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Synthesis, Structural Study, Antimicrobial Activity and Theoretical Treatment of 3d-metal Complexes Involving Schiff Base of Piperonal Derivative

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Abstract:

New VO (II), Cr (II), Co (II), Ni (II), Cu (II) and Zn (II) Schiff base complexes derived from piperonal have been synthesized and characterized by spectroscopic methods, conductivity, metal analyses and magnetic moment measurements.

The nature of the complexes formed in ethanolic solution was study following the molar ratio method. From the spectral studies, Octahedral geometry was suggested for all prepared complexes except Vanadium (IV) and zinc (II) complexes have square pyramidal and tetrahedral geometry respectively, Structural geometries of these compounds were also suggested in gas phase by using hyper chem-8 program for the molecular mechanics and semi-empirical calculations.

The heat of formation and binding energy for the prepared compounds was calculated by using PM3 and ZINDO/1 methods. The method of PM3 was used for evaluate the vibration spectra for the imine and starting material as authentic compound.

Preliminary *in vitro* tests for antibacterial and antifungal activity show that most of the prepared compounds display good activity to *(Staphylococcus aureus)*, *(Escherichia coli)* and *(Candida albicans)*

Keywords: Schiff base, Piperonal, hyper chem-8, *in vitro*, Activity.

الخلاصة:

تم تحضير الليكاند 2-hydroxy phenyl piperonalidene ومعقداته مع بعض الايونات الفلزية وتم تشخيصها باستخدام الطرق الفيزيائية المناسبة وأطياف الأشعة تحت الحمراء و تقنية الامتصاص الذري أللهبي و قياسات التوصيلية الكهربائية فضلا عن الحساسية المغناطيسية.

تم كذلك دراسة طبيعة المعقد المتكون في محلول الايثانول بأتباع طريقة النسبة المولية. من الدراسات الطيفية تم اقتراح الشكل الهندسي الثماني السطوح لجميع المعقدات ماعدا الخارصين الذي له شكل رباعي السطوح و الفناديوم له شكل هرم مربع القاعدة.

أجريت معالجة تكون المعقدات نظريا في الطور الغازي باستخدام برنامج (Hyperchem-8) بتطبيق الميكانيك الجزيئي وشبه التجريبي في الحساب وذلك باستخدام الدوال PM3 و ZINDO/1 لحساب حرارة التكوين وطاقة الترابط لليكاند ومعقداته المحضرة.

وجرى حساب التردد الاهتزازي نظرياً باستخدام الدالة PM3 لقاعدة شف ومقارنتها مع القيم المقاسة عمليا باستخدام Orthohydroxy aniline كمركب قياسي. وتم إجراء التقييم الحيوي لهذه المركبات المحضرة ضد أنواع منتخبة من البكتريا والفطريات *(Escherichia. Coli, Staphylococcus aureus, Candida albicans)* وبتركيزين مختلفين و أظهرت النتائج التأثير المتداول للفعالية لليكاند و بعض معقداته.

Introduction:

Schiff bases are utilized as starting materials in the synthesis of industrial and biological compounds [1-5].There is enormous interest presently in the field of coordination chemistry of later **3d** transition metals with Schiff bases; they have also been used as biological models [6], oxygen carriers and drugs [7]. Earlier work reported that some drugs showed increased activity, when administered as metal complexes rather than as organic compounds [8,9].

The wide range of applications of the ligand and its complexes was around our interest to prepare a new ligand formed by the condensation of 2-hydroxy aniline with piperonal.

This ligand system has both nitrogen and oxygen donor sites. It coordinates with the metal ion as a bidentate manner through enolic moiety and nitrogen atoms of azomethaine. The choice of piperonal for the aldehyde moiety in these preparations stemmed from the fact that many compounds containing the 3,4-methylenedioxy group have some biological activity[10].

Experimental:

All the chemicals used were analytical analar and of highest purity available .

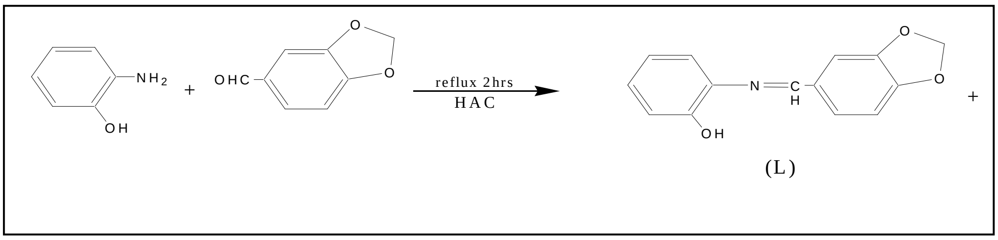
The metal analyses of the separated solid chelates for metal content were performed by using AA-680Shimadzu Atomic Absorption Spectrophotometer. The electronic spectra of the prepared compounds were recorded on a Shimadzu Uv-160 Spectrophotometer. FTIR spectra of the samples were recorded using IR Prestige-21Spectrophotometer as KBr discs. Magnetic susceptibility measurements of the complexes in the solid state were determined using Burker BM6 instrumentation at room temperature.

