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Research Article

Theoretical Study and Biological Activity of Co(II), Ni(II), Cu(II),Pd(II),Pt(IV) and Cd(II) Complexes with2-Thioxoimidazolidin-4-one Derivative

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Abstract

The workcontains a theoretical treatment of the preparedligand (3-{[(*Z*)-(4-nitrophenyl) methyli -dene] amino}-2-thioxoimidazolidin-4-one)[L] and their metal complexes[S_1-S_6]in the gas phase. Hyperchem-8 program has been used to determined structural geometries of ligand and their metal complexes. The electrostatic potential(E_p)of the ligand was calculated,furthermore binding energy(ΔE_b),the heat of formation(ΔH_f),vibration spectra and bond length for the ligand and their metal co -mplexes were calculated by PM3methods at 298K°. The theoretically calculateddata were agreed with those found experimentally. The antibacterial activity for free ligand and its metal complexes (S_1-S_6) were studied against two selected micro-organisms [(***Staphylococcusaureus***) as gram positive] and [(***Escherichiacoli***)as gram negative]. The minimal inhibitory concentrations (**MIC**) have been also studied to determine the low concentration for inhibition. The antibiotics (**Amoxcillin and Ampicillin**) have been chosen to compare their activity with those of the new compounds. Furthermore the antif -ungal activity against two microorganisms (***Candidaalbicans***) and (***Aspergillusflavus***) were studied for all compounds. The results showed great activity of the complexes relative to that of free ligand.

Keywords: 2-thioxoimidazolidin-4-one, complexes, theoretical study, biological activity.

الخلاصة

تضمن هذا العمل معالجة نظرية لليكاند المحضر[L]:-2-{amino]methylidene)-(4-nitrophenyl)-(*Z*)[(3-{ومعقداته[S_1-S_6] في الطور الغازي. أستخدام برنامج(8-Hyperchem)لأستنتاج thioxoimidazolidin-4-one) الأشكال الهندسيةلليكاندومعقداته. تم حساب حرارة تكوين(ΔH_f)والجهدالالكتروستاتيكي(E_p)وطاقة التاصر(ΔE_b)والأطياف الأهتزازيةوأطوال الأواصرلكل من الليكاندومعقداته وبأستخدام دالة PM3 وعند درجةحرارة298كلفن. ووجد بأن هنالك توافقاً كبيراً بين القيم العمليةو النظرية. تم تقويم الفعالية المضادة للبكتريا لليكاند[L] ومعقداته[S_1-S_6]واختير نوعان من البكتريا موجبة الصبغة(***Staphylococcusaurous***)وسالبة الصبغة(***Escherichiacoli***). تم دراسة أقل تركيز يحدث عندهالتثبيط(**MIC**) وتمت مقارنة فعالية المركبات المحضرة مع نوعين من المضادات الحيويةAmoxcillinوAmpicillin. كما تم اجراء التقويمالحيوي لليكاند ومعقداته ضد نوعين من الفطريات(***Candidaalbicans***)و(***Aspergillus flavus***),وقد أظهرت النتائج الفعالية العالية للمعقدات مقارنة باليكاند.

Introduction

Thioxoimidazolidin is a five membered heterocyclic ring with two nitrogen atoms and contain two groups, thion (C=S) and carbonyl (C=O) at position, 2 and 4, respectively [1] [2]. Thioxoimidazolidin are biologically active molecules widely used in medicine as drugs [3] [4] [5] [6]. It is also an effective medication for the treatment of some type of cancer [7] [8] as well as it is may be used as fungicidesandherbicides [9] [10]. In literature there are somepapers studies the crystal structure and hydrogen bonding interaction of 2-thioxoimidazolidn-4-one [11] [12]. In our previous work [13] the Schiff base [L], and its metal complexes[S_1-S_6] have been prepared andinvestigated using different chemical tech-

niques, as well as molar ratiomethod measurement in solution gave comparable results with thoseobtained from solid state studies. Continuing the studies on free ligand and it's complexes. This paper reports here the theoretical studies in the gas phase was done by using semi-empirical method in order to show the most stable conformation. The study aims to calculate the binding energy, heat of formation for all the structures geometries to find the most active sites of the [3-{[(*Z*)-(4-nitrophenyl) methylidene] amino}-2-thioxoim -idazolidin-4-one] [L] by using the electrost -atic potential calculations. The vibrational frequencies of the free ligand [L] and their metal complexes have been carried out in order to compare the results with the experi -mental vibrational frequencies to make assig -nment of the most diagnostic bands.

