The chemistry of [metal-drug]compounds is more popular now than before in importance especially the design of more biologically active drugs. Several complexes are act as {antibacterial, antifungicidal, antiviral and anticancer} bio activity .Schiff bases have important role in the development of [coordination & medicine] chemistry .Transition metal complexes containing Oxygen and Nitrogen donor Schiff base ligands have been of research interest for last years and act as active sites and thereby catalyze chemical reactions . Antimicrobial diseases are now more frequent than during the first half of the century, and still difficult to diagnose clinically .

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Schiff Base And Ligand Metal Complexes of Some Amino Acids and Drug

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Schiff Base And Ligand Metal Complexes of Some Amino Acids and Drug Substances

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Contents

Abbreviation

Abbreviation	Full meaning
A.A	Amino acid
A.A.S	Atomic Absorption Spectroscopy
^{0}C	Centigrade
DMF	\I,N- Dimethyl formamide
DMSO-d^{6}	Oeuterated dimethylsulfoxide
Dec.	Decomposition
FTIR	nfrared Transforms Infrared Spectroscopy
g/mol	Gram per mole
Am	Vlolar conductance
M.Wt	Vlolecular weight
NAm	Nicotinamid
ppm	^{3}arts per million
^{13}C-NMR	Carbon-13- Nuclear magnetic resonance
^{1}H-NMR	^{0}roton Nuclear Magnetic Resonance
UV-Vis	Ultraviolet-visible
AlaH	.-Alanine
Amox.H	Amoxcilline trihydrate
AmpiH	Ampicillin trihydrate
AnthH	Anthranilic acid
AmoxH	Amoxcilline trihydrate
4-Chlobp	4-Chlorobenzophenone
4-DMBA	4- dimethylaminobezaldehyde
M-dopa	Methyl dopa
ProH	.-proline
^■max	Wave length of maximum absorbance
E.coli	*Escherichia coli*
IR	Infrared
3D	Three dimensional
TLC	Thin layerchromatography
Cip	Ciprofloxacin
Mtf	Metformin hydrochloride
Ado	Adenosine
CT-DNA	Circulating tumor DNA
^eff	Effective magnetic moment

l.l. General introduction

The chemistry of [metal-drug]compounds is more popular now than before in importance

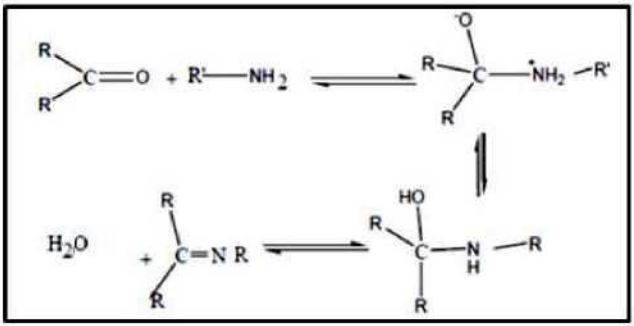
especially the design of more biologically active drugs[1]. Metal ions are known to effect the active of many drugs. The efficacy of the drugs on coordination with a metal are boost in many cases[2]. Metal ions play a basic role in a large number of widely differing medicinal processes and reliance on their concentration, and either contribute towards the health of the organism or cause toxicity [3-6]. Several complexes are act as {antibacterial, antifungicidal, antiviral and anticancer} bio activity and have been found to be more antimicrobial than the ligands themselves[7].

These compounds are played in the field of medicine,bioinorganic chemistry and are used as a starting material for the synthesis of new catalyst and drugs [5].

1.1.1.Schiff base ligands

Schiff bases have important role in the development of [coordination & medicine] chemistry as they readily form new complexes with metals [8].These compounds are played in the field of bioinorganic chemistry and various aspects of organometallic compounds[9].

Schiff base and its complexes containing azomethine group (-HC=N-) as shown in scheme(1-1). They are formed by condensation of a primary amine (RNH_2) and carbonyl compound. The (-HC=N-) group is particularly suited for binding to metal ions via the N atom lone pair (-N:) and when contain one or more donor atoms in addition to (-C=N-) group they act as[polydentate ligands or macrocycles].



Scheme (1-1): Reaction mechanism for the formation of Schiff bases (R is H and R' alky aryl OH, NHR & OR group)

Transition metal complexes containing Oxygen and Nitrogen donor Schiff base ligands have been of research interest for last years [9] and act as active sites and thereby catalyze chemical reactions [10]. Antimicrobial diseases are now more frequent than during the first half of the century, and still difficult to diagnose clinically [11].

1.1.2. SchifFs bases and their metal complexes

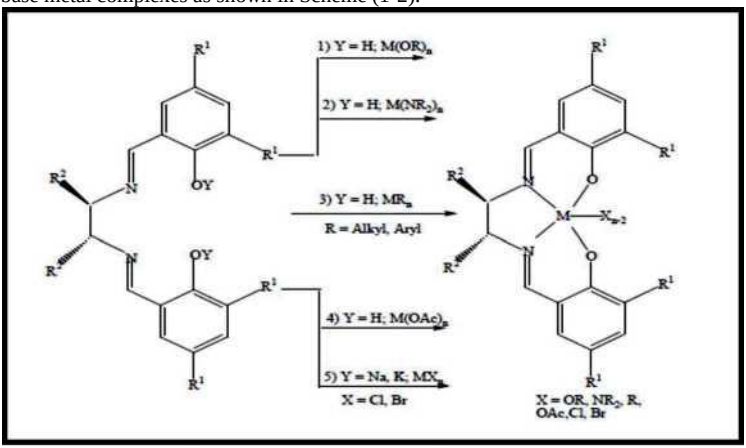
There are many literature reviews on the synthesis and characterisation of Schiff base metal complexes [12-15].

Schiff base metal complexes are generally synthesis by treating metal Halides (MXn) with Schiff base ligands under suitable experimental conditions. In special cases metal alkox1ides, metal amides, metal alkyls or metal acetates have been used for the synthesis [12]. Generally (transition metal and lanthanides) ions are used to prepare coordination complexes with different oxidation states, interesting new physicochemical properties and different coordination structures & geometries. [12-13]

The (-OH) hydroxyl group or (-SH) sulfhydryl group ortho to (-C=N-) group moiety present in the Schiff bases can induce tautomerism in the compounds and give many different structures [14,15].

Antimicrobial and antifungal studies of Schiff base ligands and their metal complexes are reported [16-17] and the biological activity of Schiff bases beside decrease or increase upon formation new compounds [18-20].

Cozzi (2004), [12] has been reported five synthetic different routes commonly as synthesis of Schiff base metal complexes as shown in Scheme (1-2).



Scheme (1-2): Schematic of (5) Synthetic different routes of Schiff base-metal Complexes

Route 1:

Involves the use of metal alkoxides [M(OR)n]. Alkoxides of early commercially available and easy to handle transition metals (M = Ti & Zr).

The use of other alkoxide derivatives is not easy for derivatives of lanthanides. Metal amides, $M(NMe_2)_4$ (M = Ti& Zr) are also employed as the precursors in the preparation of Schiff base metal complexes

Route 2:

The reaction via the elimination of the acidic phenolic proton of the Schiff bases through the formation of volatile $NHMe_2$.

Route 3:

Treatment of metal alkyl complexes with Schiff bases.

Route 4:

Treatment of metal acetates with Schiff bases under reflux conditions.

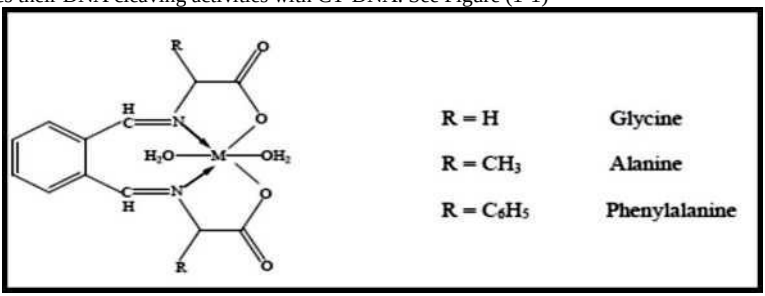
Route 5:

Obtaining salen-type metal complexes consists of a two-step reaction involving the deprotonation of the Schiff bases followed by reaction with metal halides .

Deprotonation of the acidic phenolic hydrogen by using coordinating solvents and the excess Sodium hydride (NaH) or potassium hydride (KH) can be eliminated by filtration. This step heating

the reaction mixture to reflux with not cause decomposition and is normally rapid at room temperature.

Neelakantan *et al.*, (2008) [19]. Synthesized metal {VO(II), Mn(II), Cu(II), Ni(II), Co(II), and Zn(II) }complexes of a Schiff base derived from o-phthalaldehyde and {L-amino acids=Glycine, L-Alanine, L-Phenylalanine}. The Schiff base ligands types [N_2O_2] coordinate to the metal ion via (imine Nitrogen and carboxylate Oxygen) .The complexes were studies their DNA cleaving activities with CT-DNA. See Figure (1-1)



Figure(1-1): Schiff base derived from o-phthalaldehyde and amino acids M= VO(II), Mn(II), Cu(II), Ni(II), Co(II), and Zn(II)

Shakir *et al.*, (2011) [20] have synthesized and characterized foure transition metal complexes with Schiff base N, N-bis- (2-pyridine carboxaldimine)-1,8diaminonaphthalene, Figure(1-2) derived from 2-pyridine carboxaldehyde and 1,8 diaminonaphthalene (Figure 13). The ligand is coordinated to M(II) as tetradentate type (N4) donor sites.

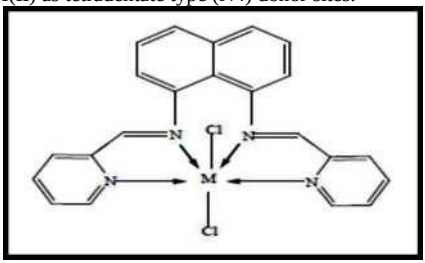


Figure (1-2): Schiff base, N,N-bis-(2- pyridine carboxaldimine) —1, 8 diaminonaphthalene-M-complexes M=Co(II),Ni(∩),Cu(∩)& Zn(II)

A tetradentate Cu(II) complex of the type, $[CuL](NO_3)_2$ by the interaction of Schiff base ligand L, N, N-bis [(E)-thienylmethylidene]-1,8- diaminonaphthalene, obtained by the condensation of thiophene-2-carboxaldehyde and 1,8 diaminonaphthalene, Figure (1-3) The ligand and its Cu(II) complex was characterized by different spectroscopic studies. The DNA cleavage studies and DNA binding of Cu(II) complex has shown considerable DNA cleavage. The results suggested a putative role of Cu(II) complex similar to various anticancer drugs [21].

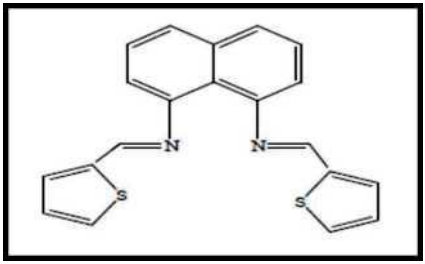


Figure (1-3): Schiff base N, N-bis[(E)-thienylmethylidene]-1,8-diaminonaphthalene

Nair, *et al,* (2012) [22], have synthesized four transition metal complexes, Figure (1-4) and Figure(1-5) of the Schiff base derived from (indole-3-carboxaldehyde) and (m- aminobenzoic acid) characterized by (C.H.N), molar conductance, IR, UV-Vis and magnetic moment. The antimicrobial activity of the synthesized ligand and its complexes were screened by disc diffusion method.

