Article

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Preparation and characterization of new ligand derived from dithiocarbamate and their metal complexes with biological study

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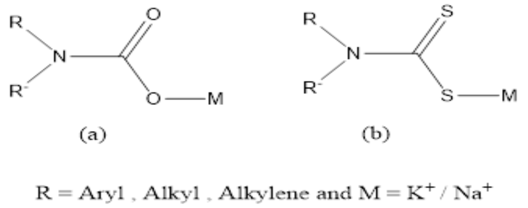
ABSTRACT

The study involved creating a new dithiocarbamate derivative ligand, which is known for its significance in both medical and industrial fields. This was accomplished by joining the CS_2 group with the substituted Schiff base 4-((1-(4-Chlorophenyl) imino) ethyl)aniline in basic medium to create the derivative sodium (4-((1-(4- Chlorophenyl) imino) ethyl) phenyl) carbamodithioate. The derivative is then reacted with the chlorides of Cu(II), Co(II), Ni(II), Pt(II) and silver nitrate Ag(I), and to create complexes of that derivative. Melting point measurements are performed using ultraviolet spectroscopy, infrared spectroscopy, mass spectroscopy, nuclear magnetic resonance spectroscopy, and other physical properties to examine the behavior of the derivative and the complexes made from it, as well as examining their biological efficacy as anticancer agents .

Keywords : Schiff base , Dithiocarbamate , anticancer , complexes .

INTRODUCATION

Dithiocaramate (DTCS) represent amide analogs of dithiocarbonic acid, characterized by a functional group in which two oxygen atoms in the carbamate group are replaced by two sulfur atoms figure(1) . In contrast, thiocarbamates involve the substitution of only one oxygen atom with sulfur, which defines the structural and functional differentiation between the two classes [1] .



Figure(1) : a-carbamate , b-dithiocarbamate

DTCs are members of the structural class of mono anionic 1,1-dithiolate ligands, which include xanthates, carbamates, and dithiophosphate among other chelating ligands. Despitethis common structural categorization the electrochemical (physochemical) characteristics of dithiocarbamate coordination products display major differences in their reactive behavior and crystalline shape compared to other ligands within its family [2], The biological action of these molecules clearly shows this difference. Non-conventional modes of action ascribed to the special interactions of the sulfur-carbon-nitrogen (S-C-N) links within their molecular surroundings are revealed by pharmacodynamic and cytotoxic investigations. In transition metal chemistry, such structural and functional distinctiveness sets dithiocarbamates as remarkable ligands [3]. Unique synthetic characteristics of DTCs allow the formatiom of great variety of structurally different complexes. Three main coordination modes help to show their remarkable binding capacity with metal ions: monodentate, bidentate, and varied denticity patterns. Two sulfur atoms inside their molecular framework are the source of this structural flexibility as they function as electron pair donors figure(2) , therefore enabling the synthesis of stable and reactive metal coordination complexes with improved thermodynamic and kintic characteristics [4] .

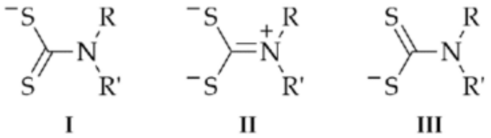


Fig (2)Forms of dithiocarbamate

One-pot synthesis is a general preparation method that uses two approaches to synthesis: the insertion reaction approach and the replacement (substitution) reaction approach. Of the two, replacement is preferable because it yields highly pure dithiocarbamate compounds[5]. Dithiocarbamate ligands and their metal derivatives have the capacity to regulate essential proteins involved in several biological processes, including apoptosis, transcription, oxidative stress, and degradation. They were also discovered to have uses as antibacterial and antifungal agents, antioxidants, and potential treatments for AIDS and cancer. The rise in the prevalence of severe invasive fungal infections and their incidence, coupled with the diminished efficacy of existing antifungal agents against specific fungal strains due to the emergence of drug resistance, has rendered the discovery of alternative medications critically important[6]. Because of their ability to increase anticancer biological activity, dithiocarbamate compounds have emerged as intriguing candidates in this investigation. There are ongoing efforts to improve these therapies' pharmacokinetic characteristics and selective cytotoxicity. A viable strategy for accomplishing these objectives is to alter the ligand's chamical structure or substitute it with other frameworks, which might lead to the creation of molecules that are more potent and have less adverse effects[7] .

