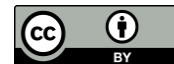




DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF MANNICH BASE SOME TRANSITION METAL COMPLEXES

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ABSTRACT

The new mannich base ligand and its metal complexes were synthesized in ethanol medium. The mannich base is derived from the condensation reaction of morpholine and Ciprofloxacin (Cp) at room temperature. This ligand and metal complexes were characterized using elemental analysis, FT-IR, UV-Vis, and NMR spectral data, molar conductivity measurements, and melting points. Elemental analysis data show that the metal complexes formed have the general formula $[Cr(L)_2ClH_2O] Cl \cdot H_2O$, $[Pt(L)_2Cl_2] Cl_2 \cdot H_2O$ and $[Au(L)_2]Cl \cdot H_2O$ where mannich base ligand (L). Based on spectroscopic analytical, coordination with metal ions involves the 'O' donor atoms of carboxylate group, and the Cr(III) and Pt(IV) complexes are a six-coordinated octahedral structure while Au(III) complex is A four-coordinated square planer structure. Molar conductivity of these complexes showed that they were electrolytic in nature. The toxicity of the free ligand and their metal complexes as anticancer agents against MDA-Mb-231 cell lines was examined with different concentration. Anticancer testing revealed that all complexes were more effective than the ligand. The Au (III) complex exhibited the most significant toxicity effect than the other compounds.

Keyword: Metal complexes, Ciprofloxacin, Mannich base, Anticancer activity.

توصيف ، تحضير والتقييم الحيوي لبعض معقدات العناصر الانتقالية لقاعدة مانخ

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الخلاصة

تم تحضير ليكاند قاعدة مانخ الجديد من تفاعل تكثيف المورفين وسيبروفلوكساسين عند درجة حرارة الغرفة وتم تحضير بعض المعقدات من هذا الليكاند. تم تشخيص الليكاند ومعقداته باستخدام تحليل العناصر، وبيانات طيفية FT-IR، و UV-Vis، و NMR، وقياسات الموصلية المولية، ودرجة الانصهار. اظهرت بيانات تحليل العناصر أن المركبات الفلزية المتكونة لها الصيغة العامة $[Cr(L)_2ClH_2O] Cl \cdot H_2O$ ، $[Pt(L)_2Cl_2] Cl_2 \cdot H_2O$ و $[Au(L)_2]Cl \cdot H_2O$ حيث ليكاند قاعدة مانخ (L). بناءً على التحليل الطيفي، يكون التناسق مع أيونات المعادن عن طريق ذرتي اوكسجين مانحة لمجموعة الكربوكسيل، ومعقدات Cr (III) و Pt (IV) سداسية التناسق ذات شكل ثماني السطوح بينما معقد Au (III) رباعي التناسق ذو شكل مربع مستوي. اظهرت الموصلية المولية لهذه المعقدات أنها ذات طبيعة إلكتروليتيّة. تم فحص سمية الليكاند ومعقداته كعوامل مضادة للسرطان ضد خطوط الخلايا من نوع MDA بتراكيز مختلفة. كشفت الاختبارات المضادة للسرطان أن جميع المعقدات كانت أكثر فعالية من الليكاند. أظهر معقد Au (III) تأثير سمية أعلى من بقية المركبات.

الكلمات المفتاحية: معقدات فلزية، سيبروفلوكساسين، قاعدة مانخ، نشاط مضاد للسرطان.

* The research is extracted from the doctoral thesis of the first researcher.

INTRODUCTION

Many pharmaceuticals and drugs contain metal moieties or metal-drug bonds that can coordinate or react with various metal ions, can affect biological activity, and can damage target biomolecules. increase (Albedair, 2021). Quinolone antibiotics (Gellert *et al.*, 1976) have many properties such as broad antibacterial spectrum (Lipinski, 2000), high bactericidal activity, low toxicity and unique mechanism. As one of the most important antibiotics, it is widely used in the clinical treatment of various infectious diseases (Tan *et al.*, 2012). Ciprofloxacin (CP) is a synthetic broad-spectrum fluoroquinolone antibiotic for oral administration (Supuran *et al.*, 2001). It is active against a wide range of aerobic Gram-negative and Gram-positive bacteria (Rawtani *et al.*, 2017). Mainly complicated and uncomplicated urinary tract infections and pyelonephritis, lower respiratory tract infections, skin infections, urethral and cervical gonococcal infections, bone and joint infections, infectious diarrhea, typhoid fever and acute sinusitis, it is approved for the treatment of (Kapoor *et al.*, 2017). The Mannich reaction is one way to accomplish this task. In addition, many of these compounds have been synthesized and studied for their antibacterial and antitumor activity, as the Mannich bases themselves possess excellent biological activity (Fu *et al.*, 2014). In the present work we are synthesis a new derivative of Ciprofloxacin with morpholine, also the metal complexes of this derivative (L) with Cr(III), Pt(IV) and Au(III) ions were synthesized. The medicinal applications as a anticancer activity was studied.

MATERIALS AND METHODS

General

Ciprofloxacin (99.5%), morpholine, formaldehyde, solvents and metal chlorides (analytical-grade) were obtained from Merck (Schnelldorf, Germany). Using an AA-6880 Shimadzu atomic absorption flame spectrophotometer (Shimadzu Corporation; Tokyo, Japan), the metal content was measured. A Bruker Avance 300 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) was used to record the ^1H and ^{13}C -NMR spectra. In order to measure the ultraviolet-visible (UV-Vis) spectra in ethanol, a Shimadzu UV-1601 spectrophotometer (Shimadzu Company; Tokyo, Japan) was used. The FT-IR 8300 Shimadzu spectrophotometer (Shimadzu Corporation; Tokyo, Japan) was used to record the Fourier transform infrared (FTIR) spectra. Direct Probe captured mass spectra. The melting points in open glass capillaries were examined. Using EA-034.mth, the elemental analyses (C.H.N.S.) were obtained. Measurements of conductivity were performed using a Corning conductivity meter 220, and they were done in an ethanol solvent with a concentration of (10^{-3} M)

Synthesis of Mannich base derived from antibiotic Ciprofloxacin 4-cyclopropyl-7-fluoro-6-(4morpholinmethyl) piperazin-1-yl)1-oxo-1,4-dihydronaphthalene-2-carboxylic acid.) (L)

General procedure for the preparation of (L) (CP, 1.65 g 0.005 mol) and morpholine (0.45 ml, 0.005 mol) in EtOH (25 mL). A solution (CH_2O) was applied and heated to reflux for 6 hours and cooled to room temperature. The precipitate was filtered and recrystallized from (ethanol in water) to give the title compound (Feng *et al.*, 2011).

