Preparation, characterization and biological activity of some transition metal (II) complexes containing cephalexin and cefotaxime sodium

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Abstract:

A series of mixed ligand complexes of cephalexin and cefotaxime sodium were prepared. All complexes were characterized by molar conductivity, IR and UV-Visible spectroscopy. All the complexes have Oh geometry with general formula $\{M(L1)(L2)(H_2O)_2\}$, where M= Co(II), Cu(II), Ni(II), V(II), L1= cephalexin, L2= cefotaxime sodium. Antibacterial activity of all the synthesized complexes and ligands were tested against some bacteria. The antibacterial activities of all compounds in case of Pseudomonas aeruginosa at DMSO (10 mg/ml) concentration exhibit not active. The Staphylococcus aureus, Escherichia coli, Salmonella some metal complexes exhibit more activity than ligand.

Keywords: Synthesis, characterization, metal complexes, cefotaxime, cephalexin, antimicrobial.

1. Introduction:

The antimicrobial agents coming on the top of the list of the most commonly misused drugs in the world [1]. The antibiotic-resistance pathogens are appeared widely as consequence for the widespread use of antimicrobial agents, which increased the need for new drugs. To increase the natural resistance of the body, it is strongly recommended to reduce the improper use of antibiotics. The reason behind developing resistance to amicrobial agents related to the failure of some of these agents to access their places of work [2]. In order to create new novel agents (complex compounds), there is a need to incorporate old antimicrobial agents with the ions of transition metals. The new created complexes will work on a broader range of microbes and widen their spectrum. Transition metal complexes may be cationic, neutral or anionic species where the ion of these transition metals is coordinated with ligands [3].

The metal complex form of the drugs has different pharmacological and toxicological behaviors which may be better or worse than the original antimicrobial agents. The mixed ligand or antibiotic metal complexes of transition metals are much better in their efficacy if compared with their parent drugs used, these complexes showing big differences in their nature of working [4].

In 2005, Anacona J.R. and Gladys D.S. prepared a series of complexes from reacting Cefotaxime (Hcefotax) with transition metal ions to give [M(cefotax)Cl] complexes (M = Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Cd(II)) [2]. They characterized the complexes by the IR and the ^{1}H-NMR spectra, which suggest that the complexes have tetrahedral geometry and cefotaxime behaves as monoanionic tridentate ligand. They screen the complexes for antibacterial activity against several bacteria, and they compared the results with the activity of cefotaxime to find that The antibiotic and the complexes presented bactericide diameters larger than 20 mm being highly sensitive. Also, they found that [Cu(cefotax)Cl] complex was found to have higher activity than that of cefotaxime against the bacteria strains studied under the test conditions.

In 2014, Aurora Reiss and et al, published an about transition metal(II) complexes with cefotaxime-derived schiff-base [5]. The characterization for the complexes were done by conductance, elemental analysis, magnetic measurements, IR, and UV-Vis spectroscopy. The low molar conductance values indicate nonelectrolyte type of complexes. An octahedral geometry may be proposed for Co(II), Ni(II), and Zn(II) complexes while a tetragonal geometry for Cu(II) complex, this based on the spectral data and magnetic moments. The synthesized complexes in this research study were tested for in vitro antibacterial activity against some pathogenic bacterial strains, namely Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacillus subtilis, and Staphylococcus aureus. The MIC values shown by the complexes against these bacterial strains in this research work revealed that the metal complexes possess superior antibacterial activity than the Schiff base.

In 2015, Abdulghani A. J. and et al. published an articles [6]. Two Schiff base derivatives of cefotaxime antibiotic (CFX) were used. They prepared metal complexes of the two Schiff base ligands with Co(II), Ni(II), Cu(II), Cd(II), Pd(II) and Pt(IV) ions by reacting each ligand with the metal salts in refluxing ethanol. The chemical structures of the two ligands as well as the stereo chemical structures and geometries of the studied metal complexes were suggested depending the results obtained from CHN and TG analysis, NMR, FTIR, atomic absorption spectrophotometry, electronic spectra, magnetic moments and conductivity measurements.

2. Methodology:

2.1 Chemicals

All the chemicals used in this work were obtained from different companies such as Fluka, Sigma-aldrich.

2.2 Instrumentation

a. Melting point and decomposition of the ligands and complexes were determined on a BÜCHI melting point B-545.
b. IR spectra were recorded in the 400-4000 cm^{-1} range using KBr disc on Shimadzu FT-IR spectrophotometer of college education in Salahaddin University.
c. The Conductivity of the ligands and complexes were determined on. ECOSCAN 6 conductivity meter, eutech instrument
d. The electronic spectra for (10^{-3}M in DMF) of the synthesized complexes were measured on Cary 100 UV-Vis Spectrophotometer.

2.3 Synthesis of complexes:

2.3.1 Synthesis of Co, Cu and Ni complexes

An amount of (3.33 mmol, 1.22 g of L1) and (3.33 mmol, 1.6 g of L2) was dissolved in 25 ml of D. W. separately and then heated in a water bath until a clear solution obtained. The solutions L1, L2 were mixed with metal (II) chloride separately of [3.33 mmol, 0.79 g of $CoCl_2.6H_2O$, 3.33 mmol, 0.49 g of $NiCl_2.6H_2O$, 3.33 mmol, of 0.50 g of $CuCl_2.6H_2O$] respectively in 1:1:1 mole ratio. The mixtures were refluxed for 4 hrs (each one), then they left to evaporate the solvent and reduced to half of their initial volumes. The products were obtained by filtration, and then washed with cold water and diethyl ether [7]. The products were Recrystallized in ethanol.

2.3.2 Synthesis of Vanadium complex

A solution was prepared by dissolving (0.416 g) of (V_2O_5) in (0.75 ml conc. H_2SO_4) and (1ml of D. W.), then a 2.08 ml of ethanol was added to the solution. The mixture was refluxed for 1-2 hrs on a hot plate, in the beginning, the color of the solution was brownish-yellow, after a duration of 15-20 minutes the color was changed to green. The final product obtained after 1-2 hrs. was blue color due to the reduction of vanadium metal, and it was allowed to cool, and then the solution was filtered.

