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Al-Nahrain University
College of Sciences
Department of Chemistry

Synthesis, Characterization and Biological Evaluation of Penicillin Derivatives Complexes with some Metal ions

A Thesis

Submitted to the College of Sciences/Al-Nahrain University as a Partial Fulfillment of the Requirements for the Degree of Master of science in Chemistry

By

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(B.Sc. 2014) Al-Mustansirya University

May 2017 **Ramadan 1438**

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We, the examining committee, certify that we have read this thesis entitled **"Synthesis, characterization and biological evaluation of Penicillin derivatives complexes with some metal ions"** and examined the student "**Yasser Hussam Sabah**" in its contents and that in our opinion, it is accepted for the Degree of Master of Science, in Inorganic Chemistry, with **(Excellence)** standing.

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

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صَدَقَ اللهُ العَظيمِ
سورة الضحى

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Thanks to the staff of the Chemistry Department, College of science, AL-Nahrain University of their support and facilities to complete analysis during the years of my research.

Also, I am very grateful to all the people who helped me during my work.

Yasser

Dedication

To My father

I wish you are here to see me but one thing I tell you that you are always in my heart.

To My wife

Thank you for the times you shared with me the suffering and gave me assistance and confidence all times, I'm really grateful that you have been my inspiration and soul mate

To my major supervisor

Thank you for the countless hours of revisions and advice on my thesis and for all the wonderful lessons that he has taught me during the last 2 years of my education.

Summary

Three new antibacterial ligands have been prepared in this work by the reaction of 6-amino penicillanic acid (6-APA) with terephthaladehyde, glyoxal and vanillin to produce L_1, L_2 and L_3 respectively.

Nine new complexes have been prepared by the reaction of the above derivative ligands with metal ions Co(II), Cu(II) and Zn (II), that L_1, L_2 and L_3 interacted with these metal ions in mole ratio [2:1], [2:1] and [1:1] metal to ligand [M:L] respectively.

The synthesized compounds were characterized using ^{1}H-NMR for (L_1 and L_2), Uv-Visible for all complexes and IR-spectroscopy, metal and elemental Micro analysis, conductivity and thermal analysis for (A_1, B_2 and C_2) The results suggested that the complexes could be with distorted octahedral geometry and the predicted formula of the new complexes were as follow: **[**Co_2 L_1Cl_4 $(H_2O)_4$].$2H_2O$ (A_1),

[Cu_2 L_1Cl_4 $(H_2O)_4$].H_2O (A_2), **[**Zn_2 L_1Cl_4 $(H_2O)_4$] (A_3),

[Co_2 L_2Cl_4 $(H_2O)_4$].$2H_2O$ (B_1), **[**Cu_2 L_2Cl_4 $(H_2O)_4$].H_2O (B_2),

[Zn_2 L_2Cl_4 $(H_2O)_4$].H_2O (B_3), [$CoL_3(H_2O)_2$ Cl_2] (C_1)

[Cu $L_3(H_2O)_2Cl_2$] (C_2) and [Zn $L_3(H_2O)_2Cl_2$].$2H_2O$ (C_3).

The antibacterial activity of the synthesized compounds were studied against two selected microorganisms (*Staphylococcus aureus* and *Pseudomonas aeruginosa)*, using the minimum inhibitory concentration (MIC) of the raw material 6-APA as a lead for the other compounds which was 10^{-3}M. The results showed that most of the prepared ligands (L_1, L_2 and L_3) compounds have higher antimicrobial activity than the 6-APA itself due to the analogy of penicillin drug in addition to the presence of β-lactam part.

Symbols and Abbreviations

6-APA	**6-amino penicillanic acid**
MIC	**Minimum inhibitory concentration**
TGA	**Thermal gravimetric analysis**
DMSO	**Dimethyl Sulfoxide**
FT-IR	**Fourier transform infrared**
M.p.	**Melting point**
^{1}H-NMR	**Proton-Nuclear Magnetic Resonance**
UV-Vis	**Ultraviolet –Visible**
υ	**Stretching**
γ	**Bending**
σ	**Sigma bond**
nm	**Nanometer**
B'	**Racah parameter**
B	**Nephelauxetic factor**
Ph	**Phenyl**
dec.	**Decomposition**
λ	**Wave length**
EA	**Elemental micro analysis**
C.T	**Charge transfer**

Symbols and Abbreviations

Cepha	**Cephalexin**
Cefaz	**Cephazolin**
Cephra	**Cephradine**
Cephalo	**Cephalothin**
Cefot	**Cefotaxime**
Amox	**amoxicillin**
Amp	**ampicillin**
NA	**Nicotinamide**

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1.1 Preface

The importance of inorganic complexes have emerged in scientific and practical life[1].For instance, there are a number of natural biological complexes such as chlorophyll, hemoglobin and vitamin B_{12} ,that all of them have complex structures[2].

It has been studied that there is a possibility of using some inorganic complexes by considering them as a therapeutic agents and entering them in pharmaceuticals[3-5], as well as the influence of the minerals on the living cells and tissues, for this reason many of experiments and researches to control the toxic and non-toxic concentrations of metal ions in living organisms by transforming them into metal complexes[6,7].This measure requires to know the common qualities between the metal ion and the ligands surrounding it to form chelate complexes whether it is ionic or neutral. These studies paved the way to do some of the applied researches that have a biological importance[8].

In the field of industry, it has been found that inorganic complexes have several applications, including using them as Anti-corrosion[9,10]. Moreover, they were used as catalysts in the preparation of many organometallic compound that have a great importance in manufacturing petrochemicals, plastics and other materials[11].

In the field of analytical chemistry, inorganic complexes used to estimate the ions, whether it is positive or negative. Often these complexes and their solutions are colorful, so this feature is adopted to be one of the coordination clues between the metal ion and the ligand[12,13].

Many researchers detect a lot of metals in form of complexes by using a number of organic reagents, in the light of what these reagents gave precipitates and colorful solutions with a number of metal ions to form chelating complexes. The stability of the metal complexes often estimated through the physical and chemical properties of the central ion and the ligands surrounding it, like the electronic distribution of the central ion[14]. The stability of the formed complex is directly proportional to the number of chelating rings formed between the metal ion and the ligand, at the same time the ligands should contain at least two donor atoms that associate with central metal ion to form the chelating rings, the five and the six-membered rings considered the most stable and common[15].

1.2 Penicillin antibiotics

Antibiotic can be defined as substances produced by living organisms, which in low concentration are able to inhibit the growth of other organisms; this is a more general definition. In another view, an antibiotic is a drug that kills or slows the growth of bacteria. Antibiotics constitute one class of antimicrobials, that antimicrobial is a larger group which also includes anti-viral, anti-fungal, and anti-parasitic drugs[(16)].

Penicillin antibiotics were among the first medications to be effective against many bacterial infections, they also considered among the most frequently utilized and least toxic antibiotics. About 10% of people report that they are allergic to penicillin; However, over 80% of this group may not actually be allergic. Serious allergies only occur in about 0.03%[(17)].

Penicillin was discovered by Alexander Fleming in 1928 in a significant break- through for medical science. Fleming saw that a mould (penicillium species) had growth inhibiting properties against a number of pathogenic bacteria[(18)].

Following on from the discovery of the penicillin, the mechanism whereby it inhibits cell growth has been extensively studied. It has been found that the penicillins and cephalosporins inhibit bacterial cell wall synthesis[(19)].

Resistance to β-lactam antibiotics by bacteria is a complex function of the elaboration of β-lactamases, the ability of some bacteria to exclude these antibiotics from their cells and to decrease the tendency of binding β-lactams to penicillin binding proteins which considered their intercellular targets. The mechanism that makes bacteria resistant to β-lactams is due to the synthesis of β-lactamase enzymes which hydrolyze penicillins and cephalosporins before they can reach their receptors and the antibiotic cannot bind to peptidoglycan layer[(20)].

Various methods have been developed to deal with these factors. For example, increased steric bulk strategically placed near the side chain amide linkage often conveys greater stability against β-lactamases without significant loss of potency[(21)].

Penicillins share the basic structure of five-membered thiazolidine ring connected to a four-membered β-lactam ring attached a side chain[22] *R*-group shown in figure (1-1).

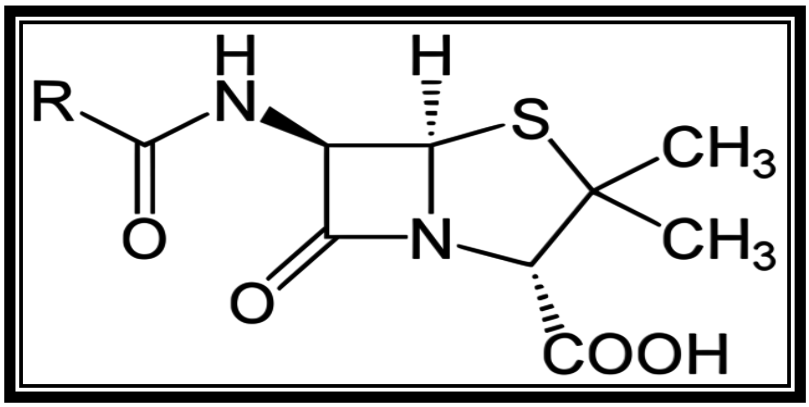


Figure (1-1): Chemical structure of penicillin

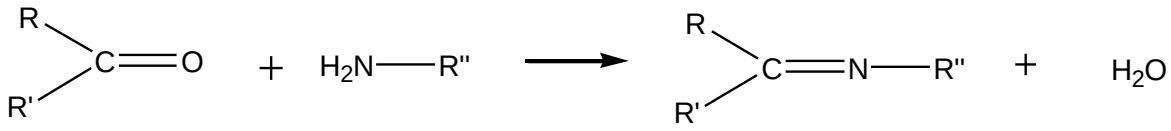
The term "penam" is used to describe the common core skeleton of a member of the penicillins. The key structural feature of the penicillins is the four-membered β-lactam ring; this structural moiety is essential for penicillin's antibacterial activity[23].

The strained β-lactam ring causes non-planarity of the molecule with large angle and torsional rotation which reduces the resonance of amide linkage and leads to β-lactam's stability[24,25].

Several advances have resulted in compounds with favorable antimicrobial and pharmacological properties[26]. They function as a broad spectrum antibiotics due to their ability to inhibit the protein synthesis in bacteria on the ribosomes by causing misreading of the genetic code[27].

1.3 Schiff base

It named after the German chemist Hugo Schiff[28] who prepared these compounds from simple condensation between aldehydes and ketones with primary amines:

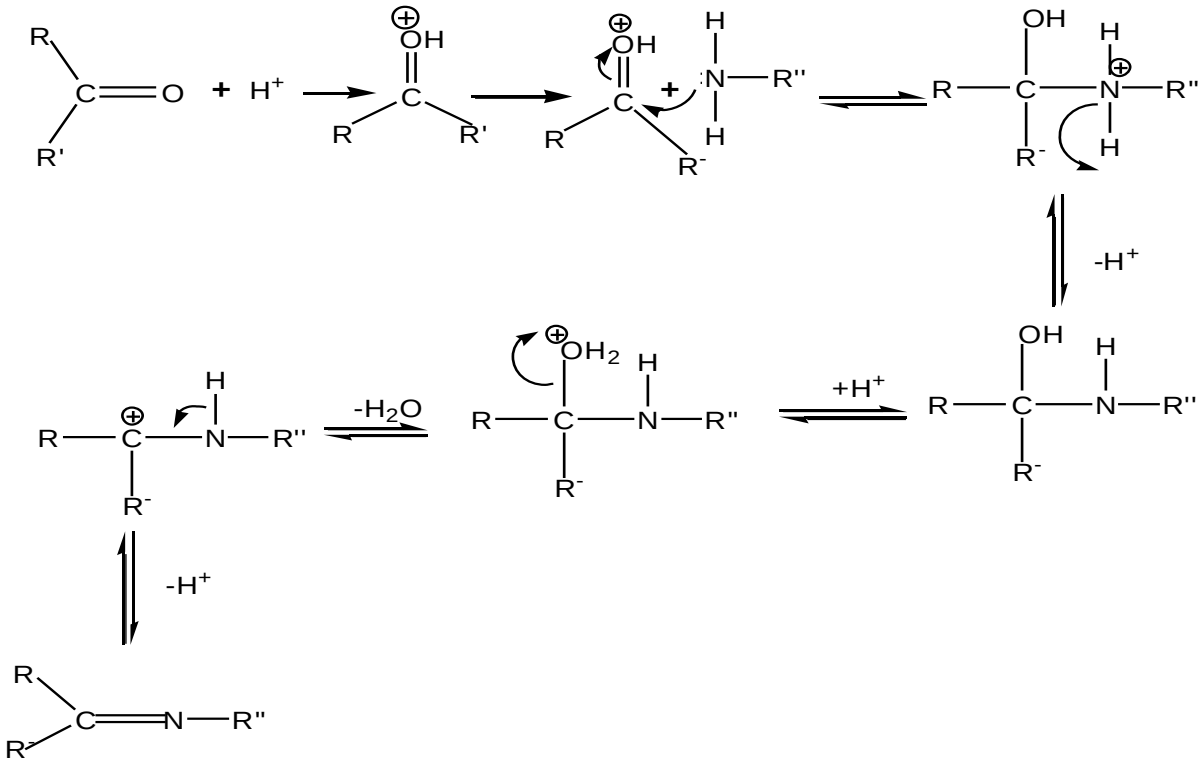


aldehyde or ketone — primary amine — schiff base (imine) — water

R, R', R" = Alkyl or aryl group

Schiff bases have been known by different names such as imines, azomethines and anils which common for Schiff bases derived from aromatic amines, aldehydes and ketones. In general the Schiff bases which have been derived from aldehydes, are called aldimine and from ketones as ketamine and the stability of the final product depends on the nature of aldehyde, ketone and amine[29,30].

The mechanism of Schiff base consisted of the addition of proton to carbonyl group to yields conjugated acid in which carbon of carbonyl group is more electrophilic, thus facilitating attack of amine on carbonyl group. The added acid will enhance elimination of water molecule to give the final product Schiff bases, thus the proper *p*H and suitable solvent is required[31]. General mechanism of Schiff base is shown below:



Schiff base (imine)

R, R', R''= Alkyl or an aryl group.

Compounds containing an azomethine group (imine) are considered important category of compounds used in the fields of medicine and pharmacology due to their biological importance[32,33] for having antitumor[34,35] anticancer[36-38], antibacterial[39,40] antifungal[41,42] and diuretic activity[43].

The widespread use of antibiotics has led to a serious medical problem of drug resistance and public health concern. Therefore, the synthesis of new

derivatives of antibiotics has become an important task to deal with drug resistance problems.

Depending on the activities associated with the antibiotics and imines, an attempt was made to synthesize and evaluate the biological activity of some novel Tri-Schiff's basses derived from 6-aminopenicillanic acid (6-APA) figure (1-2). The results also showed that the novel tri-schiff bases have better activity than 6-amino penicillanic acid alone[44].

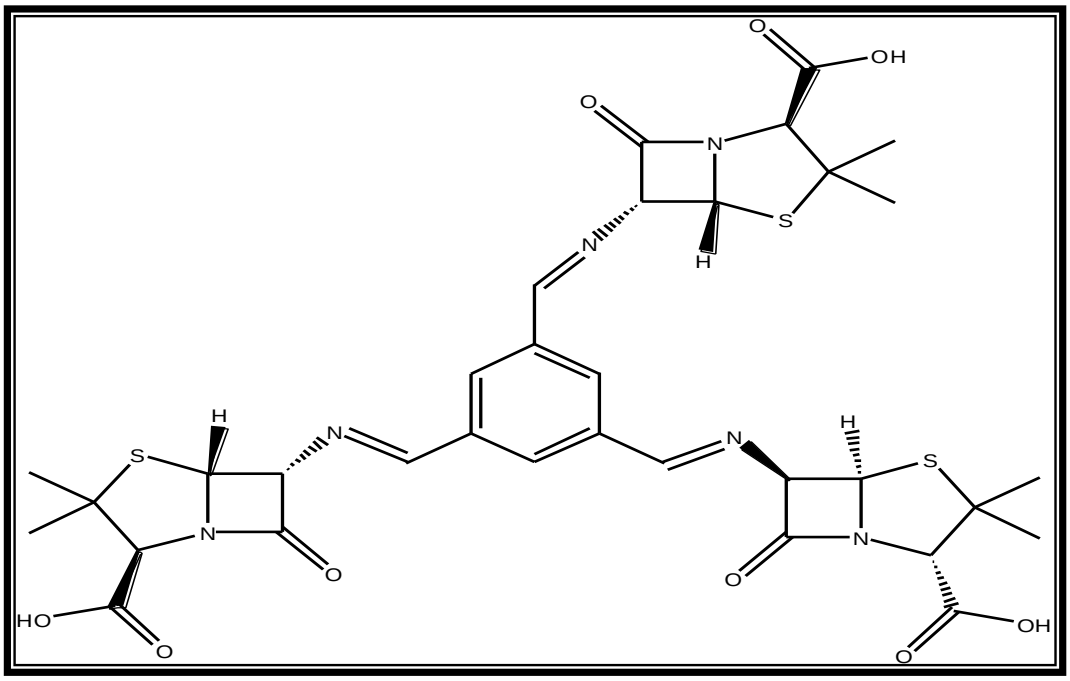


Figure (1-2): Structure of Tri-Schiff bases derived from 6-APA

Another attempt was made to generate new derivatives containing imine and amoxicillin in the same molecule. All the synthesized compounds were evaluated *in vitro* for their antibacterial activities against four microorganisms in different concentrations. The results showed that some of these derivatives have good antibacterial activities when compared to the parent drug[45].

The reason of drawing attention to the new antibiotics mentioned previously is that part of this research is about synthesis of new penicillin derivatives containing an imine group and the other part concerning involve metal ion in the preparation of imine complexes to figure out the correlation and the biological activity among the synthesized compounds.

1.4 Metal complexes of some antibiotics

The knowledge of the interactions between metal ions and antibiotics is of great importance because these reactions can influence the synthesis of metalloantibiotics depending on the idea of metal ion interaction with absorbed drugs, for example penicillins in human body can interact with metal ions which are present in a form of free ions or coordinatively bounded to proteins, enzymes, amino acids, nucleic bases, nucleotides and other bioligands [46,47].

Metals have an esteemed place in medicinal chemistry, most antibiotics do not need metal ions for their biological activities, but there are a number of antibiotics that require metal ions to function properly, such as bleomycin, streptonigrin and bacitracin drugs have gained recognition and are more effective than pure drugs[48,49]. This is due to the fact that metal ions can interact with many different kinds of biomolecules including DNA, RNA, proteins and lipids rendering their unique and specific bioactivities[50-52].

On the other hand, some metal complexes showed a high capacity to work as antifungal, antiviral antitumor and special biological activities that the efficacies of some therapeutic agents are known to increase upon coordination[53,54].

Complexes containing schiff bases in the ligand part attract many researchers because of their wide application in medicinal chemistry, food industry, analytical chemistry, dye industry, catalysis and also for their simple methods to prepare. Many studies reported several metal complexes of Schiff base derived from different antibiotics and their biological activity[55].

Some of the researches presented at recent years, which are interested in coordination field between metal ions and antibiotics.

1.4.1 Cephalosporin complexes

Cephalexin, cephazolin , cephradine and cephalothin; all of them are first-generation cephalosporin antibiotics while Cefotaxime and ceftriaxone are third-generation cephalosporin antibiotics.

Some complexes of cephalexin (cepha) ligand with Cu(II), Zn(II) and Cd(II) of composition [M(cepha)Cl.H_2O] were synthesized in [1:1] [M:L] mole ratio suggesting a tetrahedral geometry figure(1-3). It was found that Cu(II), Zn(II)

and Cd(II) complexes had increased antimicrobial activity as compared with cephalexin[56].

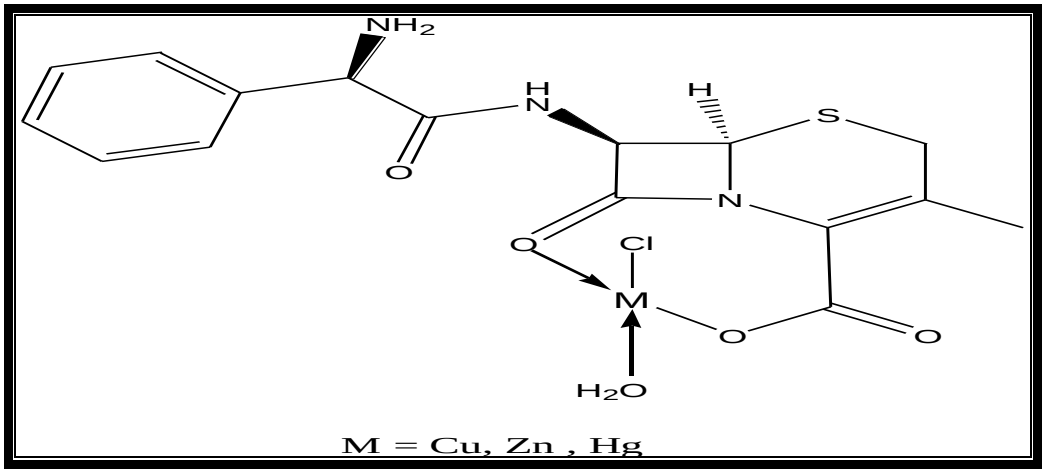


Figure (1-3): Structure of cephalexin complexes

Complexes of cefazolin (cefaz) with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Pd(II) were synthesized figure (1-4). Their spectroscopic identification suggest that cefazolin behaves as a monoanionic tetradentate ligand and the complexes of composition [1:1] [M:L] mole ratio. Pentacoordinate with one molecule of cefazolin and the chloride ion probably having tetragonal pyramidal or trigonal bipyramidal geometries. Thus, the coordination environment of each metal ion would be composed of two nitrogens from the diazole and tetrazole moieties, two oxygens from carboxylate and amide carbonyl groups, and one chloride ion. In general [Co(cefaz)Cl], [Ni(cefaz)Cl] and [Zn(cefaz)Cl] complexes were found to have higher activities than that of cefazolin against the bacteria strains studied under test conditions[57].

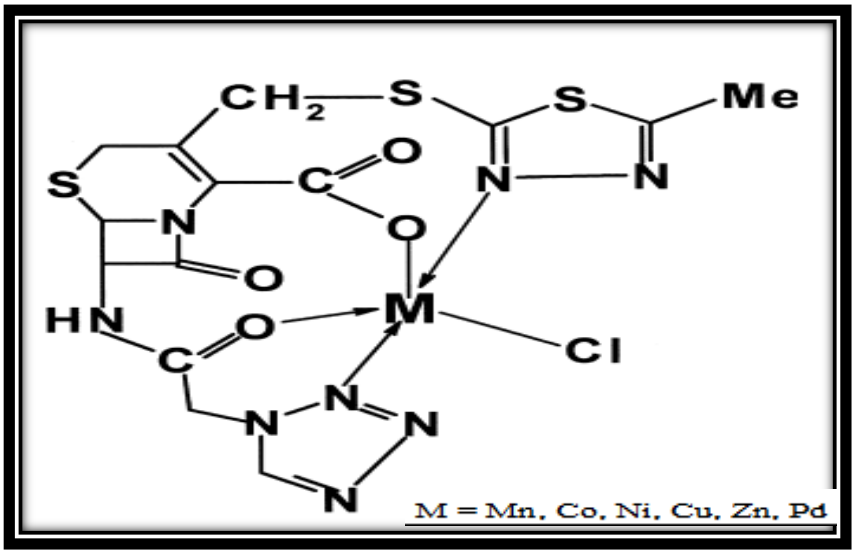


Figure (1-4): Structure of cefazolin complexes

Some complexes of cephradine (cephra) with Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) as [M(cephra)Cl] were synthesized figure (1-5). Coordination with metal ions via the amine, beta-lactam O-atom, and carboxylate groups. The divalent cations formed a tetrahedral geometry the results showed that all metal complexes tested had lower antimicrobial activity than the cephradine itself[58].

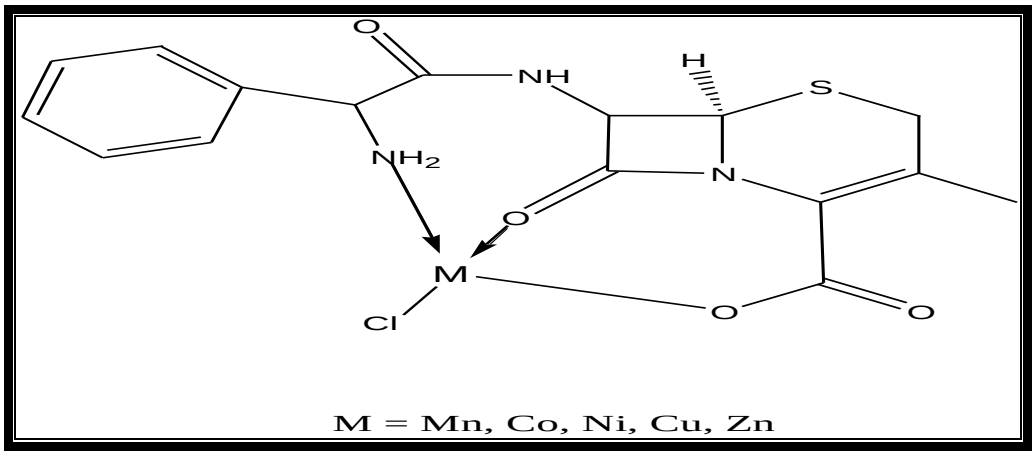


Figure (1-5): Structure of tetrahedral cephradine complexes

On the other hand, Some Co(II), Cu(II), Ni(II) and Zn(II) complexes of antibacterial drug cephradine (cephrad) have been prepared with different behavior figure (1-6). Complexes formed in [1:2] [M:L] molar ratio and formula $[M(cephrad)_2 (H_2O)_2]$ octahedral geometry, but copper complex in square planar geometry$[Cu(cephrad)_2]$. Cephradine and its complexes have been screened for their antibacterial activity against bacterial strains. The antibacterial results evidently showed that the complexation improved the antibacterial activity [59].

