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Coordination chemistry and biological activity of different types of antibiotics

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ABSTRACT

Metal complexes of antibiotics have powerful antimicrobial activities and are used in medicinal field such as silver bandages for treatment of burns, zinc antiseptic creams, bismuth drugs for the treatment of ulcers and also as anti-HIV drugs. The chelating properties of metals were used to prepare metal complexes of all the classes of antibiotics as metalloantibiotics. Although most antibiotics do not need metal ions for their biological activities but, there are some of antibiotics that require metal ions for maintaining proper structure and/or function of these antibiotics, such as bleomycin, streptonigrin and bacitracin. Metalloantibiotics can interact with several different kinds of biomolecules, including DNA, RNA, proteins, receptors, and lipids, rendering their unique and specific bioactivities. In addition to antimicrobial activity of metalloantibiotics, also show antiviral and antineoplastic activities which provide a various function of the term metalloantibiotics. Bismuth-fluoroquinolone complexes have developed as drugs against H. pylori related ailments. Antibiotics metal complexes and the mixed antibiotics metal complexes were found more effective as chemotherapy agents than their parent antibiotics.

INTRODUCTION

1. Metal complexes of cephalosporin based antibiotics:
1.1 First generation cephalosporin metal complexes:
1.1.1 Cephradine:

Cephradine is active against a wide range of Gram-positive and Gram-negative bacteria including penicillinase-producing *Staphylococci*. The synthesis and spectral characterization of cephradine –tin (II) complex of general formula [Sn (L) Cl] (L=cephradine) is characterized by physicochemical and spectroscopic methods (Figure1). The spectrum of the formed tin complex indicates that cephradine act as multidentate ligand via the amide and lactam carbonyl and carboxylate which, probably have a polymeric structure and showed an enhancement of the antibacterial activity [1-3]. Also, cytotoxicity and antibacterial activities of cephradine- tin complex was investigated against Artemia salina (brine shrip) and four bacterial strains which gives an increase in antibacterial activity compared to the parent cephradine [4].

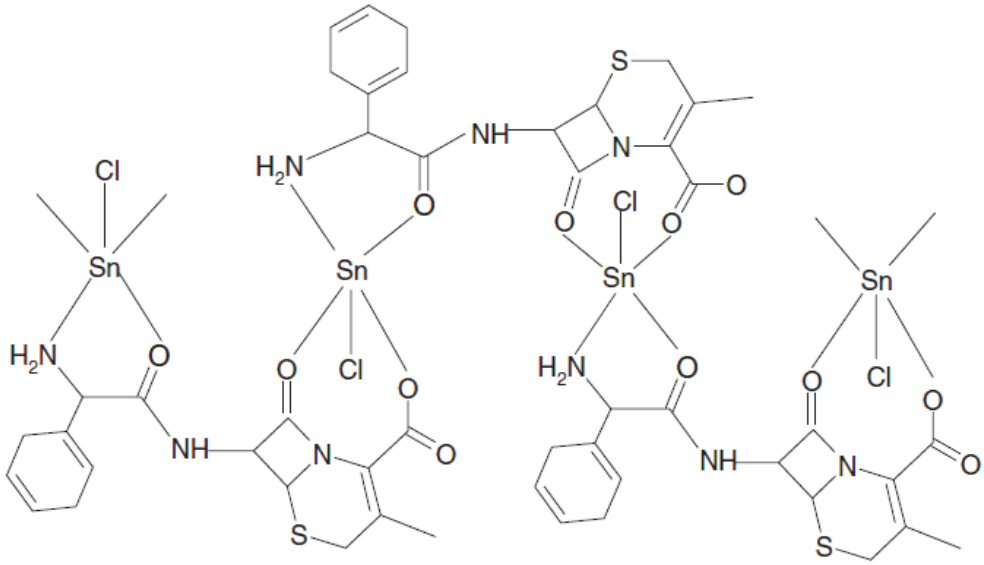


Figure 1 Suggested structure of cephradine- tin complex

Cephradine reacts with $VOSO_4.3H_2O$ in 1:1, 1:2 and 1:3 molar ratios in methanol at three different temperatures (25°C, 0°C and -10°C). Three complexes formulated as $VO(H_2O)_3L^{2-}$, $VO(H_2O)L_2^{2-}$ and VL_3^{-} (Figure 2) were formed and characterized by elemental analysis and IR spectroscopy. Biological screening tests show significant antibacterial and anti-fungal activities against various bacterial and fungal strains [5].

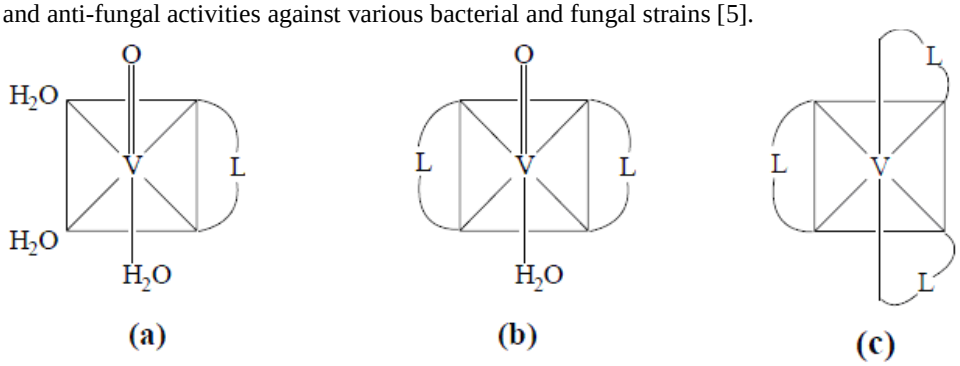


Figure 2 Proposed structures of oxovanadium (IV) complexes in (a)1:1, (b)1:2 and (c) 1:3

Solid complexes of cephradine with Mg (II), Ca (II), Mn (II), and Cr (III) [6] and Co (II), Cu (II), Zn (II) and Cd (II) [7] were obtained (Figure 3).These complexes were studied by spectral and elemental analysis. Cephradine coordinates as a bidentate ligand via the beta-lactam (N atom) and carboxylate groups. Complex formation was shown to decrease antibiotic activity.

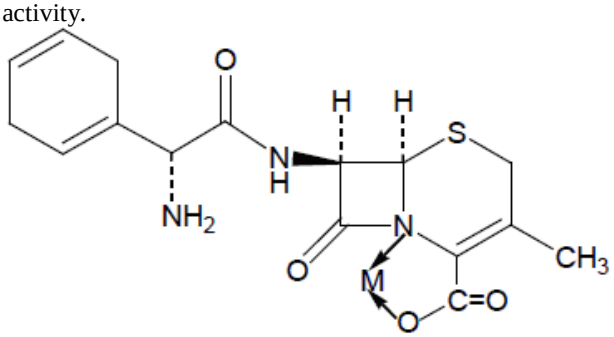


Figure 3 Proposed structure of cephradine metal complex, M= Mg (II), Ca (II), Mn (II), Cr (III),Co (II), Cu (II), Zn (II) and Cd (II)

Also, some complexes of cephradine with Fe (III) as ($FeLCl_2$) and Mn (II), Co(II), Ni(II), Cu(II), and Zn(II) as (MLCl) were synthesized and coordinated with metal ions via the amine, beta-lactam (O atom), and carboxylate groups (Figure 4), All the complexes studied had lower antimicrobial activity than cephradine itself [8].

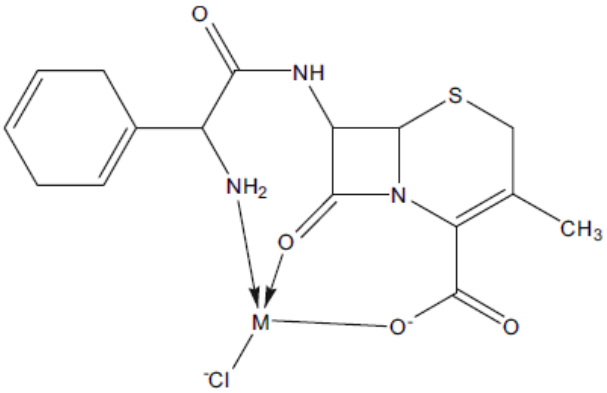


Figure 4 Structure of cephradine metal complex M= Mn (II), Co(II), Ni(II), Cu(II) and Zn(II)

Some Co (II), Cu (II), Ni(II) and Zn(II) complexes of antibacterial drug cephradine have been prepared (Figure 5). Complexes formed in 1:2 (M:L) molar ratio in octahedral geometry, but copper complex in square planar geometry (Figure 5). Cephradine and its complexes have been screened for their antibacterial activity against bacterial strains, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [9].

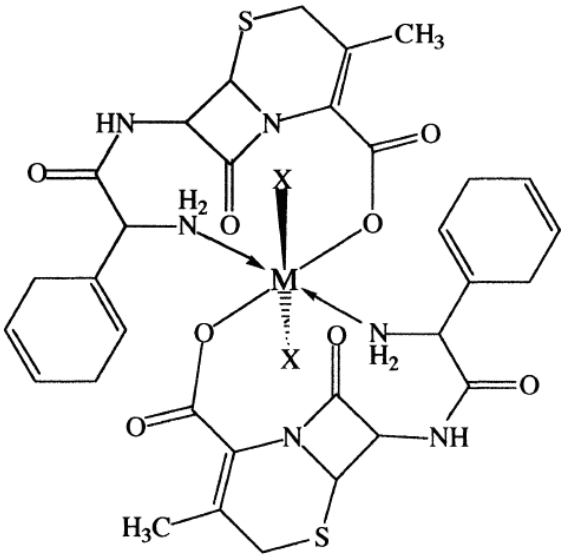


Figure 5 Proposed structure of 1:2 metal complexes of cephradine M=Co (II), Ni(II), and Zn(II),X=Cl, M=Cu(II),X=0

Also, complexes of tin(II), lead(II), manganese(II) and iron(II) with antibacterial cephradine have been synthesized and characterized by elemental analysis, IR, electronic, magnetic and NMR spectral studies with 1:2 (M:L) molar ratio in octahedral geometry. Cephradine and its complexes have been screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [10].

1.1.2 Cephadroxil: It is a semi-synthetic first generation cephalosporin which recommended for oral use, which have antibacterial activity against different kinds of bacteria. Solid complexes of cephadroxil with Fe(II), Fe(III), Co(II), Ni(II), Cu(II),Zn(II), Co(III) of composition ML and M(OH)L. Cephadroxil coordinates with metal ions via beta-lactam (O and N atoms) and the carboxylate group (Figure 6) [11].

