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Synthesis, characterization, antimicrobial and anticancer activity of Zn(II), Pd(II) and Ru(III) complexes of dehydroacetic acid hydrazone

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ABSTRACT

The solid complexes of Zn(II), Pd(II) and Ru(III)of ethylenediamine bis dehydroacetic acid hydrazone were synthesized and characterized by elemental analysis, conductometry, thermal analysis, magnetic measurements, IR, ^{1}H-NMR and UV—Vis spectroscopy and a biological studies. From the analytical and spectral data, the stoichiometry of the complexes was found to be 1:1 (metal: ligand). The physic-chemical data suggest an octahedral geometry for the Ru(III) and Zn(II) complexes and a square planar for Pd(II) complex. The thermal decomposition of all the complexes was studied by the TG–DTA method. The synthesized ligand and its metal complexes were screened for their in vitro antibacterial activity against Gram-negative (Pseudomonas aeruginosa & Sarcina SP) and Gram-positive (Micrococcus lutes&Bacillus Subtilis) bacterial strains and for in vitro antifungal activity against Aspergillus niger and Candida albicans. The results of these studies showed that the [Pd(HL)] Cl . 4H_2O complex have antibacterial and antifungal activities than the free ligand and other complexes. The cytotoxicity of the ligand (H_2L) and its complexes on human liver carcinoma HEPG2 and breast carcinoma cells lines MCF7were determined. The Pd(II) complex showed a significant more cytotoxicity activity with a lower IC50 value of 2.67 ug/ml compared to the other complexes moreover the Pd(II) complex more active than the reference drug (IC50=3.73 ug/ml) therefore we believed to possess a significant role in the medicinal area in the future.

Key words: Metal Complexes, IR, UV, Antimicrobial, Antifungal, Anticancer, Synthesis.

INTRODUCTION

Dehydroacetic acid (DHA)and sodium dehydroacetate are used in the formulation of a wide variety of products, including bath, skin care, suntan, sunscreen, fragrance, shaving, hair and nail care products, as well as eye and facial makeup. Dehydroacetic acid it is also included on FDA's list of indirect food additives for use in adhesives and in cosmetics and personal care products as a preservative and antimicrobial agent. The use of preservatives in cosmetics and personal care products is required to prevent product damage caused by microorganisms and to protect the product from inadvertent contamination by the consumer during use. Dehydroacetic acid(dha=3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one) is known to form a number of metal complexes having fungicidal property. DHA and enaminones containing 4-hydroxy-2-pyrone ring are often investigated compounds due to their use in the synthesis of organic compounds and their good complexing properties[1]. Studies on metal chelates with Schiff base of dehydroacetic acid have been reported due to their excellent chelating capacity in modern coordination chemistry [2]. The compound of dehydroacetic acid is widely used as fungicide[3], herbicide and as preservative that has powerful antimicrobial effect against bacteria, yeast and particularly molds[4]. Ruthenium complexes are presently the objective of great attention in the field of medicinal chemistry as antitumor agents with selective antimetastatic

properties and low systemic toxicity [5]. Ruthenium complexes appear to penetrate reasonably well into the tumor cells and bind effectively to DNA [6]. By the same token, hydroxyl pyrones are biologically important chelating ligands and have been reported to possess promising pharmacological properties [7,8].A series of hydroxypyrone templates has received considerable attention as potential HIV protease inhibitors owing to the interaction of the pyrone ring with enzyme active sites [9]. The metal complexes of hydroxypyrones have reasonable hydrolytic stability and significant lipophilicity [10]. In addition, the oxygen atom on the six membered ring of the ligand renders the complexes moderately water soluble [11]. Copper(II) Complexes of dehydroacetic acid thiosemicarbazone have been synthesized and characterized by electronic, I.R and N.M.R, spectral measurements and magnetic moments[12].

EXPERIMENTAL SECTION

All compounds and solvents used were pure chemicals from BDH or Aldrich and used without further purification. Elemental analyses (C, H, N and Cl) were carried out at the microanalytical Unit of the University of Cairo. Metal ions were determined using atomic absorption with a Perkin Elmer (model 2380) spectrophotometer. The IR spectra were measured as KBr discs using a Perkin-Elmer 1430 infrared spectrometer (4000-200) cm^{-1}). Electronic absorption spectra in the 200-900 nm region were recorded on a Perkin-Elmer 550 spectrophotometer.. The magnetic susceptibilities were measured at room temperature using the Gouy method with mercuric tetrathiocyanatocobaltate(II) as magnetic susceptibility standard; diamagnetic corrections were made using Pascal's constants[13]. A Bibby conductimeter MCl was used for conductance measurements.