Preparation of metal Complexes

The desired metal ions in 1mmole (0.158g, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 0.22 g, 0.409g $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ and 0.354 $\text{HAuCl}_4 \cdot 6\text{H}_2\text{O}$) were mixed with 2mmoles (0.430 g) of mannich base (L) which was

dissolved in 10ml of absolute ethanol. The mixture was refluxed for two hours, changing the color. When the solvent was evaporated the resultant precipitates were formed and recrystallization from hot ethanol and then dried to give the metal complexes.

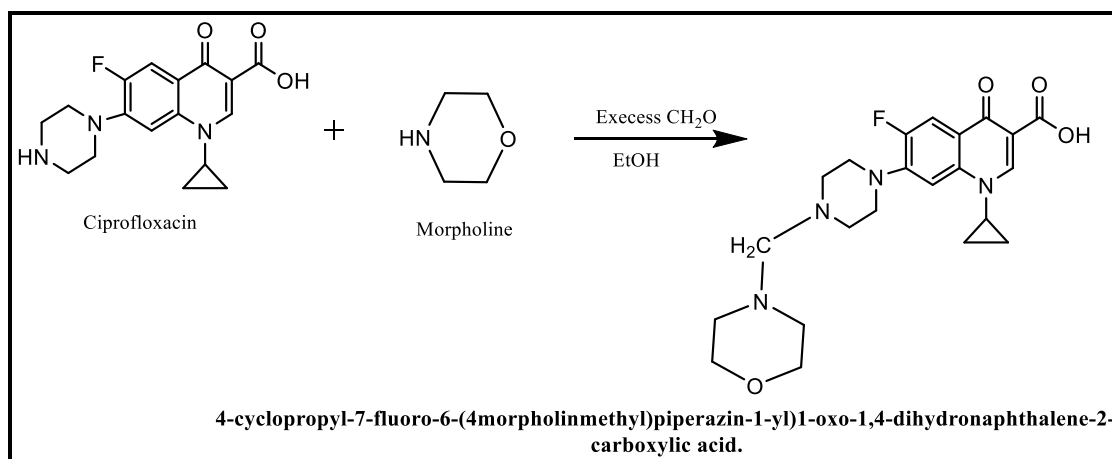
Cytotoxic studies-MTT assay

The cytotoxicity of free ligand and their metal complexes were studied against MDA cell lines by *in vitro* MTT cytotoxicity assay (Abdulameer & Alias, 2022). Cell lines were evaluated 24 hours after being exposed to the compounds at various concentrations. Results from the MTT testing utilizing a desiccator were shown for ligand and their metal complexes. All the compounds produced were characterized using spectroscopic, analytical, and physical methods, as shown in Table 4. Various concentration (400,200,100,50 $\mu\text{g/ml}$) were compared to untreated negative control culture medium.

RESULTS AND DISCUSSION

Synthesis and Characterization of the ligand and Metal Complexes

The data in Table 1 suggest that (L) and its metal ion complexes are in agreement with calculated values. The suggested molecular structure is formulated and characterized by subsequent spectral and molar ratio as well as magnetic moment.



Scheme (1): Synthesis of ligand (L).

Spectral Analysis

FT-IR Analysis:

(Figure 1 and Table 2) show the assignment of the typical bands (FT-IR spectra) of the free (L). The FT-IR spectrum of the free ligand (4-cyclopropyl-7-fluoro-6-(4morpholinmethyl)piperazin-1-yl)1-oxo-1,4-dihydronaphthalene-2-carboxylic acid displays distinct bands between (1635 and 1620 cm^{-1}), which was ascribed to (C=O). The stretching vibration of the (OH) of the COOH group is attributed to a band in the FT-IR spectrum of the free ligand at (3531) cm^{-1} . Other bands are attributed to the stretching frequency of the $\nu(\text{CH}_2\text{-N})$ and the (C=N) at (2964-2839), (1552) cm^{-1} , respectively. All complexes showed a lower frequency shift of the stretching vibration of the (OH) of the COOH group during complexation, appearing in the range (3395-3393) cm^{-1} , indicating coordination through the oxygen atom



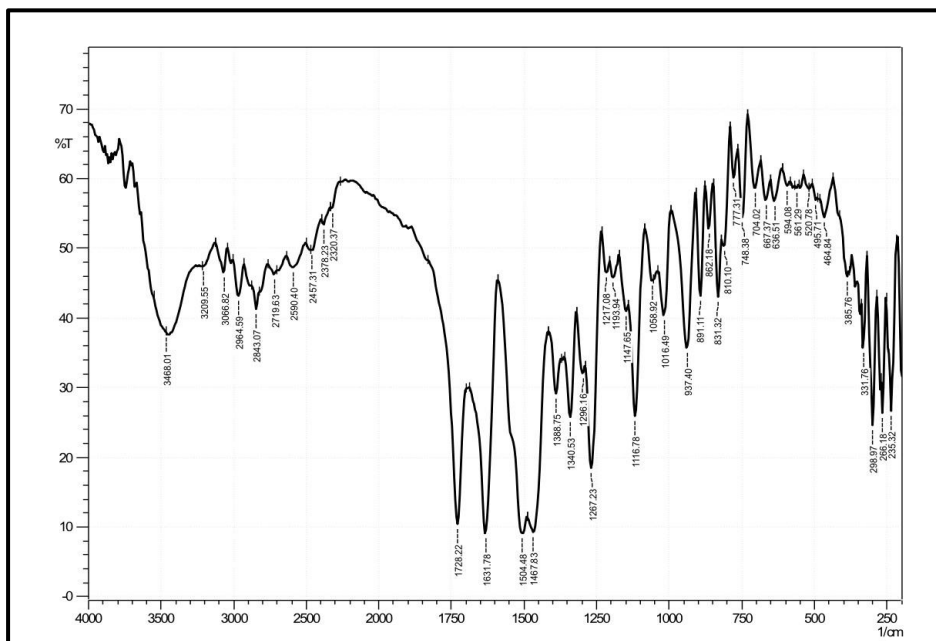
with the metal ion. The spectral data of the prepared complexes records typical frequency bands of stretching vibrations that are asymmetric (COO⁻)_{asym} and symmetric (COO⁻)_{sym} within the ranges (1595-1568) and (1409-1392) cm⁻¹, respectively. The low difference between the (COO⁻)_{asym} and (COO⁻)_{sym} values, which is less than 200 cm⁻¹, shows that the carboxylate group has bidentate binding properties (Mahmood *et al.*, 2021). The FT-IR spectrum of the complexes showed the appearance of new bands at low intensities and lower wave numbers in the ranges 484-470 cm⁻¹ attributed to ν (M-O) (Taher & Mohammed, 2011). The complexes spectra showed new weak bands in the range (352-312) cm⁻¹, which was attributed to the stretching frequency of ν (M-Cl) (Bakir, 2016). Table (2) displays the coordination of the δ H₂O and ω H₂O band with the central metal ion (aqua) in the Cr (III) complex. Bands varied between (3452-3419) cm⁻¹ appeared in all complexes referred to stretching band of H₂O incoordination (Ali & Hassan, 2022).

