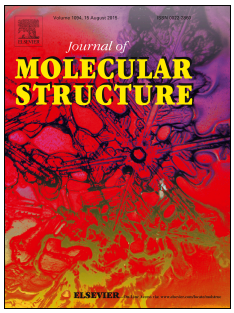

Synthesis, characterization, coordination chemistry and biological activity of some pyrimidine complexes

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SYNTHESIS, CHARACTERIZATION ,COORDINATION CHEMISTRY AND BIOLOGICAL ACTIVITY OF SOME PYRIMIDINE COMPLEXES.

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Abstract

A group of biologically active ligands: 5-(2hydroxyphenylide) barbituric acid (L^1) , 5-(phenyl azo) thiobarbituric acid (L^2) and 5-(phenyl azo) barbituric acid (L^3) and its complexes with Os(VIII) , Ru(III) ,Zr(IV) and V(III) ions were synthesized .The chemical structures of these compounds were fully identified using MALDI-TOF , FT-IR ,^{1}H-NMR , TGA and DSC techniques , magnetic susceptibility measurements helped to determine the exact geometry of the complexes under study. The dissociation constants of the ligands were evaluated by analyzing their electronic absorption spectra at different pH's. All the compounds were tested for its anticancer, antimicrobial and antioxidant activities .The collected data showed that some of the compounds can be used as drugs for the treatment of breast cancer (MCF-7 cancer cells) and as potent antibiotics for both gram-positive and gram –negative bacterial species including : *Staphelococcus Epidermisis* , *Escherishia Coli* ,*Staphyllococcus Auresis and Salmonilla* and the fungal species: *Candida Albicans* . The DPPH Radical Scavenging Activity of the compounds showed that most of the compounds can be used as good antioxidant agents.

1-Introduction

Heterocyclic compounds containing nitrogen and/or sulphur including pyrimidines represent a major component of many natural products and biologically active molecules(1).These compounds have been widely used as agrochemicals ,flavors and stains but they were mainly applied as drugs in medicinal chemistry(2). The pyrimidine nucleus is a 1,3-diazine containing two nitrogens at 1 and 3 positions. As a response to the great importance of pyrimidines in many aspects, a large number of synthetic procedures have been designed for the efficient synthesis of pure pyrimidine derivatives. The barbituric acid and thiobarbituric acid derivatives exhibited a wide range of biological activities and consequently, they are considered one the most important examined drugs(3).

Cancer is one of the most serious diseases that eventually lead to death .It involves uncontrolled cell growth forming injurious tumers that may spread in body organs .

Pyrimidine derivatives have been greatly involved in the cancer therapy and showed excellent antoxidant and antimicrobial activity[4].Breast cancer is one of the most common diseases in women and dramatic rise in its incidences occurred globally .So, it is important to develop new drugs that act against this disease. According to literature, many pyrimidine derivatives and thieir transition metal complexes are reported to exhibit potent anticancer activity against MCF-7 breast carcinoma and many other cancers[4-12] . Our research group "Masoud et al [13-44]" published a large number of papers concerning the chemistry of pyrimidines. In continuation of our research , the present work aimed to synthesize and fully characterize some biological active ligands derived from barbituric and thiobarbituric acids and their complexes using :

- ^{1}H NMR spectra to confirm the proposed structure of the ligands and to support the tautomeric behavior of the ligands.
- MALDI-TOF mass spectroscopy to determine the exact molecular weight of the compounds.
- FT-IR spectra to discuss the mode of binding in their metal complexes.
- Electronic spectra and magnetic measurements to determine the geometry of the transition metal complexes derived from Os(VIII) , Ru(III) ,Zr(IV) and V(III) salts.
- Thermal methods (TGA and DSC) of some compounds to propose the mechanism of their decomposition and their heat capacities.
- Spectrophotometric methods to evaluate the Pka values of the ligands.

2-Experimental:

2.1.Synthesis of the ligands

The prepared ligands are azo and ylide derivatives of barbituric and thio barbituric acids which are purchased from Alpha –chemika company.

2.1.1.Synthesis of 5-(2hydroxyphenylide) barbituric acid (L^1)

Barbituric acid (0.01 mol) was dissolved in 50 ml of 0.1 M HCl. A bout 15 ml of salisaldehyde slowly added to the solution with continuous stirring. The nitrogen content, colour, m. p. ºc and formula are given in Table (1).

2.1.2.Synthesis of 5-(phenyl azo) thiobarbituric acid (L^2)

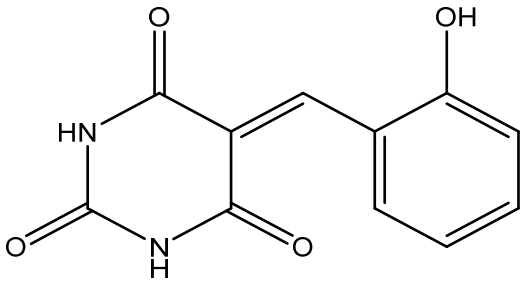
Aniline (0.01 mol) was dissolved in HCl (0.2 mol) and 25 ml distilled water. The hydrochloride compound was diazotized below 5 ºc with a solution of $NaNO_2$ (0.1 mol) and 20 ml distilled water. The diazonium chloride was coupled with an alkaline solution of 0.1 mol thiobarbituric acid / 30 ml distilled water. The solid products where filtered off and allowed to dry under suction. Table (1) collects the nitrogen content, colour, m. p. ºc and formula of the ligands.

2.1.3.Synthesis of 5-(phenyl azo) barbituric acid (L^3)

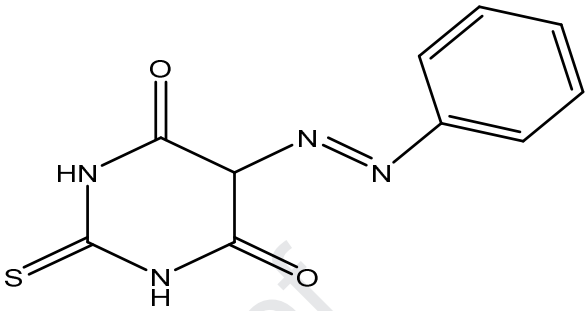
0. 01 mol of aniline acid was dissolved in 0. 2 mol HCl and 25 mi distilled water. The hydrochloride compound was diazotized below 5 ºc with a solution of $NaNO_2$ (0. 1

mol) and 20 ml distilled water. The diazonium chloride was coupled with an alkaline solution of 0. 1 mol barbituric acid / 30 ml distilled water. The observed molecular weight, colour, m. p. ºc and formula are given in Table (1).