The molar conductance of the complexes was measured in DMF as a solvent at room temperature using WTW conductometer type. Melting point apparatus of Gallen Kamp M.F.B-60 was used to measure melting points of all prepared compounds.

Synthesis of 2-hydroxy phenyl piperonalidene and its metal complexes:

A mixture of (0.15g, 1 mmole) of piperonaldehyde with (0.064 g, 1 mmole) of 2-hydroxy aniline was dissolved in (25 ml) of absolute ethanol, then to this mixture three drops of glacial acetic acid were added as catalyst. The resulting mixture was refluxed for two hours. The precipitate was separated by filtration and washed with diethyl ether and recrystallized from ethanol, then dried under vacuum; the physical properties are shown in (Table 1). The structure of the proposed ligand (L) is shown in Scheme (1).

Scheme (1): Synthesis of 2-hydroxy phenyl piperonalidene



Synthesis of complexes:

Imine complexes under investigation were synthesized as follows: The ligand dissolved in (15 ml) of absolute ethanol, to which drops of aqueous solution of potassium hydroxide (1%) were added as a catalyst, followed by the addition of (10 ml) of metal salt ethanolic solution. The reaction

molar ratio was (1:2) for vanadium, cobalt, Nickel, zinc complexes and (1:3) for chromium complex.

The mixture was refluxed for 90 minutes, the colour products were filtered and washed several time with ethanol then dried under vacuum at 50°C for two days, the physical properties are shown in (Table-2).

Study of complex formation in solution:

Complexes of imine with metal ions were studied in solution using ethanol as a solvent, in order to determine the concentration of metal to the ligand ratio in the complex following molar ratio method [11]. A series of solutions were prepared having a constant concentration 10^{-3} M for each metal ion and ligand.

The ratio was determined from the relationship between the absorption of the absorbed light and mole ratio of (M/L). The results of the complexes formation in solution were listed in (Table-1).

Table-1: Physical data of ligand (L) and its metal complexes

Comp.	Colour	m.p. °C	Yield%	Molar ratio M:L	Metal percentage		Suggested Molecular formula
					found	Calc.	
L	Brown	101-103	88	-	-	-	$C_{14}H_{11}NO_3$
VOL	Olive green	307d	94.21	1:2.5	12.29	11.9	$[VOL_2].H_2O$
CrL	Dark green	188d	60.81	1:3.5	4.78	5.77	$[CrL_3]$.3EtOH
CoL	Brick-red	164d	71.24	1:2	8.67	8.29	$[CoL_2(H_2O)_2]$.3EtOH
NiL	Green	153d	95.53	1:2	8.60	8.83	$[NiL_2(H_2O)_2]$.EtOH
CuL	Brown	>300	54.11	1:2.5	10.57	10.18	$[CuL_2(H_2O)_2]$.EtOH
ZnL	Light brown	82-84	74.51	1:2	11.66	11.64	$[ZnL_2].H_2O$

Theoretical treatment computational chemistry:

Hyperchem-8 program [12] is a sophisticated molecular modeller, editor and powerful computational package that are known for its quality, flexibility and easy of use, using 3D visualization and animation with quantum chemical calculation, mechanic and dynamic. Hyperchem-8 can plot orbital functions resulting from semi-empirical quantum mechanical calculation as well as the electrostatic potential.

The total change density or the total spin density can also be determined during a semi-empirical calculation.

This information is useful in determining reactivity and correlating calculation results with experimental data. Hyperchem offers ten semi empirical

molecular orbital methods, with options for organic and main group compounds, for transition metal complexes and spectral simulation [13,14]. PM3 level of semi-empirical method was used for calculation the heat of formation ΔH_f^o and binding energy ΔE_b^o for all metal complexes.

Antibacterial and Antifungal activity:

Disc diffusion method was used for screening the ligand and its complexes **[15]** for primary selection of the compounds as therapeutic agents.

These complexes tested against gram positive *Staphylococcus aureus*, Gram-negative *Escherichia Coli* and pathogenic fungus *Candidia albicans* in different concentration

Nutrient agar plates were incubated with DMSO of an appropriate dilution of the tested culture and the
plates were incubated at the appropriate temperature for 24 hrs.