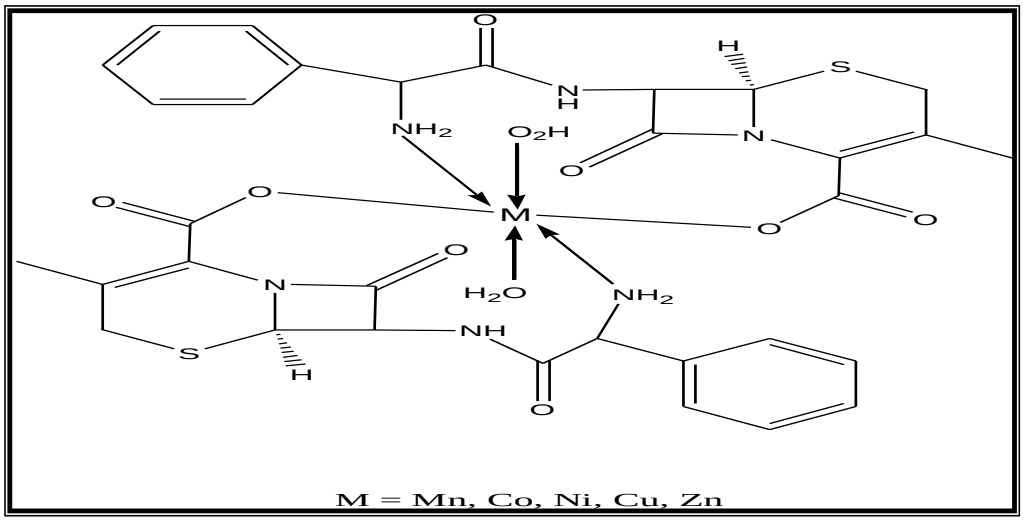


Figure (1-6): Structure of octahedral cephradine complexes

Complexes of cephalothin (cephalo) with Mn(II), Co(II), Ni(II) and Pd(II) of composition [M(cephalo)Cl] were prepared, with [1:1] [M:L] molar ratio and coordinated via oxygen atom of carboxylate, oxygen atom of beta-lactam and sulfur atom of heterocyclic side chain to give a tetrahedral geometry figure (1-7). The prepared compounds screened for their antibacterial activity against several strains and the results showed enhancement when compared with activity of cephalothin alone[60].

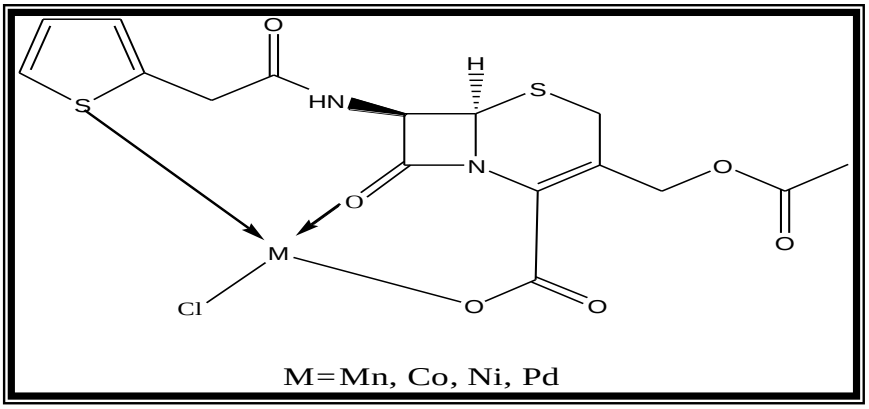


Figure (1-7): Structure of cephalothin complexes

Complexes of cefotaxime (cefot) with Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) of composition [M(cefot)Cl] with a molar ratio [1:1] [M:L] suggesting a tetrahedral geometry figure (1-8). The ligand was coordinated through carboxylate (O-atom), beta-lactam (O-atom) and aminothiazole (N-atom) group as O_2N chelation. The highest antibacterial activity was shown in the copper(II) complex against *Staphylococcus aureus* and being higher than cefotaxime activity, while the nickel(II), manganese(II) and cobalt(II) complexes did not show any activity against the same bacteria strain[61].

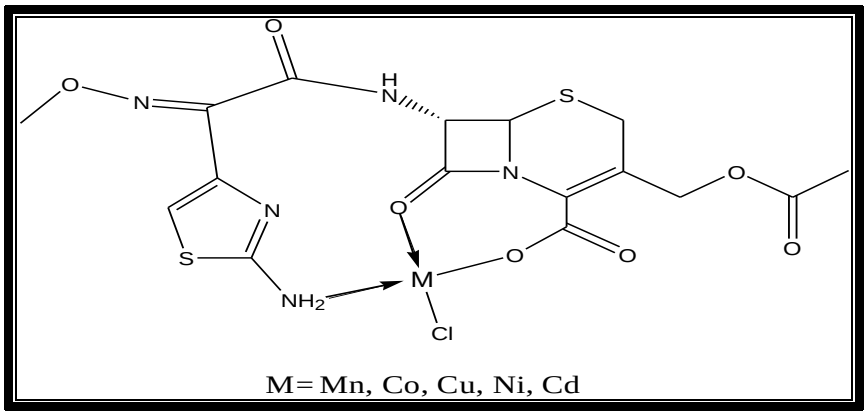


Figure (1-8): Structure of cefotaxime complexes

Ceftriaxone (ceftria) complexes with Mn(II), Co(II), Cu(II) and Cd(II) were synthesized in [1:1] [M:L] molar ratio and formula [M(ceftria)] .Their spectra indicated that the ligand is probably acting as a dianionic pentadentate chelating agent to give a tentative structure Figure (1-9). Microbiological examination showed that Cd(II) complex had greater activity than ceftriaxone, while the activities of the other complexes were similar to that of ceftriaxone[62].

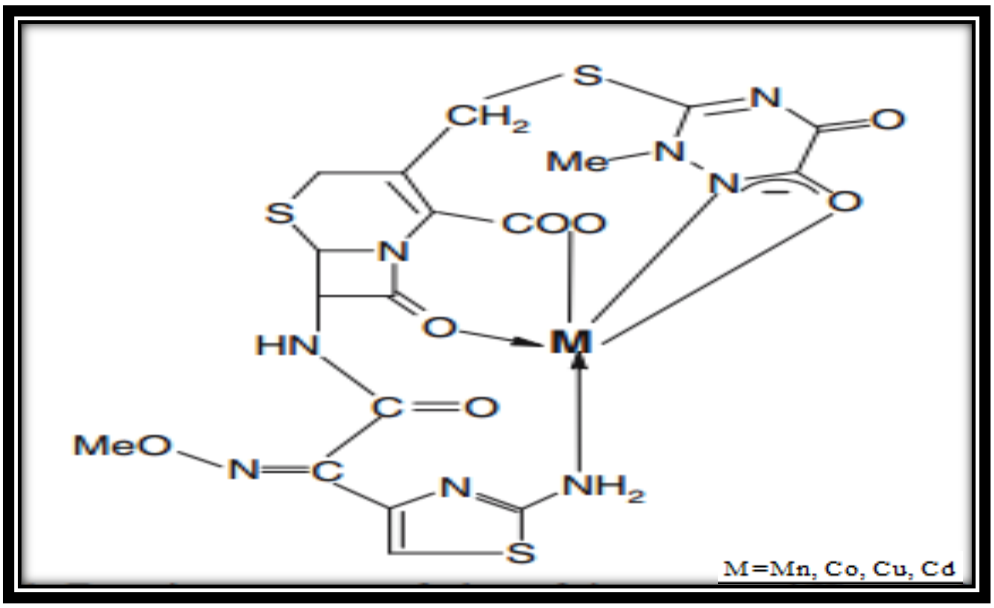


Figure (1-9): Structure of ceftraixone complexes

1.4.2 Penicillin complexes

In the early of twenty-first century several attempts were persuade profusely and excessively to synthesize metal drug complexes to find out the activity against organisms and to figure out the mechanism of action depending on structure activity relationship that the first trail was during the mid-twentieth century by A. Weiss *et al.* using benzyl penicillin as ligand. It was suggested that these complexes were coordinated through O atom of carboxylate group and N atom of the β-lactam group[63].

In 2006 Muhammad Imran and co-workers synthesized complexes of amoxicillin with some transition metal ions such as Co(II), Ni(II), Cu(II) and Zn(II) figure (1-10).Tetrahedral geometries have been suggested because amoxicillin acts as monoanionic bidentate ligand. The coordination to the metal ion was through carboxylate as well as the lactamic carbonyl group. These complexes have also screened for their antibacterial activity against several

bacterial strains. The metal complexes showed enhanced antibacterial activity as compared to simple antibiotic[64].

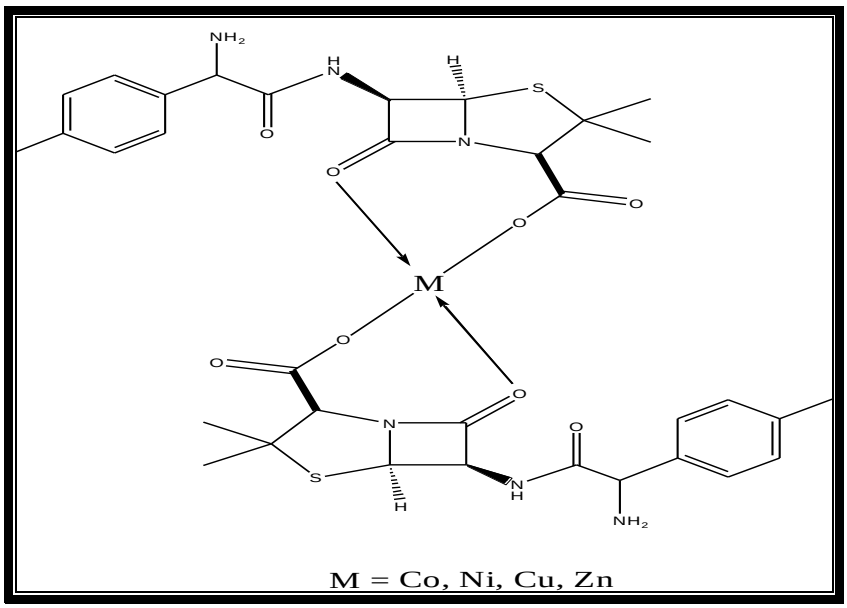


Figure (1-10): Structure of amoxicillin complexes

Another trail, the complexes of cloxacillin with Co(II), Ni(II), Cu(II) and Zn(II) were performed and the coordination occurs through oxygen of carboxylate group and nitrogen of β-lactam group . These complexes have been investigated and found that they have an octahedral geometry with formula [M(cloxa) $(H_2O)_3$ Cl] and they are non-electrolytic in nature figure (1-11). It found that the complexes have improved the antibacterial activity than the one that was found for cloxacillin alone. It was evident that overall potency of cloxacillin was enhanced on coordination with metal ions[65].

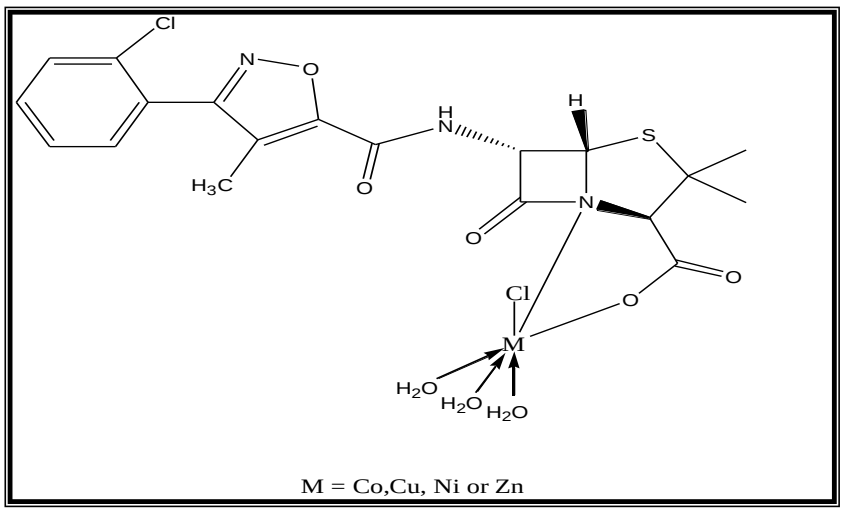


Figure (1-11): Structure of cloxacillin complexes

Solid complexes of benzyl penicillin with Fe(III), Ni(II), Zn(II), Cd(II), and La(III) were synthesized with an octahedral geometry figure (1-12). The divalent ions are coordinated by amide carbonyl, β-lactam carbonyl and carboxylate groups of benzyl penicillin, while the trivalent ions are coordinated by the carboxylate and the amide carbonyl groups only [66].

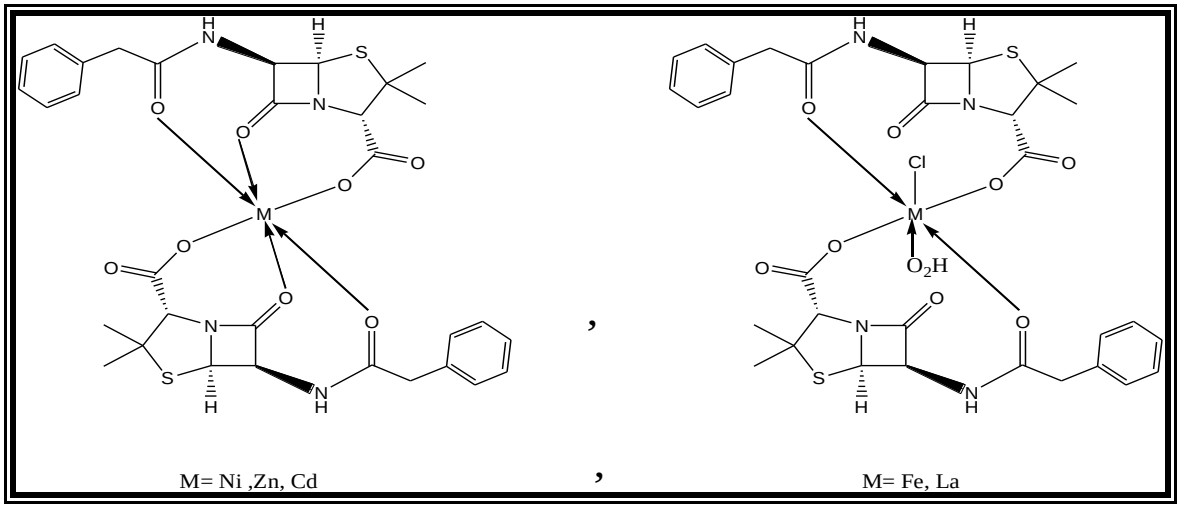


Figure (1-12): Structure of benzyl penicillin complexes

Aurora Reiss *et al*. reported Co(II) and Ni(II) complexes with Schiff base derived from amoxicillin and salicylaldehyde, which were characterized and noted as bidentate ligand that coordinated through phenolic oxygen and imino nitrogen of azomethine. The chelation was through 6-membered ring around the metal ion with an octahedral geometry of both complexes figure (1-13). Bacteriological studies were carried out against three species, the outcomes indicated increment in antimicrobial action of metal complexes as compared[67].

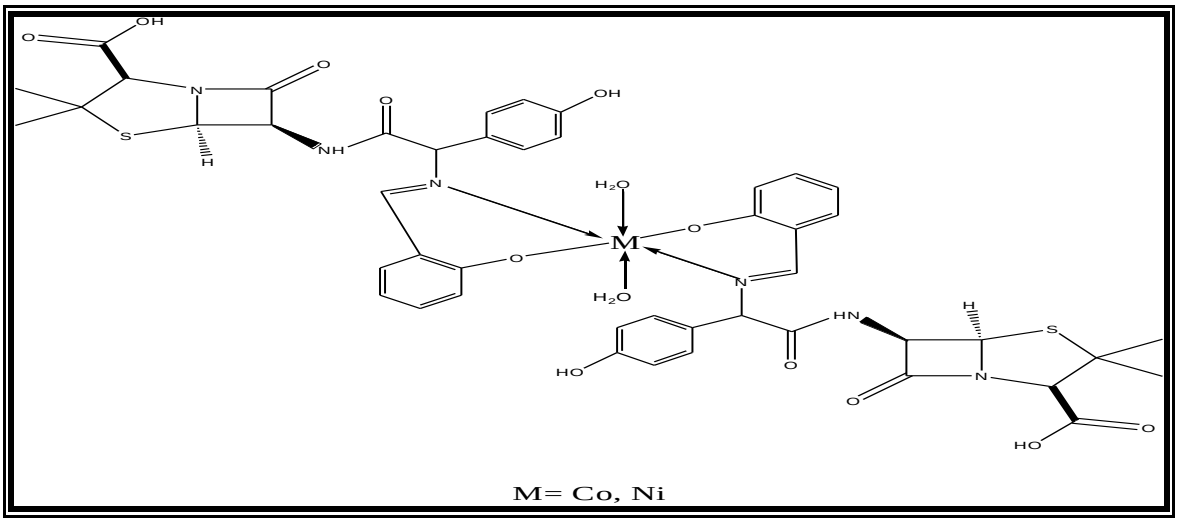


Figure (1-13): Structure of amoxicillin derivative complexes from salicylaldehyde

Eight complexes have been synthesized from divalent ions Mn(II), Co(II), Ni(II) and Zn(II) with Schiff bases derived from amoxicillin and two aldehydes (cinnamaldehyde and *p*-chlorobenzaldehyde). These complexes have been investigated and found that they have an octahedral geometry, the coordination sphere of all complexes were through imine nitrogen and phenolic oxygen figure (1-14). It found that the complexes have improved the antibacterial activity than the one that was found for free Schiff bases[(68)].

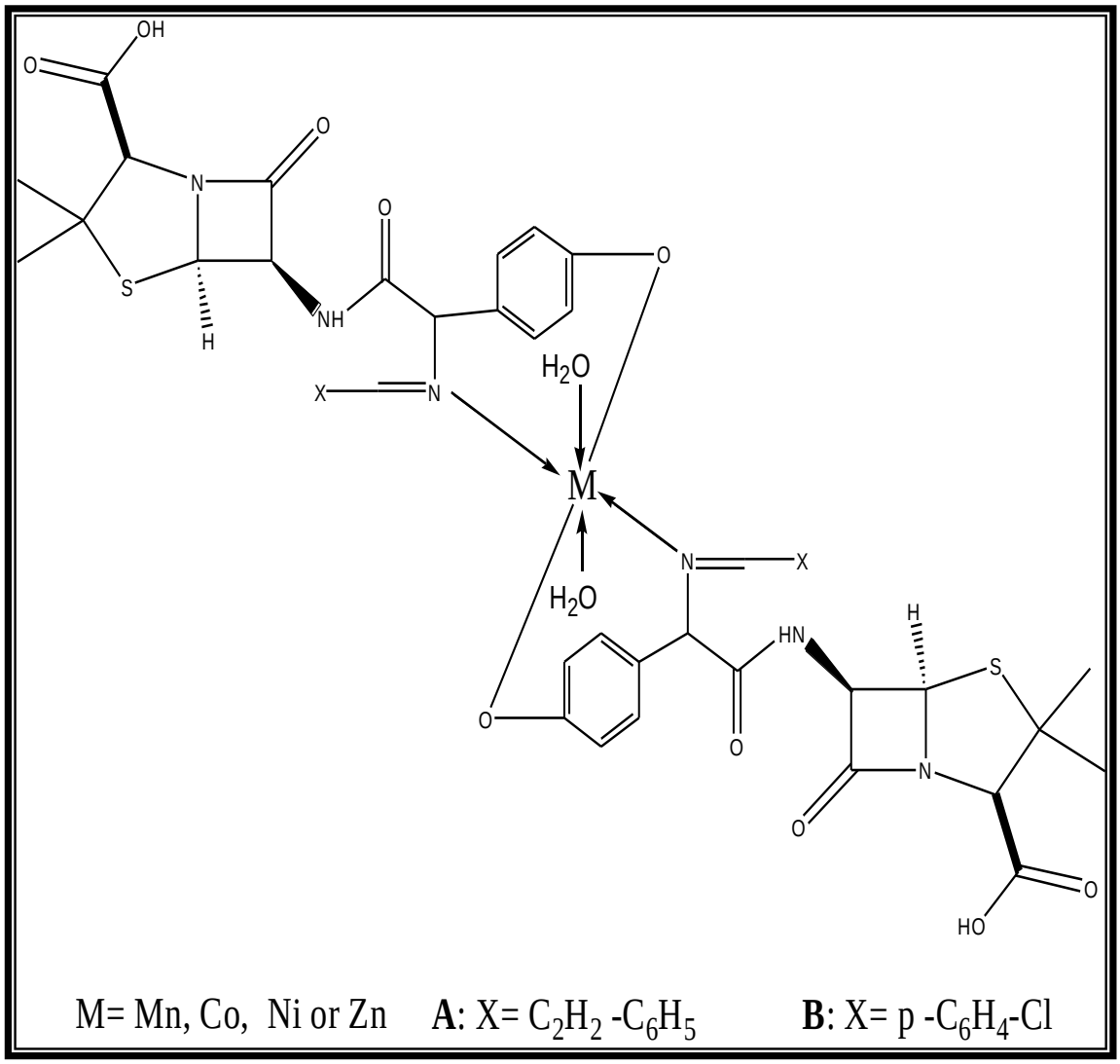


Figure (1-14): Structure of amoxicillin derivatives complexes derived from: A) cinnamaldehyde or B) *p*-chlorobenzaldehyde

Also mixed ligand complexes of Co(II) and Ni(II) with amoxicillin (amox) and ampicillin (amp) as ligands have been synthesized. The coordination of both ligands was through carboxylate oxygen, β-lactam oxygen and terminal amide nitrogen. The suggested formula was[M(amox)(amp)].$3H_2O$ and the probable geometry was octahedral figure (1-15). All the complexes and the ligands were screened for their biological activity on some selected bacterial species. The results of biological activity indicated that the Co(II) and Ni(II) complexes have increased activity against bacteria[69].

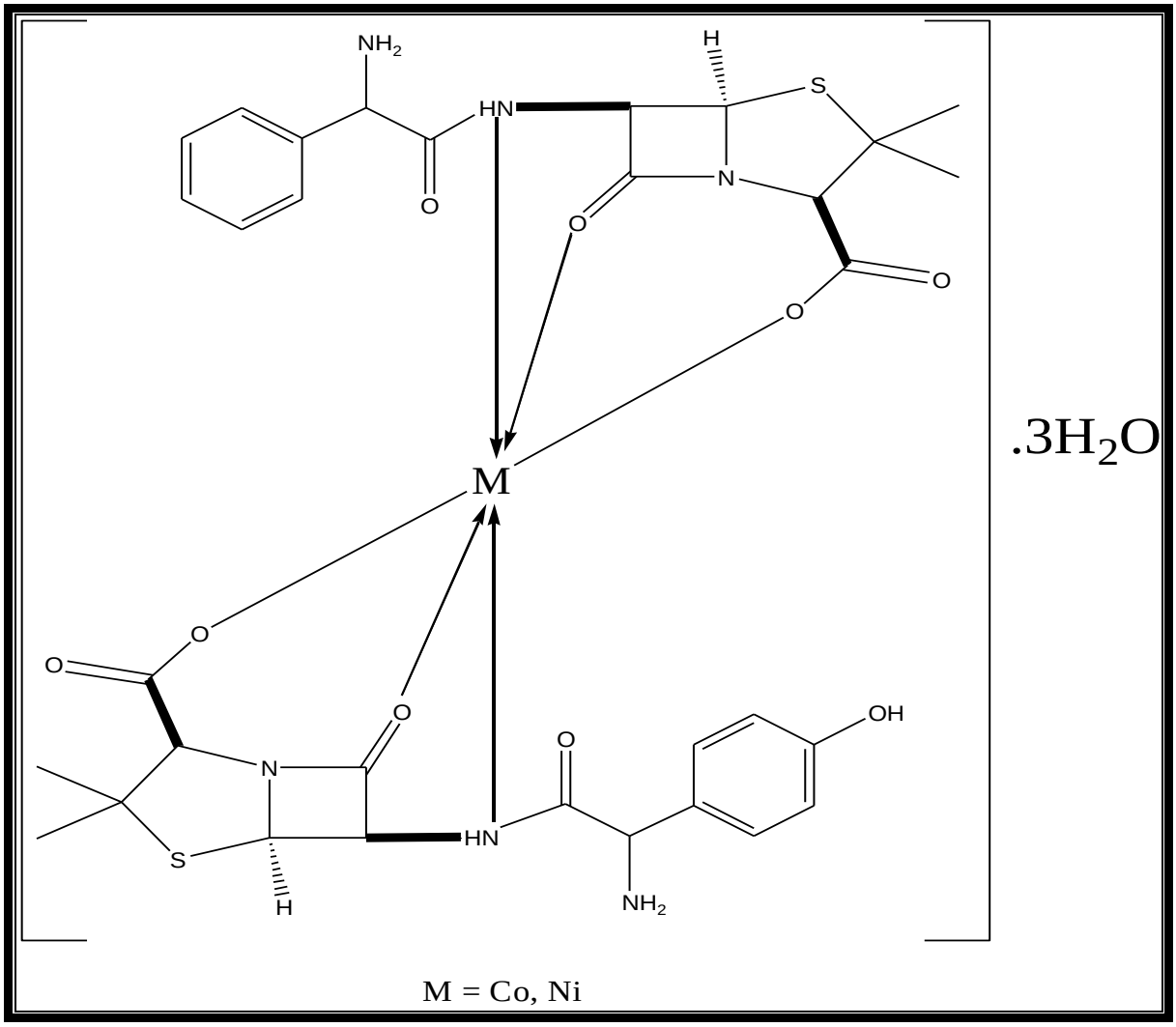


Figure (1-15): Structure of [M(amox)(amp)].$3H_2O$ complexes

Two new Schiff base ligands (HL) have been synthesized via condensation of 4-dimethylaminobenzaldehyde with amoxicillin[70] or ampicillin[71] in methanol. Generally the Mixed ligand complexes were obtained from reactions of metal ions, Ligands (HL) and Nicotinamide (NA) forming complexes with molar ratio1:1:2 respectively at the suggested formula $[M(L)(NA)_2Cl]$,where M= Co(II), Ni(II), Cu(II) and Zn(II) figure (1-16). In order to evaluate the bactericidal activity, these synthesized complexes in comparison to the uncomplexed Schiff base have been screened against five bacterial species. All metal-mixed ligand complexes were active against all five tested organisms. The antibacterial results evidently showed that the activity of the Schiff base become more upon coordination to the metal ions.