Table (1): Color, melting point, yield, and elemental composition of ligand and its metal complexes.

Compund	suggested formula	Color	melting point °C	yield %	elemental analysis Found (cal.)				
					C	H	N	S	M
L	C ₂₂ H ₂₇ FN ₄ O ₄	Light Yellow	158-160	88.5	61.45 (61.38)	5.92 (6.32)	12.92 (13.02)	---	---
L Cr(III)	[CrL ₂ Cl H ₂ O].Cl.H ₂ O	Green	184-186	68%	51.38 (51.42)	5.54 (5.56)	11.60 (11.66)	---	4.89 (4.958)
L Pt(IV)	[PtL ₂ Cl ₂].Cl ₂ .H ₂ O	Dark Yellow	236-238	67.5%	43.51 (43.54)	4.45 (4.48)	9.20 (9.23)	---	16.03 (16.06)
L Au(III)	[AuL ₂].Cl ₁ .H ₂ O	Orang	136-138	68%	47.64 (47.69)	4.88 (4.91)	10.08 (10.10)	---	17.73 (17.75)

Table (2): Selected FT-IR absorption bands of ligand and its metal complexes.

Comp.	ν OH COOH	ν COOH	ν C=O	ν COO- asy.	ν COO- sy	ν Δ	ν N-H piprazin	ν CH ₂ -N	ν M-O	Others
L	3531	1722	1629	----	----	----		2920 2837	----	----
CrL	3395	----	1635	1575	1394	181	2625	2928 2835	472	ν OH(H ₂ O) = 3419 ω H ₂ O = 1039 aqua. δ H ₂ O = 956 ν Cr-Cl = 312
PtL	3393	----	1631	1583	1398	185	2630	2926 2830	470	ν OH(H ₂ O) = 3452 ν Pt-Cl = 352
AuL	3393	----	1620	1585	1394	191	2617	2924 2834	484	ν OH(H ₂ O) = 3452



Figure(1): FT-IR spectrum of mannich base ligand

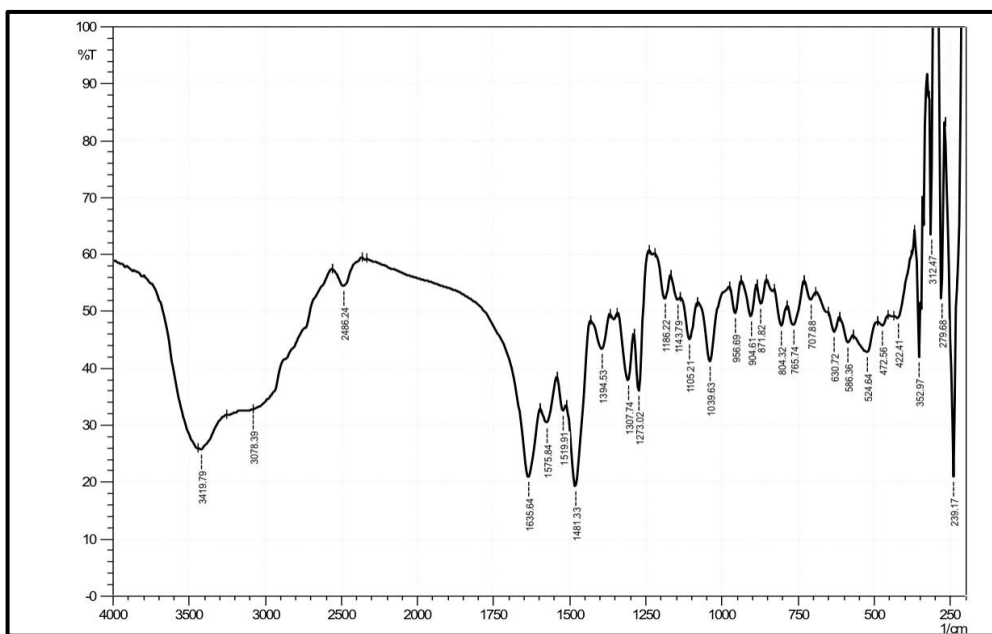


Figure (2): FT-IR spectrum of Cr(III) complex.

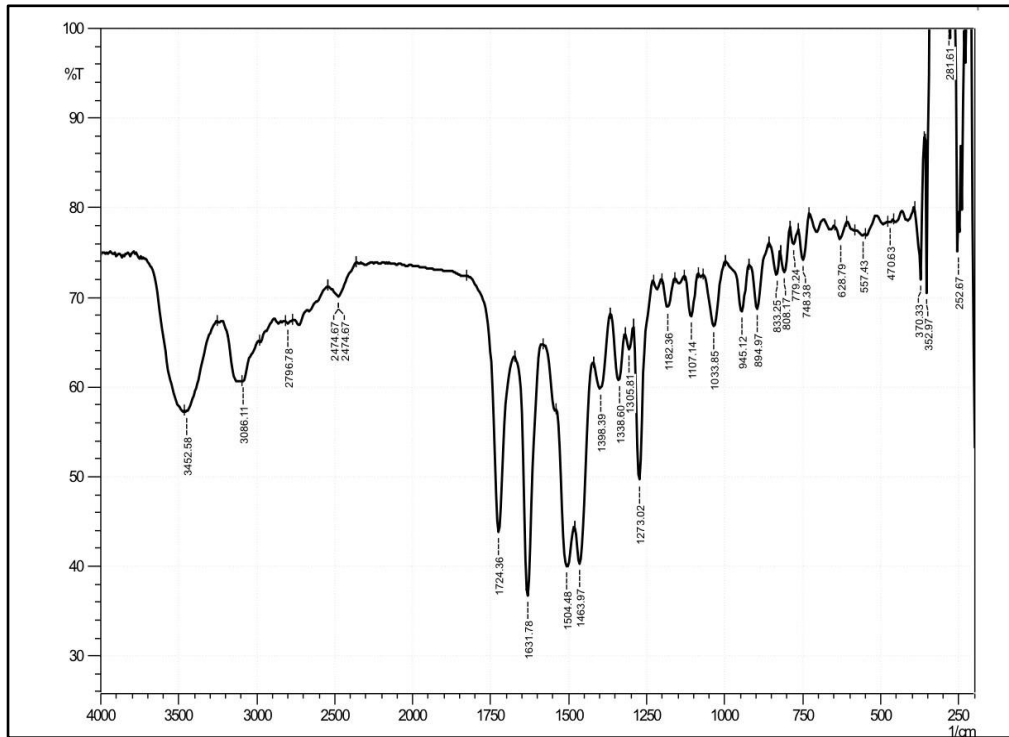


Figure (3): FT-IR spectrum of Pt(IV) complex.