Antimicrobial, antifungal and anticancer activity

The compounds were evaluated for their anti-microbial activity using the agar diffusion technique[14]. All chemical compounds were dissolved in dimethyl formamide DMF (5mg/ml). The tested organisms were Gram-negative bacteria (*Pseudomonas aeruginosa* & *Sarcina* SP), Gram-positive bacteria (*Micrococcus lutes*) and fungi (*Aspergillus niger*, Candida albicans). The bacteria and fungi were maintained on nutrient agar and Czapek's Dox agar medium, respectively [15]. DMF showed no inhibition activity. Antiviral activity effect were determined by the method previously reported [16,17]. Potential cytotoxicity of the compounds (s) were tested using the method of SHehan [18] as follows:

1-Cells were plated in 96- multiwall plate (10^4 cells/well) for 24hrs before treatment with the compound(s) to allow attachment of cell to the wall of the plate.
2-Different concentration of the compound under test (0,1,2.5,5 and 10ug/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose.
3-Monolayer cells were incubated with the compound (s) for 48hrs at 37°C and in atmosphere of 5% CO_2.
4-After 48hrs, Cells were fixed, washed and stained with Sulfo-Rhodamine-β stain.
5-Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer.
6-Color intensity was measured in ELISA reader.
7-The relation between surviving fraction and drug conc. is plotted to get the survival curve of each tumor cell line after the specified compound.

Synthesis of the ligand

The ligand ethylenediamine bis dehydroacetic acid en$(DHA)_2H$ (H_2L) was prepared by the condensation of ethylenediamene and dehydroacetic acid in (1:2) molar ratio respectively in absolute ethanol and refluxed on a water bath for three hours. The condensation product separated out was filtered off, crystallized from absolute ethanol and finally dried in a vacuum desiccator over anhydrous calcium chloride.

Synthesis of the metal complexes

metal complexes were prepared by mixed metal chloride and the ligand (H_2L) in (1:1) molar ratios in absolute ethanol by adding the hot metal chloride solution [where metals are Zn(II), Pd(II) and Ru(III) to the hot ligand solution. The mixture was cooled and the ammonia solution was added drop wise with shaking until pH = 8 was reached. The mixture was refluxed on a water bath for a time depending on the nature of the metal cation used. The complexes formed were filtered off, washed several times with pure dry ethanol and vacuum dried over anhydrous calcium chloride.

RESULTS AND DISCUSSION

The Schiff base ethylenediamine bis dehydroacetic acid hydrazone (H_2L) were prepared from condensation of dehydroacetic acid (DHA) and ethylene diamine (en) in 2:1 molar ratio. The results of elemental analysis (C, H, N)

with molecular formula and melting points are presented in Table(1). The results obtained are in good agreement with those calculated for the suggested formula. The structures of the ligand (H_2L) are given in Scheme (1)

Mass spectrum of the ligand

Mass spectral data confirmed the structure of the ligand (H_2L) as indicated by the peaks corresponding to their molecular mass Fig. (1). The appearance of final peak at m/e = 360 ($C_{18}H_{20}N_2O_6$) equal the calculated molecular mass(360) and the other peaks at 193, 180, 166, 151, 138, 109, 85, 81, 67, 55, 50 may be due to different fragments. The intensity of these peaks given an idea of the stability of these fragments.

^{1}HNMR spectra

The ^{1}HNMR spectrum of the free ligand (H_2L) in DMSO solution Fig. (2) showed that the peaks at 14 ppm are assignable to the proton of OH group which disappear in the presence of D_2O [19]. The protons of CH_3 group of azomethine group and of the ring appeared as a singlet peak at 2.6 and 2.1 ppm respectively[20]. The peak appeared at 3.9 and 3.4 ppm corresponding to two CH_2 groups of ethylene diamine part. A singlet at 5.7ppm was assigned to the vinylic proton of DHA. The ^{1}HNMR spectrum of the complex [Zn (HL) $(H_2O)_2$] Cl . $4H_2O$ was comparison with those of the parent ligand (H_2L). It was found that new peaks appeared at 12 and 9.8 ppm due to protons of H_2O molecules coordinated with Zn(II) ion and the peak of OH which appeared at 14 ppm in the free ligand disappeared in the spectrum of complex indicated that the phenolic oxygen chelating with Zn(II) ion. The signal that was observed at 3.3 Ppm with an integration corresponding to 8 protons in the complex is assigned to four water of crystallization which disappear in D_2O Fig.(3) .