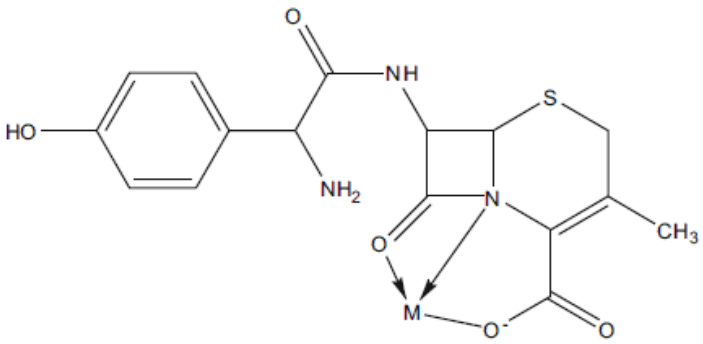
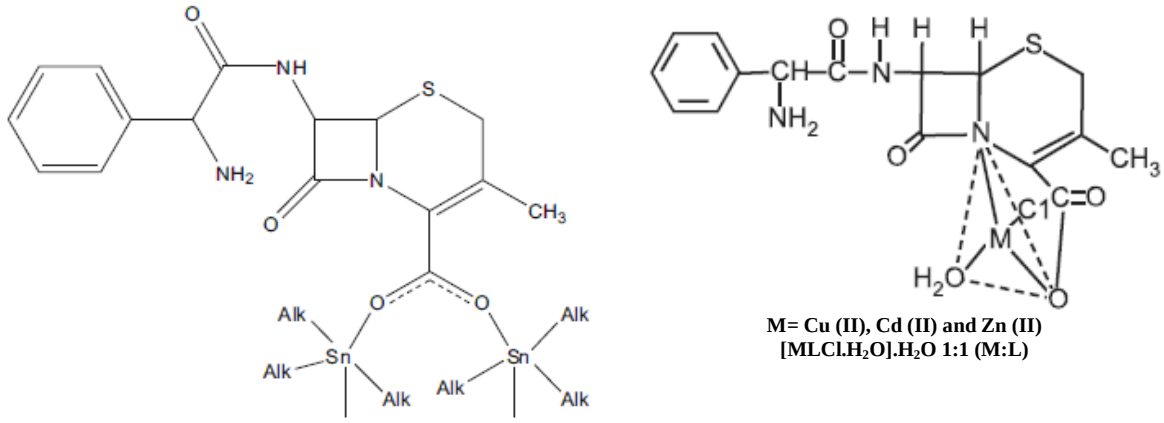


Figure 6 General structure of cephadroxil metal complex

The effect of Zn^{2+}, Cu^{2+} and Al^{3+} ions on the antibacterial activity of cephadroxil was tested. It was found that there is no significant difference between the activity of cephadroxil and its metal complexes studied towards the investigated bacterial species [12]. Potentiometic studies was used for determination of stability constants of complexes of cephadroxil with Cu^{2+}, Ni^{2+},Co^{2+}, Zn^{2+}, Mn^{2+}, Hg^{2+}, Cd^{2+}, Ca^{2+}, and Mg^{2+}, as well as the formation of ternary complexes with amino acids, Table1 [13].

1.1.3 Cephalexin: Complexes of cephalexin with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) of composition $MLCl.3H_2O$ were synthesized with molar ratio of 1:2 (M:L) [14]. Cephalexin act as a tridentate ligand coordinated in Ni(II), Cu(II) and Zn(II) complexes via the amine, amide (O atom) and carboxylate group, however, Mn(II) and Co(II) complexes via the amine beta-lactam (O atom) and carboxylate group while, Hg(II) and Cd(II) complexes via the amine, amide (O atom) and thioester group. It was found that Cu (II), Zn(II) and Hg(II) complexes had increased antimicrobial activity as compared with cephalexin. Solid complexes of cephalexin with organotin cations Alk_3Sn^+, where Alk = Me or n-Bu were prepared with a composition of 1:2 (M: L) molar ratio (Figure 7). [15]. Cephalexin formed complexes with Cu (II), Cd (II) and Zn (II) in 1:1 molar ratio M:L [16].

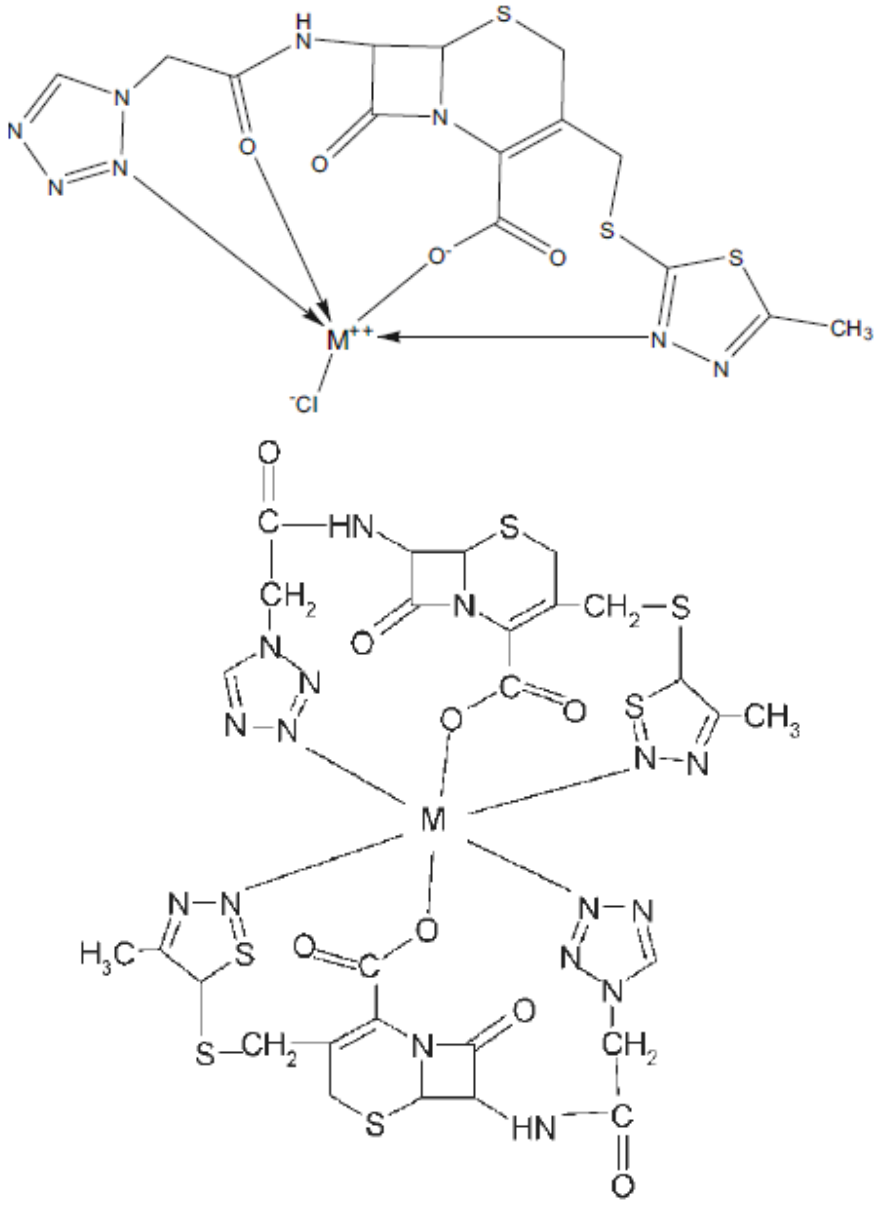


M= Cu (II), Cd (II) and Zn (II)
$[MLCl.H_2O].H_2O$ 1:1 (M:L)

7 A **7B**

Figure 7 Proposed structures of cephalexin metal complexes

1.1.4 Cephazolin: Complexes of cephazolin with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Pd(II) were synthesized [17-19]. Complexes of composition 1:1 and 1:2 were formed via the carboxylate, amide group O atom and the N atom of the heterocyclic side chain. Pd (II) also coordinated with cephazolin via the beta-lactam O atom (Figure 8A & B).

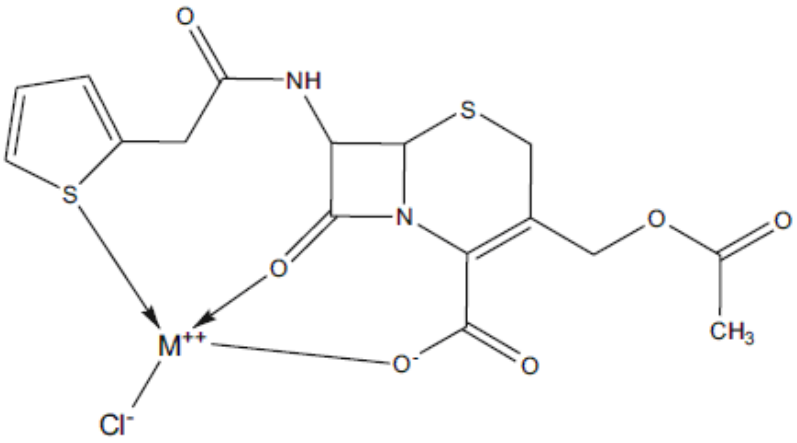


8A
M= Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)

8B
M= Co(II), Ni(II) and Zn(II)

Figure 8 Proposed structures of cephazolin metal complexes

1.1.5 Cephalothin: Complexes of cephalothin with Mn(II), Co(II), Ni(II) and Pd(II) were prepared with 1:1 (M:L) molar ratio and coordinated via the carboxylate and beta-lactam group O atoms and the S atom of the heterocyclic side chain [19-20] (Figure 9).



M= Mn(II), Co(II), Ni(II), and Pd(II)

Figure 9 Proposed structures of cephalothin metal complexes

1.2 Second generation cephalosporin metal complexes:

1.2.1 Cefaclor: Complexes of cefaclor with transition metal (II) ions such as Cu(II), Co(II) and Ni(II) to form complexes of the type [M(L)(H_2O)Cl] with molar ratio 1:1 (M:L). Cefaclor acts as a bi-dentate ligand. The UV-Vis spectra of cefaclor and its Cu(II), Co(II) and Ni(II) complexes present two absorption maxima at 265 and 301nm assigned to π- π * and n- π * transitions within the organic ligand. The spectra of the complexes contain same absorption bands in the range 588-428 nm (relatively weak, low energy bands), which may be assigned to the d-d* transition in a tetrahedral configuration. The μ_{eff} values have been found 1.70, 4.20 and 3.05 for [Cu (CEF) H_2O C)], [Co (CEF) H_2O Cl], and [Cu(CEF) H_2O Cl], respectively. The complexes have been screened for antibacterial activity and compared with the activity of the uncomplexed antibiotic.The copper complex was found to be more potent against bacterial species than the uncomplexed cefaclor (Figure 10) [21].

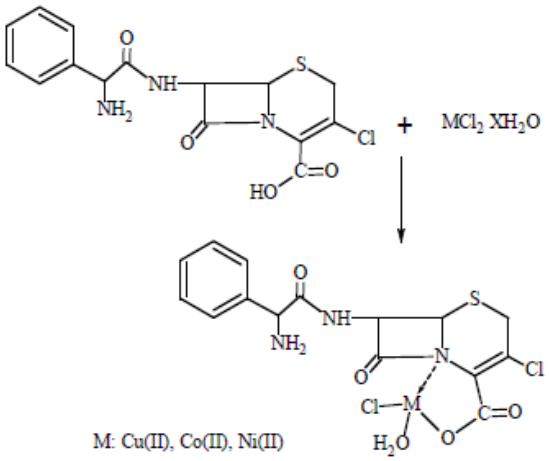


Figure 10 Proposed structure of cefaclor metal complex

Spectrophotometric methods were used to study complexes of cefaclor with Cu^{2+} and Ni^{2+} [22-24]. CuL^+ complexes (λ_{max}= 300 nm, ε = 2670 liter. $mol^{-1}.cm^{-1}$) and NiL formed in mildly acidic medium and easily hydrolyzed in mildly alkaline medium to Cu(OH)L and Ni(OH)L. At pH 8.7, the complex Ni(OH)L had λ_{max} = 316 nm and ε = 1120 liter. mol^{-1}. cm^{-1}. The presence of Cu (II) was found to have virtually no influence on the rate of hydrolysis of cefaclor. Solid complexes with Co (II) and Ni(II) had greater antimicrobial activity than cefaclor [25].

1.2.2 Cefoxitin: It interacts with transition metal ions to give 1:1(M:L) complexes [M = Fe(III), Co(II), Ni(II),Cu(II), Zn(II) and Cd(II)] (Figure 11) with a tetrahedral geometry, where the cefoxitin behaves as a monoanionic tridentate ligand. The complexes have been screened for antibacterial activity against several bacteria, the results showed that they are less active than the parent cefoxitin [26].