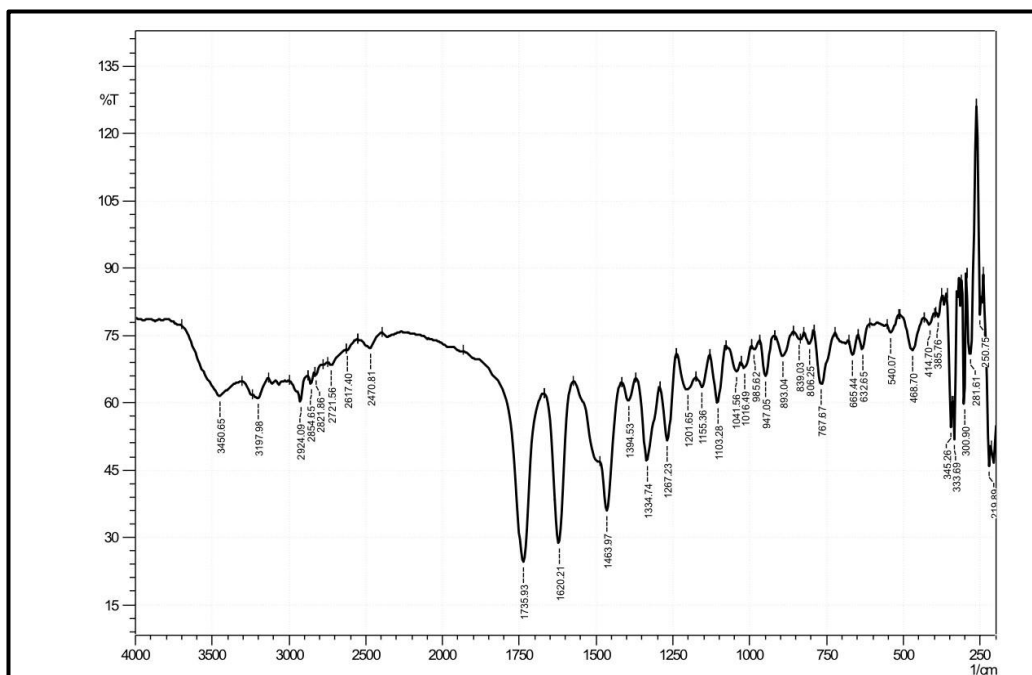


Figure (4): FT-IR spectrum of Au(III) complex.

Electronic Spectra

Four absorption bands are seen at (231 and 260 nm) (43290 and 38461 cm^{-1}) in the UV-visible spectra of the (L) (Figure 5) which attributed to $\pi-\pi^*$ transitions of the aromatic rings (Mathew, *et al.*, 2017) In addition, the absorption band at (298 and 305 nm) (33557 and 32786 cm^{-1}) that may be attributed to $n-\pi^*$ transition of the intraligand transitions (these transitions occur in the case of unsaturated hydrocarbons that contain ketone groups for ciprofloxacin) (Sarwade, *et al.*, 2015) and the $N=C$ - groups of imidazole in addition to the pyrazine ring respectively (Abdulghani & Hussain, 2015).

[CrL] The spectrum in (Figure 6) shows three bands at (611,278 and 210 nm) (16366 , 35971 , and 47619 cm^{-1}) which assigned to the transitions $^4A_{2g} \rightarrow ^3T_{2g}$ (F), $^4A_{2g} \rightarrow ^3T_{1g}$ (p), and $L \rightarrow Cr$ CT, respectively (Hasan, 2020) The theoretical second transition calculated from the equation $15B\lambda = v_3 + v_2 - 3v_1$ using Tanabe–Sugano diagram in d^3 configuration and found to be (404 nm) (24742 cm^{-1}), the ligand field parameter was calculated and can be shown in (Table 3) ionic nature was observed conductivity device. The μ effect value of this complex is 3.33 BM. This indicates that the complex has an octahedral geometry around the Cr(III) ion with three parallel electrons.

[PtL] Four bands of dark yellow Pt(IV) complex at (995,350,301, and 200 nm) (10050 , 28571 , 33222 , and 50000 cm^{-1}), which are attributed to the transitions $^1A_{1g} \rightarrow ^3T_{1g}$, $^1A_{1g} \rightarrow ^1T_{1g}$, $^1A_{1g} \rightarrow ^1T_{2g}$, and (L) $\rightarrow Pt$ (C.T) respectively. The magnetic moment of the present complex, which is (0.0 B.M) of the Pt(IV) complex in its (d^6) structure, agrees with the octahedral configuration (Abdullah *et al.*, 2016), indicating a diamagnetic characteristic. The complex ionic behavior revealed by the conductivity measurement in ethanol (Table 3, Figure 7), the two (Cl^-) ions are outside the coordination zone.

[AuL] The electronic spectrum of the synthesized orang-Au(III) complex (Figure 8) described three bands at (408,295 and 242 nm) (24509 , 33898 and 41322) cm^{-1} which are assigned to the transitions $^1A_{1g} \rightarrow ^1B_{1g}$, $^1A_{1g} \rightarrow ^1E_g$ and (L) $\rightarrow Au$ (C.T) respectively (Alibrahim *et al.*, 2018). These results suggest diamagnetic behavior since the magnetic moment of the present complex (0.0 B.M) is consistent with the suggest square planar configuration.

