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Synthesis, identification, biological activity and anti-cancer activity Studies of Hetrocyclic Ligand Azo-schiff Base with Au(III) Complex

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Abstract

This research involved preparation of 2-((E)-(1H-benzo.[d]imidazol-2-yl).diazenyl)-4-(((4-bromophenyl)imino)methyl)phenol and Au(III) complex which was prepared by mixing solution of metal salt with ligand solution at mole ratio[M:L] 1:1 . Compounds prepared were identified by FT- IR,, elemental analyses (C.H.N). Molar conductance measurements, magnetic susceptibility UV-Visb. The biological activity of the compounds prepared were examined against the susceptible organisms Streptococcus, (Gram. Positive) and Escherichia coli ,(Gram .negative), as antibacterial and Penicillium. Sp and Aspergillus Niger as antifungal, The prepared compounds checked for anti-cancer activity; activity of anti-tumor against of breast cancer for human

Key words: Azo-Schiff, Biological activity for azo ligand, anti cancer, breast cancer

1. Introduction

Azo-schiff base are compounds derived from the reaction of the azo compounds with schiff base[1,2]. As these compounds have met wide interest in all academic and applied research. Azo compounds have been used in various fields in science, medicine, and technology, It gave results of great significance in life, and azo compounds have the ability to have biological effectiveness [3,4).The compounds that have the benzamidazole group have been used in the treatment of ulcers and giadra inflammation in children [5,6).azo-schiff base were involved in many biological reactions in inhibiting DNA, RNA and protein synthesis [7-10]azo-schiff base compounds were used in the manufacture of dyes, due to the intensity of the coloration shown by these ligands, as a result of the non-positioning of the pi electrons and their containment of the azo and azo methene groups and their uses in dyeing fabrics and polyester, acrylic and nylon threads [11].In the field of analytical chemistry, the dominant color characteristic of this type of compounds and their complexes formed with metallic ions in their aqueous and organic solutions were exploited in spectroscopic analyzes, and they are called spectroscopic reagents [12]. In direct color estimation methods to estimate negative ions in solutions [13], azo compounds were used in the field of physical chemistry, in the study of adsorption on a surface of silicon dioxide [14] and in photography [15] and photo sensitizers [16-19] In photovoltaic applications [20] metallic complexes were used in the manufacture of solar cells [21].It has also been used in agriculture as insecticides and some agricultural pests, due to the presence of effective groups such as azo and azomethene [21] It has been shown in the field of medicine the possibility of using the azo-base compounds as anti-carcinogens, because they form complexes with ions of the transitional elements that have the ability to bind to the DNA bases by coordinating bonds with the nitrogen atoms in the DNA bases to form a chelate ring [22,23]While another type of azo-schiff base compounds was used as an antioxidant [24]and was also used to estimate the level of fluorine in toothpaste and mouthwash solution [12].Yingjie Zhang indicated in the case of treatment against cancerous tumors that the metal complexes exploit the difference between cancerous and normal cells in the direction of identifying harmful cells [25].

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and they can also be used. Metal complexes in increasing the pharmacokinetic effect of some drugs within what is known as the synergic effect [26]. The study of the complex compounds of the transition elements is due to the possession of these elements with special properties, including the ability to possess multiple oxidation states as well as their strong tendency to form ionic or neutral complexes [27]. The objective of this work is syntheses, characterize and study the ability of a novel ligand and its complex with gold metal for usage as antibacterial, antifungal, anti-tumor and anti cancer for breast cancer cells.

2. Experimental

All Chemicals of acceptable purity were used, purchased for Merck and Sigma. Either of the solvents used were of analytical grade. Spectrum of IR were measured by a Bruker FTIR Spectrophotometer. The electron spectra were also measured using ultraviolet light. Spectrophotometer T80-PG. The compounds prepared were examined by elemental analysis (CHN). The magnetic sensitivity of the metal compound was examined by magnetic balance device (MSB-MKI) in lab temperature by using the method of Faraday.