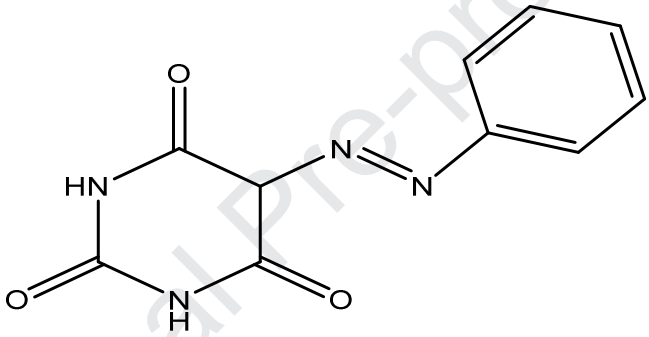
The ligands used during this work are given as follows [Figure(1)]:



5-(Salicylidene) barbituric acid (L^1)



5-(phenyl azo) thiobarbituric acid (L^2)



5-(phenyl azo) barbituric acid (L^3)

Figure (1) : The synthesized ligands

2.2.Sythesis of transition metal complexes

All complexes where prepared in the same way. The inorganic salts of $RuCl_3$,VCl_3 , $ZrOCl_2$ and OsO_4) are dissolved in distilled water, while the ligands where dissolved in ethanol. The complexes where prepared using (1:1) mole ratio of metal to ligand.

In all preparations, the reaction takes place at room temperature. Filtration of the solid products is done through suction system and then dried in a vaccum desictor over anhydrous $CaCl_2$. The analytical results are given in Table (2).

2.3.Elemental analysis

The complexes were digested and decomposed with aqua regia and the metal contents were determined either complexometrically using published procedures[45] and by means of atomic absorption spectroscopy. The chloride content in certain comolexes were determined by the usual Volhard method.

Table (1): Colour, m.p (◦c) and analytical data for the prepared ligands

Compound	m. p(c◦)	M. wt(g/mol)	Formula	Colour	[Calculated/(Found)%]			
					C	H	N	S
5-(2hydroxyphenylide) barbituric acid(L^1)	281-282	232. 20	$C_{11}H_8O_4N_2$	Red-orange	56.9 (56.53)	3.47 (3.87)	12.06 (12.56)	-
5-(phenyl azo) thiobarbituric acid (L^2)	294-295	248. 26	$C_{10}H_8O_2N_4S$	Brown	48.38 (47.99)	3.25 (3.71)	22.57 (22.86)	12.91 (12.78)
5-(phenyl azo) barbituric acid (L^3)	288-289	232. 20	$C_{10}H_8O_3N_4$	Dark violet	51.73 (52.03)	3.47 (3.35)	24.13 (24.33)	-

Table (2):Elemental analysis and physical properties of the complexes (All the complexes are with "1:1"stoichiometry)

Complex	M. wt Calculated (Found)	Colour	Formula	Calculated (Found) %				
				C	H	N	M	X
Ru. L^1. Cl_3.	438. 61 (441.23)	Dark Brown	$C_{11}H_7Cl_3N_2O_4Ru$	30.12	1. 61	6.39	23.04 (23. 88)	19. 83 (19. 36)
OsO_2. L^3. 2OH	490.45 (491.192)	Dark grey	$C_{10}H_{12}N_4O_7Os$	24.49	2.47	11.42	38.79 (38. 15)	-
V. L^3. Cl_3	388.48 (389.107)	Black	$C_{10}H_7Cl_3N_4O_3V$	30. 92	1.82	14.42	13.11 (13. 53)	27.38 (27.82)
ZrO. L^2.Cl_2	425.38 (426.285)	Brown	$C_{10}H_7Cl_2N_4O_3SZr$	28.24	1.66	13.17	21.45 (21.56)	16.67 (16.89)
ZrO. L^3. Cl_2	409.31 (408.125)	Dark Brown	$C_{10}H_7Cl_2N_4O_4Zr$	29.34	1.72	13.69	22.29 (22.59)	17.32 (17.96)
Ru. L^2. Cl_4	491.13 (492.723)	Dark Brown	$C_{10}H_{10}Cl_4N_4O_2RuS$	24.46	1.64	11.41	20.58 (20.86)	28.67 (29.01)
								-

2.4.Instrumental analysis:

2.4.1.NMR spectroscopy

NMR measurements were done using an Avance Bruker (300 MHz) instrument.

2.4.2.Infra-red spectroscopy

The IR spectra of the ligands and their complexes were recorded using Perkin-Elmer spectrophotometer model 1430 covering the frequency range 4000-200 cm^{-1}, by the KBr disc method. The analytical procedure were done at the central laboratory, Faculty of science, Alexandria university.

2.4.3.UV-VIS Specroscopy

The spectral data in the visible and ultraviolet spectral regions were recorded using Perkin-Elmer spectrophotometer model 4B Lambada scanning the wavelength range 190-900 nm at the central laboratory, Faculty of science, Alexandria university. The complexes were measured in nujol mull, following the method described by Lee, Griswold and Kleinberg[46].

2.4.4.Magnetic susceptibility measurements

Molar magnetic susceptibility measurements were carried out on a Sherwood scientific magnetic balance. The calculations were evaluated by applying the following equations (1, 2 and 3) [47].

$$x_g = C \times L (R - R^{\circ}) / 10^3 \times m \quad (1)$$

$$x_m = x_g \times M.wt \quad (2)$$

$$\mu_{eff} = 2.84 (x_m \times T)^{1/2} \quad (3)$$

x_g= the mass susceptibility per gram sample.
C =the calibration constant of the instrument.
L = the sample length in cm.
R = the balance reading for the sample and tube.
R° = the balance reading for the empty tube.
m=the mass of the sample in gm.
T =absolute temperature.