The aqueous solution of the [3.33 mmol, 1.22 g of L1 and 3.33 mmol, 1.6 g of L2] were mixed with filtrates of vanadium. To neutralize the solution (PH 7) a small amount of anhydrous sodium carbonate (Na_2CO_3) 10 g in 60 ml distilled water (using PH meter to adjust PH) were added to the solutions. The product observed by filtration. Recrystallize in chloroform and washed with cool water, diethyl ether.

2.4 Physical properties

Some physical Properties of prepared complexes illustrate in the following **Table 1**.

Table 1: Some physical Properties of prepared complexes.

Compound	Molecular formula	Molecular Weight	Color	Melting point C^0	Yield (g)
L1	$C_{16}H_{17}N_3O_4S$ H_2O	365.41	white	326.8	---
L2	$C_{16}H_{16}N_5NaO_7S_2$	477.45	Pale Yellow	163	---
$[Co(L1)(L2)(H_2O)_2]$	$Co(C_{32}H_{35}N_8NaO_{12}S_3)(H_2O)_2$	937.49	yellow	141*	2.0
$[Ni(L1)(L2)(H_2O)_2]$	$Ni(C_{32}H_{35}N_8NaO_{12}S_3)(H_2O)_2$	937.55	Yellowish-brown	191*	1.85
$[Cu(L1)(L2)(H_2O)_2]$	$Cu(C_{32}H_{35}N_8NaO_{12}S_3)(H_2O)_2$	942.40	Dark green	146*	1.20
$[V(L1)(L2)(H_2O)_2]$	$V(C_{32}H_{35}N_8NaO_{12}S_3)(H_2O)_2$	929.80	Pale Green	217*	0.93

*decomposition point.

3. Results and Discussions

3.1 Synthesis of mixed L1 and L2 complexes

Refluxing aqueous solutions of L1 and L2 with metal (II) chloride for 4 hrs. As illustrated in the following reaction **Scheme (1)**.

$$MCl_2.XH_2O \quad + L1 \quad + L2 \rightarrow \{M\,(L1)(L2)(H_2O)_2\} \quad + NaCl \; + \; HCl$$

L1= Cephalexin, L2= Cefotaxime sodium, M= Co, Ni, Cu, V

Scheme 1 : the general chemical reaction of preparation of complexes

3.2 Infrared absorption

The IR spectrum of the cephalexin (L1) **Fig.1**, contain the band at 2850 cm^{-1} due to stretching mode of NH^{3+}, confirming the presence of Zwitterionic form. A series broad bands at 3395-3000 assigned to OH from H_2O and amide NH stretch. The β-lactam carbonyl stretching appear at 1759 cm^{-1}. The Amide carbonyl stretch Appear at 1689 cm^{-1} and broad carboxylate stretching carbonyl appear at 1593 cm^{-1}. Absorption band observed at 2918 and 2883 cm^{-1}assigned to aliphatic C-H asymm, symm stretching vibration respectively. The band at 3049 cm^{-1} attribute to C-H aromatic str. [2] [7], see **Table 2**.

The ligand Cefotaxime sodium (L2) exhibits bands in the wave number regions at 3342and 3435 cm^{-1} due to the ʋs NH and ʋas NH stretching vibrations of L2 ligand. A characteristic band, arising from the stretching vibrations of the carbonyl group of the b-lactam ring, appeared at 1759 cm^{-1} in L2. **Fig.2**. [8].

Also band at 1730 cm^{-1} due to the stretching vibrations of the amide group of L2. The IR spectra of antisymmetric and symmetric stretching vibrations of the carboxylate group appear at 1608 cm^{-1} and 1386 cm^{-1} for L2 ligand [9] [10] [11].

The bands appear at 3251, 3043, 1647 and 1537 cm^{-1} attribute to str N-H, C-H aromatic C=O keton and C=N respectively in L2 ligand. [2] [6] [7] [12].

While comparing the IR spectra of ligand with complexes, a broad spectrum appeared above 3292 cm^{-1} to confirm coordinate water molecule in complexes [11].

The stretching vibrations of the carbonyl group of the β-lactam ring slightly changed the frequency in all complexes suggesting this group is not involved in complexation in both ligands.

The asymmetric and symmetric stretching vibrations of the carboxylate group appear in all complexes at lower and higher wave number. This may suggest that the caboxylate is involved in metal binding in both ligands [13].

The stretching vibrations of the amide group of L1and L2 shifted to lower frequency in all complexes suggesting the coordination of metals through amide carbonyl group in both ligands. Also appear band at 450 – 470 cm^{-1} is evidence to coordination M-O bonding [2] [5] [7] [12], see Fig. (3), Fig. (4), Fig. (5), Fig. (6).

Table 2: Some infrared data in cm^{-1} of ligand and metal complex.

Complexes	**υ(O-H)**	**υs(NH) υas(NH)**	**υ(C=O)βlacta**	**υs(C-H)str υas(C-H)str(alip)**	**υs(COO) υas(COO)**	**υ(C=O) amide**	**υM-O**
L1	3451	3273	1759	2883	1354	1689	-----
				2918	1593		
L2	-----	3342	1759	2880	1386	1730	-----
		3435		2981	1608		
{Co(L1)(L2)$(H_2O)_2$}	3319 b	-----	1759	-----	1381	1662	-----
				2945	1541		
{Ni(L1)(L2)$(H_2O)_2$}	3379 b	-----	1751	-----	1370	1670	-----
				2939	------		
{Cu(L1)(L2)$(H_2O)_2$}	3292 b	-----	1751	-----	1388	1670	470
				2939	1517		
{V(L1)(L2)$(H_2O)_2$}	3404 b	-----	-----	-----	1379	1647	450
					1533		

