Article

Synthesis, Spectroscopy characterization, theoretical study and biological activity of some new metal complexes with new Schiff base ligand derived from cefixime

Sarah A.R. Mohammed[1] and Enass J. Waheed[2*]

[1,2]Department of Chemistry, College of Education for Pure Sciences, Ibn -Al-Haitham, University of Baghdad, Baghdad, Iraq.

**Corresponding author E-mail: enass.j.w@ihcoedu.uobaghdad.edu.iq*

sarah.abd2105m@ihcoedu.uobaghdad.edu.iq

Abstract

A set newly complexes with the general formula [M(L)Cl_2] are resulting from the reaction of a new schiff base ligand [Ethyl (6R,7R)-7-((E)-2-((2-ethoxy-2-oxoethoxy)imino)-2-(2-(((E)-4-nitrobenzylidene) amino) thiazol -4- yl) acetamido) -8- oxo -3- vinyl -5- thia -1-aza bicyclo [4. 2.0] oct -2- ene -2-carboxylate] (L). This ligand was derived from the reaction of the two substances 4-nitrobenzaldehyde and precursor (P). Reaction the ligand with metal ions M= Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) afforded new complexes which are characterized by FT-IR and Electronic Spectra. These measurements indicate that the complexes have a tetrahedral geometry. The Penicillin-Binding Protein 3 (PBP3) of *Staphylococcus aureus* and the target protein was β-Lactamase belong to the family CTX-M of *Escherichia coli* were chosen to study the binding strength of the ligand and the copper complex prepared by molecular docking method as a primary measure of the biological activity of these compounds. The inhibition ability of the prepared compounds was tested against four types of selected bacteria (G^-) *Coli Escherichia* and *Klebsiella pneumoniae* & (G^+) *Staphylococcus aureus* and *Staphylococcus epidermidis* and fungi *Candida albicans*, where the results showed that the ability of the complexes to inhibit selected types of bacteria was different to the schiff base ligand.

Keywords: 4-nitrobenzaldehyde, Schiff base, heterocyclic unit, theoretical study

1. Introduction

These compounds were called Schiff bases after the scientist Huge Schiff, who prepared them for the first time in 1864 AD, as a result of condensation ketones or aldehydes with primary amines in an acidic medium. The general chemical formula for Schiff bases is ($R_1R_2C=NR_3$). The compound is named according to the nature of R_1, R_2, and R_3. That is, if a Schiff base is derived from aniline, where R_3 is a phenyl group, or a substituted phenyl, then the resulting compound can be called (Azomethine) and others names [1,2].

An antibiotic is a substance that prevents the growth of bacteria or kills them. Antibiotics belong to a large class of antimicrobial compounds that treat infections caused by microscopic organisms such as fungi, bacteria, and parasites [3].

The first person to use the phrase "antibiotics" was the scientist Waxman in 1942, describing it as any substance produced by microorganisms that then prevents the multiplication of microorganisms in a diluted medium, with the exception of natural substances that kill microorganisms but are not produced by them, such as hydrogen peroxide and fluid inside the stomach. Most antibiotics are relatively small molecules with a molecular mass of less than 2000 Daltons. With the advancement of the science of medicinal chemistry, antibiotics have become semi-synthetic or original compounds (chemically modified) in nature, such as beta-lactam compounds including penicillin, which are generated by fungi of the Penicillium class, carbapenems, and cephalosporins [4,5].

Cefixime belongs to the third-generation cephalosporin antibiotics. It is highly effective against many types of bacteria, and it fights diseases by stopping the growth of the bacteria that cause them. You should refrain from taking cefixime if you have a proven allergy to it, or to any of its similar medications, such as cefuroxime and cefprozil. The doctor should also be informed if the patient suffers from a penicillin allergy [6]. Cefixime is effective in treating infections such as laryngitis, pneumonia, otitis media, tonsillitis, gonorrhea, urinary tract infections and pharyngitis. The interactions of metal ions with antibiotics are of great importance because they influence the preparation of metal antibiotics through the idea of interaction between absorbed drugs and metal ions [7]. Like penicillin, which is present in the human body, it can be coordinated with metal ions that exist in the form of free ions or coordinated with amino acids, proteins, enzymes, nucleotides, nuclear bases, and various vital bonds. This makes metals of high value in medicinal chemistry. There are antibiotics that do not need metal ions to perform their biological activity, while there are antibiotics that require metal ions to perform their work properly, such as bacitracin, bleomycin, and streptogrin, as they are more effective than pure drugs. This is because metal ions can interact with many diverse classes of biomolecules such as RNA, DNA, proteins, and others, making their biological activity unique and specific [8]. On the other hand, some metal complexes have shown high biological effectiveness against tumors, fungi, and viruses, and their effectiveness increases after their coordination [9]. Complexes containing Schiff base ligands in their composition have received the attention of many researchers due to their wide applications in the medical, food, analytical, dyes and chemical catalysis fields due to the simplicity of their preparation [10]. The aim of the work is to prepare a ligand of Schiff bases resulting from the condensation of 4-nitrobenzaldehyde with the intermediate substance (P), which in turn reacted with the selected metal ions M= Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) to produce solid complexes. Then the

prepared compounds were characterized using several spectroscopic methods to arrive at the tetrahedral geometric shape of the complexes.

2. Experimental

2.1. Materials

Without any purification, chemicals were used as they are of high purity and prepared by certified companies (BDH, Fluka or Merck).

2.2. Instrumentation

Analysis of microelements (CHN) was performed using a device Euro EA CHNSO Elemental Analyzer. Measurement of electronic transfers of compounds prepared at laboratory temperature and with a quartz cell (1cm) was carried out using a device UV-M90 Double Beam Spectrophotometer. Infrared spectroscopy was performed for the prepared compounds within the range (4000–400) cm^{-1} with potassium bromide tablets using a device Shimadzu FTIR-8400S Spectrometer. Electrical conductivity measurement was performed at concentration (10^{-3} M) and laboratory temperature with DMSO solvent using a device Philips pw-Digital Meter Conductivity. An examination of the magnetic susceptibility of metal complexes was carried out at temperature 25 °C using a device the Sherwood Scientific's Magnetic Susceptibility Balances. The atomic absorption measurement of the prepared compounds was carried out using a device Shimadzu AA-7000 Shimadzu. ^{1}H, ^{13}C NMR spectroscopic measurements of the prepared ligand was performed using a device Bruker AVANCE NEO 400 MHz spectrophotometer with DMSO. Anti-bacterial activity was done at In the Central Laboratory, College of Science, Al-Mustansiriya University. Determination of chlorine content in the prepared compounds was carried out using 686-Titro processor – 665 Dosimat. Metrohm. Swiss. The melting point of the prepared compounds was measured using a device Stuart SMP10 Melting Point Apparatus with open capillary tube.