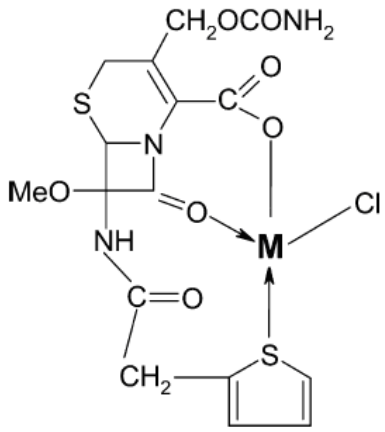


Figure 11 Structure of the cefoxitin metal complexes [M (cefoxi) Cl], [M = Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)]

1.2.3 Cefomandole and cefuroxime: Solid complexes of cefomandole and cefuroxime with Cd (II) and Cu(II) of composition 1:2 (M:L) molar ratio [27-28]. These complexes were studied by elemental analysis, IR spectroscopy and thermal analysis. These data led to the conclusion that antibiotic anions were coordinated via the O atom of the carboxylate group and the beta-lactam group N atom (Figure 12).

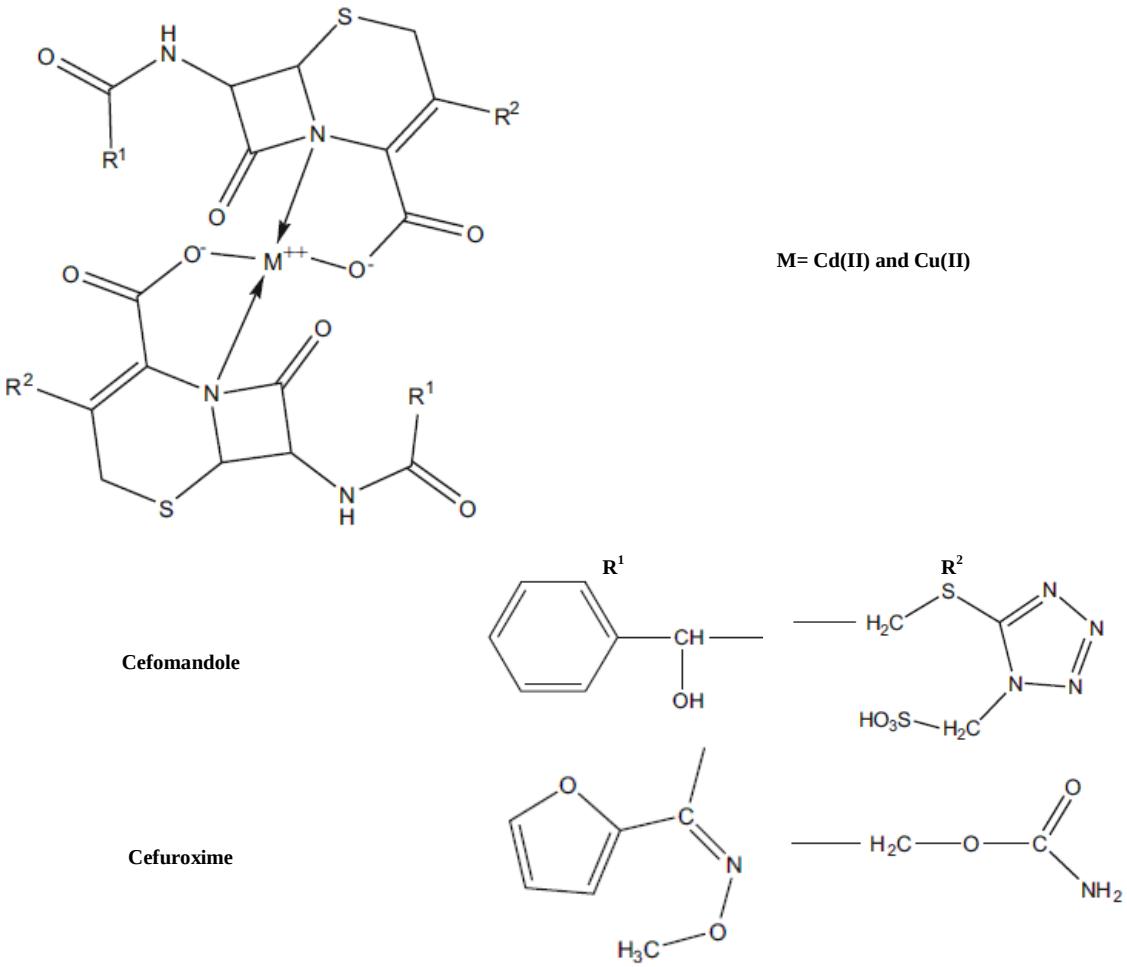
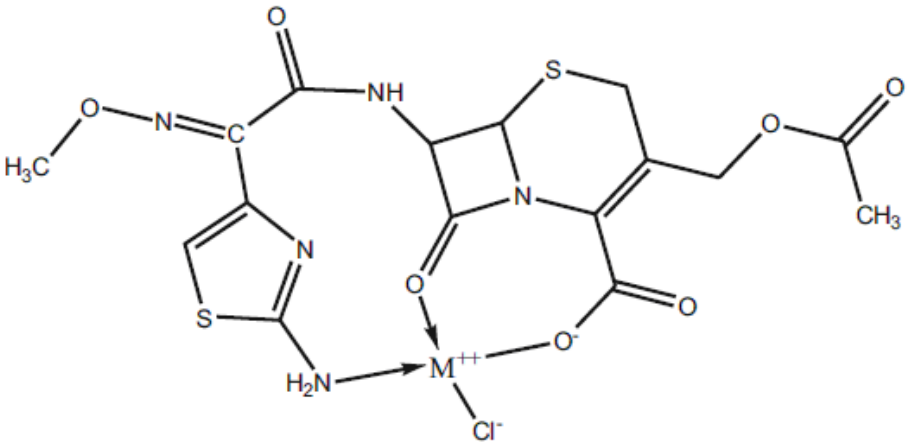


Figure 12 General structure of cefomandole and cefuroxime metal complexes

1.3 Third generation cephalosporin metal complexes:

1.3.1 Cefotaxime: Complexes of cefotaxime with Mn(II),Co(II), Ni(II), Cu(II) and Cd(II) of composition MLCl and the complex $FeLCl_2$ were synthesized with a molar ratio M:L (1:2), the ligand was coordinated via the carboxylate, beta-lactam (O atom) and aminothiazole (NH_2) group (Figure 13). Cu (II) complexes had increased antimicrobial activity as compared with cefotaxime [29].

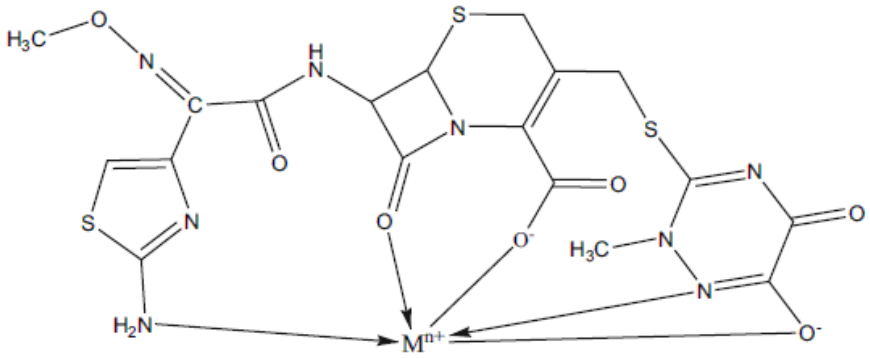


M= Mn(II),Co(II), Ni(II), Cu(II), and Cd(II)

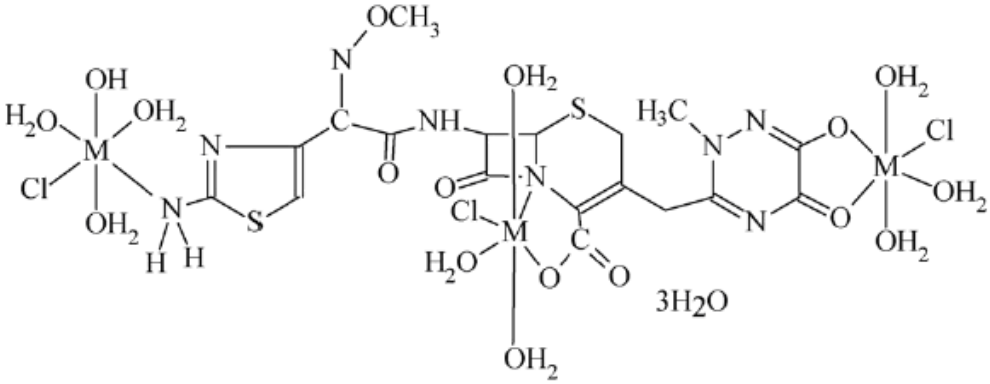
Figure 13 Proposed structure of cefotaxime metal complex

1.3.2 Ceftriaxone:

Ceftriaxone complexes with Mn (II), Co(II), Cu(II), and Cd(II) were synthesized in 1:1 (M:L) molar ratio via a pentadentate coordination of the ligand to the metal ions (Figure 14A) [30]. Microbiological examination showed that the Cd(II) complex had greater activity than ceftriaxone, while the activities of the other complexes were similar to that of ceftriaxone.



14 A
M=Mn(II),Co(II), Cu(II),andCd(II) (1:1)



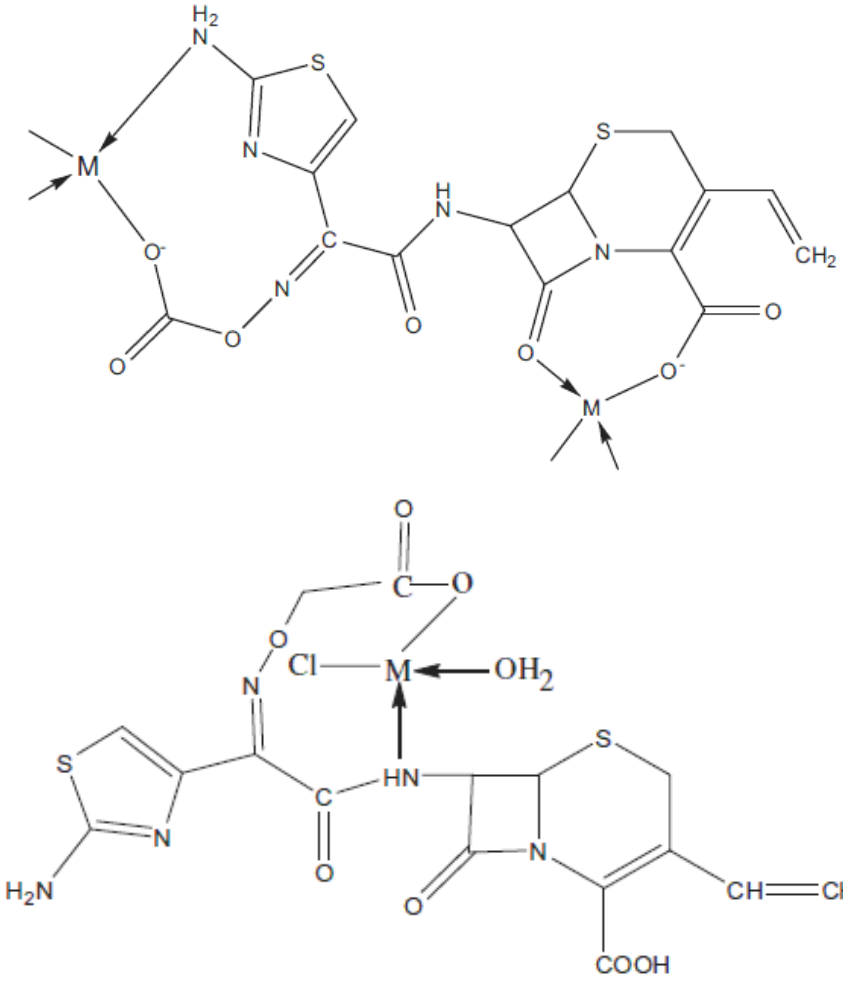
14B

M= Co(II),Ni(II), and Cu(II) (3:1)

14C

Figure 14 Structures of ceftriaxone metal complexes

Also, Iron, cobalt, nickel and copper complexes of ceftriaxone were prepared of a composition 1:3 (L:M) molar ratio with Oh geometry (Figure 14B) [31]. The antimicrobial activities of the complexes were examined and compared to that of the ceftriaxone itself.