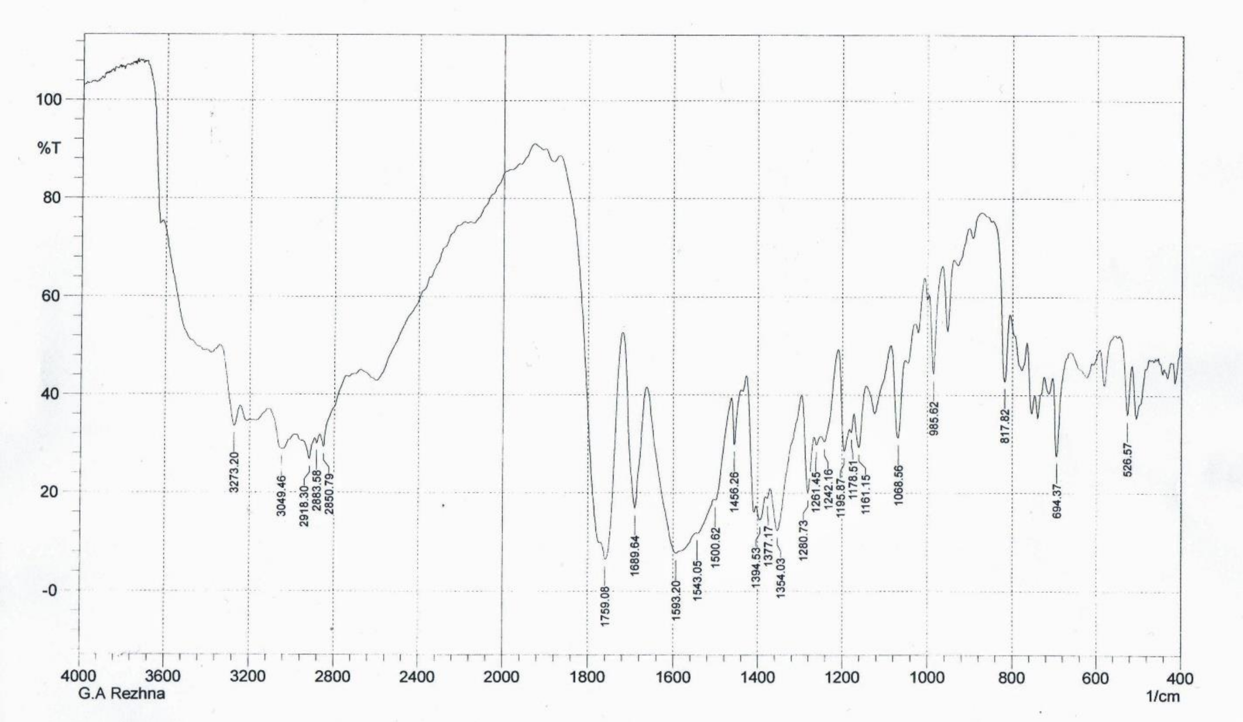

Figure 1: IR band of Cephalexin (L1).

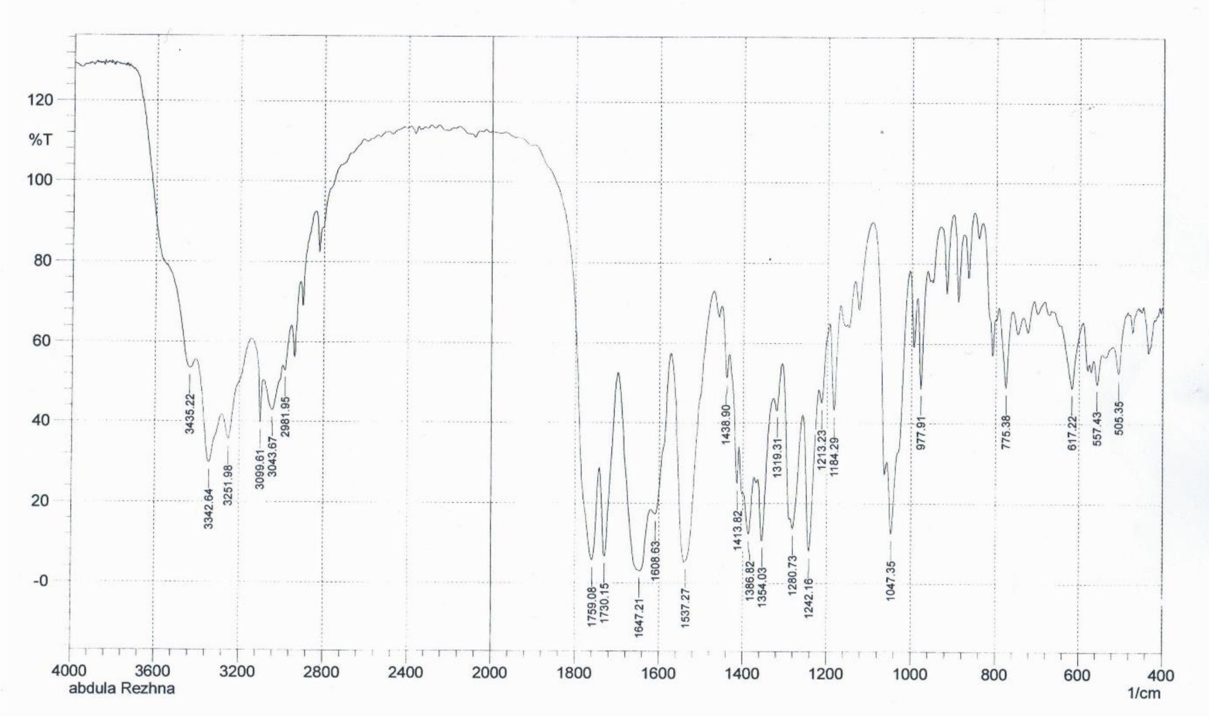

Figure 2: IR band of Cefotaxime sodium (L2).