2.3. Synthesis of New Schiff base ligand (L)

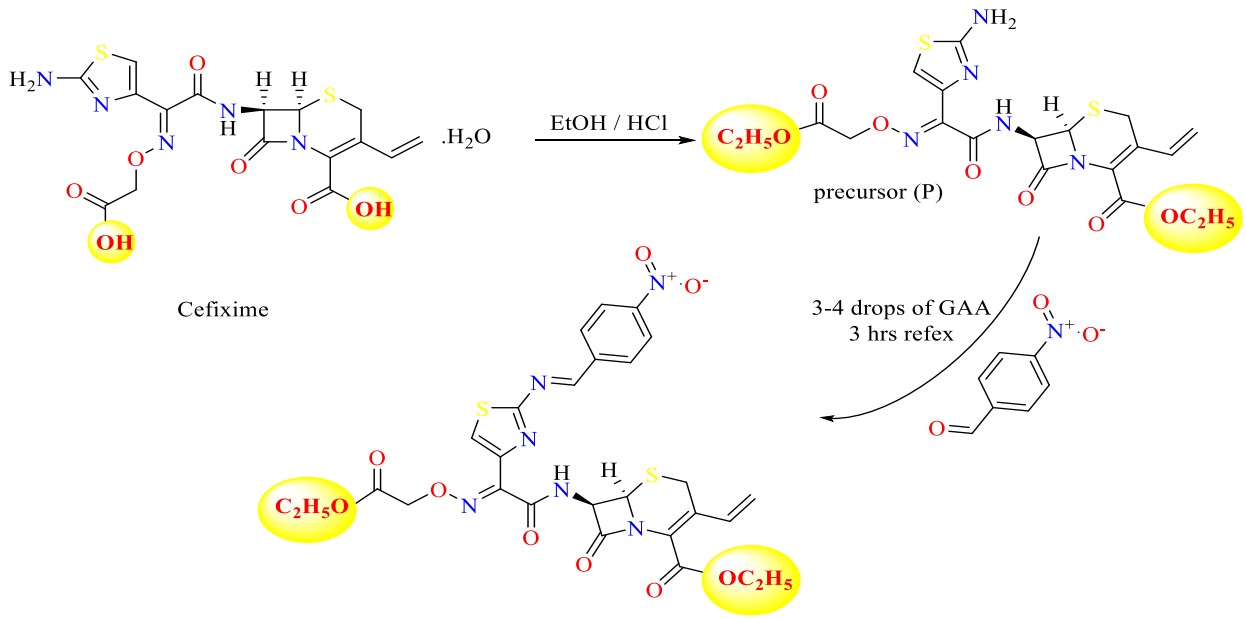
Prepare ligand (L) in two steps: -

A. Synthesis of precursor (P) [11]

Using a 100mL round flask, (0.51g, 1mmol) of cefixime was dissolved in (1mL) of absolute ethanol containing dissolved HCl, where saturated absolute ethanol was prepared. With HCl gas, by adding an amount of concentrated sulfuric acid to a flask containing an amount of sodium chloride (NaCl), and we collect the liberated gas in a flask containing ethanol, which is formed (ethanol saturated with HCl gas) and the mixture is left to stir continuously. With reflux for 3 hours, the course of the reaction was followed by TLC. After that, the mixture was cooled to obtain ester crystals and they were recrystallized using hot methanol and diethyl ether. The percentage of the product after drying the precipitate was 82% and its melting points were (109-111°C).

B. Synthesis of new Schiff base Ligand (L) [12]

The New Schiff base ligand (L) was prepared by adding a solution of the substance obtained in the first step (P) (0.51g, 1mmol) in 10 mL of ethanol to a solution of (4-nitrobenzaldehyde) (0.15g, 1mmol in 10 mL of ethanol with the addition of 3-4 drops of glacial acetic acid. After stirring for one hour, the mixture was placed under reflux for 3 hours, and then the course of the reaction was followed by TLC. After that, the mixture was filtered to obtain the desired precipitate (pale yellow), and the precipitate was recrystallized using hot methanol and diethyl ether. The precipitate was then left to dry at room temperature and was weighed to calculate the percentage of the product, which was (76%). And the melting point is (122-124) °C, Scheme 1.

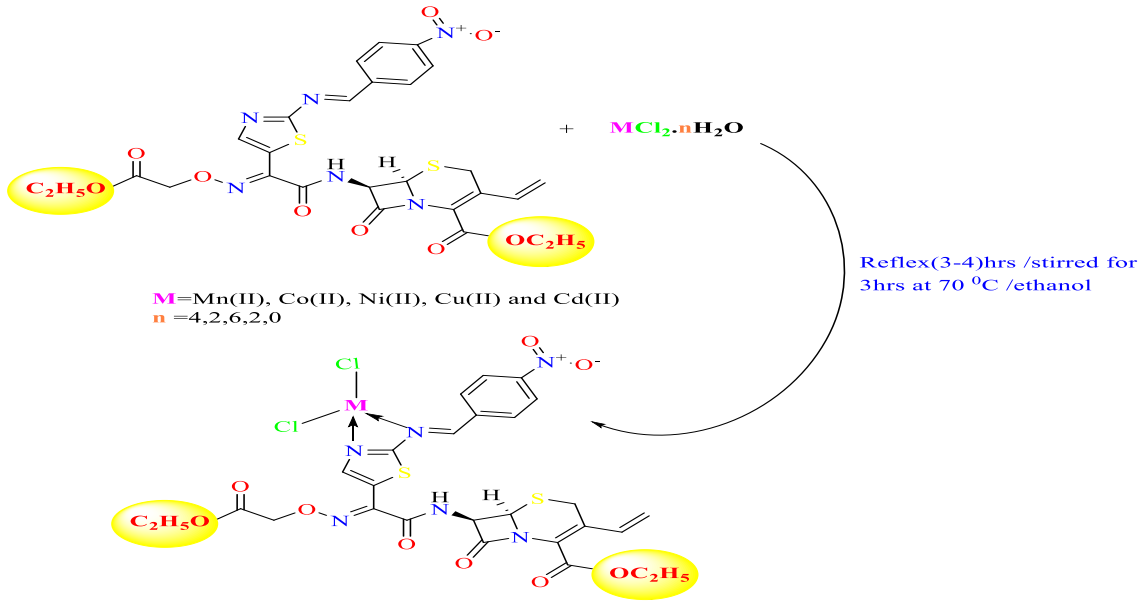


ethyl (6*R*,7*R*)-7-((*E*)-2-((2-ethoxy-2-oxoethoxy)imino)-2-(2-(((*E*)-4-nitrobenzylidene)amino)thiazol-4-yl)acetamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (L)

Scheme1. Synthesis of ligand (L)

2.4. Synthesis of the complexes [13]

The copper complex was prepared with a molar ratio of (1:1) (M:L) using a 100mL round flask by adding (0.17gm). (1mmol) of copper chloride ($CuCl_2.2H_2O$) dissolved in (10mL) ethanol to the ligand solution (L) resulting from dissolving (0.64gm, 1mmol) in (10mL) ethanol and leave the mixture at a temperature of 70 °C with continuous stirring and reflux for (3 hours). Filter the solution to obtain the precipitate (green). It was washed several times with distilled water and diethyl ether and recrystallized with absolute methanol. Then the percentage of the product, which was (73%), and the melting point (104-106)°C were calculated. Preparation of the remaining complexes M= Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) of the prepared ligand (L), these complexes were prepared by the same method mentioned, Scheme 2.