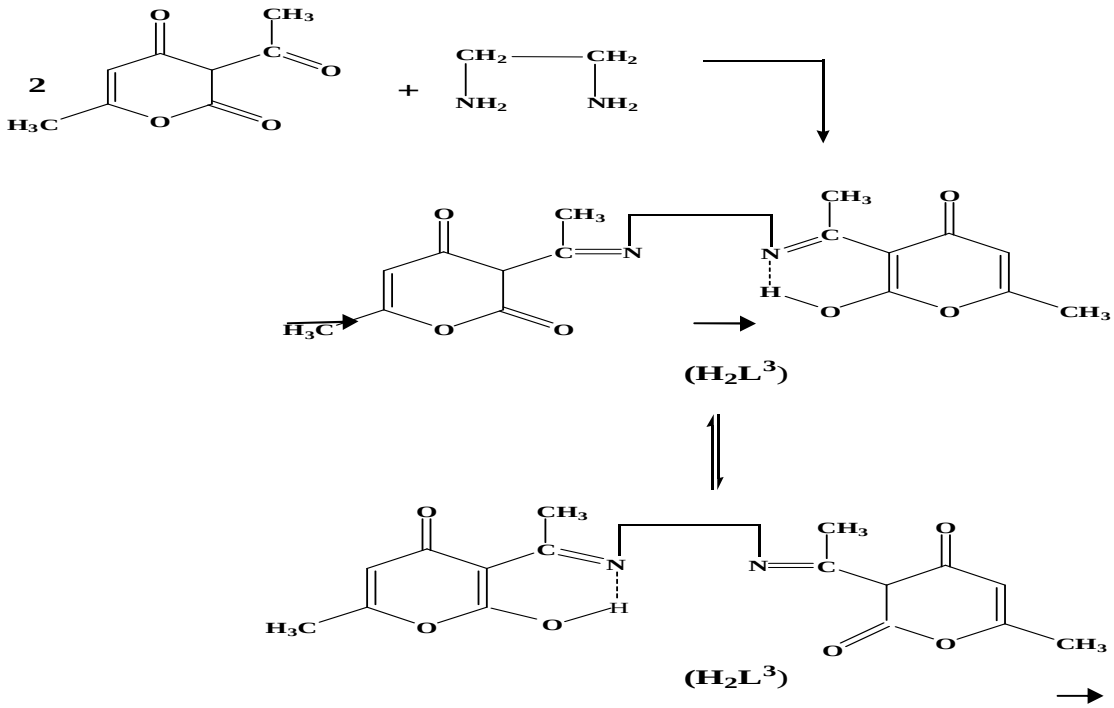
Table (2)^{1}HNMR spectra data of the ligand (H_2L) and its [Zn (HL) $(H_2O)_2$] Cl . $4H_2O$ complex

Compound	Chemical shift (δ) ppm					
	OH	H_2O (coordination)	CH_2	CH(DHA)	CH_3	H_2O (crystalization)
H_2L	14	---	3.4 3.9	5.7	2.1 2.6	---
[Zn(HL^3) $(H_2O_3)_2$]Cl .$4H_2O$	---	12 9.8	3.5 3.8	5.7	2.4 2. 6	3.3

IR spectra

The IR spectrum of the free ligand (H_2L) shows abroad band at 3430 cm^{-1} which attributed to inter – and intra molecular hydrogen bonding OH group [21 ,22]. The spectrum shows also strong three bands at 1706, 1655 and 1566 cm^{-1} are assigned to νC=O (lactone), νC=O (carbonyl)and νC=N respectively[23] .Depending on the above resulted and the elemental analyses Table (1). the ligand (H_2L) has the structure as showen in Scheme 1. The IR spectra of the complexes were compared with those of the free ligand Table(3) in order to determine the coordination sites that may be involved in chelating. The position and or the intensities of these peaks are expected to change upon chelation.. In all the complexes νC=O (lactone) remains unaltered .The spectra of the complexes show abroad band in the range 3589-3000 cm^{-1} suggesting the presence of water molecules [24-27]. Upon comparison it was determined that the νC=O and νC=N stretching vibration is found in the free ligand at 1655-1566 cm^{-1} this bands were shifted to higher wave numbers in the complexes indicating their participation in coordination [28,29]. In all complexes the absence of νOH at 3400 cm^{-1} suggests the deprotonation of the one phenolic oxygen prior to coordination. New bands are found in the spectra of the complexes in the regions 665-584 cm^{-1} which are assigned to νM-O stretching vibrations and the bands at 581-504 cm^{-1} assigned to νM-N [30]. In the spectra of Ru(III) complexe the band of νM-Cl appeared at 443 cm^{-1}. Therefore from the IR spectra it is concluded that the ligand (H_2L) behaves as monobasic tetradentate ligand coordinating through C=O and deprotonated phenolic oxygen and the azomethine N.

Depending on the above resulted and the elemental analyses Table (1). the ligand (H_2L) have the following structure.



Scheme 1

Electronic spectra of the ligand (H_2L) and their complexes.

The electronic obsorption spectra of the ligand (H_2L) show three bands with maxima at 412 , 305 and 228 nm due to the various n - π^* and π - π^* transition . The electronic spectra of the complexes under study are summarized in Table(4). The spectrum of Ru(III) complex display two electronic spectral bands at 650,522 nm assignable to $^4T_1g(F) \longrightarrow {}^4A_2g(F)$ and $^4T_1g(F) \longrightarrow {}^4T_1g(P)$ transitions characteristic of octahedral geometry [31]. The electronic spectra of the complexes show also bands below 400 nm which can be assigand to various types of intra π - π^* and C.T. interactions. The palladium complex show different bands at 637 and 486 nm suggesting square planar geometry [32,33]. The room tempereture magnetic moments of the Pd(II)and Zn(II) complexes are diamagnetic.

Ruthenium (III) complex shows a magnetic value 2.1 B.M. indicating an octahedral structure [34].

TGA, DTA and DTG of the ligand (H_2L) and their complexes.

From the DTA and TG curves of the ligand(H_2L) the following facts can be establised.

(a) The weight of the ligand (H_2L) remains constant up to 152 °C.