Experimental and Apparatuses

substances (purity 99.9%) utilized. The weigh-in was conducted using an electric Metler balance (BL, Satorius, 2015). The melting point device utilized was the Stuart Melting Point SMP10. The Digital Conductivity Series Ino.Lab.720 was used to measure the molar conductance in ethanol.The Shimadzu FTIR 8400S Spectrophotometer was used to capture infrared spectrum analyses in the 400–4000 cm-1 range. The Shiadzu240-UV-V spectrophotometer captured the (UV-visible) spectra of all the substances under study using ethanol in the 200–1000 nm range. The BRUKER 500MHZ was used to perform the H-NMR spectra measurements with ethanol as the solvent. The Agilent 5975c Mass Smpectrometer USA was used to record mass spectrum measuremen.

Preparation of Schiff base

The Schiff base 4-((1-(4-chlorophenyl)imino)ethyl)aniline was synthesized by combining 2.5514 g (0.02 mol) of 4-chloroaniline with 2.7 g (0.02 mol) of aminoacetophenone, along with addition(2-3) drops of glacial acetic acid, and heating for 25 hours at 78°C [8].

Preparation of Dithiocarbamate ligand

2.445 g of 4-(1-((4-chlorophenyl)imino)ethyl)aniline (0.01 mol) is dissolved in 50 ml of absolute alcohol with 99% purity to prepare the organic compound solution. The basic solution is prepared by dissolving (0.4 g) of sodium hydroxide (0.01 mol) in 10 ml of distilled water and subsequently adding it to the aforementioned organic compound solution. Then, (0.76 ml) of CS_2 (0.01 mol) is added dropwise to the reaction flask, which is maintained in an ice bath with continuous stirring for a duration of 3 hours. The resultant solution was thereafter transferred into a watch glass and allowed to evaporate at ambient temperature, after which it was collected and recrystlization from hot ethanol [9].

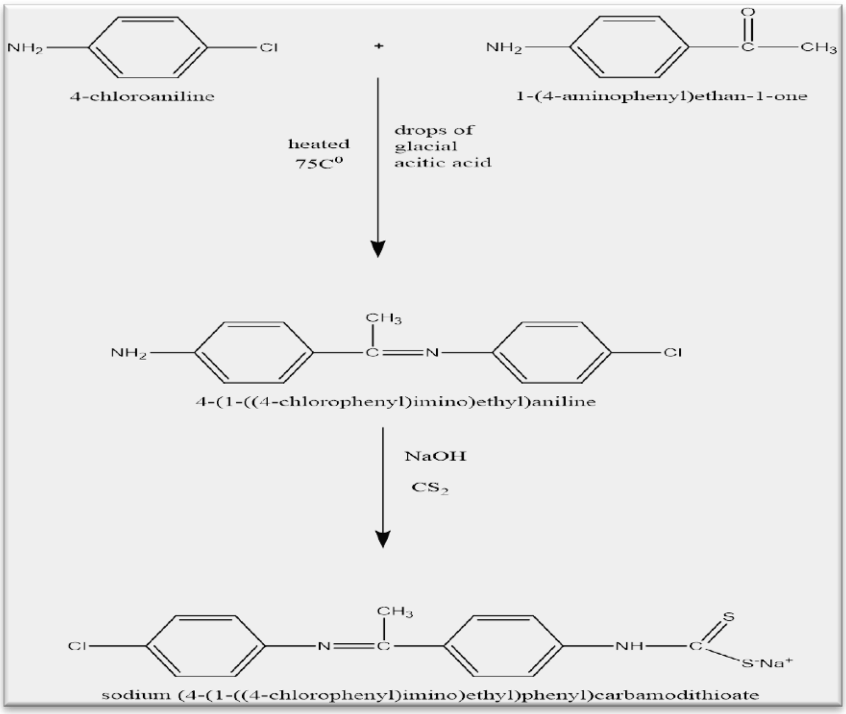


Fig (3) synthesis of ligand

Preparation of ligand complex

Complexes of ligand 4-((1-(4-chlorophenyl) imino) ethyl) phenyl) were prepared by dissolving metal chloride salts of Cu(II), Ni(II), Co(II), , Pt(II) and Ag(I) (0.001mol) in ethanol (10ml) and adding them to the ligand solution prepard by dissolving (0.2055g) (0.002 mol) in mole ratio (1:2) expected Ag(I) (1:1) (metal : ligand) [10].

Results and discussion

The ligand is a pale green powder, whilst the complexes likewise manifest as powders, differing according to the type of metal used. These compounds are distinguished by their chemical stability and insolubility in water, however they exhibit partial solubility in organic solvents such as methanol, ethanol, and acetone [11]

Element investigation

Table (1) present the analytical and physical data of the ligand and its corresponding chemical complex .