2.1. Synthesis of Schiff base (E)-4-(((4-bromophenyl)imino)methyl)phenol

The Schiff base compound (Scheme 1) was synthesized through 4-bromoniline condensation Benzaldehyde (1.72 g, 1% mol) with 4-hydroxybenzaldehyde (1.22 g, 1% mol) was mixed in 70 ml of ethanol solvent by adding 3 drops as a catalyst from glacial acetic acid. and refluxed six hours,The product of compound was concentrated with vacuum for removing excess ethanol, reddish yellow color, then distilled water is used for washing, recrystallized, drying at (70 ° C) for two hours. The yield78% of crystals (reddish orange) and melting point =187°C.

2.2. Synthesis Azo-Schiff base [2-((E)(1Hbenzo[d]-imidazol-2yl)-diazenyl)-4-(((4-bromophenyl)imino)methyl)phenol]ligand

The Azo-Schiff base was synthesized by the following procedure with some **change** the process as described below [28, 29]. (schem-1), (1.33 gm, 0.01mol) of 2.Amino Benzimedazole HCl(37%) and (35) mL distilled water. (0.75 gm, 0.01mol) of sodium nitrite($NaNO_2$)was dissolved in (25)mL distilled water and has been added by droping at the temperature between 0-5°C to the mixture with continuous rapid stirring. Then diazonium salt was added successively drop wise with continuous stirring to a cold in alkaline solution of (E)-4-(((4-bromophenyl) imino) methyl)phenol (2.76gm,0.01mol) and the mixture was mixed well for (2) hours at (0-5 °C),the precipitate was taken, filter and wash with distilled water, as well as(6) mL of ethanol solution for surplus of non-reactive materials, it was recrystallized with ethyl alcohol then drying for two hours at (60)° Cs. The percentage of yield was (82)% of dark red crystals and melting point = (170 ° C)