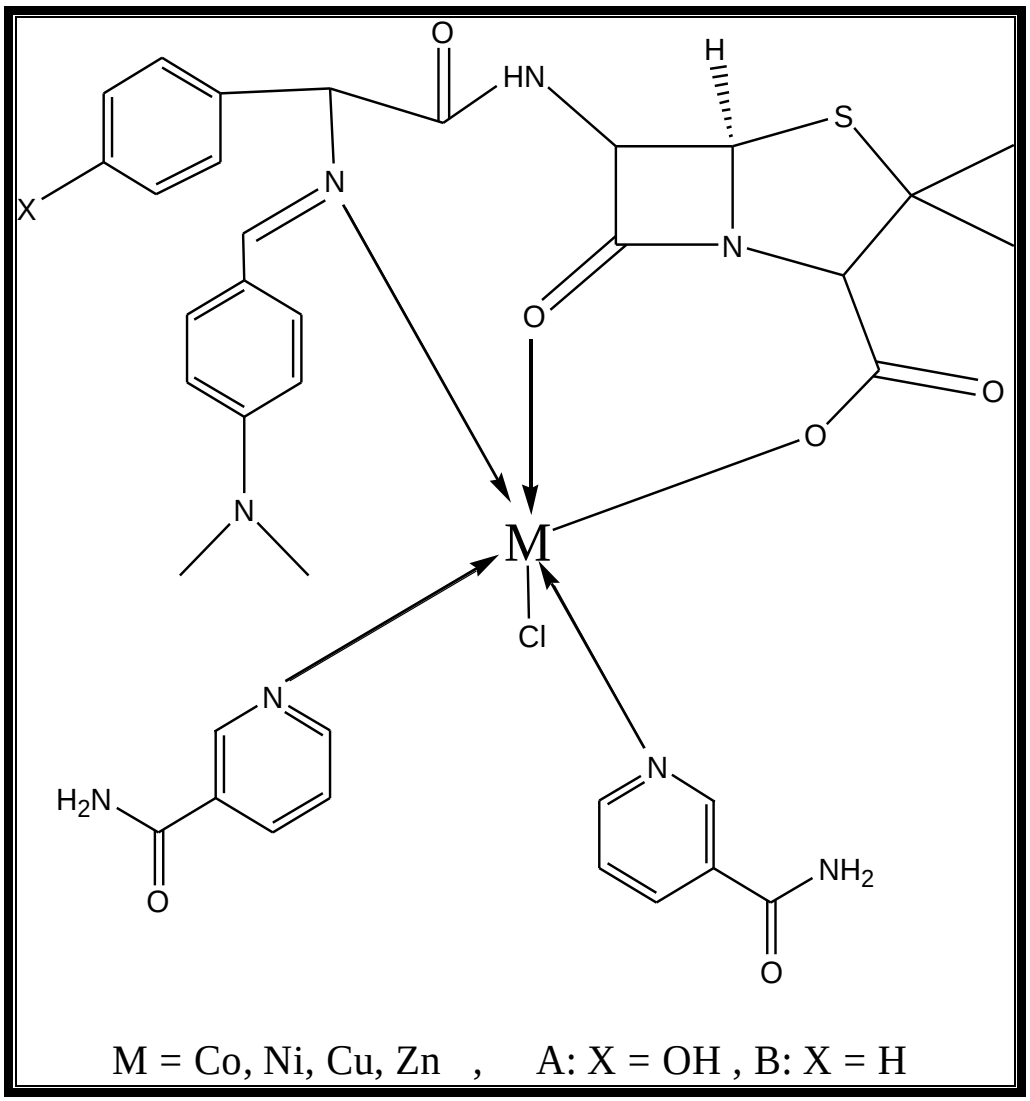


Figure (1-16): Structure of mixed-ligand complexes of Schiff base derived from: A) amoxicillin or B) ampicillin

In 2012 M.O. Bamigboye and co-workers[72] synthesized three complexes of mixed sulfamethoxazole - cloxacillin drugs. Both sulfamethoxazole and cloxacillin acts as bidentate ligands towards Mn(II), Cu(II), Zn(II) metal ions. The geometry is in octahedral which is assigned to all three complexes. Coordination of metal ion with cloxacillin is through carbonyl oxygen and lactam ring oxygen, while sulfamethoxazole the coordination is through sulphone oxygen and amine nitrogen group and to complete the coordination of octahedral geometry two chloride ions were intruded figure (1-17). Investigation of antimicrobial activities of the complexes against the tested microorganisms were found to be more active than their parent ligands.

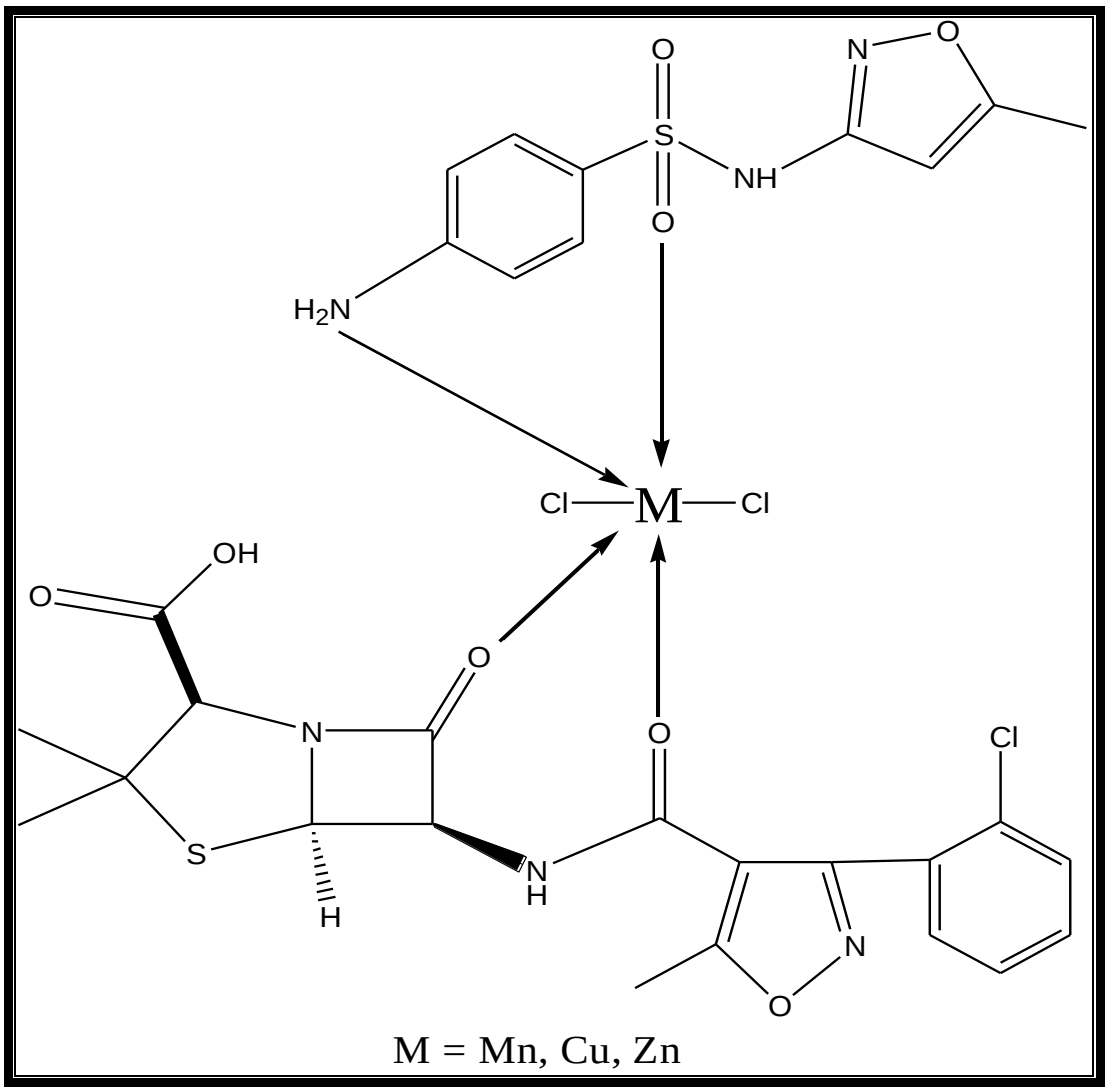


Figure (1-17): Structure of mixed ligand complexes of sulfamethoxazole and cloxacilin drugs

Lanthanides complexes have been prepared recently ,some trivalent lanthanides were interacted with cloxacillin drug in [1:2] [M:L] mole ratio. In all complexes, cloxacillin acts as a tridentate ligand with coordination involving the oxygen of carboxylate, endocyclic nitrogen of β-lactam ring and nitrogen of amide. Complexes of the lanthanides: La(III), Pr(III), Nd(III), Sm(III), Dy(III), Ho(III) and Er(III) were eight coordinated using two additional water molecules figure (1-18). Finally the complexes have been screened for their antibacterial activity and found to be more potent against uncomplexed cloxacillin[73].

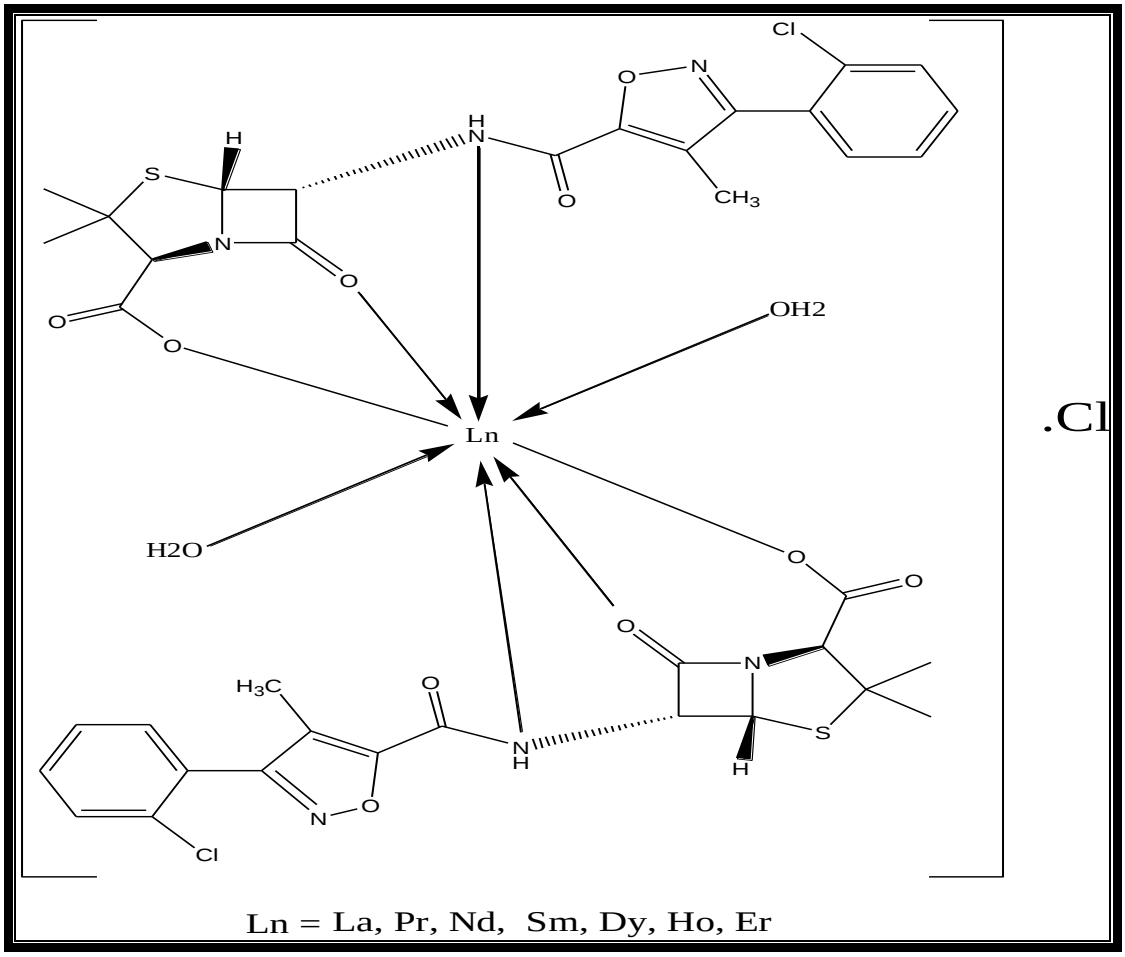


Figure (1-18): Structure of lanthanides complexes

In this work we hope to obtain novel penicillins that have one or more of the following advantages: (i) broader antimicrobial spectra, (ii) more favorable absorbance patterns and (iii) reduced undesirable side effect. Therefore; we have planned a synthetic strategy to synthesize a set of new penicillin derivatives with bioavailable and bifunctional antibacterial property, this coincides with the synthesis of their metal complexes.

1.5 Aim of the work: -

In the light of what have been presented in this chapter, it has been found a continuous extending work to prepare sets of antibacterial compounds and their metal complexes in recent years. Eventually we should consider the followings:

1- An academic study was required to explore the behavior of the complicated multidentate ligands towards metal ions.

2- Find out the capability of the mononuclear complex using ligand derived from a natural bioavailable compound to design new model of antibiotic.

3- Find out the capability of the binuclear complexes using bifunctional antibacterial (two β-lactams) and explore the expected double action of the new designed compounds.

4- Figure out the final structure of the compounds using all suitable techniques.

5- Study the antibacterial activity of all the compounds aginst two bacterial strains: *staphylococcus aurues* (gram positive) and *pseudomonas aerginosa* (gram negative) to make comparsion between them.

2.1 Chemicals

All the chemicals used in this work were obtained from different companies with variable purities as shown in Table (2-1).

Table (2-1): Purity of the chemicals and their suppliers

Compound	Purity %	Company
6-Aminopenicillanic acid	98%	Fluka
Terephthaladehyde	Purum	Fluka
Glyoxal monohydrate	Purum	B.D.H
Vanillin	99.99%	Sigma-Aldrich
Absolute ethanol	99.99%	B.D.H
Diethyl ether	99%	Sigma-Aldrich
Glacial acetic acid	98%	Fluka
Cobalt(II)chloride hexahydrate	98%	B.D.H
Cupper(II)chloride dihydrate	98%	B.D.H
Zinc(II)chloride hexahydrate	98%	B.D.H

2.2 Instrumentation

A- Infrared Spectrophotometer

The Fourier transform infrared spectrophotometer FT-IR of the prepared compounds were recorded using FTIR 8300 of *SHIMADZU* Company as KBr disc in the wave number range of (400-4000) cm^{-1} at Al-Nahrain University, Department of Chemistry and Ministry of Industry /Ibn Sina State Company.

B- Ultra violet-visible spectroscopy

The electronic spectra of the synthesized complexes were obtained using Shimadzu Uv-Vis. 160A - ultra violet spectrophotometer using the quartz cell in the range (200-1100) nm at Al-Nahrain University, Department of Chemistry.

*C- Melting Point Instrumen*t

The melting points were determined by the open capillary tube method using hot stage, *Gallenkamp*, England and were not corrected at Al-Nahrain University, Department of Chemistry.

D- Conductivity Measurements

Molar conductivity of the complexes were recorded at room temperature of 10^{-3}M solution for each sample using Corning Conductivity Meter 220 at Al-Nahrain University, Department of Chemistry.

E- Proton-nuclear magnetic resonance analysis

^{1}H-NMR spectra were recorded on nuclear magnetic resonance Bruker spectrophotometer model Ultrasheild 400 MH_z using tetramethylsilane internal standard and DMSO-d_6 as solvent at Isfahan University of Technology (IUT), Iran.

F- Thermal analysis

Thermal gravimetric analysis (TGA) was performed with 4000 Perkin–Elmer thermal analyzer maintained at 2000 C^{o} min^{-1} heating rate at Al-Nahrain University, Department of Chemistry.

G- Elemantal analysis (C.H.N.S)

Element analysis technique were recorded on EuroEA Elemental analyser (2000 $^{\circ}$C) at Al-Nahrain University, Department of Chemistry**.**

H- Metal analysis

Metal content of the complexes was measured using flame atomic absorbtion techniques by Agilent 30A at Al-Nahrain University, Department of Chemistry**.**

2.3 Methods of Synthesis

2.3.1. Synthesis of [L_1-L_3] ligands

A- Synthesis of [L_1] and [L_2] ligands:-

2mmoles of 6-APA was dissolved in 10 ml of absolute ethanol then mixed with 1mmole of terephthaladehyde or glyoxal to prepare L_1 and L_2 respectively. The reaction was refluxed for 4 hours with stirring and the proper *p*H[31] was adjusted to ≈ 4 by addition of several drops glacial acetic acid (the process followed up by *pH* paper test). The color of the reaction mixture has been change and a precipitates were formed after cooling and evaporation of the solvent.

L_1 and L_2 ligands recrystallized by using diethyl ether and ethanol solvents to give the titled compounds. The color, melting point and yield percentage are shown in Table (2-2).

B- Synthesis of [L_3] ligand:-

1mmole of 6-APA was dissolved in 10 ml of absolute ethanol then mixed with 1mmole of vanillin. The reaction was refluxed for 4 hours with stirring to prepare L_3. The proper *p*H[31] was adjusted to ≈ 4 by the addition of several drops of glacial acetic acid (the process followed up by *pH* paper test). The color of the reaction mixture has change been and a precipitates were formed after evaporation of the solvent.

L_3 ligand recrystallized by using diethyl ether and ethanol solvents to give the titled compound. The color, melting point and yield percentage are shown in Table (2-2).

2.3.2 Mole ratio method

The mole-ratio method were followed to determine the metal**:**ligand [M:L] ratio in absolute ethanol as solvent and at λ_{max} for each complex. The results suggested that L_1, L_2 and L_3 interacted with the metal ions in mole ratio [2:1], [2:1] and [1:1] metal to ligand [M:L] respectively[74].

2.3.3 Synthesis of [L_1-L_3] ligands complexes

A- Synthesis of [A_1-A_3] and [B_1-B_3] Complexes

1mmole of L_1 or L_2 dissolved in 10ml of absolute ethanol then was mixed with 2mmoles of the desired metal ion ($CoCl_2.6H_2O$, $CuCl_2.2H_2O$ or $ZnCl_2.6H_2O$). The mixture was refluxed for 2 hours and the color has been changed. The resulting precipitates were formed after evaporation of the solvent and recrystallized by two solvents: diethyl ether and absolute ethanol to give the following complexes:

$[Co_2L_1Cl_4(H_2O)_4].2H_2O$ (A_1) , $[Cu_2L_1Cl_4(H_2O)_4].H_2O$ (A_2), $[Zn_2L_1Cl_4(H_2O)_4]$ (A_3), $[Co_2L_2Cl_4(H_2O)_4].2H_2O$ (B_1), $[Cu_2L_2Cl_4(H_2O)_4].H_2O$ (B_2) and $[Zn_2L_2Cl_4(H_2O)_4].H_2O$ (B_3).

The melting point, color and yield percent are summarized in Table (2-2).

B- Synthesis of [C_1-C_3] complexes

1mmole of L_3 dissolved in 10ml of absolute ethanol then was mixed with 1mmoles of the desired metal ion ($CoCl_2.6H_2O$, $CuCl_2.2H_2O$ or $ZnCl_2.6H_2O$). The mixture was refluxed for 2 hours and the color has been changed. The resulting precipitates were formed after evaporation of the solvent and recrystallized by two solvents: diethyl ether and absolute ethanol to give the following complexes: **$[CoL_3Cl_4(H_2O)_4].2H_2O$ (A_1), $[CuL_3Cl_4(H_2O)_4].H_2O$ (A_2) and $[ZnL_3Cl_4(H_2O)_4]$ (A_3)**.

The melting point, color and yield percentage are given in Table (2-2).

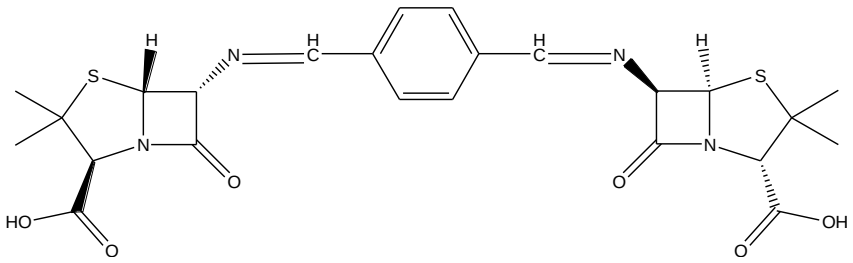
Table (2-2): Physical properties of synthesized compounds

Symbol	Empirical formula	Color	M.p °C	Yield %
L_1	$C_{24}H_{26}N_4O_6S_2$	Orange	224-226	81
A_1	$Co_2L_1Cl_4(H_2O)_4].2H_2O$	Green	202dec.	85
A_2	$[Cu_2L_1(H_2O)_4Cl_4].H_2O$	Green	270dec.	80
A_3	$[Zn_2L_1(H_2O)_4Cl_4]$	Orange	241-243	77
L_2	$C_{18}H_{22}N_4O_6S_2$	Pale yellow	231-233	84
B_1	$[Co_2L_2(H_2O)_4Cl_4].2H_2O$	Pale Green	158-160	78
B_2	$[Cu_2L_2(H_2O)_4Cl_4].H_2O$	Green	172dec.	74
B_3	$[Zn_2L_2(H_2O)_4Cl_4].H_2O$	Yellow	252-254	79
L_3	$C_{16}H_{18}N_2O_5S$	Orange	233-235	76
C_1	$[CoL_3(H_2O)_2Cl_2]$	Green	198dec.	84
C_2	$[CuL_3(H_2O)_2Cl_2]$	Pale green	182dec.	87
C_3	$[ZnL_3(H_2O)_2Cl_2].2H_2O$	Yellow	246-248	86

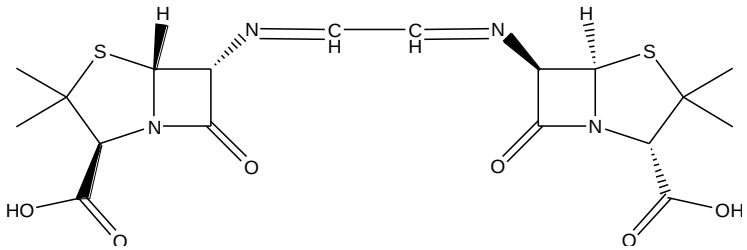
Note:
dec. = decomposition

Our study is to illustrate the behavior of the synthesized multidentate ligands L_1, L_2 and L_3 towards the metal ion. The property of several coordination sites were discussed to figure out the probable path of the ligand during the reaction with metal ion .Therefore, the ligand expected to flip around or polymerized due to the bifunctional property or using another mole ratio like [2:2] [M:L] rather than the suggested one [2:1] [M:L] as complexes. In addition to the preparation of the complicated compounds, the possession of the two antibacterial parts derived us to discover the double action as drugs *in vitro* and to make comparison between the parent 6-APA and the synthesized compounds.

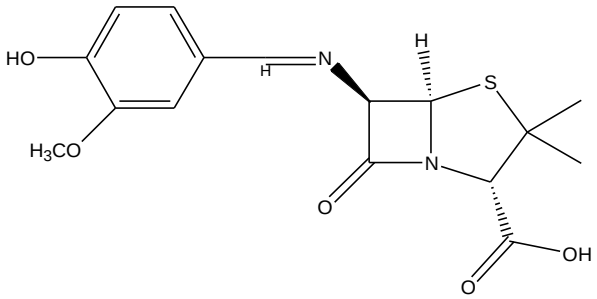
The final suggested structure of our task compounds were presented depending on the usual available techniques.



L_1



L_2



L_3

3.1 Proton-Nuclear magnetic resonance (NMR) spectra

The ^{1}H correlated NMR analysis were used to characterize the ligands to insure the synthesis process through the illustrated new formed functional groups in addition to the other present ones.

3.1.1 ^{1}H-NMR spectrum of [L_1]

The ^{1}H-NMR spectrum of ligand **[L_1]** shows a singlet peak at δ = 10.33 ppm[75] equivalent two protons of the carboxylic acid hydroxyl O–H. The signal obtained at δ =8.36 ppm was assigned for singlet peak due to two protons of imine group N=C–H[75,76]. The multiplet signals obtained in the range δ= (7.9-7.1) ppm is due to aromatic hydrogen of carbons[75,76].

A doublet peak presented by CO–CH group of β-lactam ring appeared at the range δ = (4.1-4.6) ppm. S–CH group on the dihydrothiazine ring was observed in the range δ= (2.90-3.66) ppm as doublet peak[70,71].

Finally a single peak appeared at δ =1.57 ppm could be attributed to methyl groups of 5-membered dihydrothiazine ring[70,71].

According to the above signals the ligand characterized especially through the presence of imine group and disappearance of precursor amine group.

3.1.2 ^{1}H NMR spectrum of [L_2]

^{1}H-NMR spectrum of **[L_2]** in DMSO-d6 showed signal at δ= 13.2 ppm of O-H of carboxylic acid[75]. The singlet peak obtained at δ= 8.46 ppm was due to two proton of imine group CH=N in the ligand[75,76]. This gives an evidence of the formation of imine group.

A double peak given by CO–CH of the β-lactam ring appeared at the range δ= (4.1-4.7) ppm. S–CH group on the dihydrothiazine ring was observed in the δ= (3.23-3.66) ppm[70,71]. Finally a single peak could be attributed to methyl groups of 5-membered dihydrothiazine ring appeared at δ =1.57 ppm[70,71].

Also **[L_2]** characterized especially through the presence of imine group and disappearance of precursor amine group.