2.4.5.Thermal analysis

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were carried out for the prepared ligands and their complexes. The rate of heating was 5º c / min. The cell used was platinium, the atmospheric nitrogen rate flow was 20 ml/min. The instrument is located at the central laboratory, Faculty of Science, Alexandria university.

2.4.6. Matrix Assisted Laser Desorption Ionization Time-of-flight (MALDI-TOF) mass spectroscopy

The instrument used for the analysis of the prepared compounds is MALDI Ultraflextreme for Bruker Daltonics company of software flex analysis at the Faculty of Medicine , proteomic department, Alexandria University.

2.5.Biological activity

2.5.1.Disc diffusion method

Disc diffusion method was determined by Kirby-Bauer's [48] disc diffusion method as National Committee for Clinical Laboratory Standards (NCCLS) recommendations. Nutrient agar media plates were cultured with inoculums of each bacterium isolate using sterile cotton swabs. The discs of the prepared compounds placed on the inoculated plates. The compounds were dissolved in DMSO which was used as control [49]. Different concentrations of each compound were prepared (in DMSO).The bacterial and fungal growth were examined in absence and presence of the compounds at 37° C for 2 days and later, applied to bacteria grown on agar plates. Inoculation was performed with the help of a platinum wire loop,which was made red-hot in flame and used for the application of bacterial strains after cooling. Sterilized forceps were used to apply paper disc on inoculated agar plates. The inhibition zone diameters were measured and recorded for the investigation of both antibacterial and antifungal activity of the prepared compounds.

2.5.2.Antioxidant Assay:

The antioxidant activity of extract was determined at the Regional Center for Mycology and Biotechnology (RCMB) at Al- Azhar University *by* the DPPH free radical scavenging assay in triplicate and average values were considered.

DPPH Radical Scavenging Activity:

Freshly prepared (0.004%w/v) methanol solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical was prepared and stored at 10C in the dark. A methanol solution of the test compound was prepared. A 40 µL aliquot of the methanol solution was added to 3ml of DPPH solution. Absorbance measurements were recorded immediately with a UV-visible spectrophotometer (Milton Roy, Spectronic 1201). The decrease in absorbance at 515 nm was determined continuously, with data being recorded at 1 min intervals until the absorbance stabilized (16 min). The absorbance of the DPPH radical without antioxidant (control) and the reference compound ascorbic acid were also measured. All the determinations were performed in

three replicates and averaged. The percentage inhibition (PI) of the DPPH radical was calculated according to the formula:

$$PI = [\{(AC - AT)/ AC\} \times 100] \quad (4)$$

Where *A*C = Absorbance of the control at t = 0 min and *A*T = absorbance of the sample+DPPH at t = 16 min [(50)].

2.5.3.Anticancer activity:

Cell culture:

All the prepared compounds were tested for their anticancer activity against human breast adrenocarcinoma MCF-7 cells which are obtained from VACSERA company, Alexandria, Egypt .Cells were cultured in complete culture medium: DMEM (Dulbecco's Modified Eagle Medium) purchased from LONZA company, U.S.A, supplemented with 10%fetal bovine serum (SIGMA-ALDRICH, U.S.A) at 37 ºC in a humidified incubator (NUAIRE, U.S.A) with 5% CO_2 atmosphere.

Cell viability examination using MTT test

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was used for the evaluation of the antiproliferative and /or cytostatic effect of the tested compounds on cancer cells. In this procedure. Trypsinized cells were suspended in complete culture medium before seeding in 96-well plates (3000 cells per well). Incubation proceeded for 24 hours at 37 ºC in 5% CO_2 atmosphere. Maximum concentarion of 100 µg/ml was applied followed by two-fold serial dillutions. Different concentrations of the tested compounds were added to the MCF-7 cells and then the plates were incubated at 37 ºC with 5% CO_2 atmosphere for 48 hours after which old medium was removed followed by washing with saline solution (0.89%) and the addition of 100 µL of MTT solution (0.5mg/ml). After a period of 4 hours of incubation, the supernatants were carefully separated and the precipitates of formazan crystals were dissolved 100 µL of dimethyl sulfoxide (DMSO). At last, the absorbances at 490 nm were measured using a 96-well plate reader spectrophotometer [(51)]. A dose response curve was constructed, to conclude the IC_{50}, using the concentration as x-axis and the % viability as Y axis.

3.Results and discussion :

3.1.^{1}HNMR Spectra in d6-DMSO:

^{1}HNMR spectrum of the ligands (L^1, L^2 and L^3) showed the following peaks : δ(6.8-8.0 ppm) assigned for the(4H) in the phenyl group, δ(2.4-4.0 ppm) are due to –CH protons, δ(3.47 ppm-1H) of –OH group in $L^1$and δ(2.47 ppm-1H) of –SH group in L^2. The absence of

the signals assigned for O–H in L^2 and L^3 is an evidence for the keto rather than the enolform.(52) The singlet band of the proton of C-H group appeared at (6.9 ppm) for L^2, and also the proton of the OH group of thiobarbituric acid (TBA) appeared at δ(12.0 ppm), are due to denote keto-enol forms(53).

3.2. MALDI-TOF spectroscopy

All the prepared compounds were analyzed using MALDI-TOF technique. The experimental and calculated molecular weights of the compounds are collected in Table (3) .Based on the obtained data , it is obvious that the experimentally determined molecular weights are either equal or matching with the theoretically calculated ones which give a clear evidence for the accuracy of the proposed structures of the prepared compounds.

Table (3):Summary of the experimentally observed molecular weights and the theoretical ones for the prepared compounds.