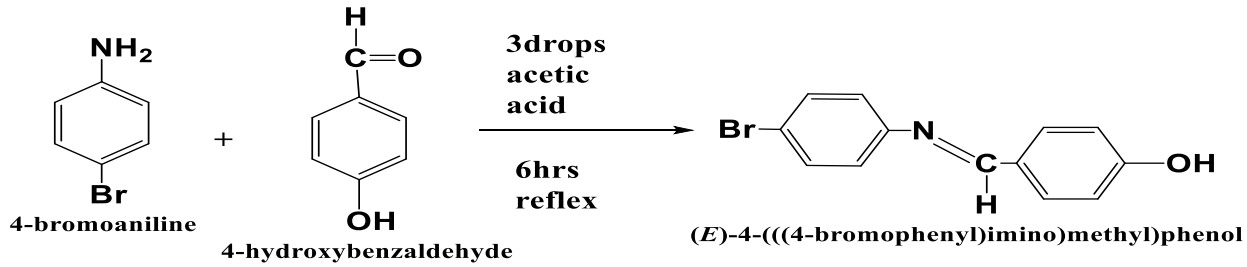
2.3. Preparation of Gold complex

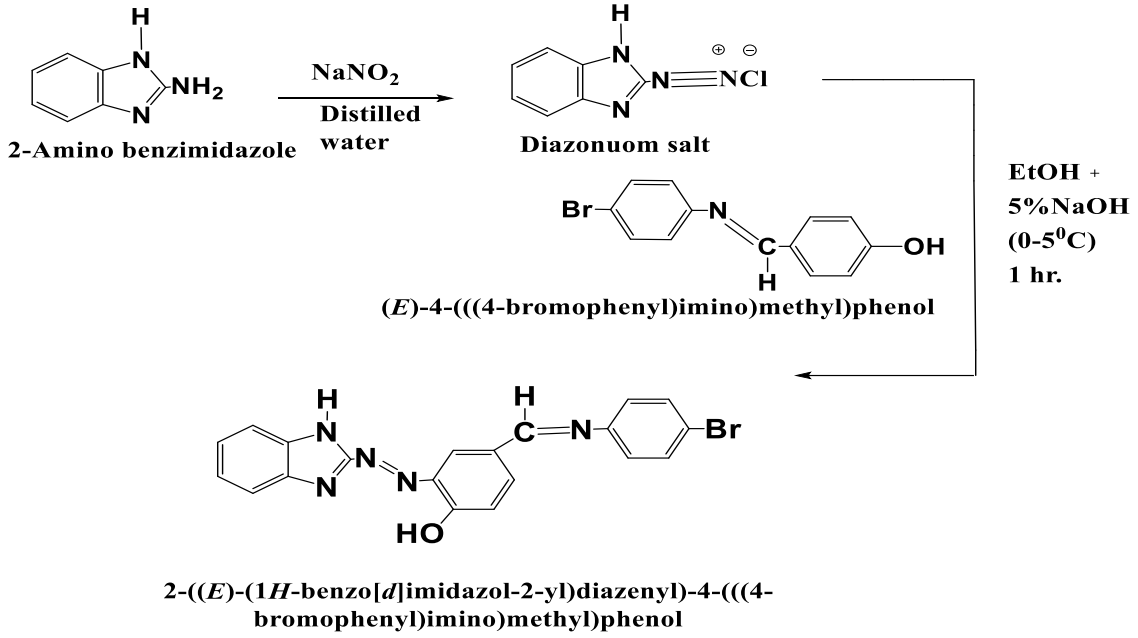
The gold complex was prepared by using Au (III) chlorides where the amount of ligand of (0.42g ,0.001 mol) was **dissolved** in(60)mL methanol. That was added gradually with stoichiometric stirring to amount of (0.001 mol) [1:1] [M:L]. For Au (III) salt dissolved in (60) mL of methanol as a solvent and heated the mixture to (50-70) degrees Celsius at 3 hours left overnight. The solid of complex was filtered then washed by deionized water (DDW) with a warm of ethanol in order to remove the unreacted materials. Finally, the gold complex was dried in vacuum dryers .The physical and analytical data of the ligand and Gold complex are presented in the table (1).

3. Result and Discussion

3.1. Proton Nuclear Magnetic Spectra

The spectra of ligand in figure.1 was measured using the solvent (DMSO-d_6) in (TMS) which used as internal reference (500MHz). The recorded parameters for the compound are in table 2.





Scheme(1):- Synthesis of azo-schiff base ligand

Table (1): Physical properties and elemental analysis for prepared compounds

Compounds	Color	Melting point C°/	Yield percentage	M.f (molecular weight)	Found (Calc.)%			
					C	H	N	M
Ligand	reddish orange	123-127	80	$C_{20}H_{14}BrN_5O$ 420.27)	(57.16) 58.43	(3.63) 4.01	(16.66) 16.88	
[Au(L)CL].CL.H_2O	Reddish purple	215.9-217.2	77	$C_{21}H_{16}AuBrClN_5O$(666.71)	(37.83) 38.77	(2.42) 2.55	(10.5) 11.2	(29.54) 30.1