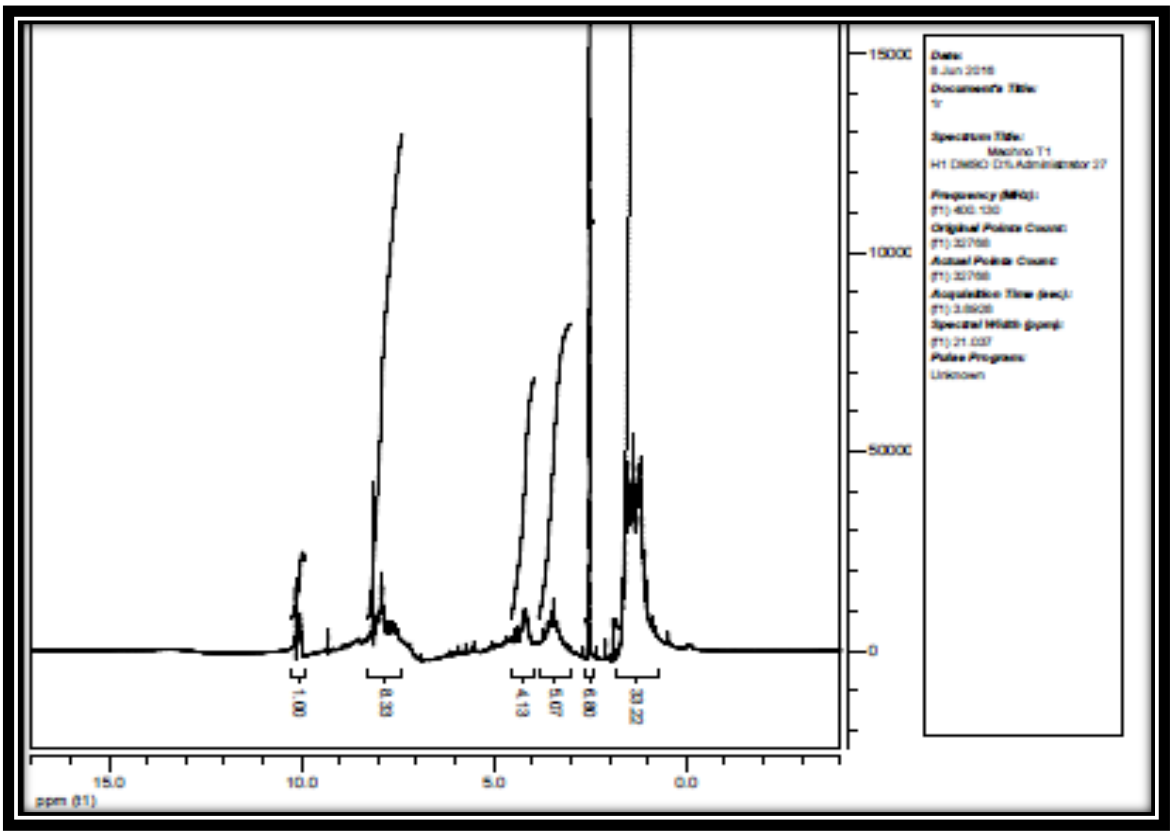


Figure (3-1): ^{1}H-NMR spectrum of [L_1]

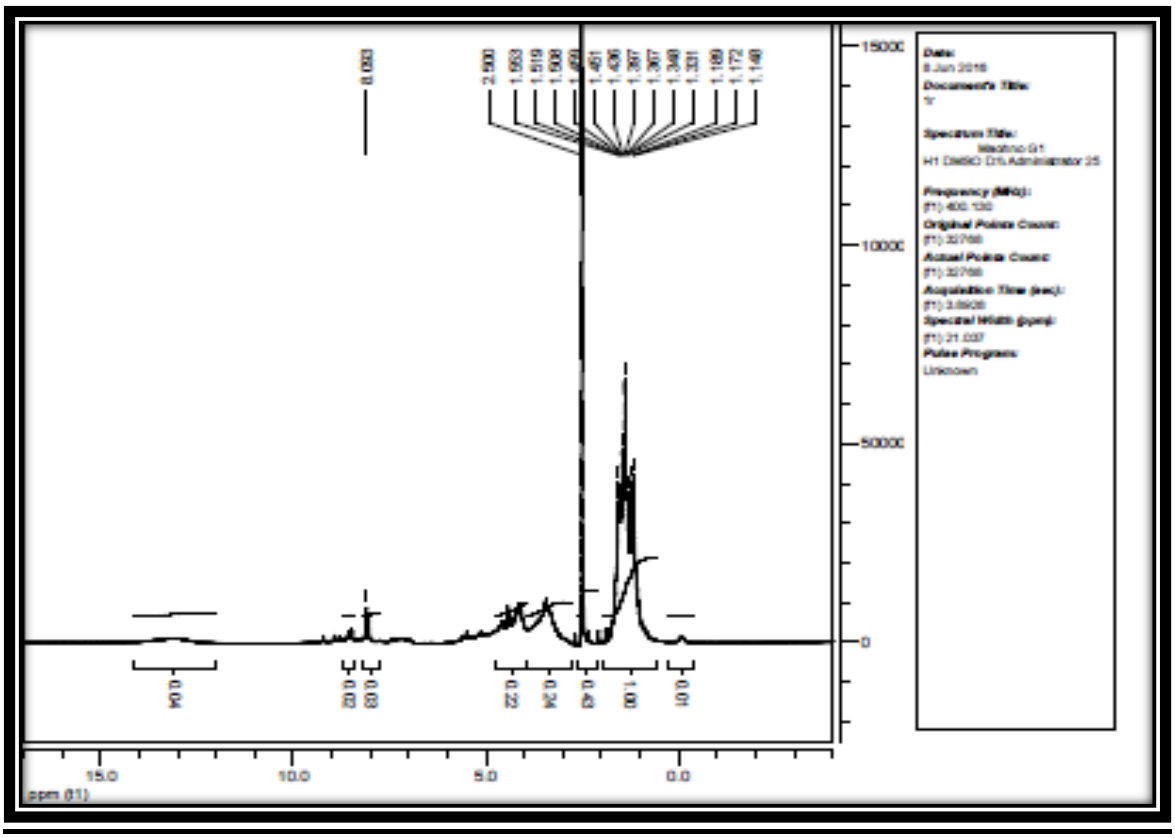


Figure (3-2): ^{1}H NMR spectrum of [L_2]

3.2 FT-IR spectra

The FT-IR spectra of the ligands and complexes were discussed and compared with each other to predict the coordination mode and the expected final shape depending on ligand behavior and other coordinating molecules such as water molecule and chloride ion.

3.2.1 FT-IR spectra of [L_1-L_3] ligands

The FT-IR spectra of the synthesized ligands [L_1], [L_2] and [L_3] exhibit a strong bands at 1697cm^{-1}, 1681cm^{-1} and 1681cm^{-1} respectively due to the presence of carboxylic carbonyl (C=O) that appears usually around 1700 cm^{-1} [77,78].

Generally azomethine (imine group) absorption band appears in the region (1610-1680) cm^{-1} depending on the nature of groups linked to it[77,79].The bands at 1635cm^{-1}, 1654cm^{-1} and 1651cm^{-1} of [L_1], [L_2] and [L_3] respectively were assigned to imine group (C=N), the appearance of imine group in the ligand spectrum confirms the formation of Schiff base ligand.

β-lactam carbonyl group (C=O) for all the synthesized ligands occurred at a significant value 1732 cm^{-1}. The other important characteristic peaks in the FT-IR spectra were assigned in Table (3-1) and shown in figures (3-3) to (3-5).

Table (3-1): Bands of FT-IR spectra of the synthesized ligands

Compound	υ (O-H)	υ (C-H) Aromatic Aliphatic	υ (C=O) β –lactam	υ (C=O) Carboxylic	υ (C=N) Imine	υ (C=C) Aromatic	υ (C-N) υ (C-O)
L_1	3383	3078 2974	1732	1697	1635	1608	1300 1211
L_2	3340	- 2974	1732	1681	1654	-	1338 1215
L_3	3294	3070 2970	1732	1681	1651	1589	1292 1211

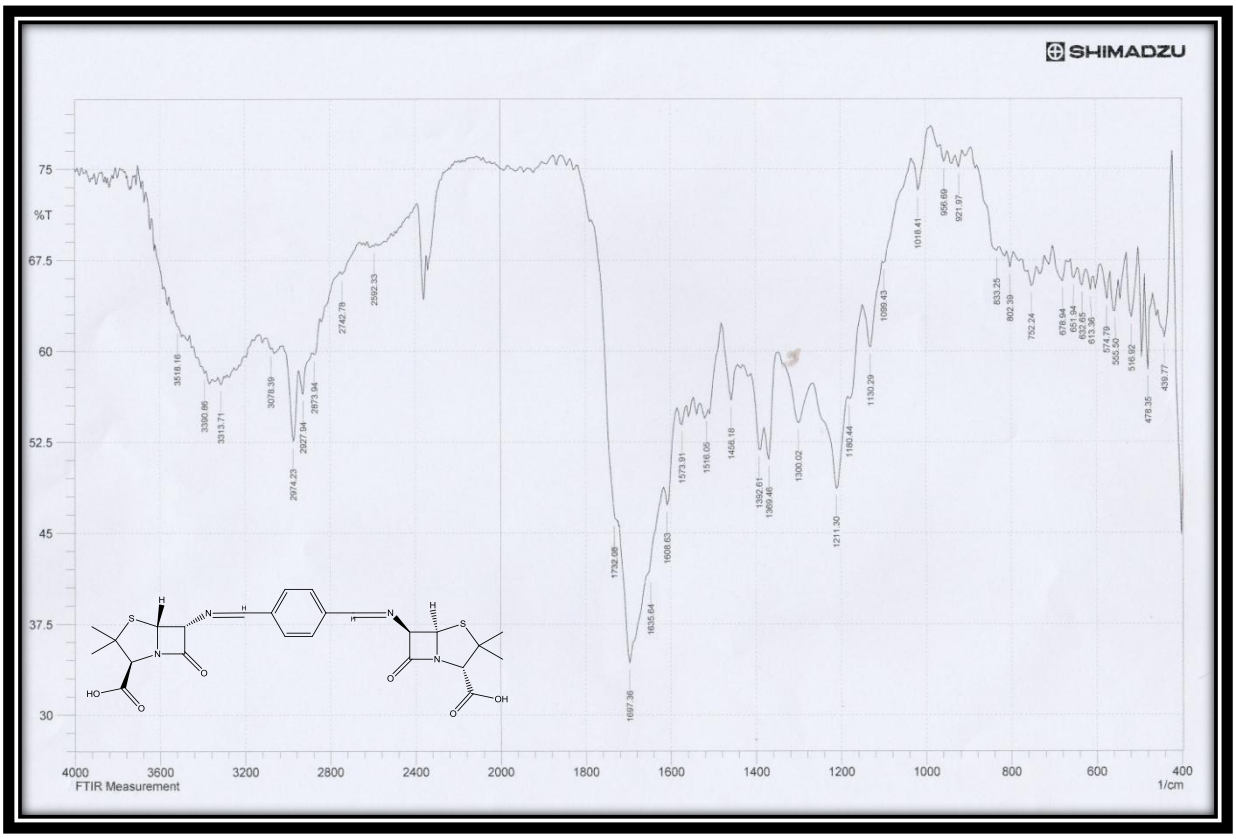


Figure (3-3): FT-IR spectrum of [L_1]

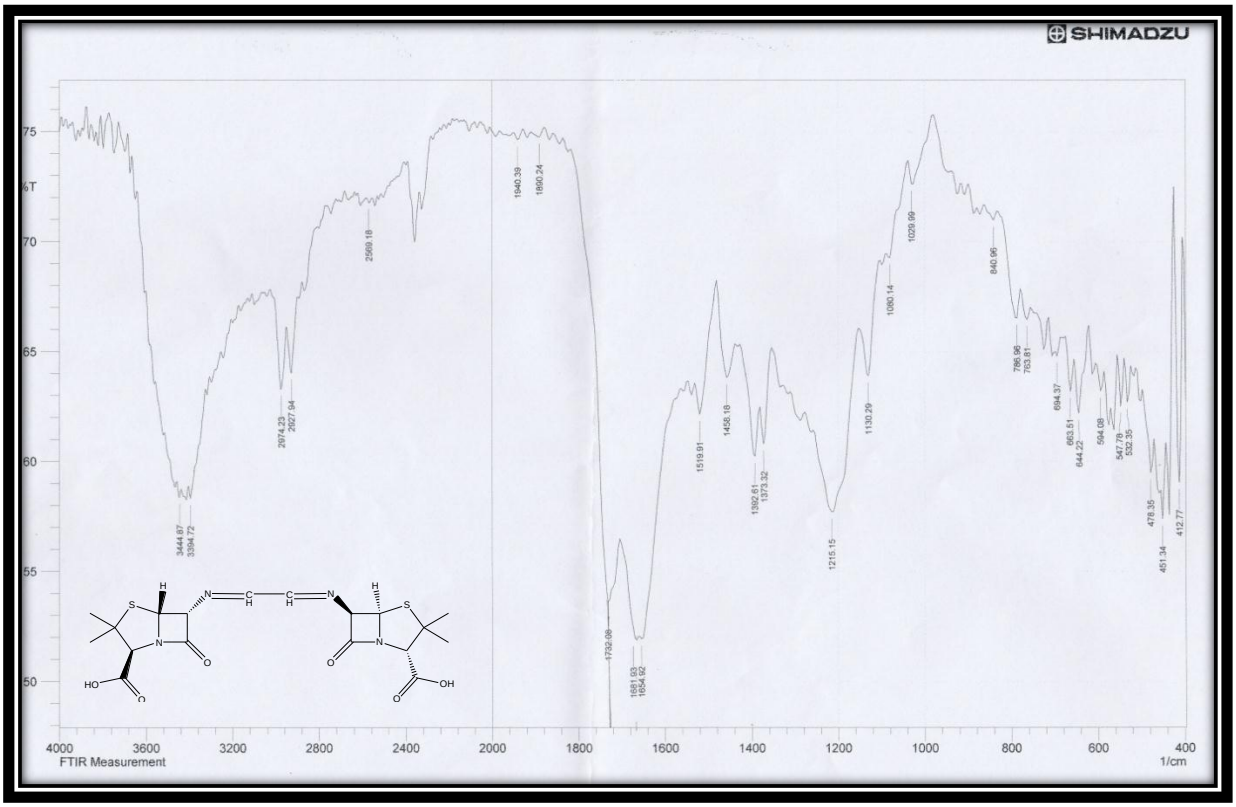


Figure (3-4): FT-IR spectrum of [L_2]

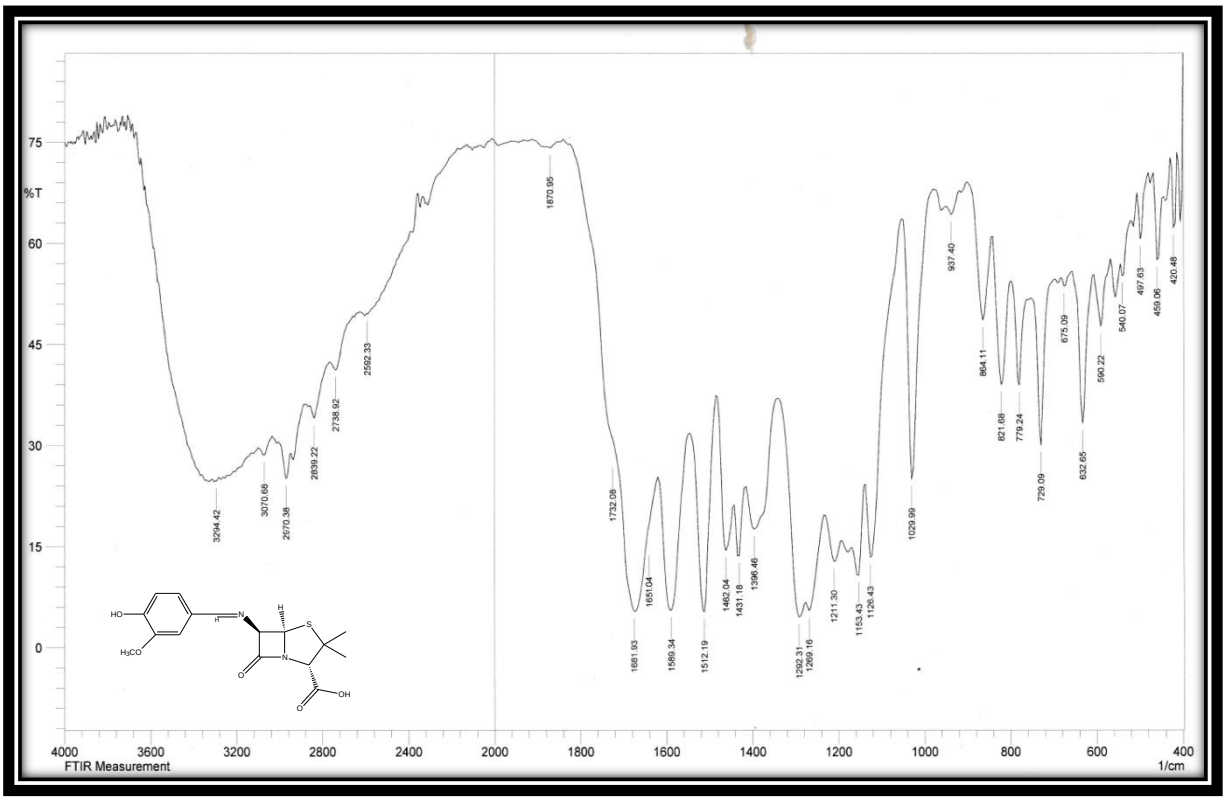


Figure (3-5): FT-IR spectrum of [L_3]

3.2.2 FT-IR spectra of [A_1-A_3],[B_1-B_3] and [C_1-C_3] Complexes

The bands which were attributed to the carboxylic carbonyl (C=O) of [L_1], [L_2] and [L_3] mentioned previously were shifted to lower wave number in all complexes [A_1-A_3], [B_1-B_3] and [C_1-C_3] by (4-12) cm^{-1}, (7-11) cm^{-1} and (7-11) cm^{-1} respectively, indicating that carboxylic groups were involved in complex formation[77,78].

The band at 1732 cm^{-1} of β-Lactam carbonyl group (C=O) does not shifted in all complexes, therefore oxygen of carbonyl C=O does not participate in coordination, but participation occurs through amide nitrogen atom of β-lactam which is situated in a favorable position to form 5-memberd ring because its bended out of plane with respect to the other three carbon atoms in β-lactam ring[63,65,80]. The coordination through oxygen atom of C=O and nitrogen atom of β-lactam are further supported by the occurrence of M-O and M-N bands in the spectra of the complexes at the range mentioned in literatures[81,82]. The other important characteristic peaks were observed in the FT-IR spectra were assigned in Table (3-2) and shown in Figures from (3-6) to (3-14).

Table (3-2): Bands of FT-IR spectra of the synthesized metal complexes

Compound	υ (O-H)	υ (C-H) Aromatic Aliphatic	υ (C=O) β –lactam	υ (C=O) Carboxylic	υ (C=N) Imine	υ (C=C) Aromatic	υ (C-N) υ (C-O)	υ (M-N) υ (M-O)
A_1	3402	3078 2978	1732	1685	1635	1608	1330 1207	505 447
A_2	3371	3167 2985	1732	1689	1635	1600	1338 1199	493 412
A_3	3409	3205 2974	1732	1693	1635	1608	1307 1245	462 405
B_1	3379	- 2975	1732	1670	1654	-	1330 1207	555 428
B_2	3437	- 2978	1732	1674	1654	-	1199 4343	462 420
B_3	3409	- 2958	1732	1670	1654	-	1233 4343	478 410
C_1	3379	3070 2970	1732	1674	1651	1589	1273 1207	547 401
C_2	3367	3186 2978	1732	1670	1651	1600	1288 1207	540 401
C_3	3402	3045 2927	1732	1674	1651	1608	1276 1211	501 435

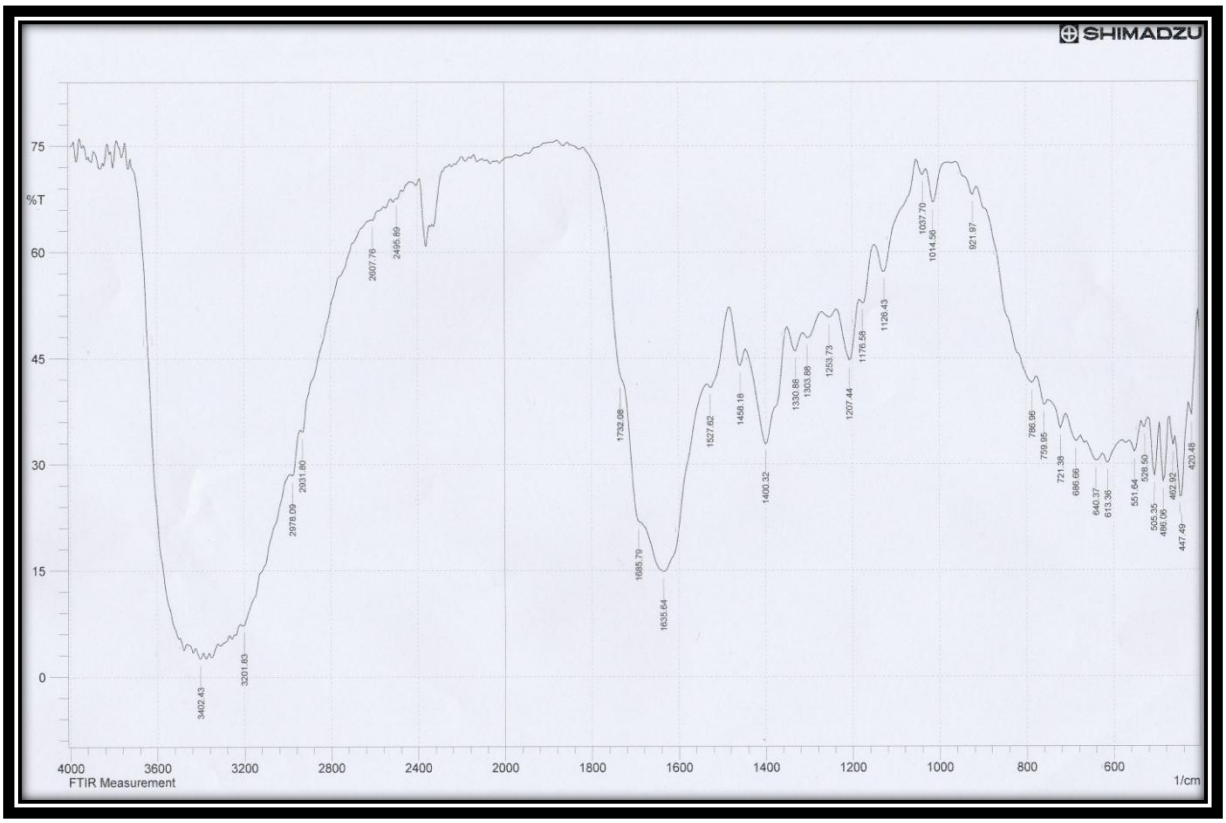


Figure (3-6): FT-IR spectrum of [A_1]

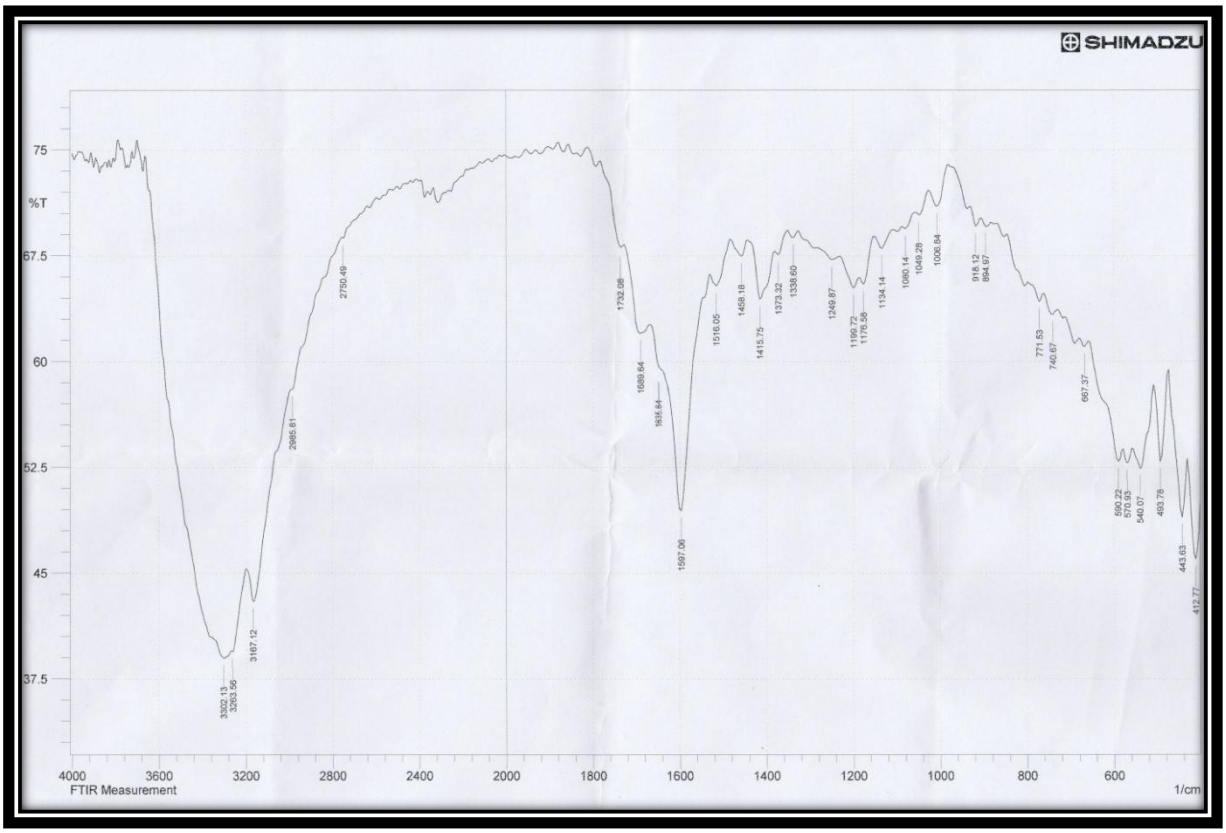


Figure (3-7): FT-IR spectrum of [A_2]

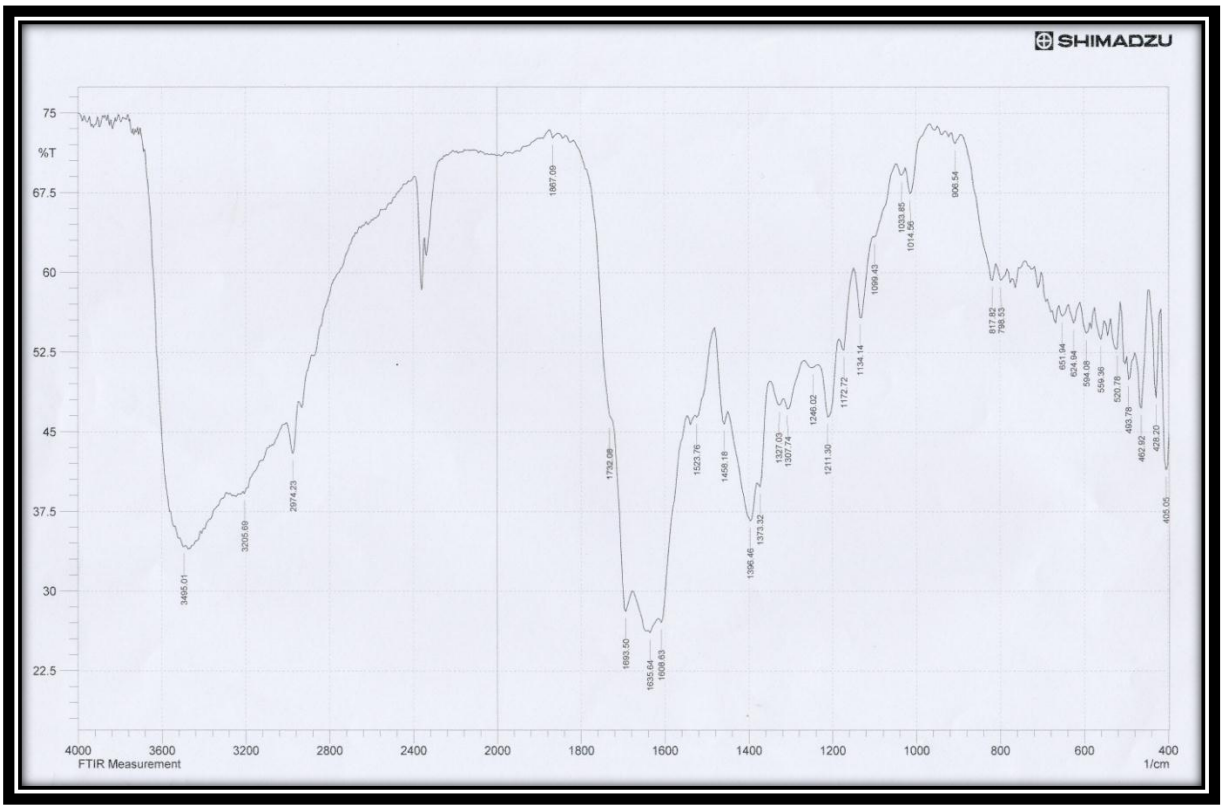


Figure (3-8): FT-IR spectrum of [A_3]