Scheme2. The preparation method of complexes $[M(L)Cl_2]$

3. Result and Discussion

Thermal stability and the nature of the colored solid are the most important characteristics of the prepared metal complexes. The theoretical and practical data of (CHN) Microanalysis for all prepared complexes were approximated, Table 1.

Table 1. Different physical data of ligand with complexes

Com.	Color	M.wt	m. p (°C)	Found (Calc.) (%)						Λ_M ($cm^2\ \Omega^{-1}$ Mol^{-1})
				M	C	H	N	S	Cl	
(L)	Yellow	642.66	122-124 °C	-	50.32 (50.46)	4.11 (4.08)	13.15 (13.08)	9.82 (9.98)	-	-
$[Mn(L)Cl_2]$	Yellow	768.50	244-246 °C	7.39 (7.15)	42.34 (42.20)	3.35 (3.41)	10.87 (10.94)	8.39 (8.34)	9.28 (9.23)	17.5
$[Co(L)Cl_2]$	Green	772.49	112-114 °C	7.59 (7.63)	41.70 (41.98)	3.56 (3.39)	10.76 (10.88)	8.12 (8.30)	9.24 (9.18)	20.2
$[Ni(L)Cl_2]$	Brown yellow	772.25	250-252 °C	7.55 (7.60)	41.78 (41.99)	3.36 (3.39)	10.92 (10.88)	8.31 (8.30)	9.22 (9.18)	21
$[Cu(L)Cl_2]$	Green	777.10	104-106 °C	8.23 (8.18)	41.81 (41.73)	3.45 (3.37)	10.83 (10.81)	8.29 (8.25)	9.26 (9.12)	18
$[Cd(L)Cl_2]$	Yellow	825.97	135-137 °C	13.65 (13.61)	39.33 (39.26)	3.19 (3.17)	10.49 (10.17)	7.83 (7.76)	8.60 (8.58)	14

3.1. FT-IR spectrum of new Schiff base ligand

In Table 2, the ligand (L) was identified by studying its infrared spectrum shown in Figure 1, where strong band at (3340) cm^{-1} cm was observed, is attributed to the frequency υ(N–H)str. As for the two sharp, strong bands at wave numbers (1751)cm^{-1} and (1689)cm^{-1}, they are attributed to the stretching frequency bands of the carbonyl group υ(C=O)ester and υ(C=O)amide respectively, with the appearance of other stretching frequency bands at (1597)cm^{-1}, (1454)cm^{-1} and (1215,1099)cm^{-1} belong to the aggregates $\upsilon(C=N)_{five\ ring}$, $\upsilon(N\text{-}H)_{bend,}$ $\upsilon(C\text{-}O\text{-}C)_{ester}$ respectively and finally a band appears at the wave number (1620)cm^{-1} is due to $\upsilon(CH=N)_{imine}$ for the Schiff base ligand [14].

3.2. FT-IR spectrum of metal complexes

The prepared complexes were identified by following their infrared spectra and comparing them with the spectrum of the prepared ligand (L). It was observed that some bands shifted and new bands appeared while other bands remained stable. The infrared spectra of the metal complexes of the ligand showed (L) represented by Figure 1 is absorption bands within the range (3394-3275) cm^{-1}, (1724-1743) cm^{-1} and (1674-1647) cm^{-1} attributed to $\upsilon(N–H)_{str.}$, $\upsilon(C=O)_{ester}$ and $\upsilon(C=O)_{amide}$ respectively, which did not participate in the coordination of the prepared complexes, while the coordination of the ligand (L) with the metal ions was revealed through absorption bands of the order of (1635-1616) and (1600-1593) cm^{-1} , which are attributed to the groups of $\upsilon(C=N)_{imine}$ and $\upsilon(C=N)_{five\ ring}$ respectively, which were shifted towards different frequencies compared to their absorption band in the free ligand (L). What enhances this consistency is the appearance of weak absorption bands in the range (570-528) and (532-439) cm^{-1} attributed to the υ(M-N) band in the complexes.[15-17], Table 2.

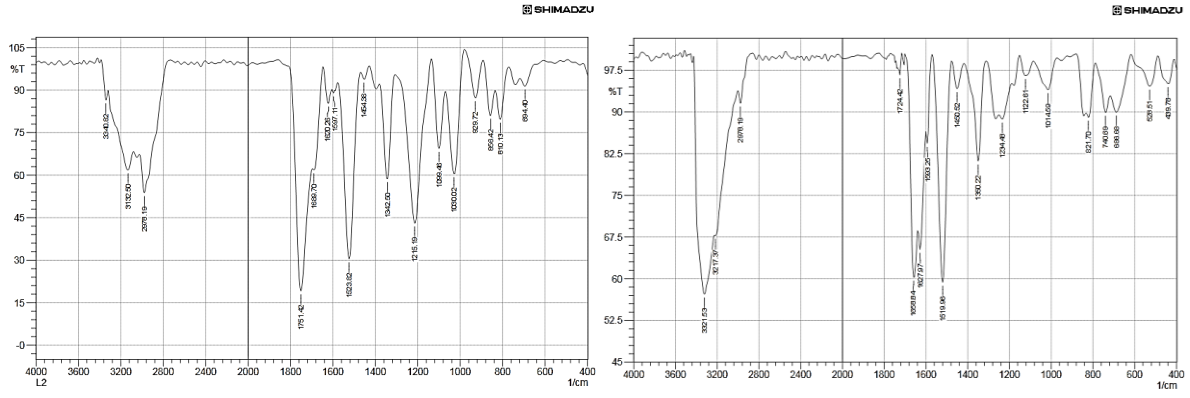


Figure 1. FTIR spectrum of L and $NiLCl_2$

Table 2. FTIR data of ligand with complexes

Com.	υ (N-H)$_{str.}$ υ (N-H)$_{bend}$	υ (C=O) υ (C-O-C) ester	υ (C=N) five ring	υ (C=O) amide	υ (C=N) imine	υ (M - N) υ (M - N)
(L)	3340 1454	1751 1215 1099	1597	1689	1620	—— ——
[Mn(L)Cl$_2$]	3340 1450	1728 1265 1122	1608	1647	1624	536 470
[Co(L)Cl$_2$]	3394 1454	1743 1230 1176	1600	1651	1616	570 520
[Ni(L)Cl$_2$]	3321 1450	1724 1234 1122	1593	1658	1627	528 439
[Cu(L)Cl$_2$]	3294 1446	1739 1230 1180	1604	1674	1635	570 516
[Cd(L)Cl$_2$]	3275 1450	1724 1230 1122	1600	1647	1631	563 532

3.4. ^{1}H,^{13}CNMR spectra

The Proton NMR spectral data of ligand L is listed in Table 3, Figure 2 [18].