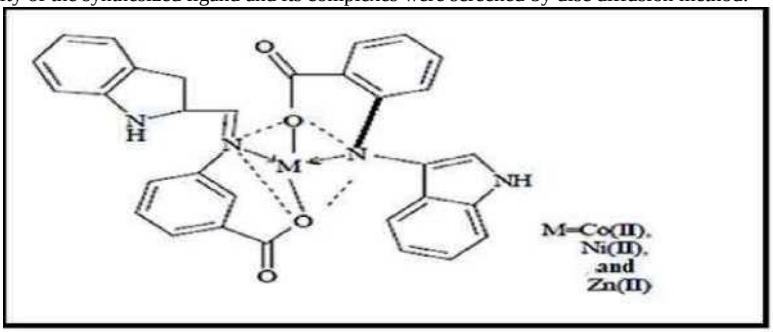


Figure (1-4): Complexes of the Schiff base derived from (indole-3-carboxaldehyde) & (m-aminobenzoic acid)

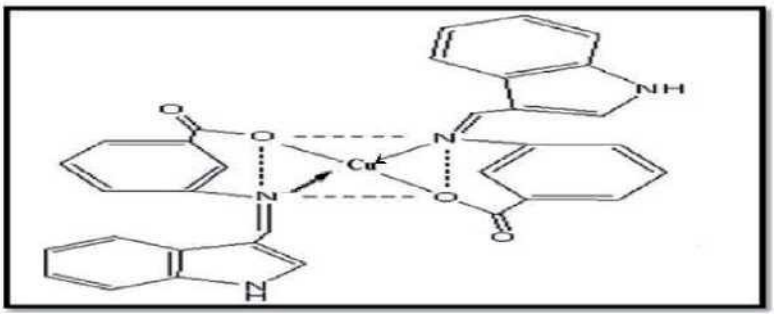


Figure (1-5): Proposed structure of Schiff base metal complex is square planar geometry for Cu (II) complex

Bharti *et al.,* (2013) [23], reported the schiff bases derived from sulfa drugs with some transition metal ions. The metal complexes of {Co(II) & Fe(II)} have been synthesized with Schiff base derived from react (salicylaldehyde) and sulfamethoxazole [4-amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide]**,** Figure (1-6) . Conductometric titrations have suggested metal:

ligand ratio of (1:2) for two ions [Co(II) & Fe(II)] complexes and the ligand behaves as a bidentate with (O, N) donor atoms.

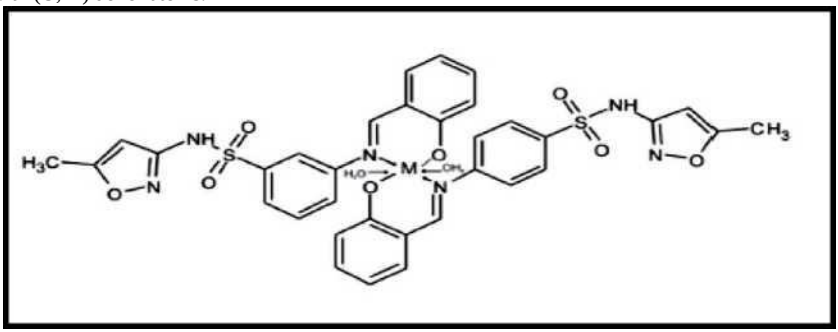


Figure (1-6): Structure of [Sulfamethoxazole-Salicyladimine -M] complexes M= Fe (II) and Co(II)

Islam *et al.,* (2013) [24] reported of the four synthesized and characterized Schiff base complexes derived from (Salicylaldehyde) and Gly with some transition metals in very good yield through a fast, simple, and efficient methodology, Scheme (1-3)

$(SGCo)_2$= [N-salicylidene glycinato diaqua cobalt (II) dimer]

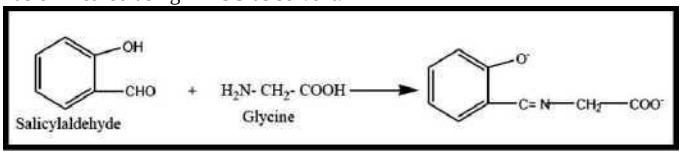
$(SGN)_2$ =[N- salicylideneglycinato-di-aqua-nickel(ll)dimer]

(SGC) = [N-salicylideneglycinato-aqua-copper(II)]

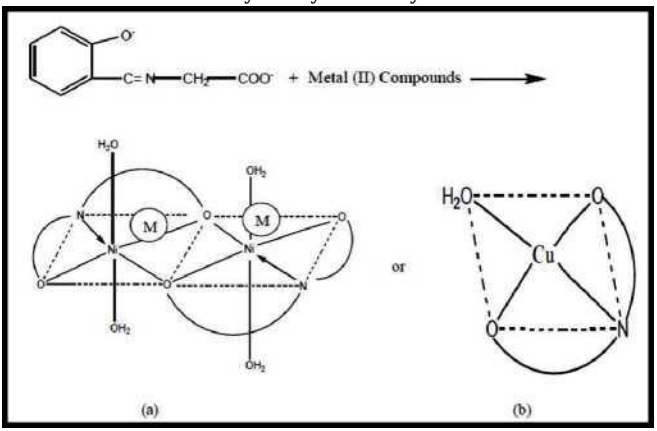
$(SGZ)_2$= [N-salicylidene glycinato diaqua Zinc(II) dimer], Scheme (1-4).

These compounds were screened for *in vitro* antibacterial activities against six pathogenic bacteria, *{Escherichia coli,Shigella sonnei,, Sarcina lutea, Staphylococcus*

aureus Pseudomonas arioginosa and Bacilus subtilis}. The antibacterial activity was determined by the disc diffusion method using DMSO as solvent.

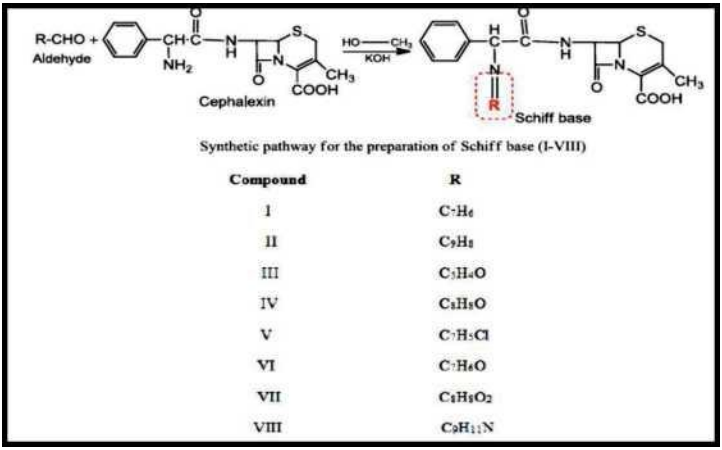


Scheme (1-3): Synthesis of Schiff base derived from Salicylaldehyde and Glycine



Scheme (1-4): Synthesis of Schiff base complexes {a= dimeric octahedral for M= Zn (II) Co (II), & Ni (II) (b) Cu(II) complex =Square planar}

Arun & Gowramma (2014) [25], reported the synthesis series of Schiff bases of Cephalexin complexes by condensation of 5-thia-1-azabicyclo [4.2.0] oct-2-ene-2- carboxylic acid, 7-[(amino phenyl acetyl) amino]-3-methyl-8-oxo, monohydrate with selective aldehydes. The purity of the compounds were determined by TLC. Complexes have been characterized by (C.H.N), [FT- IR and UV-Vis spectral studies]. All the synthesized compounds were subjected for the screening of biological activity against {(2 pathogenic fungi)and (3 bacteria)}.



Synthetic pathway for the preparation of Schiff base (I-VIII)

Compound	R
I	C_7H_6
II	C_9H_8
III	C_3H_4O
IV	C_8H_8O
V	C_7H_5Cl
VI	C_7H_6O
VII	$C_8H_8O_2$
VIII	$C_9H_{11}N$

Scheme (1-5): Synthesis of Schiff bases derived from selective aldehydes & Cephalexin (I-VIII)

A fast, clean and environmentally benign exclusive synthesis of Schiff bases and their complexes with Cu(II) have been developed using condensation of salicylaldehyde and drugs such {Amoxicillin (L_1H), Cephalexin (L_2H), sulphamethoxazole (L_3H) and Trimethoprim (L_4H), Figure(1-7). All the complexes under investigation possess method provides several uses such as environmental friendliness, short reaction times, non- hazardous, and excellent yield of products and simple work-up procedure.

The compounds were characterized by C.H.N, thermal gravimetric analysis, magnetic and spectroscopic studies [26]. Schiff bases were bidentate (NO donor) ligands. Salicylidenesulphamethoxazole-Cu(II) monohydrate was five co-ordinate whereas all other complexes were found to be six co-ordinate dihydrates and ML_2 [1:2 (metal: ligand) ratio] type. The antibacterial activity showed the following order:

Cu(II)-complexes > Schiffbase ligands > parent drugs.

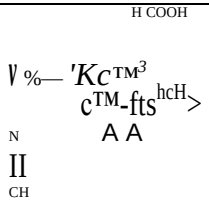
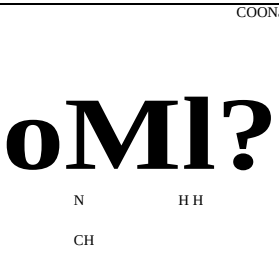
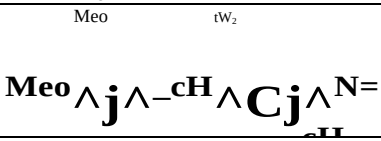
L_1H = SalicylideneAmoxicillin	
L_2H = SalicylideneCephalexin	
L_3H = Salicylidenesulphamethoxazole	
L_4H = SalicylideneTrimethoprim	

Figure (1-7): Structure Formula of salicylaldehyde and Amoxicillin (L_1H), Cephalexin (L_2H), sulphamethoxazole (L_3H) and Trimethoprim (L_4H)

1.1.3. Metal Complexes of Antibiotics

Antibiotic is a substance or compounds which inhibit the growth of bacteria[27]. Synthesis in presences of alcohol and acidic reagent was reported in 2010. Antimicrobial study of Sulfonamides derived from different substituted sulfonamide drug and aromatic aldehyde helps to formation of Schiff bases [27].

Suresh & Prakash (2010) [28], synthesized bidentate Schiff base Figure (1-8), from Vanillin and 1-phenyl 2,3-dimethyl-4-aminopyrazol-5-one (4- aminoantipyrene) and forms stable complexes with {Mn(II), Co(II), Ni(II), Cu (II), Zn (II) Cd (II) and Cr (III)}.Their structures were investigated by C.H.N, [FT-IR, Uv-Vis, NMR] Spectroscopy; and (TG- DTA) analysis studies suggested the antibacterial nature of the complexes. On the basis of the studies the coordination sites Figure (1-9) were showed through Nitrogen of the (-CH = N) group and Oxygen of the ring (-C=O).

cix and SO4

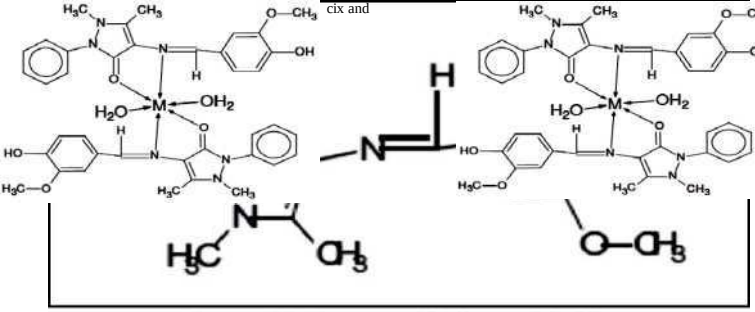
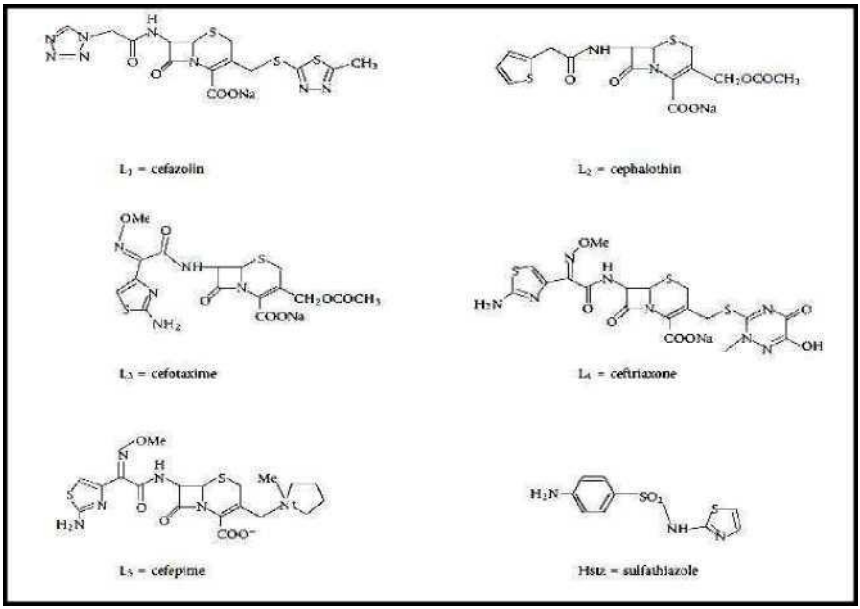


Figure (1-8): Structure of bidentate Schiff base

Figure (1-9): Structure of 1-phenyl 2, 3-dimethyl-4-aminopyrazol-5-one (4-aminoantipyrene) and Vanillin complexes

Anacona and Maried (2012) [29], reported the synthesis and reaction Nickel (II) with Cephalosporins and Sulfathiazole (Hstz) to form the following mixed-ligand complexes of general formula

[Ni(L)(stz)(H_2O)x] .n (L=1,4, x = 1; L2,3,x = 0; L=monoanion of Cefazolin (HL_1), Cephalothin (HL_2), Cefatoxime (HL_3), Ceftriaxone (HL_4) and, [Ni(L_5)(stz)].Cl (Cefepime L_5) which were Charaterized by physicochemical and spectroscopic methods. Their spectra indicated that cephalosporins as shown in Figure (1-11) are acting as multidentate ligands, via the carboxylate, lactam carbonyl, and N azomoieties where the,[Ni(L_5)(stz)]Cl complex is (1:1) electrolyte. They have been screened for antibacterial activity. See Figure (1-10) .