The biological activities for free ligand [L], and its metal complexes [S_1-S_6] were employed in the present study to show the effect of introducing the azomethian group in the(2-thioxoimidazolidin-4-one) ring to compare the biological activity of the ligand and their complexes with the main ring structure.

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Materials and Methods

(A)-Theoretical treatment

Hyperchem is a sophisticated molecular modeler; it is a powerful computational package, that is known for their quality and ease of use [14] [15]. It can plot orbital wave functions resulting from semi-empirical quantum mechanical calculations, the total charge density or the total spin density and the electrostatic potential can be determined during semi-empirical calculation, this information is useful in determining reactivity and correlating calculation results with experimental data.

1-Computational methods:

a) Semi -empirical quantum mechanical,
b) Molecular mechanics, c) Mopac 2000

2-Types of calculations:

The types of prediction possible of Molecules are [14]: Geometry optimization calculations used energy minimization algorithms to locateBond distances, stable structures, Molecular dynamics which gave the thermodymemic calculations and dynamic behavior of molecules, Plot the electrostatic potential field (HOMO and LUMO),and Vibrational spectrum (I. R and Raman spectra).

(B)-Study of biological activities for (L) ligand and their Metal Complexes (S_1 –S_6)

The bioactivities of the free ligand(L) and its complexes(S_1-S_6) were studied against selected types of bacteria which include ***(Escherichia coli)*** and ***(Staphylococcus aureus)***cultivated in Nutrient agar medium, DMSO was used as a solvent and as a control, the concentration of the complexes of this solvent was (10^{-3}M)[15, 16]. The new complexes (S_1-S_6) were tested for their ***in vitro*** growth inhibitory activity against further pathogenic fungi, i. e., [***Candida albicans***and ***Aspergillus flavus***] on potato dextrose agar medium and incubated at 30 °C for 72 hours. DMSO was used as a solvent and as a control for both techniques.

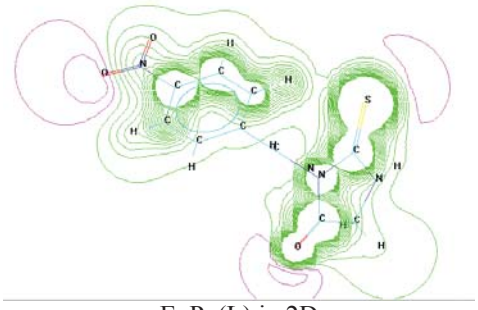
The concentrations of the compounds in this solvent were (10^{-3}M). The inhibition of fungal growth expressed in percentage terms, were determined on the growth in test plates compared to the respective control plates.

Results and Discussion

Study Complexes in Gas Stat (Theoretical studies): Electrostatic Potentials:

The electrostatic potential (E. P) describes the interaction of energy of the molecular system with a positive point charge. The active side can be found by calculating (E. P) in a molecule;

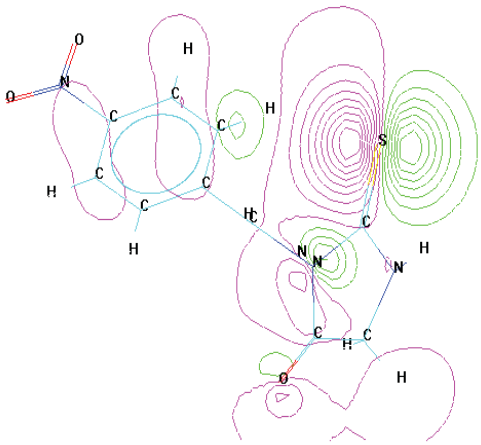
positively charged species tend to attack a molecule where the electrostatic potential is strongly negative (electrophonic attack)[14] [17] [18]. The (E. P) of the ligand (L) were calculated and plotted as 2D and 3D contours to investigate the reactive sites of the molecules, Figure1. The results of calculate -ions show that the LUMO of transition metal ions prefer to react with the HOMO of two-donor atoms of sulfur of thion group and nitrogen of the azomithane group for free ligand (L),Figure2.