15A
M=Mn(II), Co(II),Ni(II), and Cd(II)

15B
M=Ni(II), Cu(II), Zn(II) and Cd(II)

Figure 15 Structures of cefixime metal complexes

1.3.3 Cefixime: Complexes of cefixime with Mn(II), Co(II), Ni(II) and Cd(II) of composition1:1(M:L) were prepared [32-33]. Their compositions were identified by elemental analysis, IR and EPR spectra and UV/Visual spectra for suspensions in nujol. (Figure 15A). Also, Cu(II), Zn(II), Cd(II), Fe(III) and Ni(II) have been synthesized (Figure 15B), the prepared complexes exhibit square planar geometry, except Fe (III) complex, which exhibits octahedral geometry. The complexes showed a slightly higher antimicrobial activity than the cefixime drug. Among the metal complexes, Fe (III) was found to be more active than other complexes when tested against bacterial species *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa* and fungal species *Aspergillus niger*, *Rhizopus stolonifer*, *Aspergillus flavus*, *Rhizoctonia bataicola* and *Candida albicans* [34]

1.3.4 Ceftazidime: It interacts with transition metal (II) ions to give octahedral complexes with [M=Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Cd(II)] in 1:1(M:L) molar ratio. The formed complexes probably have polymeric structures (Figure 16). The antibacterial activity of the metal complexes was lower than that of free ceftazidime [35].

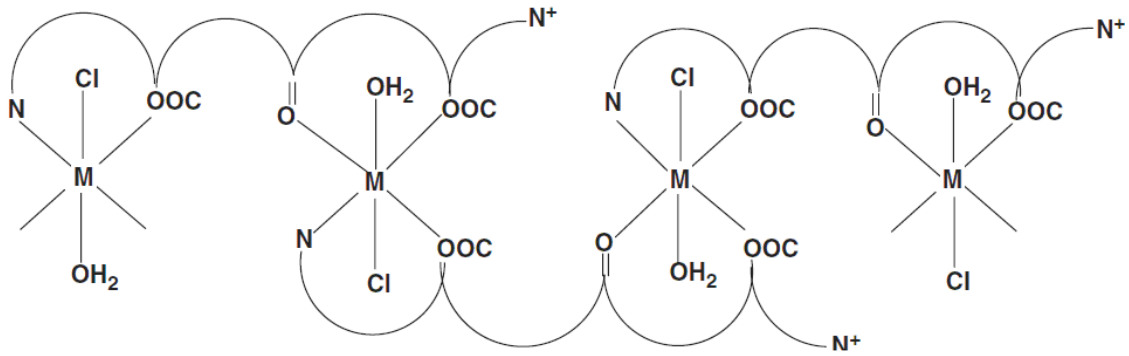
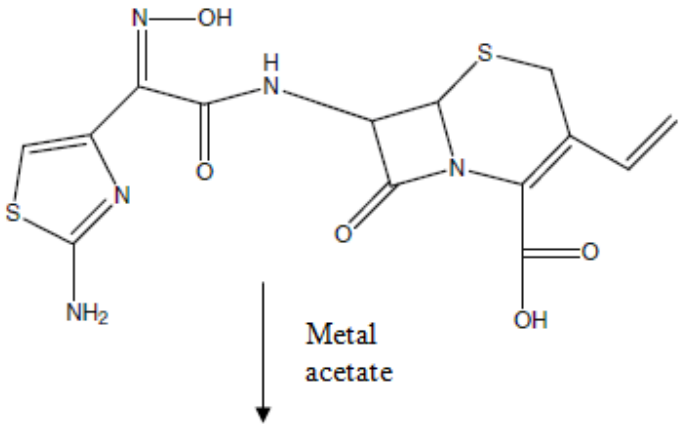


Figure 16 Suggested structure of [M (L)(H_2O)Cl] complexes

1.3.5 Cefdinir: Cefdinir metal complexes with Cu (II) and Zn (II) were described and characterized on the basis of analytical and spectral studies (Figure 17). The prepared complexes were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*. The result showed that the metal complexes possessed the better antibacterial activity against the selected species of bacteria than cefdinir, so, these metal complexes could be applied in the treatment of common bacterial infections [36].

The interaction between cefdinir with Fe (II) and Fe (III) was done by potentiometric and spectrophotmetric methods, where 1:1, 1:2 and 1:3 (M:L) complexes were observed[37], where Fe(II) coordinated with cefdinir via the thiazole ring and the oxime group nitrogen, while Fe(III) coordinated the ligand via the amide and oxime group oxygen. cefdinir did not form complexes with Ca(II) [38].



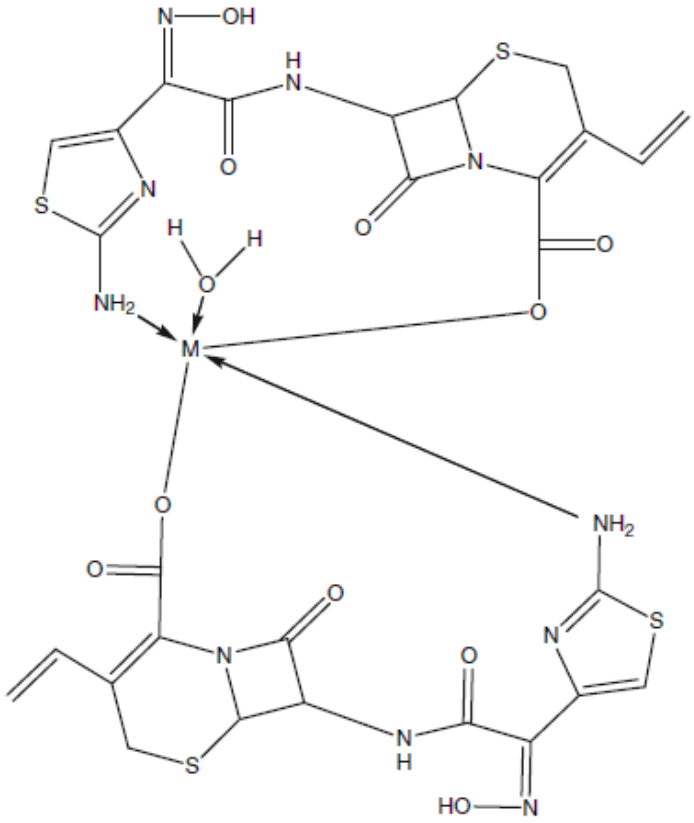


Figure 17 The synthesis of metal complexes of cefdinir M = Cu (II) and Zn(II)

1.3 Fourth generation cephalosporin metal complexes:

1.3.1Cefepime: It is a parenteral cephalosporin that has been described as a fourth generation broad-spectrum antibiotic [39-40]. It is active against some bacteria that are resistant to other antibiotics and used to treat Gram-negative and Gram-positive bacteria especially those causing infections in the lungs, kidneys, bladder, skin, and abdomen [41-42]. Cefepime interacts with transition metal (II) ions to give 1:1(M:L) complexes with (M=Mn(II), Co(II), Ni(II), Cu(II), and Zn(II)), which were characterized by physicochemical and spectroscopic methods (Figure 18). The complexes have been screened for antibacterial activity against several bacteria and showed activity less than that of free cefepime [43].

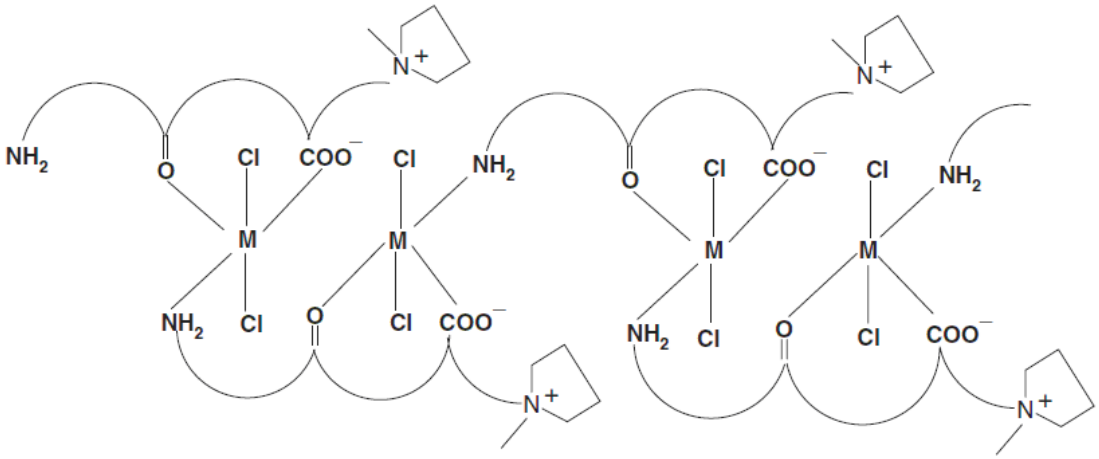
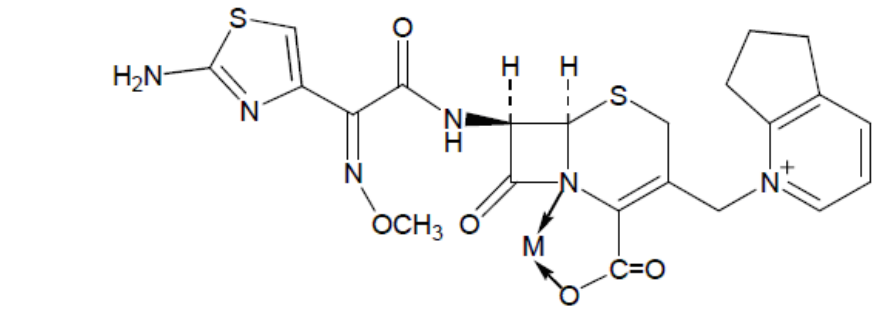
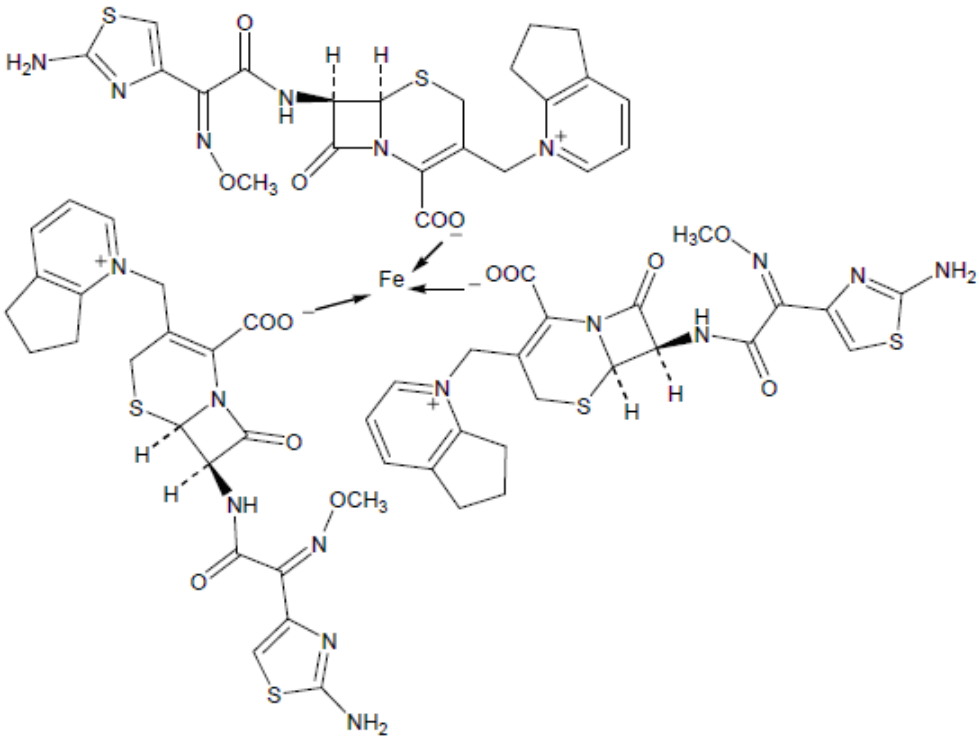


Figure 18 Suggested structure of cefepime metal complexes, M=Mn(II), Co(II), Ni(II), Cu(II), and Zn(II)

1.3.1 Cefpirome: Complexes of cefpirome with Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) were prepared with 1:1 molar ratio via the carboxylate group of dehydrothiazine ring and β-lactam nitrogen (Figure 19A) [44]. The maximum complexation were observed with ferric and chromium chloride with 1:3 molar ratio (Figure 19B). The stability constant of some selected cephalosporin are summarized in Table1.