Figure(1-10):The structure of the (Cephalosporins and Sulfathiazole) ligands

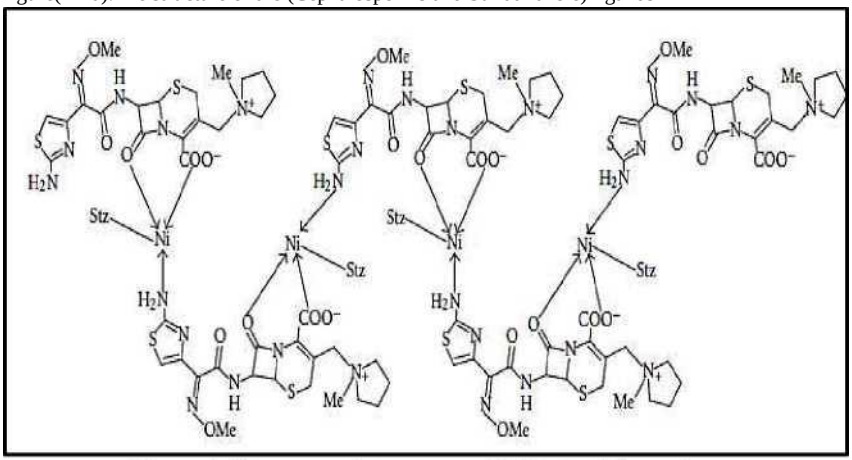


Figure (1-11): proposed structures of $[Ni(L_5)(stz)]^+$ complex

The minimum inhibitory concentrations (bacteriostatic) (MIC) and the minimum bactericidal concentrations (MBC) of the ligands and iron (III) complexes of Ciprofloxacin ($[Fe(Cip)_2Cl_2]Cl.6H_2O$ as shown in Figure (1-12) and (H_3Cip) $[FeCL_|]Cl.H_2O$) have been determined. The ligand and iron complexes showed antimicrobial effect against the tested organism species except against the molds of *{Aspergillus & Penicillim}* as literature [30].

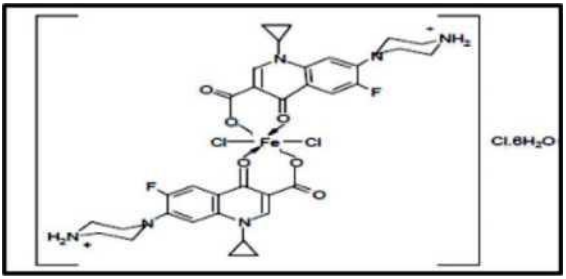


Figure (1-12): Proposed Structure of [Fe(Cip)2Cl2lCl.6H20

1.1.4. Metal complexes amino acids

All the 20 amino acids are (a- amino acids) are the basic structural units of proteins consisting of an amino group, (-NH_2) acarboxyl (-COOH) group a hydrogen (H) atom and a (variable) distinctive (R) group. All of the substituents in amino acid are bonded to a central a carbon atom, (a carbon bonded to the carboxyl (acidic) group [31J .The general formula for amino acids as shown in Figure (1-13).

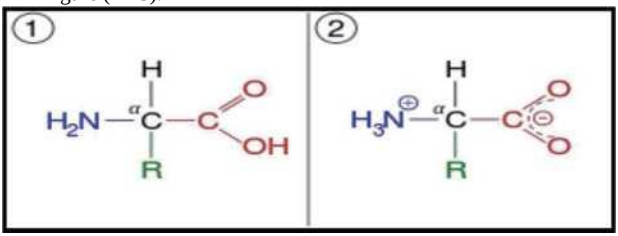


Figure (1-13): (1) General formula of an amino acid (left) & (2) zwitterionic (dipolar) In neutral solution(right)

- (-NH_2) =A basic amino group
- (-COOH) =An acidic carboxyl group
- (-H) = A hydrogen atom
- (-R) =A different side chain

This classification is based on the functional property of amino acids for the organism.

1. Essential Amino Acids[31-32J

Amino acids which arc not synthesized in the body and must be provided in the diet to meet ananimal's metabolic needs are called essential amino acid (10).

2. Non- Essential Amino Acids

These amino acids are need not be provided through diet, because they can be biosynthesized in adequate amounts within the organism [33].

Essential and non- essential} amino acids are as shown in the Table(1-1)

Table (1-1): Essential & Non-Essential L-Amino Acids In Mammals

Non-Essential	Essential
Alanine, Asparagine, Aspartic Acid, Glutamine, Glycine, Proline , Serine, Cysteine, Glutamic Acid, & Tyrosine	Arginine, Threonine, Tryptophan, Valine Histidine, Isoleucine, Leucine, Lysine, Methionine & Phenylalanine,

Complex combinations of metal ions with amino acids are important because of their biological applications. In [34] many studied the synthesis of complex combinations of [Zn(II) and Ni(II)] with [D-Penicilamine & L-Cysteine]. These complex combinations have therapeutically, biologi cal activities and metabolic enzymatic activities [35-36].

20's recent year the research field of bioorganometallic chemistry {mixed area between organometallic and biochemistry] chemistry is increasingly drawing much interest [37]. In 1957,the first example of ferrocene amino acid bioconjugate was synthesized using Alanine .See Figure (1-14) [38].

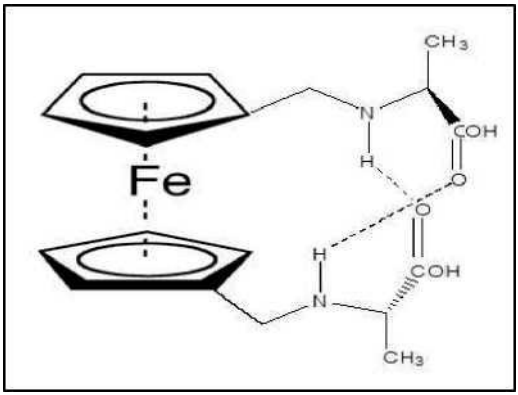


Figure (1-14): Structure of Ferrocenyl -Alanine

From literature (barbituric acid aryl-azobenzimidazol) and their derivatives are important in bioinorganic chemistry because their imidazolic and barbituric parts are contained in enzymes, proteins and nucleic acids [39, 40]. In literature [41-43] are qualify the biological and therapeutical activities of ternary complex combinations using different L-(a- amino acids) as a primary ligand and imidazol as a secondary ligand.

Zahid *et al.*, (2006) [44], were reported a series of antibacterial and antifungal L- (a- amino acids) -derived compounds and their Co (II),Cu(II), Ni (II), and Zn (II) metal complexes which were investigated by spectroscopic methods and physicochemical. Ligands (L_1)-(L_5) Figure (1-15), were prepared by condensation of y§-diketones with different amino acids as {glycine, phenylalanine, valine, and histidine} and act as bidentate towards metal ions [Co (II),Cu(II), Ni (II), and Zn(II)] via the azomethine-N and deprotonated-O of the respective amino acid. The stoichiometric reaction between the metal(II) ion and synthesized ligands in molar ratio of M: L

resulted in the formation of the metal complexes of :

1) $[M(L)(H_2O)_4]Cl$ (where M = Co(II), Cu(II), and Zn(II))and M: L (1:1)
2) $[M(L)_2(H_2O)_2]$ (where M= Co(II), Cu(II), Ni(II), and Zn(II). See Figure (1-16)

The electronic spectral and magnetic moment data suggested for the complexes to have an octahedral geometry around the central metal atom. Elemental analyses and NMR spectral data of the ligands and their metal(II) complexes agree with their proposed structures. compounds, were screened for their in vitro antibacterial activity against *(4Gram-negative=Shigella flexeneri, Escherichia coli, Salmonella typhi and Pseudomonas aeruginosa)* and (2 Gram-positive = *Bacillus subtilis* and *Staphylococcus aureus*) bacterial strains and for in vitro (6 antifungal activity against = *Candida albicans, Trichophyton longifusus, Microsporum canis, Aspergillus flavus, Fusarium solani, and, Candida glaberata.* The results of these studies show the metal(II) complexes to be more antibacterial/antifungal against one or more species as compared to the free ligands.

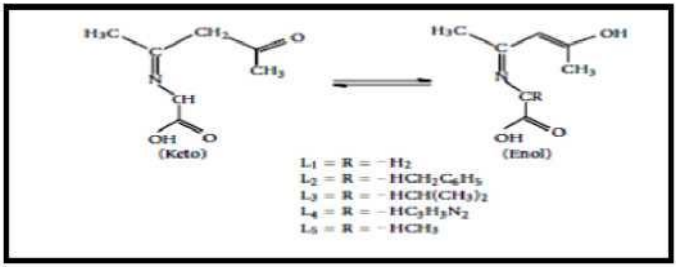


Figure (1-15): Proposed structure of the (L_i) to (L_5) ligands

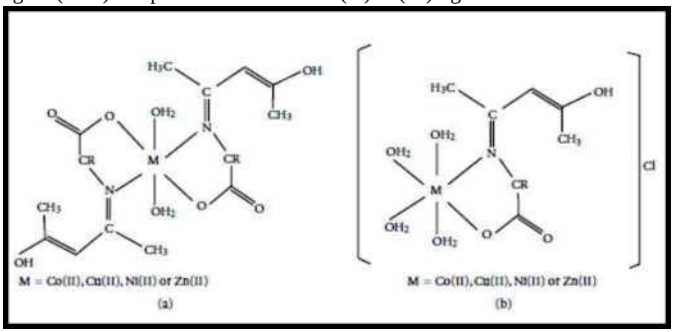


Figure (1-16): Proposed structures of the metal (II) complexes

Solution Chemistry of {Co(II), Ni(II),Cu (II),Zn(II } ions with p-amide a- aminosuccinate (Asparagine) / a-aminoisoverate (Valine) (A) and 5-methyl 2,4- dioxopyrimidine (Thymine) (B) ligands have been analyzed. Formation constant of quaternary metal complexes and complexation equilibria at 30±1°C and at constant ionic strength (I= 0.1M NNO_3) have been explored potentiometrically. Formation of
quaternary species in addition to hydroxyl, protonated{binary & ternary}species have been reported in literature [45].See Figure (1-17) and Figure (1-18).

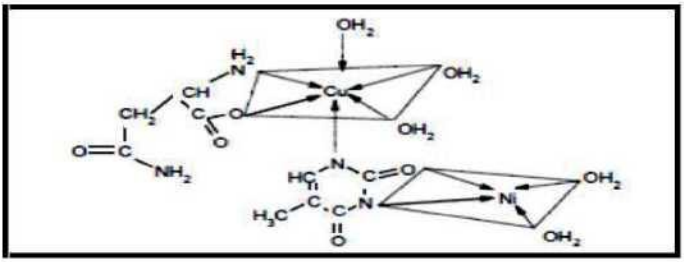


Figure (1-17): Proposed structure of Quaternary
Cu(II)-Ni(II)-Asparagine- Thymine

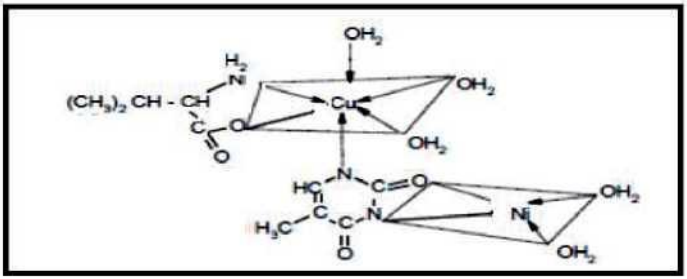


Figure (1-18):Proposed structure of Quaternary
Cu(II)-Ni(II)-Valine-Thymine

Survey of literature reveals that no systematic study of complexes of [Cobalt (II) - antibacterial drugs - amino acids] have been reported and investigated ternary complexesation of Cobalt (II) with different drugs as {Metformin hydrochloride(Mtf), Imipramine hydrochloride (Imp) and Adenosine(Ado)} as primary ligand and a series of [amino acids = Glycine (Gly), DL-Alanine (Ala), L-Glutamic acid (Glu-acid), DL- Isoleucine (Ile), DL-Methionine (Met), DL-^-phenyl alanine (Phe), DL- Serine (Ser) and DL-Valine (Val) as secondary ligands in 20% ethanol-water(v/v) medium [46].