Table 1. Some analytical and physical information on the ligand and its complexes

Compound	**M.Wt g/mol**	**m.p c^0**	**color**	**M:L**	**Conductivity $S.mol^{-1}.cm^2$**
$C_{15}H_{12}N_2S_2ClNa$	342.5	70	Light green	-----------	---------
$[Co(C_{15}H_{12}N_2S_2Cl)_2(H_2O)_2]$	378.44	120 decompose	Dark green	1:2	3.8
$[Ni(C_{15}H_{12}N_2S_2Cl)_2(H_2O)_2]$	378.19	130 decompose	Yellow green	1:2	3
$[Cu(C_{15}H_{12}N_2S_2Cl)_2(H_2O)_2]$	384.24	135 decompose	yellow	1:2	4
$[Ag(C_{15}H_{12}N_2S_2Cl)(H_2O)_2]$	427.37	106 decompose	Dark brown	1:1	2.1
$[Pt(C_{15}H_{12}N_2S_2Cl)_2]H_2O$	514.59	161 decompose	Very dark yellow	1:1	10.6

Infrared Spectra of dithiocarbamate ligand

FT-IR Spectra of the produced complexes and ligand carried out and it was found that , the presence of variable bonding modes due to numerous coordination sites in the ligand , FT-IR Spectrum of free ligand and its complexes are givenin table(2) .

The Spectrum of ligand showed absorbing bond at 3375Cm^{-1}and 3217Cm^{-1} with attributed to the N-H stretching vibration of amine group [12]. And showed bond at 1645Cm^{-1}assigned to (C=N) stretching vibration of azomethine group[13] which unchanged according to spectra complexes , indicating that azomethine nitrogen was not participating in coordination . Ligand showed frequencies at 1170Cm^{-1}and 1043Cm^{-1}wich attributed to (C=S) and (C-S) groups[14] where comparing with IR Spectra of complexes we find that all metal complexes bind to ligand through the (C=S) and (C-S) at higher or lower frequencies .

Tabe2 . FT-IR Spectral information and its complexes

compound	H2O	N-H	C=N	C=S C-S	M-S	M-O H2O
LNa	-------------	3375 3217	1645	1170 1043	----------------	------------------
$[Co(L)_2(H_2O)_2]$	3400 839	3334 3230	1645	1176 1031	420	499
$[Ni(L)_2(H_2O)_2]$	3396 837	3334 3232	1645	1176 1026	430	480
$[Cu(L)_2(H_2O)_2]$	3414 829	3336 3219	1643	1193 1036	460	499
$[AgL(H_2O)_2]$	3394 833	3332 3226	1645	1188 1016	422	497
$[Pt(L)_2]H_2O$	3394	3334 3228	1647	1178 1003	410	470