Compound (Chemical formula)	Calculated Molecular weight(g/mol)	Observed Molecular weight(g/mol)
$L^1(C_{11}H_8O_4N_2)$	232.20	236.35
$L^2(C_{10}H_8O_2N_4S)$	248.26	248.70
$L^3(C_{10}H_8O_3N_4)$	232.20	234.80
$OsO_2.L^3.2OH(C_{10}H_{12}N_4O_7Os)$	490.45	491.19
Ru. L^1. $Cl_3(C_{11}H_7Cl_3N_2O_4Ru)$	438.61	441.23
Ru. L^2. $Cl_4(C_{10}H_{10}Cl_4N_4O_2RuS)$	491.13	492.72
V. L^3. $Cl_3(C_{10}H_7Cl_3N_4O_3V)$	388.48	389.10
ZrO. L^2.$Cl_2(C_{10}H_7Cl_2N_4O_3SZr)$	425.38	426.28
ZrO. L^3.$Cl_2(C_{10}H_7Cl_2N_4O_4Zr)$	409.31	408.12

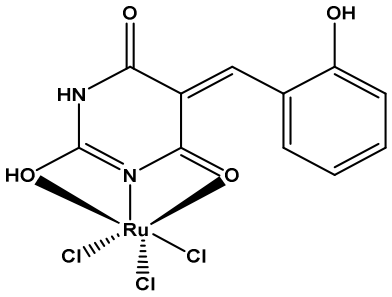
3.3.FT-IR spectra :

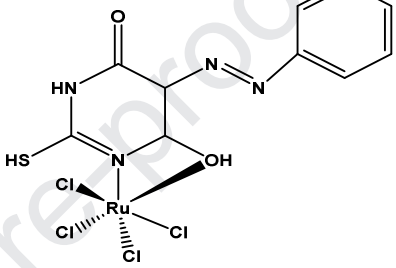
The ligands (L^1,L^2 and L^3) showed spectral bands at 3398,3325 and 3331 (cm^{-1}) respectively due to νO-H. The bands showed at 3212,3086 and 3112 (cm^{-1}) respectively are due to νN-H stretching overlapped with hydrogen bonds of the type N–H· · · O, O· · ·H–O and O–H · · ·N. The bands at 1620–1700 cm^{-1} region are assigned to *ν*C=O, and those at 1588–1595 cm^{-1} are due to *ν*C=N.The bands due to **ν**O–H · · ·N are shown in the region(2500-2850 cm^{-1}).The ligand containing sulphur (L^2) exhibited the four thioamide bands at : 1535,1392,1149 and 824 cm^{-1}**.** The presence of *ν*OH and *ν*C=O denoting keto↔ enol tautomerism, beside the presence of thioamide bands and *ν*S–H indicating thiol↔ thione tautomerism. (54,55) The νC-O bands are detected at 1232, 1297 and 1260 for L^1,L^2 and L^3 respectively. C–N stretching bands appeared 1357, 1392 and 1333 respectively. The Ligands (L^2 and L^3) show bands due to stetching vibration of the azo group (νN=N) at 1441 and 1470 (cm^{-1}) respectively.(56)

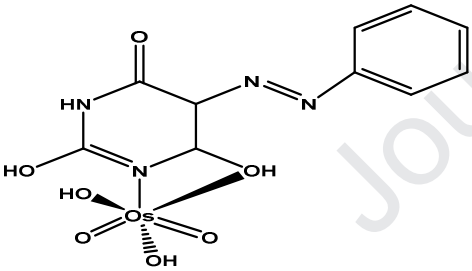
The bands due to both νN-H and **ν** C=O stretching disappeared in the IR spectra of the complexes and the appearance of new spectral bands in the regions (2400-2600 cm^{-1}),(1594-1650 cm^{-1}) and (1350-1402) are assigned for νO-H_{iminol}, ν C=N and νC-O respectively provide a strong evidence that tautomerization of the NH group with the adjacent carbonyl and thiocarbonyl groups takes place before complexation.The psudo aromaticity of the iminol

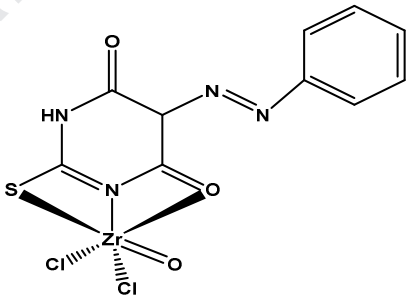
structure can stabilize the enol form as compared to the keto form.The spectra of the azo complexes do not show any shift in the frequencies of νN=N indicating that N=N do not participate in the coordination with the metal ions.The broad bands appeared at 3405,3433,3401,3440,3436 and 3451 (cm^{-1}) in , $Zr.L^3.H_2O$, $V.L^3.H_2O$, $Ru.L^1.H_2O$, $Ru.L^2.H_2O$ and $Os.L^3.H_2O$ respectively are due to the the existence of a coordinated water molecule.[57] The four thioamide bands in -azothiobarbituric acid complexes: $Zr.L^2.H_2O$ and $Ru.L^2.H_2O$ are affected on complexation with different degrees to give a proof for the M–S bonding. [58]

From the previous findings, together with the elemental analysis data, Table (2), the following structures are suggested for the prepared complexes[Figure(2)]:









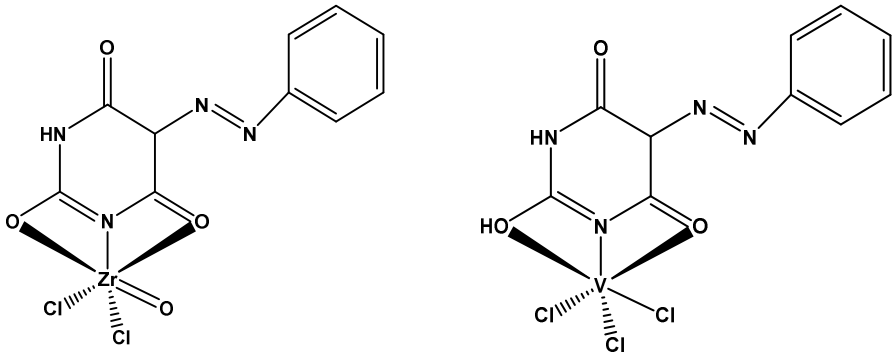


Figure (2) : The prepared complexes

3.4. Magnetism and electronic spectral studies:

The electronic absorption spectra of diamagnetic complexes $Zr(IV)O.L_2.CL_2$, $Zr(IV)O.L_3.CL_2$ and $Os(VIII)O_2.L_3.(OH)_2$ showed the bands due to π-π* at 289 ,289 and 252 nm respectively .The bands assigned to n-π* for these complexes appeared at 349 ,366 and 363 nm respectively[59].