(b) The decomposition of the ligand (H_2L) proceeds without melting in two steps , the first step with weight loss is 55.2% at 152 - 414 °C which may be due to the loss of ($C_{10}H_{12}NO_3$) as CO_2 and NO_2 gases and appeared as endothermic peak in DTA and the second step of decomposition proceeds at 414-600°C due to loss of ($C_7H_4NO_3$) with weight lost 41.94(found) and 41.7(calc.) and appeared as exothermic peak in DTA curve . The TG curves of the complexes show thermal decomposition at 144 – 158 °C due to the loss of crystalline water [35]. The HCl molecule or Cl_2 molecules are liberated at a temperature above 300 °C [36]. The product is stable up to 500°C when the organic constituents of the complexe start decomposing finally leaving the decomposition products at (550-600°C) [37-39].The loss of crystalline water appears as endothermic peak and all the further decomposition appears as exothermic peaks

Biological activity

Antimicrobial activity

Compounds were tested for their antimicrobial activiting using the Gram positive bacteria *(Micrococcus lutes*) and gram negative bacteria *(Pseudomonas aeruginosa* & *Sarcina* SP**)**. The results are summarized in Table (5) and represented in figs .4,5 which showed that, the tested compounds were found to possess different antibacterial activities towards all the gram positive and negative bacteria, On chelation[40,44]the polarity of the metal ion was reduced greatly due to overlap of the ligand orbital and the partial sharing of its positive charge with donor groups and also due to delocalization of the π-electrons over whole chelate ring .The [Pd(HL)] Cl . $4H_2O$ complex has antibacterial activities towards *Micrococcus lutes* as gram positive and *Pseudomonas aeruginosa* & *Sarcina* SP. as negative bacteria. The compounds were tested for their antimicrobial activities using fungi *(Aspergillus niger*,

Candida albicans) and yeast *Candida albicans*, the results are represented in fig.6 the ligand and Pd(II) complex showed antifungal activity towards *Aspergillus niger* .The Ru(III) complex only showed antifungal activity against Candida albicans. All the ligand and its complexes showed no any antiviral activity.

Antitumor activity

Anticancer liver HEPG2 activity of the ligand (H_2L) and its complexes

The cytotoxicity of the ligand (H_2L) and its Zn(II), Ru(III) and Pd(II) Fig.7 on human liver carcinoma cells lines HEPG2 were determined and from the IC50 values are 24, 19.5, 20.1 and 2.76 ug/ml for the ligand (H_2L) and its Zn(II), Ru(III) and Pd(II) complexes respectively. From the data it was found that the complexes are more active against HEPG2 cells than the ligand (H_2L) and the Pd(II) complex showed a significant more cytotoxicity activity with a lower IC50 value of 2.67 ug/ml compared to other complexes moreover the Pd(II) complex more active than the reference drug (IC50=3.73 ug/ml) therefore we believed to possess a significant role in the medicinal area in the future.

Anticancer breast MCF7 activity of the ligand (H_2L) and its complexes

The cytotoxicity on breast carcinoma cells lines MCF7 of the ligand (H_2L) and its Zn(II), Ru(III) and Pd(II) complexes Fig.8 are 20.5, 20.3, 19.6 and 3.28 ug/ml respectively. From the data it was found that the ligand (H_2L) and its Zn(II) and Ru(III) complexes have the same effect on MCF7 these means lower than the reference drug (IC50=2.97 ug/ml) but the Pd(II) complex have significant more cytotoxicity activity with IC50 value of 3.28 ug/ml approximately equal to IC50 of the reference drug therefore it may be used in medicinal uses.

Table (1) : Elemental analyses of the ligand en$(DHA)_2H$ (H_2L) and its complexes

Comp. no	Molecular formula	M.wt.	Colour	Yield	M.P.^{0}C	Found (calco.) %					$\Omega^{-1}mol^{-1}cm^2$
						C	H	N	Cl	M	
1	H_2L	360	White	97%	260°C	59.20 (60.00)	5.66 (5.60)	7.80 (7.80)	----	----	2.62
2	[Ru (HL)Cl_2] $2H_2O$	567.1	Black	95%	246°C	38.20 (38.10)	4.40 (4.10)	6.11 (4.90)	12.20 (12.50)	---- (17.8)	25.00
3	[Pd(HL)]Cl. $4H_2O$	570.9	Grey	92%	274°C	38.10 (37.70)	4.50 (4.70)	4.80 (4.90)	6.70 (6.20)	19.00 (18.6)	93.00
4	[Zn$(HL(H_2O)_2]$Cl. $4H_2O$	566.4	Bage	85%	188°C	37.80 (38.10)	4.80 (5.50)	5.00 (4.90)	6.60 (6.30)	10.00 (11.6)	97.90

