Structural chemistry and biological activity of some pyrimidine compounds and their transition metal complexes.

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Abstract— Some pyrimidine derivatives : 5-[Carboxy phenyl azo] thiobarbituric acid [L^1], 5-[2hydroxyphenylide] thiobarbituric acid [L^2] and of 5-[Carboxy phenyl azo] barbituric acid [L^3] and their Cu[II] ,Ni[II] and Co[II] complexes were synthesized and fully characterized using elemental analysis and spectral methods including: H^1-NMR, C^{13}-NMR, FT-IR and UV-Visible spectroscopy . Phenomenon of tautomerism was discussed using spectral methods. The electronic absorption spectra of the ligands are studied at different pH's to evaluate and discuss the dissociation constants of the prepared ligands. The compounds were tested invitro for their antimicrobial and antioxidant activity .The results showed that complexes: $Ni.L^1.2H_2O.SO_4$, $Ni.L^2.3H_2O$, $Ni.L^2.3H_2O$, $Co.L^1.2H_2O$, $Co.L^3.2H_2O$, $Cu.L^2.Cl$ and $Cu.L^3.H_2O$ moderate to good antimicrobial activity against the species: Staphylococcus Aureus [S.A], Streptococcus Pyogenes [S.P], Micrococcus Luteus [M.L], Pseudomonas aeruginosa [Ps], Proteus Mirabilis [P] and NisseriaSaprophytica [N].The parent ligands showed excellent antifungal activity against the fungi: Helminthosporiumorezae which is a harmful pathogen to rice crop. In addition, the complexes : $Ni.L^1.2H_2O.SO_4$, $Ni.L^2.3H_2O$, $Ni.L^2.3H_2O$, $Co.L^1.2H_2O$ and $Cu.L^2.Cl$ can be used as good antioxidants .

Index Terms— Bioinorganic , Nucleic acids , Pyrimidines , Barbiturates, Thiobarbiturates, Antimicrobial , Antioxidant

1 Introduction

Barbituric and thiobarbituric acid derivatives are used as precursors in the synthesis of biologically active compounds. Such barbiturate-based drugs are considered to exhibit a wide range of medicinal activities including: antimicrobial, antitubercular, anticonvulsant, antitumor and anti-inflammatory activities. In addition, they can act as enzyme inhibitors and consequently, can control many mechanisms in biological systems[1].These great activities of barbiturates can be a result of structural changes at positions N1, N3, C2 and especially C5. For example, 5-benzylidene or 5-methylene derivatives, usually prepared by their reaction with benzaldehydes or triethyl orthoformate,respectively. Moreover, a large number of 5-arylidene barbiturates and thiobarbiturates have been evaluated for their antimicrobial activity against a number of Gram-positive and Gram-negative bacteria, as well as against fungal species[2]. It was important to synthesize barbituric acid containing a diarylazo group. The chemistry of azo compounds is included with a few imperative biological reactions, for example, protein synthesis, carcinogenesis, azo reduction monoamine oxidase inhibition, mutagenic, immunochemical affinity marking, nitrogen fixation, and critical medical and industerial uses [3] .In our lab, Masoud et al [4-36] published a large number of papers about the chemistry of biologically active ligands and their complexes. Some Co[II], Ni[II] and Cu[II] complexes of three arylazo and ylide deravatives of barbituric and thiobarbituric acids have been synthesized. The present work is intended to study the structural chemistry and biological activity of arylazo and ylide derivatives of barbituric and thiobarbituric acid and their complexes utilizing: ^{1}H NMR and ^{13}C NMR spectra to confirm the proposed structure of the ligands and to support the tautomeric behavior of the ligands, 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, 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 and biological methods to evaluate both antimicrobial and antioxidant activity.

2 Experimental section

2.1 Synthesis of the ligands

Synthesis of 5-[Carboxy phenyl azo] thiobarbituric acid [L^1]

Anthranilic acid (0.01 mol) was dissolved in HCl [0.2 mol] and 25 ml distilled water. The hydrochloride compound was diazotized below 5 ^{o}c 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.

Synthesis of 5-[2hydroxyphenylide] thiobarbituric acid [L^2]

Thiobarbituric acid (0.1 mol) was dissolve in 50 ml of 0.1 M HCl. A bout 15 ml of salisaldehyde slowly added to the solution with continuous stirring.

Synthesis of 5-[Carboxy phenyl azo] barbituric acid [L^3]

0. 01 mol of anthranilic acid was dissolved in 0. 2 mol

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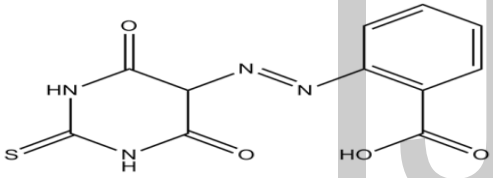
HCl and 25 mi distilled water. The hydrochloride compound was diazotized below 5 ºC with a solution of $NaNO_2$ (0.1 mol) and 20 ml distilled water. The diazonium chloride was coupled with an alkaline solution of 0. 1 mol barbituric acid / 30 ml distilled water.

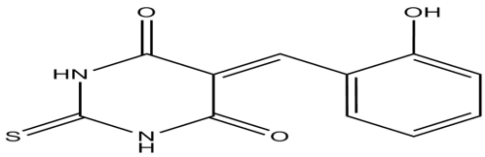
2.2 Synthesis of transition metal complexes

All complexes where prepared in the same way. The inorganic salts of (Cu, Co and Ni) as chlorides 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.