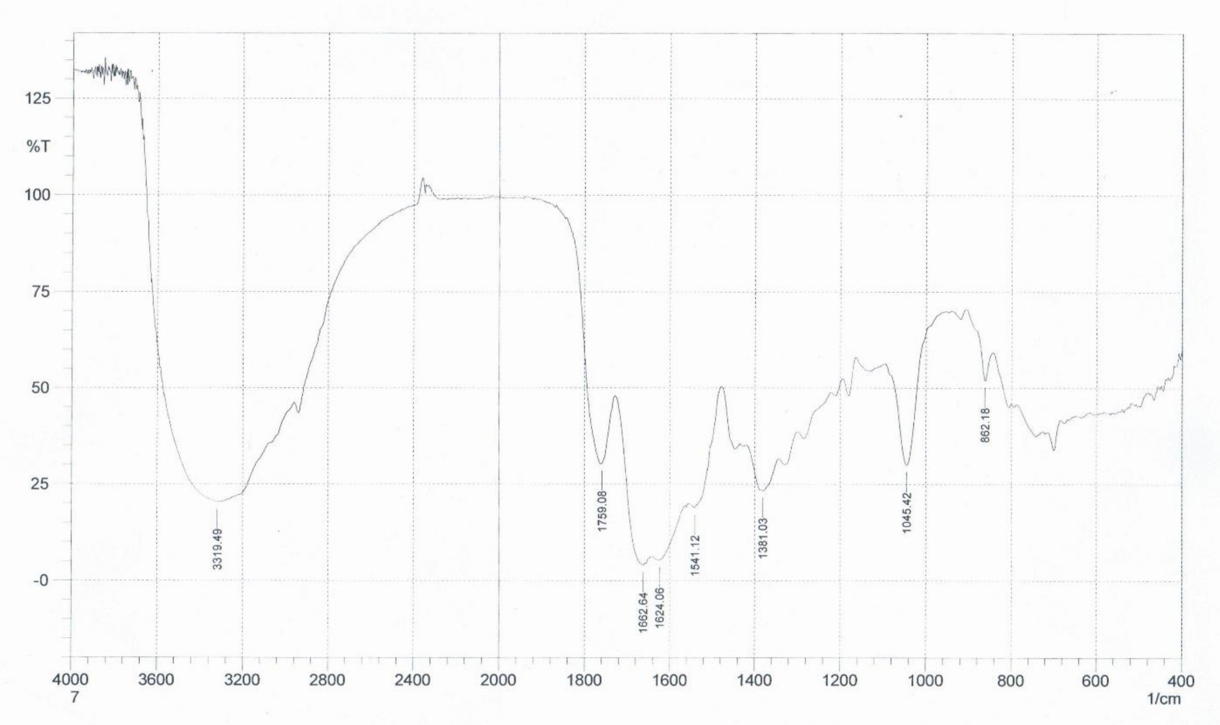

Figure 3: IR band of {Co(L1)(L2)$(H_2O)_2$}

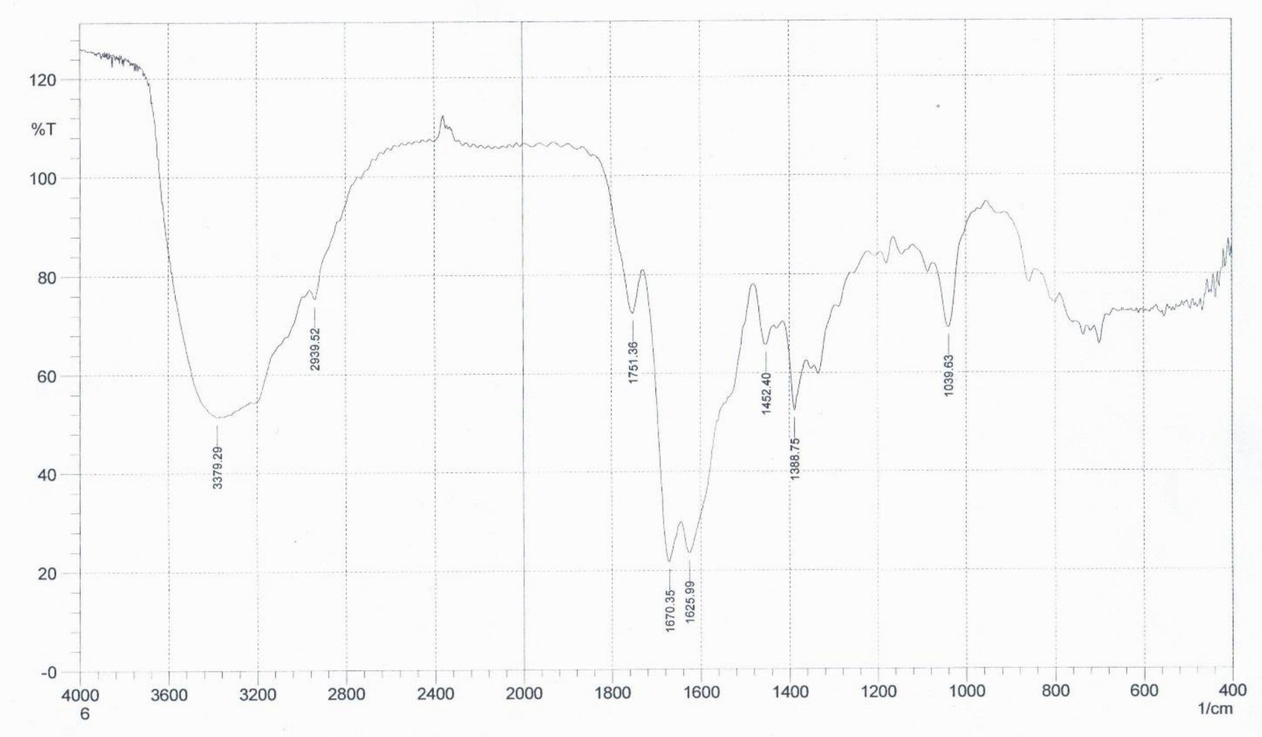

Figure 4: IR band of {Ni(L1)(L2)$(H_2O)_2$}

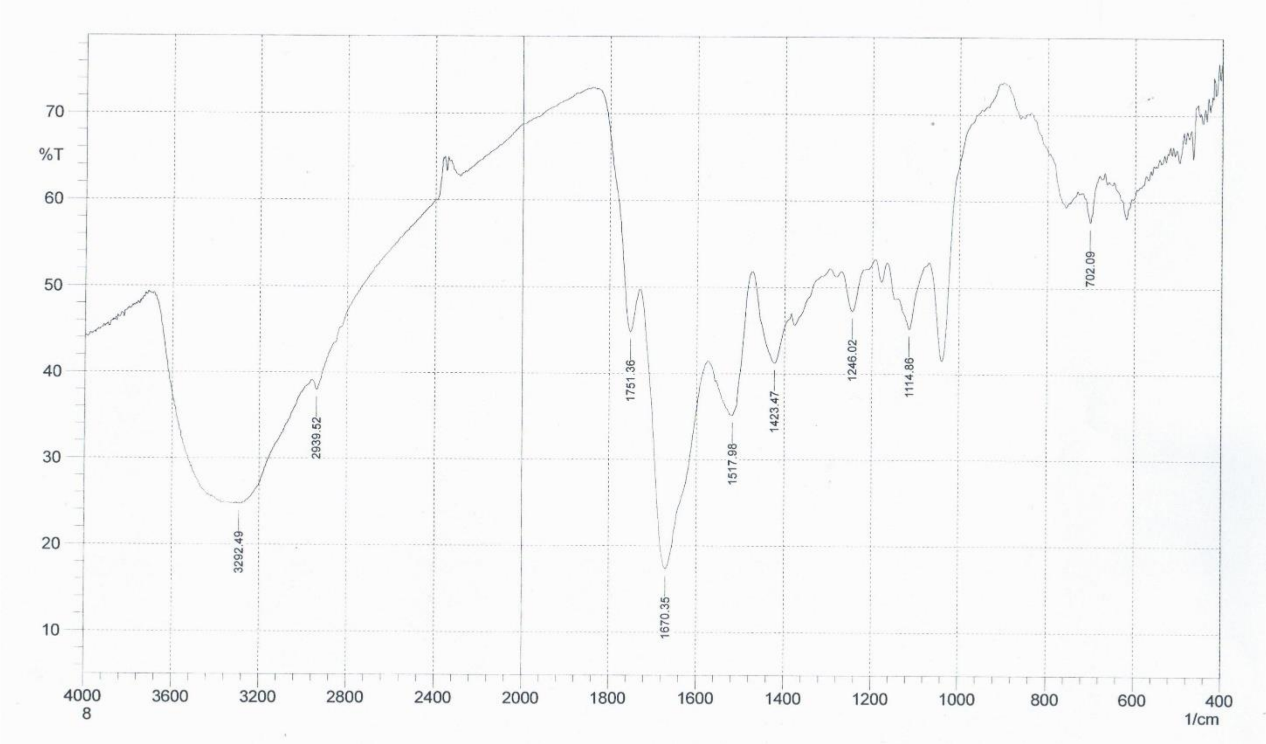

Figure 5: IR band of {Cu(L1)(L2)(H_2O)$_2$}

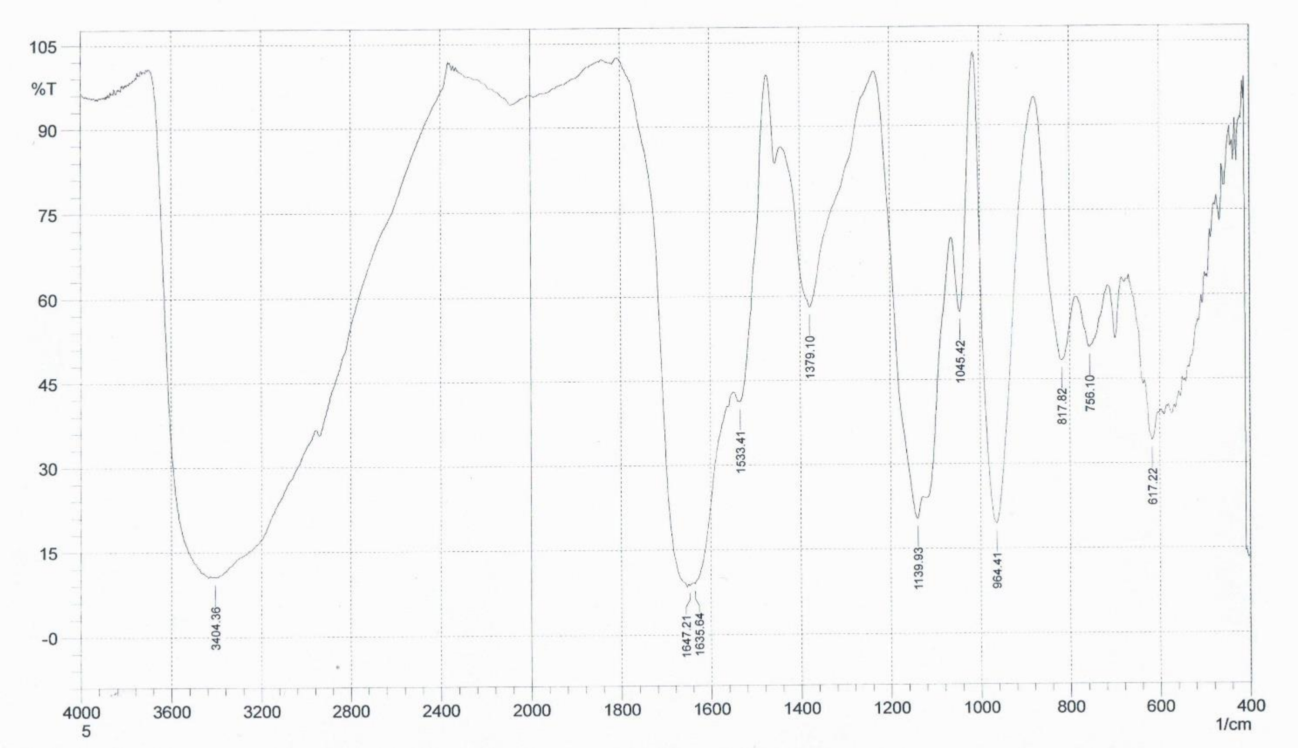

Figure 6: IR band of {V(L1)(L2)(H_2O)$_2$}

3.3 Electronic spectra of metal complexes

In this work the (UV-Vis) spectra of 10^{-3} M of L1 and L2 in DMF as a solvent, showed a bands at 306 nm which assigned to n-π*in L2 ligand. The band at 207 nm and 274nm which assigned to π-π* in L1 and L2 respectively.