Table (3): Important I.R. spectral of the ligand (H_2L) and its complexes

Comp. no	Molecular formula	ν_{OH}	$\nu_{C=O}$ DHA	$\nu_{C=N}$	ν_{M-O}	ν_{M-N}	ν_{M-Cl}
1	H_2L	3433(s)	1706(s) 1655(s)	1566(s)	--------	--------	--------
2	[Ru (HL) Cl_2] . $2H_2O$	3433(br)	1702(s) 1670(m)	1570(s)	584(m)	504(w)	443(w)
3	[Pd(HL)] Cl . $4H_2O$	3589(w) 3463(w)	1691(s) 1680(w)	1572(s)	640(s)	534(s)	--------
4	[Zn(HL) $(H_2O)_2$] Cl . $4H_2O$	3300-3000 (br)	1703(s) 1690(w)	1590(s)	612(s)	509(s)	--------

br: broad m: medium w: week s: strong

Tabel(4): Uv.Vis spectra of the ligand (H_2L) and its complexes

Comp. no	Molecular formula	λmax (nm)	μeff
1	H_2L	412(Є = 1.7 x 10^{-6}) , 305(Є = 5.20 x10^{-4}) , 228(Є = 5.01 x 10^{-4})	------
2	[Ru (HL) Cl_2] $2H_2O$	650(Є = 1.09 x 10^{-4}) , 522(Є = 3.88 x 10^{-5}) , 388(Є = 1.09 x 10^{-4}) , 313.5(Є = 1.49 x 10^{-3}) , 222.5(Є = 1.45 x 10^{-3})	2.1
3	[Pd(HL)] Cl . $4H_2O$	637.5(Є = 1.42 x 10^{-4}) , 486.5(Є = 1.64 x 10^{-4}) , 248.5(Є = 8.05 x 10^{-4})	diamagnetic
4	[Zn(HL) $(H_2O)_2$] Cl . $4H_2O$	389.5(Є = 1.10 x 10^{-5}) , 302.5(Є = 8.11 x10^{-4}) , 219.5(Є = 7.87 x 10^{-4})	diamagnetic

Table (5): Thermal analysis of the ligand (H_2L) and its metal complexes

Comp no	Molecular formula	DTA Peaks		TGA Peaks			Assignment
		Temp C°	Peak	Temp C°	Wt. Loss%		
					Calcd.	Found	
1	H_2L	257 498	Endo. Exo.	152-414 414-600	53.9 41.7	55.27 41.94	Loss of ($C_{10}H_{12}NO_3$) as (CO_2 and NO_2). Loss of ($C_7H_4NO_3$) .
2	[Ru (HL) Cl_2] $2H_2O$	264 384	Endo. Exo.	58-158 158-371 371-518	3.2 58.2	3.6 57.2 32.3	Loss of one lattice water. Loss of one lattice water, Cl_2, $2CH_3$, ($C_8H_9NO_3$) and CO_2. Further decomposition.
3	[Pd(HL)] Cl . $4H_2O$	74 132, 236 319, 336 416	Endo. Endo. Exo. Exo.	144-288 288-358 358-457	9.4 31.9	8.2 31.4 28.3	Loss of three lattice water. Loss of one lattice water and ($C_8H_7NO_3$). Further decomposition.
4	[Zn(HL)(H_2O)$_2$] Cl . $4H_2O$	176 333 371 620	Endo. Endo. Exo. Exo.	120-470 470-620 620-800	40.7	41.1 21.2 24.1	Loss of four lattice water,$2H_2O$, HCl and $2(CO_2)$. Further decomposition. Further decomposition.

n. number of stages of decomposition Exo. Exothermic peak Endo. Endothermic peak*

Table (6): Antimicrobial and antifungal activity of the ligand (H_2L) and its complexes:

Mean Values of inhibition zones (in mm)	Compound			
	H_2L	[Zn(HL)(H_2O)$_2$] Cl . $4H_2O$	[Ru (HL) Cl_2] $2H_2O$	[Pd(HL)] Cl . $4H_2O$
Bacillus subtilis	0	0	0	0
Micrococcus lutes	20	22	0	19
Pseudomonas aeruginosa	22	0	20	23
Sarcina SP	0	30	0	29
Aspergillus niger	25	0	0	26
Candida albicans	0	0	23	0

Table(7) Anticancer liver HEPG2 activity data of the ligand (H_2L) and its complexes

conc: ug/ml	DRUG CYTOTOXICITY (HEPG2)				
	DOX.	H_2L	[Zn(HL)(H_2O)$_2$] Cl . $4H_2O$	[Ru (HL) Cl_2] $2H_2O$	[Pd(HL)] Cl . $4H_2O$
0.0	1.000000	1.000000	1.000000	1.000000	1.000000
5.0	0.331906	0.841392	0.837912	0.886265	0.091568
12.5	0.211934	0.682701	0.656723	0.689455	0.073060
25.0	0.188967	0.486555	0.376217	0.371382	0.069886
50.0	0.262134	0.235757	0.259238	0.276611	0.093474
IC50: ug/ml	3.73	24	19.5	20.1	2.67