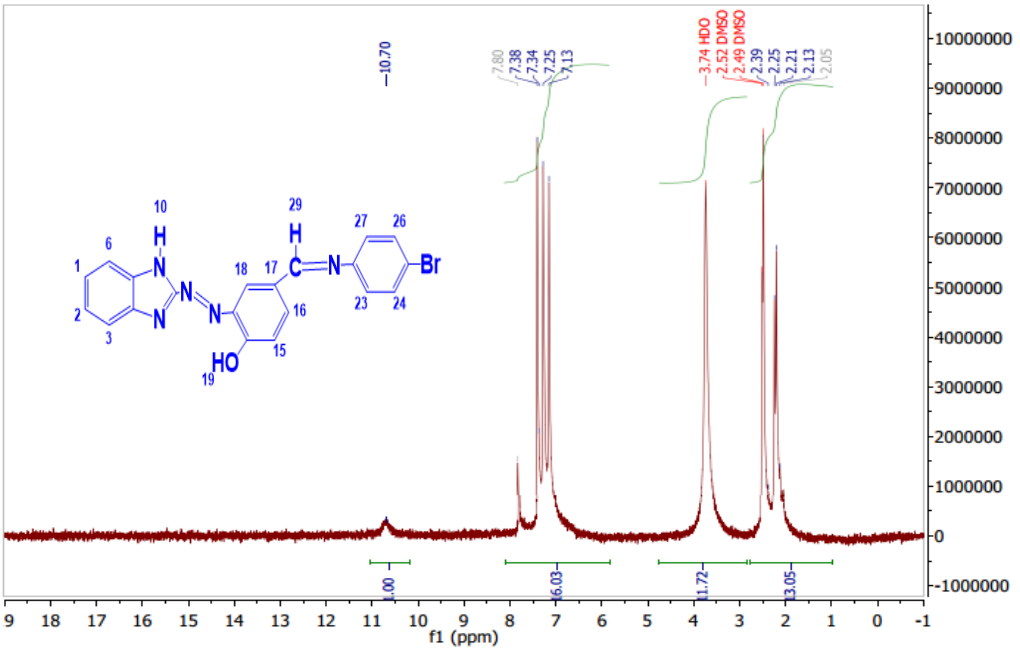


Figure (1):- spectrum of Azo – Schiff base ligand by ^{1}H-NMR

Table (2): (^{1}H-NMR)spectra of preparedligand

ligand L\H ,δ, ppm, (H atoms, peak, assignment)
2.52 solvent proton
7.13-7.25(4H,d,23,24,25,27)
7.34-7.38, (4H,d,1,2,3,6)
7.80 (1H,S,29)
10.7 (1H,S,19)

Where s= singlet,d= doublet

3.2. Molar conductivity measurement

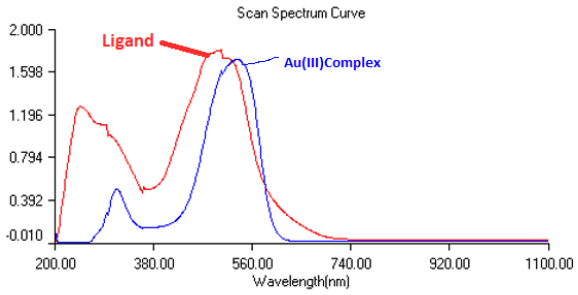
The molar conductance of The Au (III) compound was studied at room temperature with DMSO as solvent. The results are shown in Table (3).

Table (3): Measurement of Molar conductivity for the ligand

Metal ion	Optimal Conc.×10^{-4} M	Molar. conductivity.S.cm^{-1}Mol^{-1}
Au(III)	1.50	37.55

3.3. Magnetic susceptibility and electronic spectra measurement

The electronic spectra of synthesized ligand and gold ions were measured in ethyl alcohol (0.0001 M) at lab temperature .The results are listed in table(4). Figures (2).illustrate that both of ligand and gold ions have low magnetic in value so it is a dia *Magnetic* indicate square planer geometry



Figure(2): UV Visible spectra of prepared ligand and its gold ions

Table (4):electronic Spectra (cm-1and nm), hybridization and geometry proposed Au(III)Complex

compounds	λ_{max} nm	absorption Bands (cm^{-1})	transitions	geometry	hybridization
ligand	490	20408	n→π*	----	----
	247	40485	n→π*		
[Au(L)Cl].Cl.H_2O	530	18867	$^1A_{1g}$ ⟶ $^1B_{1g}$	Square planer	dsp^2

3.4. Infrared (spectra) of ligand and its Au(III) complex

Table.5, demonstrate the stretching vibration bands of the functional group those are appeared in ligand and [Au(L)Cl]Cl.H_2O in the measurement range (400-4000) cm^{-1}.

Table (5):- stretching vibration of function groups for ligand and its Au(III) complexes

Compounds	ν(OH)	ν(N-H)	ν(C=N) azomethine	ν(C=N)	ν(C=C)	ν(M–O)	ν(M–N)
ligand	3354m.br	3155m	1674s	1464s	1253s	---------	-------
[Au(L)Cl]Cl.H_20	---------	3202m	1668m	1438s	1354m	528w	458w

Table (6):-Antibacterial and antifungal activity (zone of inhibition in millimeter)of the(ligand) and gold .complex.

Compound	Activity of anti. bacterial		Activity of anti.fungal	
	streptococcus	*Escherichia coli*	*penicillium*	*Aspergillus niger*
Ligand	++	++	++	++
[Au(L)CL]C L.H_2O	+	-	+++	+++

(+++):-activehigh (zone of inhibition)> 12 millimeter,,(++);-active moderate- (zone of inhibition) = 9--12 millimeter , (+): - active slightly-(zone of inhibition) = 6--9 millimeter ,, (-): -inactive.

