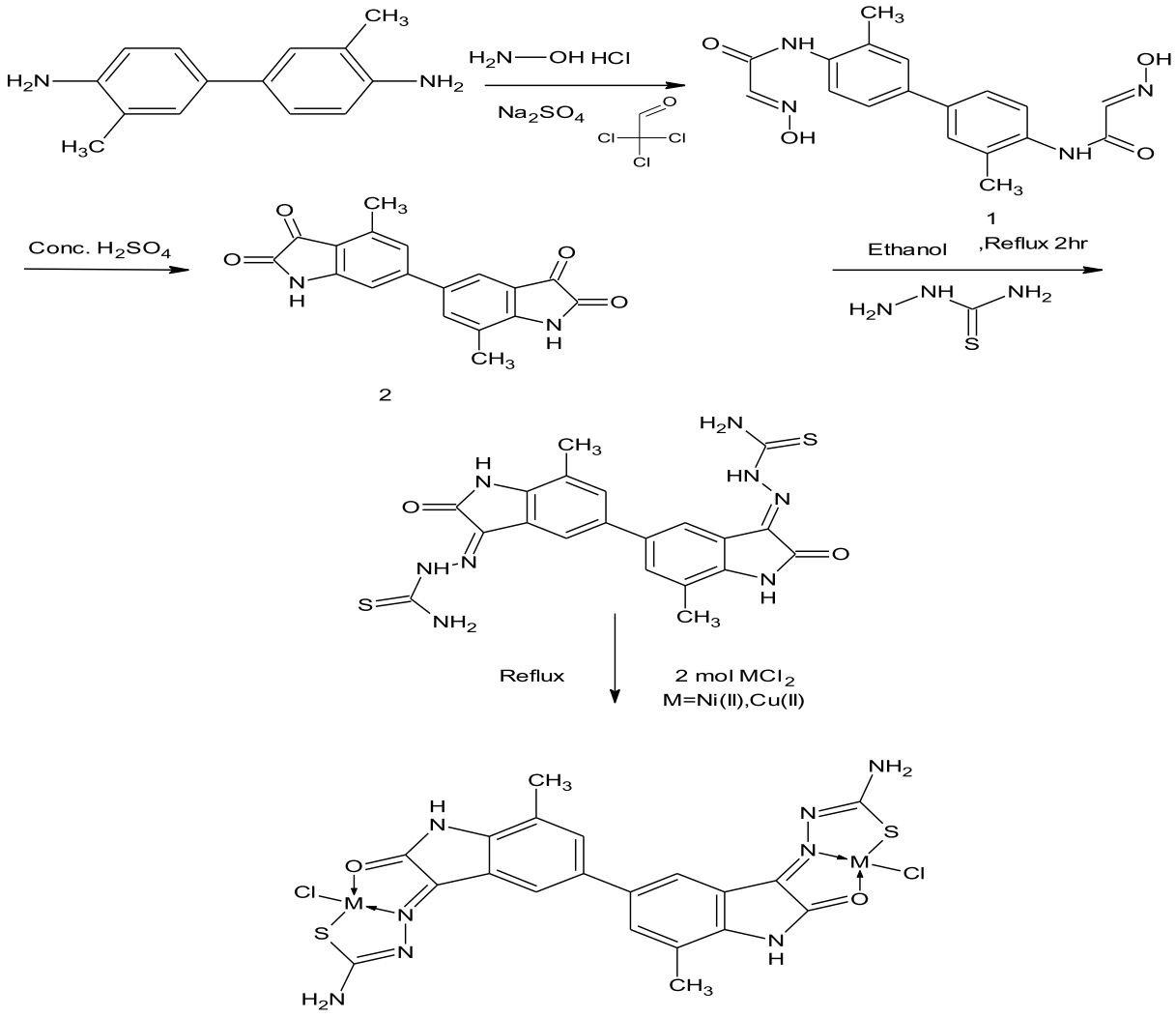
Dihydrazinecarbothioamide: L

A solution of chloral hydrate (30 mmol, 4.96 gm) in 40 ml of water was poured into a round-bottomed flask, followed by the addition of (60 g) of crystallized sodium sulfate, then a solution of o-tolidine (20 mmol) in 30 ml of water and (4 ml) of strong hydrochloric acid. A (40 mmol, 2.78 gm) hydroxylamine hydrochloride solution in 50 ml of water was added, along with 40 ml of 100% ethanol. The reaction mixture was refluxed, and vigorous boiling proceeded within approximately 45 minutes. After a brief period of one to two minutes of vigorous boiling, the reaction reached completion. Throughout the heating phase, compound (1) Scheme Scheme 1 crystals began to precipitate. Upon cooling with a stream of water, the product solidified completely. It was then isolated through suction filtration and air-dried.

After heating 6 ml of concentrated sulfuric acid to 50° C in a round-bottomed flask, 15 mmol of compound 1 Scheme Scheme 1 was added at a rate adequate to maintain the temperature between 60–70 °C. To complete the reaction, the temperature of the solution was raised to 75 °C after the addition, and it was maintained at this temperature for 10 minutes. After cooling to room temperature, the reaction mixture was poured over crushed ice while being agitated. The separated product was filtered after half an hour, washed with small volumes of cold water several times, and air dried. 20 ml of ethanol and 2 drops of glacial acetic acid were added to the solution of compound 2 and thiosemicarbazide and refluxed for 2 hours at 60–70 °C. The crude product was purified via recrystallization with DMSO and water.

Synthesis of the Ni(II) and Cu(II) complexes

The Ligand (1 mole) was refluxed with (2 moles) of $NiCl_2.6H_2O$ and $CuCl_2.2H_2O$ for 2 hours at 50–60 °C, Scheme 1. The precipitates formed were filtered and rinsed with cold ethanol. Table 1. summarizes the physical properties of the end products.



Scheme 1. Syntheses of the complexes.