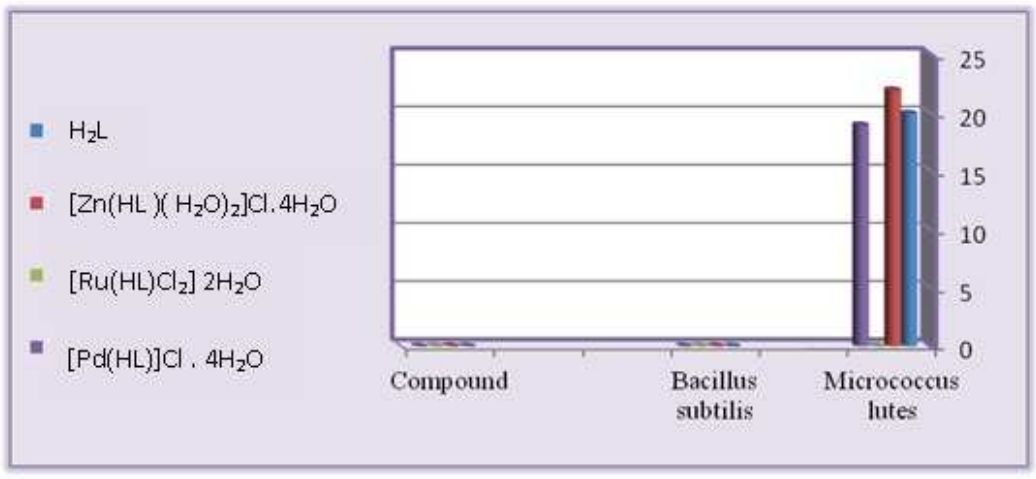


Fig.(4) Antimicrobial activity of the ligand (H_2L) and its complexes against Gram positive bacteria

Table(8) Anticancer effect breast MCF7 activity data of the ligand (H_2L) and its complexes

conc: ug/ml	DRUG CYTOTOXICITY (HEPG2)				
	DOX.	H_2L	$[Zn(HL)(H_2O)_2]$ Cl . $4H_2O$	[Ru (HL) Cl_2] $2H_2O$	[Pd(HL)] Cl . $4H_2O$
0.0	1.000000	1.000000	1.000000	1.000000	1.000000
5.0	0.194273	0.916826	0.881609	0.912174	0.166956
12.5	0.171715	0.801870	0.743348	0.770565	0.146665
25.0	0.185526	0.323187	0.350143	0.278117	0.119130
50.0	0.201330	0.206378	0.123913	0.218261	0.136813
IC50: ug/ml	2.97	20.5	20.3	19.6	3.28

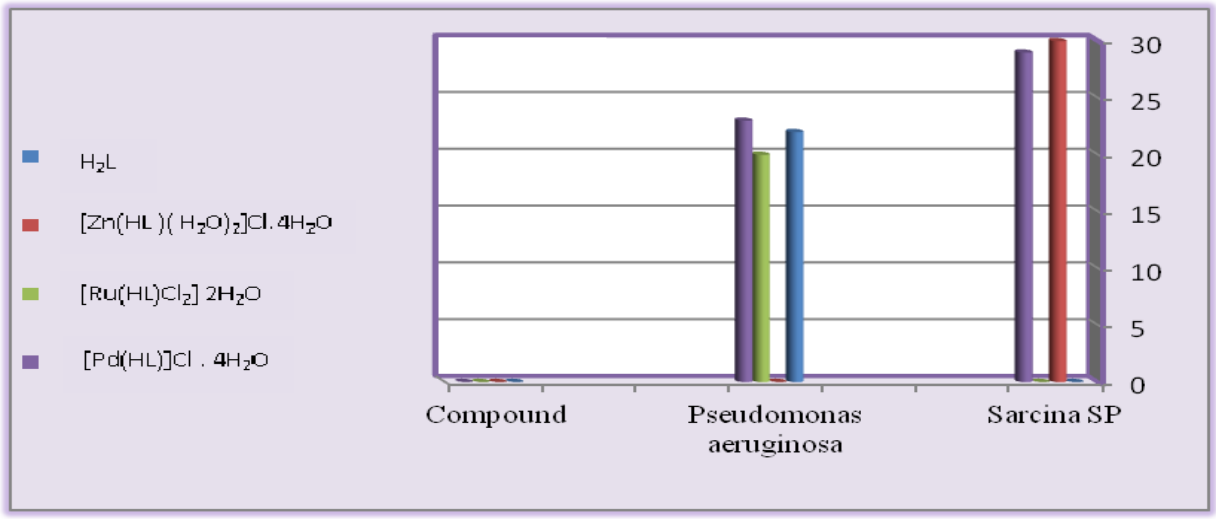


Fig.(5) Antimicrobial activity of the ligand (H_2L) and its complexes against Gram negative bacteria