19A
M=Co(II), Ni(II), Cu(II), Zn(II) & Cd(II)



19B

Figure 19 Proposed structures of cefpirome metal complexes

Table 1 Stability constant of some selected cephalosporins metal complexes

Antibiotic	Complex	Log β	Conditions of identification
Cephradine[45]	UO_2L^+	5.78 ± 0.07	25°C, 0.1 M $NaNO_3$, potentiometry
Cephalexin [46-51]	MnL^+	0.75 ±0.06	
	Mn(OH)L	6.0±0.1	
	CoL^+	1.83 ±0.02	
	Co(OH)L	7.97 ±0.03	
	NiL	2.38 ±0.02	
	Ni(OH)L	8.41 ±0.03	
	ZnL^+	1.86 ±0.02	
	Zn(OH)L	8.84 ±0.04	
	CdL	1.58 ±0.03	
	Cd(OH)L	7.93 ±0.04	
	$Al(OH)L^+$	14.1 ±0.1	
	$Al(OH)_2L$	23.9 ± 0.1	
	NdL^{2+}	2.78 ± 0.04	
	$Nd(OH)L^+$	8.8 ± 0.1	
	UO_2L^+	4.76±0.15	25°C, 0.1 M $NaNO_3$, potentiometry
	UO_2(-H)L	0.43± 0.05	
	CuL_2	9.44	25°C, *I* = 0.2, pH 8.7, polarography
	CoL^+	3.09	25°C, *I* = 0.2, pH 7.5, polarography
	NiL^+	3.16	
	CaL^+	3.47	25°C, 0.1 M KNO_3, potentiometry
	ZnL^+	4.41	
	PbL^+	4.98	
	LaL^{2+}	5.57	
	CuL^+	6.06	
	CaGlyL	8.97	25°C, 0.1 M KNO_3, potentiometry
	ZnGlyL	10.61	
	PbGlyL	11.40	
	CuGlyL	13.11	
	NiGlyL	8.13 ±0.05	20°C, 0.1 M KNO_3, potentiometry
	CoGlyL	6.42 ±0.05	
Cephadroxil [13,51]	CuL	8.11 ± 0.01	25°C, 0.1 M $NaNO_3$, potentiometry
	$CuHL^+$	12.89 ± 0.11	
	NiL	3.72 ± 0.03	
	$NiHL^+$	11.62 ± 0.05	
	CoL	3.12 ± 0.03	
	$CoHL^+$	10.87 ±0.14	
	CdL	3.85 ± 0.04	
	$CdHL^+$	11.58 ±0.09	
	CaL	2.61 ± 0.05	
	$CaHL^+$	11.18 ± 0.09	
	BaL	3.10 ± 0.05	
	$BaHL^+$	11.75 ±0.07	
	MnL	3.78 ± 0.07	
	$MnHL^+$	11.73± 0.12	
	MgL	1.93 ± 0.09	
	$MgHL^+$	10.66 ± 0.17	
	HgL	6.96 ± 0.01	
	$HgHL^+$	13.14 ± 0.07	
	CaL	3.6	25°C, spectrophotometry
	ZnL	4.81	
	PbL	5.67	
	PbL	5.87	
	CuL	9.2	
Ceftriaxone [52-53]	CuL	2.5	30°C
	(VO)L	2.5	
	Pd_2L	6.06	25°C, spectrophotometry
	CuL	2.5	30°C
	(VO)L	2.5	
	Pd_2L	6.06	25°C, spectrophotometry
Ceftizoxime [52-53]	CuL	2.5	30°C
	(VO)L	2.5	
	Pd_2L	6.52	25°C, spectrophotometry

Cefpodoxime[53]	Pd_2L	6.51	25°C, spectrophotometry
Ceftazidime[53]	Pd_2L	6.74	
Cefoperazone[51]	CaL^+	4.27	25°C,0.1M KNO_3, potentiometry
	ZnL^+	5.97	
	PbL^+	6.70	
	LaL_2^+	7.01	
	CuL^+	7.50	
Cefixime [51]	Pd_2L	6.53	
Cephaloridine [51]	CaL^+	3.75	20°C, 0.1M KNO_3, potentiometry
	ZnL^+	5.25	
	pbL^+	8.00	
	LaL_2^+	8.55	
	CuL^+	8.7	
Cefdinir [37]	$Fe^{II}L$	7.53	
	$Fe^{II}L_2$	14.44	
	$Fe^{II}L_3$	18.33	
	$Fe^{III}L$	10.43	
	$Fe^{III}L_2$	20.40	
	$Fe^{III}L_3$	27.54	

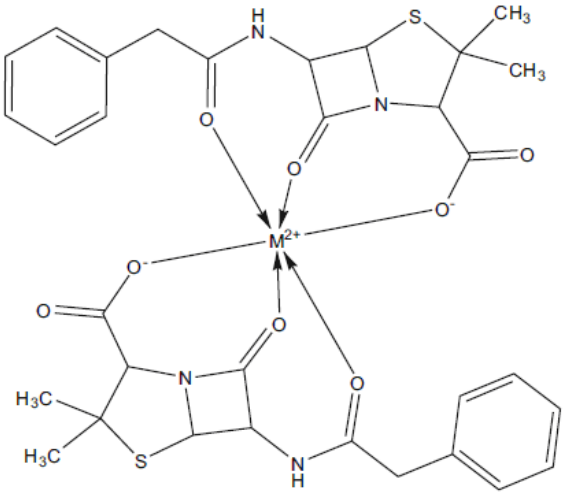
2. Metal complexes of penicillin based antibiotics:

2.1 Benzyl penicillin and methyl penicillin:

Solid complexes of benzyl penicillin with Ni(II), Zn(II), Cd(II), Fe(III) and La(III) were formed in aqueous solutions, where Fe(III) and La(III) complexes coordinated via the O atoms of the carboxylate and amide groups, while coordination in Ni(II), Zn(II) and Cd (II) complexes involve the O atoms of the beta-lactam group (Figure 20 A) [54].

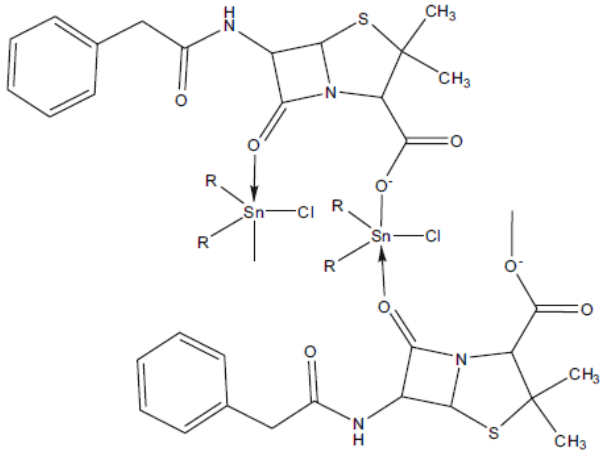
Benzyl penicillin with R_2SnCl_2 and R_3SnCl (R= Me, Bu, Ph) were prepared (R_2SnCl L and R_3SnClL) and characterized by IR spectroscopy and elemental analysis. The coordination of bezyl penicillin to the metal ions via the beta-lactam O atom and the carboxylate atom O group (Figure 20B), while, in the R_3SnClL complex, the benzyl penicillin anion behaved as a monodentate ligand coordinated via the beta-lactam O atom. The complexes were monomeric but linked to each other via amide group hydrogen bonds [55]. The interaction of benzyl penicillin with Cu^{2+} ions in aqueous solution was studied by an ion exchange method. The formation constants of CuL^+ and CuL_2 complexes were determined in which the chelation occurs through the O atom of the carboxylate group and the N atom of the beta-lactam group (Figure 20C) [56].

20A



M= Ni(II),Zn(II) and Cd(II)

20B



$M=R_2SnCl_2$

20 C

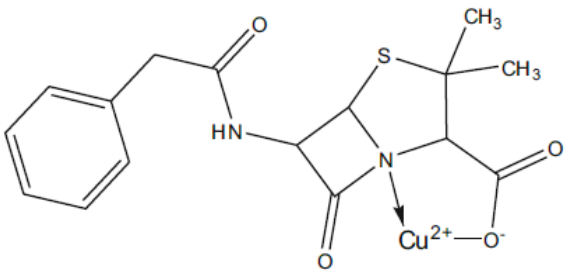


Figure 20 Proposed structure of metal-Benzyl penicillin and methyl penicillin complexes

2.2 Methicillin: Tin complexes of methicillin ($R_2SnClL.\ H_2O$) were coordinated via the carboxylate and beta-lactam O atoms with formation of a chelate ring [57] (Figure 21).

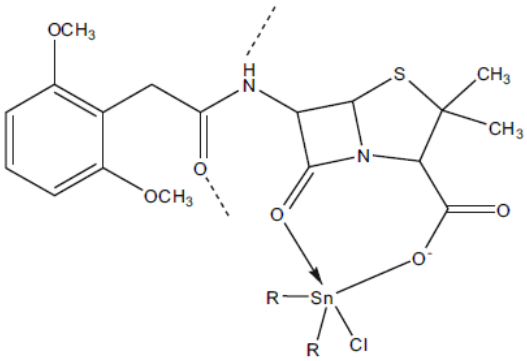


Figure 21 Proposed structure of tin methicillin complex

2.3 Cloxacillin: Zn (II) and Co (II) complexes with the anionic cloxacillin were prepared [58]. It is coordinated with Zn^{2+} ion via the oxygen atoms of the amide and beta-lactam group (Figure 22). Also, the complexes of cloxacillin with Cu(II), Ni(II), Co(II) and Zn(II) were performed and the coordination occur through the carboxylate group and the N atom of the beta-lactam group [59].