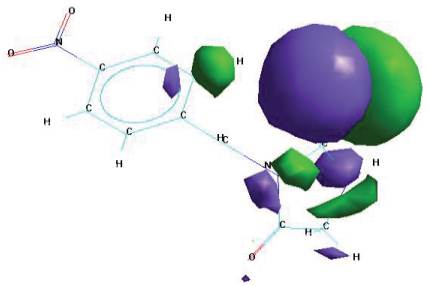
E. P. (L) in 2D

E. P. (L) in 3D

Figure 10 : Electrostatic Potential as 2D&3D Counters for ligand L



HOMO and LUMO in 2D for (L).



HOMO and LUMO in 3D for (L)

Figure 11: HOMO and LUMO Sites for the L

Optimized energies: The heat of formation (ΔH_f^o), binding energy (ΔE_b), and total energy (ΔE_T) for ligand (L) and its metal complexes(S_1-S_6) were calculated ,by using the semi-empirical (PM3) and (AMBER) methods, Table 1.

Table 1 : Conformation energetic (in KJ. mol^{-1}) for the L and their metal complexes (S_1-S_6).

No.	PM3			AMBER
	ΔH^o_f	ΔE_b	ΔET	ΔE_T
L	226	-11573	-291004	
S_1	-1145	-25476	-720062	
S_2	-425	-24696	-743800	
S_3	1640	-22538	-755897	
S_4	-----	-----	------	520
S_5	1124	-22849	-681625	
S_6	1911	-21798	-582825	

Optimized vibrational spectra for ligand (L):
The vibrational spectra of the prepared ligand (L) and its metal complexes (S_1-S_6) have been calculated, Table 2. The results of theoretic -cally calculated wave numbers for ligand and its complexes showed that some of deviations from the experimental values, these devia -tions are acceptable in theoretical calculations[14] [18] [19] [20] [21] Tables 2.

Table 2: Comparison between the experimental and theoretical vibrational frequencies (cm-1) for free ligand (L) and their metal complexes.

Comp.	υN-H	υC=N	υC=O	υC=S	υM-N	υM-S
L	3329* 3404** 2.203***	1633* 1606** 1.681***	1708* 1800** 5.11***	1099* 1030** 6.699	-	-
S_1	3336* 3243** 2.87***	1618* 1609** 0.56***	1707* 1727** 1.158***	1072* 1077** 0.464***	535* 530** 0.943***	462* 477** 3.114***
S_2	3267* 3404** 4.02***	1614* 1592** 1.38***	1703* 1797** 5.23***	1068*,1076* 1051**,1088** 1.62***,1.1***	530* 532** 0.375***	458* 455** 0.659***
S_3	3299* 3381** 3.522***	1619* 1728** 6.195***	1705* 2000** 14.75***	1078* 1073** -0.465***	528* 551** 4.174***	460* 471** 2.335***
S_4	3240* 3232** 0.247***	1608* 1571** 2.36***	1710* 1671** 2.333***	1072* 1088** 1.47***	533* 524** 1.171***	455* 457** 0.437***
S_5	3172* 3200** 0.88***	1620* 1674** 3.225***	1708* 2000** 14.6***	1082* 1111** 2.61***	530* 552** 3.985***	462* 457** 1.094***
S_6	3240* 3263** 0.70***	1593* 1598** 0.31***	1710* 1720** 0.58***	1051*,1064* 1044**,1059** 0.67***,0,47***	533* 537** 0.744***	458* 450** 1.777***

***: Experimental frequencies **: Theoretical frequencies ***Error %**

Optimized geometries of ligand (L) and their metal complexes

Theoretically chosen structures of ligand and its metal complexes have been calculated to find the most possible model building stablestructure for ligand and its metal complexes, as shown in Figure 3.