The room temperature magnetic susceptibility measurements of the $Ru(III)L^1.CL_3$ and $Ru(III)L^2.Cl_4$ complexes showed that these complexes are paramagnetic with one unpaired electron with effective dipole moments (μeff): 1.39 and 1.74 B.M respectively. Such values of μeff gave a strong evidence for the existence of these complexes in the octahedral geometry and their trivalent nature [60].The bands showed at (327-335 nm) ,(369-375 nm) and (586-593 nm) respectively in the spectrum of Ru(III) complexes are assigned for $^2T_2g \rightarrow {}^2A_2g$, $^2T_2g \rightarrow {}^4T_2g$ and $^2T_2g \rightarrow {}^4T_1g$ electronic transitions [61].

The effective dipole moment value (μeff=2.82 BM) of the paramagnetic complex ($V.L^3.Cl_3$) agreed with the conclusion that the complex exists in an octahedral geometry [62].The electronic absorption spectrum of this complex shows an absorption band at 247 nm which is assigned for π-π* transitions. On the other hand , the absorption peaks at 402 nm and 600 nm are due to n-π* and d-d($^3T_1g \rightarrow {}^3T_2g$) transitions in an octahedral ligand field respectively[63].

3.5.Thermal analysis:

3.5.1. Thermogravimetry (TG)

The thermal stability of the ligands was studied by heating the sample at a control rate of 10 k/minute under air atmosphere except for 5-(phenyl azo) barbituric acid (L^3) the rate was 10 ^oC/minute under nitrogen atmosphere . All the prepared ligands were stable up to (187.5-236.5^oC) giving a strong evidence for the absence of lattice water [64]. Typically in TGA, the loss of lattice water occurs at low temperature in the range 60–120 ^oC, whereas coordinated water requires a temperature in the range 120–230 ^oC .Accordingly, all the prepared ligand do not contain lattice water. L^1 begins to undergo thermal decomposition at 236.2^oC and its thermogram shows Three distinct decomposition stages. The first stage started at 236.2^oC with a loss of

weight (Obs.; 7.34%,Calc.;7.32%) could be due to loss of one hydroxyl radical. The second fragmentation between 236.4 and 342.4 ^{o}C shows the weight loss (Obs.; 19.46%, Calc.; 20.0%)due to loss of the organic fragment ($CHNO^{2\bullet}$) in the form of gaseous radical product leaving carbon residue. The final stage involved the loss of another organic moiety ($C_3H_2NO^{3\bullet}$) (Obs.; 34.87%,Calc.; 39.53%) as a gaseous radical between 342.4 and 499.8^{o}C.The second ligand (L^2) starts decomposing at 187.5^{o}C in three distinct stages, the first stage started at 187.5 ^{o}C with weight loss (Obs.; 24.63%,Calc.; 23.75%) where the radical ($CHNS^{2\cdot}$) was lost.The second stage started at 340.7 ^{o}C with weight loss(Obs.; 25.34%,Calc.; 22.75%) giving out a small organic moiety ($CHNO^{2\cdot}$) as a gaseous product. In the third stage a larger organic moiety was given out ($C_6H_5^{\cdot}$) (Obs.; 50.11%,Calc.; 52.74%)leaving a carbon residue between 340.70 and 499.10 ^{o}C .For (L^3), the thermal decomposition took place in three stages of thermal degradation ; the first gave out ($C_6H_5N_2^{\cdot}$) (Obs.; 48.14%,Calc.; 45.24%) in the temperature range (193.91-220.04^{o}c), the second stage started between (302.54-324.01^{o}c) giving out the radical($O^{2\cdot}$) (Clac; 12.58%,Obs.; 12.81%),the third stage occurs between (324.01-400.00^{o}c) with weight loss (Clac; 35. 71%,Obs.; 35.446%) due to loss of an organic moiety ($C_7H_5O^{\bullet}$) as a gaseous radical, in the final stage (338.08-432.06^{o}c) another organic moiety is lost (Clac; 63.95%,Obs.; 62.25%) leaving a carbon residue.

The TGA curve of the complexes gives a three-stage decomposition pattern for $V.L^3.Cl_3$,$ZrO.L^2.Cl_2$ and $ZrO.L^3.Cl_2$ complexes. In case of the thermograms of $OsO_2.L^3.(OH)_2$ and $Ru.L^2.Cl_4$ complexes four-stage thermal degradation stages are observed. The complex $Ru.L^1.Cl_3$ showed a five stage decomposition pattern .The complex $V.L^3.Cl_3$ started to decopose in temperature range (39.9-119.1^{o}C) with weight loss (Clac; 23.16%,Obs.; 23.37%) is due to the loss of an organic moiety ($C_6H_5N^{2\bullet}$) as a gaseous product. The second stage gave out another organic moiety ($C_2H_4N_2O^{2\bullet}$) (Clac; 24.00%,Obs.; 24.44%) at 329.5^{o}C , finally the third stage occurred at 498.4 ^{o}C to give out the rest of the molecule leaving a metal oxide residue. For $ZrO.L^2.Cl_2$ the first stage occurs in the temperature range (23.6-190.3^{o}C) with weight loss(Clac; 12.85%,Obs.; 13.16%) due to loss of ($CHNO^{2\bullet}$), the second stage gave out ($CHNO^{2\bullet}$) at (190.3-407.5^{o}C),the final one gave out ($CH_2S^{3\bullet}$) at 691.5^{o}C and a residual metal oxide is obtained. The $ZrO.L^3.Cl_2$ complex starts decomposition at 189.7^{o}C indicating the loss of ($C_7H_6N_2^{2\bullet}$), the second decomposition stage gave out an organic moiety ($C_2HNO_2^{3\bullet}$) Clac; 28.84 %,Obs.; 29.28%) at 295.5^{o}C.The final decomposition stage occurs in the range (295.5-669.4^{o}C) to complete the loss of the rest of the complex yielding the metal oxide residue. The $OsO_2.L^3.(OH)_2$ complex strated the first stage at 140.1^{o}C giving out ($C_5H_5^{3\bullet}$)(Clac; 13.65%,Obs.; 13.69%), the second stage also gave an organic fragment($C_4H_4N_3O_2^{5\bullet}$) (Clac; 30.20%,Obs.; 32.30%) at 225.6^{o}C, at 392.5 ^{o}C the third stage occurs with the loss of ($CH_3NO^{3\bullet}$) (Clac; 27.10%,Obs.; 28.64%) .The fourth stage occurred at 499.5 ^{o}C leaving the residue. The $Ru.L^2.Cl_4$ complex lost a ($SH^{\cdot}$) gaseous radical(Clac; 6.68%,Obs.; 6.08%) in the first decomposition stage at 116.85^{o}C , the second stage involved the loss of ($C_8H_7N_3O^{2\bullet}$) radical at 292.18 ^{o}C,the third stage is accompanied with the loss of ($C_2H_2NO^{5\bullet\cdot}$) (Clac; 18.84%,Obs.; 19.61%) at 382.57 ^{o}C,finally the last decomposition stage gave out the rest of the molecule at 457.85^{o}C leaving the metal oxide residue. For the complex $Ru.L^1.Cl_3$ gave out ($Cl^{\cdot}$, $C_3H_3O^{3\bullet}$, $C_4H_3^{5\bullet}$and $C_2H_2NO^{3\bullet}$) leaving the metal residue at 600 ^{o}C.