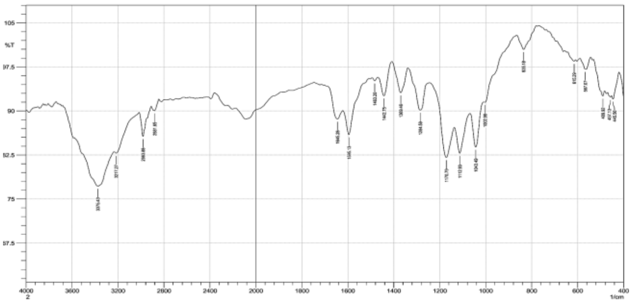


Fig 4 . IR of ligand

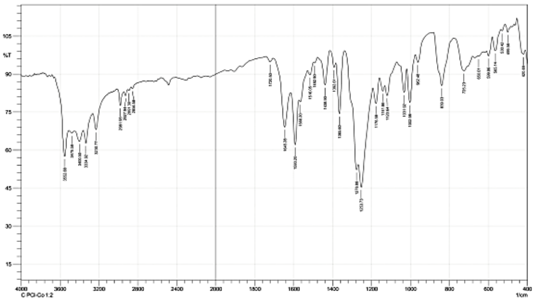


Fig 5 . IR $[Co(L)_2(H_2O)_2]$

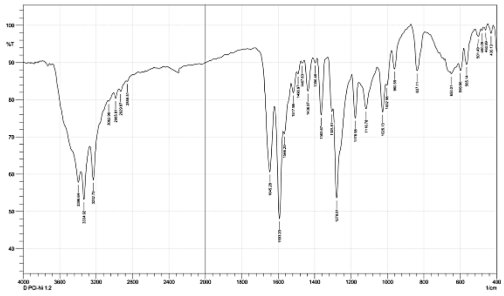


Fig 6 . IR $[Ni(L_2)(H_2O)_2]$

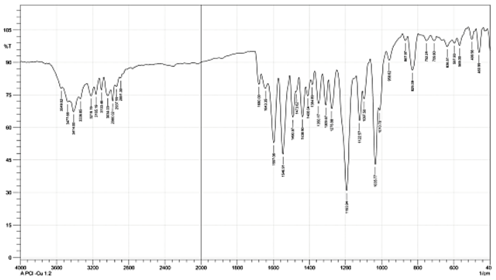


Fig 7 . IR $[Cu(L)_2(H_2O)_2]$

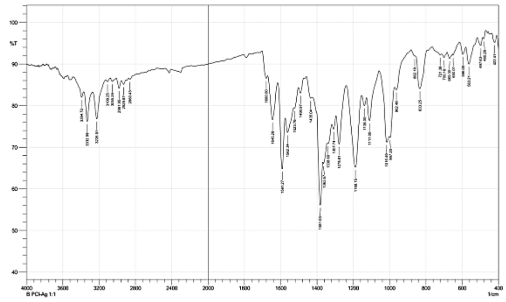


Fig 8 . IR $[AgL(H_2O)_2]$

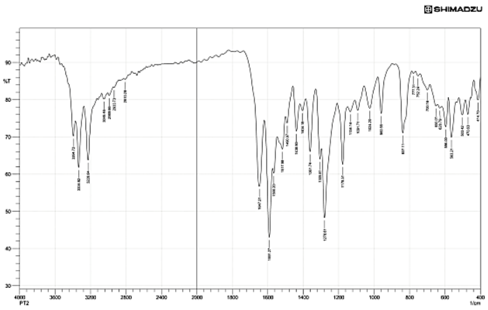


Fig 9 .IR $[Pt(L)_2]H_2O$

The dithiocabamate ligand Mass Spectrum

The mass Spectrum of ligand is represeuted in Figure.(10) . The Spectrum exhiits successive fragments related to ligand structure . The parent ion peak for the ligand is aboserved at m/z = 341.4 which correspond to $C_{15}H_{12}N_2S_2ClNa$.

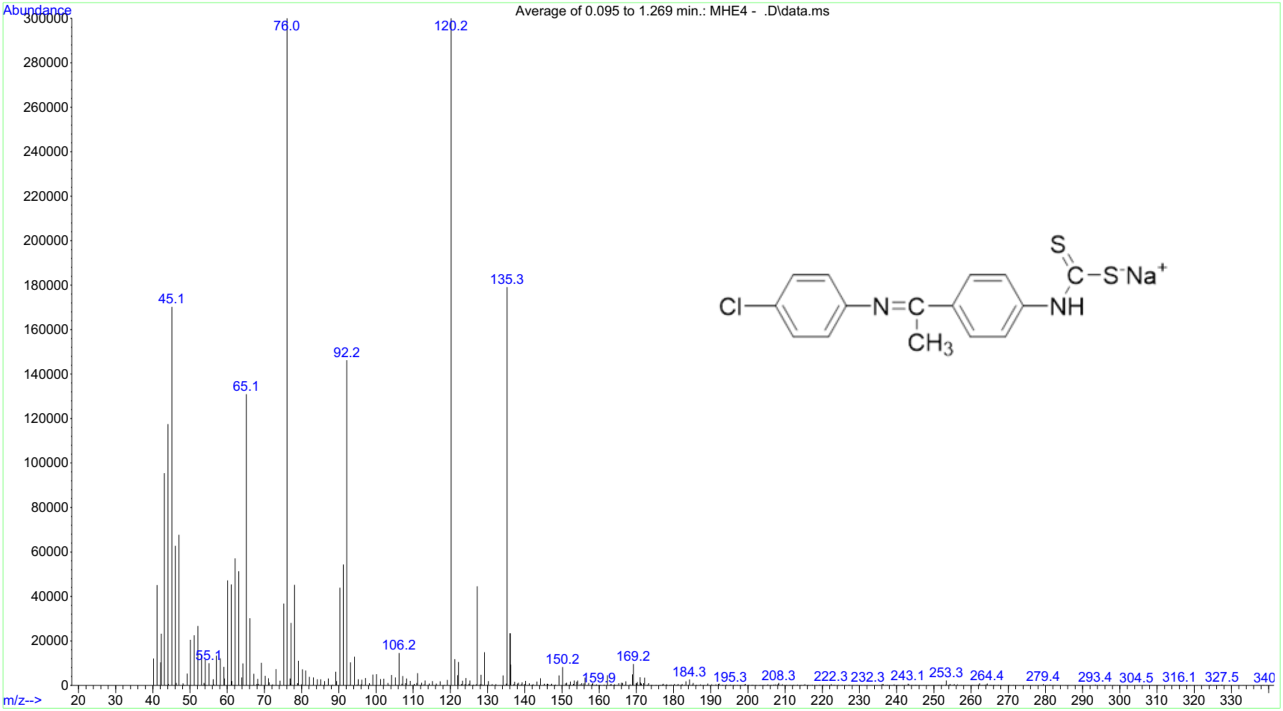


Fig (10) Mass of ligand

The dithiocabamate ligand ^{1}HNMR Spectrum

The ^{1}HNMR Spectrum for ligand Fig (11) singal at (1.4) ppm which attributed to (CH_3) group, multiplete aromatic protons at (6.5 – 7.5) ppm and chemical shift signal at (4.08)ppm assigned to (NH) group of the ligand . while the singlet signal at (2.54)ppm attributed of (DMSO-d_6) solvent .