Table 3. Proton NMR data for ligand with DMSO-d6

Ligand	Protons Type	Protons number	δ (ppm)
L	6H, proton 2CH$_3$ group	H11	0.83-1.74 (m)
	2H, proton S-CH$_2$ group	H4	3.37-3.72 (m)
	6H, proton 3O-CH$_2$ group	H10, H26	3.94-4.30 (m)
	5H, proton C-H group	H6, H7, H12, H13	4.78-5.17 (m)
	2H, proton C-H $_{aromatic}$ group	H23	7.30-7.80 (m)
	2H, proton C-H $_{aromatic}$ group	H24	7.95-8.39 (m)
	1H, proton NH group	-------	9.04 (s)
	1H, proton N=CH group	H21	9.18 (s)
	1H, proton C=CH-S group	H20	10.16 (s)

The Carbon NMR data of ligand L is listed in Table 4, Figure 2 [19].

Table 4. Carbon NMR data for ligand with DMSO-d6

Ligand	Carbons kind	Carbons number	δ (ppm)
L	2C, CH_3	C11	14.51
	1C, S-CH_2	C4	29.81
	1C, N-CH	C7	61.19
	2C, O-CH_2	C10	61.56
	1C, S-C-N	C6	67.84
	1C, $NOCH_2$	C26	72.39
	1C, =CH_2	C13	118.30
	1C, N-C=	C2	123.78
	1C, S-CH=	C20	124.07
	2C, CH aromatic	C23	124.75
	1C, =CH	C12	127.79
	2C, CH aromatic	C24	131.14
	1C, C aromatic	C22	131.27
	1C, C-Cl	C25	139.91
	1C, =C	C3	140.50
	1C, =C	C19	146.97
	1C, C=N	C15	151.03
	1C, C=N	C21	160.73
	1C,NHCO	C14	161.93
	1C, NC=O	C8	163.90
	1C, OC=O	C9	167.44
	1C, OC=O	C27	168.82
	1C, N=C-N	C17	169.28

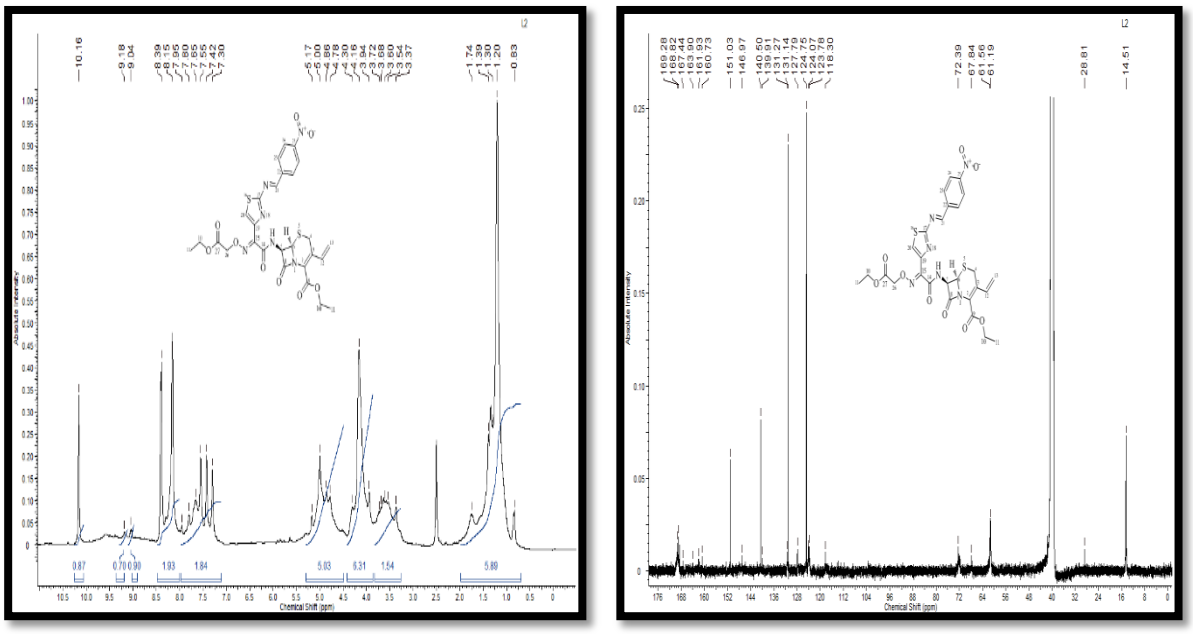


Figure 2. $^{1}H,^{13}C$NMR spectrum of ligand L

3.5 Electronic spectra

The electronic transition of the prepared ligand and its complexes [20,21]are listed in the Table 5 and Figure 3.

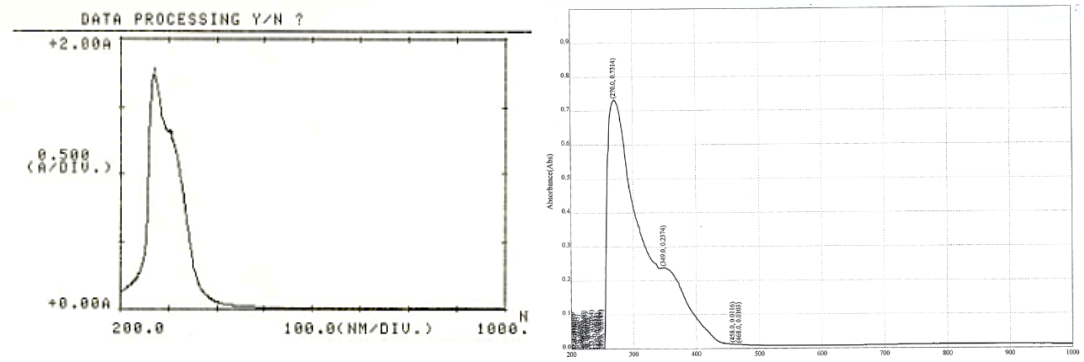


Figure 3. Electronic spectrum of ligand L and $[CuLCl_2]$ complex

Table 5. UV/Vis data of ligand with complexes.