3.5.2. Differential scanning calorimetery (DSC)

Typical DSC method was applied for the ligands (L^1 and L^2) and the complexes ($Ru.L^1.Cl_3$,$ZrO.L^2.Cl_3$ and $ZrO.L^3.Cl_3$), which are done under air at heating rate10 °C /min in the temperature range 25-700 ^{0}C. The heat capacity can be determined by dividing the heat flow by the heating rate. The variation of Cp versus T can be represented using Debye model as the following relations[65].

$$C_P = \alpha T^3 + \gamma T \,, \quad \frac{C_P}{T} = \alpha T^2 + \gamma \quad , \text{Cp} \simeq \text{Cv}$$

Where, α is the slope of the line and γ is the intersection of the line with y-axis (Cp axis), C_p is the specific heat at constant pressure ,C_v is the heat capacity at constant volume, γ is constant equals10^{-4}cal/gram.mole.

According to Debye model [66], $\alpha = \frac{234R}{\theta_D{}^3}$, $\theta_D = \sqrt[3]{\frac{234R}{\alpha}}$ (5)

R is the universal gas constant equals 8.3 J/mole/^{o}K and θ_D is Debye temperature, which defined as the temperature separate between the high temperature range and the low temperature range. By plotting C_p/T as y-axis and T^2 as x-axis(Figure(3)), a straight line is obtained with a slope equals α, also the intersection with y-axis gives the coefficient (γ), Table (4).

The entropy change (ΔS) for any phase change can be obtained from the relation [67]:

$$\Delta S = \Delta H / T_m \, (6)$$

Where , ΔH : the enthalpy change at any peak temperature (T_m).

The studied compounds showed exothermic peaks at lower temperatures with negative ΔS values which give an indication that the activated transition states are ordered [68].

Figure(3): Typical C_p/T against T^2 plot.

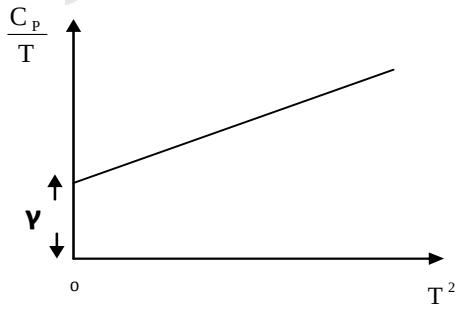


Table (4): Slopes and intercepts for DSC curves of some compounds.

3.5. Effect of pH on the electronic absorption spectra and determination of dissociation constants

The pKa values of the ligands were evaluated using Half – height method[69,70], Modified limiting absorption method[71]and Colleter method [72,73].The data obtained is collected in Table(5).

Table (5): pK's values of the ligands

Compound	λmax (nm)	Isobestic points (nm)	Half height		Modified limiting		Number of ionized protons (n)		Colleter		Average	
			pk1	pk2	pk1	pk2	n_1	n_2	pk1	pk2	pk1	pk2
L^1	420, 241	400.7,242.1	6.4	10.7	6.1	10.2	1	1	6.42	10.33	6.3±0.2	10.41±0.3
L^2	344.8,285	344.8,283.4	7.0	11.0	6.8	10.9	1	1	7.3	11.23	7.03±0.4	11.04±0.3
L^3	407, 285	388,282	5.5	9.1	6.00	9.7	1	1	6.23	9.26	5.91±0.3	9.18±0.02

Compound	Heat range °C	T_m °C	ΔH J/g	ΔS J/g.°C	$C_p = aT + b$ a	B	$\frac{C_p}{T} = \alpha T^2 + \gamma$ α	γ
L^1	25.1-341.1 569.4-611.6	82.3 589.2	-1206.462 3340.854	-14.66 5.67	0.0033	-0.8842	6.0×10^{-8}	-0.0023
L^2	22.0-341.1 519.0-581.8	96.4 459.3	-4307.51 4833.435	-44.68 10.52	0.0364	-8.4113	9.0×10^{-8}	0.0015
$Ru.L^1.Cl_3$	22.6-393.5 453.0-488.9	80.5 465.0	-4542.956 -58.9281	-47.82 -0.127	0.038	-11.085	1.0×10^{-7}	-0.0089
$ZrO.L^2.Cl_3$	23.2-352.8 494.5-593.7	95.0 550.1	-3333.924 1515.701	-35.09 2.76	0.0846	-24.157	4.0×10^{-7}	-0.0311
$ZrO.L^3.Cl_3$	33.7-147.0 215.0-507.6	95.8 466.2	-889.2633 4369.964	-9.28 9.37	0.105	-30.559	5.0×10^{-7}	-0.0383

3.6.Biological activity

3.6.1.Antimicrobial activity

The *in vitro* antibacterial activity of compounds was evaluated against both gram positive and gram negative bacteria including two gram-positive species : Staphylococcus aureus "ATCC 6538" and Staphylococcus Epidermidis"ATCC12228" and two gram-negative species :Escherichia coli"ATCC 25922" and Salmonella"ATCC 25566" .In addition, all the compounds were tested for their antifungal activity against the species: Candida albicans"ATCC 10231". Nutrient agar plates were inoculated with the test strains and the results were expressed by measuring the diameter of the zone of inhibition (in mm) around the disc and collected in Table (6).