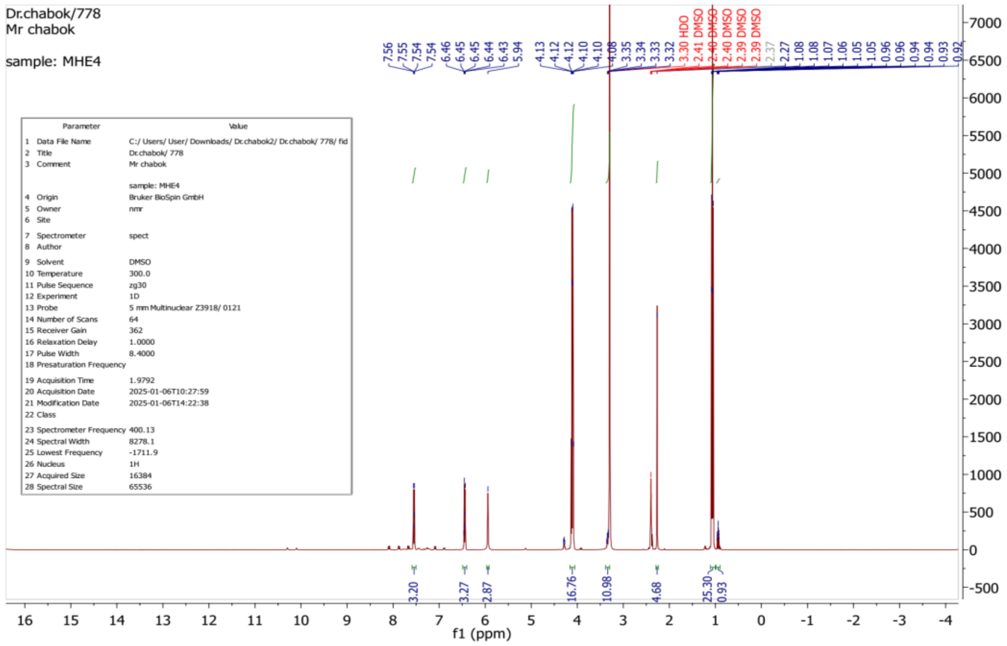


Fig (11) ^{1}HNMR of ligand

Electronic Spectra and magnetic moment measurement.

The electronic absorption of the ligand and solid complexes meseared in ethanol absolute solution within a rang between 200 and 1100 nm. The position of the peak at 305nm in 252nm ligand Spectrum which attributed of (n- π^*) and (π- π^*) . While the Spectrum of Co(II) appering three peaks which due to ($^4T_1g_{(F)}\rightarrow{}^4T_1g_{(P)}$) , ($^4T_1g_{(F)}\rightarrow{}^4A_2g_{(F)}$) at region 623nm ,958nm and 349nm , 479nm which referred to transition (ILCT) , (C.T)

Spectrum of Ni(II) appering three peaks which due to ($^3A_2g_{(F)}\rightarrow{}^3T_1g_{(P)}$) , ($^3A_2g_{(F)}\rightarrow{}^3T_1g_{(F)}$) at region 415nm ,477nm and 344nm which referred to transition (C.T) while the Spectrum of Cu(II) Which apperes two peaks which assigned to trasition (ILC.T) and (C.T) at region 385nm and 567nm repectivly . For all complexes of Co(II),Ni(II) and Cu(II)these electronic transitions referred to octahedral geometry . The magnetic moment of the complexes were found to be (4.3) , (3.4) and (1.78) resectivity .

The diamagnetic of Ag(I) complex possess atetrahedral structure in the electronic spectrum of Ag(I) complex appered one absorption bonds found at

383nm and assigned to (C.T).For Pt(II) complex, The two obsorption bands at 319nm and 392nm assigned to (ILCT) and (MLCT) respectively in a siqure plannar geometry confirmed by the diamagnetic properties [15] .