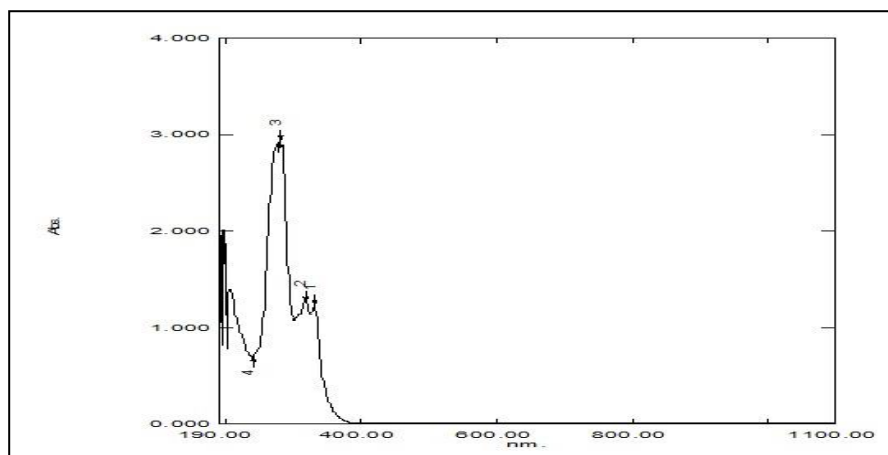


Figure (5): Electronic spectrum of (L).

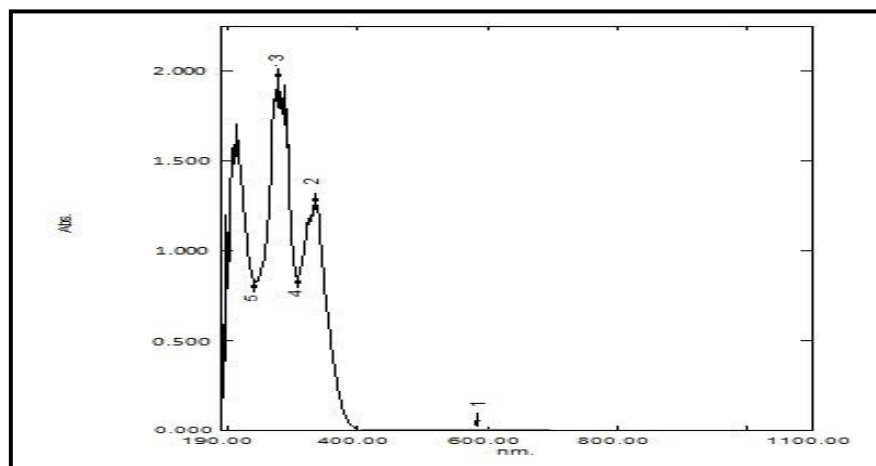


Figure (6): Electronic spectrum of Cr(III) complex.

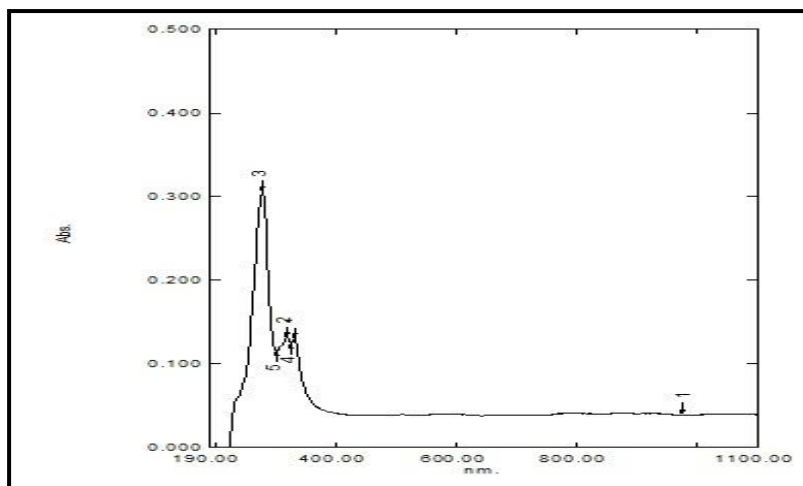


Figure (7) : Electronic spectrum of Pt(IV) complex.

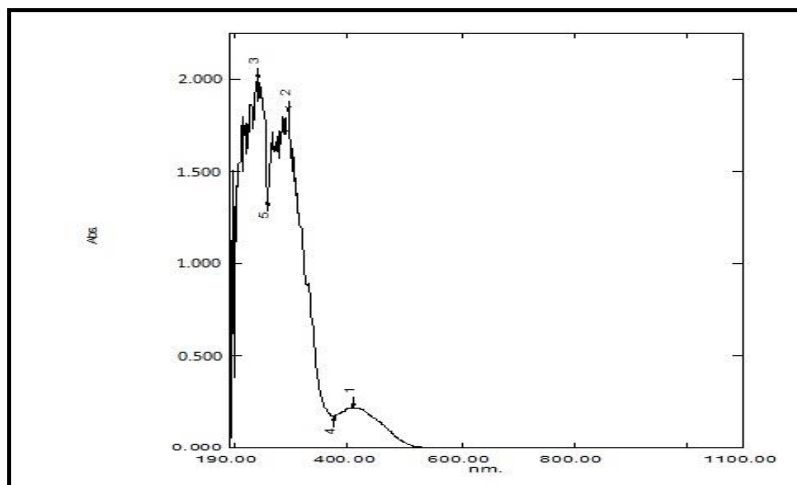
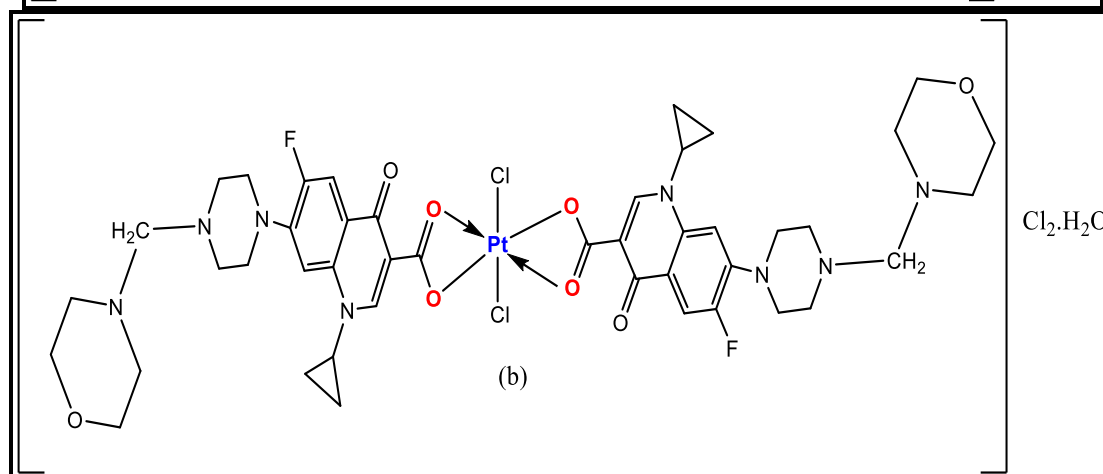
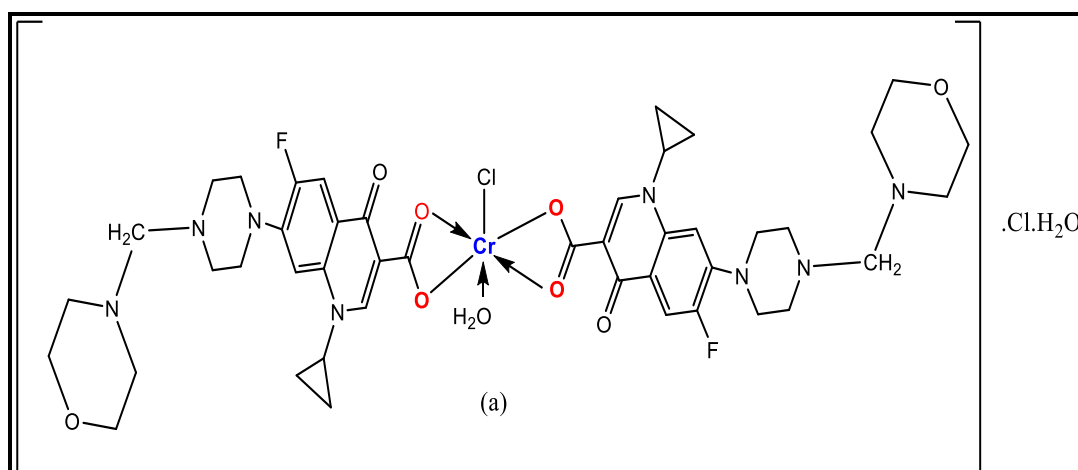