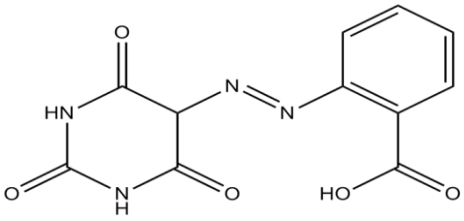
In all preparations, the reaction takes place at room temperature except for Cu. L^2.Cl complex which were refluxed for about 45 minutes. Filtration of the solid products is done through suction system and then dried in a vaccum dessicator over anhydrous $CaCl_2$. The complexes were digested and decomposed with aqua regia and the metal contents were determined either complexometrically using published procedures[37] and by means of atomic absorption spectroscopy. The chloride and sulphate contents in certain comolexes were determined by the usual Volhard method[38] and simple gravimetric method [39]respectively. The ligands used during this work are given as follows:



5-[2-Carboxy phenyl azo] thiobarbituric acid [L^1]



5-[2-hydroxyphenylide] thiobarbituric acid [L^2]



5-[2-Carboxy phenyl azo] barbituric acid [L^3]

TABLE 1: Colour, m.p [◦c] and analytical data for the prepared ligands

Compound	m. p(c◦)	Formula	Colour	[Calculated/(Found)%]			
				C	H	N	S
5-(2-Carboxy phenyl azo) thiobarbituric acid (L^1)	322	$C_{11}H_8O_4N_4S$	Orange	45.16 (45.54)	2.76 (2.87)	19.16 (19.56)	10.95 (11.2)
5-(2 hydroxy phenylide) thio barbituric acid. (L^2).	285	$C_{11}H_{10}O_4N_2S$	Buff	49.57 (49.96)	3.78 (3.42)	10.51 (10.96)	12.0 (12.4)
5-(2-Carboxy phenyl azo) barbituric acid (L^3).	288	$C_{11}H_{10}O_6N_4$	Yellow	44.89 (45.10)	3.40 (3.25)	19.04 (19.35)	- -

TABLE 2 :Elemental analysis and physical properties of the complexes

Complex	Colour	Formula	Calculated (Found) %					
			C	H	N	S	M	X
Ni. L^1. SO_4. $2H_2O$	Pale Blue	$C_{11}H_{13}O_{10}N_4S_2Ni$	27. 29 (27. 12)	2. 71 (2. 54)	11. 57 (11. 75)	13. 25 (13. 54)	11. 57 (11. 46)	19. 83 (19. 36)
Ni. L^2. 3 H_2O	Pale Blue	$C_{11}H_{15}O_6N_2SNi$	36. 5 (36. 52)	4. 18 (4. 22)	7. 74 (7. 76)	8. 86 (8. 72)	16. 21 (16. 32)	-
Ni. L^3. $3H_2O$	Yellow-Green	$C_{11}H_{16}O_9N_4Ni$	32. 46 (32. 55)	3. 96 (3. 85)	13. 75 (13. 11)	-	14. 42 (14. 53)	-
Co. L^1. H_2O	Orange	$C_{11}H_{12}O_6N_4SCo$	34. 12 (34. 54)	3. 12 (3. 14)	14. 47 (14. 60)	8. 28 (8. 30)	15. 22 (15. 35)	-
Co. L^3. H_2O	Yellow	$C_{11}H_{14}O_7N_4Co$	35. 40 (35. 62)	3. 78 (3. 40)	15. 01 (15. 12)	-	15. 79 (15. 23)	-
Cu. L^2. Cl	Brown	$C_{11}H_9O_4N_2CuCl$	39. 77 (39. 72)	2. 73 (2. 61)	8. 43 (8. 30)	-	19. 13 (19. 52)	10. 67 (10. 22)
Cu. L^3. H_2O	Green	$C_{11}H_{11}O_6N_4$ Cu	36. 82 (36. 72)	3. 09 (3. 14)	15. 62 (16. 11)	-	17. 71 (17. 56)	-

2.3 Instrumental measurements

NMR spectroscopy

NMR measurements were done using an Avance Bruker [300 MHz] instrument.

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.

UV-VIS Specroscopy

The spectrophotometric measurement in the visible and ultraviolet spectral regions were recorded using Perkin-Elmer spectrophotometer model 4B Lambada covering the wavelength range 190-900 nm . The complexes were measured in nujol mull, following the method described by Lee, Griswold and Kleinberg.

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] [40].

$xg = C \times L [R - R\circ] / 103 \times m$ (1)

$xm = xg \times M.wt$ (2)

$\mu eff = 2.84 [xm \times T]1/2$ (3)

xg= the mass susceptibility per gram sample.

C =the calibration constant of the instrument.

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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.

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.

2.4 Biological methods

Disc diffusion method

Disc diffusion technique was created by Kirby-Bauer's [41] 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 [42]. 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.

Effect of the compounds on oxidative stress

Determination of Malondialdehyde [MDA]

Malondialdehyde [MDA], a product formed due to the peroxidation and decomposition of polyenic fatty acids of the lipids,was determined by the thiobarbituric acid [TBA] test [43]. Thiobarbituric acid reactive substances [TBARS], including lipid hydroperoxides and aldehydes are expressed in terms of MDA equivalents. Under an acidic condition and elevated temperature, one molecule of MDA reacts with two molecules of TBA with the production of a pink colored product with an absorption maximum at 532 nm.