Results and Discussion:

A. Chemistry:

Stable complexes were isolated in all cases based on the metal analysis data, spectroscopic spectra, molar conductance and magnetic susceptibility studied, the general formula of the complexes can be depicted as; $[ML_2].H_2O$ where M=VO,Zn; $[ML_2(H_2O)_2].nEtOH$ where M=Co,Ni.Cu; n=3,2,1 respectively and $[CrL_3].3EtOH$.

The piperonalidene derivative is a potential ligand capable to form chelating group through oxygen of hydroxyl moiety and nitrogen of azomethaine group **[16,17]**. So it expected that FT-IR measurements are highly informative with respect to the complexation behaviour with various metal ions. The characteristic frequencies of the free ligand and its complexes were readily assigned based on comparison with literature references [16,18].

The ligand (L) exhibited a strong band at (1627) cm^{-1} which was ascribed to stretching of azomethiane group **[16,19]** and the spectrum showed a band at (655) cm^{-1} assigned to the out of the plane γ-OH bending vibration [16].

This assignment is supported by disappearance of the band when hydrogen is replaced by the metal. The phenolic C-O stretching asymmetric vibration that appeared at (1253) in the ligand [19,20], underwent a shift toward higher frequencies with splitting in all complexes. This shift confirms the participation of oxygen in C-O-M bond **[16,17,20]** and the azomethaine band also underwent higher frequencies for the prepared complexes, this band was attributed to take place the complexation through nitrogen of azomethaine as clarified in (Table 2) These absorptions were further indicated by the appearance of υM-N, υM-O and υM-X respectively, (Table2). A band was observed around (3313-3441) cm^{-1} in the spectra of all compl exes, assigned to the υ-OH suggested in the crystal lattic of the complexes **[21]**.

Another set of a sharp and strong bands were also observed at (1037) and (1219) cm^{-1} due to the symmetrical and asymmetrical υC–O–C stretching vibrations respectively **[16]**.

No appreciable change is taken place in the vibration modes of this band in the prepared complexes, which excluded the possibility oxygen atom participation in coordination with all prepared complexes.

Ultraviolet-visible spectroscopy, magnetic moment and conductivity measurements:

The electronic spectra of the metal complexes were recorded in their solution in DMF in the range (200-1100) nm. The spectrum of the free ligand (L) showed three bands:

The first absorption band appeared at 285 nm (35087 cm^{-1}) which can be attributed to ($\pi \rightarrow \pi^*$) transition for the aromatic system.

The second absorption band is attributed to ($\pi \rightarrow \pi^*$) transition of imines group, which appeared at 350 nm (28571 cm^{-1}). This band was not significantly affected by chelating.

The third absorption band appeared at 435 nm (22988 cm^{-1}) is assigned to ($n \rightarrow \pi^*$) transition **[23]** which is shifted to a longer wavelength (red shift) upon formation of the complexes.

This shift may be attributed to the donation of the lone pairs of the nitrogen atoms of the Schiff base to the metal ion (N:→M) [22].

Table-2: The most diagnostic FT-IR bands of L and its metal complexes

Comp.	υ C=N	υ C-O	δ -OH	υ C-O-C	υ M-N	υ M-O	Others
L	1627	1265	648	1037 1219	-	-	υOH=3356
VOL	1681	1284 1282	-	1037 1219	540	478	V=O = 972 υOH=3321
CrL	1654	1284 1253	-	1037 1220	540	486	υOH=3379
CoL	1655	1276 1273	-	1033 1219	536	455	Coord.δ_{H2O}=848 υOH (H_2O,EtOH)=3387
NiL	1654	1276 1273	-	1033 1220	555	474	Coord. δH_2O=840 υOH (H_2O,EtOH)=3313
CuL	1620	1284 1270	-	1033 1219	578	509	Coord. δH_2O=845 υH_2O(H_2O,EtOH)=3441
ZnL	1685	1284 1270	-	1033 1219	540	486	υOH=3360

VL: The olive green spectrum of vanadyl (II) complex shows three prominent d-d absorption bands, (Table 3), which are assigned to the transition $^2B_2g\rightarrow{}^2Eg$, $^2B_2g\rightarrow{}^2B_1g$ and $^2B_2g\rightarrow{}^2A_1g$ respectively in a square pyramidal geometry **[23,24]**. The value of magnetic moment is (1.89) BM which indicates a higher orbital contribution and the conductivity measurement in DMF showed that the complex is non-ionic (Table 3).

CrL: Two bands are observed within the range of measurement. They have maxima at about (20022) and (23696) cm^{-1}.