Table 3. The Magnetic moment and U.V-Visible spectral data

Compound	λ(nm)	Assignments	Suggested structure	Hybridization
L	252 305	π- π* n- π*		
$[Co(L)_2]$	958 623 479 349	($^4T_1g_{(F)}\rightarrow{}^4A_2g_{(F)}$) ($^4T_1g_{(F)}\rightarrow{}^4T_1g_{(P)}$) (C.T) (ILC.T)	Octahedral	SP^3d^2
$[Ni(L)_2]$	477 415 344	$^3A_2g_{(F)}\rightarrow{}^3T_1g_{(P)}$ $^3A_2g_{(F)}\rightarrow{}^3T_1g_{(P)}$ (C.T)	Octahedral	SP^3d^2
$[Cu(L)_2]$	385 567	(ILC.T) (C.T)	Octahedral	SP^3d^2
$[AgL(H_2O)_2]$	383	(C.T)	Tetrahedral	SP^3
$[Pt(L)_2]H_2O$	392 319	(MLTC) (ILCT)	Square planner	dSP^2

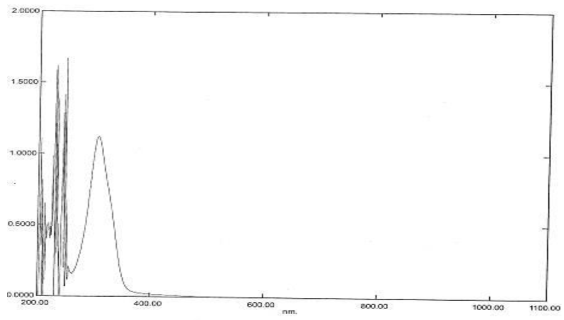


Fig 12. UV-Vis of ligand

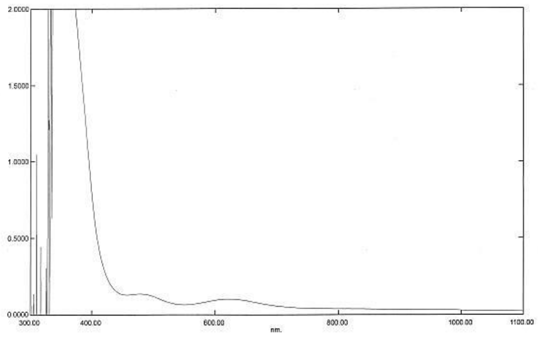


Fig 13. UV-Vis of $[Co(L)_2(H_2O)_2]$

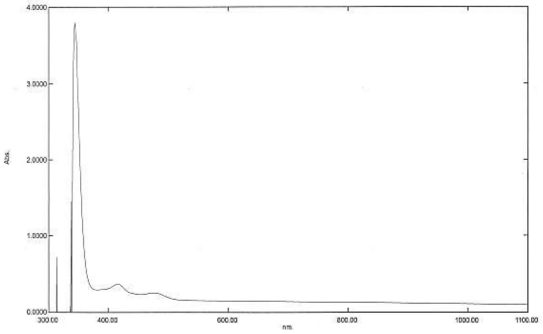


Fig 14. UV-Vis of $[Ni(L)_2(H_2O)_2]$

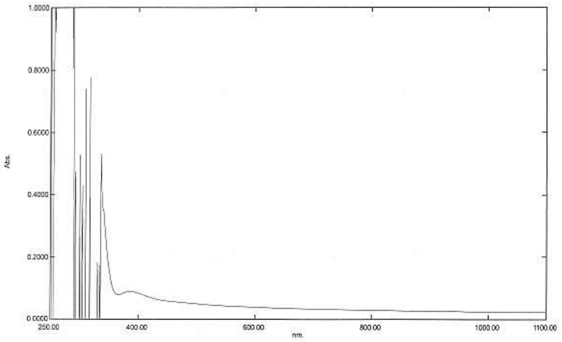


Fig 15. UV-Vis of $[Cu(L)_2(H_2O)_2]$

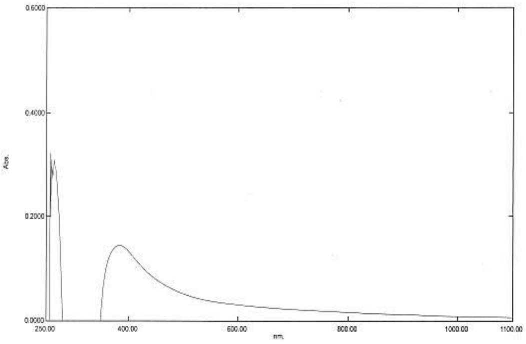


Fig 16. UV–Vis of.$[Ag(L)(H_2O)_2]$

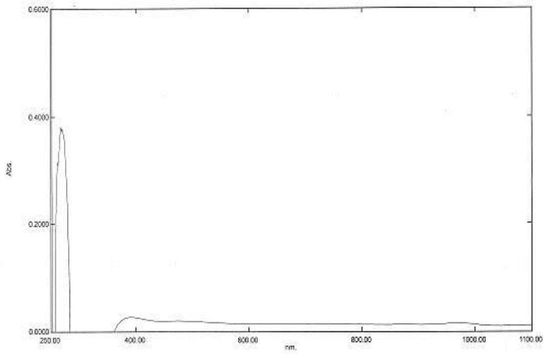


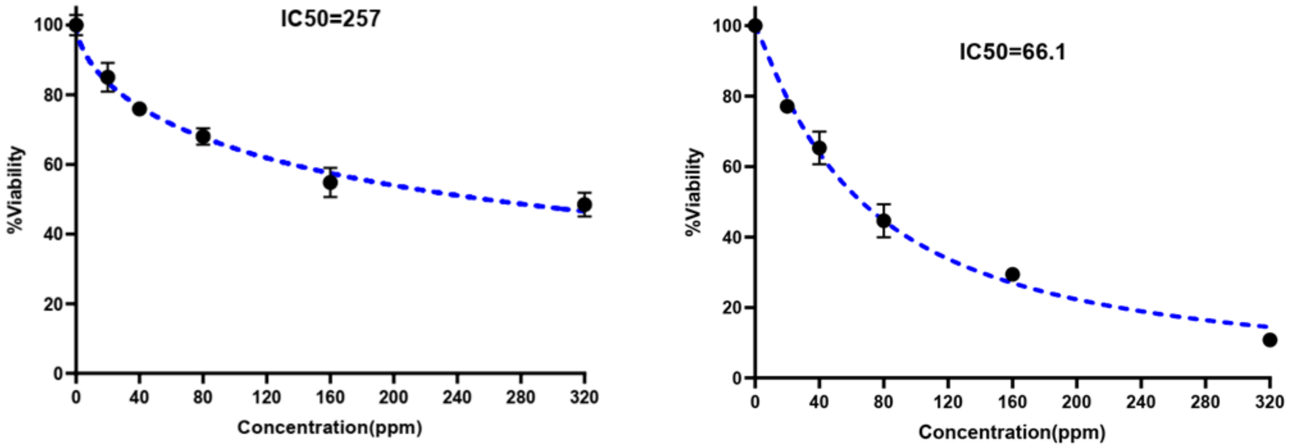