Fayad *et al.,* (2012) [47], were reported the synthesis of new six mixed ligand complexes of metals (II) with L-Valine (Val H) as a primary ligand and Saccharin (SacH) as a secondary ligands. All the prepared complexes have been investigated by spectroscopic methods and physicochemical. The complexes with the formulas $[M(Val)_2(Sac)_2]$
M(II) = Mn (II), Fe (II), Co(II),Ni(II), Cu (II),Zn(II) & Cd(II)
L- Val H= (C_5H ,,NO_2) & SacH =$C_7H_5NO_3S$.

The study shows that these complexes have octahedral geometry; the metal complexes have been screened for their microbiological activities against bacteria. Based on the reported results, it may be concluded that the deprotonated ligand (L-valine) to (valinate ion (Val^-) by using (NaOH) coordinated to metal ions as bidentate ligand through the Oxygen atom of the carboxylate group, and the Nitrogen atom of the amine group, where the saccharin (SacH) coordinated as a monodentate through the Nitrogen atom. See Figure (1-19).

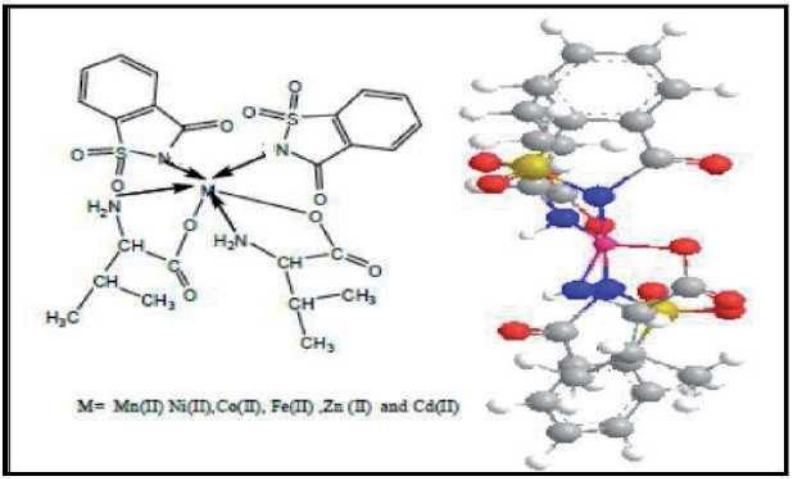
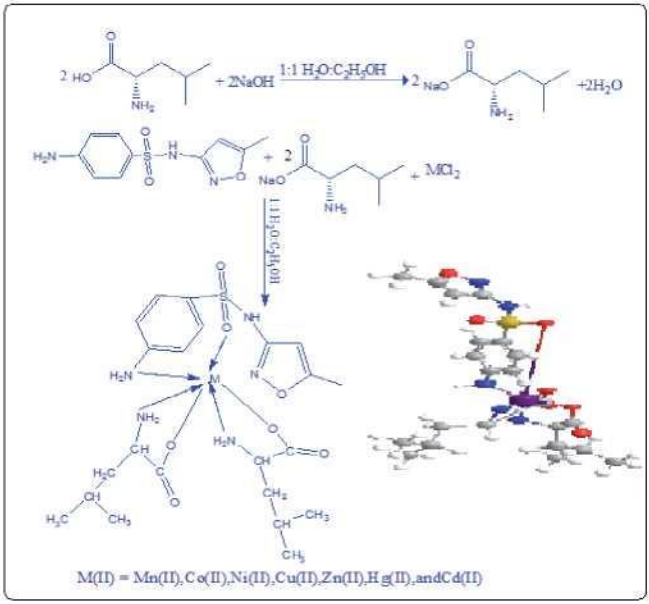


Figure (1-19): Proposed Structures & 3D-Geometrical Structure of The Complexes

The antibacterial activity of mixed ligand complexes against *Staphylococcus aureus(+ve)*, and *Escherichia coli(+ve), Aeruginosa(-ve)* and *Salmonella typhi* were carried out by measuring the inhibition diameter.

Raheem et al(2014) [48], reported the synthesis and investigated of the mixed ligands complexes of M(II) ions in general composition,[M(Leu)2 (SMX)]where L-leucine ($C_6H_{13}NO_2$) = (LeuH) as primary ligand and Sulfamethoxazole ($C_{10}H_{11}N_3O_3S$) = (SMX) as a secondary ligand, Scheme (1-6). The reaction required the following, [(metal: 2(Na+Leu$^-$): (SMX)], molar ratios with M (II) ions, where M (II)= Mn(II), Co(II), Ni(II), Cu(II), Zn(II),Cd (II), and Hg(II).

The UV-Vis and magnetic moment data revealed an octahedral geometry around M(II).The conductivity data show a non-electrolytic nature of the complexes.



Scheme (1-6): Preparation of $[M(Leu)_2(SMX)]$ complexes

1.1.5. Mixed ligand metal complexes of some drugs

Many researchers have studied the characterization, antimicrobial and toxicological activity of mixed ligand complexes of transition metals [49,50]. The role of mixed ligand complexes in biological process has been well recognized [51].

Anti-tumor activity of some mixed ligand complexes has also been reported [52]. The antibacterial and anti-fungal properties of a range of Copper(II) complexes.

Mixed ligand complexes of Ni(II) with 1,10-phenanthroline (1,10-Phen) and Schiff bases L_1(MIIMP); L_2(CMIIMP); L_3(EMIIMP); L_4(MIIMNP); Ls(MEMHMP); L6(BMIIMP); L_7(MMIIMP); L8(MIIBD) Figure (1-20) have been synthesized [52]. These complexes have been characterized by C.H.N, IR, ^{1}H-NMR, ^{13}C-NMR, Mass, UV-Vis, magnetic moments, and thermogravimetric analysis. Spectral data showed that the (1,10- Phenyl) acts as neutral bidentate ligand coordinating to the metal ion through (2N: donor atoms in ring) and Schiff bases act as monobasic bidentate coordinating through NO donor atoms. All Ni(II) complexes Figure (1-21) appear to have an octahedral geometry [53].

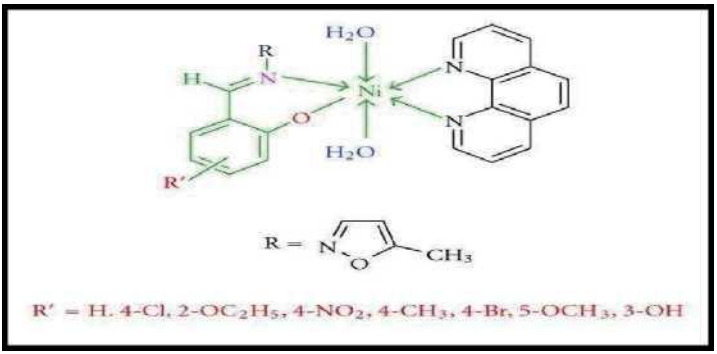


Figure (1-20): Proposed structure of the Nickel (II) complexes

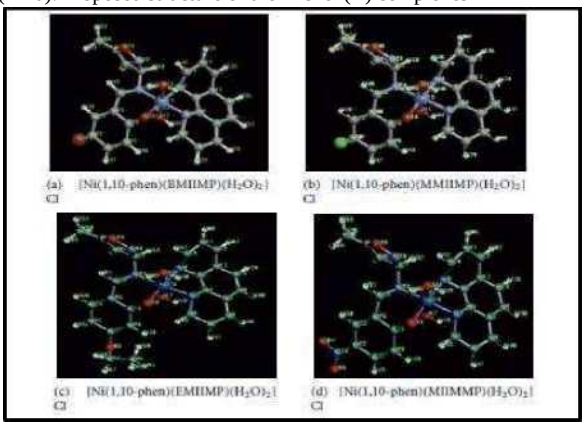


Figure (1-21): The Optimized Structural Geometry of Ni(II) Complexes

Epton Marr *et al.,* in the 1970s described the synthesis of ferrocene analogues of well-established antibacterial and published a series of papers drugs such as penicillins and cephalosporins [54-55].

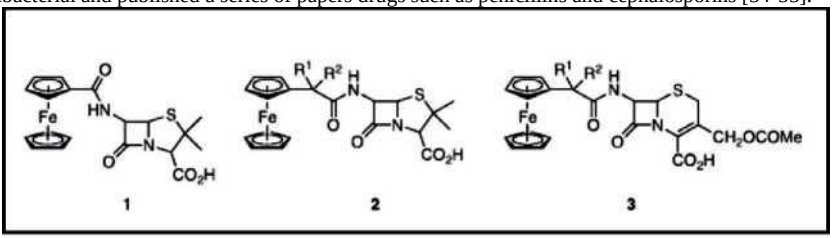
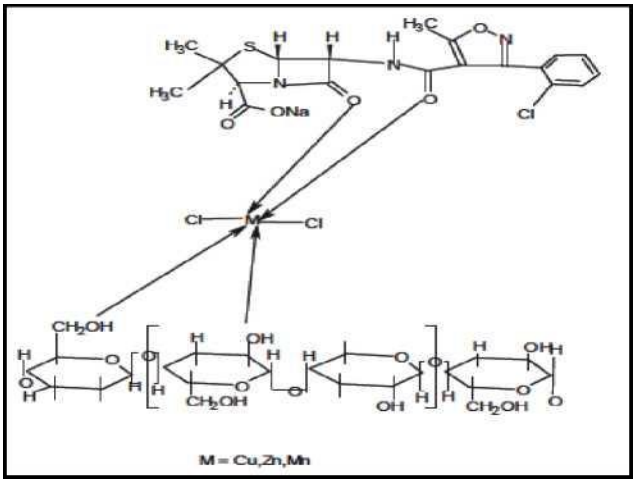


Figure (1-22): Structures of Ferrocenoyl-Penicillin (1), Ferrocenyl-Penicillin 2, & Ferrocenylcephalosporin

Telia *et* a/.,(2011)[56], investigated the possibility of metals coupling of antibiotics into cellulose. Complexes of three [M- cellulose - Antibiotics], M = Co(II), Zn(II) and Mn(II) Figure (1-23) .



Figure(1-23): Metal -Cellulose-Antibiotics complexes

1.2. Ligands and starting materials compounds and related in this study:

1- Trimethoprim antibiotic drug (TMP) and its metal complexes

2- ^-lactam antibiotic drug (Ampicillin (AmpiH) & Amoxicillin(AmoxH) and their Metal complexes

3- Aldomet (Methyldopa) (M-dopa) drug and its metal complexes

4- Vitamins

[Vitamin L= Anthranilic acid (AnthH) & vitamin B3= Nicotin amid(NAm)] and their Metal complexes

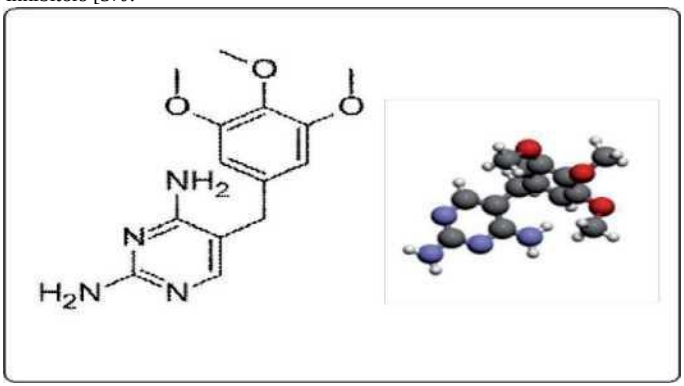
5- Amino Acids [L- Proline (ProH)& L-Alanine (AlaH)] and their metal complexes.

6- (4-chlorobenzophenon) and its metal complexes

1.2.1. Trimethoprim Antibiotic Drug (TMP) And Its Metal Complexes

1.2.1.1, Medical Uses

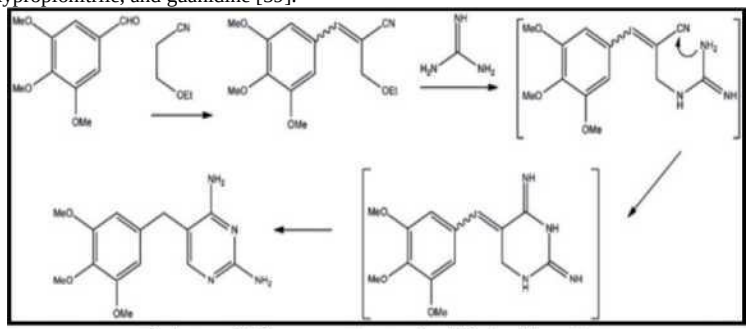
Trimethoprim is a bacteriostatic antibiotic used mainly in the prevention and treatment of urinary tract infections. It belongs to the class of chemotherapeutic agents known as dihydrofolate reductase inhibitors [57J.