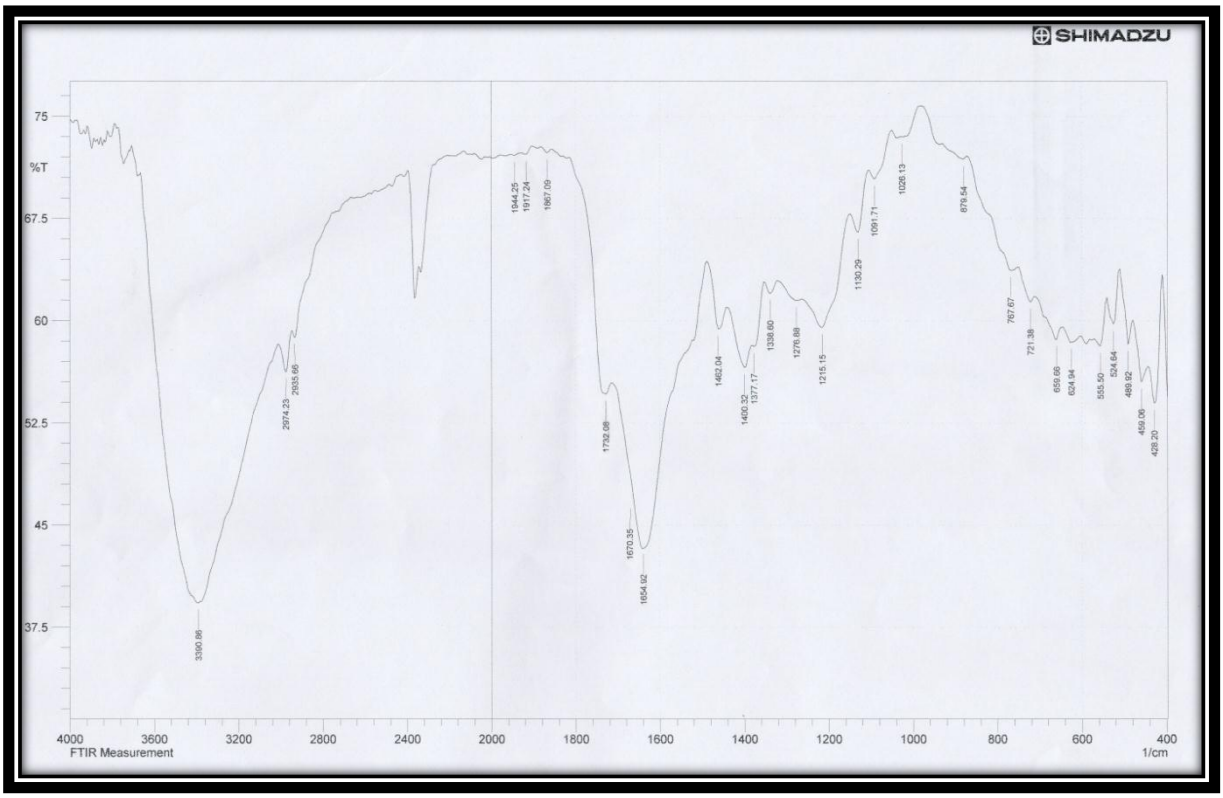


Figure (3-9): FT-IR spectrum of [B_1]

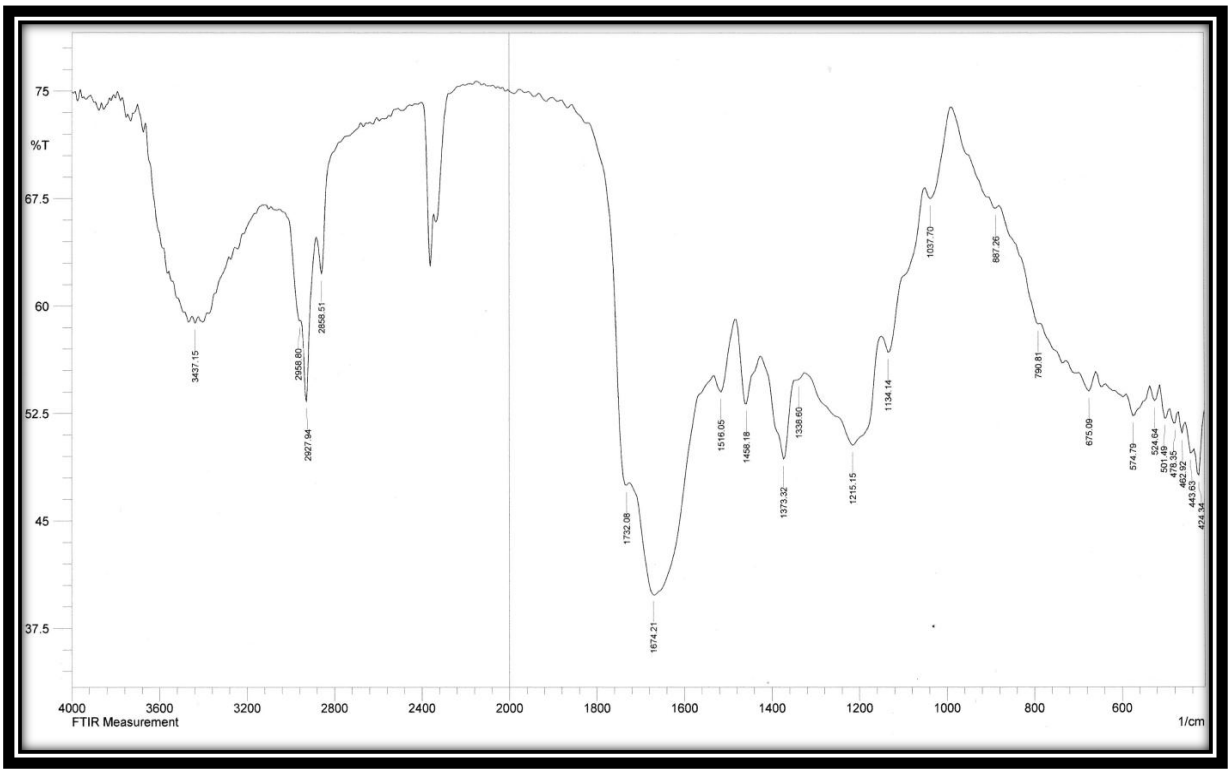


Figure (3-10): FT-IR spectrum of [B_2]

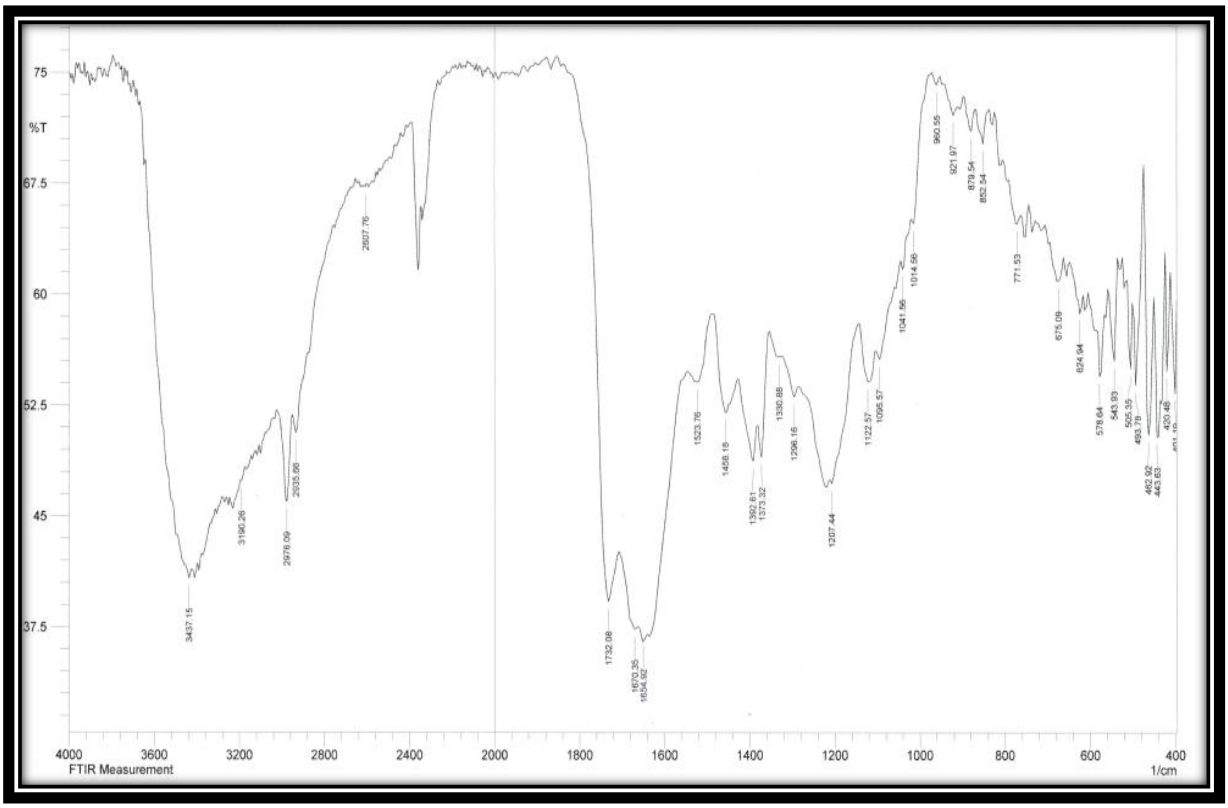


Figure (3-11): FT-IR spectrum of [B_3]

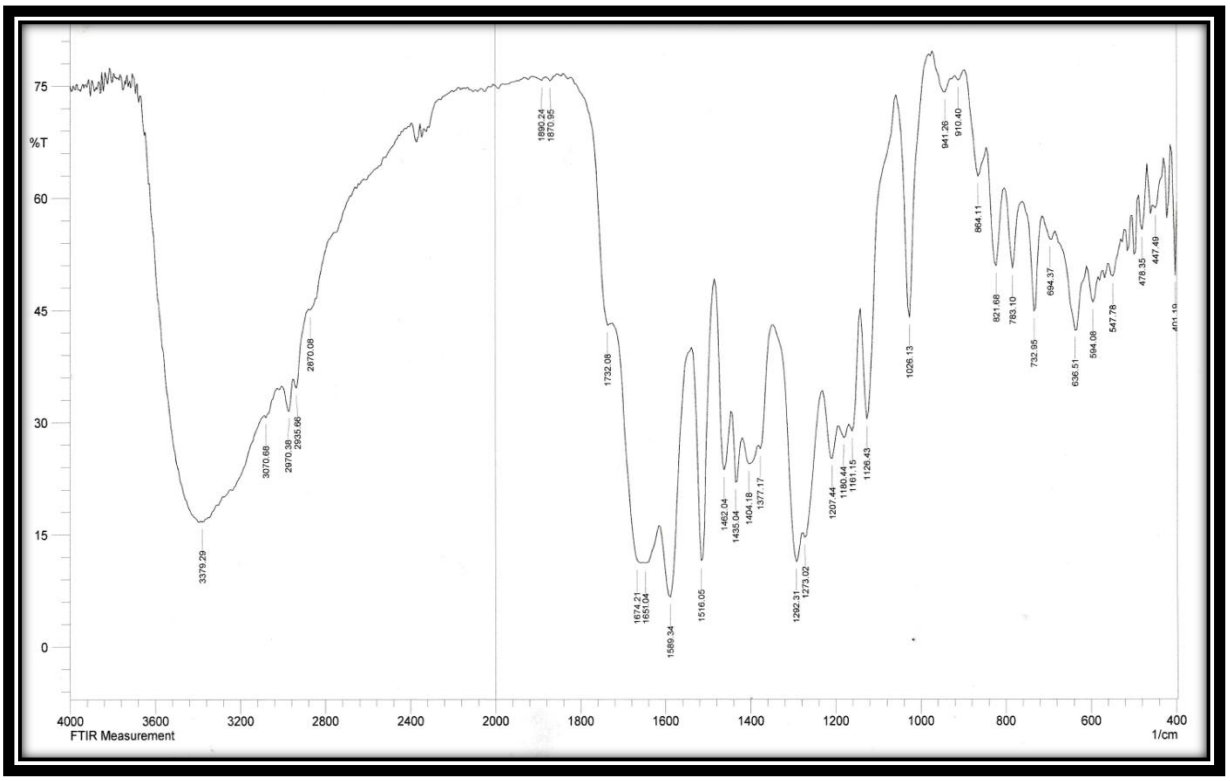


Figure (3-12): FT-IR spectrum of [C_1]

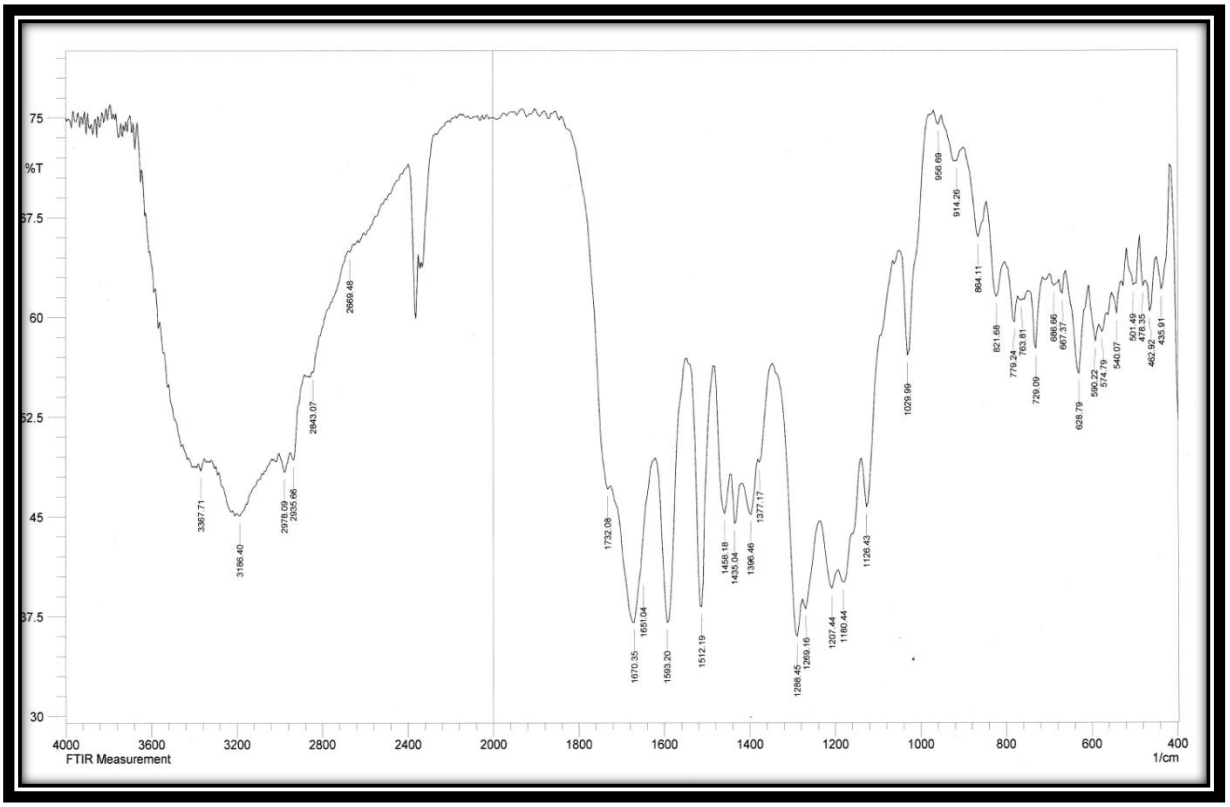


Figure (3-13): FT-IR spectrum of [C_2]

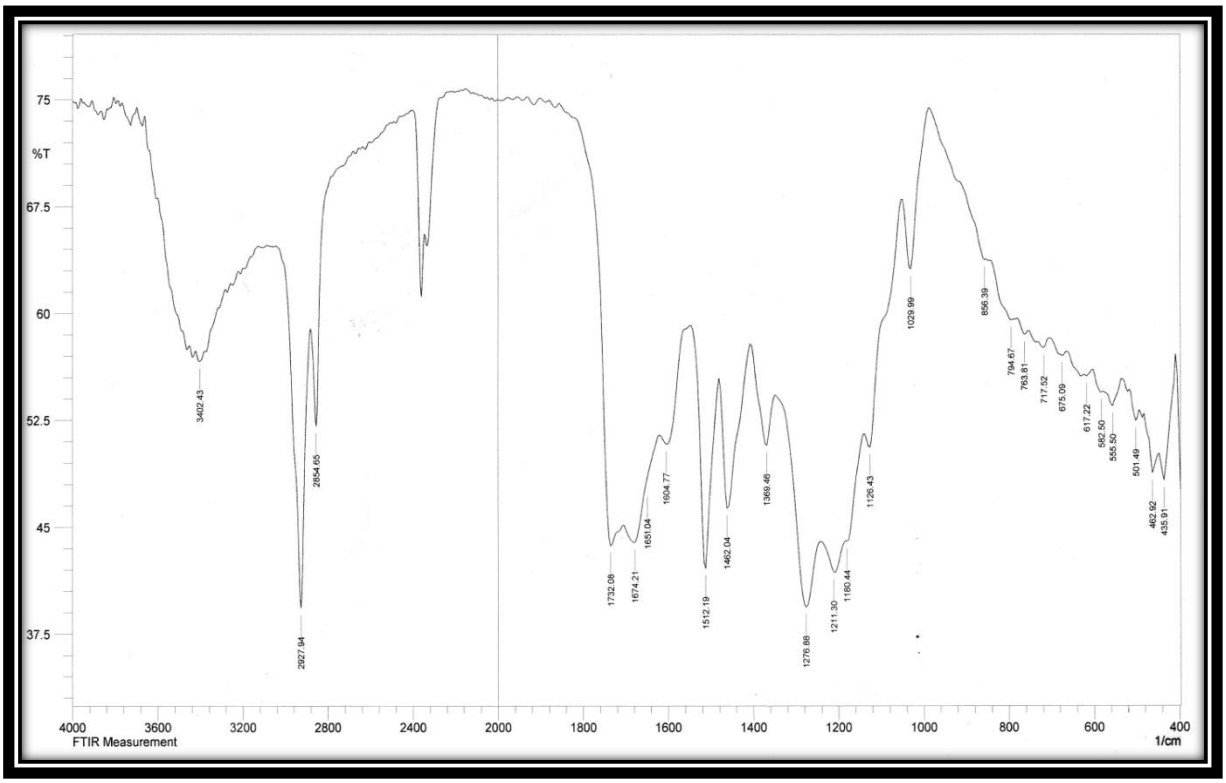


Figure (3-14): FT-IR spectrum of [C_3]

3.3 Study of the electronic spectra of ligands and metal complexes

Electronic absorption spectra of transition metal complexes are usually attributed to the electronic transitions of metal partially filled d-orbital except Zn; the energy required for such transitions is that of near UV and visible regions.

The spectra helped us to predict the suggested geometry according to the shape and number of observed peaks beside the calculated ones depending on the information of Racah parameter (B'), 10Dq and nephelauxetic factor (β) using Tanabe- Sugano diagram. The electronic spectra of the prepared ligands did not help us to predict the coordination behavior by shifting to lower or higher field due to the variation of n→π*and π→ π* transitions presented on the complicated ligands.

3.3.1 Uv-Vis. Spectra of Ligands [L_1], [L_2] and [L_3]

The electronic spectra of the prepared ligands showed several peaks between 200-400nm which were assigned to n→π* and π→ π* transitions as shown in table (3-3) and figures (3-15) to (3-17).

Transitions related to coordinated groups in complexes were shifted, but either obscured or interfered with non-coordinated groups of the ligand field.

Table (3-3): Electronic Spectral data of the prepared ligands

symb.	*λ nm*	*ύ cm $^{-1}$*	*Assignments*	*Suggested Structure*
L_1	**236** **288**	**42,372** **34,722**	***π→ π**** ***n→π****	***Distorted Octahedral***
L_2	**230** **243**	**43,478** **41,152**	***π→ π**** ***n→π****	***Distorted Octahedral***
L_3	**249** **275**	**34,018** **36,363**	***π→ π**** ***n→π****	***Distorted Octahedral***

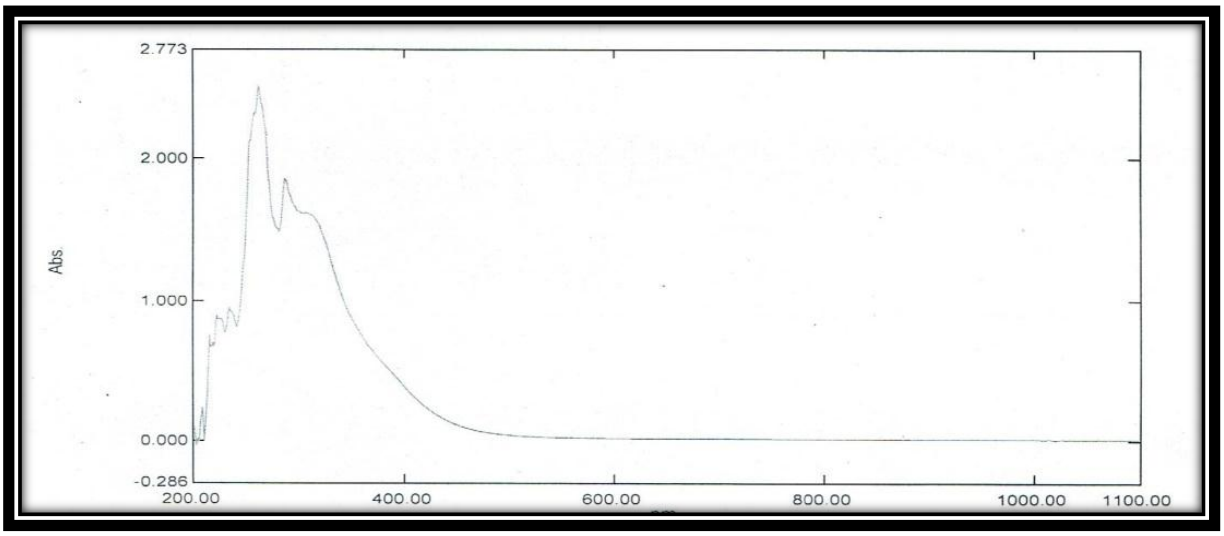


Figure (3-15): Electronic Spectrum of [L_1]

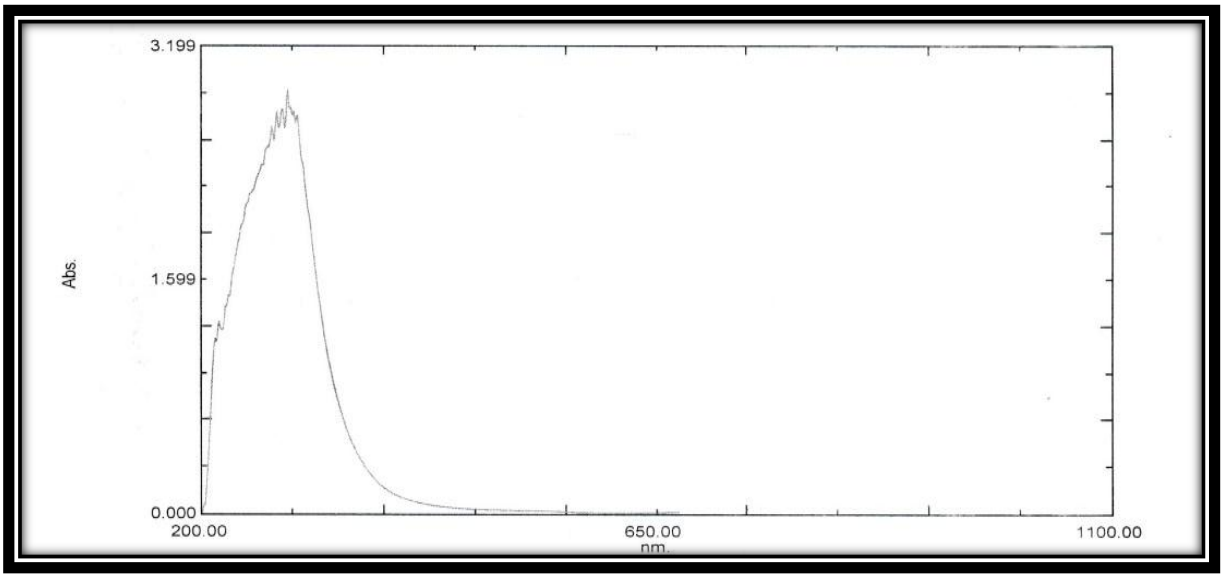


Figure (3-16): Electronic Spectrum of [L_2]

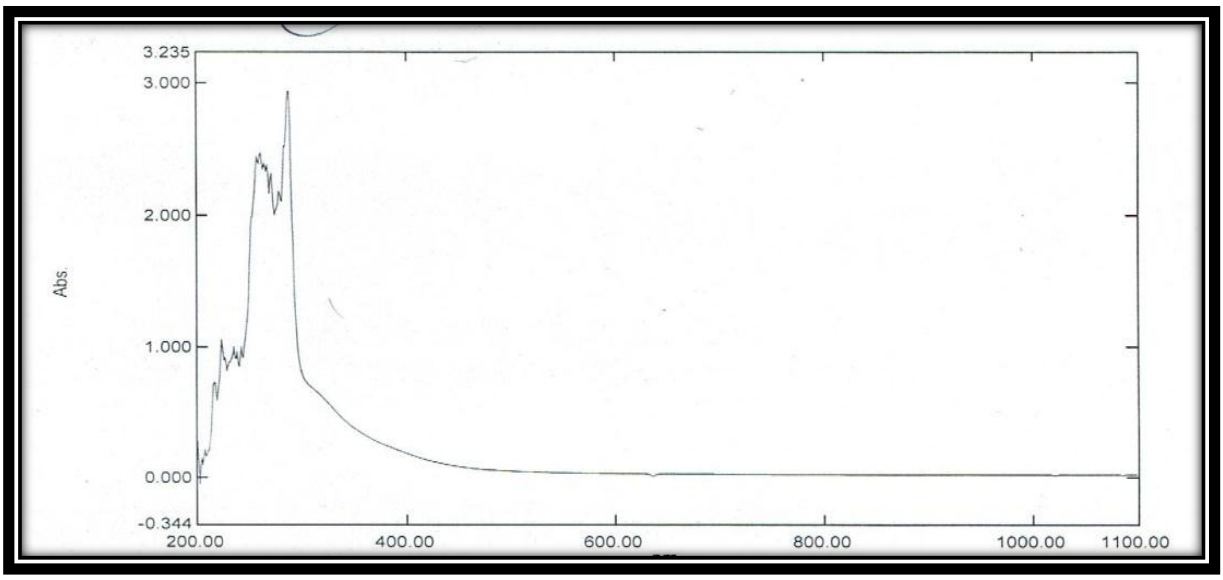


Figure (3-17): Electronic Spectrum of [L_3]