These are spin-allowed and laborite-forbidden d-d transition. The third band $υ_3$ and other ligand field parameter β, B\, 10Dq were calculated refers to Tanaba-Sugano diagram for d^3 configuration (Table 3).

The magnetic value (3.21) B.M., of chromium (III) is observed and this value agreement with octahedral geometry around Cr(III) ion [22,23,25-27].

The conductance measurements indicate that the complex is non-ionic behaviour.

CoL: Three bands were observed in the spectrum of Co(II) complex, one at (10256)cm^{-1} and the two others at (15384) cm^{-1} and (22522) cm^{-1} which are referred to the transitions of $υ_1$, $υ_2$ and $υ_3$ respectively **[25,26]**.

The different ligand field parameters have been calculated using the Tanabe-Sugano diagram of d^7 configuration, and the results are found in (Table 3). The value of the calculated neuphelauxetic factor β is (0.421), this low value refers to the high covalent character of the bonding between the cobalt and the donor atom of the ligand [27,28].

The magnetic moment is (4.94) B.M, which shows the complex to be paramagnetic, indicating a high-spin octahedral configuration. The formula was further confirmed to be non-ionic by conductivity measurement.

NiL: Square planar nickel (II) complexes are commonly orange or red, but green colour is also known **[29]**.

The green colour of the present complex is postulated to be distorted octahedral. Three transitions bands are shown in the spectrum of nickel complex and their assigned can be shown in (Table 3).

The value of constant field splitting (10Dq=10505 cm^{-1}) which equal to the first transition $υ_1$. The transition observed at 13368 cm^{-1} assigned to the spin-forbidden transition $^{3}A_{2}g\rightarrow{}^{1}Eg$ **[30]**.

The assigned values of second and third transition and the calculated υ_1 as well as $B^{\backslash}$, β and 10Dq are all in a good agreement with octahedral geometry of nickel(II) complexes having similar donor atom groups **[24,30]**.

The quite low value of β suggests a considerable covalent bonding between metal and ligand atoms. Magnetic moment is (3.05) B.M, and the conductivity measurement shows that the complex is to be non-electrolytic.

CuL: The greenish brown complex shows a broad band at (15649) cm^{-1} which can be assigned to $^{2}Eg\rightarrow{}^{2}T_{2}g$ transition, this band refers to the distortion of octahedral geometry (Jahn-Teller distortion) [23,29,30].

The magnetic moment value at room temperature of this complex is (1.83) B.M This value is in the range of mononuclear octahedral geometry **[31]**.

Conductivity measurements show that the complex is non ionic (Table 3)

ZnL: The complex is diamagnetic which is expected for d^{10} ion. The spectrum shows a relative change in the bands position compared to that of the free ligand **[32]**, as listed in (Table 3).The conductivity measurements showed to be non-ionic for this complex.

Solution study:

Molar ratio method was followed to determine the M:L ratio. The results of complexes in ethanol solution, suggest that the metal to ligand ratio was (1:2) for vanadium, cobalt, Nickel, zinc complexes and (1:3) for chromium complex, which were comparable to those obtained from isolated solid state study, (Table-1), (Fig-1).

Table-3: Electronic spectra, conductance in DMF solvent and magnetic moment (B.M.) for the present prepared metal complexes of L

Compound	VOL	CrL	CoL	NiL	CuL	ZnL
Absorption Bands(cm^{-1})	10040 16501 23696	20022 23696 30129 (cal.)	10256 15384 22522	13368 11135 10668(cal.) 21283 23529	15649	23094 29411 36101
Assignments	$^{2}B_{2}g\rightarrow{}^{2}Eg$ $^{2}B_{2}g\rightarrow{}^{2}B_{1}g$ $^{2}B_{2}g\rightarrow{}^{2}A_{1}g$	$^{4}A_{2}g\rightarrow{}^{4}T_{2}g$ $^{4}A_{2}g\rightarrow{}^{4}T_{1}g$ $^{4}A_{2}g\rightarrow{}^{4}T_{1}g_{(P)}$	$^{4}T_{1}g\rightarrow{}^{4}T_{2}g$ $^{4}T_{1}g\rightarrow{}^{4}A_{2}g$ $^{4}T_{1}g\rightarrow{}^{4}T_{1}g_{(P)}$	$^{3}A_{2}g\rightarrow{}^{1}Eg$ $^{3}A_{2}g\rightarrow{}^{3}T_{2}g$ $^{3}A_{2}g\rightarrow{}^{3}T_{1}g$ $^{3}A_{2}g\rightarrow{}^{3}T_{1}g_{(P)}$	$^{2}Eg\rightarrow{}^{2}T_{2}g$	ILCT
B		918	1128	1035		
B`		518.7	475.8	550		
B		0.564	0.421	0.531		
Dq/B`		3.85	2.1	1.91		
10Dq		19972	9991	10505		
15B`		7780.5	7137	8250		
B.M.	1.89	3.21	4.94	3.05	1.83	0.00
μscm^{-1}	51	38	53	49	40	16
suggested geometry	Square Pyramidal	O.h	O.h	O.h	O.h	T.d