Table 1. Physical properties and analytical data of ligand and their complexes.

Complex	Color	Yield%	M.Wt g/mol	d.P. (°C)	(Calculated) Found %			
					C	H	N	M
L	Brawn	65%	466.54	238.6	(51.49) 52.08	(3.89) 3.96	(24.02) 224.82	….
$Ni_2(L)Cl_2$	Reddish brown	77%	652.82	>300	(36.80) 35.37	(2.47) 3.25	(17.16) 17.91	(17.98) 18.35
$Cu_2(L)Cl_2$	Brawn	75%	662.52	>300	(36.26) 36.87	(2.43) 3.22	(16.91) 17.7	(19.18) 19.89

Results and discussion

Infrared spectroscopic study

Table 2 lists selected vibrational bands of the ligand and the two metal complexes. When the spectra of shift bases are compared, all of the complexes exhibit a band at 3190–3155 belonging to the amide group's v(N-H) stretching mode. Aromatic C-H stretching was allocated to the bands that appeared near 3078–3062 cm^{-1}, while aliphatic C-H stretching was assigned to the bands that showed near 2817–2877 cm^{-1}. C=O vibration is assigned to the bands seen at about 1693–1654 cm^{-1}. The band shift to

Table 2. The selected IR spectra bands (cm^{-1}) of the free ligand and its complexes.

Comp.	υ N-H	C-H str. Aleph.	C-H str. Arom.	υ C=O	υN-N	υC=N	υ C=S	υ C-S	υ M-S
Ligand	3190	2877	3062	1693	1153	1622	819	...	.....
$Ni_2(L)Cl_2$	3130	2800	3066	1654	1099	1499	...	702	450
$Cu_2(L)Cl_2$	3155	2817	3078	1681	1078	1604	.....	698	420

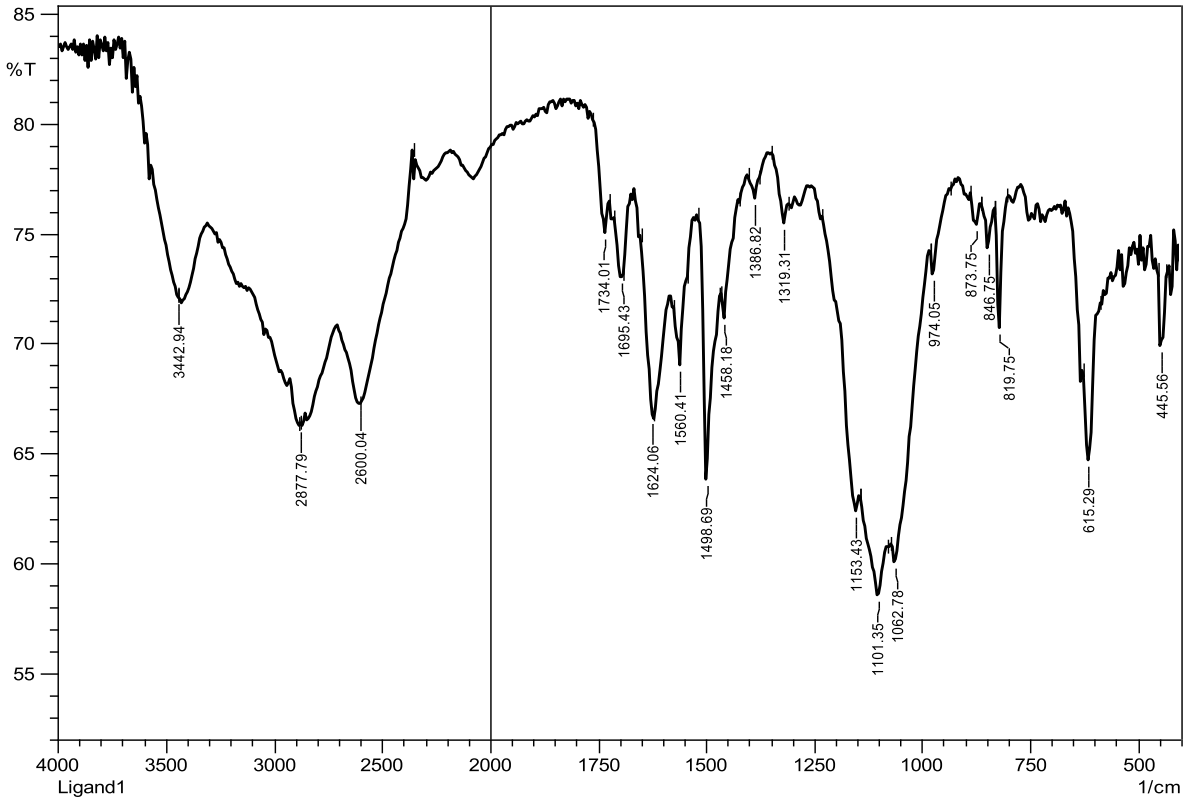


Fig. 1. The infrared spectrum of (L) ligand.

lower wavenumbers shows that carbonyl oxygen is coordinated with the metal ion.[24] The v(C=N) band at 1622–1499 cm^{-1} in metal complexes is moved to lower wavenumbers, showing that nitrogen of the azomethine group is coordinated to the metal ion.[25] The free ligands have an (N-N) band at 1153 in their IR spectra. This band shifted to lower wavenumbers 1099 in nickel complex spectra and 1078 in copper complex spectra, showing the participation of this group in complexation.[26]

The band corresponding to the C=S stretch shows at 819 cm^{-1} in the spectra of the ligands. The v(C-S) band of the two metal complexes in the range of 702 for the Ni complex and v(698) for the Cu complex suggested coordination of (C-S) to the metal ions. This is corroborated by the occurrence of new bands in the 450–420 cm^{-1} range attributed to vM-N bands.[27] The IR spectrum results support the tridentate complexation of the Schiff base with metal ions. The infrared spectrum for the three complexes is shown in Figs. 1 to 3.