Figure (8): Electronic spectrum of Au(III) complex.

Table (3): Electronic transitions, conductivity, and suggested geometry of metal complexes

Comp.	Absorption cm^{-1}	Assignments	B°	B'	β	15 B'	10Dq	μ_{eff} B.M	ϵ_{max} $\text{Mol}^{-1} \cdot \text{L}^{-1}$	Suggested Geometry
L	43290 38461 33557 32786	$\pi \rightarrow \pi^*$ $\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ $n \rightarrow \pi^*$	---	---	---	---	---	---	---	---
Cr(III)	16366 24742(Cal.) 35971 47619	${}^4A_{2g} \rightarrow {}^4T_{2g}$ ${}^4A_{2g} \rightarrow {}^4T_{1g}$ ${}^4A_{2g} \rightarrow {}^4T_{1g}(p)$ L \rightarrow Cr C.T.	918	771	0.83	11565	16962	3.80	38	Octahedral
Pt(IV)	10050 28571 33222 50000	${}^1A_{1g} \rightarrow {}^3T_{1g}$ ${}^1A_{1g} \rightarrow {}^1T_{1g}$ ${}^1A_{1g} \rightarrow {}^1T_{2g}$ (L) \rightarrow Pt C.T	---	---	---	---	---	0.00	88	Octahedral
Au(III)	24509 33898 41322	${}^1A_{1g} \rightarrow {}^1B_{1g}$ ${}^1A_{1g} \rightarrow {}^1E_g$ (L) \rightarrow Au C.T	---	---	---	---	---	0.00	44	square planner



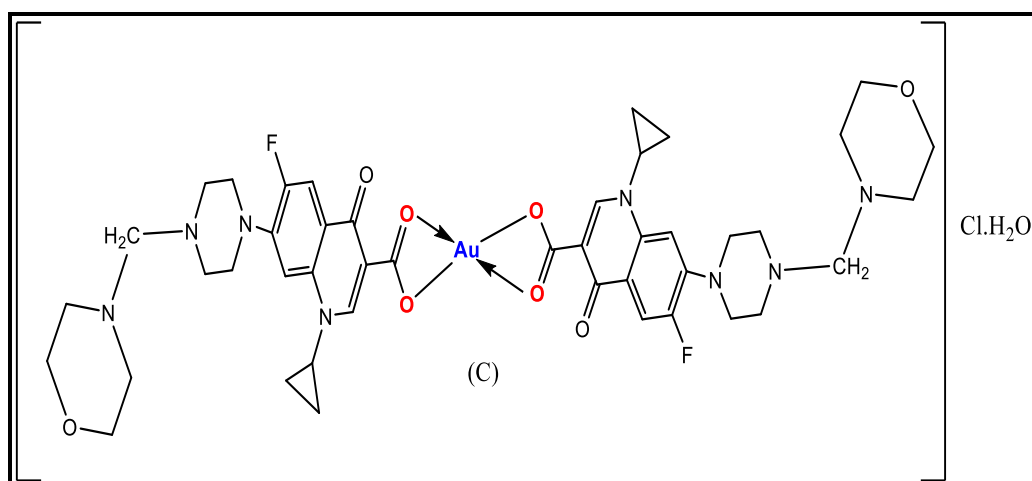


Figure (9): Proposed Structure of (a): Cr (III) complex, (b) Pt(IV) complex and (c) Au(III) complex.

Mass Spectroscopy

The molecular weight of the prepared (L) can be calculated using the mass spectrum, and it can be determined the fragmentation belongs to the compounds being studied. The mass spectrum of the synthesized ligand in (Figure 10), was compatible with the suggested structural formula $C_{22}H_{27}FN_4O_4$. One of the bands, which was found at 430.4 m/z for the ligand, was associated with the molecular ion and was recorded for the ligand in their spectra. Additional distinct peaks revealed in the mass spectra for each ligand were resulting from the successive fragmentation.