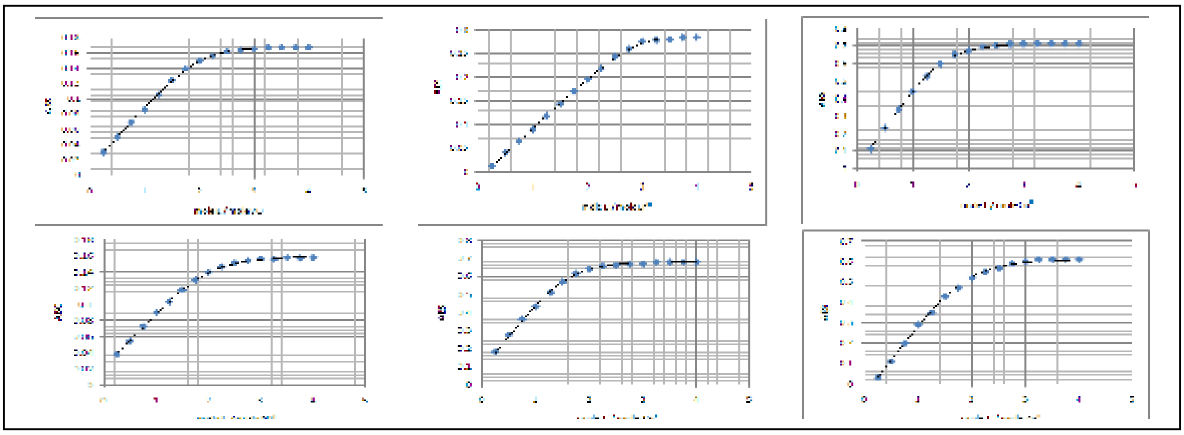


Fig-1: Molar ratio plot of the complexes

Theoretical study:

(i) The program Hyper Chem-8 was used for the semi-empirical and molecular mechanics calculation at optimized geometries energies, the result of PM3 and ZINDO/1 methods of calculation in gas phase for heat of formation and binding energy for the ligand and its complexes were calculated and tabulated in (Table 4).

Also PM3 was used for evaluation the vibration spectra of the amine (A) and Schiff base to compare the theoretically calculated wave numbers with experimental values.

Theoretically calculated wave numbers for these ligands showed some deviations from the experimental values, these deviations are generally acceptable in theoretical calculation and are described in (Table 5 and 2).

Table-4:Conformation energetic (in kJ.mol^{-1}) for the Schiff base and its metal complexes

Comp.	PM3		ZINDO/1	
	ΔH°_{f}	ΔE_{b}	ΔH°_{f}	ΔE_{b}
A	-64.52595409	-6603.0587591	-	-
L	-165.1768378	-13793.54849	-	-
VOL	-	-	-55456.40066925	-83040.5629012
CrL	-1022.143706	-40966.950698	-	-
CoL	-2037.288259	-30656.852418	-	-
NiL	-1749.411078	-30370.648838	-	-
CuL	-1098.015816	-29626.787176	-	-
ZnL	-1342.651129	-27088.828185	-	-

Table-5: Comparison of experimental and theoretical vibrational frequencies for the starting material and Schiff base compound

Symb.	υ_{asy} NH_2	$\upsilon_{sy}NH_2$	υC-O phenolic	υ C=N	υOH	δOH	υ_{as} C-O-C	υ_{sy} C-O-C
A	*3545.84 **3310 ***-7.09	*3487.26 **2990 ***-16.62	*1340 **1275 ***-5.09	_	*3865.04 **3450 ***-12.03	*591.15 **650 ***-9.05	_	_
L	_	_	*1321.23 **1265 ***-4.44	*1836.53 **1627 ***-12.84	*3854.92 **3356 ***-14.86	*553 **648 ***14.62	*1068.37 **1037 ***-3.02	*1215.76 **1219 ***0.265

Where: * Theoretical frequency, ** Experimental frequency, ***: Error % due to main difference in the experimental measurements and theoretical treatment of vibrational spectrum.