3 Results and discussion

3.1 H^1-NMR

The 1H NMR spectra of the ligands were recorded in d6-DMSO, and gave the following signals: δ[6.8-8.0 ppm] due to the four phenyl protons , δ[2.4 ppm] assigned for The S-H proton in L2 ,consequently, it predominates in the thiol form while Signals for S–H group are not detected in L1 spectrum, So L1 exist in the thione structure, δ [2.4-3.5 ppm] are due to –CH protons. The two signals : δ [6.9 ppm] for L2 of the singlet band of the proton of C-H group and δ [12.3 ppm] of the proton of the OH group of thiobarbituric acid (TBA) are denoting keto-enol tautomerism [44] . The broad band at δ [3.3–3.9 ppm] for L^2[45] is due to the OH group proton of of salicylidine. No signals assigned for O–H in the azo-ligands which is an evidence that the keto structure predominates. The absence of signal due to carboxylic proton in the azo-ligands could be due to the resonance of the acidic hydrogen between the two oxygen atoms of the carboxylic group [46].

3.2 ^{13}C-NMR

The ^{13}C-NMR spectra of the azo ligands (L^1 and L^3) were recorded in d6-DMSO, and gave the following signals: δ [158-162 ppm] [3 C] assigned for the two amide carbons and the carboxylic carbon, δ [179-180 ppm] [1 C] due to the thioamide carbon in [L1], δ [152 ppm] [1C] for the [-HN-C[O]-NH-] carbon, δ [39-40 ppm] [1C] confirmed the presence the carbon between the two carbonyl group in the barbiturate nucleus, δ[143-150 ppm] due to the carbon in the benzene ring directly attached to the azo group [-C-N=N] [1C], δ[116.5-135 ppm] assigned for the five phenyl carbons[5C].

3.2 IR spectra

The ligands [L^1,L^2 and L^3] showed spectral bands at 3439,3332 and 3563 [cm^{-1}] respectively due to νO-H. The bands showed at 3080,3213 and 3181 [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 strong bands at 1675–1720 cm^{-1} region are assigned to νC=O, and those at 1601–1666 cm^{-1} are due to νC=N.The bands due to νO–H ….N are shown in the region[2601-2925 cm^{-1}].The ligands containing sulphur [L^1 and L^2] showed the four thioamide bands in the regions : [1564-1576],[1312-1388],[1148-1196] and [832-863] cm-1 respectively. The presence of νOH and νC=O indicating keto↔ enoltautomerism, beside the presence of thioamide bands and νS–H indicating thiol↔ thione tautomerism[47].

The νC-O bands appeared at 1294, 1257 and 1301 respectively. C–N stretching bands appearat 1330, 1312 and 1338 respectively. Ligands 1 and 3 [L^1 and L^3] show bands due to stetching vibration of the azo group [νN=N] at 1431 and 1427 [cm^{-1}] respectively.

By comparing the IR spectra of the prepared ligands and those of their transition metal complexes helped to indicate the bonding sites in the complexes. The broad bands appeared at 3437,3438,3553,3563 and 3445 [cm^{-1}] in Ni.L^1.SO_4.2H_2O, Ni.L^2.3 H_2O, Ni.L^3.3 H_2O, Co.L^1. H_2O, Co.L^3. H_2O and Cu.L^3.H_2O are due to the the existence of a coordinated water molecule.[45] The four thioamide bands in -azothiobarbituric acid complexes are affected on complexation with different degrees to support the M–S bonding. [48]

Both νN-H and ν C=O bands are absent in the IR spectra of the complexes and the appearance of new spectral bands in the regions [2248-2800 cm-1],[1609-1672 cm^{-1}] and [1302-1391] are assigned for νO-Himinol, ν C=N and νC-O provides an evidence that tautomerization of the NH group with the adjacent carbonyl and thiocarbonyl groups takes place before complexation. The spectra of the azo complexes do not show any shift in the position of νN=N bands so N=N do not participate in the coordination with the metal ions.

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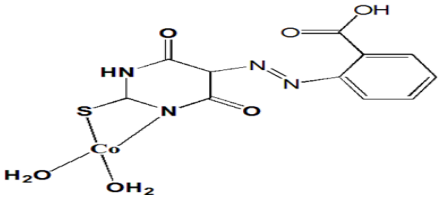
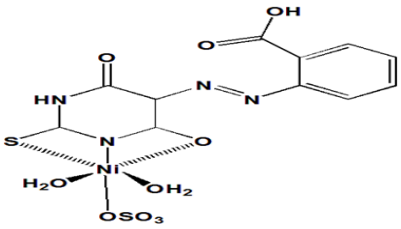
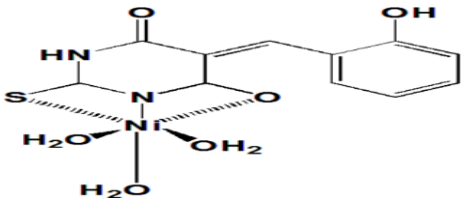
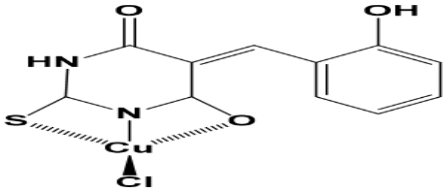
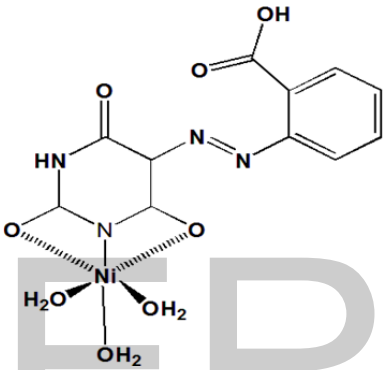
From the previous findings, together with the elemental analysis data, TABLE 2, the following structures are proposed for the prepared complexes:

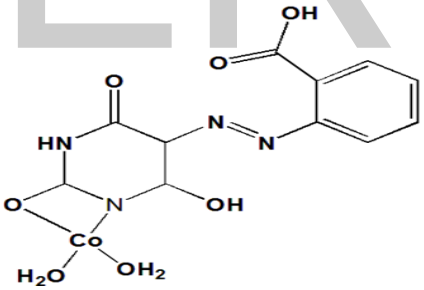












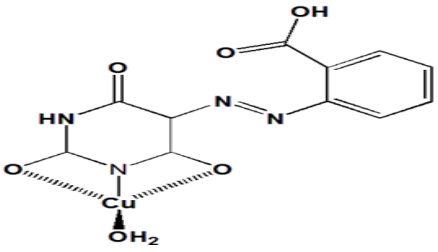


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TABLE 3 : Fundamental Infra-Red bands [cm^{-1}] of the ligands and their metal complexes.

L^1	L^2	L^3	$Cu.L^3.H_2O$	$Cu.L^2.Cl$	$Co.L^3.H_2O$	$Co.L^1.H_2O$	$Ni.L^3.3H_2O$	$Ni.L^2.3H_2O$	$Ni.L^1.2H_2O SO_4$	Assignment
3439	3332	3563	3445	3436	3563	3553	3438	3437	3437	νO-H
3080	3213	3181	-	-	-	-	-	-	-	ν N-H
2601	2925	2830	-	-	-	-	-	-	-	ν O–H · · ·N+νS-H
1576	1564	-	-	-	-	-	-	-	-	Thiamide I
1388	1312	-	-	-	-	-	-	-	-	Thiamide II
1148	1196	-	-	1044	-	1146	-	1098	1098	Thiamide III
863	832	-	768	718	773	728	775	785	784	Thiamide IV
1675	1712	1720	-	-	-	-	-	-	-	ν C=O
1601	1607	1666	1616	1609	1665	1632	1664	1638	1638	ν C=N
1294	1257	1301	1364	1367	1305	1383	1302	-	-	ν C-O
1330	1312	1338	-	-	-	-	-	-	-	ν C-N + δOH
1431	-	1427	1479	1454	1494	1477	1497	-	-	ν N=N
764	769	-	-	-	-	-	-	-	-	ν C=S
-	-	-	2797	2800	2824	2803	2396	2249	2248	νO-H$_{minol}$
-	-	-	698	640	617	650	629	628	629	νM-O
-	-	-	488	495	439	521	460	470	471	νM-N and νM-S

3.3 Magnetism , electronic and ESR spectral studies

According th the data ,the nujol mull electronic spectra of the nickel complexes $Ni.L^1.2H_2O.SO_4$., $Ni.L^2.3H_2O$. and $Ni.L^3.3H_2O$. gave bands in the wavelength ranges of 300-350 nm, 300-465 nm and 300-670 nm respectively due to $3A_2g \rightarrow 3T_1g[P]$ and $3A_2g \rightarrow 3T_1g[F]$ transitions, respectively and the magnetic moment values [3.32 and 3.42 and 3.44 B.M.], to assign a high spin octahedral structure is assigned[49].

Octahedral, tetrahedral and square-planar cobalt [II] complexes show magnetic moment between 4.7-5.2, 4.2-4.8 and 2.2-2.9 B.M., respectively[50]. The room temperature effective Bohr magneton numbers fot the cobalt[II] complexes range between [2.2-2.35 B.M].These μeff values lie in the range corresponding to one unpaired electron for the square planar stereochemistry around the Co[II],d7ion.In solution electronic absorption spectra of Co[II] complexes showed four absorption bands are indicative of D2h symmetry for the cobalt [II] d7 planar geometry [51].A well-defined strong band occurring at[318-340 nm] is assigned to the transition $2Ag \rightarrow 2B_1g$ and $2Ag \rightarrow 2B_3g$.A shoulder around 310nm and another strong band at [370-420 nm] are metal-to-ligand charge transfer bands. These are assigned to $2Ag \rightarrow 2B_2u$ and $2Ag \rightarrow 2B_3u$ transitions respectively.

The electronic absorption spectra of Cu[II] complexes, the brown complex $[Cu.L^2.Cl]$ and the green complex $[Cu.L^3.H_2O]$ gave broad bands with maxima at 336, 365 nm and 345, 378 nm respectively. The presence of the bands at 365 and 378 nm in the copper complexes may be due to the destabilization of the energy of the lone pairs of electrons on complex formation and they are assigned to the transition 2T2g→2Eg of a tetrahedral structure is further deduced from the μeff values, which equals 2.34 and 2.26 B.M, respectively.

The room-temperature ESR of $Cu.L^2.Cl$ and $Cu.L^3.H_2O$ complexes are nearly of similar spectral pattern. All are isotropic in nature with gs= 2.02 and 2.019 respectively and A=1000 for both complexes. This confirm a perfect tetra hedral geometry of these complexes

TABLE 4 : Nujol mull wavelengths, magnetic moments , geometry and Room temperature ESR spectral data of the metal complexes

Complex	Nujol mull λ (nm)	μeff	Geometry	g_s	A
$Ni.L^1.2H_2O.SO_4$.	347,424,301	3.32	Octahedral	-	-
$Ni.L^2.3H_2O$	301,347,465	3.42	Octahedral	-	-
$Ni.L^3.3H_2O$	305,346,670	3.44	Octahedral	-	-
$Co.L^1.H_2O$	305,318, 347,420	2.35	Square Planar	-	-
$Co.L^3.H_2O$	310,345,333,379	2.22	Square Planar	-	-
$Cu.L^2.Cl$	336,365	2.34	Tetrahedral	2.02	1000
$Cu.L^3.H_2O$	345,378	2.26	Tetrahedral	2.019	1000