Compound	Band position (λnm)	υ^-(cm^{-1})	Extinction coefficient ε_{max} dm^3 mol^{-1} cm^{-1})	Assignment
$C_{27}H_{26}N_6O_9S_2$ (L)	269	37174	1741	$\pi \rightarrow \pi^*$
$[Mn(L)Cl_2]$	272 353 533 559	36764 28328 18761 17.889	220.7 91.3 13.3 7.8	I.L C.T $^6A_1 \rightarrow {}^4T_{1(G)}$ $^6A_1 \rightarrow {}^4T_{1(G)}$
$[Co(L)Cl_2]$	338 356 465 615 682	29.585 28.089 21.505 16.260 14.662	494.0 555.1 23.8 94.9 6	I.L I.L C.T $^4A_2 \rightarrow {}^4T_{1(P)}$ $^4A_2 \rightarrow {}^4T_{1(P)}$
$[Ni(L)Cl_2]$	270 338 355 538 750	37,037 29.585 28.169 18.587 13.333	1251.8 446.4 504.0 14.3 18.5	I.L I.L C.T $^3T_1 \rightarrow {}^3T_{1(P)}$ $^3T_{1\,(F)} \rightarrow {}^3A_{2(F)}$
$[Cu(L)Cl_2]$	349 458 468 551 940	28.653 21.834 21.367 18.148 10.638	237.4 11.6 10.3 15.4 162.0	I.L C.T C.T C.T $^2T_2 \rightarrow {}^2E$
$[Cd(L)Cl_2]$	338 355 475	29.585 28.169 21.052	744.4 837.7 150	I.L I.L C.T

CT = Charge of Transfer IL=Intra of Ligand

3.5. Magnetic moments and Conductivity measurements

The Mn(II), Co(II), Ni(II), and Cu(II) complexes exhibit μeff (5.96, 4.69, 3.72 and 2.03) B.M respectively of L these normal values are consistent with tetrahedral complexes. The non- electrolytes nature of all metal complexes was confirmed by molecular conductivity measurements [22].

3.6. Study of biological activity

An examination of the biological effectiveness of the prepared compounds against bacteria (G^-) *Coli Escherichia* and *Klebsiella pneumoniae* & (G^+) *Staphylococcus aureus* and *Staphylococcus epidermidis* and fungi *Candida albicans* were carried out using the diffusion study. With Muller Hinton Agar to grow the selected bacteria, concentration ($1x10^{-3}$M) and solvent (DMSO), the chemical solutions prepared for the study were first prepared and the dishes were incubated at a temperature of (37°C) for one day. Then the effectiveness was determined by the ability of the compounds to inhibit the selected bacteria by calculating the diameter of inhibition for each sample [23], Table 6 and Figure 4.

Table 6. Anti-bacterial activity data for the prepared compounds

NO.	*Com.*	*S. aureus*	*S. epidermidis*	*E. coli*	*K. spp.*	*C. albicans*
1	Cefixime (Antibiotics)	29	44	10	22	-----
2	L	25	20	20	20	24
3	$[Mn(L)Cl_2]$	24	27	22	25	28
4	$[Co(L)Cl_2]$	32	34	29	29	29
5	$[Ni(L)Cl_2]$	32	29	20	17	25
6	$[Cu(L)Cl_2]$	27	26	25	22	25
7	$[Cd(L)Cl_2]$	29	30	24	25	25

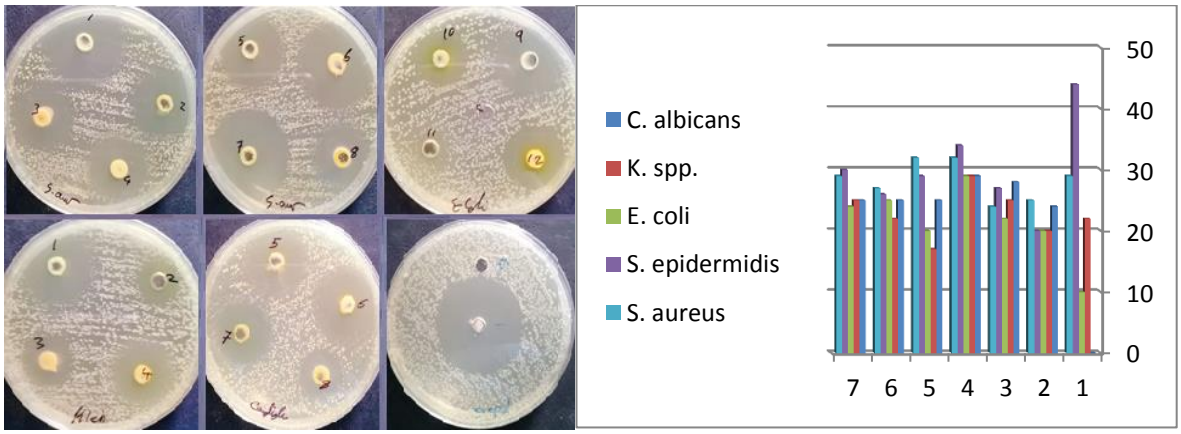
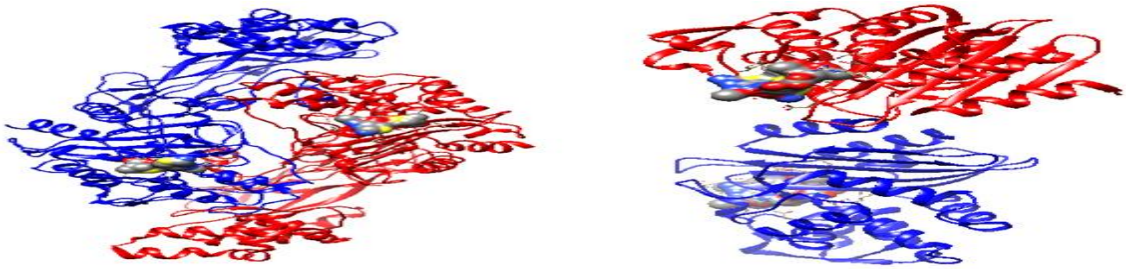


Figure 4. Effect of prepared compounds on selected bacteria

3.7. Theoretical study (docking study)

The deposited protein structures from the PDB database were in pdb format, Autodock4 software [24] for preparing protein structures (deletes waters, repair missed atoms, adding polar hydrogens, add charges, delete ligands and unwanted peptide chains). Building and optimizing molecular structures was performed using Avogadro [25]. Docking process was done using CB-Dock2 online tool [26], with benefiting from templet cavity search to focus docking process to the reported active site. Chimera software [27] was used in image processing and analysis of the docking results. The 2D interaction plot was instructed by LigPlot+ tool [28].