Bond lengths measurements for (L) and their metal complexes

The Gaussian suite of software was employed throughout this study optimizations were carried out for the model systems represented in Figure 4, Table 3, for the free ligand and its metal complexes by using the semi-empirical (PM3) method at geometry optimization (0.001Kcal/mol). The data results gave excellent agreement with the experimental data [14] [19] [22].

Table 3:Bond length of Ligand and their Metal Complexes.

Comp.	C=N	C=S
L	1.289	1.6224
S_1	1.3126	1.6507
S_2	1.2835	1.6569
S_3	1.3187	1.7627
S_4	1.3261	1.6768
S_5	1.3138	1.7069

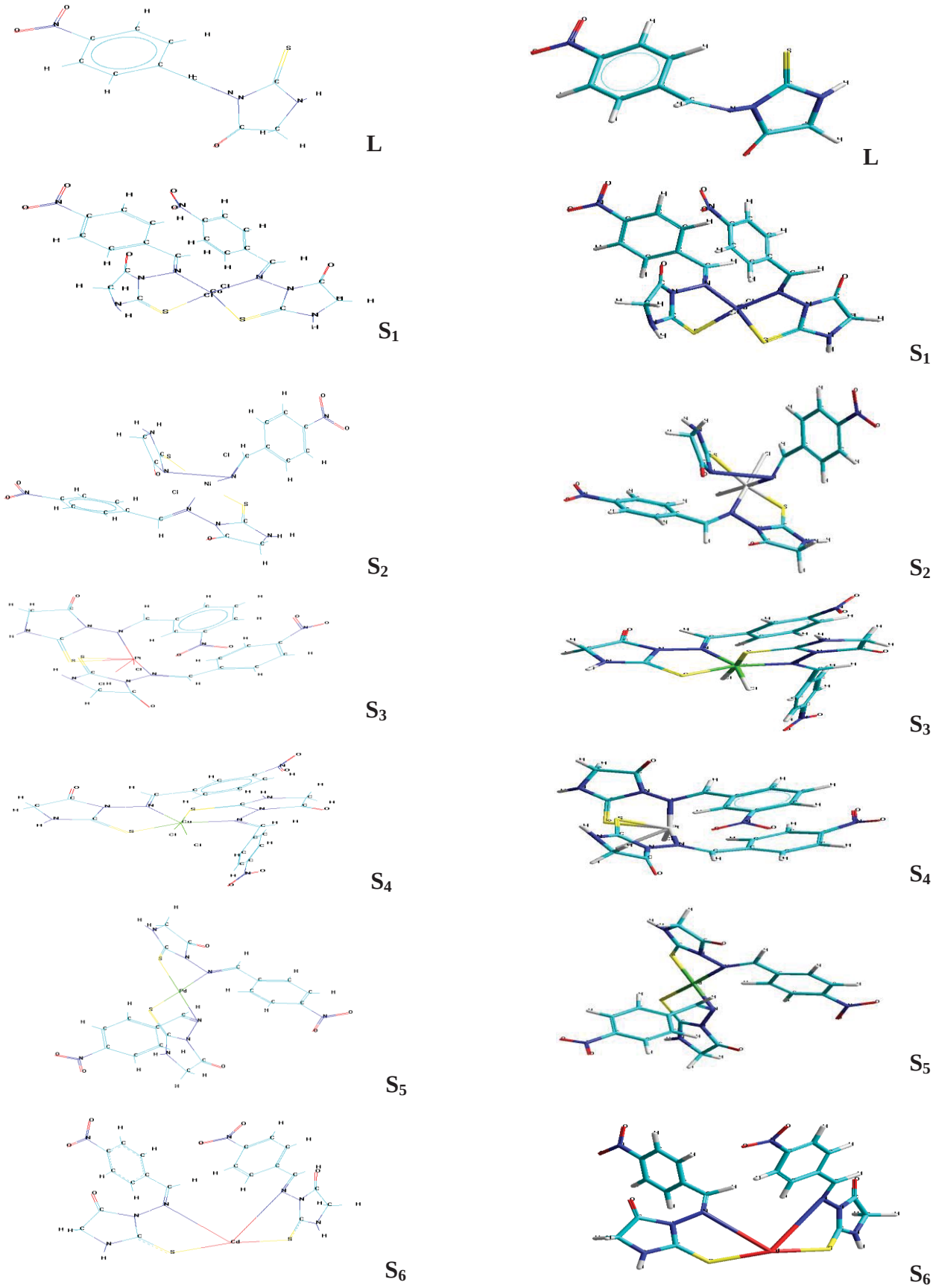
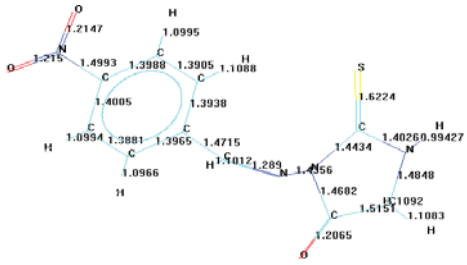
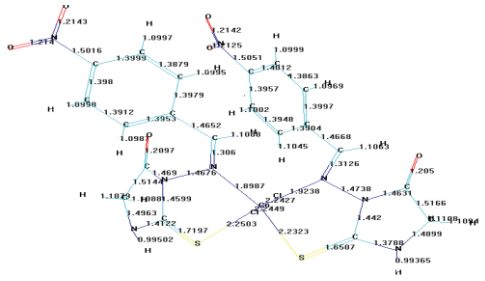