According to the data given in Table (6) it can be concluded that, The ligand (L^2) showed great inhibitory effect on the bacterial cell growth of both gram positive and gram negative strains under study with inhibition diameters: 12,13,13 and 12mm for the species Staphylococcus aureus, Staphylococcus Epidermidis, Escherichia coli and Salmonella respectively . Also, L^2 exhibit good antifungal activity against Candida albicans with inhibition zone diameter of 15 mm. A moderate antimicrobial activity was shown by (L^3) as it affects only the gram-positive strains: *Staphylococcus Aureus and Staphylococcus Epidermidis* with inhibitory zone of diameters 17 and 24 mm respectively. However, L^3 have the greatest antifungal effect with inhibition diameter of 23 mm against Candida albicans. On the other hand,(L^1) showed the least activity as it cause an inhibition diameter of 15 mm against the fungal species under study.

The species : Escherichia coli , Salmonella and Candida albicans showed complete resistance against all the prepared transition metal complexes .However , the collected data clarified that all the complexes exhibited a moderate to good antibacterial activity against the gram-positive species :Staphylococcus aureus and Staphylococcus epidermidis. Among these complexes, "$OsO_2.L^3.(OH)_2$" gave the highest bacterial cell growth inhibitory action with diameters 16.5 and 20 mm followed by " $Ru.L^1.Cl_3$" with 13.5 and 20 mm , "$ZrO.L^3.Cl_2$" with 11.5 and 16 mm , "$V.L_3.Cl_3$" with 11 and 15 mm," $Ru.L^2.Cl_4$" with 11.5 and 15 and the complex "$ZrO.L_2.Cl_2$" with the smallest diameters 10 and 14 mm against Staphylococcus Aureus and Staphylococcus Epidermidis respectively.

The antimicrobial action of the tested ligands follows the descending order : $L^2 > L^3 > L^1$.Such variation in activity may be attributed to the presence of sulfur atom in L^2 that improve the antimicrobial effect of this compound which is a thiobarbituric acid deravative [(74)] The cell wall of bacteria contains lipids which are non-polar materials[(75)],so a successful anti-microbial agent should have some lipophilic groups. Since, the nature of the tested ligands are mainly lipophilic,they showed good antimicrobial activity.

The antibacterial activity of the tested complexes increases in the order : $OsO_2.L^3.(OH)_2 > Ru.L^1.Cl_3 > ZrO.L^3.Cl_2 > V.L^3.Cl_3 > Ru.L^2.Cl_4 > ZrO.L_2.Cl_2$, these variations in antibacterial activity cannot be clearly explained. The gram negative bacteria show higher resistance than gram positive ones, this is attributed to intrinsic resistance of the gram negative bacteria. The membrane of the gram negative bacteria functions as a barrier and prevents penetration of the drug molecules, that's why the gram-negative strains under investigation exhibited full resistance against the tested complexes [(76)]. In general all the metal(II) complexes possess higher anti-

bacterial action against gram-positive species than ligands and this may be due to the change in structure due to coordination and chelating tends to make metal complexes act as more powerful and potent bactereostatic agents, thus inhibiting the growth of the microorganisms. Moreover, coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with the donor groups within the chelate ring system formed during the coordination[68].This process, in turn, increases the lipophilic nature of the central metal atom, which favors its permeation more efficiently through the lipid layer of the microorganism, thus destroying them more aggressively. Increased activity of the metal chelates is due to the lipophilic nature of the metal ion in complexes[77]. Furthermore,The metal ion interaction is preferred with the lipidsand polysaccharides which are the important constituents of the cell wall and membranes. Other components of cell wall, many phosphates, carbonyl and cysteinyl ligands which maintain the integrity of the membrane by acting as a diffusion barrier also provide suitable sites for binding[76].This would suggest that the chelation could facilitate the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory[78].The pathogens secreting various enzymes, which are involved in the breakdown of activities, appear to be especially susceptible to inactivation by the ion of complexes. The metal complexes facilitate their diffusion through the lipid layer of spore membrane to the site of action and ultimately killing them by combining with the OH and C=N groups of certain cell enzymes. [79]

Table (6): *In vitro* Antibacterial activity of the complexes against some reference strains

Species	Inhibition Zone (mm)								
	L^1	L^2	L^3	$OsO_2.L^3.(OH)_2.$	$ZrO.L^2.Cl_2$	$ZrO.L^3.Cl_2$	$Ru.L^1.Cl_3$	$Ru.L^2.Cl_4$	$V.L^3.Cl_3$
Staphylococcus Aureus.(S.A)(ATCC 6538)	-	12	17	16.5	10	11.5	13.5	10.5	11
Streptococcus Epidermidis.(S.E)(ATCC 12228)	-	13	24	20	14	16	20	15	16
Eschirichia Coli.(E.C)(ATCC 25922)	-	13	-	-	-	-	-	-	-
Salmonilla.(S)(ATCC25566)	-	12	-	-	-	-	-	-	-
Candida Albicans.(C.A)(ATCC 10231)	15	15	23	-	-	-	-	-	-

3.6.2.Antioxidant activity

The in vitro antioxidant activity of the tested compounds was evaluated using 1,1-diphenylpicrylhydrazyl (DPPH) radical scavenging method [80] at eight different concentrations(640,320,160,80,40,20,10 and 5 µg/mL) . By analyzing the collected data in table (7),it was found that the parent ligands showed a weak to moderate antioxidant activity as indicated from the IC_{50} values:118, 49.5 and 53.6 µg/mL for L^1 ,L^2 and L^3 respectively compared

to the IC_{50} =14.2 µg/mL of the reference drug: Ascorbic acid.On the other hand, the complexes : $Ru.L^1.Cl_3$ and $OsO_2.L^3.(OH)_2$ exhibited a great antioxidant effect as compared to the reference compound with IC_{50} values:9.2 and 19.4 µg/mL respectively. The other tested complexes: $Ru.L^2.Cl_4$,$V.L^3.Cl_3$ and $ZrO.L^3.Cl_2$ gave rise to very high IC_{50} values:268.7 ,258.7 and 118.2 µg/mL respectively, which is an evidence for the very weak antioxidant activity of these complexes.