^{1}H-NMR data

Figs. 4 to 6 show the ^{1}H-NMR spectra of substances ((L), $[Ni_2(L)Cl_2]$, and $[Cu_2(L)Cl_2]$) in DMSO, with peak assignments given in Table 3. In DMSO solution, the ^{1}H-NMR spectra of the complexes (L, $[Ni_2(L)Cl_2]$, and $[Cu_2(L)Cl_2]$) were recorded. The findings revealed that the signals at (11.36, 11.33) attracted the N-H proton of istain. Aromatic ring protons were found at 7.36, 7.44, and 7.52 for Ni, Cu, and L complexes, respectively. Finally, the methyl group of indoles emerged as a singlet at the (L), $[Ni_2(L)Cl_2]$, and $[Cu_2(L)Cl_2]$ ranges of 2.51, 2.31, and 2.51, respectively.

Conductivity measurement

Complexes [L], Ni(II) complex, and Cu(II) complex have molar conductivities in DMSO of 24, 52, and 94 (Ω^{-1} cm^2 mol^{-1}), respectively, showing that they are electrolyte complexes Table 4.

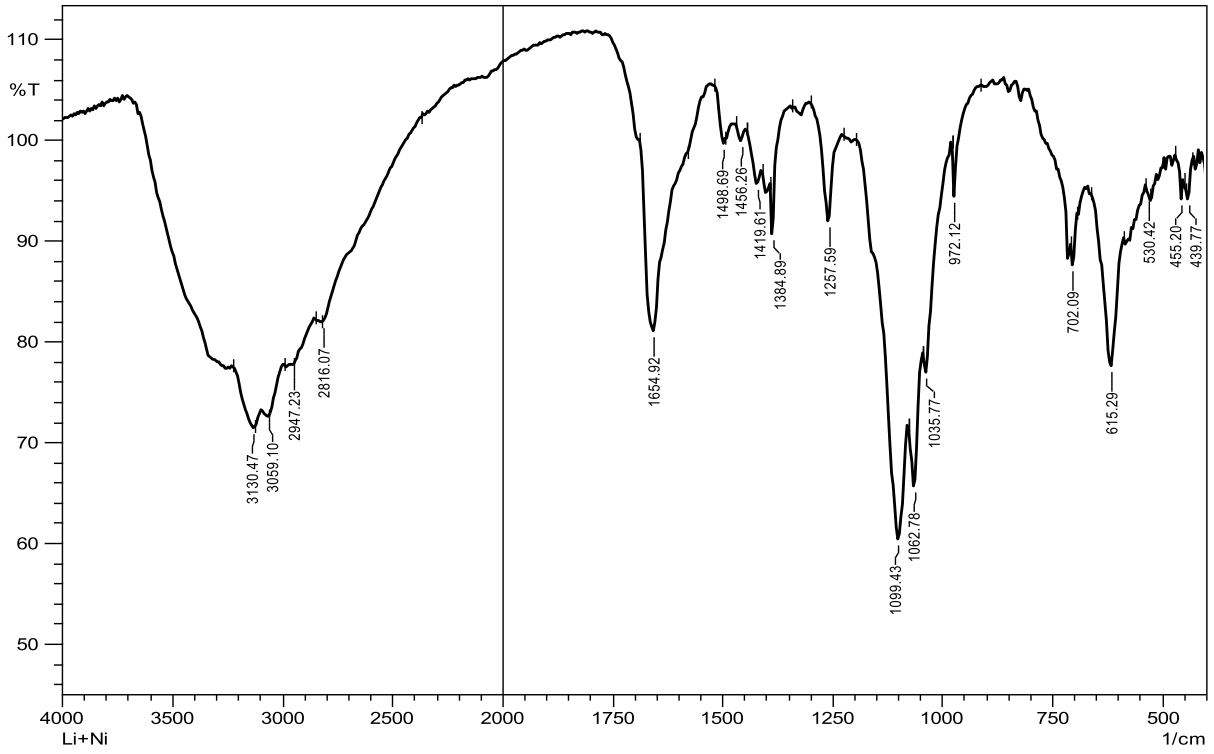


Fig. 2. The infrared spectrum of $[Ni_2(L)Cl_2]$.