3.4 THERMAL ANALYSIS

3.4.1 Thermogravimetry (TG)

The thermal stability of the ligands was studied by heating the sample at a control rate of 15 oC per minute under nitrogen atmosphere. 5-[2-carboxy phenyl azo] thiobarbituric acid [L^1] is stable up to 200oC indicating the absence of lattice water [52].The TGA data of the ligands are collected in Table 5. 5-[2-hydroxyphenylidene] thiobarbituric acid [L^2] and 5-[2-carboxy phenyl azo] barbituric acid [L^3] must contain lattice water. The loss below 100°C is attributed to moisture and hygroscopic water [53]. L1 starts decomposing above 200oC and thermogram exhibits three distinct decompositions at 200 and 480 oC.

According to the data collected in Table 5, the TGA curve of the complexes gives a three-step decomposition pattern except $Cu.L^3.H_2O$ complex which gave four-step and $Ni.L^3.2H_2O$ with five step decomposition processes. The thermogram of $Ni.L^1.SO_4.2H_2O$ complex showed three distinct decomposition steps .

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Table 5 : Thermal decomposition data of the ligands

Compound	steps	Temperature range(°C)	Mass loss/ %	Cal. Mass loss/%	Probable assignments
L^1	I	226.34-299.48	4.201	4.11	Loss of (-CH)
	II	299.48-334.92	36.145	35.00	Loss of($C_2H_2N_2OS^{2-}$)
	III	334.92-598.78	21.329	21.92	Loss of ($C_5H_4^{4-}$)
L^2	I	101.80-115.92	2.295	-	Loss of Moisture
	II	158.29-196.14	9.976	9.013	Loss of (H_2O & C_2^{4-})
	III	258.85-447.26	23.093	22.15	Loss of ($CHNS^{2-}$)
	IV	447.26-599.51	37.159	34.92	Loss of ($C_6H_5O^{-}$)
L^3	I	34.69-41.47	0.747	-	Loss of Moisture
	II	67.71-95.65	5.419	6.123	Loss of (H_2O)
	II	274.58-338.08	35.446	35. 71	Loss of ($C_7H_5O^{\bullet}$)
	IV	338.08-432.06	16.082	14.96	Loss of ($CH_2NO^{\bullet}$)

Table 6 : Thermal decomposition data of the complexes

Compound	steps	Temperature range(°C)	Mass loss/ %	Cal. mass loss/%	Probable assignments
$Ni.L^1.SO_4.2H_2O$	I	92.84-139.66	23.668	25.00	Loss of ($C_7H_5O_2^{\bullet}$)
	II	139.66-202.38	8.85	8.88	Loss of ($CHNO_2^{\bullet}$)
	III	307.79-340.06	2.748	2.725	Loss of (CH)
$Ni.L^3.3H_2O$	I	88.30-133.06	16.219	15.47	Loss of ($CHO_2^{\bullet}$) and moisture.
	II	133.06-188.02	6.15	6.88	Loss of (N_2^{2-})
	III	188.02-333.91	7.493	6.90	Loss of ($CO2^{\bullet}$)
	IV	333.91-359.29	11.895	11.898	Loss of ($CH_3N_2^{3\bullet}$)
	V	359.29-508.13	7.228	-	Loss of rest of the molecule
$Co.L^1.2\ H_2O$	I	23.71-61.57	8.234	-	Loss of Moisture
	II	288.73-348.34	47.225	49.07	Loss of ($C_9H_6N_2O_3^{2\bullet}$)
	III	348.34-598.67	32.775	-	Loss of rest of the molecule
$Co.L^3.2H_2O$	I	58.48-118.86	10.227	-	Loss of Moisture
	II	314.94-366.57	63.333	62.44	Loss of ($C_{10}H_6N_2O_4^{4\bullet}$)
	III	366.57-556.44	21.295	-	Loss of rest of the molecule
$Cu.L^3.H_2O$	I	97.59-132.11	7.574	7.80	Loss of ($CO^{2\bullet}$)
	II	136.60-154.28	3.254	5.017	Loss of ($HO^{\bullet}$)
	III	307.79-340.06	46.239	44.053	Loss of ($C_9H_6N_2O_4^{\bullet}$)
	IV	340.06-361.67	13.445	-	Loss of rest of the molecule

3.4.2. Differential scanning calorimetery [DSC]

Typical DSC curves are obtained for 5-[2-carboxy phenyl azo] barbituric acid [L^3] and its complexes, which are done under a flow of N_2 at heating rate10 °C /min in the temperature range 25-200 0C.From the experimental curves one can notice that there are no glass transition temperatures [Tg] for the compounds under study, where the crystallization temperatures [Tc] for L^3 and its complexes are at 122 ^{0}C for L^3 and 162 ^{0}C, 120^{0}C and 122^{0}C for $Cu.L^3.H_2O$,$Ni.L^3.2H_2O.SO_4$ and $Co.L^3.2H_2O$ respectively. The heat capacity can be evaluated by dividing the heat flow by the heating rate. The variation of Cp against T can be represented using Debye model as the following relations[54]:

,

Where, α is the slope of the line and γ is the intersection of the line with y-axis [Cp axis], Cp is the specific heat at constant volume, γ is constant equals10-4cal/gram.mole.