3.3.2 Uv-Vis. Spectra of Co(II) complexes [A_1],[B_1] and [C_1]

Electronic spectra of [A_1], [B_1] and [C_1] complexes in Figures (3-18), (3-19) and (3-20) respectively showed two electronic transition bands. The regular transition bands of Co(II) complexes are three bands ν_1: ^4T_1g (F) → ^4T_2g (F) 7000 – 12000 cm^{-1}, ν_2: ^4T_1g (F) → ^4A_2g (F) 14000 – 16000 cm^{-1} and ν_3: ^4T_1g (F) → ^4T_1g (P) 18000 – 21000 cm^{-1}[1(14,83)]; Therefore the missing third in the synthesized complexes band was calculated using Tanabe- Sugano diagram depending on the information of Racah parameter (B'), 10Dq and nephelauxetic factor (β). Table (3-4) shows the absorption bands and their assignments

Table (3-4): Electronic Spectral data of Co(II) complexes

sym	*λ nm*	*ύ cm $^{-1}$*	*Assignments*	*B*	*B′*	*B*	*10Dq*	*Suggested Structure*
A_1	**238** **575** **657** **1388**	**42,016** **17,391** **15,220** **7201(Cal.)**	***π→ π*, n→π**** ***$^4T_1g(F)\rightarrow{}^4T_1g\ ^4(P)$*** ***$^4T_1g(F)\rightarrow{}^4A_2g\ ^4(F)$*** ***$^4T_1g(F)\rightarrow{}^4T_2g\ ^4(F)$***	**1128**	**758**	**0.65**	**8019**	***Distorted Octahedral***
B_1	**214** **539** **652** **1372**	**46,729** **18,552** **15,337** **7285(Cal.)**	***π→ π*, n→π* π*** ***$^4T_1g(F)\rightarrow{}^4T_1g\ ^4(P)$*** ***$^4T_1g(F)\rightarrow{}^4A_2g\ ^4(F)$*** ***$^4T_1g(F)\rightarrow{}^4T_2g\ ^4(F)$***	**1128**	**728**	**0.64**	**8052**	***Distorted Octahedral***
C_1	**231** **548** **662** **1394**	**43,290** **18,248** **15,105** **7170(Cal.)**	***π→ π*, n→π**** ***$^4T_1g(F)\rightarrow{}^4T_1g\ ^4(P)$*** ***$^4T_1g(F)\rightarrow{}^4A_2g\ ^4(F)$*** ***$^4T_1g(F)\rightarrow{}^4T_2g\ ^4(F)$***	**1128**	**717**	**0.6**	**7935**	***Distorted Octahedral***

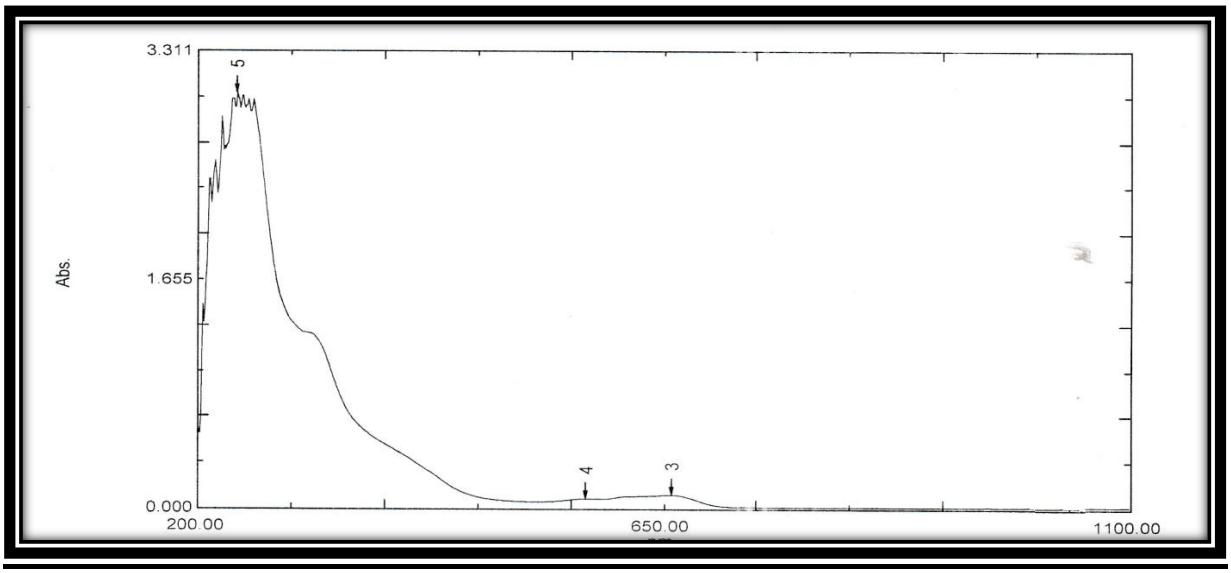


Figure (3-18): Electronic Spectrum of [A_1]

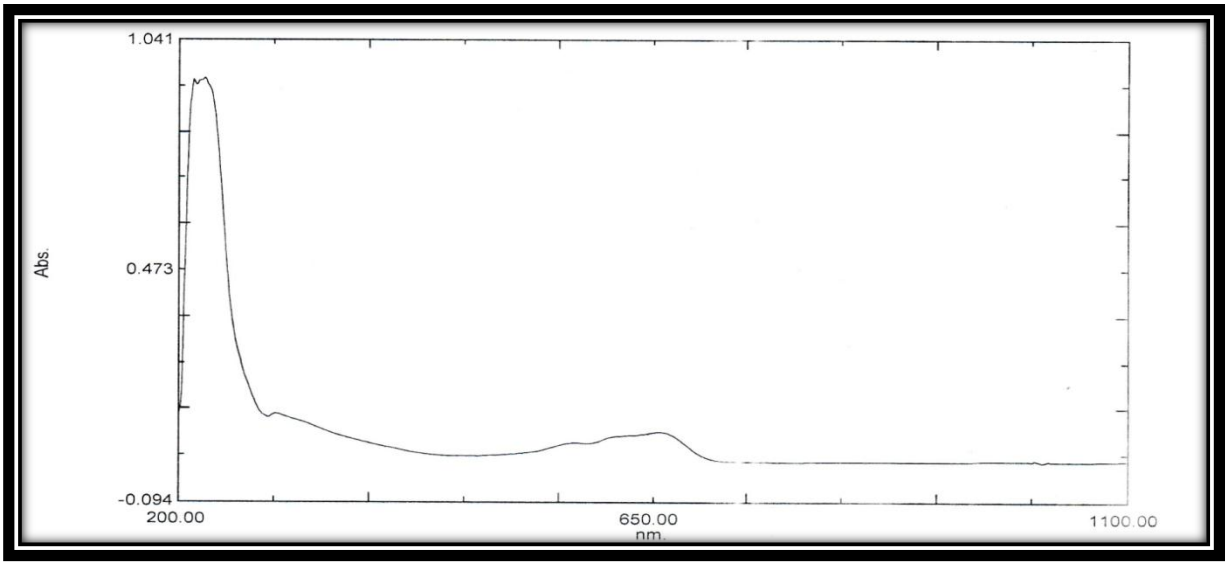


Figure (3-19): Electronic Spectrum of [B_1]

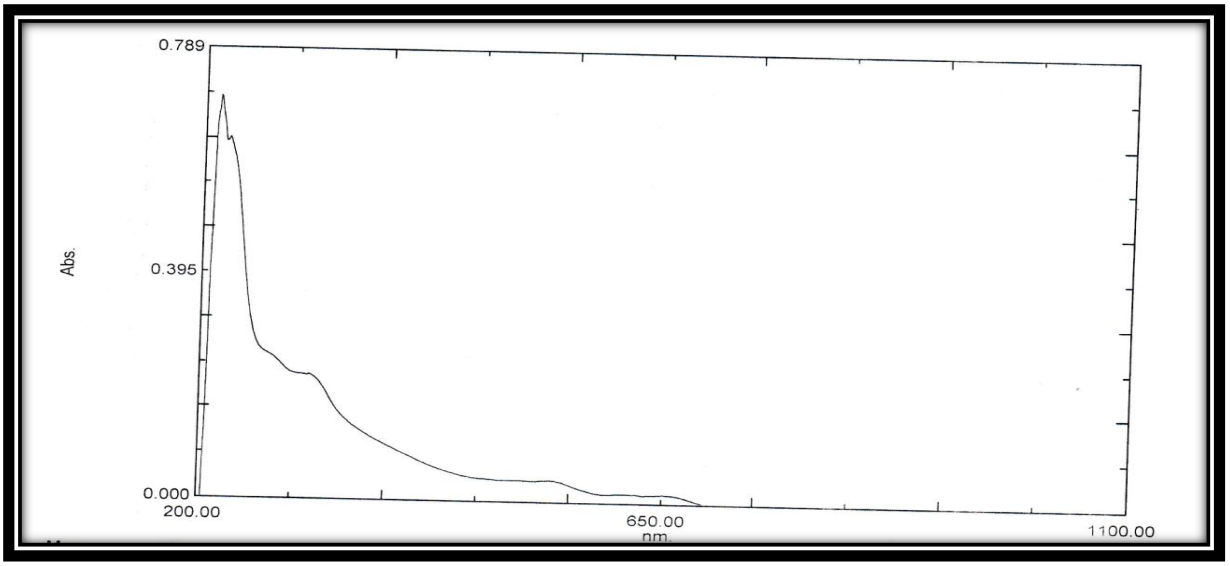


Figure (3-20): Electronic Spectrum of [C_1]

3.3.3 Uv-Vis. Spectra of Cu(II) complexes [A_2],[B_2] and [C_2]

Electronic spectra of [A_2],[B_2] and [C_2] are shown in Figures (3-21), (3-22) and (3-23) respectively. A single broad band appeared in the range (11,000-16,000) cm^{-1} representing octahedral geometry[84]. The suggested complexes were with distorted octahedral geometries due to Jahn-Teller distortion[85,86] and the appearance within the mentioned range. Table (3-5) shows the absorption band and their assignments.

Table (3-5): Electronic Spectral data of Cu(II) complexes

symb.	*λ nm*	*ύ cm $^{-1}$*	*Assignments*	*Suggested Structure*
A_2	**241** **340** **654**	**41,493** **29,411** **15,290**	***π→ π**** ***n→π**** ***$^2Eg \nrightarrow {}^2T_2g$***	***Distorted Octahedral***
B_2	**234** **352** **648**	**42,735** **28,409** **15,432**	***π→ π*, n→π**** ***(C.T)*** ***$^2Eg \nrightarrow {}^2T_2g$***	***Distorted Octahedral***
C_2	**251** **388** **671**	**39,840** **25,773** **14,903**	***π→ π**** ***n→π**** ***$^2Eg \nrightarrow {}^2T_2g$***	***Distorted Octahedral***

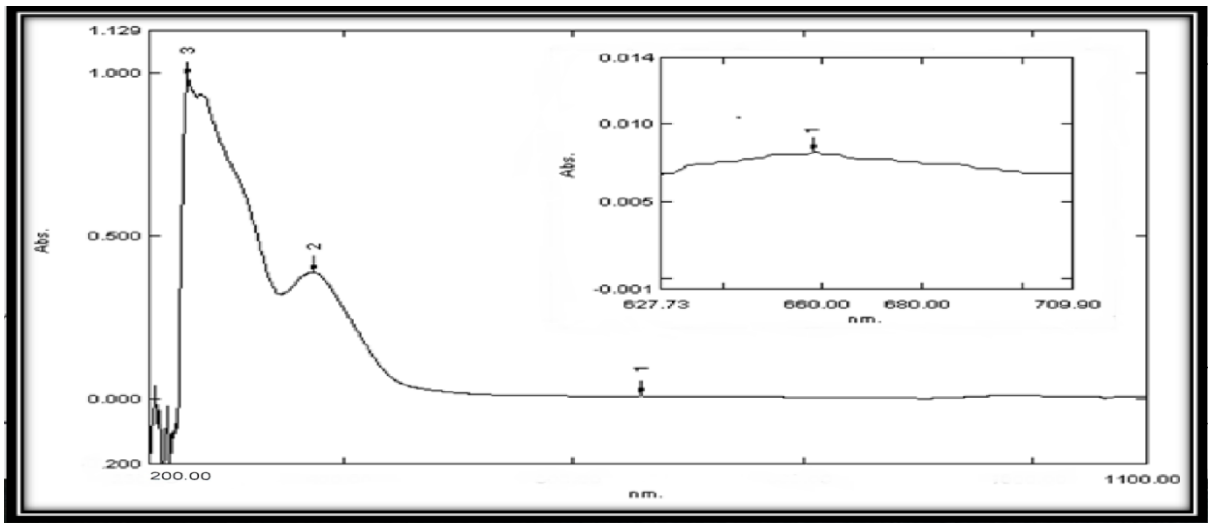


Figure (3-21): Electronic Spectrum of [A_2]

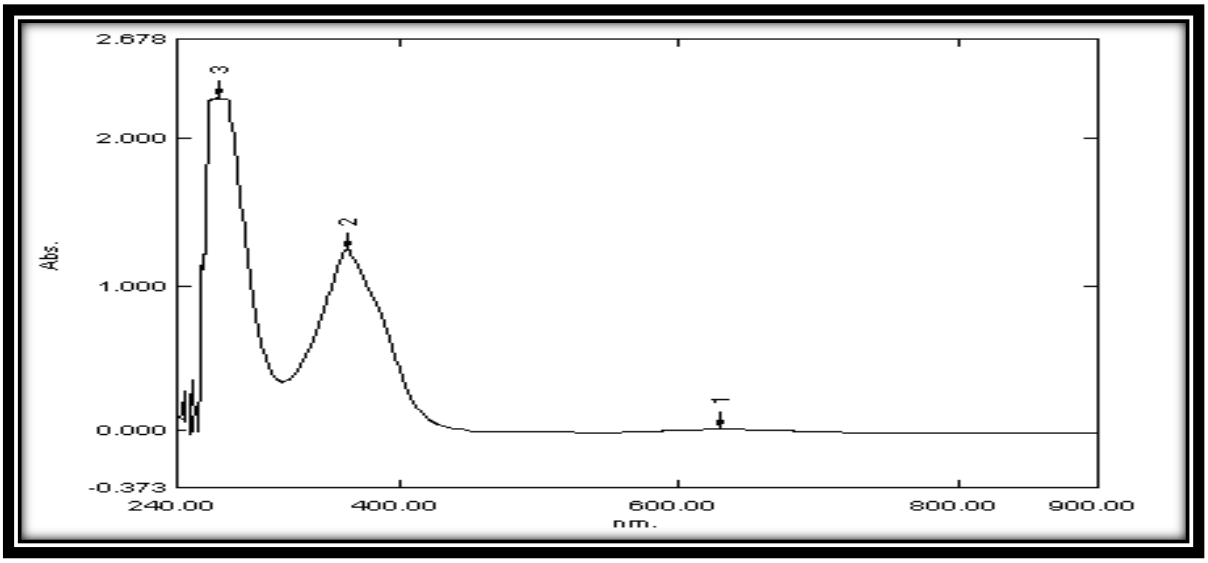


Figure (3-22): Electronic Spectrum of [B_2]

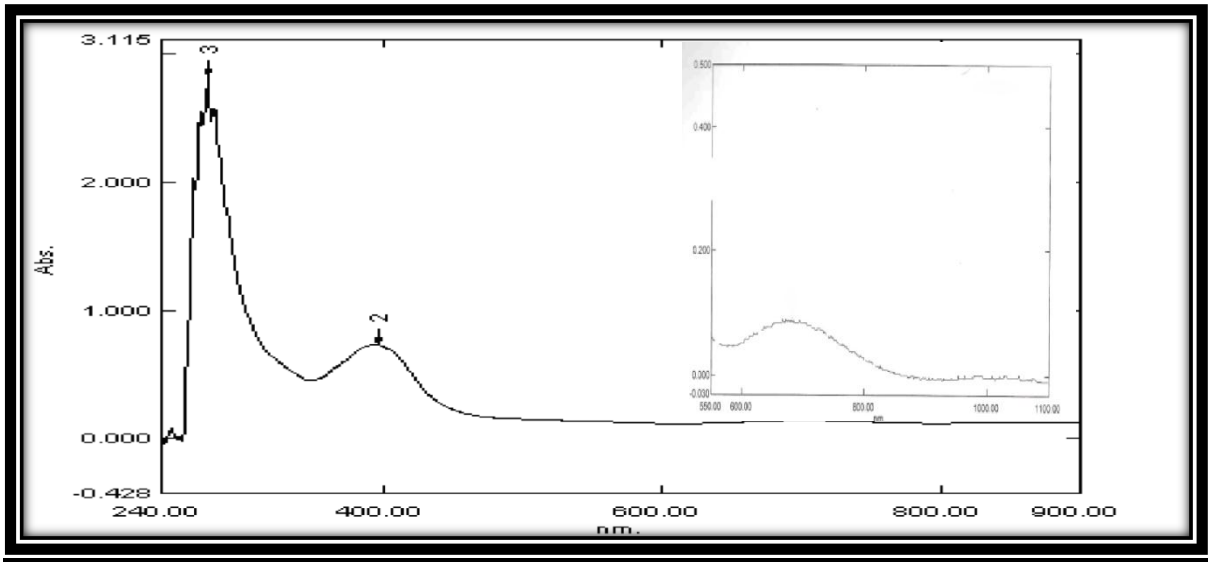


Figure (3-23): Electronic Spectrum of [C_2]

3.3.4 Uv-Vis. Spectra of Zn(II) complexes [A_3],[B_3] and [C_3]

Generally Zinc ion complexes with d^{10} electronic configuration do not expected to show d-d electronic transition because of the filled d-orbital[85,86], thus [A_3], [B_3] and [C_3] spectra in Figures (3-24), (3-25) and (3-26) respectively, did not show clear bands in the visible region, only ligand field bands can be recognized in the spectra. Table (3-6) shows the absorption band and their assignments.

Table (3-6): Electronic Spectral data of Zn(II) complexes

symb.	*λ nm*	*ύ cm $^{-1}$*	*Assignments*	*Suggested Structure*
A_3	**257** **307**	**38,910** **32,573**	***π→ π**** ***n→π****	***Distorted Octahedral***
B_3	**232** **316**	**43,103** **31,645**	***π→ π**** ***n→π****	***Distorted Octahedral***
C_3	**237** **279** **312** **471**	**42,194** **35,842** **32,051** **21,231**	***π→ π**** ***n→π**** ***n→π**** **C.T**	***Distorted Octahedral***

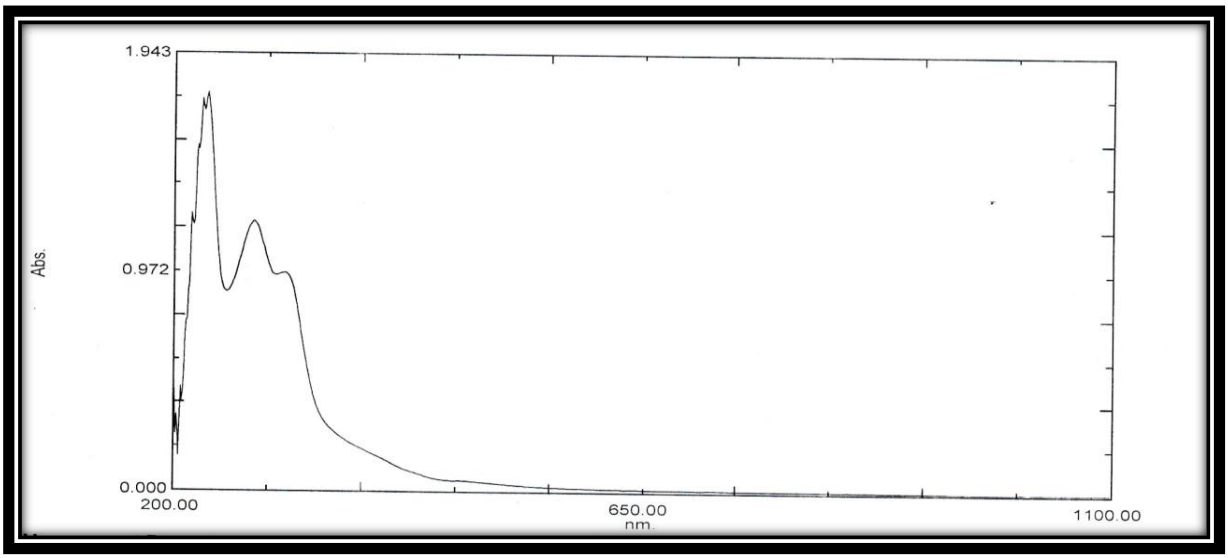


Figure (3-24): Electronic Spectrum of [A_3]

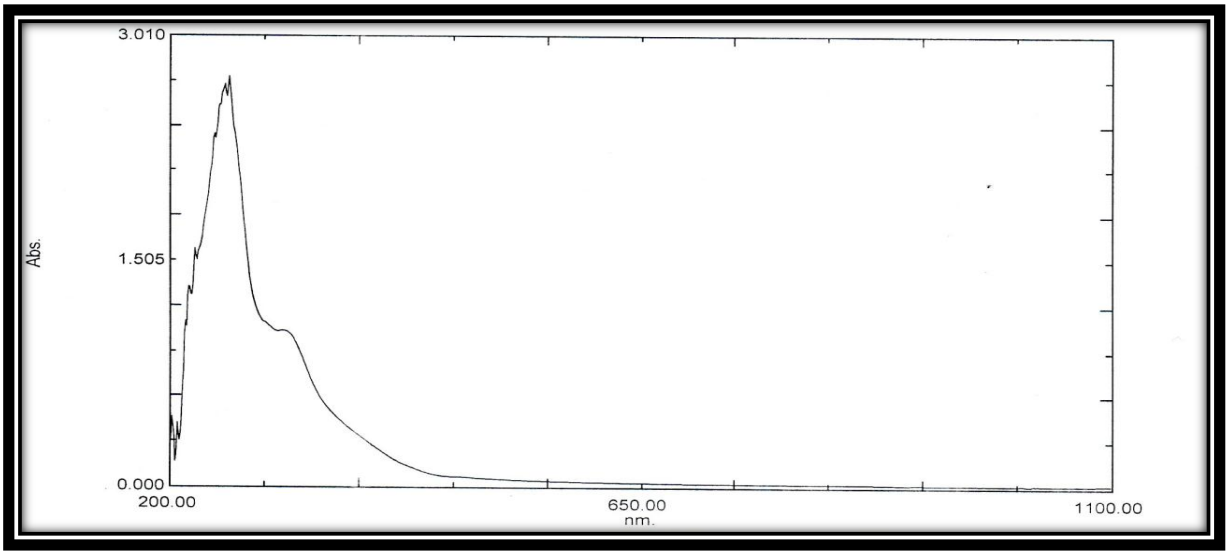


Figure (3-25): Electronic Spectrum of [B_3]

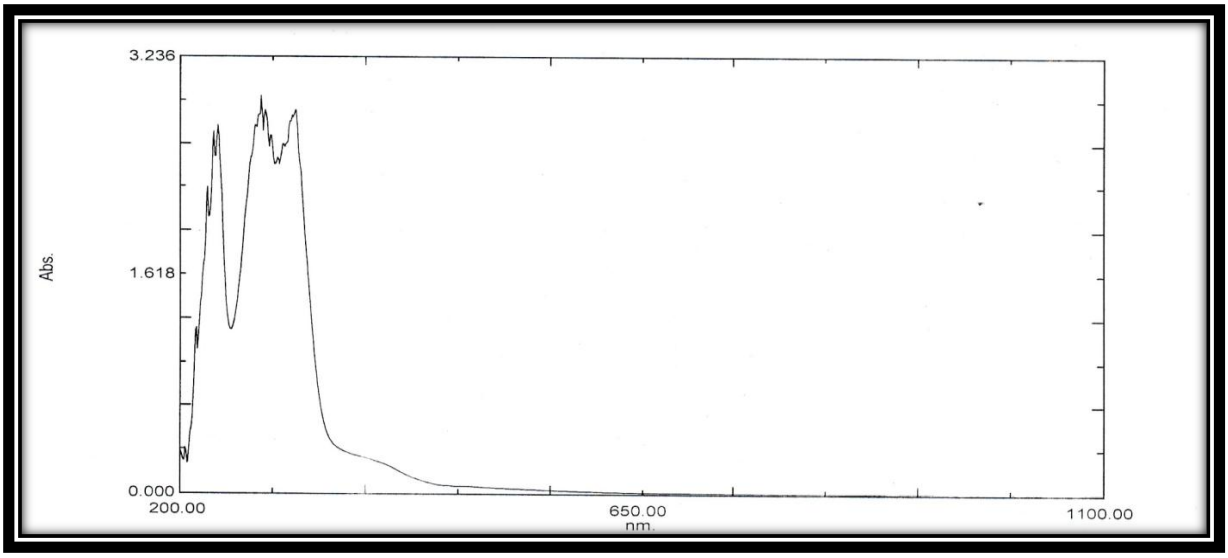


Figure (3-26): Electronic Spectrum of [C_3]

3.4 Metal and Elemental Micro analysis (C.H.N.S.)

Micro elemental analysis (C.H.N.S.) of the synthesized complexes played an important role in predicting the final structure and formula accompanied with metal analysis by using atomic absorption spectroscopy. Table (3-7) shows that calculated theoretical values were in good agreement with found experimental values.

Table (3-7): Elemental analysis of synthesized compounds

Symbol	Empirical formula	Elemental and metal analysis Found (Calc.)				
		C%	H%	N%	S%	Metal %
L_1	$C_{24}H_{26}N_4O_6S_2$	54.14	5.02	10.23	11.92	-
		(54.33)	**(4.90)**	**(10.57)**	**(12.07)**	-
A_1	$[Co_2L_1(H_2O)_4Cl_4].2H_2O$	31.90	4.28	5.98	7.27	12.89
		(32.07)	**(4.23)**	**(6.23)**	**(7.12)**	**(13.14)**
A_2	$[Cu_2\ L_1\ (H_2O)_4Cl_4].H_2O$	32.17	4.09	6.15	7.05	14.01
		(32.39)	**(4.04)**	**(6.29)**	**(7.19)**	**(14.28)**
A_3	$[Zn_2\ L_1\ (H_2O)_4Cl_4]$	32.66	3.95	6.32	7.03	14.78
		(32.91)	**(3.88)**	**(6.41)**	**(7.31)**	**(14.97)**
L_2	$C_{18}H_{22}N_4O_6S_2$	47.33	4.45	12.10	14.30	-
		(47.56)	**(4.88)**	**(12.33)**	**(14.11)**	-
B_1	$[Co_2\ L_2\ (H_2O)_4Cl_4].2H_2O$	26.12	4.25	6.98	7.58	14.28
		(26.27)	**(4.13)**	**(6.81)**	**(7.78)**	**(14.35)**
B_2	$[Cu_2\ L_2\ (H_2O)_4Cl_4].H_2O$	26.34	4.06	7.02	7.28	15.45
		(26.56)	**(3.93)**	**(6.88)**	**(7.87)**	**(15.62)**
B_3	$[Zn_2\ L_2\ (H_2O)_4Cl_4].H_2O$	26.61	3.71	6.52	7.74	15.93
		(26.43)	**(3.91)**	**(6.85)**	**(7.83)**	**(16.03)**
L_3	$C_{16}H_{18}N_2O_5S$	54.54	5.02	7.73	8.92	-
		(54.85)	**(5.14)**	**(8.00)**	**(9.14)**	-
C_1	$[Co\ L_3\ (H_2O)_2Cl_2]$	36.90	4.28	5.98	6.27	11.89
		(37.28)	**(4.27)**	**(5.43)**	**(6.21)**	**(11.45)**
C_2	$[Cu\ L_3\ (H_2O)_2Cl_2]$	36.57	4.09	5.15	6.05	12.01
		(36.99)	**(4.23)**	**(5.39)**	**(6.16)**	**(12.23)**
C_3	$[Zn\ L_3\ (H_2O)_2Cl_2].2H_2O$	34.66	4.95	5.32	5.03	11.78
		(34.47)	**(4.66)**	**(5.02)**	**(5.74)**	**(11.66)**

3.5 Molar conductivity measurement for the complexes

The conductivity measurement of a compound is used to determine the conductance property (electrolyte or non-electrolyte nature.