(ii) Electrostatic potential: It describes the interaction of energy of the molecular system with a positive point charge, so it useful for finding sites of reaction in molecule positive charge species tend to attack a molecule where the E.P is strongly negative electrophilic attach [33,34]. The E.P of the free ligand was calculated and plotted as 2D and 3D contour to investigate the reactive sites of the molecules (Fig-2). The results of calculation showed that the LUMO of transition metal ion prefer to react with the HOMO of oxygen and nitrogen atoms of Schiff base ligand (Fig-3).

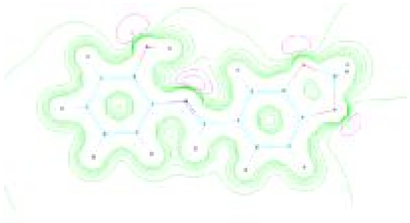
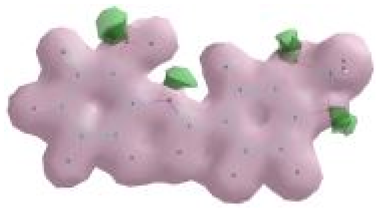
E.P L 2D 	E.P L 3D 

Fig-2: Electrostatic Potential as 2D&3D Contours for Schiff bases

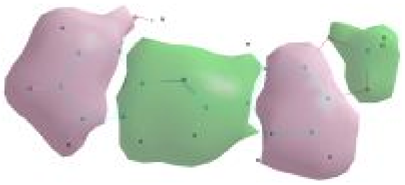
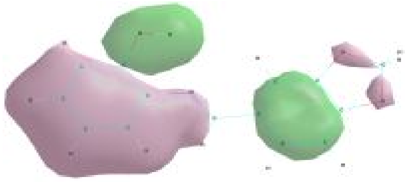
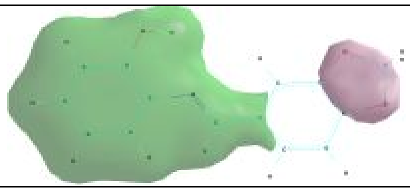
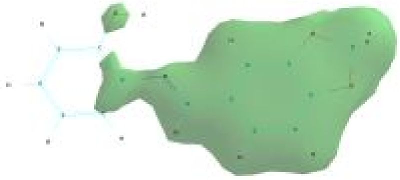
	
-25.30496 Ev	-26.66133 eV
	
-33.06469 Ev	-36.58794 eV
	
-40.53282 Ev	-42.14537 eV

Fig-3: HOMO & LUMO as 3D Contours for L

(iii) Optimized geometries and energy of metal complexes for the ligand: All theoretically probable structures of metal complexes with ligand have been calculated to search for the most probable model building stable structure these shapes (Fig 4 and 5), show the calculation optima geometries for the imine and its complexes. The results of PM3, methods of calculation in gas phase for the $\Delta H_f°$ and ΔE_b of Cr (III), Co (II), Cu (II) and Zn (II) while ZINDO/1 method used for the VO (II) complex, and are described in (Table-4).

B. Antibacterial and Antifungal Activates:

The data of the antifungal and antimicrobial activities of the prepared ligand and its complexes are given in (Table-6), (Fig 6,7 and 8).

The data reveal that some complexes have higher activities than free ligand. This enhancement of the complexation activity can be explained by the structure of these complexes and the oxidation states of metal ions, or these results would suggest that to cross the cell membranes [35,36].

The chelating theory considerably reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization over the whole chelating ligand.

Such coordination could also enhance the lipophilic character of the central metal atom, which subsequently favours its permeation through the lipid layer of the cell membranes [37].