Fig 17. UV-Vis of $[Pt(L)_2]H_2O$

Anticancer effectiveness

Sulfur cmpounds have demonstrated significant activity against certain type of cancer[16]. Defferent concentration of complex $[Pt(C_{15}H_{12}N_2S_2Cl)_2]H_2O$ were utilized , and its effects on breast cancer cells (MCF-7) were evaluated , revealing a pronounced ability to ihibit cancer growth, since it is (IC50=66.1) for cancer cells among us are lower toxicity to normal cells (IC50=257) Fig(18), which can be attributed to the chamical structures present within the complexes that enhance the efficacy of biological active substance . The presence of electron- withdrawing groups (C=S) and the existence of hydrogen bond donors oracceptors (N-H) are considered fundamental requirements influencing the activity of these compouds[17] .

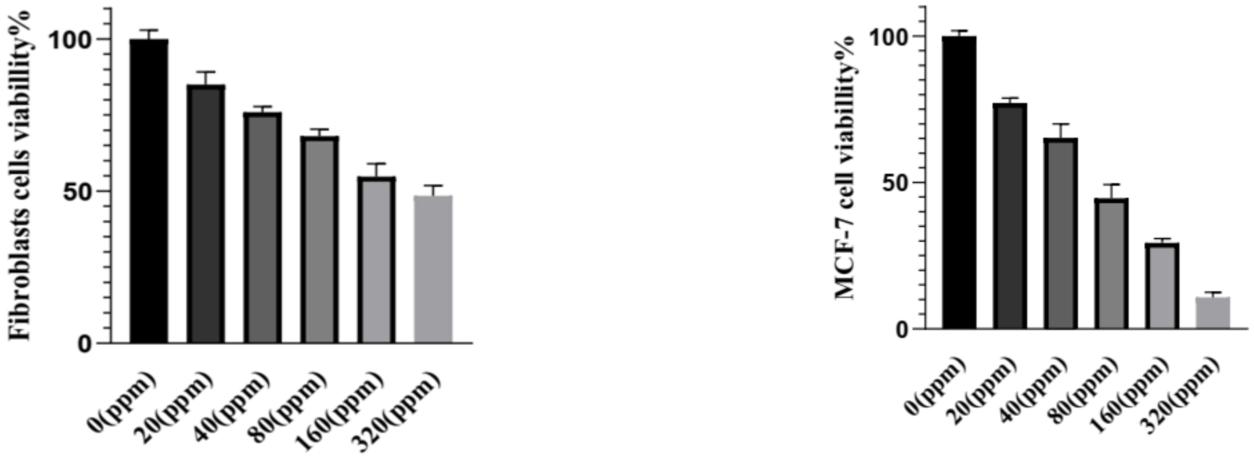
Table 3: Comparison between fixed cancer cells (MCF-7) with normal suppressed cells (WRL-65) in the same formulations for 24 hours for $[Pt(C_{15}H_{12}N_2S_2Cl)_2]H_2O$ complex .