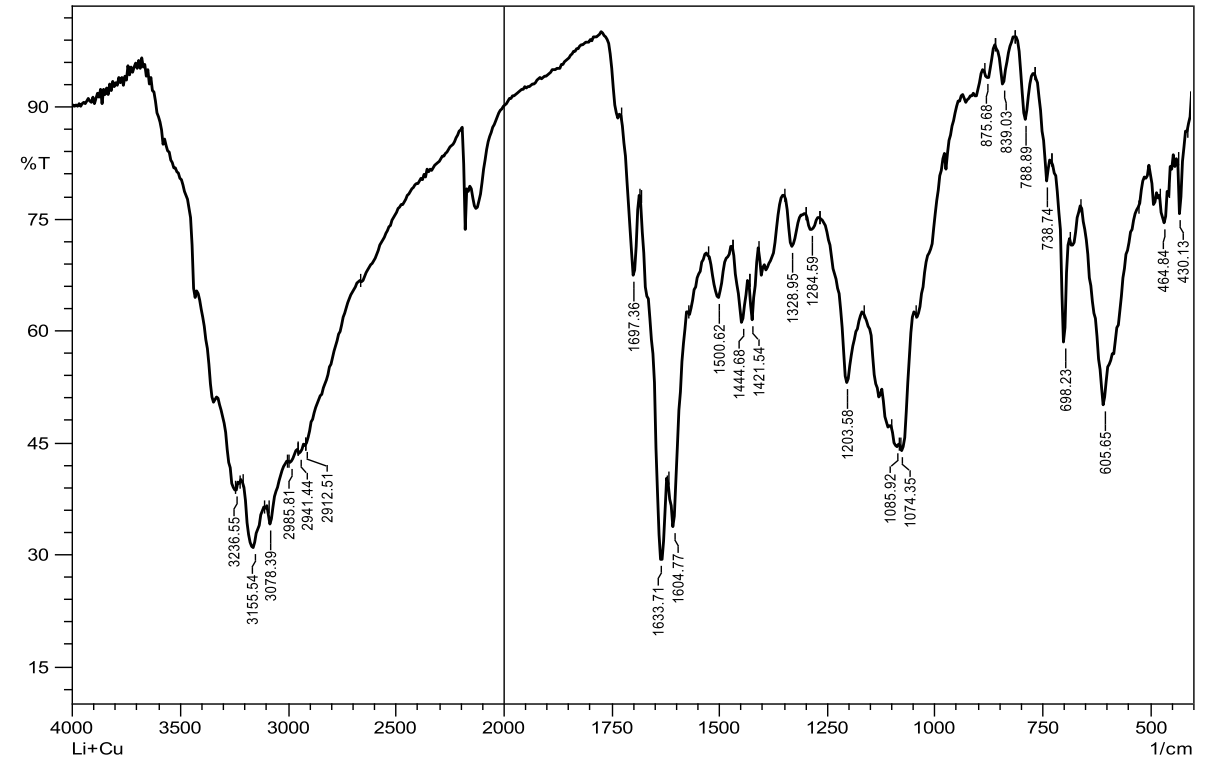
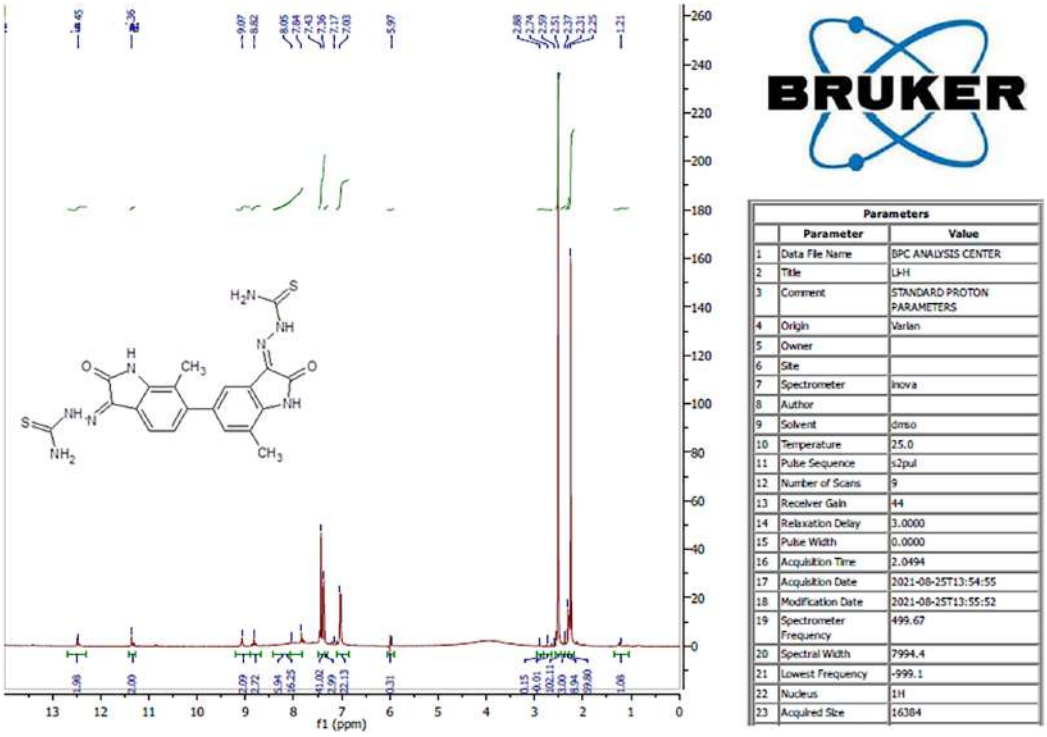


Fig. 3. The infrared spectrum of $[Cu_2(L)Cl_2]$.



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8	Author	
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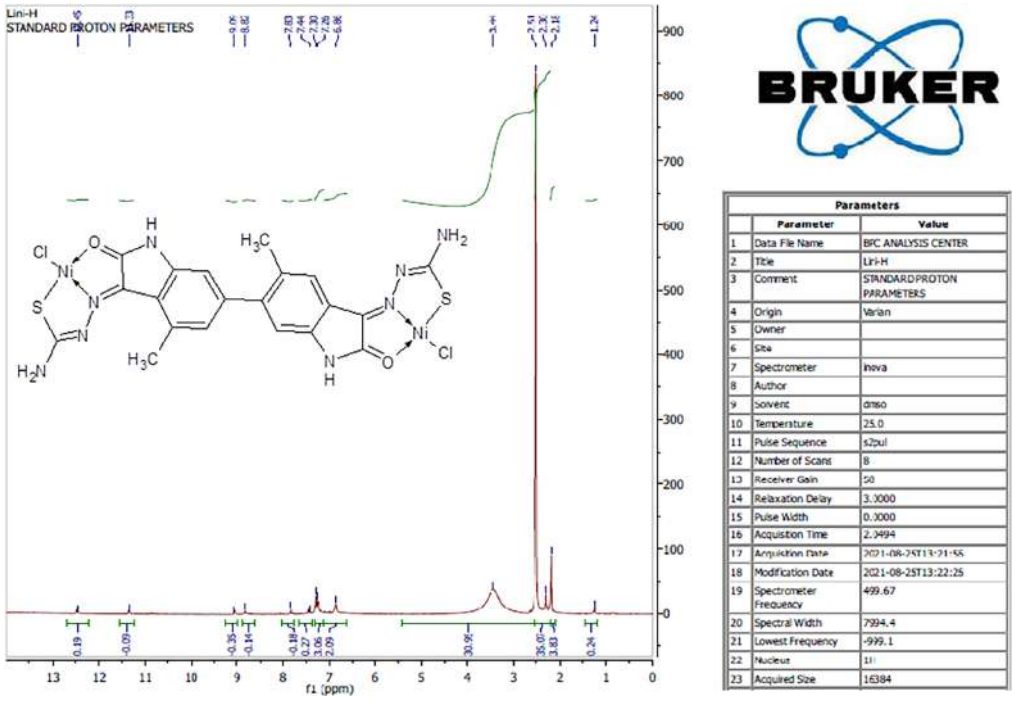
20	Spectral Width	7994.4
21	Lowest Frequency	-999.1
22	Nucleus	1H
23	Acquired Size	16384