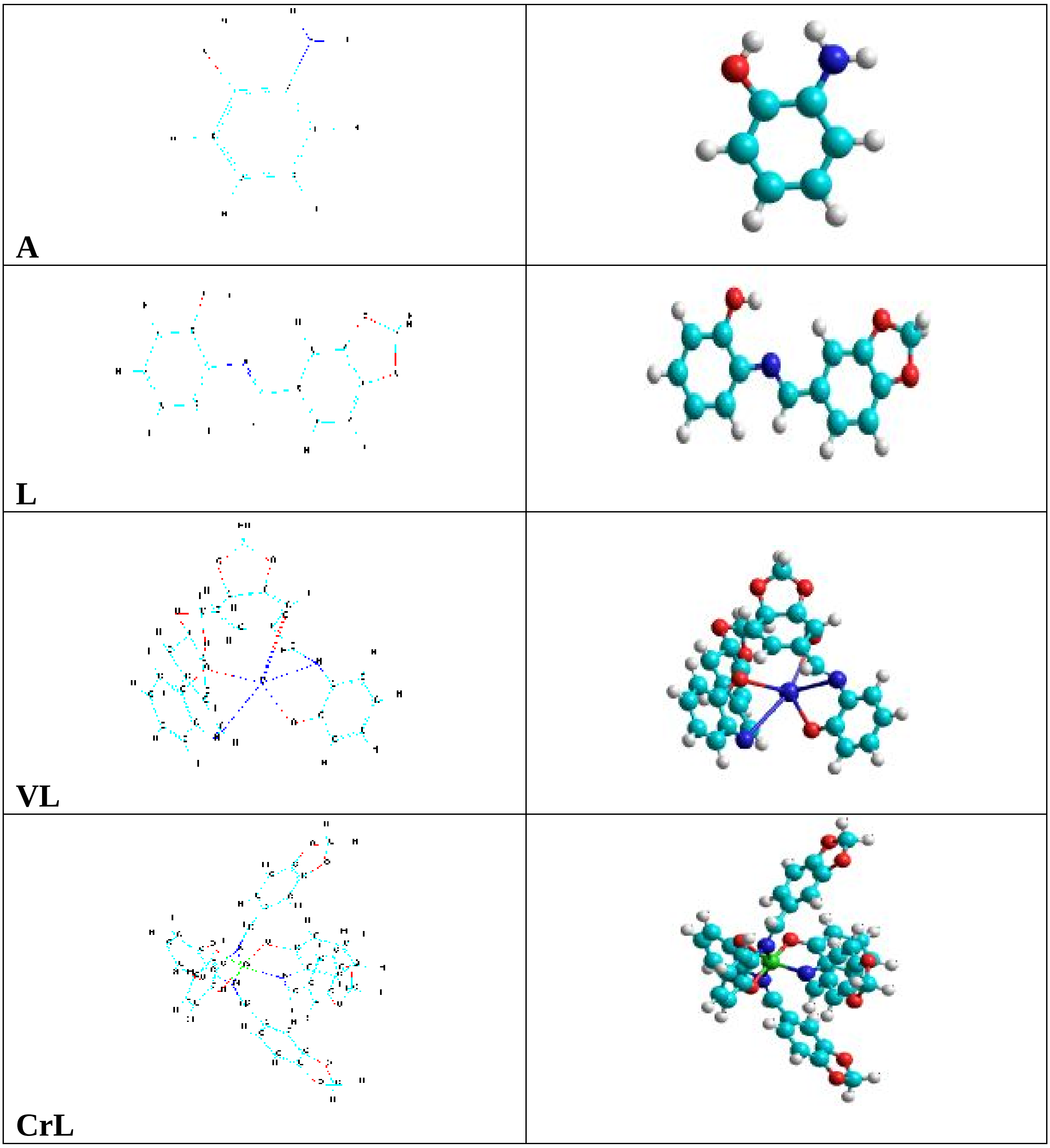
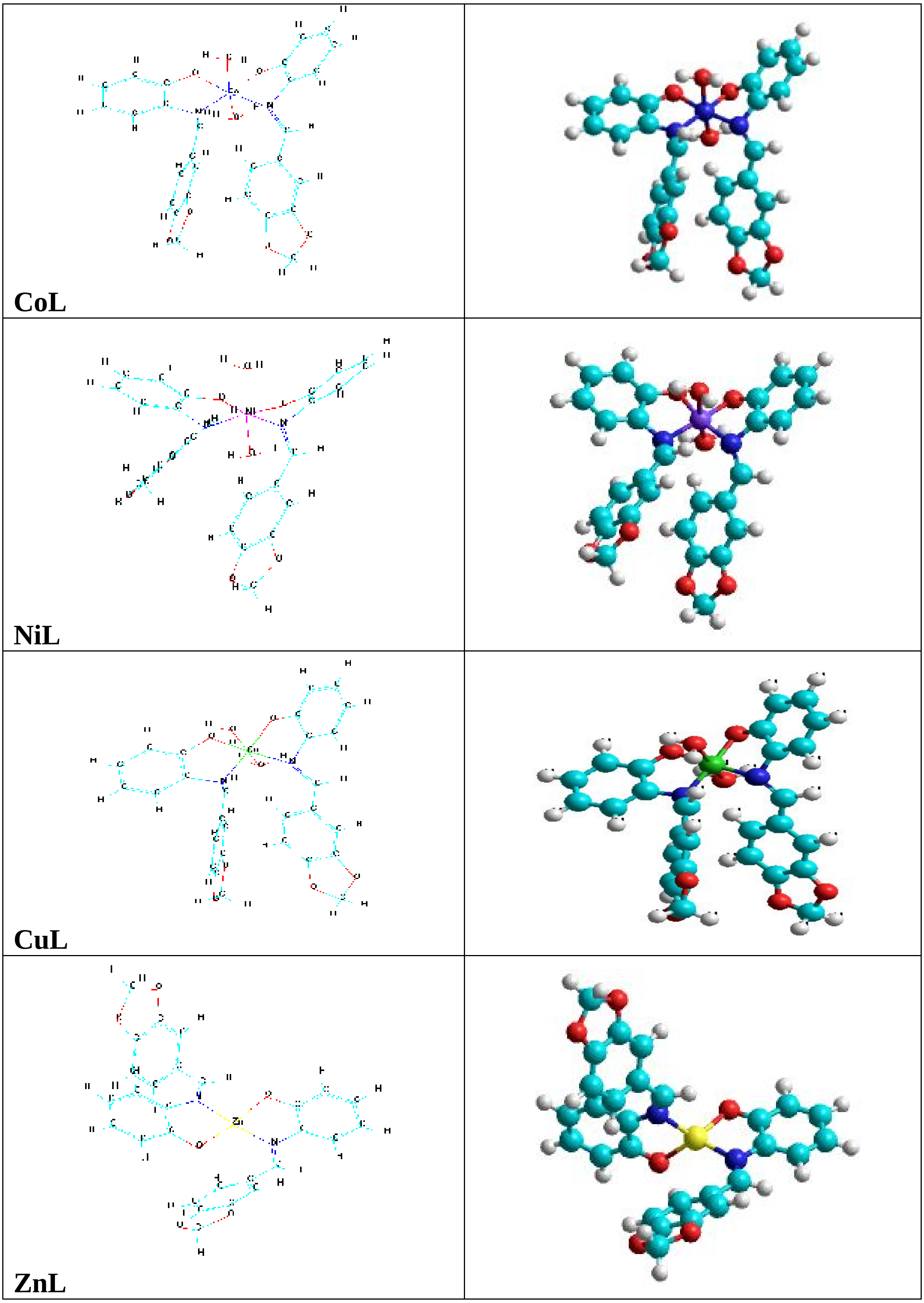