The anti-oxidant activity depend on the presence of the active groups (OH- and NH_2)[81]. Since phenolic compounds are good electron donors, they may accelerate the conversion of H_2O_2 to H_2O. Phenolic compounds are known as powerful chain breaking antioxidants. This indicated that the parent ligands (L^1,L^2 and L^3) had fair inhibitory effect on the oxidation process since they can generate free radicals.This may be related to their structure since they exist mainly in the enol or thiol forms as proved by FT-IR analysis .On the other hand, the complexes: $Ru.L^1.Cl_3$ and $OsO_2.L^3.(OH)_2$ have electron donating groups and atoms (OH- and Cl-) which enhance their antioxidant activity and consequently these complexes exhibited significant antioxidant activity at all examined concentrations[82].

Table (7):The *in vitro* antioxidant activity(DPPH scavenging %) of tested compounds using DPPH method.

Compound	Concentrations(µg/mL)								
	640	**320**	**160**	**80**	**40**	**20**	**10**	**5**	**IC_{50}**
L^1	92.10	88.70	64.30	37.00	17.30	8.60	4.50	1.30	118.00
L^2	92.40	91.10	89.60	78.60	41.10	14.40	5.70	1.90	49.50
L^3	91.20	90.40	84.70	72.20	38.50	12.70	4.90	1.40	53.60
$Ru.L^1.Cl_3$	95.00	94.80	94.50	93.90	92.30	88.40	56.30	18.10	9.20
$OsO_2.L^3.(OH)_2$	93.50	93.10	92.20	89.80	81.10	52.20	14.10	4.40	19.40
$Ru.L^2.Cl_4$	81.40	55.90	37.50	20.20	11.30	5.60	2.80	0.70	268.70
$V.L^3.Cl_3$	85.30	56.40	39.70	21.40	12.30	5.90	3.00	0.80	258.70
$ZrO.L^3.Cl_2$	90.50	82.20	68.70	32.90	13.10	6.10	3.10	0.90	118.20
Ascorbic acid	-	-	-	-	92.84	70.94	17.49	11.78	14.20

3.6.2.Anticancer activity

The synthesized compounds were tested for their *invitro* cytotoxic activity against the human breast cancer (MCF-7) cell line using the MTT assay technique. Different concentrations (ranging from 3.9 to 500 µg/ml) of the compounds were applied to the cancer cells as doses of treatment. The values of the half maximal inhibitory concentration (IC_{50}) of the compounds were listed in table (8).Based on the data collected in table (8) ,it is clear that L^2 exhibited the greatest

activity with IC_{50} : 22 µg/ml followed by L^3(IC_{50} : 28.98 µg/ml) and $[Ru.L^2.Cl_4]^-$ (IC_{50} : 37.8 µg/ml) respectively. According to the structure-activity relationship (SAR) investigations [83] , it was concluded that thiooxy pyrimidine derivatives have exhibited a more potent anticancer action than the oxy pyrimidines and this may account for the excellent activity of the compounds containing sulfur. The compounds : L^1 , $ZrO.L^3.Cl_2$ and $V.L^3.Cl_3$ showed moderate anticancer activity against the tested cells giving IC_{50} values:52.53 , 59.70 and 72.05 µg/ml respectively. On the other hand the rest of the tested drugs have a little effect on the the human breast cancer (MCF-7) cells .

Table (8):Cytotoxic activity of the compounds against MCF-7 cell line expressed as IC_{50}.

Compound	IC_{50} (µg/ml)
L^1	52.53±2.6
L^2	22 ± 0.9
L^3	28.98±3.1
$Ru.L^1.Cl_3$	203 ± 5.3
$[Ru.L^2.Cl_4]^-$	37.8 ± 1.3
$OsO_2.L^3.(OH)_2$	237± 7.4
$V.L^3.Cl_3$	72.05±5.3
$ZrO.L^2.Cl_2$	222 ± 6.8
$ZrO.L^3.Cl_2$	59.7 ± 3.4

4.conclusion:

In conclusion, our research group synthesized three biologically active ligands (L^1,$L^2$and L^3) derived from barbituric and thiobarbituric acid and six of their transition metal complexes($Ru.L^1.Cl_3$,$[Ru.L^2.Cl_4]^-$,$OsO_2.L^3.(OH)_2$, $V.L^3.Cl_3$, $ZrO.L^2.Cl_2$, $ZrO.L^3.Cl_2$) .All the prepared compounds were fully characterized and tested for their antimicrobial, antioxidant and anticancer activities. The collected data showed that L^2 is the most effective anticancer agent as compared to the other compounds against MCF-7 cells with "IC_{50}=22 µg/ml" .The ligands (L^2 and L^3) exhibited great antimicrobial action against both gram positive and gram negative species and the fungal species under study.Moreover, the complex: $Ru.L^1.Cl_3$ is recommended to be used as excellent antioxidant as seen from the DPPH radical scavenging technique.

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- The research paper focused on bioinorganic chemistry of barbiturates and thiobarbiturates.
- IR,NMR, MALDI-TOF ,UV-VISIBLE spectral methods are used to identify the prepared compounds.
- The compounds were tested for their anticancer, antimicrobial and antioxidant activities.
- The compound L^2 exhibited the greatest anticancer activity (IC_{50}=22µg/ml).
- Some of the compounds exhibited excellent antioxidant, antimicrobial(against both gram positive and negative species) and anticancer (against breast cancer) activity.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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