Figurc(I-24): Structure and 3D-geometrical structure of the Trimethoprim

Trimethoprim, Systematic (IUPAC) name: 5-(3,4,5-Trimethoxybenzyl) pyrimidine - 2,4-diamine (TMP), widely used in conjunction with sulfamethoxazole (SMX), is an effective antimicrobial agent used, for example, in the treatment of urinary tract infections and as a powerful bacteriostatic agent, because the antimicrobial activity is greater than that when the sulfa-drug is used alone [58,591-

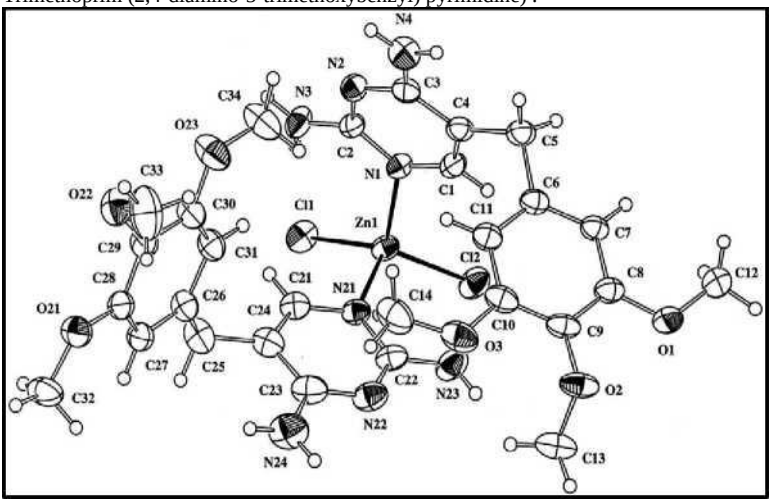
Trimethoprim is a broad-spectrum antimicrobial and also exhibits antparasitic activities [58,59]. Trimethoprim can be prepared from 3,4,5-trimethoxybcnzaldehydc, 3-ethoxypropionitrile, and guanidine [59].



Scheme (1-7): preparing rote of Trimethoprim

1.2.1.2. Metal complexes of Trimethoprim

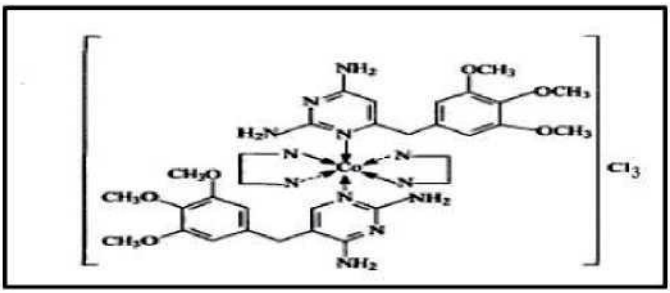
Simo *et al.*, (2000) [60], reported the interaction of [Zinc(II), Copper (II) and cadmium(II)] with Trimethoprim (2,4-diamino-5-trimethoxybenzyl) pyrimidine) .



Figure(1-25): Crystal Structure of [Zn(Trim)Cl]

Peter (2005), [61], was reported the synthesizes Co(III) complex of Trimethoprim (TMP) synthesized from {Trimethoprim and *trans- or cis-* $[Co(en)_2Cl]Cl_2$ in two solvents (Methanol and Ethanol) Figure(1-26).

Microanalyses showed that there was no coordination in ethanol when the reaction was carried out in a (1:1) mole ratio. However, when the preparation was done at(2:1) mole ratio the trans~complex was isolated. The complex obtained is formulated as $[Co(en)_2(TMP)_2]Cl_3$.

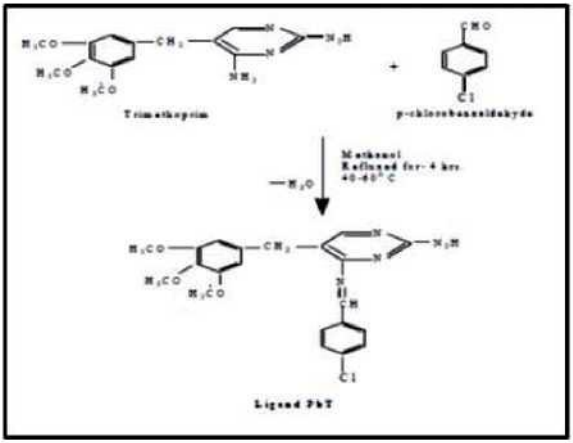


Figure(1-26): Proposed structure for $[Co(en)_2(TMP)_2]Cl$

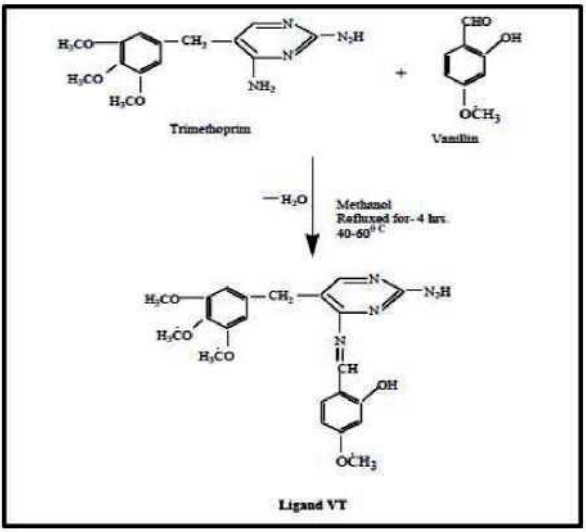
Sunil *et al* (2010) [62] have been synthesized Schiff bases by the condensation of Trimethoprim with p-Chlorobenzaldehyde and Vanillin respectively in methanol (Ligand pbT and ligand VT) Schemes (1-8 and 1-9). Further their metal complexes have been synthesized by react

metal salts of {Mn (II), Co (II), Ni (II) and Zn (II)}, Figure(1-27) characterization data of these compounds have been made on the basis of Mol. wt , A_m, Peff , C.H.N, UV, IR and NMR Spectra.

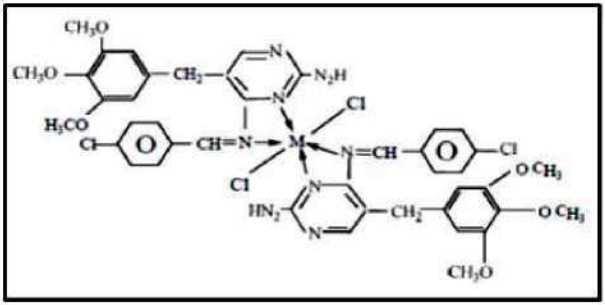
The synthesized compounds were screened for their in vitro growth inhibiting activity against bacteria viz., gram negative(-) *{Escherichia coli)* & gram positive (+) *{Staphylococcus aureus, Bacillus licheniformis, Micrococcus luteus}and* were compared with the Oflaxocin as (standard antibiotic).



Scheme (1-8):Schiff base ligand (pbT)

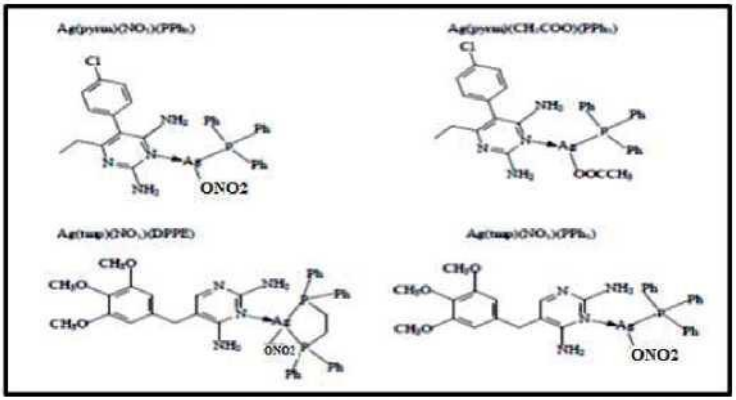


Scheme (1-9): Schiff base ligand(VT)



Figure(1-27): Structures of Metal Complexs PbTM Where M= Mn (II), Co (II), Ni (II) and Zn (II)

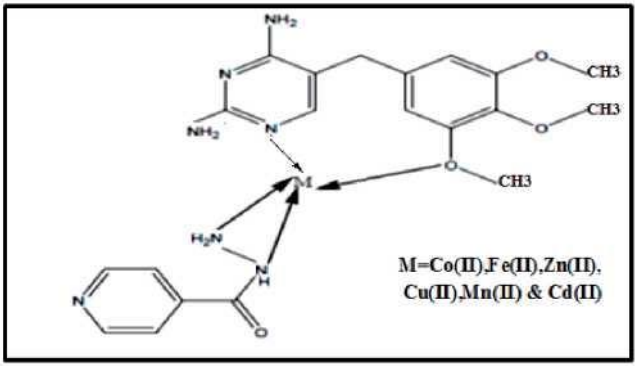
Omoruyi *et al.,* (2012), [63], reported the silver Ag(I) complexes of Trimethoprim and pyrimethamine drugs Figure(1-28) have been synthesized and characterized by (C.H.N), (FTIR) and (UV-Vis) spectroscopy, and electrical conductivity measurement. The metal complexes formed a three and four coordinate geometry with the ligands acting as a monodentate molecule bonding to the Ag(I) in each case through the pyrimidine N (1) Nitrogen. The complexes have non-electrolyte behaviour in (DMF) solution with its low conductivity values. All the silver complexes showed enhanced antibacterial activities compared to their free ligands {Trimethoprim and pyrimethamine} drugs .



Figure(1-28):Proposed structures of silver(I) complexes

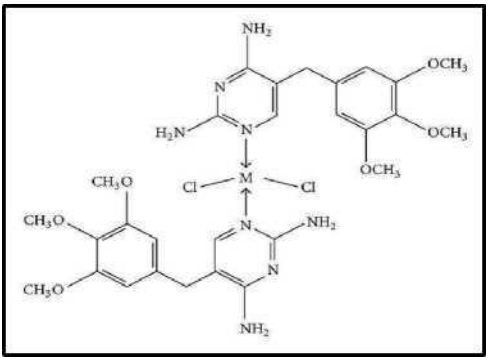
Bamigboye *et al.,* (2012), [64], reported the syntheses and biological screening of mixed [Trimethoprim -M -Isoniazid] complexes, M= Mn(II), Fe(II), Cu(II), Co(II),Zn(II) and Cd (II) See Figure (1-29).

The complexes were characterized by using solubility, melting point, conductivity measurement and spectroscopic studies. Trimethoprim complexes of coordination of the metal to the ligands is through the Nitrogen of the pyrimidine group and coordination through the Nitrogen of the amine group. The Antimicrobial Properties of the complexes were carried out against *six organisms.*



Figure(1-29): Proposed structure for [Trimethoprim -M -Isoniazid]

Peter & Omoruyi (2013) [65], synthesized Pd(II) and Pt(II) complexes of Trimethoprim and pyrimethamine, Figure(1-30) and characterized by (C.H.N),UV-Vis, FTIR, and NMR spectroscopy. The complexes are formulated as four coordinate square planar species containing two molecules of the drugs and two chloride or thiocyanate ions. The coordination of the metal ions to the pyrimidine Nitrogen atom of the drugs was confirmed by spectroscopic analyses. The complexes were screened for their antibacterial
activities against eight bacterial isolates. They showed varied activities with the active metal complexes showing more enhanced inhibition than either Trimethoprim or pyrimethamine. The Pd(II) complexes of pyrimethamine showed unique inhibitory activities against *P. aeruginosa & B. pumilus*, and none of the other complexes or the drugs showed any activity against these bacteria isolates.



Figure(1-30): Proposed structures for the metal complexes M= Pd(II) & Pt (II)

Srivastava *et al.*, (2014) [66],were reported microwave irradiation as a green approach for fast, efficient, clean and environmentally benign exclusive synthesis with excellent yields of Schiff bases as new ligands and their complexes with Cu(II) have been developed using condensation of pyridoxal and {antibiotics = Amoxicillin(L_1),
Cephalexin(L_2), sulphamethoxazole (L_3) and Trimethoprim (L_4)}, See Figure (131). All the

complexes under investigation possess antibacterial activity. This method provides several uses such as environmental friendliness, short reaction times, non- hazardous and simple work-up procedure. The compounds were characterized by (C.H.N), thermo-gravimetric, magnetic and spectroscopic studies . The complexes are coloured and stable in air and found to be six co-ordinate dihydrates and ML_2 (1:2), [(metal: ligand) ratio] type.