According to Debye model [55].

$$\alpha = \frac{234R}{\theta_D^{\ 3}} \qquad \theta_D = \sqrt[3]{\frac{234R}{\alpha}}$$

R is the universal gas constant equals 8.3 J/mole/oK and θ_D is Debye temperature, which defined as the temperature separate between the high temperature range and the low temperature range. By plotting Cp/T as y-axis and T^2 as x-axis, a straight line is obtained with a slope equals α, also the intersection with y-axis gives the coefficient [γ], Table [7].

Table 7: Slopes and intercepts for DSC curves of L3 and its complexes

Compound	$C_p = aT + b$		$\frac{C_P}{T} = \alpha T^2 + \gamma$	
	A	B	γ	A
L^3	0.01768	-0.2260	-0.5753	5.472 x 10^{-6}
Co- L^3	0.02186	-1.759	-0.2092	1.96x10^{-6}
Cu- L^3	1.477	-522.6	-0.7276	5.806 x 10^{-6}
Ni- L^3	0.04612	-10.89	-0.002368	1.423 x 10^{-7}

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

The pKa values of the ligands were calculated by means of Half-height method[56],Modified limiting absorption method[57] and colleter method[58]and collected in Table 8.

Table 8 : 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	429.5,267.5,228	430,265,229	7.1	10.2	7.06	10.6	1	1	7.42	10.13	7.2±0.1	10.3±0.3
L^2	378.5,265	259,215	5.0	10.9	6.23	11.0	1	1	5.96	10.98	5.7±0.7	10.96±0.03
L^3	402.5,214	400,235	6.1	8.8	6.13	8.6	1	1	6.16	8.43	6.13±0.03	8.6±0.2

3.6. Molecular modeling

Molecular modeling utilizes theoretical methods and computational techniques to model the behaviors of molecules.[59] .The data were evaluated by optimizing bond lengths, bond angles and dihedral angles of the ligands.

Barbituric and thiobarbituric acids coordinate to various metal ions through N[1], O[8] and O[23] in case of barbituric acid derivatives [L^3] and through N[5],O[8] and S[10] in case of L^1 and through N[1],O[8] and S[12] in case of L^2. These atoms carry more electronegative charge indicating active sites for

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coordination. The charge density values for N[5], O[8] and S[10] in L1 are -0.230, -0.218 and -0.135 respectively and those for N[1], O[8] and S[12] in case of L2 are -0.285, -0.143 and -0.125 respectively while for N[1], O[8] and O[23] in [L3] are -0.175, -0.152 and -0.189 respectively. For all ligands the bond lengths are approximately 1.4 A°. This value decreases for N[1]-H[2]= 1.012, C[4]-O[8]= 1.208, C[3]-O[9] = 1.208, N[5]-H[6]= 1.012, N[12]-N[13]= 1.248, C[11]-H[24]= 1.113, C[17]-H[26] C[18]-H[25],and C[16]-H[27]= 1.100 and O[21]-H[22]=0.992 in L1. For L2 the average bond length decreases for N[1]-H[2]and N[5]-H[6]=1.012, C[3]-O[8], C[22]-O[23], and C[4]-O[7] =1.208, C[10]-H[24], C[15]-H[23],C[14]-H[25], C[16]-C[17]and C[16]-H[22]=1.100. Also, short bonds in L3 are N[1]-H[2]and N[5]-H[6]=1.012, C[4]-O[7]and C[3]-O[8]=1.208, C[9]-H[24]=1.113, N[10]-N[11]=1.248, C[16]-H[25], C[14]-H[27], C[15]-H[26]and C[13]-H[28]=1.100 and O[19]-H[20]=0.972.

The bond angles of the prepared compounds were found to be around 110◦ and 120◦.These angles are attributed to sp2 and sp3 hybridization of the atoms. The dihedral angles indicated the near planarity of the ligand molecules, where the angles were of nearly 180◦ and 0◦. The difference is due to the syn and anti-positions of the ligands atoms, where the anti gives 180◦ and the syn gives 0◦.

$X = -[EHomo+ELumo]/2$

$\Lambda = [ELumo-EHomo]/2$

$\sigma = 1/\Lambda$ $\quad Pi = -X$

EHOMO is a quantum chemical parameter which confirm the electron donating ability of the molecule. The energy of the lowest unoccupied molecular orbital, ELUMO, indicates the ability of the molecule to accept electrons. The parameters, X and Pi are related to each other. The inverse of the universal hardness is known as the softness, σ[60]. All these quantum chemical parameters were evaluated for the ligands. Based on the frontier molecular orbital theory, the chemical reactivity depend on interaction between HOMO and LUMO levels of the reacting species. The higher the value of EHOMO of a compound, the easier it can donate its electrons to the empty d-orbital of metal ion.

Based on the calculations given in Table 9, high energy EHOMO is assigned for the ligands, which are expected to have an excellent coordination ability to metal ions.

The HOMO level is mostly localized on N[5],O[8] and S[10] in case of L1, N[1],O[8] and S[12] in case of [L2] and N[1],O[8] and O[23] in case of [L3].This means that these moieties with high coefficients of HOMO density were directed toward the metal ions. The energy gap [HOMO-LUMO gap, ΔE] indicates stability. The high value of ΔE confirmed that the ligands has high tendency to bind to the metal ion. Absolute hardness, Λ and softness, σ are helpful in measuring the molecular stability and reactivity. The harder the molecule, the higher the energy gap, while as softness increases, the energy gap decreases. It can be concluded that the ligands have a proper value σ value has a good tendency to coordinate to metal ions effectively. This is also confirmed from the calculated chemical potential, Pi.