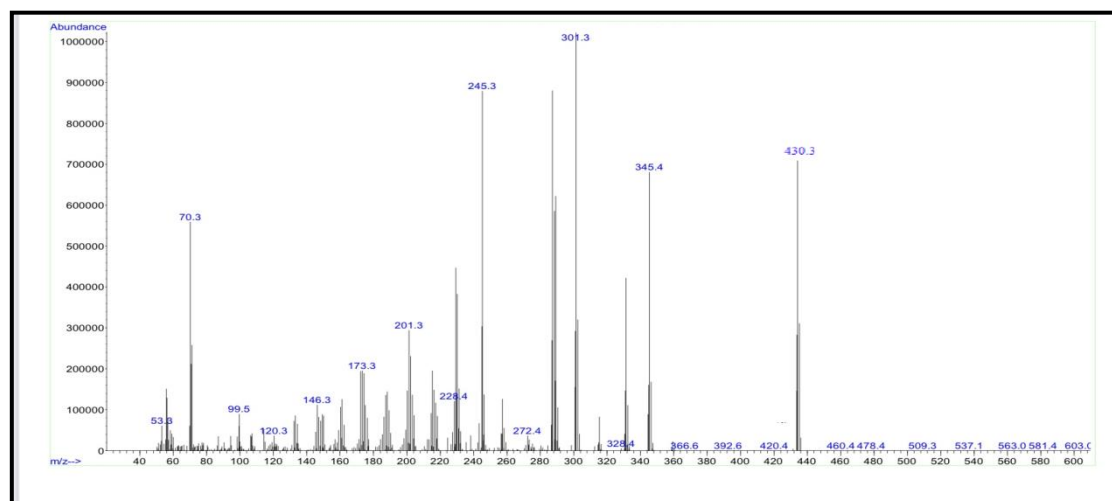
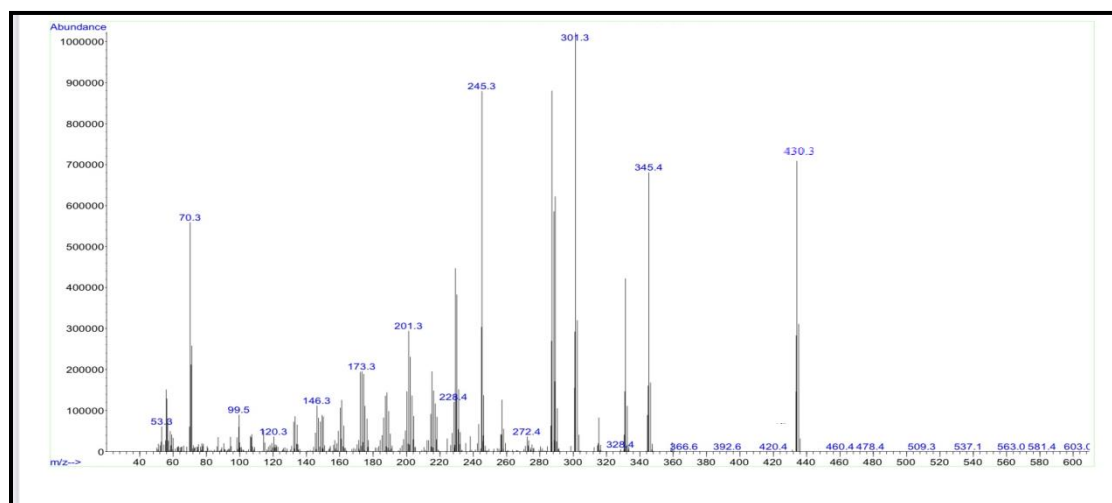


Figure (10): Mass spectrum of Ligand.

HNMR Spectra

The ^1H NMR spectrum of the (L) in (Figure 11) shows proton peaks at 2.5 ppm that are likely due to the solvent protons in DMSO. The spectra of the ligand also show proton bands at 1.19, 1.32–1.34, 3.64, and 7.58–8.66 ppm that are characteristic of ciprofloxacin (**Kowalczyk et al., 2021**).

The ^1H NMR spectrum of the ligand also display signals peak at δ 7.588 ppm (d,H,H6), 7.87ppm (d,H,H9) respectively which belong to the aromatic protons. The peak which exhibited chemical shift at (5.55) ppm (d,2H,H5 are attributed to the $\text{CH}_2\text{-N}$ groups of Mannich bases are present in ligand (**Abdulghani& Hussain, 2015**) . The signals peak at δ 3.59 ppm (t, 2H, H12, 13) and δ 2.61 ppm (t, 2H, H11, 14) are attributed to the -O-CH_2 and N-CH_2 proton of the morpholine moiety for the ligand, respectively (**Jandourek et al., 2017**). The ^1H NMR spectra of the Au (III) complex, which are examined in DMSO d6 (Figure 12).

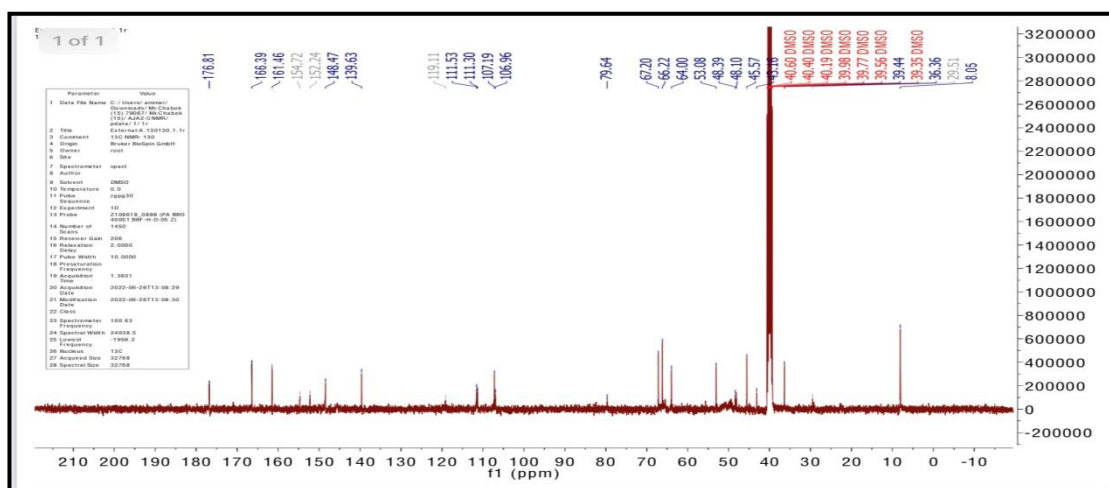


Figure (13): ^{13}C NMR spectrum of (L).