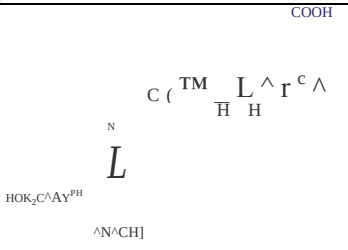
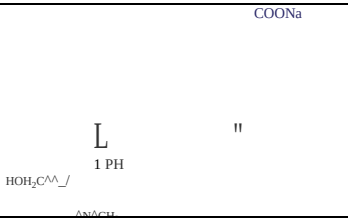
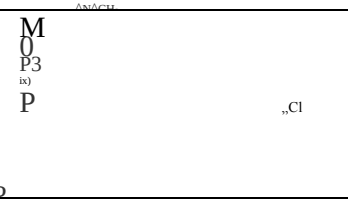
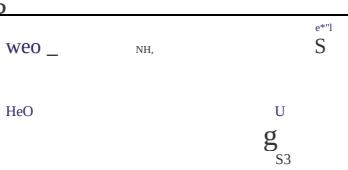
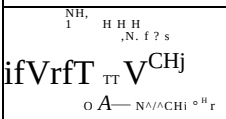
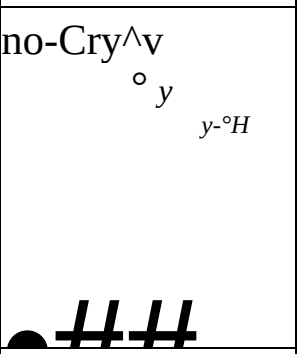
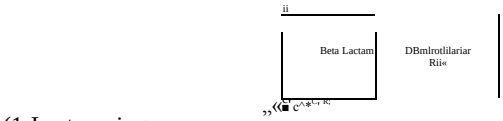
L_1 = PyridoxylideneAmoxicillin	
L_2 = PyridoxylideneCephalexin	
L_3 = Pyridoxylidenesulphamethoxazole	
L_4 = PyridoxylideneTrimethoprim	

Figure (1-31): Structure Formulae of the (H_1 to H_4) Schiff bases of pyridoxal & antibiotics

1.2.2. p-lactam antibiotic drug (Ampicillin & Amoxicillin) and Schiff Base

The p -lactams are a family of antibiotics that are characterized by the presence of P-lactam ring Figure (1-32). They are a diverse and varied family which include the penicillins, cephalosporins and carbapenems, and are the most commonly prescribed antibiotics in Europe .^-lactams antibiotics uses (AmpiH & AmoxH) and their derivative's (Schiff base) are multi-dentate ligands [22,67].

	Ampicillin (AmpiH)	Amoxicillin(AmoxH)
		
Systematic (IUPAC) name	(2S,5R,6R)-6-([(2R)-2-amino-2-phenylacetyl].amino)-3,3-dimethyl-7-oxo-4-thia-1 -azabicyclo[3.2.0J heptane- 2-carboxylic Acid	2S,5R,6R)- 6-{,[(2R)-2- amino-2-(4-hydroxyphenyl)- acetyl] .amino}- 3,3-dimethyl- 7-oxo- 4-thia- 1 -azabicyclo[3,2.0]hcptane- 2-carboxylic acid



(1-Lactam ring

Figure (1-32): Structural formulas of (Amp H & AmoxH)

Penicillin behaves as bidentate,Figure (1-33) (A) or tridentates ligand, Figure (1-33) (B). In bidentate mode, coordination occurs through the carboxylate and lactamic Oxygen atoms to the metal and in case of tridentale mode, coordination occurs through the carboxylate, lactamic Oxygen and amide carbonyl group to the ions [67-68J.

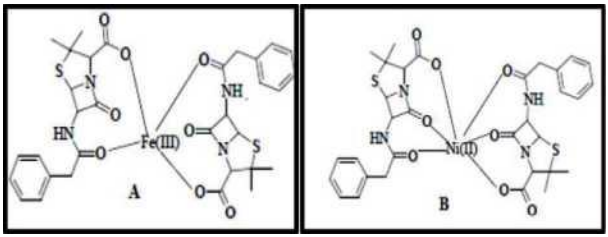


Figure (1-33): Fe(IU)& Ni(II) complexs of Benzy (penicillin, (Bidentate mode) (A) and (Tridentate mode) (B)

Manhel (2013) f 69],was reported the synthesis and characterization of the six tridentate Schiff bases ligands (HLi- HU) derives from selected p-lactam antibiotics (Amoxcilline trihydratc, Ampicillin trihydrate and Cephalexin, with 4 (dimcthylamino) benzaldehyde) and

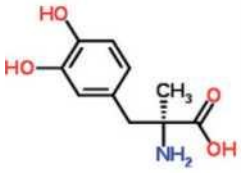
Table (1-2): Tridentate Schiff bases ligands (HLi- HLf,) derives from selected p-lactam antibiotics

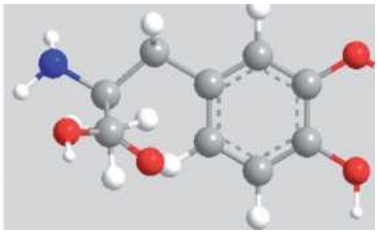
Symbol	Chemical formula	Schiff bases derives form
HL,	$C_{25}H_{26}N_4O_4S$	Cephalexine + 4(dimethylamino)benzaldehyde
HL_2	$C_{25}H_{28}N_4O_5S$	Amoxcilline + 4(dimethylamino)benzaldehyde
HL_3	$C_{23}H_3HN_4O_4S$	Ampicillin trihydratc + 4(dimethylamino)benzaldchydc
HL_4	$C_{24}H_{23}N_3O_6S$	Cephalexine + Vanillin
HL_5	$C_{24}H_2SN_3O_7S$	Amoxcilline + Vanillin
HU	$C_{24}H_{25}N_3O_6S$	Ampicillin trihydrate + Vanillin

Vanillin containing (N,0 and O) as donor atoms type (O N O) shown Table (1-2).

1.2.3. Aldomct (Methyldopa) (M-dopa) drug and its metal complexes

Methyldopa (M-dopa), the L-isomcr of alpha-Methyldopa, is levo-3-(3,4-dihydroxyphenyl)-2-methylalanine. Its empirical formula is $CioH_{|3}N0_4$ [70,71]. See its structural formula in Figure (1-34).





IUPAC Name

(S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid
Or 3-Hydroxy-a-methyl-L-tyrosine

Figure (1-34): Structures and 3D-geomelrical structure of the Methyldopa

1.2.3.1. Medical uses

Methyldopa is used in the clinical treatment of the following disorders:

- Hypertension (or high blood pressure) Gestational hypertension (or pregnancy-induced hypertension) .
- Aldomet (L-Methyldopa) is an antihypertensive drug and is an aromatic-amino-acid decarboxylase inhibitor in animals and in man [71].

1.2.3.2. Metal complexes of Methyldopa (M-dopa)

Patil & Mhaske, (2001) [72] have studied the stability constants (Ks) of four metals with (Iminodiacetic and /or Nitrilotriacetic) acids as primary ligands and (Methyldopa and /or levodopa) as secondary ligands potentiometrically.

Mouayed *et al.,* (2009), [73] were reported spectrophotometric determination of dopamine hydrochloride and Methyldopa in pharmaceutical preparations using flow injection analysis (FIA). The method is based on oxidative coupling reaction of drug with 2-Furoic acid hydrazide ($C_5H_6N_2O_2$) in the presence Sodium nitroprusside in (NaOH) medium to form soluble product that has a maximum absorption at 487 nm. The various physical and chemical variables were optimized. The results obtained were in good agreement with those obtained by British Pharmacopoeia method.

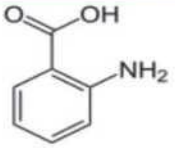
Patil (2012), [74] was studied the stability constants of ternary complexes of [Mn (II), Co (II), Ni (II), Cu (II) and Zn (II)] ions with aspartic acid(ASP) and Glutamic (Glu) acid as primary ligands and levodopa and Methyldopa as secondary ligands,also all complexes have been carried out (pH-metrically) at the same conditions.

1.2.4.Vitamins [Vitamin L = Anthranilic acid (AnthH) & vitamin B3= Nicotinamid (NAm)] and their Metal complexes

1.2.4.1. Vitamin L [Anthranilic acid (AnthH)] and its metal complexes

Anthranilic acid (2-aminobenzoic acid, (AnthH) is the biochemical precursor to the amino acid tryptophan, as well as a catabolic product of tryptophan in animals.

Anthranilic acid ($C_6H_4(NH_2)COOH$) is one of the best compound used by degrading ancient dye indigo [75].

Anthranilic acid (AnthH)	
	
IUPAC name	
2-aminobenzoic acid or *o*-aminobenzoic acid, vitamin L	

Figure(l-35):Structure and 3D-geometrical structure of the Anthranilic acid

It is a white solid amino acid in pure form whereas commercially available in yellow form. Its molecule consists of a benzene ring with two adjacent functional groups, a carboxylic acid and an amine [75-76J.

Al-Noor *et al.*, (2013), [77] reported the synthesized mixed ligand complexes M(II), of the composition [M(An)2((PBu3)2] in (1:2:2) (M:Anth:(PBu3). molar ratio, (where Anth =Anthranilate ion, (PBu3)= tribulylphosphine. M= Co(II),Ni(TI),Cu(TT) and Zn(II). See Figure(l-36).

The prepared complexes were used Characterized, the data of these compounds have been made on the basis of Mol. wt, A_m, p^ff, UV-Vis, FT-IR and tested in vitro against three types of pathogenic bacteria microorganisms to assess their antimicrobial properties. The study shows that all complexes have octahedral geometry; in addition, it has high activity against tested bacteria. The results showed that the deprotonated ligand(AnthH)to anthranilate ion (Anth') by using (KOH) coordinated to metal ions as bidentate ligand through the (O)atom of the carboxylatc group (—COO), and the (N) atom of the amine group(-NH_2), where thc,(PBu3) coordinated as a monodentate through the (P) atom.

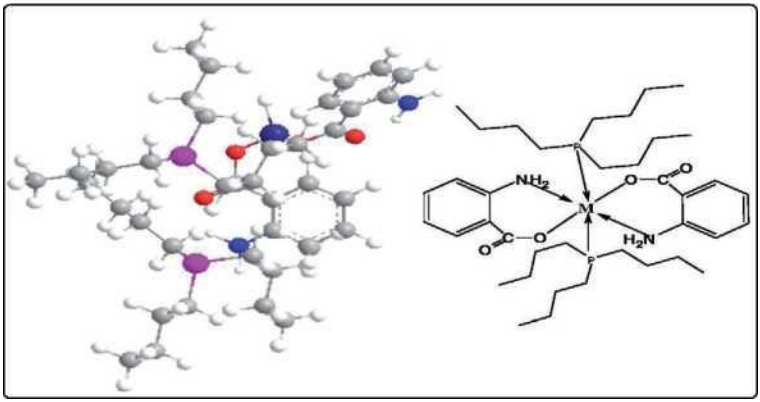


Figure (l-36):The proposed structure & 3D-geomelrical structure of the complexes[$M(A)_2$ ($PBu_3)_2$], M = Co(II),Ni(II),Cu(II) and Zn(II)

Saleem Raza (2013), [78] reported synthesized the complexes of anlhranilic acid and pthalic anhydride ligands with Co(II),Cu(II), Cd(II), Pb(Il) and Sn(II) .The antibacterial potential of the complexes was assessed against *Staphylococcus* .

Rawatc (2014), [79] reported the synthesis a mixed ligand complexes of Zn(II), Cd(II) and Cu(TT), with {Anlhranilic,phthalic, and Succinic] acids. The complexes have been characterized on the basis of analytical data, thermogravimetric studies, IR and NMR. IR spectral studies suggest that bidentate chelating behavior of three acid in its complexes.

Pandey & Shahi (2014) [80], reported the synthesis of some mixed ligand complexes of Co(II), Ni(TT), Cu(TT), Ru(TT)and Zn(IT) with tribenzyl phosphine and anthranilic acid see Figure (1-37) . The antimicrobial activities of ligand and complexes against three types of bacteria, *{Klebsiella,Bacillus* and *Staphylococcus* are tested.