	(MCF-7)		**(FBS)**	
Conc. Mg/ml	Cell viability	Cell inhibition	Cell viability	Cell inhibtion
20	85.04	14.96	98.09	1.91
40	75.91	24.09	96.88	3.12
80	68.04	31.96	95.48	4.52
160	54.80	45.2	88.97	11.03
320	48.46	51.54	86.77	13.23



(FBS) (MCF-7)

Figure(18). Comparison of inhibitory concentration for cancercells(MCF-7) and commonsins(WRL-68) concentration for complex [Pt(L_2)]

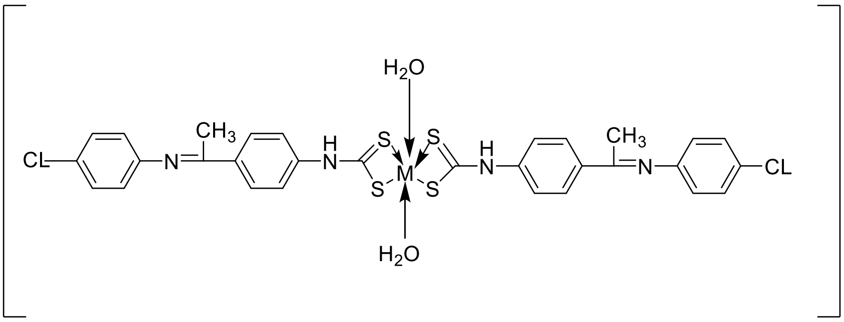


(FBS) (MCF-7)

Fig (19) anticancer activity of [Pt($C_{15}H_{12}N_2S_2Cl$)$_2$]H_2O complex

Conclusion

The conclusions were reachedbased on the spectroscopic analysis of the ligand and its complexes , which demonstrated the stability compounds . The platinum(II) complex adopted atetrahedral geometry , while the silver (I) complex was tetrahrdral , and theothercomplexes exhibited octahedral geometries . All complexes displayed high stability .



M= Co(II) , Ni(II) and Cu(II)

Fig (20) structure for complex

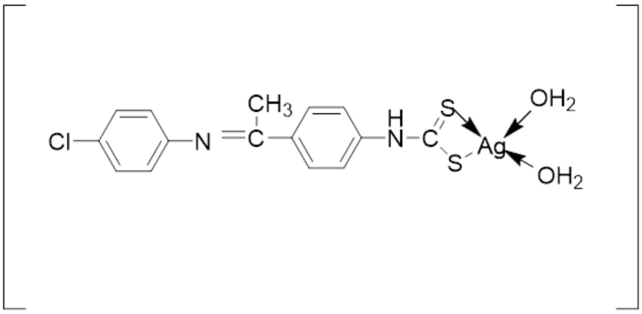


Fig (21) structure for [Ag(L)(H_2O)$_2$] complex

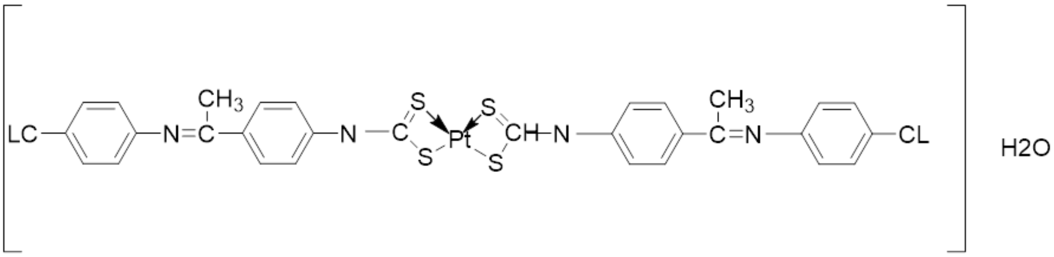


Fig (22) structure for [Pt($C_{15}H_{12}N_2S_2Cl$)$_2$]H_2O complex

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