All complexes show the non-electrolytic property in absolute ethanol. This was indicated according to the measured values in Table (3-8) which occurred within the range mentioned in literature [87,88].

Table (3-8): The molar conductivity of the complexes

symbol	Empirical formula	Λ_m S.cm^2.mole^{-1}	Property
A_1	$[Co_2L_1(H_2O)_4Cl_4].2H_2O$	11.2	Non-electrolyte
A_2	$[Cu_2 L_1 (H_2O)_4Cl_4].H_2O$	17.1	
A_3	$[Zn_2 L_1 (H_2O)_4Cl_4]$	14.7	
B_1	$[Co_2 L_2 (H_2O)_4Cl_4].2H_2O$	12.7	
B_2	$[Cu_2 L_2 (H_2O)_4Cl_4].H_2O$	12.6	
B_3	$[Zn_2 L_2 (H_2O)_4Cl_4].H_2O$	20.4	
C_1	$[Co L_3(H_2O)_2Cl_2]$	16.5	
C_2	$[Cu L_3(H_2O)_2Cl_2]$	15.2	
C_3	$[Zn L_3(H_2O)_2Cl_2].2H_2O$	13.3	

3.6 Thermal analysis

The thermal behaviors of the complexes were studied using thermal gravimetric analysis (TGA) .The thermal decomposition data of complexes were shown in Table (3-9) and figures (3-27), (3-28) and (3-29). The thermal decompositions of A_1, B_2 and C_2 complexes occur in four or three steps in air were observed. According to the mass losses, the following degradation patterns might illustrate the proposed structures of the complexes.

All the compounds decompose step by step upon time that started by dehydration process, lattice water molecules decompose first followed by leaving of the coordinated water molecules. In the second step, weight losses were observed as gases such as leaving carbon monoxide (CO), hydrochloric acid (HCl) and hydrogen (H_2) gases [89, 90].

The observed mass loss at the final steps as temperature raise, A_1, B_2 and C_2 complexes loss their ligands[91,92] leaving the metal oxide in form of (M_2O) or (MO) residue of fragments at the end [93,94].

Table (3-9): Thermo analytical results (TGA) of metal complexes

Complexes	*TG range/°C*	*Mass loss% obs.*	*Assignments*
A_1	**0-120**	**4.22**	***-Loss of two lattice water molecules***
	224-248	**8.44**	***-loss of four coordinated H_2O, -2CO***
	248-510	**59.12**	***-2Cl ,Removal of L_1***
	510-560	**12.66**	***-2HCl ,2O***
	>560	**15.56**	***-Leaving Co_2O residue***
B_2	**0-180**	**6.89**	***-Loss of one lattice water molecules and two coordinated H_2O***
	180-419	**29.32**	***-$2H_2O$, -4Cl ,-2H ,-2CO***
	419-561	**48.72**	***-Removal of L_2 ligand***
	>561	**15.07**	***-Leaving Cu_2O residue***
C_2	**0-130**	**5.55**	***-Loss of two coordinated H_2O***
	278-474	**31.63**	***-CO ,Removal of vanillin part (Schiff base decomposition)***
	474-619	**47.88**	***-Removal of penam part***
	>619	**14.94**	***-Leaving CuO residue***

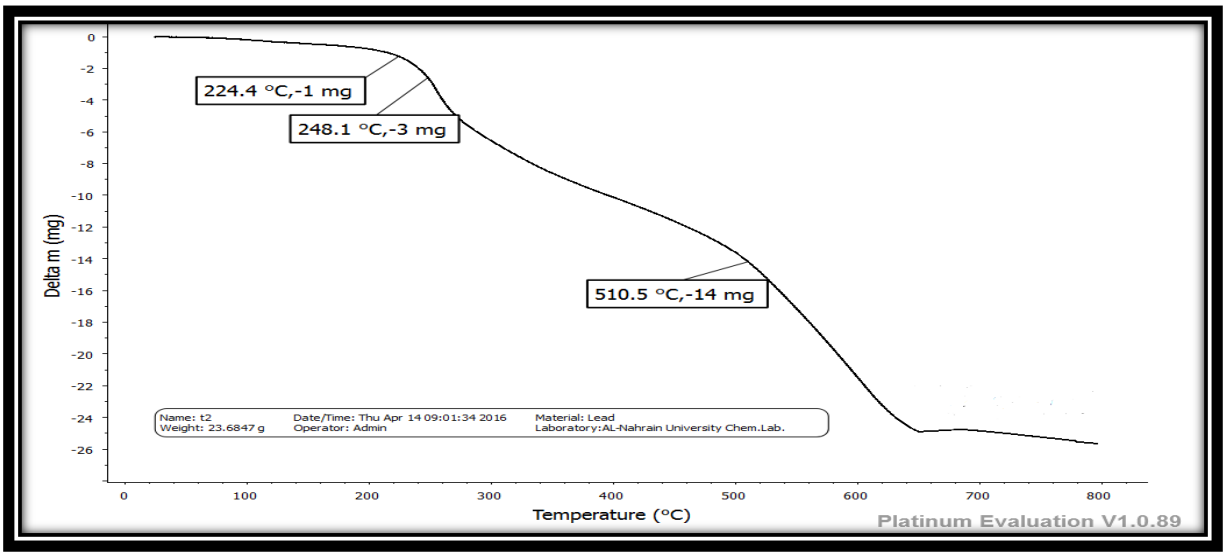


Figure (3-27): TGA of [A_1] complex

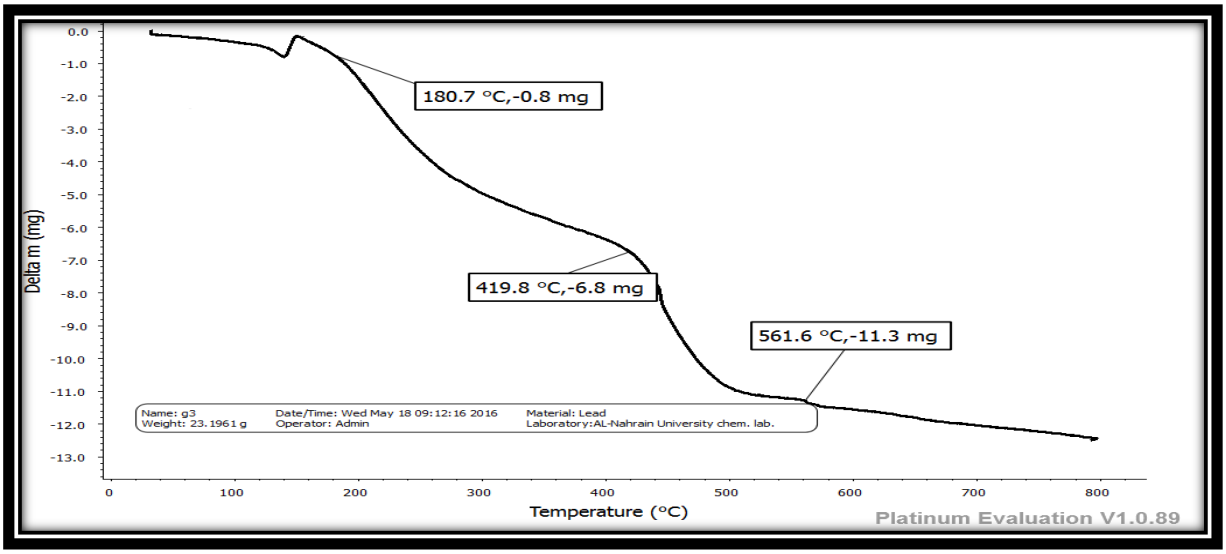


Figure (3-28): TGA of [B_2] complex

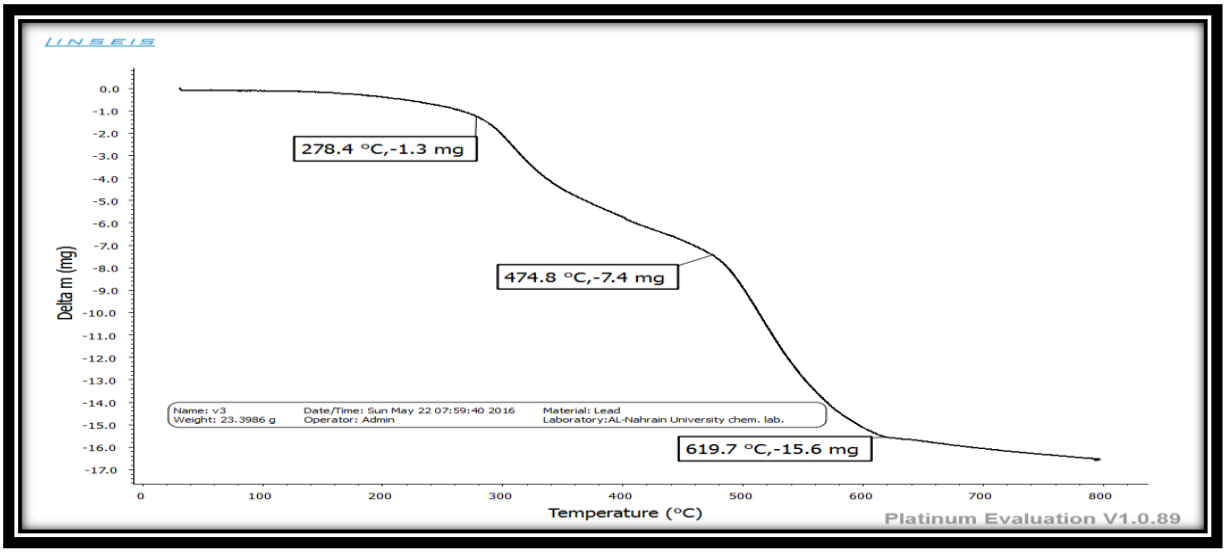


Figure (3-29): TGA of [C_2] complex

3.7 Biological study results:

Pathogenic microorganisms cause different kinds of diseases to human and animals. The Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases. The microorganisms have the ability to develop resistance to these chemotherapeutic agents and such strains which are resistant causing major problem in treatment of microbial infections. Searching for new antimicrobial agents become something very necessary; Therefore a great efforts have been employed to find new antibiotics or new compounds with good antimicrobial activity which might be suitable to be used as chemotherapeutic agents[٩5,96].

In this study, the synthesized compounds were evaluated for their *in vitro* antimicrobial activity against some of the pathogenic bacteria, two bacterial species were used: Gram positive (*Staphylococcus aureus)* and Gram negative bacteria (*pseudomonas aeruginosa).* The minimum inhibition concentration (MIC) was followed up for precursor 6-APA as a leading compound for the others derivatives as long as they can be synthesized from the parent 6-APA. Concentration 10^{-3}M was the MIC of 6-APA depending on dilution method and considered as the proper concentration for all the penicillin derivative compounds.

Some of the synthesized compounds as penicillin derivatives showed a significant inhibition zone due to the isostere effect with penicillin compounds. As long as 6-APA is represented as semisynthetic compound for penicillin derivatives. All the synthesized ligands $[L_1][L_2]$ and $[L_3]$ showed greater antibacterial activity with comparison to 6-APA alone which is obviously shown in the inhibition zone area. However; 6-APA located in the terminals of the synthesized compounds will enhance the biological activity due to emerge two β-lactam parts on the same molecule of L_1 and L_2, while L_3 showed a slight increment of inhibition zone area when compared with the other ligands, this could be due to small molecular size of using bioavailable vanillin molecule, eventually the variation was because of the structure activity relationship.

Furthermore; the presence of the metal ions in the complexes will affect in variable behavior on the final biological screening *in vitro*.

The results can be shown in table (3-10) and in vitro study can be shown in all the figures from (3-30) to figure (3-47).

Table (3-10): Antibacterial activity of the prepared compounds

No.	Compound	*Staphylococcus aureus*	*Pseudomonas aeruginosa*
1	6-APA	+	+
2	L_1	++	+
3	A_1	+	--
4	A_2	--	+
5	A_3	--	--
6	L_2	++	+
7	B_1	+	+
8	B_2	--	--
9	B_3	--	--
10	L_3	++	++
11	C_1	++	++
12	C_2	+	+
13	C_3	--	--