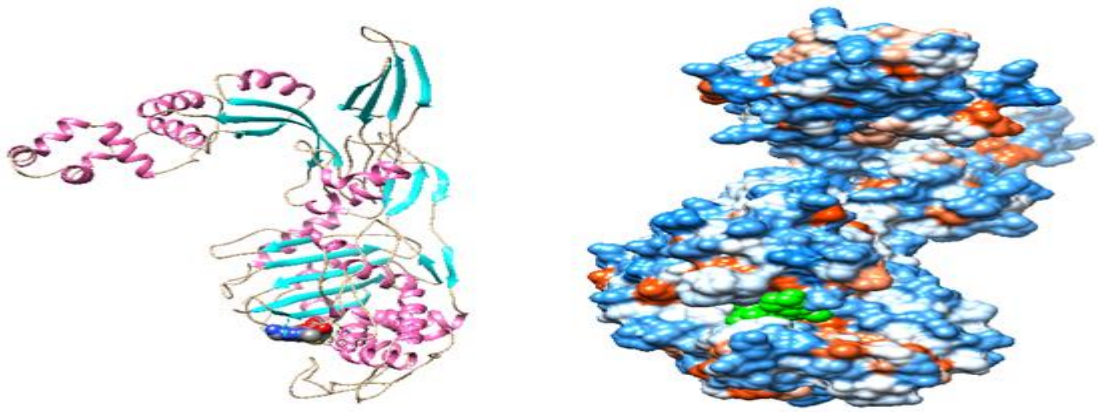
The crystal structures of Penicillin-Binding Protein 3 (PBP3) have been described by [29] the protein was identified as a dimer consists of two identical peptide chains from methicillin-resistant *Staphylococcus aureus* bacteria, in the complex form with cefotaxime antibiotic. The protein was indexed in the PDB database https://www.rcsb.org/structure/3vsl. By the symbol 3vsl as shown in Figure 5. In *Escherichia coli* bacteria, the target protein was β-Lactamase belong to the family CTX-M which indexed in PDB database by 3hlw https://www.rcsb.org/structure/3hlw. The structure of this protein also determined by X-ray single crystal with its complex with cefotaxime by [30] the protein also formed from 2 chains but topologically and structurally different from that of *Staphylococcus aureus* bacteria, the structure is shown in Figure 5. In both proteins chain A was selected to perform docking studies.



(a) (b)

Figure 5. (1a) 3D structure of the protein 3vsl complex with cefotaxime, (1b) 3D structure of the protein 3hlw complex with cefotaxime.

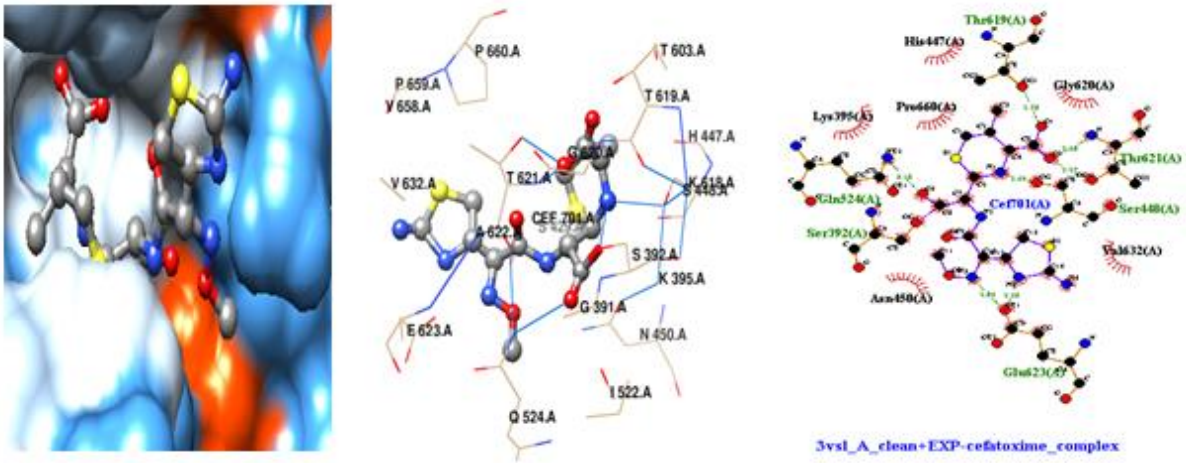
3vsl_A active site located at the edge of plane consists of five parallel β-sheets surrounded by ten randomly distributed α-helixes at a cavity contain both hydrophobic and hydrophilic regions as well, so the cefotaxime molecule complement with the cavity as shown in the in Figure 6.



(a) (b)

Figure 6. Active site location at the protein 3vsl_A (a) ribbon mode, (b) surface hydrophilicity mode.

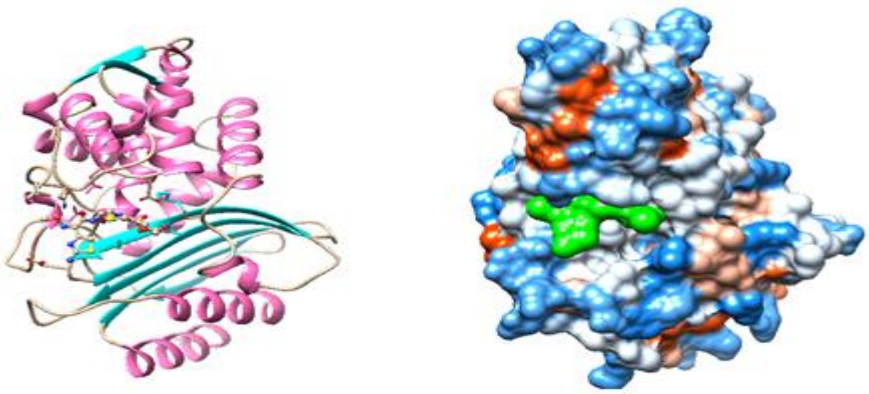
Figure (7) shows the β-lactam ring of cefotaxime was already opened and formed covalent bonding with S392 beside a net of hydrogen bindings with T619, T621, S448, G623 and G524 of the protein 3vsl_A.



(a) (b) (c)

Figure 7. Cefotaxime interaction in the 3vsl_A active site, (a) polarity environment. (b) 3D interaction plot. (c) 2D interaction plot.

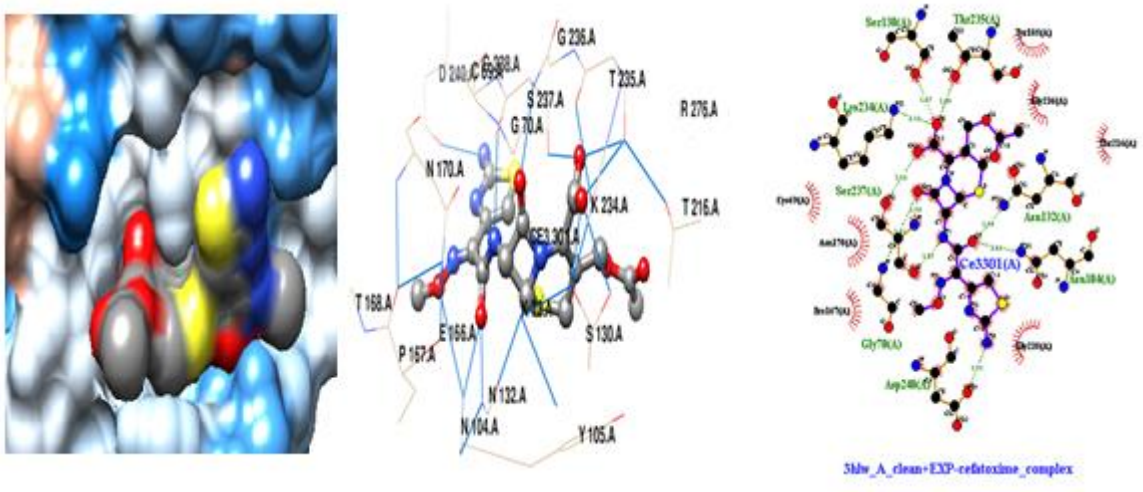
In the protein 3hlw_A, active site located also at the edge of plane of 5 β-sheets but not at the side part of the protein; instead it is mediated between the β-sheets and the collection of randomly oriented α-helixes as shown in in Figure 8.