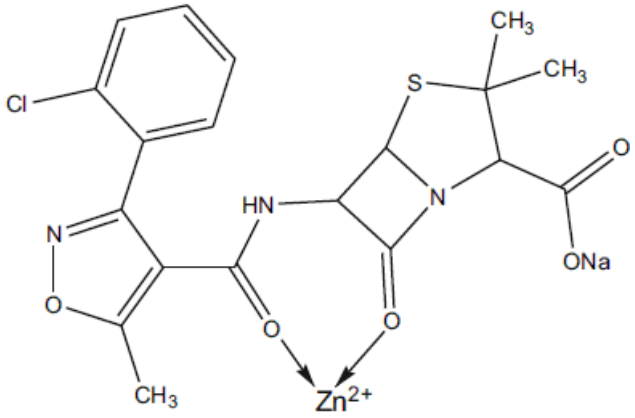


Figure 22 Proposed structure of Zn (II)- cloxacillin complex

2.4 Dicloxacillin: Solid complexes of dicloxacillin with Cu (II), Co(II), Ni(II), Fe(II), and Fe(III) were prepared and coordinated via the carboxyl group O atom and the beta-lactam group N atom [60].

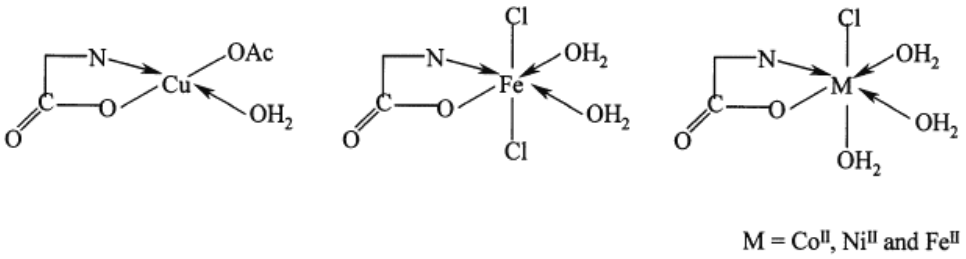
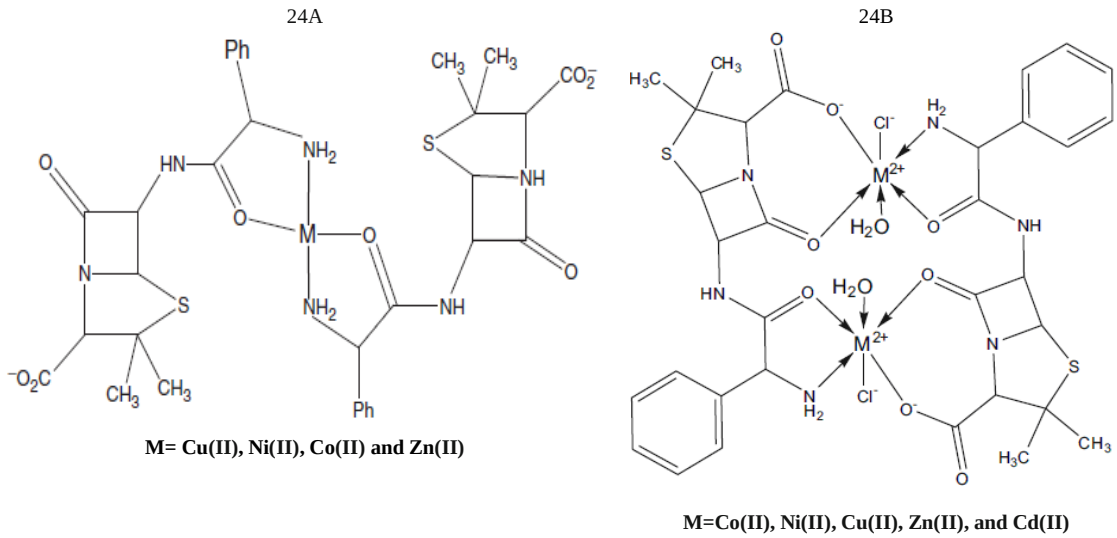


Figure 23 Structural formula of dicloxacillin metal complexes

2.5 Ampicillin: The coordination of ampicillin with Cu, Ni, Co and Zn via the amino group and the amide carbonyl oxygen atom was suggested in Figure 24A [61-63]. Solid dimeric complexes of ampicillin with Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) of composition $(MLCl)_2.2H_2O$ with a molecular ratio of 1:1 in which the ligand was coordinated via amino, amide (O atom), beta-lactam (O atom) and carboxylate groups Figure 24B [64].



M= Cu(II), Ni(II), Co(II) and Zn(II)

M=Co(II), Ni(II), Cu(II), Zn(II), and Cd(II)

Figure 24 Proposed structures of metal- ampicillin complexes

2.6 Amoxicillin: Solid complexes of amoxixillin with Cu(II), Ni(II), Cu(II), Zn(II), Fe(II) and Fe(III) were prepared at pH 8.5 [65]. It was found that amoxicillin coordinates via the amine, amide (N atom) and beta-lactam (O atom) groups (Figure 25). Also, complex formation in amoxicillin solution with Mn^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+} and Cd^{2+} cations was studied [66-68].

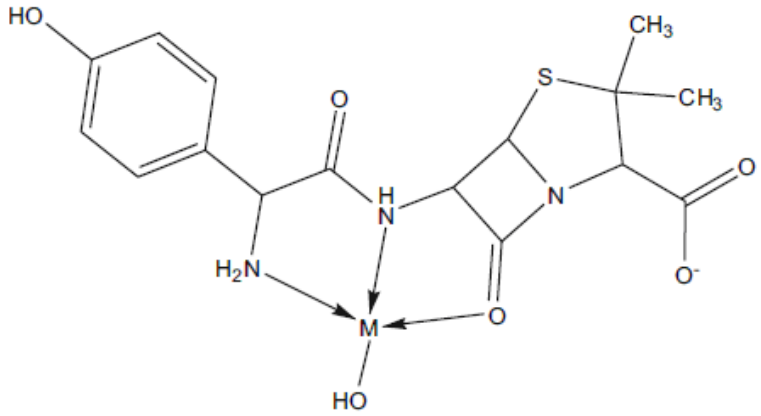


Figure 25 Proposed structures of metal- amoxicillin complex

Table 2 The stability constant β of some selected penicillin

Antibiotic	Complex	Logβ	Condition of identification
Benzylpenicillin [56,69-71]	CuL^+	4.8	25°C, ion exchange
	CuL_2	7.1	
	CuL^+	2.61± 0.01	30°C, I=0.01
	CuL^+	2.65	37°C, spectrophotometry
	NiL^+	1.74	25°C, 0.15M $NaClO_4$, potentiometry
Methicillin[70]	CuL^+	2.91	37°C, spectrophotometry
Phenoxymethyl penicillin [69,72-73]	CuL^+	2.09±0.09	30°C, I=0.01
	AgL	4.8	20°C, I=0. 1
	pbL^+	4.9	
	ZnL^+	4.9	
	CoL^+	1.67	20°C, methanol, spectrophotometry
	CoL_2	5.76	
Ampicillin [45,47,61-62,66,74-81]	CuL^+	1.62	25°C, 0.1M KCl, potentiometry
	CuL_2	1.77	
	$Fe^{III}L_2^+$	6.08	
	$Fe^{III}L_2^+$	6.13	
	ZrL^{3+}	12.47	
	$ZrL2^{2+}$	20.62	
	$CoAmp^+$	3.21±0.04	37°C, 0.1M $NaCO_3$, potentiometry
	NiL^+	3.66±0.04	
	CuL^+	4.79±0.04	
	ZnL^+	2.98±0.04	
	CuL^+	5.0	25°C
	CuL_3^-	14.5	
	CuL^+	5.11±0.05	25% ethanol,25°C, 0.3M KCl, potentiometry
	CoL^+	8.46±0.05	
	NiL^+	3.25±0.05	
	FeL^+	3.28±0.05	
	FeL_2	6.87±0.05	
	HgL^+	11.43±0.05	
	pbL^+	3.16±0.05	
	ZnL^+	3.28±0.05	
	CdL^+	3.32±0.05	
	CaL^+	3.13±0.05	
	Uo_2L^+	5.78±0.05	25°C, 0.1M $NaNO_3$, potentiometry
	$UO_2(-H)L$	1.64±0.08	
	AgL	3.37±.02	25°C, 0.1M KNO_3, potentiometry
	AgL_2^-	6.24±0.05	
	MnL^+	2.78±0.04	

	CoL^+	3.68±0.04	
	NiL	4.25±0.03	
	NiL_2	7.54±0.08	
	ZnL^+	3.45±0.03	
	CdL	3.10±0.05	
	$Al(OH)L^+$	13.40±0.06	
Amoxicillin [47,66-67,77-80]	NdL^{2+}	2.51±0.04	
	$Nd(OH)L^+$	9.2±0.1	
	CoGlyL	8.48±0.09	
	CoGlyL	7.48±0.08	
	$CuHL^+$	15.51±0.03	25°C, 0.1M $NaNO_3$, potentiometry
	$NiHL^+$	13.01±0.06	
	NiL	5.46±0.05	
	$Ni(-H)L^-$	-3.29±0.07	
	CoL^+	12.98±0.07	
	CoL	4.95±0.06	
	$Co(-H)L^-$	-3.47±0.07	
	$ZnHL^+$	12.12±0.06	
	ZnL	4.13±0.07	
	$Zn(-H)L^-$	-3.10±.003	
	AgL	3.26±0.04	25°C, 0.1M KCO_3, potentiometry
	AgL_2^-	6.0±0.1	
	MnL^+	2.09±0.03	
	Mn(OH)L	7.1±0.1	
	CoL^+	2.79±0.03	
	Co(OH)L	7.86±0.05	
	NiL	3.56±0.05	
	Ni(OH)L	8.9±0.2	
	ZnL^+	3.19±0.02	
	Zn(OH)L	9.14±0.03	
	CdL	3.03±0.02	
	Cd(OH)L	8.64±0.03	
	$Al(OH)L^+$	14.53±0.08	
	$Al(OH)_2L$	22.3±0.1	

β: stability constant.

3. Metal complexes of amino glycoside based antibiotics:

3.1 Gentamicin: It is used for the treatment of serious infections caused mainly by Gram-negative and some Gram-positive bacteria [81]. Gentamicin complexes with Co (II), Ni (II), Cu (II) and Bi (V) were synthesized. The gentamicin complexes were found to possess better activity (lesser MIC value) than that of ligand as well as bismuth (V) [82]. Co (II), Ni (II), Cd (II) and Sn (II) complexes of gentamicin are monomeric and involve coordination through the tertiary alcoholic OH group giving square planar geometries [83].