Fig. 4. ^{1}H-NMR of (L) ligand.



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20	Spectral Width	7994.4
21	Lowest Frequency	-999.1
22	Nucleus	1H
23	Acquired Size	16384

Fig. 5. ^{1}H-NMR of $Ni_2(L)Cl_2$.

Electronic spectral studies

The electronic spectra of the ligands and their complexes in 10^{-3} M solution DMSO were recorded, and the results are listed in Table 4, giving two peaks of ligand (L), at 33783, 26178 cm^{-1}, which are assigned to the π-π* and n-π* transitions inside the ligands, respectively. The UV-visible spectra of Ni(II)

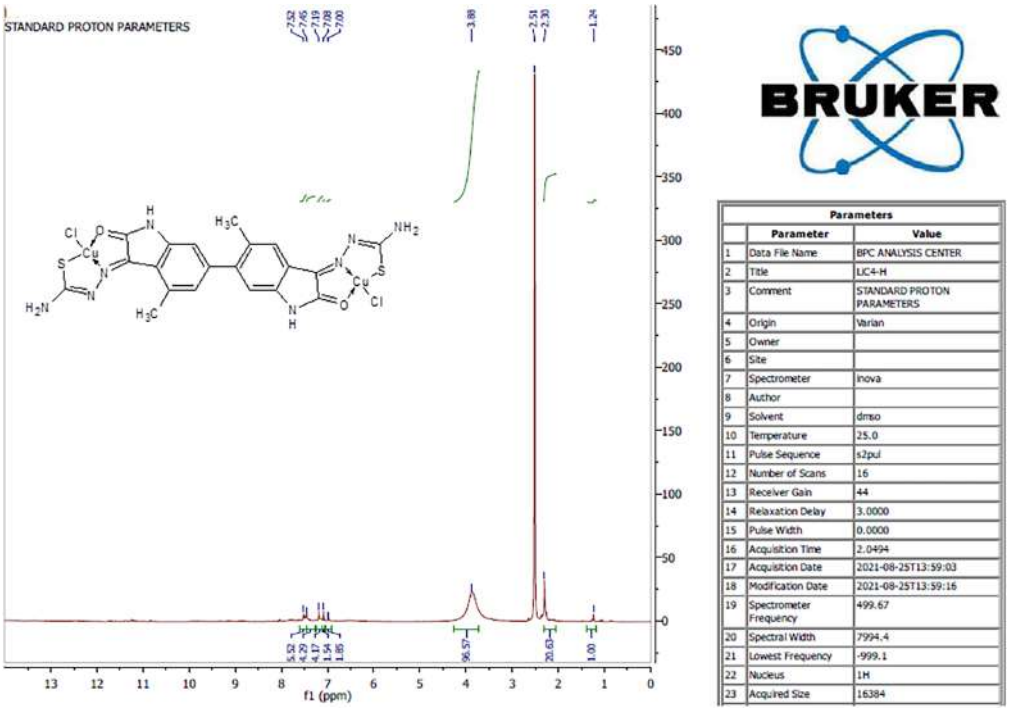

Fig. 6. ^{1}H-NMR of $[Cu_2(L)Cl_2]$.

Table 3. Assignment of ^{1}H-NMR spectral data of compounds.

Compound	(δ) in ppm (multiplicity, intensity, assignment)
Ligand	11.36(s,3H,NH), 7.36(m,6H,ArH), 7.08(S,2H,=CH), 2.51(s,6H,Ar-CH3)
$[Ni_2(L)Cl_2]$	11.33(s,2H,NH), 7.44(m,6H,ArH), 2.3(s,6H,Ar-CH3)
$[Cu_2(L)Cl_2]$	7.52(m,6H,Ar-H), 6.86(s,2H,N-H), 2.51(s,6H,Ar-CH3)

Table 4. Electronic spectra and molar conductivity of the ligand and complexes.

Compounds	Absorption band Nm	Absorption band cm^{-1}	Transition assignment	ε_{max} ($L.mol^{-1}$ cm^{-1})	Molar conductivity (ohm^{-1}. cm^2. mol^{-1})
L	296	33783	$\pi \rightarrow \pi^*$	578	24
	382	26178	n$\rightarrow \pi^*$	122	
	292	34246	$\pi \rightarrow \pi^*$	1346	
$[Ni_2(L)Cl_2]$	307	32573	M.L.C.T	1212	52
	380	26315	$^{1}A_{1(g)} \rightarrow {}^{1}B_{1(g)}$	412	
	440	22727	$^{1}A_{1(g)} \rightarrow {}^{1}A_{2(g)}$	111	
	265	37735	$\pi \rightarrow \pi^*$	1791	
$[Cu_2(L)Cl_2]$	307	32573	C.T.	1201	94
	369	27100	C.T	834	
	442	22624	$^{2}T_2 \rightarrow {}^{2}E_2$	211	

complex gave four spins permitted transitions at 34246, 32573, 26315, and 22727 cm^{-1}, which were ascribed to transitions $\pi \rightarrow \pi^*$, M.L.C.T, $^{1}A_{1(g)} \rightarrow {}^{1}B_{1(g)}$ and $^{1}A_{1(g)} \rightarrow {}^{1}A_{2(g)}$ respectively. It's feasible to assign square planar geometry. The UV-visible spectra of Cu(II) complex revealed four spins permitted transitions at 37735, 32573, 27100, and 22624 cm^{-1}, which were attributed to transitions $\pi \rightarrow \pi^*$, C.T., C.T and $^{2}T_2 \rightarrow {}^{2}E_2$, respectively. Fig. 7 These transition values are indicated to square planar geometry. [28]