Fig-4: Conformation structure the A, ligand and its complexes(VOL&CrL)



CoL

NiL

CuL

ZnL

Fig-5: Conformation structure of the complexes (CoL,CuL,NiL &ZnL).

Table-6: Diameter of zone of inhibition (mM)

Comp.		**Control**	**L**	**VOL**	**CrL**	**CoL**	**NiL**	**CuL**	**ZnL**
Escherichia. Coli	5 mM	-	8	-	8	22	14	16	14
	10 mM	-	10	10	10	26	21	24	15
Staphylococcus aureus	5 mM	-	10	25	20	20	17	23	20
	10 mM	-	12	26	25	20	20	26	26
Candida albicans	5 mM	-	13	35	33	25	30	-	31
	10 mM	-	18	35	35	28	35	20	36

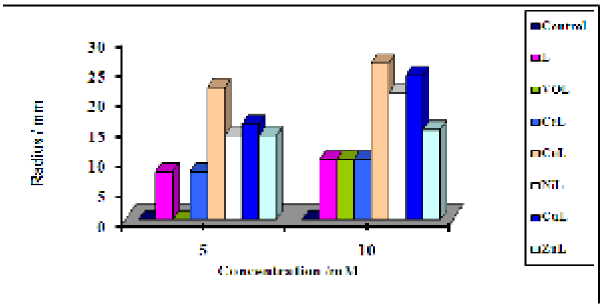


Fig-6: Effect of the ligand and its complexes toward *E.Coli* bacterial

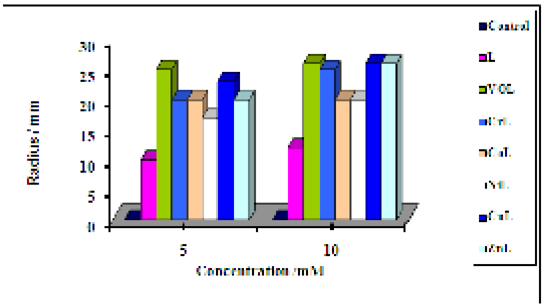


Fig-7: Effect of the ligand and its complexes toward *S.aureus* bacterial

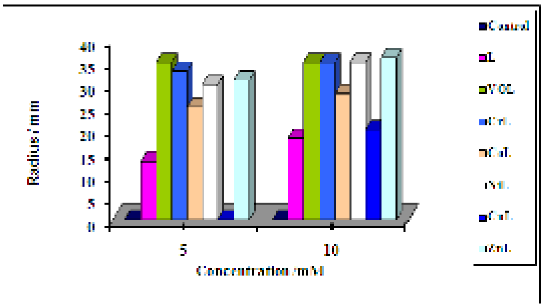


Fig-8: Effect of the ligand and its complexes toward *C.albican* fungus

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