The (UV-Vis) spectra of 10^{-3} M of four metal complexes, display absorption spectra of π-π* which are shifted to lower and higher wavelengths due to complexation. The disappearance of the peak n-π* transition which confirm the coordination through N or O atom, the data summarized in the **Table 3** [11].

The d-d transition in these complexes may appear in visible region but does not appear due to the low intensity of the d-d transition. The disappearances of the d-d transition confirm the Oh geometry of the complexes [5] [6] [7], see **Table 3**, **Fig. 7**, **Fig. 8**, **Fig. 9**, **Fig. 10, Fig. 11,** and **Fig. 12**.

Table 3: electronic absorption spectral data (nm)

Complex	π—π*	n—π*
L1	207	-----
L2	274	306
{Co(L1)(L2)(H_2O)$_2$}	217	------
{Cu(L1)(L2)(H_2O)$_2$}	307	363
{Ni(L1)(L2)(H_2O)$_2$}	280	------
{V(L1)(L2)(H_2O)$_2$}	212	----

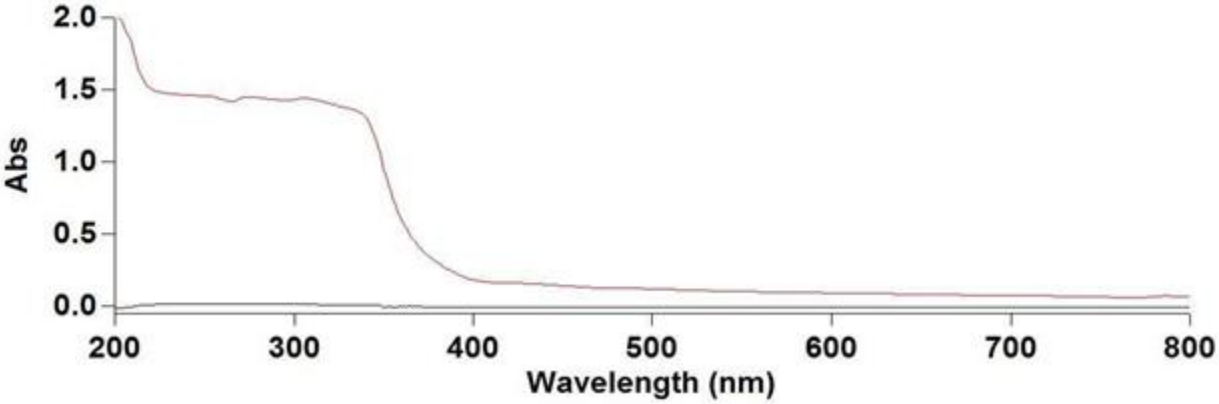

Figure 7: UV-Vis of L2

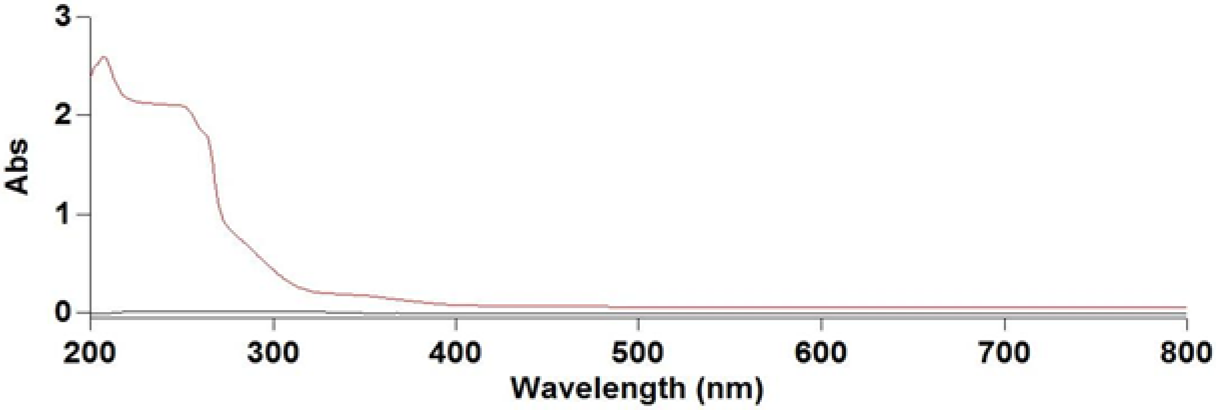

Figure 8: UV-Vis of L1

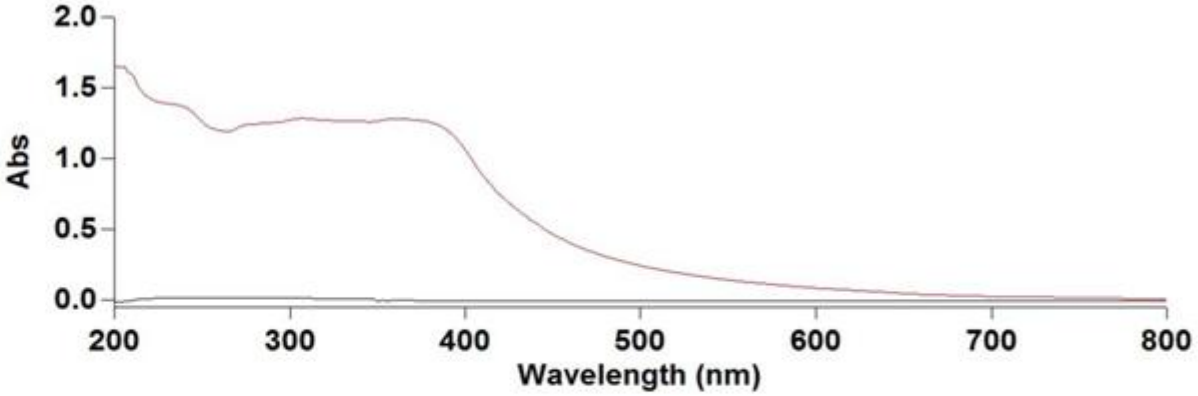