Cytotoxic activity

Maintenance of cell cultures

MCF-7 and Normal human fibroblast (NHF) cell lines were grown in the minimal essential media (MEM) with 10% fetal bovine, 100 units/mL

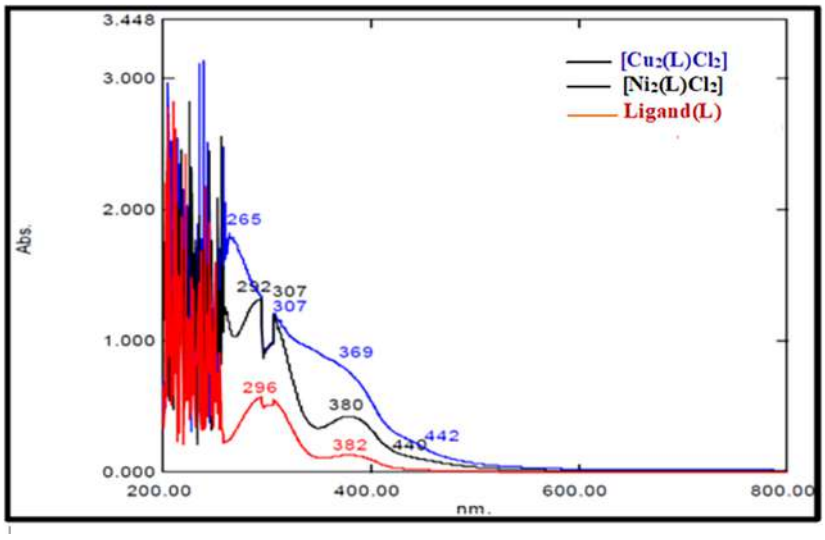

Fig. 7. Electronic spectrum of Ligand (L) and its complexes.

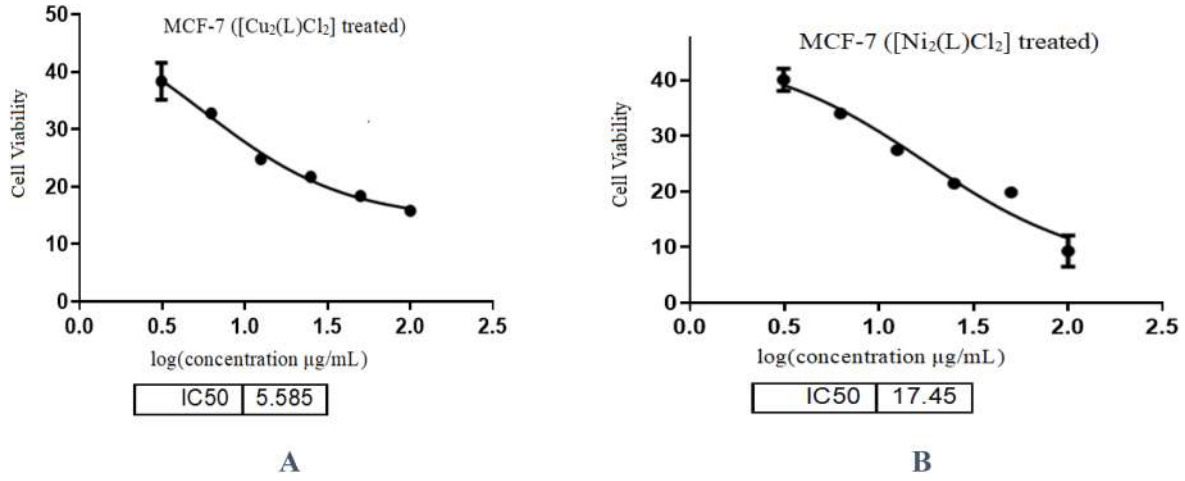

Fig. 8. Breast cancer cells 72 h MTT assay for: A $[Ni_2(L)Cl_2]$ and B of $[Cu_2(L)Cl_2]$ on MCF-7 cell line.

penicillin, and 100 μg/mL streptomycin. Cells were passaged twice a week with Trypsin-EDTA, reseeded at 50% confluence, and incubated at 37 °C.[29]

Cytotoxicity assays

The MTT cell viability assay was performed on 96-well plates to detect the cytotoxic effect.[30] Cell plating was performed on cells that had reached a confluence of 70–80%. Cell lines were planted at a density of 1×10^4 cells per well. Cells were treated with the tested chemical after 24 hours or when a confluent monolayer was established. After 72 hours of treatment, cell viability was determined by removing the medium, adding 28 μL of 2 mg/mL MTT solution, and incubating the cells for 1.5 hours at 37 °C. After discarding the MTT solution, the crystals in the wells were solubilized using 130 μL of DMSO (Dimethyl sulphoxide), followed by a 15-minute incubation at 37 °C with shaking.[31] The absorbency was measured using a triplicate microplate reader at 492 nm (test wavelength). The following equation was used to calculate the cell growth inhibition rate (the percentage of cytotoxicity)[32]:

The stated procedure leads to the calculation of:

1- % of cell viability or % of cell proliferation
2- Lowest concentration that kills 50% of cells (LC_{50}).