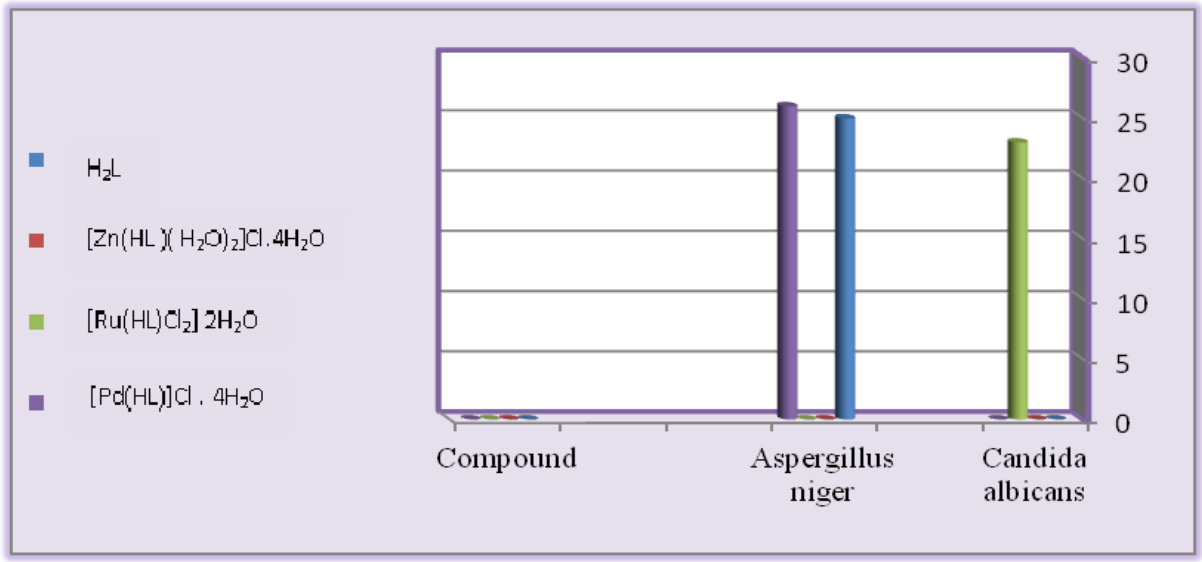


Fig. (6) Antifungal activity of the ligand (H_2L) and its complexes

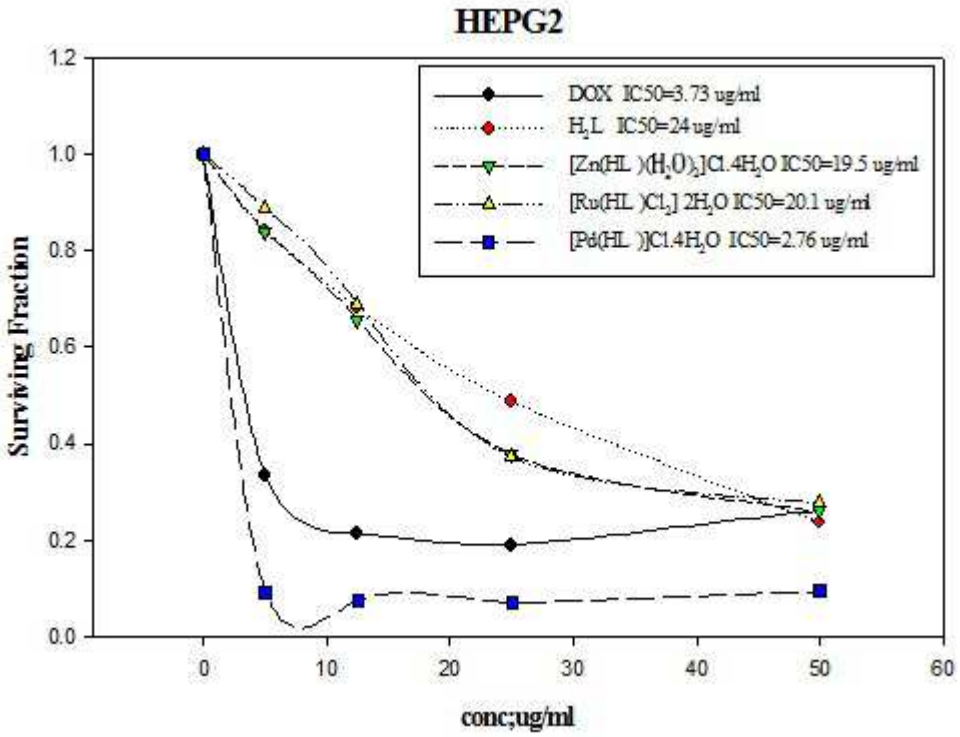


Fig. (7) Anticancer livare HEPG2 activity of the ligand (H_2L) and its Zn(II), Ru(III) and Pd(II) complexes