3.4. Pharmacology Results

3.4.1. Antimbacterial and antifungal activity

Two types of bacteria (***Streptococcus***[bacteria of gram, positive] and ***Escherichia coli***[bacteria of Gram Negative]) and two types of fungi (***Penicillium*** and ***Aspergillus. Niger***), were selected to study activity of ligand and Au(III) as antifungal and antibacterial. The results of this study are listed in table.6

3.4.2. Examination of cytotoxicity in vitro

Chemotherapy is the approach for all kinds of cancer that have spread [30-33]. The test (MTT) was used to In order to check the viability for cells. It was observed that azo ligand was found to have breast cancer viability (MCF-7)(65.83%) at 200 µg / mL, while the viability for normal, cell (WRL--68) - was

showed in similarity in the concentration (86.66%). The gold complex was showed the viability for cancer of breast (MCF--7) (58.55%). in the 400 µg / mL of concentration while the results noticed that the viability of normal cell (WRL--68) in same concentration which was (78.323%). Table 7 and table 8 and figures 3 and 4, the effect of ligand and Au (III) .complex on the MCF-7 cells and compared to normal cell line is demonstrated with the same of quantity by MTT assay under 37 °C.

Table (7):-Effect of prepared ligand on MCF-7. cells and its comparison with the normal cells line with the same concentration by the MTT assay for 24hours at 37°C

Conc. (µg.mL^{-1})	Ligand			
	Infected cells line breast cancer MCF-7		normal line cells WRI-68	
	mean	Std error of (mean)	mean	Slandered deviation error of (mean)
6.25	95.44	0.346	94.62	0.3434
12.5	94.35	0.535	94.50	0.433
25	96.74	0.322	93.77	0.355
50	93.16	1.27	94.88	0.311
100	88.17	2.478	93.331	1.055
200	65.83	1.650	86.66	3.233
400	63.79	2.758	75.66	3.322

Table (8): Effect of gold complex on MCF-7 cell and its comparison with the normal cells line with same concentration the MTT assay for 24hours at 37°C

Cons. (µg.mL^{-1})	Gold complex			
	Infected cells line breast cancer MCF-7		normal line cells WRI-68	
	mean	Std error of (mean)	mean	Slandered deviation error of (mean)
6.25	95.33	0.752	95.567	0.244
12.5	96.22	0.5434	93.453	1.134
25	95.45	0.434	94.788	0.443
50	95.343	0.2055	94.346	0.212
100	91.32	0.345	92.343	1.657
200	68.78	0.635	84.242	1.657
400	58.55	0.543	78.323	1.544

Among the important things that were obtained through the tests that tested the ligand and its complexes, MCF-7) cells and normal cells, which is called the inhibition concentration, fifty (IC_{50}) [34].It is a concentration that kills nearly half the cells. When using ligand, selective cytotoxicity was demonstrated against the tumor cell line with IC_{50} = 73.43 µg / ml, while it was 213.7µg \ mL for the normal cells, either when using the gold complex was 331howed against tumor cells line with IC_{50} = 125.7µg \ ml while it was 271.397µg \ ml subordinate to normal cells, Figures (5) and (6) show the IC_{50} µg / ml values for tumor cell lines and (normal cell) line of ligand and gold complex from the results obtained, it is found that the prepared compounds can be used with some modifications for the purpose of treating some human cancer diseases.

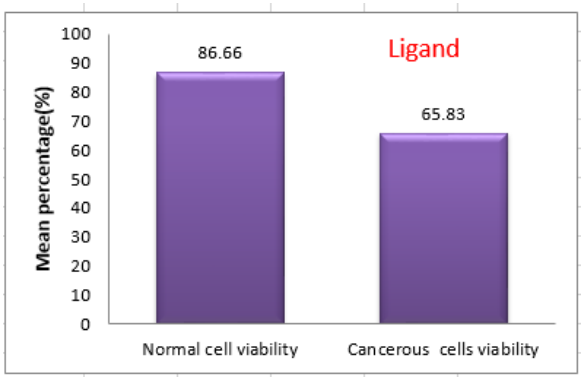


Figure (3):Comparison of cancer's viabilitynormal cells at a concentration of 200 µg / mL for ligand