Table 9 : Molecular modeling parameters of the ligands

Ligand	Parameter						
	Calculated value						
	HOMO (e.v)	LUMO (e.v)	ΔE(e.v)	X(electro-negativity)	P_i (chemical –potential)	π(hardness)	σ (softness)
L^1	-9.8	-5.5	4.3	7.63	- 7.63	2.17	0.46
L^2	-8.6	-3.8	4.4	6.24	- 6.24	2.4	0.42
L^3	-9.0	-4.1	3.9	6.54	- 6.54	23.47	0.41

3.7. Anti-microbial activity

3.7.1 Anti-bacterial activity

The antibacterial activity of compounds was evaluated against both gram positive and gram negative organisms. Nutrient agar plates were inoculated with the test strains: Staphylococcus Aureus [S.A], Streptococcus Pyogenes [S.P], Micrococcus Luteus [M.L], Pseudomonas aeruginosa [Ps], Proteus Mirabilis [P] and NisseriaSaprophytica [N] .

According to the data obtained, it can be concluded that, the ligands [L1,L2 and L3]had no effect on both gram positive and gram negative strains. Staphylococcus Aureus.[S.A] and Pseudomonas aeruginosa.[Ps] species show complete resistance for all tested compounds.The species S. aureus cause several infections including endocarditis, osteomyelitis, and arthritis. S. aureus is one of the major reasons of hospital originated nosocomial infections [61]. The complexes of copper and $Co.L^1.Cl$ complex show no antibacterial activity for the bacterial species under study. However, the complexes: $Ni.L^1.SO_4.2H_2O$, $Ni.L^2.3H_2O$, $Ni.L^3.3H_2O$ and $Co.L^3.2H_2O$ affect on the bacterial growth of both gram positive and gram negative bacteria. The $Ni.L^1.SO4.2H_2O$ complex showed a relatively good antibacterial activity against a gram positive bacteria [Micrococcus Luteus.[M.L]] with inhibition diameter of 10 mm and gram negative bacteria [Proteus Mirabilis.[P] and NisseriaSaprophytica.[N]] with inhibition diameter of 10 and 11 mm respectively,while the species: Staphylococcus Aureus [S.A], Streptococcus Pyogenes [S.P] and Pseudomonas aeruginosa [Ps]showed complete resistance for this complex. Also, $Ni.L^2.3H_2O$ complex showed the relatively highest antibacterial activity against Streptococcus Pyogenes.[S.P] which is a gram positive species with inhibition diameter of 12 mm ,in addition it showed a fair activity against Micrococcus Luteus.[M.L] [grampositive] and NisseriaSaprophytica.[N] [gram negative]species with inhibition diameters of 8 mm and 9 mm, respectively. However this complex did not affect the gram positive species: Staphylococcus Aureus [S.A] and the gram negative species : Pseudomonas aeruginosa [Ps], Proteus Mirabilis [P]. The complex Ni.L3.3H2O affected only the bacterial growth of the gram positive species Micrococcus Luteus.[M.L] with inhibition diameter of 9 mm, in contrast this complex had no effect on the species Staphylococcus Aureus [S.A], Strepto-

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coccus Pyogenes [S.P], Pseudomonas aeruginosa [Ps], Proteus Mirabilis [P] and NisseriaSaprophytica [N].The Co.L3.2H2O complex showed activity against Streptococcus Pyogenes.[S.P] only with inhibition diameter of 11 mm.The antibacterial activity of the tested compounds increases in the order : $Ni.L^2.3H_2O$ > $Ni.L^1.SO_4.2H_2O$ > $Co.L^3.2H_2O$ > $Ni.L^3.3H_2O$, these variations in antibacterial activity may be related to the differences in their structures. 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 derivative molecules [62].The cell wall of bacteria is made of lipids which are non-polar materials,so a successful anti-microbial agent should have some lipophilic groups.Since, the nature of the tested complexes are mainly lipophilic ,they showed good antimicrobial activity. In general all the metal[II] complexes possess higher antimicrobial activity 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 [62].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 [63]. Furthermore, the metal ion interaction is preferred with the lipids and 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 with metal ions[64].This would suggest that the chelation could enhance the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory[65].The pathogens secreting various enzymes, which are involved in the depression 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.

3.7.2. Antifungal activity

The prepared compounds showed significant antifungal activity against the species Helminthosporiumorezae, the rice brown spot pathogen, produces a host specific toxin. Its toxin may play an important role in the suppression of the defense mechanisms of the host to permit colonization of the pathogen [66] .Most of the prepared compounds showed significant antifungal activity against the species under study.

The parent ligands [L^1,L^2 and L^3] showed the greatest antifungal activity with inhibition zones : 1.48, 3.5 and 3.43 cm respectively as compared to the control.Among the metal complexes, the nickel complexes[$Ni.L_1.SO_4.2H_2O$, $Ni.L_2.3H_2O$ and $Ni.L_3.3H_2O$] showed good resistance against the species under study with inhibition zones 1.33, 1.23 and 1.03 cm respectively, while the $Co.L^1.2H_2O$ gave an inhibition zone of 2.03 cm as compared to the control. The copper complexes [$Cu.L^2.Cl$ and $Cu.L^3.H_2O$] and $Co.L^3.2H_2O$ showed no resistance .Large size carboxylic acid moieties are known to show excellent anti-microbial activity such as L^1 and L^2 The rigidity of the large moiety, probably, was one of the factors responsible for the enhancement of activity.