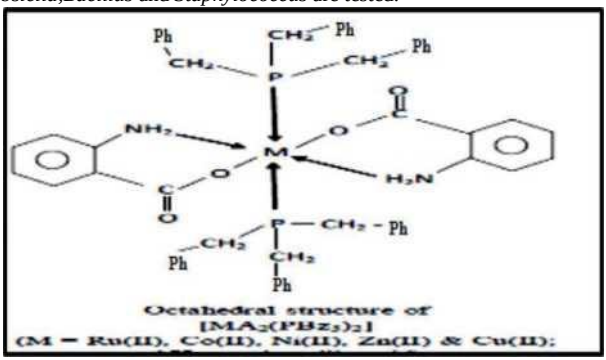
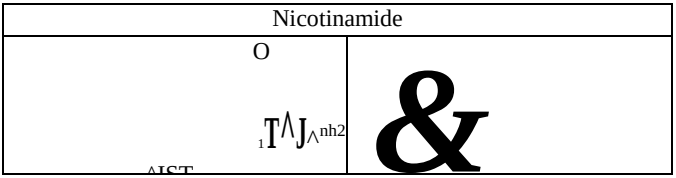


Figure (1-37): The proposed structure metal - tribenzyl phosphine and Anthranilic acid complexes

I.2.4.2. Vitamin B3= Nicotinamid(NAm)J and its metal complexes

Nicotinamide (NAm),Figure (1-38) is a water-soluble vitamin and is a part of the vitamin B group,[70,81,82].



1UPAC name:
pyridine-3-carboxamide
Other names 3-pyridinecarboxamide ,niacinamide,nicotinamide
,nicotinic acid amide, Vitamin B3

Figure (1-38) :Structure and 3D-geometrical structure of the (NAm)

Nicotinamide has demonstrated as anti-inflammatory actions that may be of statement to patients with inflammatory skin conditions [82J and conflicts as a chemo- and radio-sensitizing agent/canccr-growth-promotcr by boosting tumor blood flow, thus reducing tumor hypoxia. And it is an activator (but inhibits at higher doses) and has been reported to restore cognition in Alzheimer's disease [82,83].

Al-Noor *et al.*, (2012), [84] were reported the synthesis and investigatation of two types complexes of the ligand (AnthH) and (NAm) with Sn(II) & Pb (II) Figure (1-39).

A) The mixed Ligand complexes of composition,$[M(Anth)_2 (NAm)_2]$ where AnthH = Anthranilic acid = $C_7H_7N0_2$, M(II) = Sn(II) & Pb (IT).

B) The mono Ligand Complexes of (AnthH) or (NAm) with Pb (II) & Sn(II).

The results showed that the deprotonated ligand (anthranilic acid) to anthranilate ion [A] by using (NaOH) coordinated to metal ions as bidenlate uninegative charge ligand through the (O) atom of the carboxylate group [-COCT], and the (N) atom of the amine group [NH_7J, where the (NAm) coordinated as a monodentate through the (N) atom in ring.

The complexes of the ligand with metal ions (for mono complexes) were studied in ethanol and /or water in order to determine the M : L ratio in

the complex following the continues variation method (Job's method) A series of solutions were prepared having a constant concentration (0.001 M) of the M(II) and (AnthH). The results of complexes formation in solution (M:L = 1 : 2) ratio.

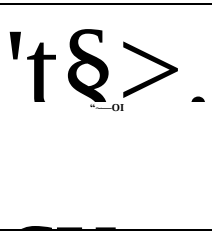
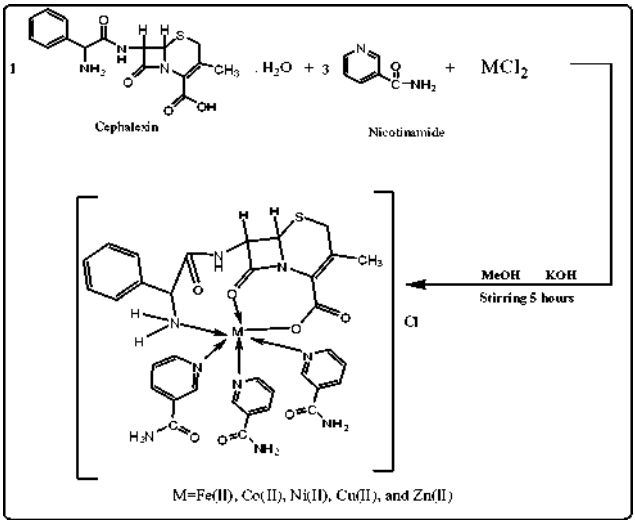
Complexes	proposed structure	3D-geometrical structure
[Sn (Anth)$_2$]		
[Pb(Anlh)$_2$]		
[Sn (NAm)$_2$(H_20)$_2$]C1$_2$ [Pb (NAm)$_2$(H_20)$_2$]C1$_2$		
[Sn(Anlh)$_2$(NAm)$_2$]		
[Pb(Anth)$_2$(NAm)$_2$]		

Figure (1-39): The proposed structure and 3D-geometrical structure complexes of the ligand (AnthH) & (NAm) with Sn(II) & Pb (II)

Al-Noor *et al.,* (2013) [85J,reported mixed ligand complexes of M(II) = [Co(Il), Ni(II), Cu(II) and Zn (II)] of the composition, [M(Ceph) (NAm)j] Cl in 1:1:3 molar ratio, (where Ceph = Cephalexin and NAm = Nicotinamide have been synthesized and characterized by repeated melting point determination, solubility, A_m, determination of the (M%) in the complexes by flame(A.A.S), FT-IR, (peff) measurements and electronic spectral data. The compounds were screened for their antimicrobial activity against six bacteria gram (+ve) and gram (-ve). See Scheme (1-10).



Scheme (1-10):Schematic route of synthesis
[M(Ceph)(NAm)3]Cl complexes

Also, Al-Noor *et al* .,(2014) [86] were reported Schiff base ligand (E)-6-(2-(4-(dimethylamino)benzylideneamino)-2-phenylacetamido)-3,3-imethy-l-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid = (HL),was prepared via condensation of (AmpH) and (4-DMAB=4-dimethylaminobenzaldehyde) in methanol . See Figure (1-40).

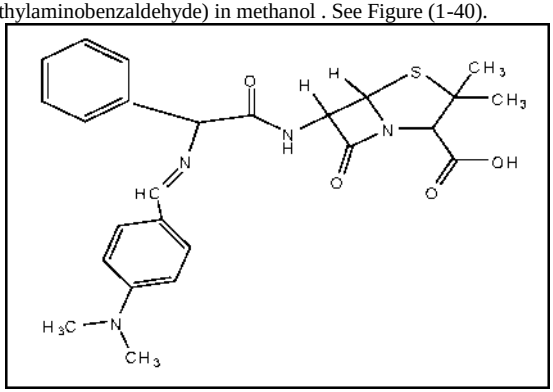
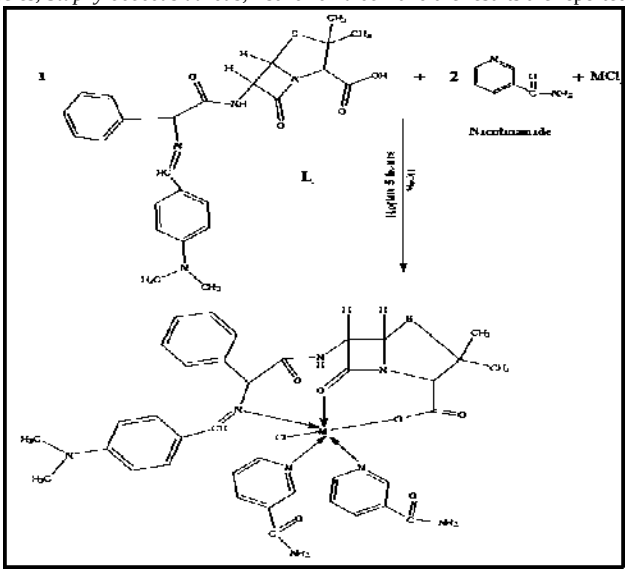


Figure (1-40): The molecular structure of (HL)

Polydentate mixed ligand complexes were obtained from (1:1:2) molar ratio reactions with M (II) and HL, 2(NAm)on reaction with [MCl_2 .nH_2O] salts yields complexes corresponding to the formulas [M(L)$(NAm)_2$Cl],where M = Fe(II),Co(Π),Ni(Π),Cu(Π),and Zn(II) and NAm=nicotinamide, Scheme (1-11).

The complexes were structurally studied through AAS, FT-IR, UV-Vis, A_m, Chloride contents and (peff). All complexes are non-electrolytes in DMSO solution. And octahedral geometries have been suggested. In order to evaluate the effect of the biological activity, these synthesized complexes, in comparison to the un complexed (HL) has been screened against bacterial species, *Staphylococcus aureus*, *Escherichia coli* and the results are reported.

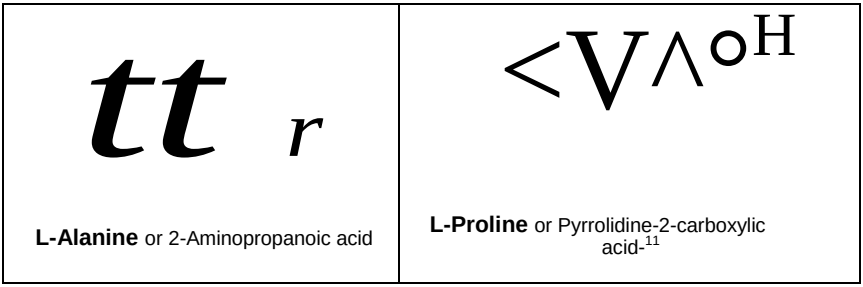


Scheme. (1-11): Synthesis of [M(L)(NAm)j]Cl complexes

1.2.5. L- a- Amino Adds [L-AIanine (AlaH) and L-I'roline (I*roH)J and their metal complexes

The L- a- amino acids and their compounds are used in biology, pharmacy, laboratory reagents and industry [87J. L- alanine and L-proline are a-amino acid, [88,89J Figure (1-41).

Amino acids are ideal ligands from both chemical [891 and nutritional [901 points of view. Metal amino acid (M-AA) complexes are similar to these compounds which allow the metal to be carried in with the amino acids during absorption and can be used to build proteins or provide energy.



L-Alanine or 2-Aminopropanoic acid

L-Proline or Pyrrolidine-2-carboxylic acid-[11]

Figure (1-41): Structure and 3D-geometrical structure of the [L-Alanine and L- Prolinelamino acids

Anna *el al*., (2014) [91J,reported the reactions of [Ru(NO)Clsj^2 with eight amino acids = (Gly), (L-Ala), (L-Val), (L-Pro), (D-Pro), (L -Scr), (L -Thr), and (L -Tyr) in n- propanol or n-butanoi formed eight new complexes, which were characterized by C.H.N, (EST-MS), 'H-NMR, UV-visible and, cyclic voltammetry, and X-ray crystallography.The general formula [RuCli(AA H)(NO)J⁻,where AA = eight amino acids.

The compounds were characterized by C.H.N, electrospray ionization mass spectrometry (ES1-MS), 'H-NMR, UV-Visible and FT-1R spectroscopy, cyclic voltammetry, and X-ray crystallography.

X-ray crystallography studies have proved that in three theoretically possible the same isomer type (from) was isolated, *Trans* (N0,0) -3[RuCl3(AA-H)(NO)l.as 3D- geomctrical structure . Figure (1-42)

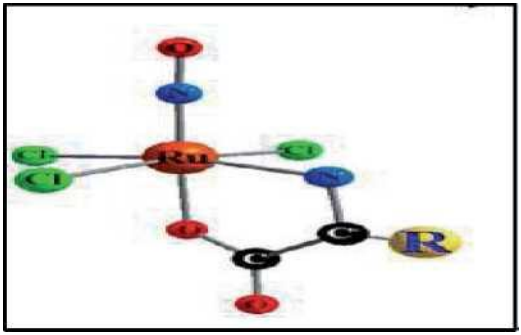


Figure (1-42):3D-geometrical structure of
<rans(NO,O)- [Rua_3(AA-H)(NO)]complexes

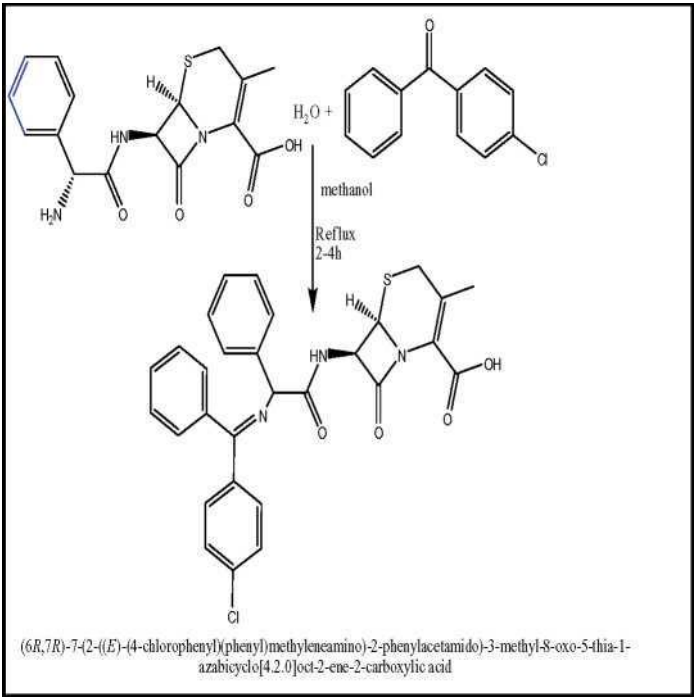
1.2.6. [4-Chlorobenzophenon] and its metal complexes

4-Chlorobenzophenone was detected, not quantified, in one sample of human adipose tissue collected in fiscal year 1982 during the Environmental Protection Agency's National Human Adipose Tissue Survey (NHATS) [92].