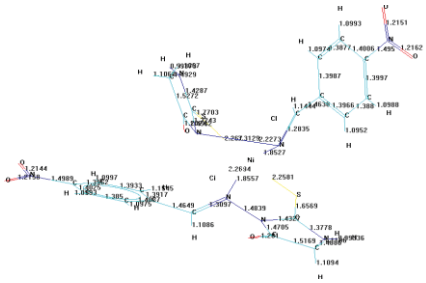
Figure 12: Conformation structure of Ligand (L) and their metal complexes using Hyperchem 8 Program



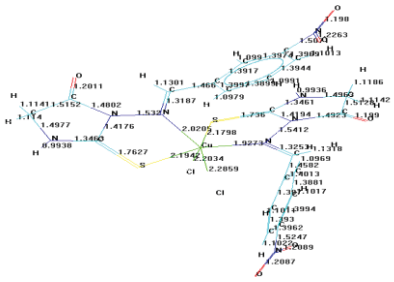
L



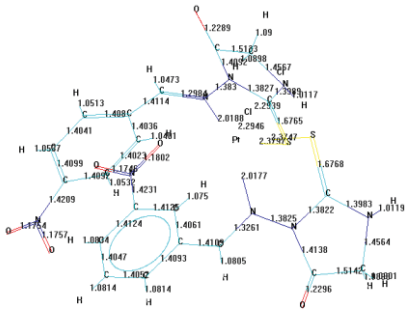
S_1



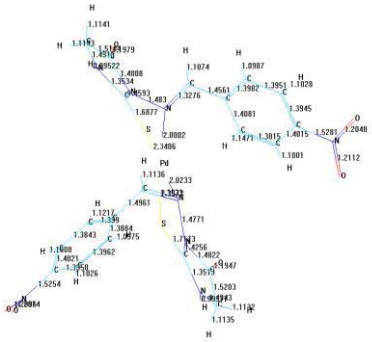
S_2



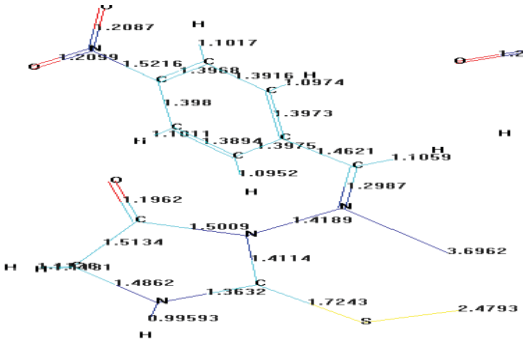
S_3

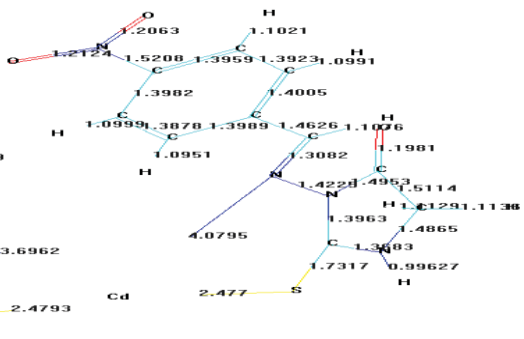


S_4



S_5





S_6

Figure 13:Bond length of Ligand and their metal complexesUsing Hyperchem.

Biological Studies

The ligand (L) and theirmetalcomplexes (S_1-S_6) were screened ***in vitro*** for their ability to inhibit the growth of representative [(***E. coli***) as gram negative] and [(***Staph. aureus***) as gram positive] are shown in Table (4). Also the study was done against (***Candida albicans***and***Aspergillus flavus***) fungus, in DMSO as a solvent, Table4. As aresult from the above mentioned studies, the following points were concluded:

1) The study of antibacterial activities gave that the ligand (L), exhibited high activity against the studied bacteria ***Staph. aureus*** while against ***E. coli.*** was moderately active.

2) (S_1-S_6) complexes showed highly active against two types of bacteria compared with the freeligand (L).

3) Results of the antifungal activity of the new compounds, Table 4 showed that the metal ion complexes (S_1-S_6) were more toxic compared with their parent ligand (L) toward the same micro-organism and under the identical experimental conditions. The increase in the antifungal activity of metal chelates may be due to the effect of the metal ion on the normal cell process; these activities may be explained by Tweedy's Chelation theory [15]. According to this theory