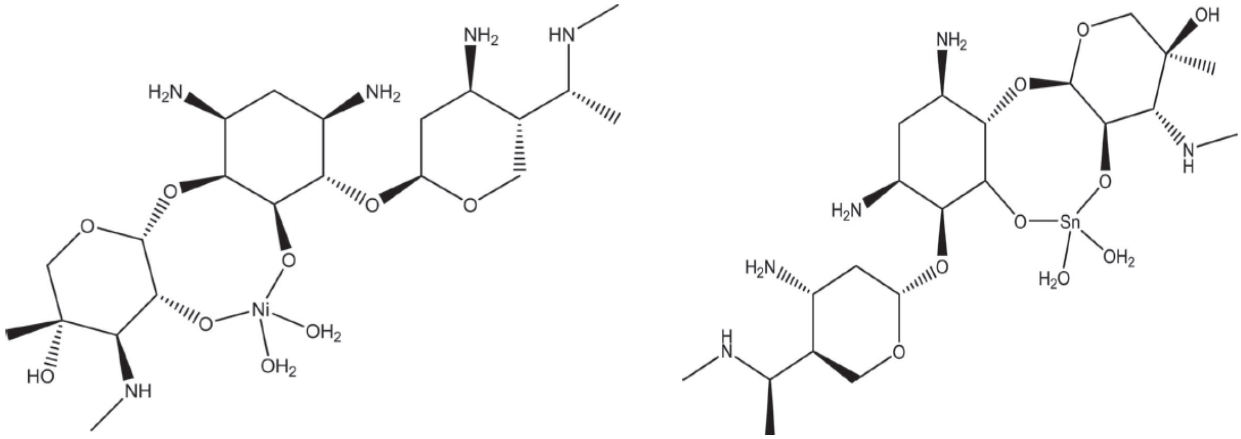


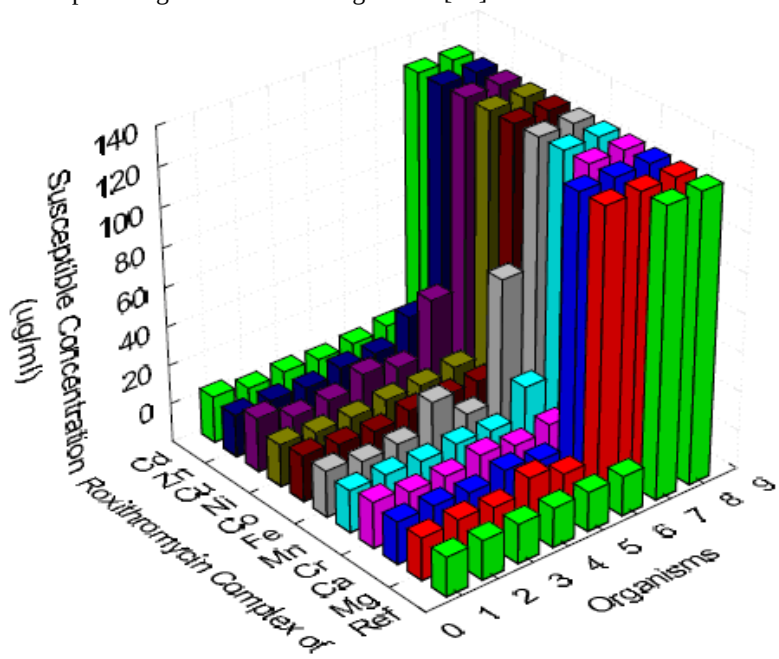
Figure 26 Stereo structure of gentamicin metal complexes

3.2 Neomycin: Solid complexes of neomycin with M= Co (II), Ni(II), Cu(II) and Zn(II) have been prepared $[M(L)(H_2O)_x]$. The complexes have been prepared and characterized by elemental analysis, conductance, magnetic moment measurements and IR, which indicates the bonding between neomycin and metal ions takes place through M-O bonds. The biological activity of the complexes formed has been tested towards eight microorganisms and compared with the activity of neomycin itself [84].

4. Metal complexes of macrolide based antibiotics:

4.1 Clarithromycin: Metal complexes of clarithromycin with magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc and cadmium has been tested for their antibacterial activity and compared with zone of inhibition of complexes against both Gram negative and Gram positive microorganisms. It was found that formation of clarithromycin complexes results in synergistic effect i.e., antimicrobial activity of complexes of clarithromycin increased with respect to parent clarithromycin drug and minimum inhibitory concentration of drug metal complexes decreased [85].

4.2 Roxithromycin: Magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc and cadmium complexes were prepared and their activity were investigated against various microorganisms, *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Salmonella typhi*, *Proteus vulgaris*, *Shigella dysentery*, *Klebsiella pneumoniae* and *Staphylococcus epidermidis* were illustrated in Figure 27. The results show an antagonistic behavior of these complexes against few microorganisms [86].



Organisms:

1 = *Staphylococcus aureus* 2 = *Enterococcus faecalis*

3 = *Escherichia coli* 4 = *Salmonella typhi*

5 = *Proteus Vulgaris* 6 = *Shigella dysentery*

7 = *Klebsiella pneumoniae* 8 = *Staphylococcus epidermidis*

Figure 27 Susceptibility of roxithromycin metal complexes against various organisms

5. Metal complexes of quinolone based antibiotics:

5.1 Norfloxacin: Complexes of tin (II) and tin (IV) with norfloxacin were prepared and characterized by elemental analysis, infrared, mass spectra and thermal analysis. The results support the formation of complexes with 1:2 and 1:3 (M:L) molar ratio through the carbonyl oxygen atom and one oxygen atom of the carboxylic group forming six-membered rings with the tin ions [87]. Also, complexes of norfloxacin with M= Zn(II), Cd (II), Hg(II), Fe (III) and Co(II) in1:2 (M:L) molar ratio have been synthesized and studied using elemental analysis, electronic (UV–vis, mid

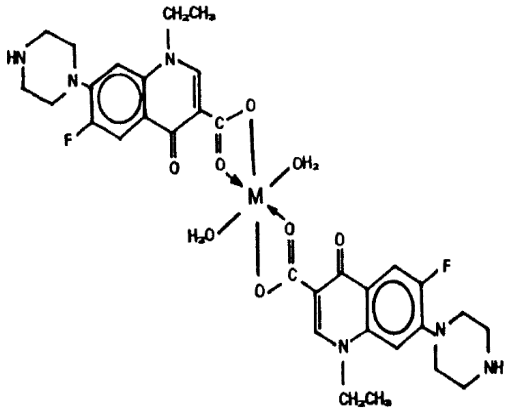
infrared, mass, and ^{1}H-NMR spectra), ligand coordinated to the metal ions via the deprotonated carboxylate O and carbonyl groups with tetrahedral geometry[88].

The interaction between norfloxacin antibiotic and two lanthanide (lanthanum (III) and cerium (III)) metal ions which prepared in normal and nano-features with chemical formulas [La $(L)_3$] $3H_2O$ and [Ce $(L)_3$] $2H_2O$. Lanthanum and cerium (III) ions coordinated toward norfloxacin with a hexadentate geometry were showed in Figure 28B. The highest antibacterial and antifungal activities data of the nano-particles complexes were observed with more potent than the free norfloxacin and normal lanthanide complexes [89].

Complexes of norfloxacin with Fe (III), Co (II) and Zn (II) have been prepared. Norfloxacin was coordinated through two carboxyl oxygen atoms. Octahedral and tetrahegon geometries have been proposed for Fe (III), Co (II) complexes and Zn (II) complex, respectively. *In vitro* test of susceptibility of Fe(III) and Zn(II) complexes showed stronger activity than that of norfloxacin against Gram (-) *E.Coli* and *bacillus dysenteriae* bacteria [90].

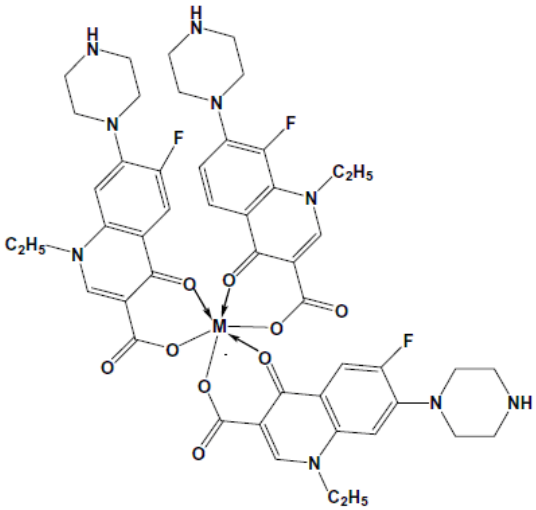
The reactions of norfloxacin and ciprofloxacin with iron (II) and iron (III) perchlorate have been investigated with formation of four complexes for each oxidation state with 1:1, 1:2, 1:3 and 1:4 metal to ligand molar ratios. The IR spectra indicate that norfloxacin bind to the iron ion as bidentate ligands through the carbonyl oxygen atom and one of the oxygen atoms of the carboxylate group [91].

28A



M=Zn(II), Cd(II), Fe (III), Co (II), Sn(II) and Hg(II)

28B



M = La(III), Sn (IV) and Ce(III).

Figure 28 Proposed structures of norfloxacin complexes

5.2 Ciprofloxacin: Complexes of ciprofloxacin-imines derived from ciprofloxacin were synthesized in 1:2(M:L) molar ratio were illustrated in Figure 29. These ligand as well as their metal complexes were also screened for their antibacterial activity against several bacterial strains, such as *Staphylococcus aureus*, *Bacillus subtilus*, *Salmonella typhae* and *E. coli*. It was found that metal complexes are more antibacterial as compared to uncomplexed ligands [92-93]. Toxicity analysis indicated that metal coordination did modify the toxicity of the antibiotics and that antibiotic, metal, and their complex acted primarily as concentration addition [95].

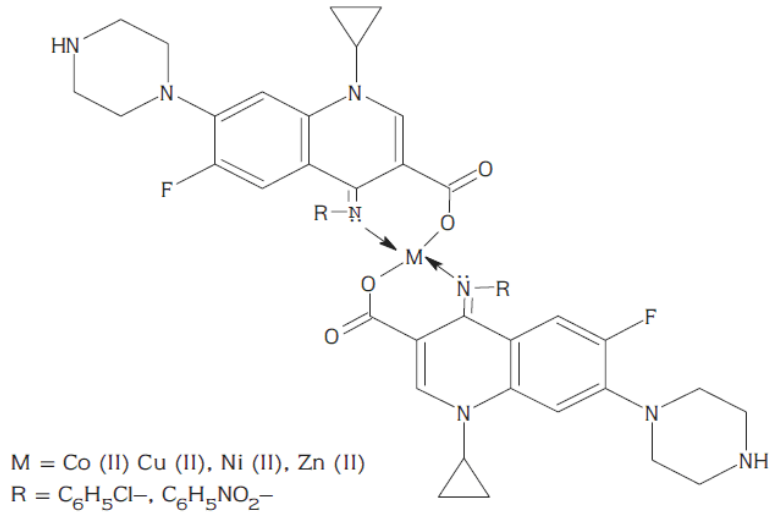


Figure 29 Proposed structures of ciprofloxacin metal complexes

5.3 Levofloxacin: Copper (II) complexes of levofloxacin were obtained and their structures were showed in Figure 30. Both ligands and complexes were assayed against Gram-positive and Gram-negative bacteria. The inhibitory effects of the ligands and complexes on the leukemia HL-60 cell line were measured.The results indicated that the complexes have stronger inhibitory effect [95].

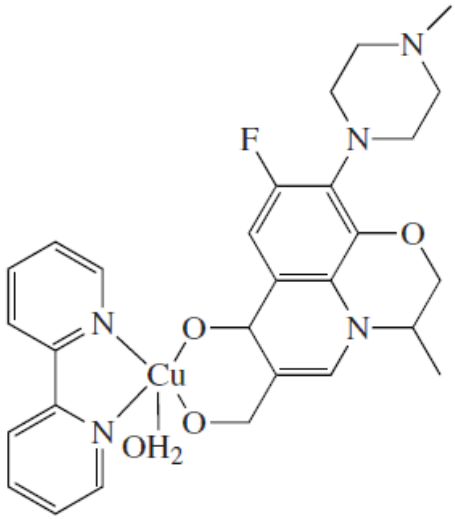
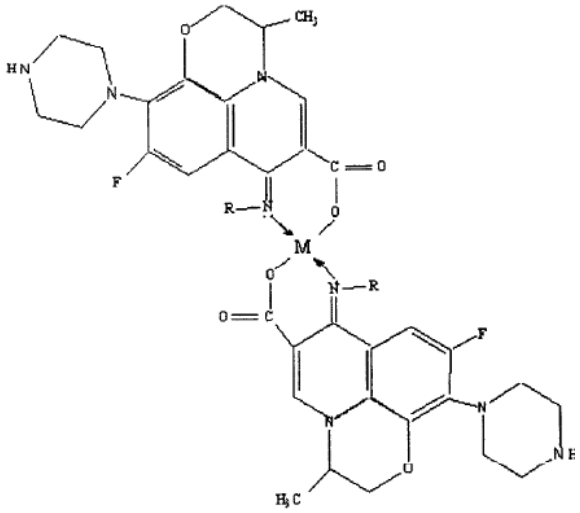


Figure 30 Possible structure of Cu (II) complex

5.4 Ofloxacin: Co (II), Ni (II), Cu (II) and Zn (II) complexes with ofloxacin-imines derived from ofloxacin and p-substituted anilines have been prepared Figure 31 and were evaluated for their antibacterial activity against some bacterial strains. The antibacterial activity demonstrated that metal complexes are more antibacterial as compared to uncomplexed imines and parent antibiotic [96].