% Cell viability = (Absorbance of treated cell/ Absorbance of non-treated cell) × 100
% Cytotoxicity = 100 – cell viability

Statistical analysis

The acquired data were statistically examined using an unpaired t-test and GraphPad Prism 6 software.[33]

The results were provided as the mean standard deviation of three measurements. [34]

Cytotoxicity results

The effect of varying doses of the two complexes on the MCF-7 tumor cell line (3.125 μg to 100 μg/mL) demonstrated considerable cytotoxic effects, where all test complexes inhibited cell growth at high concentrations and reduced it at low concentrations, with the Cu(II) complex having the most robust growth inhibitory impact, followed by the Ni(II) complex. The highest cytotoxic activity of the complexes was achieved at high concentrations (100 μg/mL), and the least activity was observed

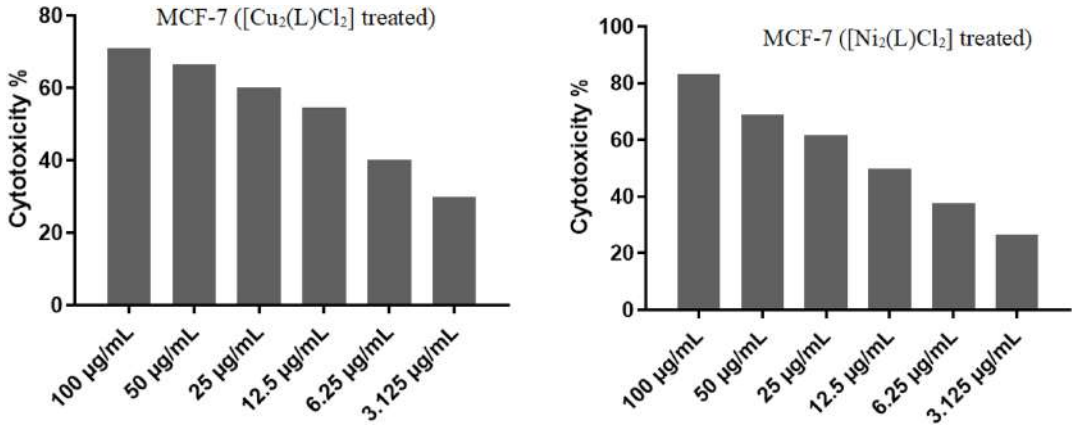

Fig. 9. A) Cytotoxic effects of $[Cu_2(L)Cl_2]$ on MCF-7 cell line, B) Cytotoxic effects of $[Ni_2(L)Cl_2]$ on MCF-7 cell line.

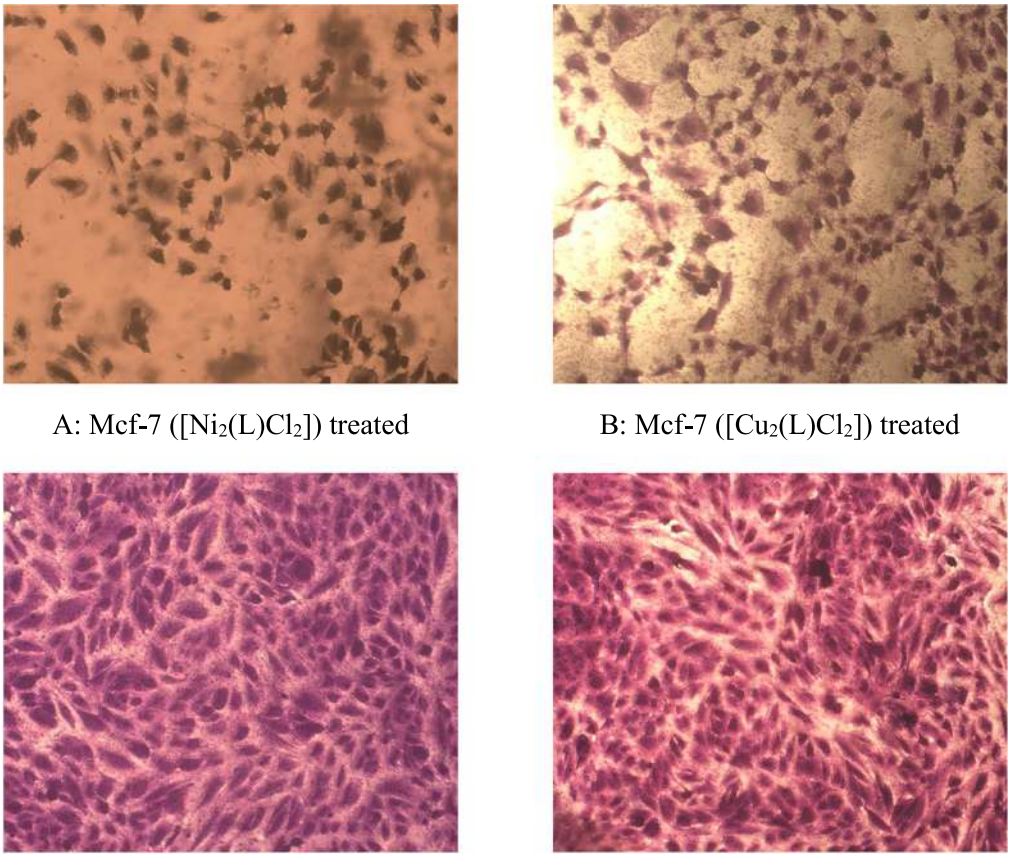

Fig. 10. In vitro morphology of the MCF-7 breast cancer cell line: (A) treated with $[Ni_2(L)Cl_2]$, (B) treated with $[Cu_2(L)Cl_2]$, and (C) control cells under an inverted microscope at 10x.