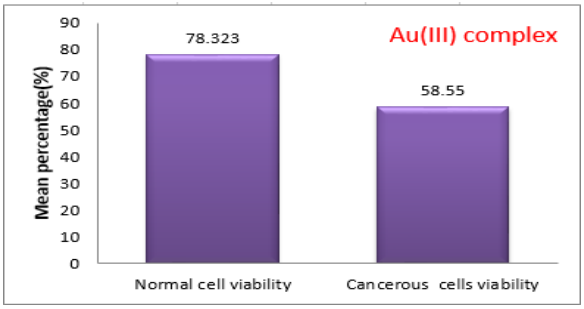


Figure (4):Comparison of cancer's viability normal cells at a concentration of400 µg / ml for Au(III)complex

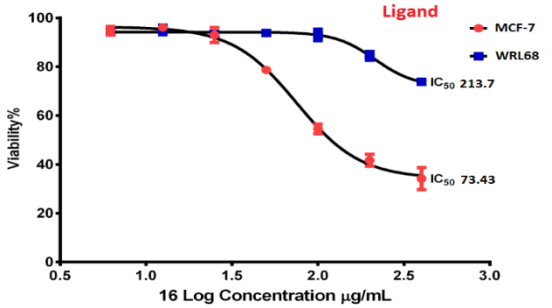


Figure (5):IC_{50} µg/ml value of the tumor cell lines and The normal cells line for the ligand

According to the obtained results by several techniques, the proposed structure for the metal complex as shown in figure 7.

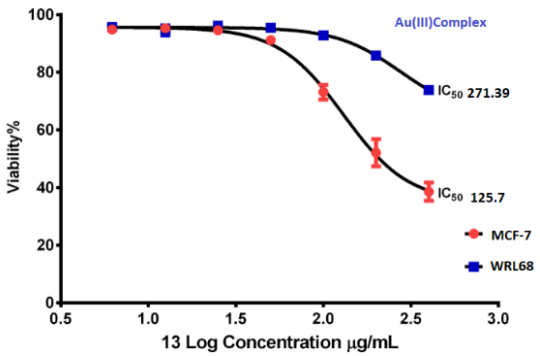


Figure (6):-IC_{50} µg/ml values of the tumor cell lines and normal .cell line of Au(III) complex

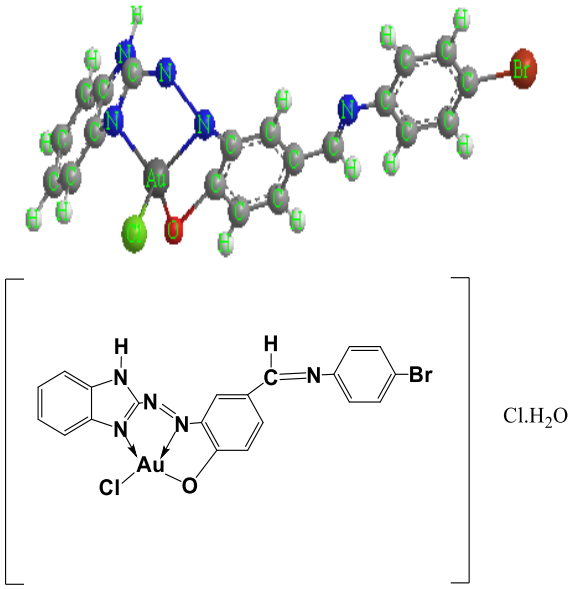


Figure (7):-The proposed of chemical structure for Au(III)complex

Conclusions

The results those based on this study were concluded that the ligand and its complex with gold ion that have low magnetic value, which indicate the geometry type square planer with hybridization type dsp^2. The gold complex appears the viability for cancer of breast (MCF--7) (58.55%). in the 400 µg / mL of concentration while it was (78.323%) for normal cell (WRL--68) in same concentration. The study also included, the use of two types of pathogenic bacteria isolated and diagnosed in the laboratory using chemical and microscopic tests positive for chromium dye *Streptococcus* and negative for the chromium dye *Escherichia coli* and two types of fungi *Aspergillus Niger* and*penicilliumsp* , the isolated fungi were considered to be the reason of some common disease.

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