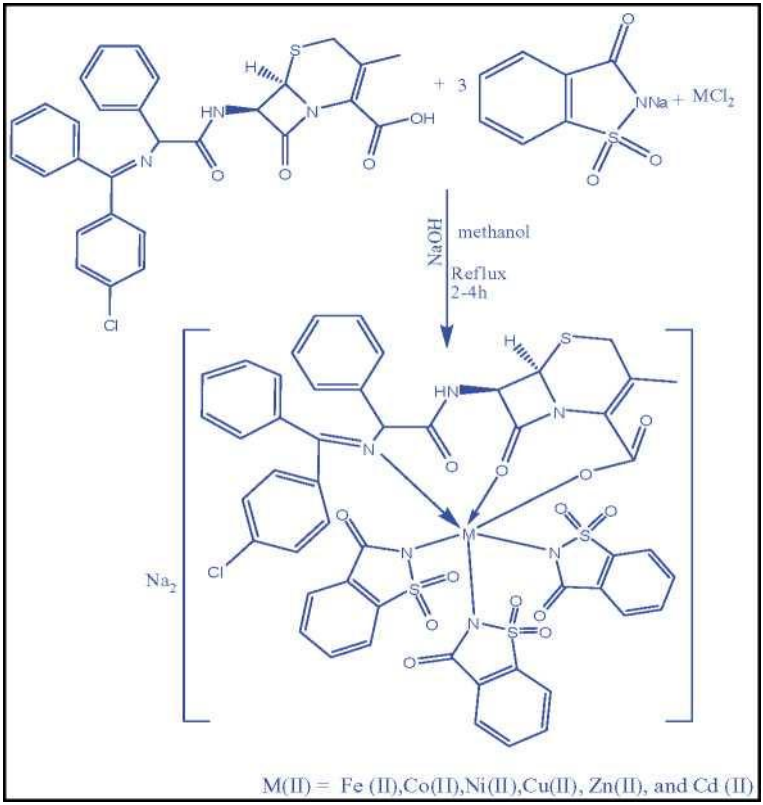
o^D Cl	
IUPAC name Molecular formula $C_{13}H_9ClO$	p-Chlorobenzophenone Other names: Benzophenone,4-Chloro-methanone, (4-Chlorophenyl)phenyl-p-CBP

Figure (1-43): Structural formula of 4-chlorobenzophenone

Al-Noor *et al.,* (2014) [93], were reported the synthesis and studying of Fe(II), Co(II), Ni(II), Cu(II),Zn(II) and Cd(II) complexes with tridentate Schiff base (HL) derived from ^-lactam antibiotic [(Cephalexin monohydrate)- 4-chlorobenzophenone] as a primary ligand and Saccharin (Sac) as secondary ligand Schemes (1-12) and (1-13) respectively .



Scheme (1-12): Schematic representation the synthesis Schiff base (derivative from p-lactam antibiotic
[(Cephalexin monohydrate)-4-chlorobenzophenone]

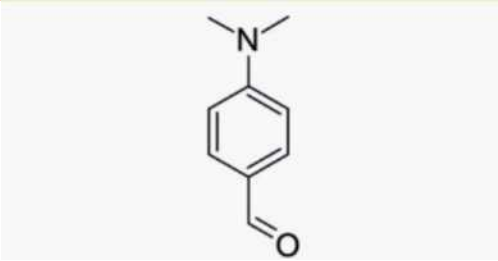


Scheme (1-13): The synthesis route of [HL -M(II)-Sac] Complexes

1.2.7.[4-dimelhylamino-benzaldehyde] and its metal complexes

para-Dimethylaminobenzaldehyde is an organic compound containing amine and aldehyde [94].

para-Dimethylaminobenzaldehyde



4-Dimethylaminobenzaldehyde

p-Dimethylaminobcnzaldchydc; 4-Formyl-A'^V-dimelhylaniline; A·,A·-Dimethyl-4-formylaniline

Figure (l-44):Structural formula of 4-Dimethylaminobenzaldehyde

James *et al.*, (1986) [95]. were reported infrared and Raman spectra and vibrational assignments for 4-(dimethylamino)benzaldehyde (DABA) and its zinc complex .

Paulo *et al.*, (2010) [96] were reported the crystal structure landscapes from combined vibrational spectroscopy and initio calculations 4-(Dimethylamino) benzaldehyde .

Taghrced and Lcqa [97-99] were reported the synthesis and characterization of:

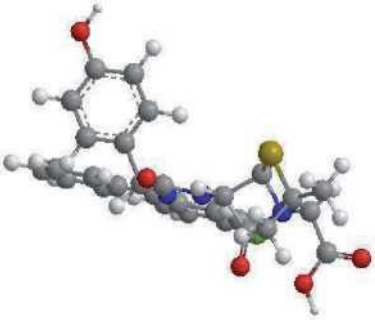
A) The two Schiff bases ligands (HL1- HL2) derives from selected (3-lactam antibiotics (Amoxcilline and Ampicillin trihydrate) with 4-Chlorobenzophenon.

B) One Schiff bases ligand HL3 derive from drug Mcthyldopa with 4(dimcthylamino)benzaldehyde as shown table below:

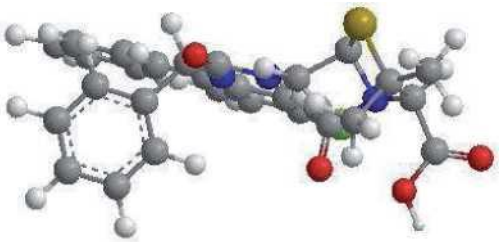
Symbol	Chemical formula	Schiff bases derives from
HLi	$C_{?9}H_{,6}ClN_3O_5S$	Amoxcilline(AmoxH) + 4-chlorobenzophenone
HL_2	$C_{?,}H_{M}C1N,0,,S$	Ampicillin (AmpiH)+ 4-chlorobenzophcnone
HL_3	$C_{I9}H_{??}N_?O_{,,}$	Methyl dopa (M-dopa)+ 4-(dimethylaminobezaldehyde)

The ligands containing (N ,O and O) as donor atoms type (O N O) for (HL_1 and HL_2) and (N.O) for HL_3 .

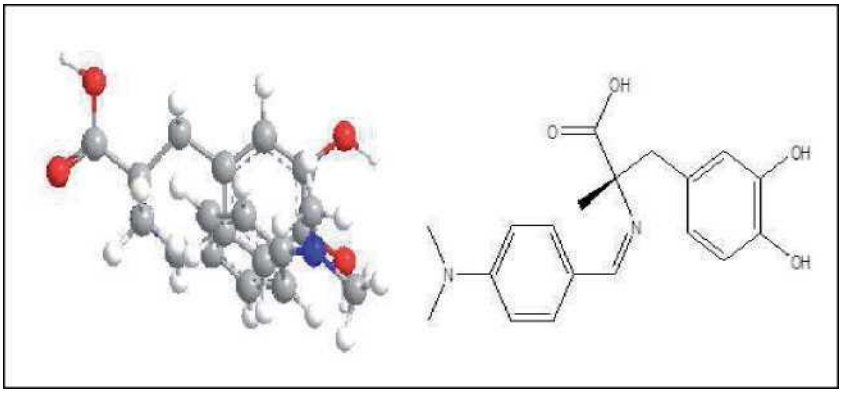
The prepared ligands (HL_1-HL_3) were characterized by (^{1}H-NMR) and (^{13}C-NMR) spectra . FT-I.R . U.V-Vis spectroscopy. (C.H.N.S). melting point and thermal analysis for (HL_1 and HL_2) . According to the results obtained from ^{1}H-NMR . ^{13}C-NMR and FT- IR. U.V/vis. . The proposed molecular structure Ligands (HL_1-HL_3) were drawing by using Cs chem office 3D Ultra program package (2006). As shown are shown in Figures below (three dimensional view of ligand).



6-[2-{[(4-Chloro-phenyl)-phenyl-methylene]-amino}-2-(4-hydroxy-phenyl)-acetylamino]- 3.3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid(HL_1)



6-(2-{[(4-Chloro-phenyl)-phenyl-methylene]-amino}-2-phenyl-cetylamino)-3.3- dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid(HL_2)



3-(3,4-Dihydroxy-phenyl)-2-[(4-dimethylamino-benzylidene)-amino]-2-methyl-propiomc acid(HL_3)

Synthesized of mixed ligand complexes :

1) Two Schiff bases ligands (HL_1-HL_2) uses as primary ligand with Nicotinamide (NAm), as a secondary ligands with M (II) and M(III) shown table below:

2) Schiff base ligand HL_3 use as primary ligand with Anthranilic acid (AnthH) , as a secondary ligands with M (II) and M' (III) shown table below:

	Mixed ligand-Metals omplexes	Compositions
Schiff bases ligand	Schiff bases ligand HL_1 + Nicotinamid(NAm) + Metal Chloride	$[M(L_1)(NAm)_3]Cl$ M=Co(II),Ni(II),Cu(II),Cd(II),and Hg(II) $[M'(L_1)(NAm)_3]Cl_2$, M'=Cr(III),Fe(III)
	Schiff bases ligand HL_2 + Nicotinamid (NAm) + Metal Chloride	$[M(L_2)(NAm)_3]Cl$ M=Co(II),Ni(II),Cu(II),Cd(II),and Hg(II) $[M'(L_2)(NAm)_3]Cl_2$, M'=Cr (III),Fe(III)
	Schiff bases ligand HL_3+ amino acid (Anthranilic acid)+ Metal Chloride	K $[M(L_3)(Anth)]$ M= Co(II),Ni(II),Cu(II),and Cd(II) $[M'(L_3)(Anth)_2]$, M'=Cr(III),Fe(III)

3) The antibiotics Trimethoprim as primary ligand with Anthranilic acid (AnthH) , L-proline (ProH) and L-alanine (AlaH) as a secondary ligands with M(II) shown table below:

	Mixed ligand-Metals Complexes	Compositions
Trimethoprim Drug (TMP)	Trimethoprim+ amino acid (Anthranilic acid) + Metal Chloride	[M $(Anth)_2$ (TMP) (H_2O)] M=Co(II), Ni(II), Cu(II), Zn(II),Cd(II) and Hg(II)
	Trimethoprim+ amino acid (L-prolin)+ Metal Chloride	[M $(Pro)_2$ (TMP)(H_2O)] M=Co(II), Ni(II), Cu(II), Zn(II),Cd(II) and Hg(II)
	Trimethoprim+ amino acid(L-Alanine)+ Metal Chloride	[M $(Ala)_2$ (TMP)(H_2O)] M=Co(II), Ni(II), Cu(II),Zn(II),Cd(II), and Hg(II)

Products were found to be solid crystalline complexes, which have been characterized through the following techniques :Molar conductivity ,Spectroscopic Method (FT-IR), (UV- Vis) and A.A additional measurement magnetic suspeliblity.

The measurement magnetic suspeliblity with the electronic spectra data suggested an octahedral geometry for all the complexes .The antimicrobial activity of the synthesized compound as well as their free ligands was studied by the zone of inhibition (ZI) technique .

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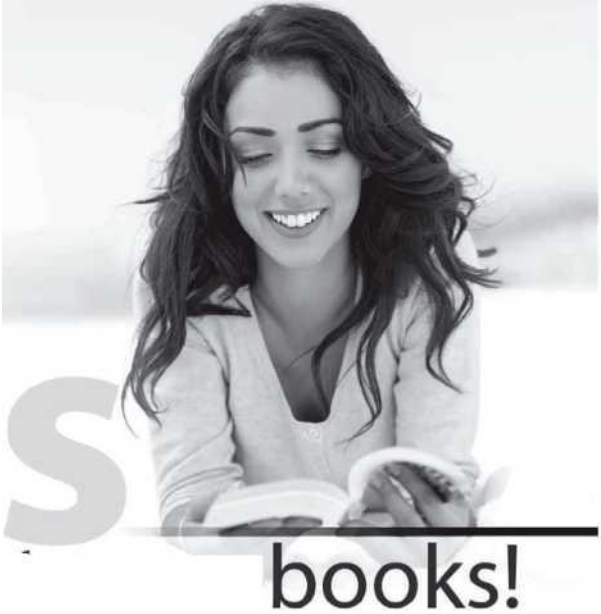

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