at lower concentrations (3.125 μg/mL) after a 72 h exposure period. The cytotoxic activity increased with concentration Figs. 8 to 10. Histopathologically, the MCF-7 tumor cells in the control group showed continuous cell growth and monolayer formation, while the tumor cells treated by the tested agents showed cell detachment and had lower cell density Fig. 8. The graphic shows that the number of cells falls noticeably when compared to the control. The $[Ni_2(L)Cl_2]$ molecule has a mild inhibitory effect on cell growth. The logarithmic equation was used to obtain the IC_{50} values for the two complexes $[Ni_2(L)Cl_2]$ and $[Cu_2(L)Cl_2]$ on the MCF-7 cell line. They were 26.73μM (17.45 μg/mL) and 8.43 μM (5.53 μg/mL), respectively. Both compounds are more active against the MCF-7 cell line than cisplatin (34.29 μM 10.29μg/mL).[35] The procedure presented was MCF-7 compliant. The anticancer activities of the produced complexes were evaluated using NHF cell lines as a reference, and the results showed that the $[Ni_2(L)Cl_2]$ complex had higher cell viability than the $[Cu_2(L)Cl_2]$ complex.

Conclusion

Elemental and spectrometry studies have validated the structures of three novel thiosemicarbazone derivatives. According to the spectroscopic results, both complexes of $[Ni_2(L)Cl_2]$ and $[Cu_2(L)Cl_2]$ exhibit a square planar geometry, with the metal ions coordinating to the ligand via nitrogen, oxygen, and sulfur centers. The cytotoxicity of the two complexes $[Ni_2(L)Cl_2]$ and $[Cu_2(L)Cl_2]$ against the breast cancer cell line (MCF-7) was assessed, and the results of in vitro anti-proliferative activity against the human breast cancer cell line revealed that $[Cu_2(L)Cl_2]$ demonstrated considerable cytotoxicity. The IC_{50} values for $[Ni_2(L)Cl_2]$ and $[Cu_2(L)Cl_2]$ on the MCF-7 cell line were 26.73 μM (17.45 μg/mL) and 8.43 μM (5.53 μg/mL), respectively. Both compounds have higher anti-MCF-7 cell line activity than cisplatin (34.29 μM 10.29 μg/mL).

In conclusion, the $[Cu_2(L)Cl_2]$ complex holds promise as a potential novel anticancer drug targeting breast cancer among thiosemicarbazone derivatives. However, further confirmation of its toxicity profile and alignment of its in vitro activity with in vivo efficacy are necessary for its further development.

Acknowledgments

I would like to offer a special thanks to the late Dr. Hikmat Ali Mohamad for his great help and inspiration.

Authors' declaration

- Conflicts of Interest: None.
- I hereby confirm that all the figures and tables in the manuscript are mine. Furthermore, any figures and images, that are not mine, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Authors signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at Salahaddin University.

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تحضيروتشخيص والفعالية المضادة للسرطان في المختبر لمعقدات النيكل (II) والنحاس (II) الجديدة المعتمدة على مشتقات ايستين ثايوسيميكاربازيد

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المستخلص

تم تحضيرالمركب --7,7')-2,2')-ثنائي ميثيل-2,2'-ديوكسو-1,1,2,2'-رباعي هيدرو-5,5'3- ,3,H H'-ثنائي إندول-3,3' -ديليدين) ثنائي هيدرازين كاربو ثيواميد) يشار إليه بـ L من تفاعل o-tolidine مع chloral hydrate و hydroxylamine hydrochloride في وجود كبريتات الصوديوم وتم التفاعل بطريقة التفاعل التكثيفي باستعمال الإيثانول المطلق كمذيب مساعد. تم تحضير معقدات Ni(II) و Cu(II) مع الليكاند L من تفاعل مول واحد من L مع مولين من NiCl2 وCuCl2 لإنتاج معقدات ذات الصيغة العامة [M2LCl2] [حيث M يمثل نيكل (II)أو النحاس)II([. جميع والأطياف المرئية فوق البنفسجية، ودراسات التحليل العنصري (المعقدات الثلاثة جديدة ولهم اشكال هندسية رباعية السطوح. ينسق أيون المعدن الموجود في المركبين الفلزين مع اللجند L عبر مراكز النيتروجين والأكسجين والكبريت. تم استخدام التحليل الطيفي FT-IR، والتحليل الطيفي CHNS، 1H-NMR) للتوصيف. غالبًا ما تواجه العوامل المضادة للسرطان الموجودة تحديات مثل المقاومة الخلايا والآثار الجانبية الضارة. تهدف هذه الدراسة إلى سد هذه الفجوة البحثية من خلال تصنيع مركبات الجديدة وتقييم نشاطها المضاد للسرطان في المختبروبالتالي المساهمة في تقدم علاجات السرطان. تؤكد الدراسة المضادة للتكاثر في المختبر صحة إمكانات المركبين المعدنيين المضادة للسرطان ضد خط خلايا سرطان الثدي البشري لمؤسسة ميشيغان للسرطان -7 (MCF-7). فقد اظهرت كلا المركبين ليكونا أكثر فعالية ضد خط الخلايا MCF-7 من عقار سيسبلاتين المضاد للسرطان المستخدم على نطاق واسع. في تقييم النشاط المضاد للتكاثرفي المختبر ضد خط الخلايا MCF-7، أظهر [Cu2(L)Cl2] سمية خلوية ملحوظة، مع (5.53 µg/mL) 8.43 µM ,IC50)، متجاوزًا السيسبلاتين (34.29 µg/mL 10.29 µM or ( ). وكان IC50 لـ (17.45 µg/mL) 26.73 µM [Ni2 (L)Cl2]. تسلط هذه النتائج الضوء على إمكانات [Cu2 (L)Cl2] كمرشح واعد لمزيد من البحث في علاج السرطان.

الكلمات المفتاحية: النشاط المضاد للتكاثر، معقدات Ni(II) وIC50، Cu(II)، شاردة الإيساتين، أطياف.