M = Co (II), Cu (II), Ni (II), Zn (II)

R = C_6H_5Cl- , $C_6H_5NO_2-$

Figure 31 Proposed structures of ofloxacin metal complexes

5.5 Nalidixic acid: Complexes of nalidixin acid with transition metals have been prepared. It has been found that the antibiotic drug nalidixic acid behaves as monoprotic bidentate ligand coordinating through oxygen of C=O and COO^- groups in 1:1 and 1:2 (M:L) molar ratio. All the prepared metal complexes with antibiotic drug nalidixic acid are screened for their antibacterial and antifungal activities. Probable structures of the complexes are shown in Figure 32 [97].

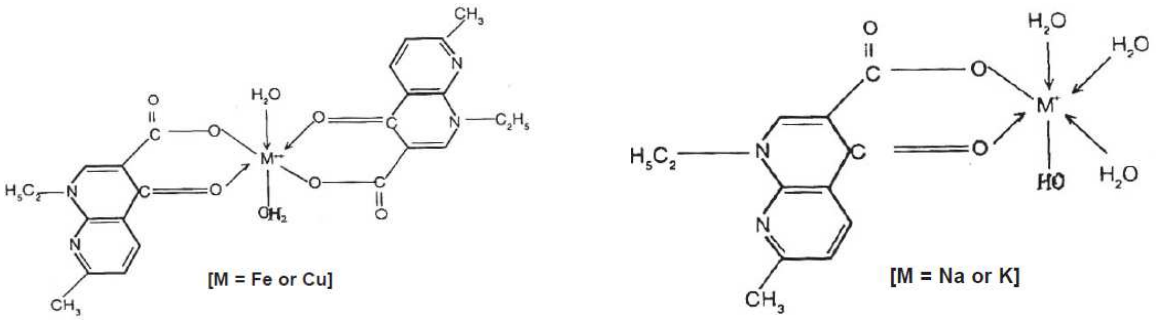


Figure 32 Proposed structures of nalidixin acid metal complexes

6. Metal complexes of nitroimidazole based antibiotics:

6.1 Metronidazole: Complexes of metronidazole were prepared. The antifungal activity tests of the compounds were assayed against three fungi: *Aspergillus niger, Aspergillus flavus* and *Rhizopus* species. The antifungal activity shows that metronidazole complexes are active against all the fungi species. Generally all the complexes have greater inhibitory activity on the organism compared to its free metronidazole [98].

7. Metal complexes of polypeptide based antibiotics:

7.1 Bacitracin: This antibiotic interacts with Zn (II), Co (II), Ni (II) and Cu (II) to form metal complexes [99]. The Mn(II)–bacitracin complex, Figure 33, it is potentially useful as an effective agent against oxidative stress. Mn–bacitracin may be involved in the respiratory burst mechanism of white blood cells that could enhance bacterial killing by synergistic process to convert superoxide radical into hydrogen peroxide. Also of its antibiotic mechanism could be useful for bacterial and oxidative stress treatment [100].

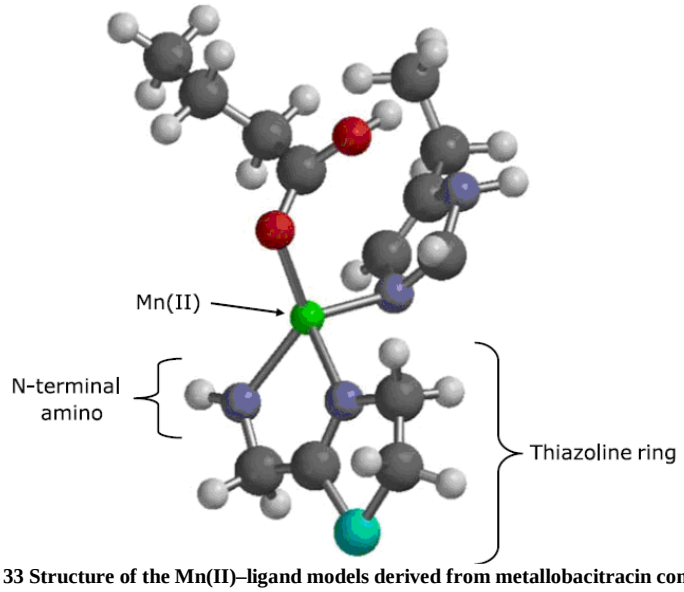


Figure 33 Structure of the Mn(II)–ligand models derived from metallobacitracin complexes

8. Metal complexes of sulphonamide based antibiotics:

8.1 Sulphadiazine: Complexes of sulfadiazine with Fe (III), Ru (III), Rh (III) and Cr (III) were also synthesized and their structures were illustrated in Figure 34. The complexes were tested for *in vitro* activity against cultures of the resistant strains of Plasmodium falciparum, tripamastigotes T. b. rhodesiense and amastigotes L. donovani to determine their antiprotozoal activities. The Fe (III) complex is more active than the other complexes against the parasitic protozoa [101-102].

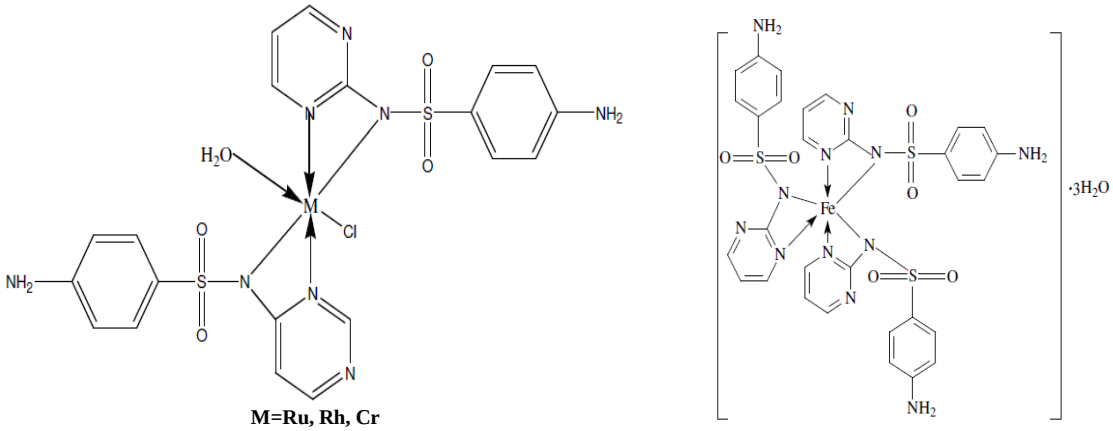


Figure 34 Structures of metal sulfadiazine complexes

8.2 Sulfasalazine: Some of complexes of sulfasalazine with Mn(II), Hg(II), ZrO(II),VO(II), Cr(III) and Y(III) in 1:1 (M:L) molar ratio have been investigated and were shown in Figure 35. Sulfasalazine behaves as a monoanionic bidentate ligand. The thermal decomposition of the complexes as well as thermodynamic parameters (ΔE*, ΔH*, ΔS* and ΔG*) were estimated [103].

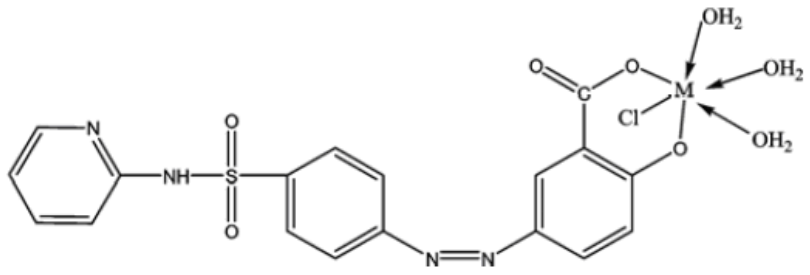


Figure 35 Structures of metal sulfasalazine complexes: M=Mn(II), Hg(II), ZrO(II) VO(II),Cr (III) and Y(III)

9. Metal complexes of tetracycline based antibiotics:

9.1 Tetracycline and oxytetracycline : Ln^{III}–tetracycline complexes of the type $[Ln(L)Cl_3]\ 2H_2O$ [Ln = lanthanum, praseodymium, neodymium, samarium, gadolinium, terbium, dysprosium and yttrium] have been synthesized. A pentagonal bipyramidal structure has been tentatively proposed for the new complexes. The ligand and the new complexes were tested against the bacteria *Escherichia coli* and *Staphylococcus aureus* [104]. Also, the interaction of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), Hg(II), pb(II), Al(III) and UO_2(II) ions with tetracycline were studied by potentiometric titration. The formation constants of different binary complexes were calculated [105].

9.2 Chloramphenicol: The presence of heavy metals such as Cd, Cr, Mn and Zn can significantly affect the activity of chloramphenicol. Various complexes of chloramphenicol with Ni (II), Fe (III) and Co (II) chloride salts were prepared and compared with their parent antibiotics, there was increase in the values of the physical properties of the metal complexes. The antibacterial activity were significantly ($P<0.05$) increased by the complexes at the concentration of 1% (w/v) [106-108].

The complexation of Ni complex with Chloramphenicol was studied on the basis of elemental analysis and molar conductance. The geometries of the complex have been proposed on the basis of magnetic moment, electron, x-ray diffraction data to study coordination behavior of Ni in the presence of VO_3 anion and infrared spectral data. The Ni- Chloramphenicol structure was shown in Figure 36 [109].

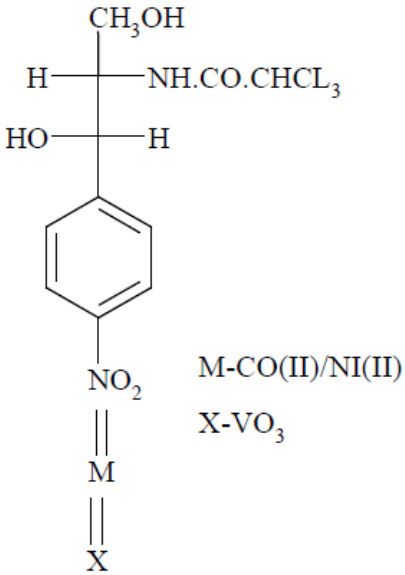


Figure 36 Structure of chloramphenicol –Ni (II) complex

10. Metal complexes of glycopeptides based antibiotics:

10.1 Vancomycin: Dimers of vancomycin linked by a rigid metal complex, $[\ Pt\ (en)\ (H_2O)_2\ ]^{2+}$, exhibit potent activities (MIC 0.8 μg/mL, 720 times more potent than that of vancomycin itself). The result suggests that

combining metal complexation and receptor/ ligand interaction offers a useful method to construct multivalent inhibitors [110].

CONCLUSION

Metals were proved to good chelating agents and antibiotics were considered as useful ligands in the formation of metalloantibiotics. Metalloantibiotics can interact with several different kinds of biomolecules, including DNA, RNA, proteins, receptors and lipids, making them very unique and specifically. Physical, chemical and biological changes in antibiotics were seen after combining with metals as metalloantibiotics. The stability and binding behavior of various antibiotics were studied using electron spray ionization Mass spectrometry. In an attempt of making novel metalloantibiotics with enhanced antimicrobial activity, various mixed effects of metals on antibiotics were seen. Metal produced synergistic, antagonistic and toxic effects on complexation with various antibiotics. Hence it has been concluded that complete biological study along with the stability and binding behavior is required before the synthesis of various metalloantibiotics.

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