(a) (b)

Figure 8. Active site location at the protein 3hlw_A (a) ribbon mode, (b) surface hydrophilicity mode

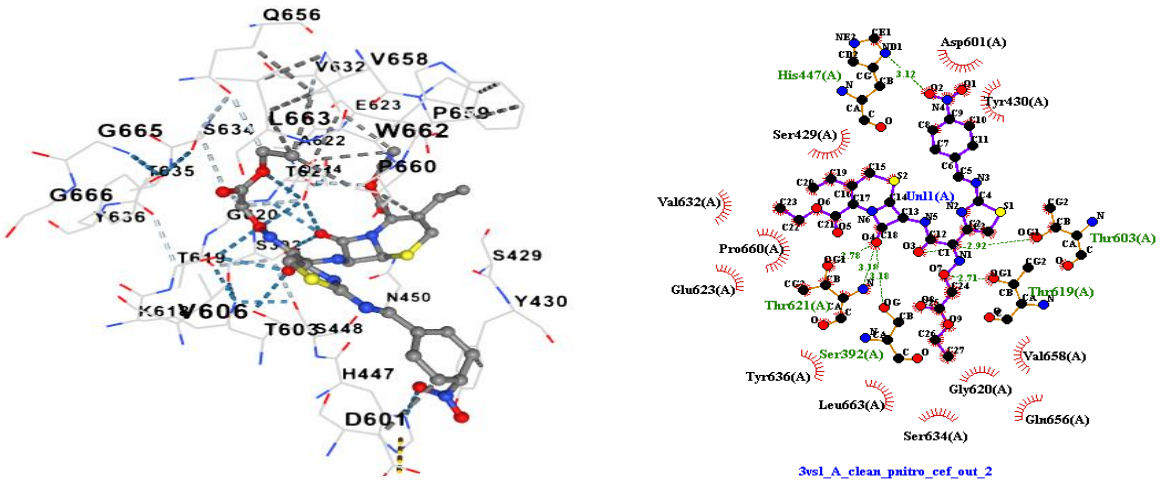
The hydrophilic environment is common character of the active site. By examining the active site interaction details it is found another difference, which is β-lactam ring of cefatoxime is conserved and the interactions are limited to physical forces, like hydrogen bindings which include S130, K234, T235, N132, N104, D240, G70, S237. As shown in in Figure 9.



(a) (b) (c)

Figure 9. Cefatoxime interaction with active site cavity of 3hlw_A. (a) active site poket. (b) 3D interaction plot (c) 2D interaction plot

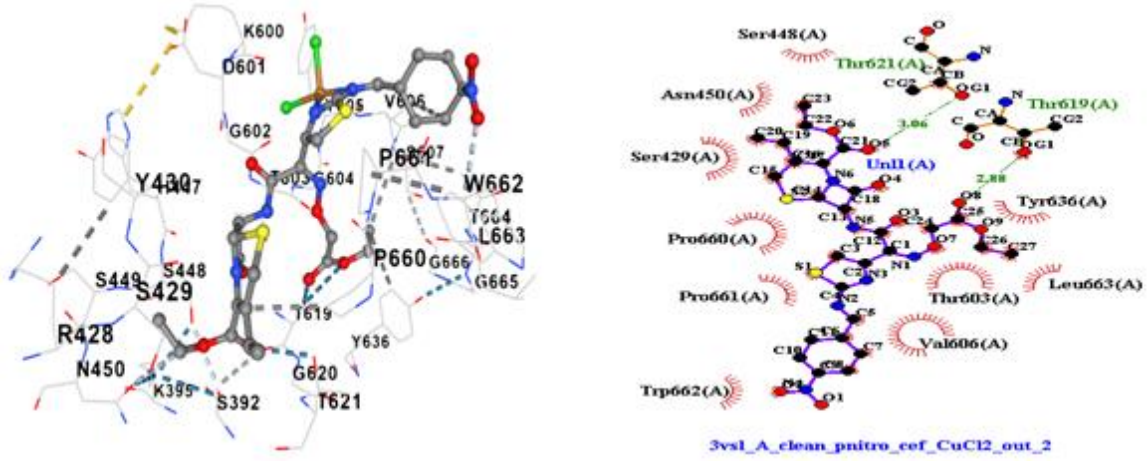
L ligand further increase the strength of the interaction with 3vsl_A active site, mainlly by hydrogen bonding, these interactions are {T621, S392} with β-lactam carbonyl, T619 with oxime group, T603 with external amide and H447 with nitro group. As shown in Figure 10.



(a) **(b)**

Figure 10. Interactions plot of L with active site cavity of protein 3vsl_A. (a) 3D plot. (b) 2D plot.

The less number of hydrogen bindings in the 3vsl_A active site took place in the interaction with $LCuCl_2$ coordination complex which limited to T621 with ethyl carboxylate group and T619 with oximic side chain, but from the vina score the strength of the interaction is more larger than that of the previous coordination complex which is due to the other physical forces (dipole-diple, electrostatic and Van der Waals) are more appreciable in this system. The interaction is shown in Figure 11.

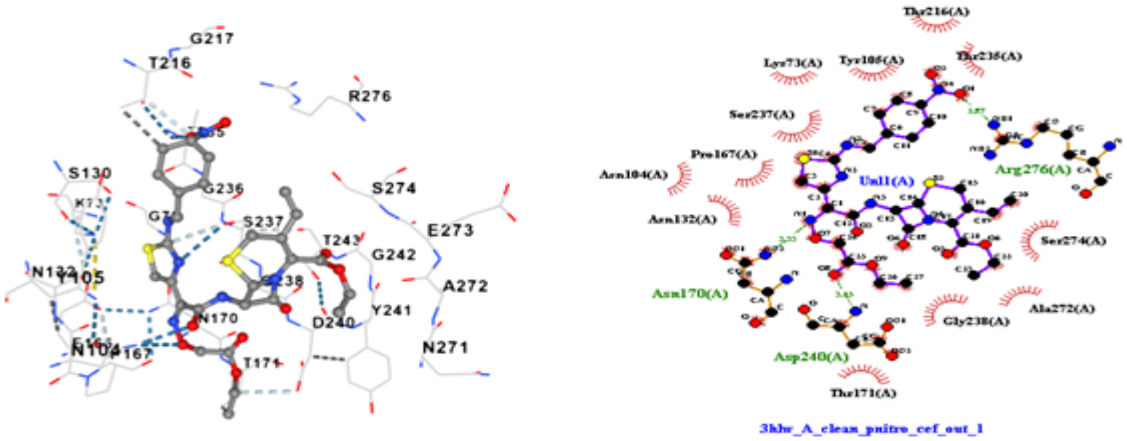


(a) **(b)**

Figure 11. Interaction plots of LCuCl2 with active site cavity of protein 3vsl_A. (a) 3D plot. (b) 2D plot.