Table 10 : In vitro Antibacterial activity of the complexes against some reference strains

Species	Inhibition Zone (mm)			
	$Ni.L^1.2H_2O.SO_4$	$Ni.L^2.3H_2O$	$Ni.L^3.3H_2O$	$Co.L^3.2H_2O$
Staphylococcus Aureus.(S.A)	-	-	-	-
Streptococcus Pyogenes.(S.P)	-	12	-	11
Micrococcus Luteus.(M.L)	10	8	9	-
Pseudomonas aeruginosa.(Ps)	-	-	-	-
Proteus Mirabilis.(P)	10	-	-	-
NisseriaSaprophytica.(N)	11	9	-	-

Table 11: Minimal inhibitory concentrations [MICs] [mg/ml] of the complexes against bacteria

Species	Minimal inhibitory concentrations (MICs)(mg/ml)						
	$Ni.L^1.2H_2O.SO_4$	$Ni.L^2.3H_2O$	$Ni.L^3.3H_2O$	$Co.L^1.2H_2O$	$Co.L^3.2H_2O$	$Cu.L^2.Cl$	$Cu.L^3.H_2O$
Staphylococcus Aureus.(S.A)	-	-	-	-	-	-	-
Streptococcus Pyogenes.(S.P)	-	90	-	-	80	-	-
Micrococcus Luteus.(M.L)	80	90	90	-	-	-	-
Pseudomonas aeruginosa.(Ps)	-	-	-	-	-	-	-
Proteus Mirabilis.(P)	90	-	-	-	-	-	-
NisseriaSaprophytica.(N)	80	90	-	-	-	-	-

Table [14]: In vitro Antifungal activity and Minimal inhibitory concentrations [MICs] [mg/ml] of the compounds against Helminthosporiumorezae species.

Compound	Inhibition Zone (Cm)	(MICs)(mg/ml)
L^1	1.84	50
L^2	3.5	60
L^3	3.43	70
$Ni.L^1.2H_2O.SO_4$	1.33	80
$Ni.L^2.3H_2O$	1.23	80
$Ni.L^3.3H_2O$	1.03	80
$Co.L^1.2H_2O$	2.03	90
$Co.L^3.2H_2O$	-	-
$Cu.L^2.Cl$	-	-
$Cu.L^3.H_2O$	-	-

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3.8. Anti-oxidant activity

The parent ligands [L^1,L^2 and L^3] show no activity on MDA concentrations as compared to the control, while the complexes[Ni.L^1.2H2O.SO4, Ni.L^2.3H2O, Ni.L^3.3H2O, Co.L^1.2H2O and Cu.L^2.Cl] showed significant decreases in MDA concentrations by about91.6%,83.13%,88.74%, 83.1% and 94.38 % respectively as compared to the control. However, the complexes [Co.L^3.2H_2O and Cu.L^3. H_2O] caused significant increases in MDA concentrations by about three times and four times respectively as compared to the control.

The anti-oxidant activity depend on the presence of the active groups [OH- and NH_2][67-71]. 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 no effect on the oxidative stress since they did not generate free radicals. This may be related to their structure since they exist in the keto form as proved by IR analysis .On the other hand, after complexation process, the ligands exist in the enol-form which enable the metal complexes[Ni.L^1.2H_2O.SO_4,Ni.L^2.3H_2O,Ni.L^3.3H_2O, Co.L^1.2H_2O and Cu.L^2.Cl] to act as antioxidants with different degrees following the order : Cu.L^2.Cl > Ni.L^1.2H_2O.SO_4> Ni.L^3.3H_2O > Ni.L^2.3H_2O> Co.L^1.2H_2O.These variations in their antioxidant power may be related to their structures were Cu-L2contains the largest number of active groups and thus showed the highest antioxidant power. On the hand, the complex Co.L^1.2H_2O showed the least antioxidant activity as it contains the smallest number of active groups. In the literature, the antioxidant capacity generally increases with increasing number of –OH groups. The concentrations of complexes that decreases MDA concentration to half of its initial value was expressed as IC50 values. The complexes which increased the oxidative stress [Co.L^3.2H_2O and Cu.L^3.H_2O] may be used as anticancer or pesticides since they may induce the apatotic process. However, the complexes which reduced the oxidative stress [Ni.L^1.2H_2O.SO_4 , Ni.L^2.3H_2O , Ni.L^3.3H_2O , Co.L^1.2H_2O and Cu.L^2.Cl] can be used as drugs with no effect on cell death.

Table 13 : IC50 values for the complexes [Ni.L^1.2H_2O.SO_4,Ni.L^2.3H_2O,Ni.L3.3H_2O, Co.L^1.2H_2O and Cu.L^2.Cl]

Complexes	IC_{50} (μM)
Ni.L^1.2H_2O.SO_4	125
Ni.L^2.3H_2O	281
Ni.L^3.3H_2O	223
Co.L^1.2H_2O	398
Cu.L^2.Cl	239

4 Conclusion

In conclusion, our research group synthesized and characterized some barbituric and thiobarbituric acid derivatives which were used as ligands to prepare six transition metal complexes containing: Ni[II] ,Cu[II] and Co[II] ions. The structures of the prepared compounds and geometries of the complexes were confirmed by means of a combination of spectroscopic techniques together with the magnetic susceptibility measurements. The parent ligands [especially L^3] showed excellent antifungal activity and can be recommended as fungicides against Helminthosporiumorezae species. On the other hand, the complex: Ni.L^1.2H_2O.SO_4 can be used as a good antioxidant. The complexes which increased the oxidative stress rate can be used as anticancer drugs in our future work.

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