Figure 9: UV-Vis of {Cu(L1)(L2)$(H_2O)_2$}

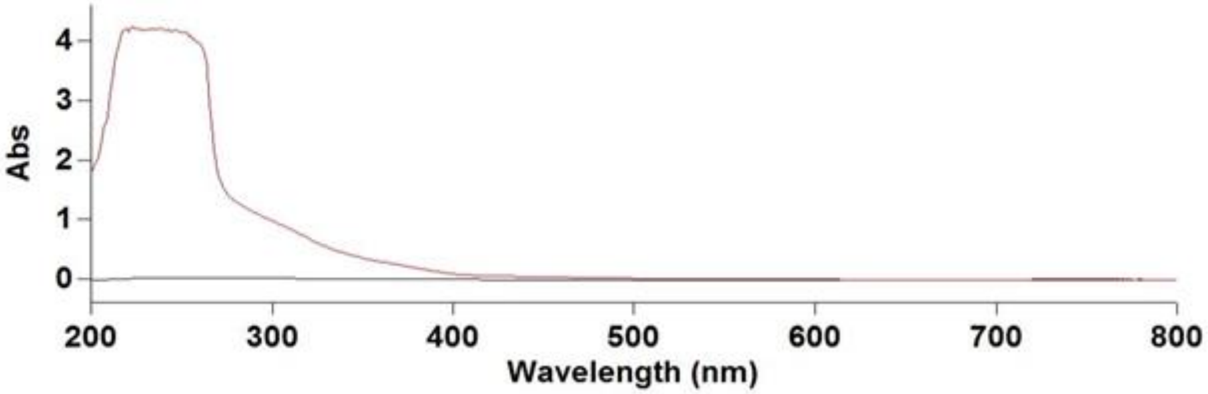

Figure 10: UV-Vis of {Ni(L1)(L2)$(H_2O)_2$}

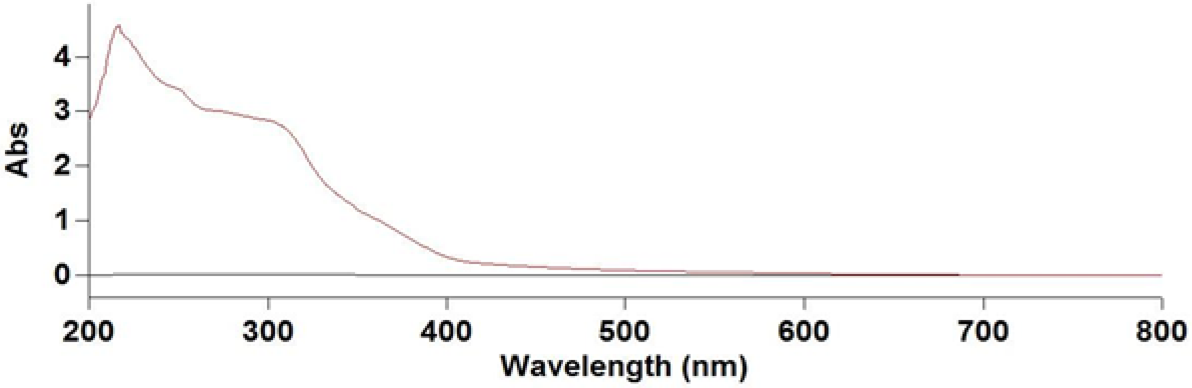

Figure 11: UV-Vis of $\{Co(L1)(L2)(H_2O)_2\}$

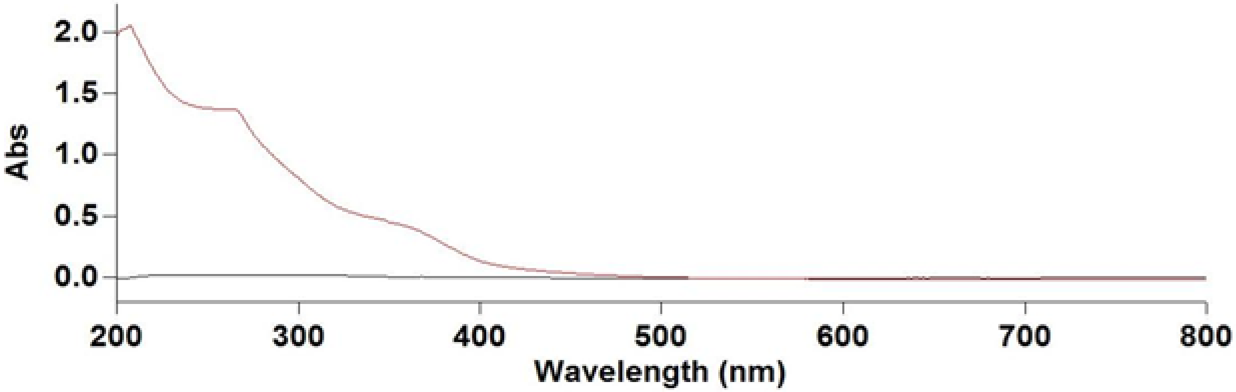

Figure 12: UV-Vis of $\{V(L1)(L2)(H_2O)_2\}$

3.4 Conductivity Measurement

The molar conductivity values of the complexes were measured in DMSO (10^{-3} M) at R.T. The lower value of molar conductivity indicates the nonelectrolyte nature of these complexes. This data confirms the structure of complexes [6] [8]. The conductivity of all compounds as shown in the **Table 4**.

Table 4: Molar conductivity ($S.cm^2.mol^{-1}$) of (10^{-3} M) of complexes

Compounds	Molar conductivity ($S.cm^2.mol^{-1}$)
DMSO	1.08
L1	8.02
L2	87.3

{Co(L1)(L2)(H_2O)$_2$}	14.67
{Ni(L1)(L2)(H_2O)$_2$}	9.8
{Cu(L1)(L2)(H_2O)$_2$}	15.58
{V(L1)(L2)(H_2O)$_2$}	19.9

According to FTIR spectroscopy, electronic spectra and conductivity, the proposed structure of all synthesized complexes are illustrated in the **Fig. 13**.