Notes:
-- = No inhibition **+ = (5-10) mm** **++ = (11-20) mm**

Figure (3-30): The effect of Compound [L_1] on *Staphylococcus aureus*

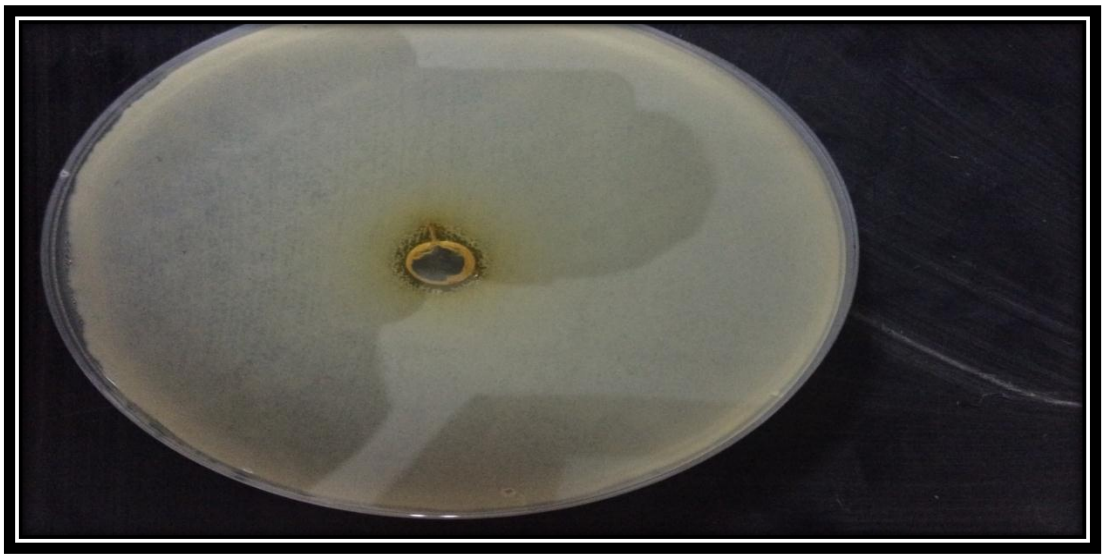


Figure (3-31): The effect of compound [A_1] on *Staphylococcus aureus*

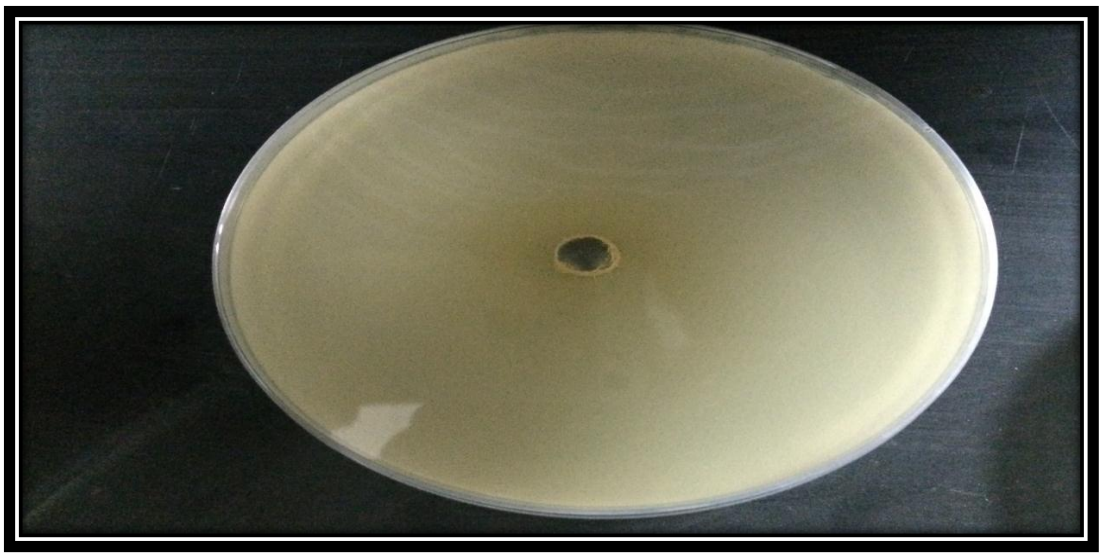


Figure (3-32): The effect of compound [A_2] on *Staphylococcus aureus*

Figure (3-33): The effect of compound [L_2] on *Staphylococcus aureus*

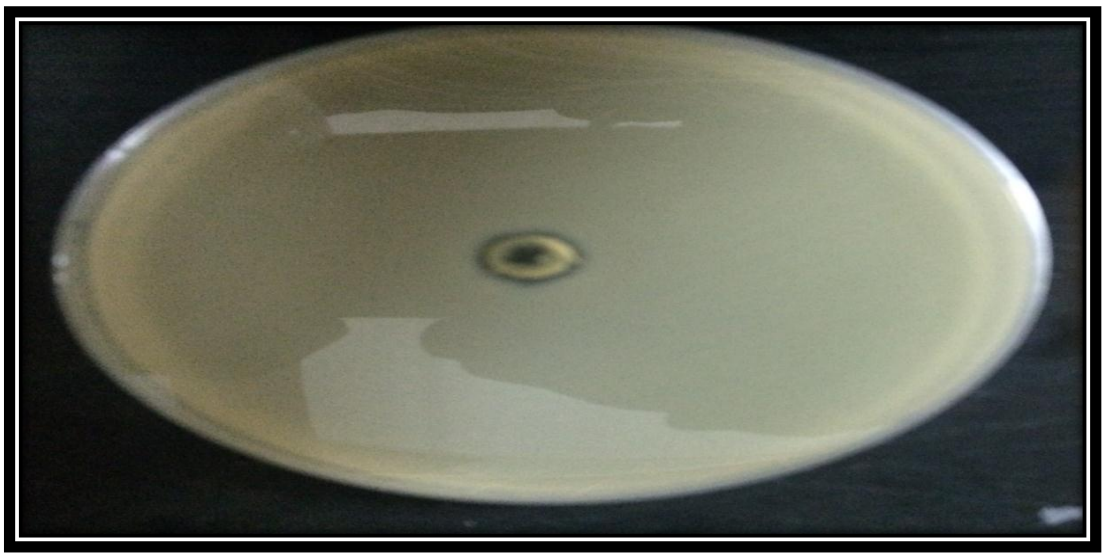


Figure (3-34): The effect of compound [B_1] on *Staphylococcus aureus*

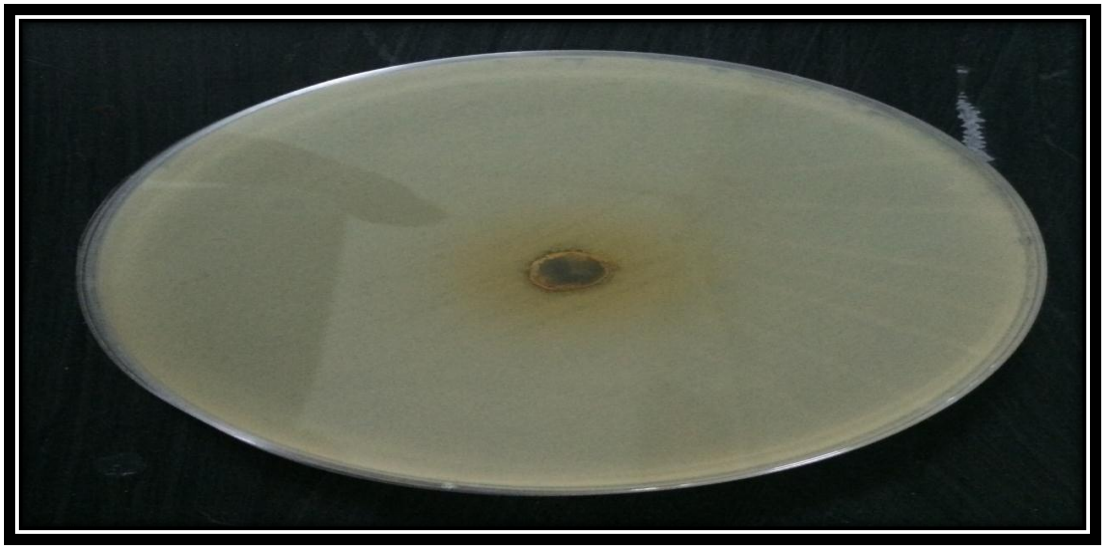


Figure (3-35): The effect of compound [B_2] on *Staphylococcus aureus*

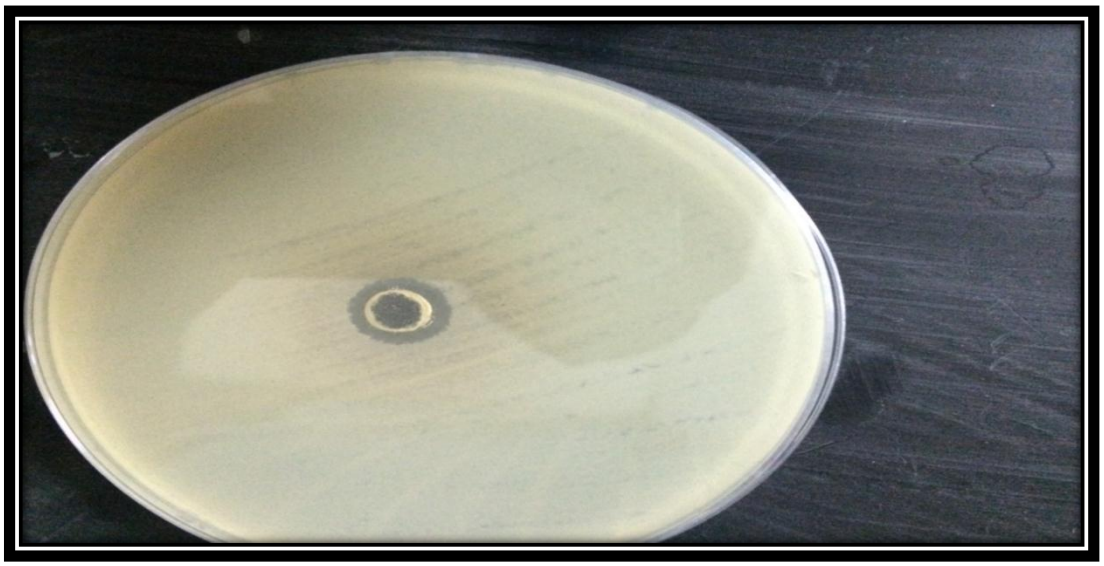


Figure (3-36): The effect of compound [L_3] on *Staphylococcus aureus*

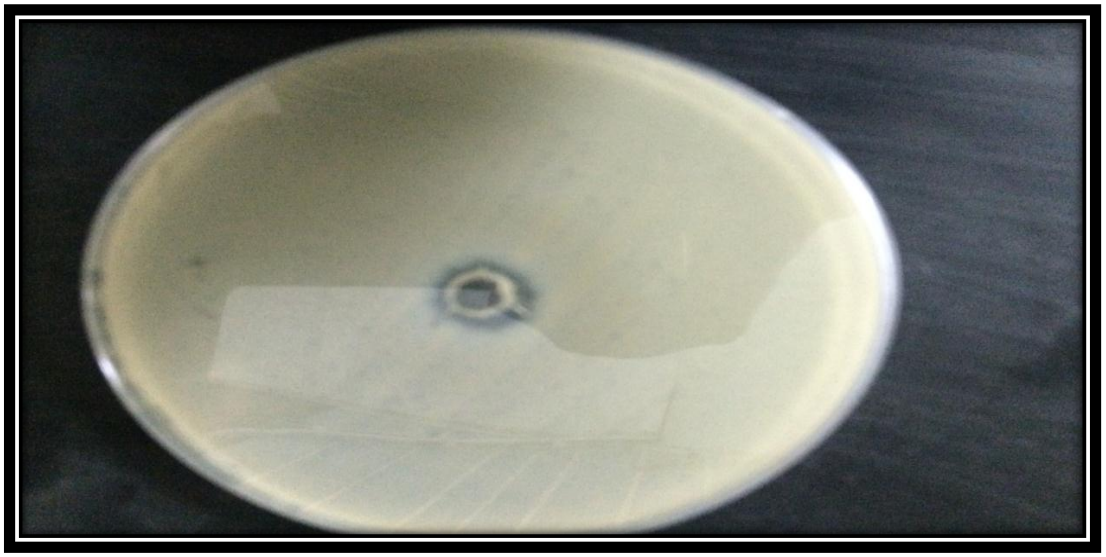


Figure (3-37): The effect of compound [C_1] on *Staphylococcus aureus*

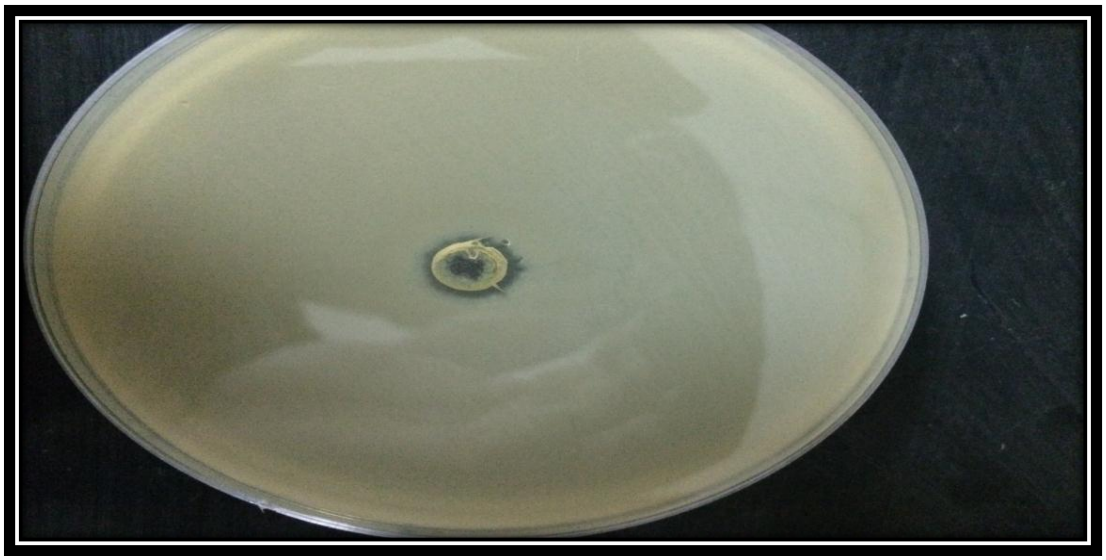


Figure (3-38): The effect of compound [C_2] on *Staphylococcus aureus*

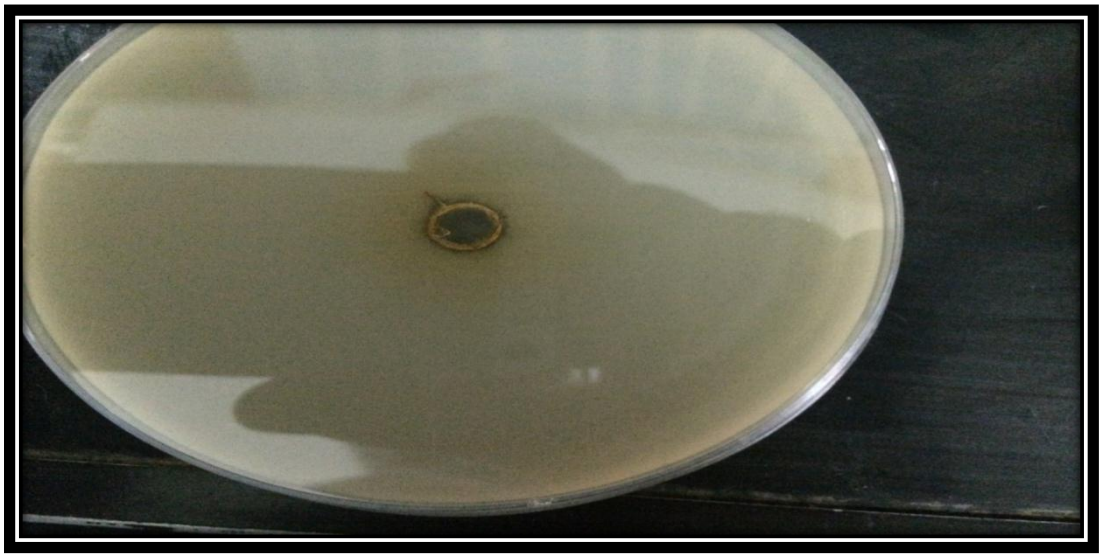


Figure (3-39): The effect of compound [C_3] on *Staphylococcus aureus*

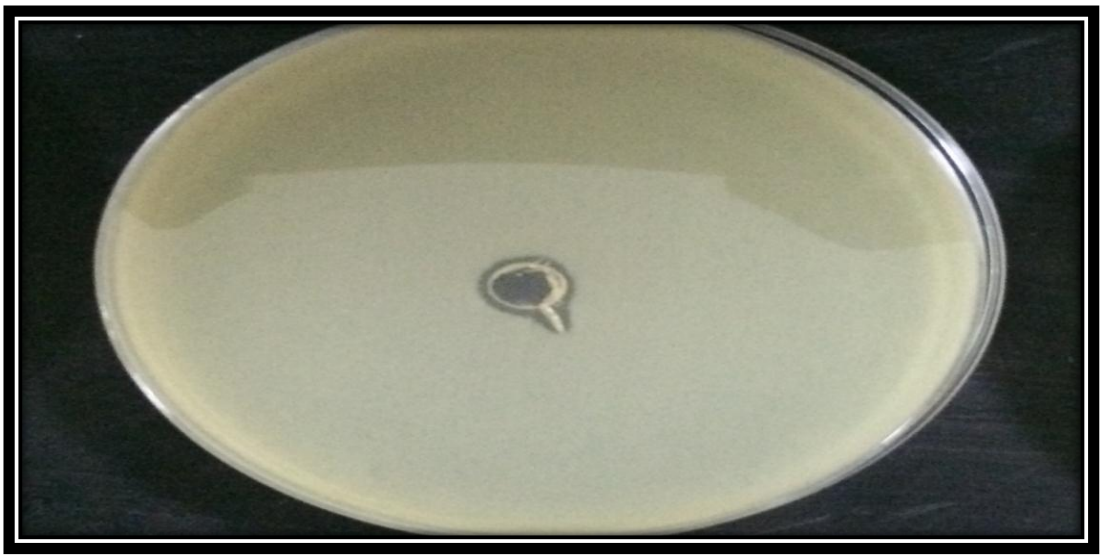


Figure (3-40): The effect of compound [L_1] on *Pseudomonas aeruginosa*

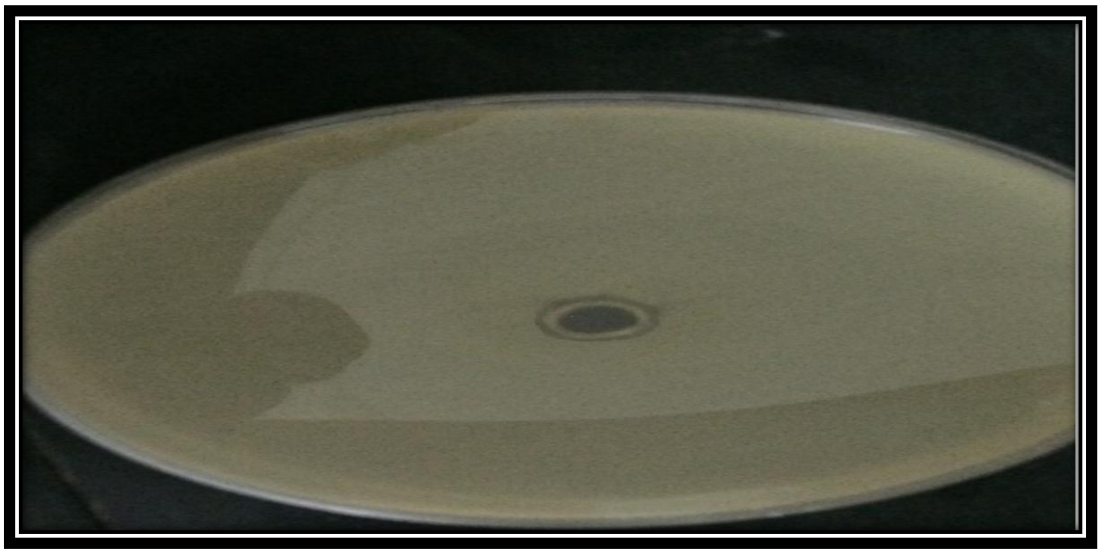


Figure (3-41): The effect of compound [A_2] on *Pseudomonas aeruginosa*

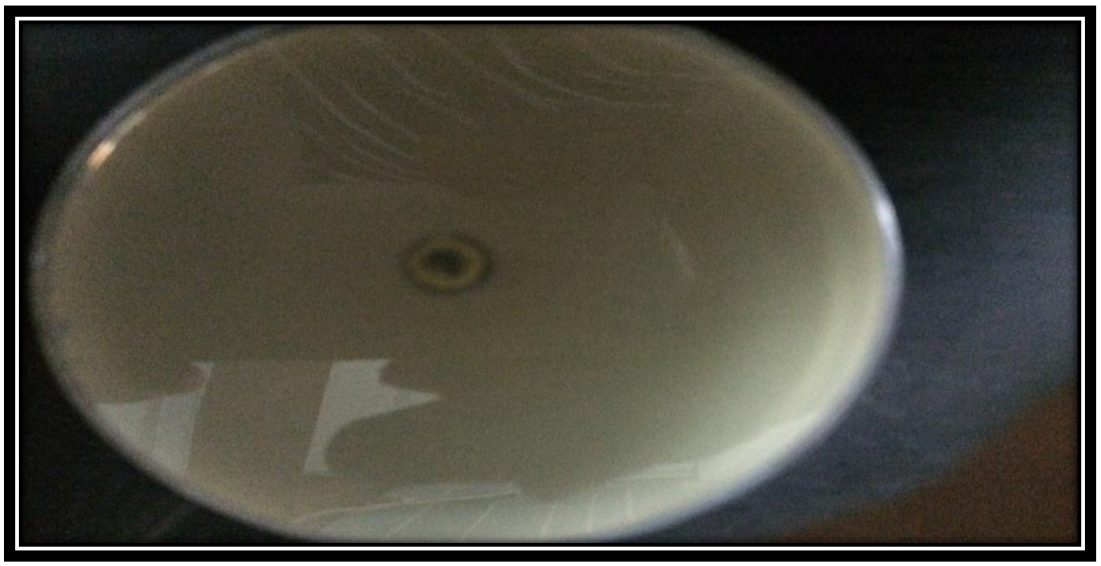


Figure (3-42): The effect of compound [L_2] on *Pseudomonas aeruginosa*

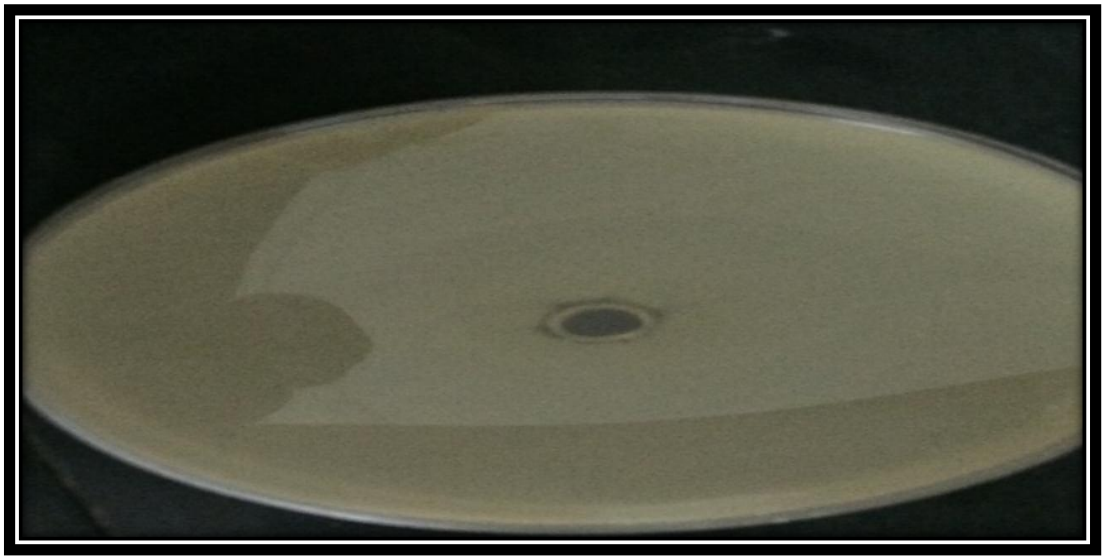


Figure (3-43): The effect of compound [B_2] on *Pseudomonas aeruginosa*

Figure (3-44): The effect of compound [L_3] on *Pseudomonas aeruginosa*

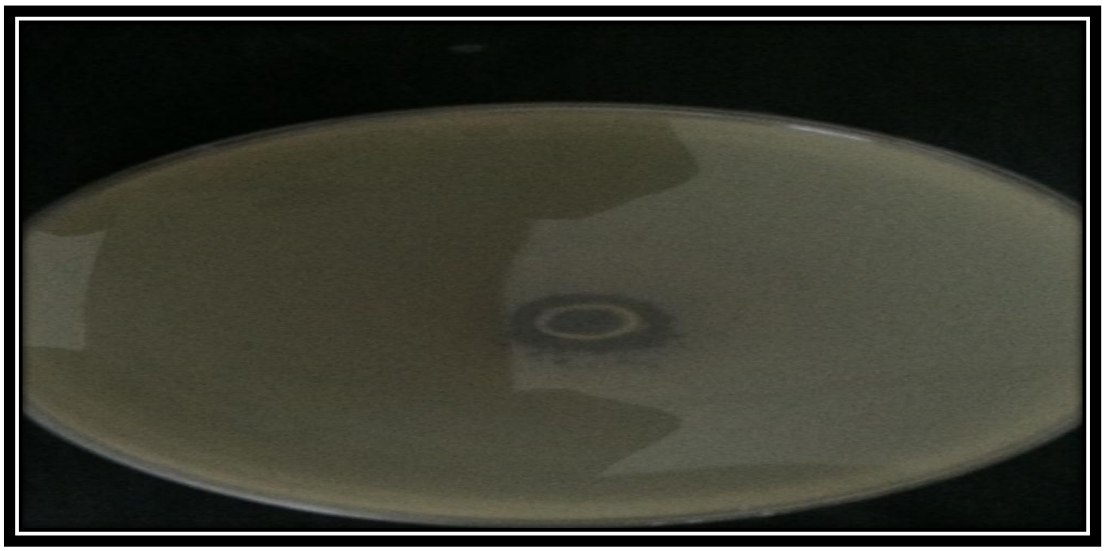


Figure (3-45): The effect of compound [C_1] on *Pseudomonas aeruginosa*

Figure (3-46): The effect of compound [C_2] on *Pseudomonas aeruginosa*

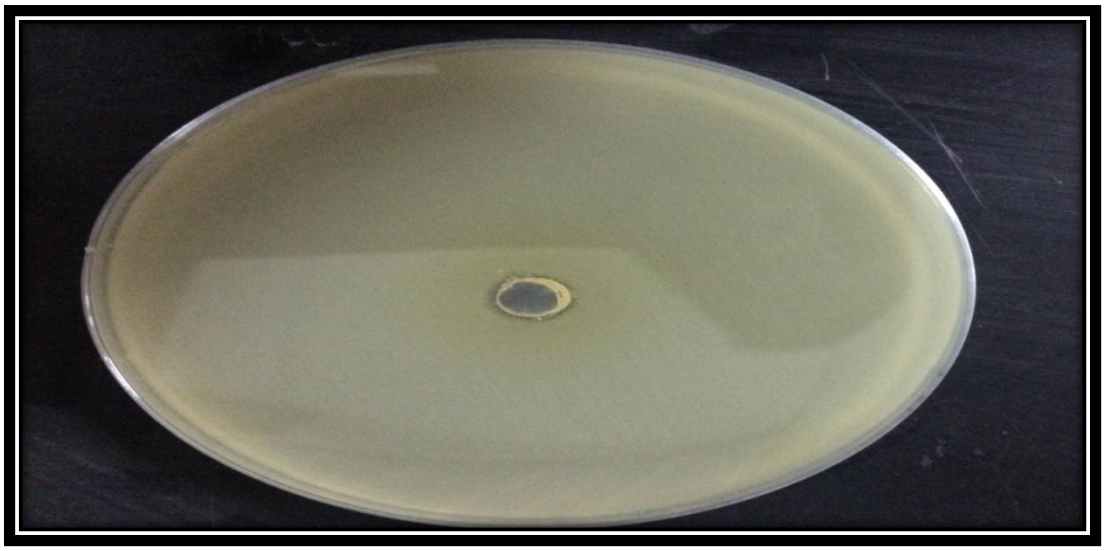


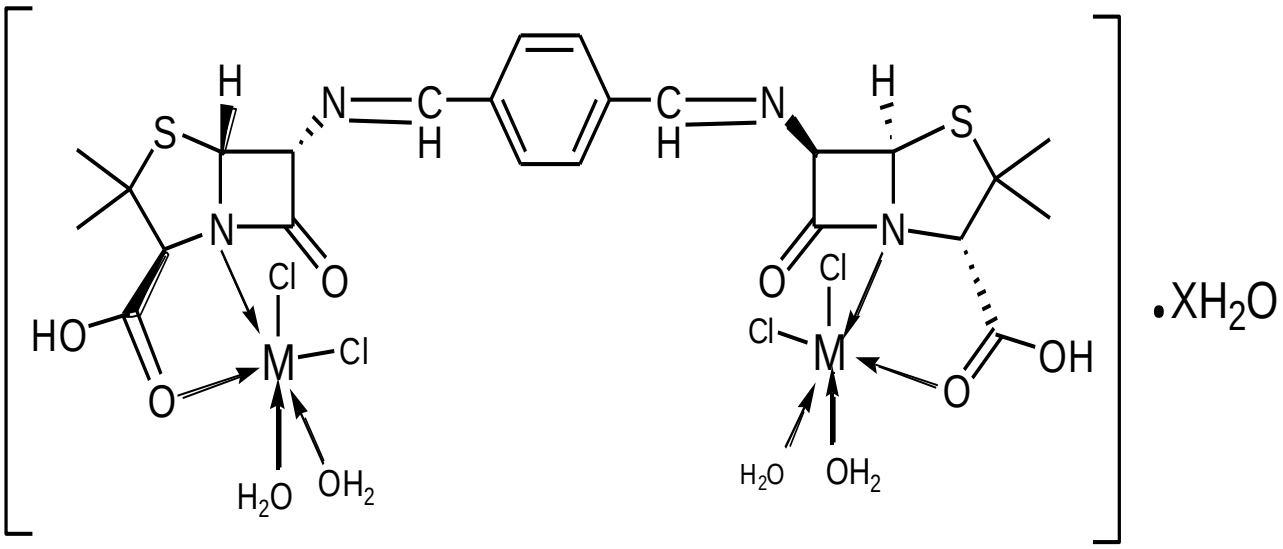
Figure (3-47): The effect of compound [C_3] on *Pseudomonas aeruginosa*

3.8 Conclusion

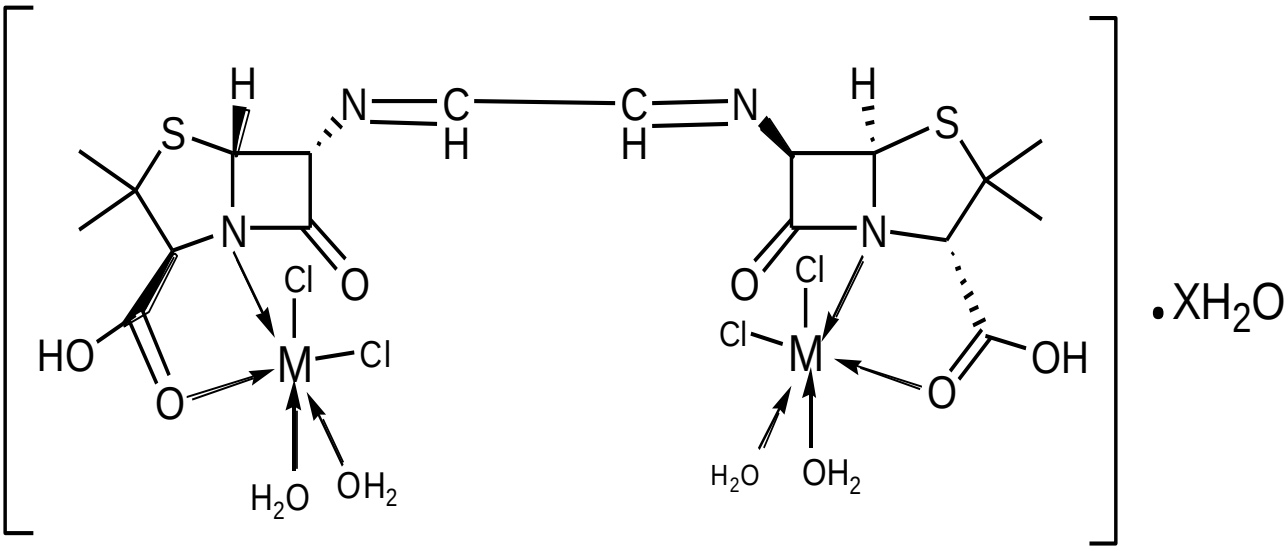
According to the above results we can conclude that:

1- The suggested structure for all complexes could be distorted octahedral geometries
2- The bidentate ligands interacted with the metal ion in five membered ring pattern through carboxylic acid and cyclic amide nitrogen (β-lactam) ,water molecules and chloride ions satisfied the six-coordination number.
3- The mole ratios [M:L] were [2:1],[2:1] and [1:1] for [A_1-A_3], [B_1-B_3] and [C_1-C_3] respectively.
4- All the synthesized ligands [L_1][L_2] and [L_3] showed greater antibacterial activity when comparison with 6-APA alone.
5- The presence of the metal ions in the complexes will affect in variable behavior on the final biological screening.

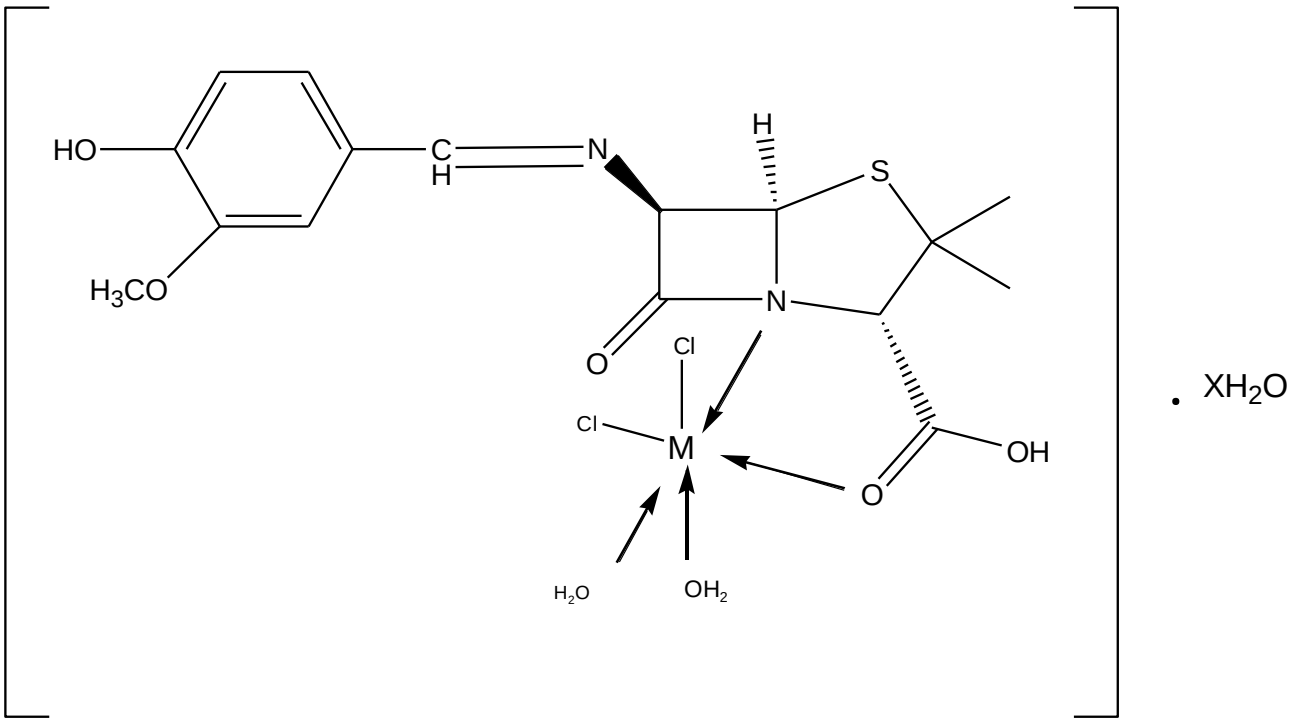
The chemical formula of the synthesized complexes along with the suggested geometrical structure are shown below:



$[M_2L_1Cl_4\ (H_2O)_4].XH_2O$, X:Natural number , M = Co, Cu or Zn



$[M_2L_2Cl_4\ (H_2O)_4].XH_2O$, X: Natural number , M = Co, Cu or Zn



$[ML_3Cl_2\ (H_2O)_2].XH_2O$, X:Natural number , M = Co, Cu or Zn

3.9 Suggestion for future work:

i. Synthesis of new Schiff base derivatives using different aldehydes.
ii. Synthesis of new sets of complexes for all ligands using other set of metal ions.
iii. Evaluation of antibacterial activity of synthesized compounds *in vitro* against different types of bacteria (Gram Positive and Gram Negative).
iv. Conducting further biological studies on the prepared compounds, such as evaluation of MIC, cytotoxic effect, *in vivo* study of interaction with various biological systems.

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الملخص

تضمن هذا العمل تحضيرثلاث ليكندات جديده وذلك بمفاعله 6-amino penicillanic acid (6-APA) مع terephthaldehyde أو glyoxal أو vanillin لتحضير L_1، L_2، L_3على التوالي.

تم تحضير تسع معقدات جديده من تفاعل الليكندات المذكوره اعلاه مع مجموعه من ثلاثه ايونات من العناصر انتقاليه [Zn(II), Cu(II), Co(II)] وتم ذلك بتفاعل L_1، L_2، L_3 مع هذه العناصر الانتقاليه بنسبه موليه [2:1] [2:1] [1:1] [ليكند:فلز] على التوالي.

تم تشخيص المركبات المحضره بواسطه طيف الرنين النووي المغناطيسي للبروتون ^{1}H-NMR ، اطياف الاشعه تحت الحمراء FT-IR ،الاشعه فوق البنفسجيه والمرئيه .Uv-Vis ، التحليل الدقيق للمعادن والعناصر ، التوصيليه الكهربائيه و التحليل الحراري. فقد بينت هذه الدراسات أن الشكل الفراغي المقترح لجميع المعقدات المحضره هو ثماني السطوح المشوه والصيغ التركيبيه لهذه المعقدات هي كالاتي:

[$Co_2\ L_1Cl_4\ (H_2O)_4].2H_2O$ (A_1),**[**$Cu_2\ L_1Cl_4\ (H_2O)_4].H_2O$ (A_2),

[$Zn_2\ L_1Cl_4\ (H_2O)_4]$ (A_3), **[**$Co_2\ L_2Cl_4\ (H_2O)_4].2H_2O$ (B_1),

[$Cu_2\ L_2Cl_4\ (H_2O)_4].H_2O$ (B_2), **[**$Zn_2\ L_2Cl_4\ (H_2O)_4].H_2O$ (B_3),

$[CoL_3(H_2O)_2\ Cl_2]$ (C_1) $[Cu\ L_3(H_2O)_2Cl_2]$ (C_2) and

$[Zn\ L_3(H_2O)_2Cl_2].2H_2O$ (C_3).

تم دراسة النشاط المضاد للبكتيريا للمركبات المحضره ضد نوعين من الكائنات الحية الدقيقة المختارة (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) وذلك باستخدام الحد الأدنى للتركيز المثبط (MIC) للماده الأوليه 6-APA تمهيدا لغيرها من المركبات التي كان تركيزها 10^{-3} مولاري. ولقد أظهرت النتائج ان أغلب المركبات المحضره تمتلك فعالية مضاده للبكتريا أعلى من 6-APA نفسه وذلك بسبب التشابه الجزئي لادويه البنسلين أضافة ألى تواجد جزء بيتا لاكتام.

جمهورية العراق
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قسم الكيمياء

تخليق وتشخيص وتقييم الفعالية البايولوجية لمعقدات مشتقات البنسيلين مع بعض ايونات الفلزات

رسالة
مقدمة إلى مجلس كلية العلوم / جامعة النهرين
كجزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل

ياسر حسام صباح

بكالوريوس علوم كيمياء ٢٠١٤
(الجامعة المستنصرية)

بإشراف

الدكتور

عمار جهاد صادق العبدلي

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