the polarity of the metal atom mainly reduce the polarity of metal ions, because of the partial sharing of its positive charge with the donor groups of the ligand, which favors permeation of the complexes through the lipid layer of cell membrane [16, 22].

4) The results of the (MIC) were compared with those of the two antibiotics, Table 5. The new compounds were more active at low concentration, Table 5.

Table 4: Antibacterial and antifungal activities for ligand (L) and their metal complexes (S_1-S_6) (10^{-3}µgm. ml^{-1})

No.	*E. coli*	*Staph. aureus*	*Cand. albic*	*Asper . flav*
Con DMSO	-	-	-	-
L	4	6	30	27
(S_1)	6	8	27	20
(S_2)	8	10	23	25
(S_3)	10	12	20	22
(S_4)	14	16	18	20
(S_5)	8	10	24	26
(S_6)	18	14	19	16

Table 5: Minimal inhibitory concentration (MIC) for Schiff base (L) ligand and [S_1-S_6] their metal complexes (µgm. ml^{-1})

Symb.	*Escherichia coli*					*Staphylococcus aurous*				
	0.025	**0.05**	**0.075**	**0.1**	**0.5**	**0.025**	**0.05**	**0.075**	**0.1**	**0.5**
(L)	+	+	**(MIC)**	-	-	+	**(MIC)**	-	-	-
(S_1)	+	**(MIC)**	-	-	-	+	**(MIC)**	-	-	-
(S_2)	+	**(MIC)**	-	-	-	+	**(MIC)**	-	-	-
(S_3)	**(MIC)**	-	-	-	-	**(MIC)**	-	-	-	-
(S_4)	**(MIC)**	-	-	-	-	**(MIC)**	-	-	-	-
(S_5)	+	**(MIC)**	-	-	-	+	**(MIC)**	-	-	-
(S_6)	**(MIC)**	-	-	-	-	**(MIC)**	-	-	-	-
Ampicillin	+	+	+	**(MIC)**	-	+	+	+	+	**(MIC)**
Amoxicillin	+	+	+	**(MIC)**	-	+	+	+	+	**(MIC)**

Conclusion

Hyperchem-8 program has been used to predict structural geometries of all compounds in gas phase. The free ligand (L) and its metal complexes [1-6] show significant antimicrobial activity. The all complexes are found more effective than the free ligand.

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