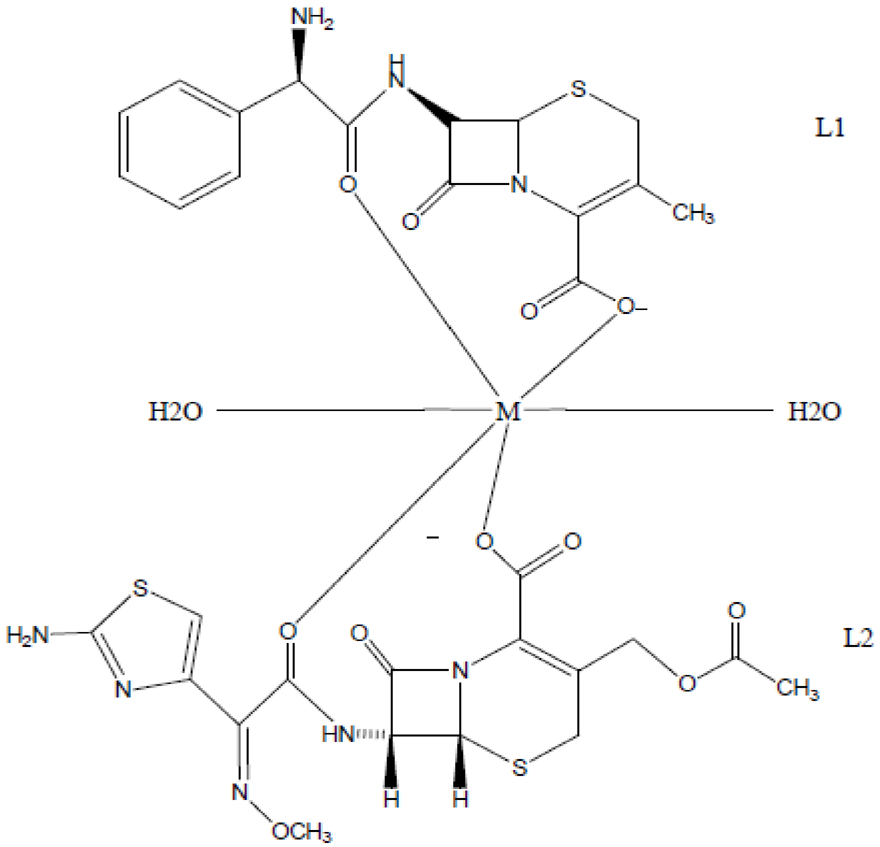

Figure 13: The chemical structure of all complexes (M = Cu, Ni, V, Co)

3.5 Biological activity

Antibacterial activity of the ligand L1, L2 and their complex have been tested against some type of bacteria as shown in **Table 5** by Kirby bauer Disc diffusion method. The test organism was grown on nutrient agar medium in petri plates. The compounds have been prepared in DMSO (10 mg/ml) and soaked in filter paper disc. The disc was placed on the previously plates and incubated at 37 C° and the diameter inhibition zone around each disc has been measured in mm.

The antibacterial activities of all compounds in case of Pseudomonas aeruginosa at this concentration exhibit not active [13].

In case of Staphylococcus aureus, the complex of Co, Ni exhibit activity around 107mm,5mm respectively.

In case of Escherichia coli, the V and L1 have bioactivity around 9,4 respectively.

In case Salmonella, the complex of Co, Ni exhibit activity around 10mm, 8mm respectively [2] [5].

Table 5: The biological activityof ligands and prepared complexes.

compounds	**Pseudomonas aeruginosa (Gram negative)**	**Staphylococcus aureus (Gram positive)**	**Escherichia coli (Gram negative)**	**Salmonella**
L1	-	-	4	-
L2	-	-	-	-
{$Co(L1)(L2)(H_2O)_2$}	-	107	-	10
{$Ni(L1)(L2)(H_2O)_2$}	-	5	-	8
{$Cu(L1)(L2)(H_2O)_2$}	-	-	-	-
{$V(L1)(L2)(H_2O)_2$}	-	-	9	-

4. Conclusion

In this research work, a series mixed ligand Complexes were prepared by reacting 1:1:1 mol ratio of metal (II): cephalexin: cefotaxime sodium. The molar conductivity, IR and UV-Visible spectrum for the ligand and complexes suggest that all the complexes most probable to be octahedral geometry. In all complexes the metal which coordinate through the COO-carboxylate and C=O amid in both ligands. It is concluded that both ligand act as bidentate ligand. The antibacterial activities of all complexes in case of Pseudomonas aeruginosa at DMSO (10 mg/ml) concentration exhibit not active. The Staphylococcus aureus, Escherichia coli, Salmonella some metal complexes exhibit more activity than ligand.

حضير وتشخيص و نشاط بيولوجي لبعض معقدات الفلزات الأنتقالية (II) تحتوي على سيفالكسين و سيفوتاكسيم صوديوم

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الخلاصة:

تم تحضير سلسلة من معقدات ليكاندات المختلطة من سيفالكسين و سيفوتاكسيم صوديوم. تم تشخيص جميع معقدات بلتوصيلية المولية والأشعة تحت الحمراء و الأشعة فوق البنفسجية المرئية. جميع معقدات لها شكل هندسي ثماني السطوح مع الصيغة العامة $\{M (L1) (L2) (H_2O)_2\}$**، حيث أن** M **هو أحد الفلزات** M **هي أحد الفلزات** ((Cu(II), Co(II), Ni(II) V(II))، L1**= سيفالكسين،** L2= **سيفوتاكسيم صوديوم. تم اختبار النشاط المضاد للبكتيريا لجميع معقدات وليكاندات ضد بعض أنواع البكتيريا, إن الأنشطة المضادة للبكتيريا** (Pseudomonas aeruginosa) **بتركيز** (10 **مجم/مل) في** (DMSO) **تظهر غير نشطة لجميع المركبات، بينما في حالة** (Staphylococcus aureus)، (Escherichia coli)، (Salmonella) **تظهر نشاطًا أكثر من ليكاندات.**

الكلمات الدالة: **تحضير، تشخيص، معقدات فلزات، سيفوتاكسيم، سيفالكسين، مضاد الميكروبات.**

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