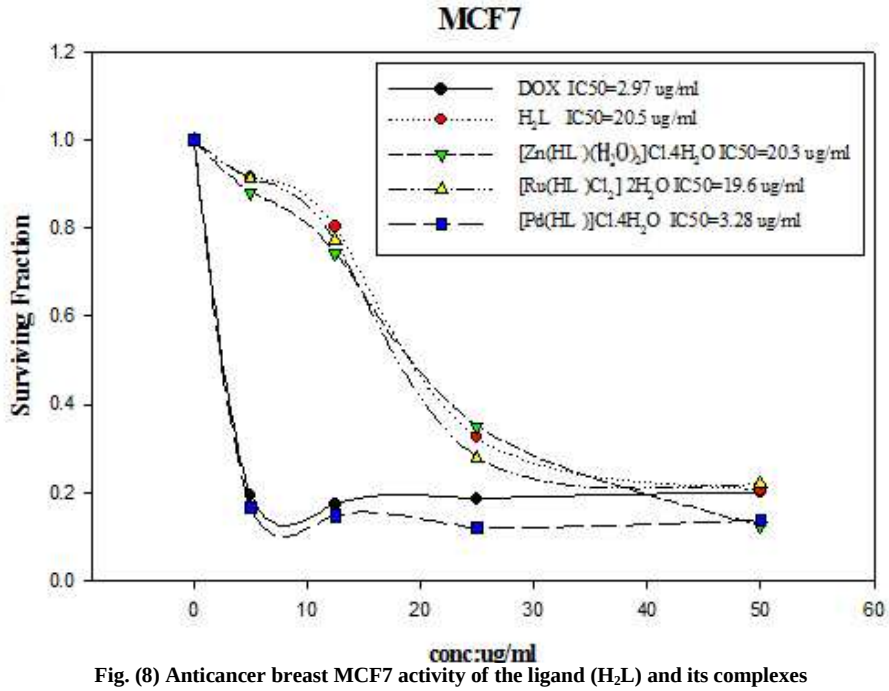
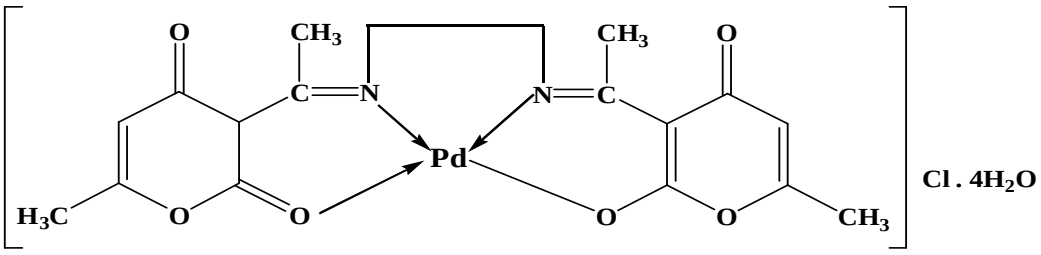
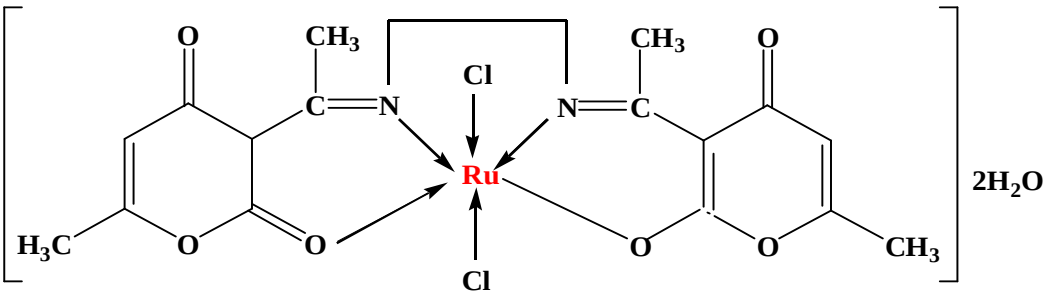


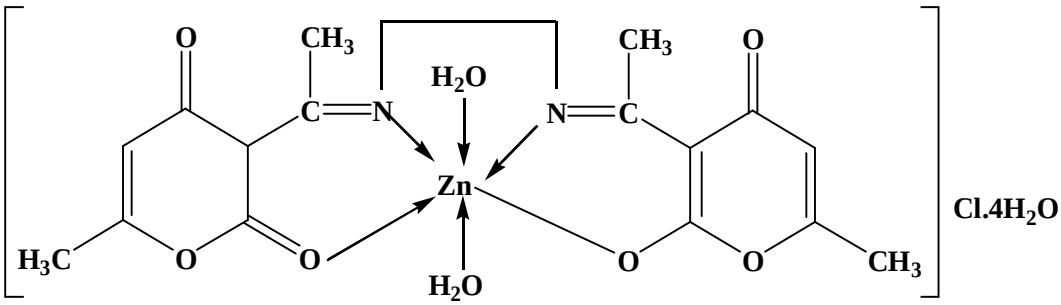
Fig. (8) Anticancer breast MCF7 activity of the ligand (H_2L) and its complexes



[Pd(HL)] Cl.4H₂O



[Ru(HL)Cl₂] 2H₂O



[Zn(HL)(H₂O)₂] Cl . 4H₂O

Fig. (9) The structure of the complexes of the ligand (H_2L)

CONCLUSION

Dehydroacetic acid hydrazone and their complexes have been prepared. The molecular structures of the resulted complexes were evaluated by physicochemical analyses. the IR spectra concluded that the ligand (H_2L) behaves as monobasic tetradentate ligand coordinating through C=O, deprotonated phenolic oxygen and the azomethine N. The Zn (II) and Ru(III) complexes have octahedral geometry but pd(II) complex has square planar geometry. The decomposition of the ligand (H_2L) proceeds in two steps and for the complexes in three steps. The ligand and their complexes were found to possess different antibacterial activities towards all the gram positive and negative bacteria. The Ru(III) complex only showed antifungal activity against Candida albicans. All the ligand and its complexes showed no any antiviral activity. The Pd(II) complex show more cytotoxicity against liver carcinoma cells lines HEPG2 active than the reference drug (IC50=3.73 ug/ml) therefore we believed to possess a significant role in the medicinal area in the future.

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