The effect of strong withdrowing property of the NO_2 group have an appresiable effect on the totla polarization of the the whole molecule making the interaction on stronger with hydrophilic active site of the protrein 3hlw_A even

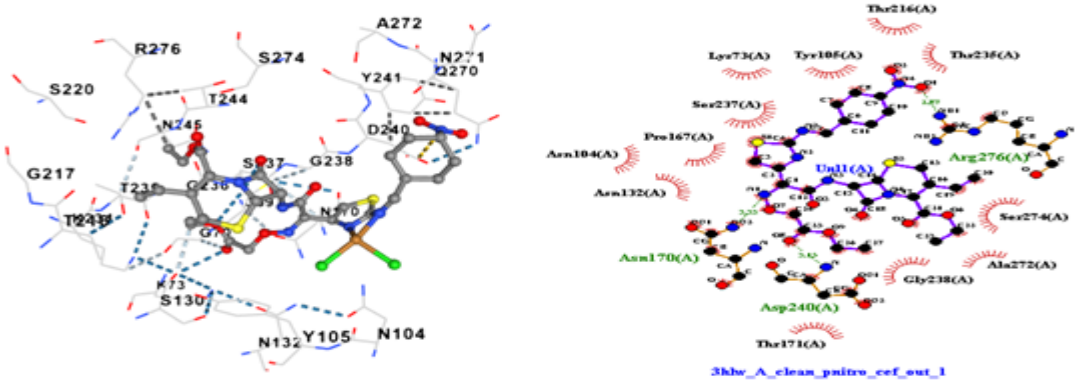
with small number of hydrogen bonds. L ligand interacts by hydrogen bonding through {R276 with nitro group, N170 with oximic nitrogen and D240 with ethyl carboxylate} as shown in Figure 12.



(a) (b)

Figure 12. Interactions plot of L with active site cavity of protein 3hlw_A. (a) 3D plot. (b) 2D plot.

$LCuCl_2$ coordination complex have 3 HB interactions with 3hlw_A active site, these interactions are {R276 with NO_2, N170 with oximic N and D240 with ethyl carboxylate} which are shown in Figure 13



(a) (b)

Figure 13. Interactions plot of LCuCl2 with active site cavity of protein 3hlw_A. (a) 3D plot. (b) 2D plot.

The docking study for the above compounds with 3vsl_A and 3hlw_A proteins is summarized in Table 7:

Table 7. The docking Results and the practical biological activity

3vcl_A					
Ligand Molecule	Vina Score (kcal/mole)	Cavity volume (Å3)	Center (x, y, z)	Docking size (x, y, z)	prac_bio
cefotaxime	-7.5	2955	19, -50, 25	26, 22, 12	29
L	-8	2955	19, -50, 25	28, 28, 28	25
$LCuCl_2$	-7.4	2955	19, -50, 25	26, 22, 12	32

3hlw_A					
Ligand Molecule	Vina Score (kcal/mole)	Cavity volume (Å3)	Center (x, y, z)	Docking size (x, y, z)	prac_bio
cefotaxime	-7.1	857	22, 55, 14	24, 24, 24	10
L	-7.1	857	22, 55, 14	28, 28, 28	20
$LCuCl_2$	-6.9	857	22, 55, 14	26, 26, 26	20

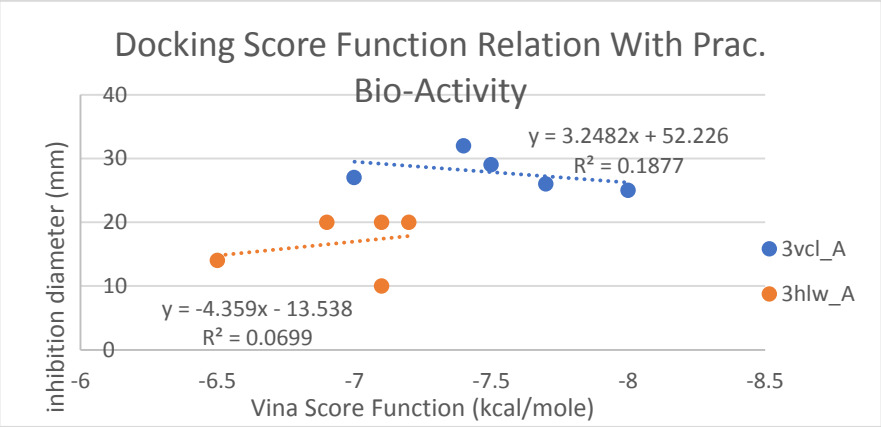


Figure 14. A plot of estimate the relation of the calculated docking score with results of the biological activity

From the resulted R2 values in Figure 14, we can estimate a weak causualty relation between the two quantities. This can be explained with three asumptions, the simplest one is that: the grouth inhibition behavior that effected by the prepared compounds, dosen't depend in their action on the studied proteins, but on the other enzymatic systems. This asumpsion urge to further computational investigation to another proteins or enzymatic systems for the above bacterial species.

The second assumption states that: the increasing strength of the interaction between the studied compounds and the active site of the proteins acts to increase the compound biological activity (grouth inhibition), by sabatge the ability of these enzymes to hydrolize β-lactam ring. If this asumption is true this means the mutations that performed on the original structure of cefotaxime was increased the protection of the β-lactam ring from the enzymatic hydrolysis. This situation can be realized if there is a direct proportion between docking score and bio-activity similar to the 3hlw_A apparent behavior.

The last asumption raies from reverse proportion between these parameters, which means: the structural modification of the cefatoxime compound act to produse weaklly interacted compounds with active site of β-lactamase enzymes resulting a new antibiotics less varunable to these enzymes. The second and third asumption require a larger set of the tested compounds to deduse which proportion is true one direct or reverse [32,33].

4. Conclusion

The summary of the work is to prepare a Schiff base ligand with five metal complexes that were characterized by different methods, and from the results of these measurements, the tetrahedral geometric structure was proposed. The biological activity of the prepared compounds was examined, which showed different results between the ligand and its complexes. Molecular docking was studied and the results were discussed for the highest interaction modes between the studied compounds and the target proteins in terms of the type of binding and binding energy**.**

Acknowledgement

Sincere thanks and appreciation to the staff of the Chemistry Department for their cooperation throughout the research period.

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