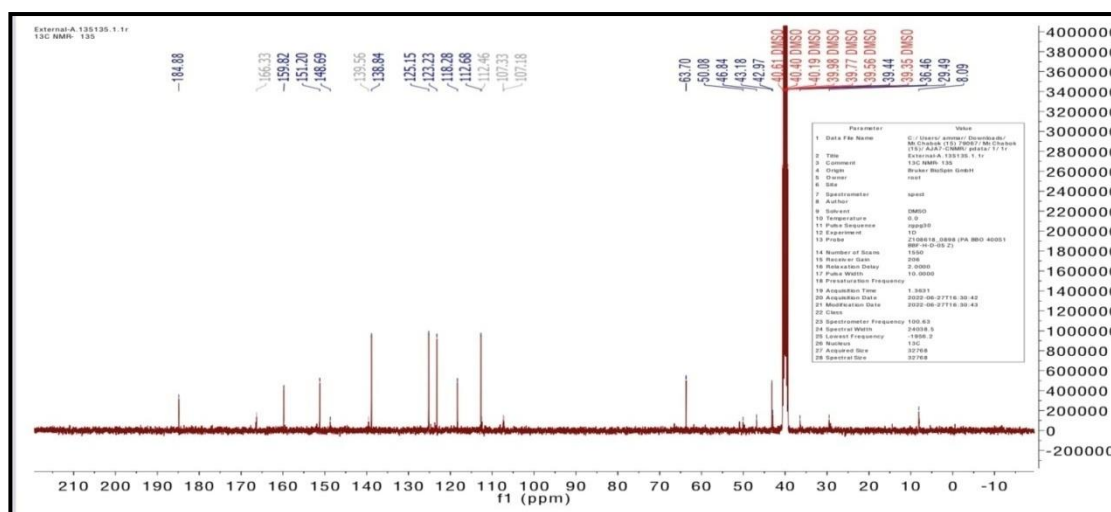


Figure (14): ^{13}C NMR spectrum of Au (III) complex.

Anticancer activity

We have examined the cytotoxic activity and mode of action for the synthesized (L) against MDA cell lines using MTT assay after incubation for 24 hours at 37C and with concentrations (50, 100, 200, and 400 $\mu\text{g}/\text{mL}$) (Kyhoiesh *et al.*, 2021). This was done using a cell viability assay. The chosen compounds reduced the growth of the MDA cell lines in a variety of ways, and by comparing the percentage inhibition of cell growth to the control, the level of toxicity was determined. At a 400 g/ml concentration, the ligand inhibited tumor cell death with a (65%) cytotoxic effectiveness. Contrastingly, the Complexes inhibited MDA cell to a concentration of (90.1%), (85.4%), and (80.2%) for Au (III), Cr (III), and Pt(IV), respectively. Furthermore, it can be concluded that all investigated substances were inhibited greatest when concentrations of (400 g/ml) were incubated for (24) hours, and least when concentrations of (50 g/ml). Due to the fact that many Au(I) and Au (III) compounds inhibit the proliferation of cancer cells, gold complexes have demonstrated excellent anticancer therapeutic efficacy. These complexes interact with several intracellular targets, including cysteine, nitrogen bases, glutathione reductase, thioredoxin reductase, and selenocysteine,

causing DNA damage, inhibiting mitochondrial function, and cytotoxicity (Sun *et al.*, 2012). The complex Au (III) showed a greater inhibition rate in comparison to the Cr(III) and Pt(IV) complexes. This could be because these complexes have square planer geometry, which is more favorable to cells than octahedral geometry. We conclude that Pt (IV) compounds are considerably more inert based on the fact that octahedral Platinum(IV) complexes can substitute ligands through a dissociative mechanism as compared to an associative mechanism for Platinum (II) (Warad *et al.*, 2013). The overall results in this section show that coordination of the ligand with specific metal ions resulted in the increased anticancer effects. The positive charge of the metal ion increased the coordinating protonated ligand's acidity, enhancing its ability to form stronger negatively charged hydrogen bonds with the DNA of cancer cells, which resulted in the higher cytotoxicity shown with metal complexes. Design changes in the compounds geometry and coordination site tend to get the most effects on biological activity.

Table (4): Evaluation of cytotoxicity of ligand and their complexes against MDA cell lines after incubation (24 hrs) at (37 °C).

Comp.	%Cell Inhibition			
	Conc. $\mu\text{g/ml}$			
	400	200	100	50
L	65	50	27	15
Au L	90.1	66	42	30
Cr L	85.4	58	35	22
Pt L	80.2	58	38	18

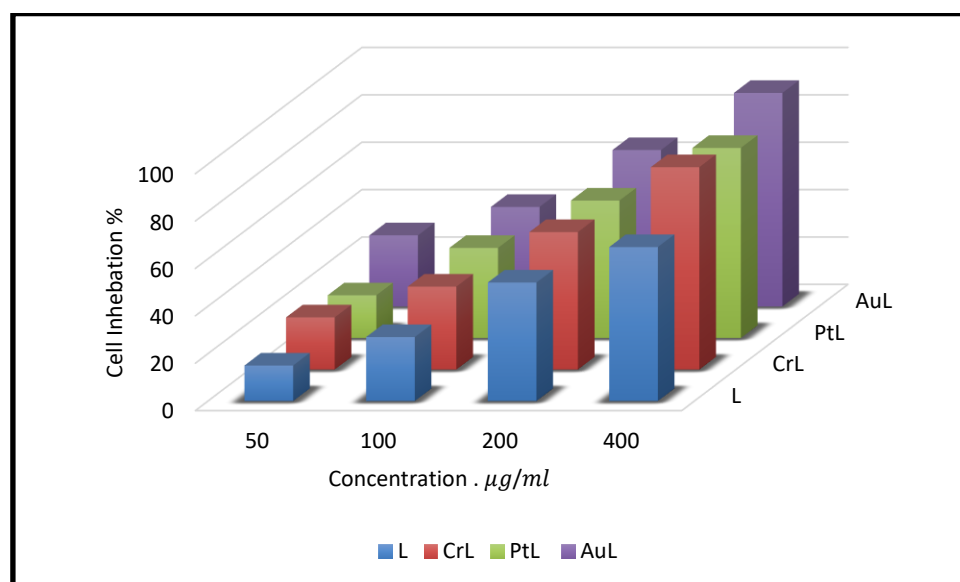


Figure (15): The percentage inhibition in (400,200,100,50 $\mu\text{g/ml}$) after exposure to ligand and its complex at 24 hrs.



CONCLUSION

This study focuses on the synthesis novel bidentate O donor mannich base (L) from morpholine and ciprofloxacin, a series of Cr (III), Pt (IV), and Au (III) complexes were synthesized. These complexes were then examined using various physicochemical methods. The physicochemical data suggested that the Au (III) complex has a four- coordinate square planner structure while the Cr (III) and Pt (IV) complexes have six-coordinate octahedral structures. The complexes molar conductance values confirmed the electrolytic nature of the compounds. Also, to evaluate the anticancer effects of the mannich base ligand (L) and its complexes on MDA cell lines. At high concentrations (400 $\mu\text{g/ml}$), it was observed that all complexes were more active than the free ligand, and Au (III) complexes exhibited stronger anti-proliferative properties at all applied concentrations.

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