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Review Article

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Metalloantibiotics in Therapy: An overview

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ABSTRACT

Antibiotics, also known as antibacterial, that destroys or slows down the growth of bacteria. Growing resistance of bacteria to established drugs is a major health concern. Antibiotics can interact with a variety of biomolecules, which may result in inhibition of the biochemical or biophysical processes associated with the biomolecules. Metal complexes of antibiotics in particular offer great promise for such novel activity. Metalloantibiotics is a broad logical term, many metalloantibiotics derivatives and metal complexes of synthetic ligands and donors demonstrating antibacterial, antiviral, and antineoplastic activities were included. In this review, we focus on few synthetic metalloantibiotics to provide a view of the term ''metalloantibiotics.'' Metal ions play a key role in the actions of synthetic and natural metalloantibiotics, and are involved in specific interactions of these antibiotics with proteins, membranes, nucleic acids, and other biomolecules including DNA, RNA, proteins, receptors, and lipids.

Keywords: Metal complex; Metal; Antibiotics; Metalloantibiotics; Fluoroquinolones; DNA interaction; Cytotoxicity.

INTRODUCTION

Metals have an esteemed place in medicinal chemistry. Some antibiotics do not need metal ions for their biological activities. Some metal complexes are known to exhibit remarkable antitumour, antifungal, antiviral and special biological activities and the efficacies of some therapeutic agents are known to increase upon co-ordination. [1] Research has shown significant progress in utilization of transition metal complexes as drugs to treat a variety of diseases and disorders like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorder. DNA can bind many different biomolecules and synthetic compounds, synthetic metal complexes and organometallic compounds. [2] Various research groups studied the influence of some metallic therapeutic compounds on the pharmacokinetics of orally administered drugs in healthy human volunteers.

The advances in inorganic and medicinal chemistry provide better opportunities to use metal complexes as therapeutic agents. The mode of action of metal complexes on living organism is differing from non metals. These complexes show a great diversity in action. Metal coordination to biologically active molecules can be used to enhance their activity. The activity of biometals is attained through the formation of complexes with different bioligands and the mode of biological action for complexes depends upon the thermodynamic and kinetic properties. The term antibiotic refers to natural or synthetic/semisynthetic compounds that in, minute concentrations, inhibit the growth of or kill microorganisms completely. Metal ions play a key role in the actions of metalloantibiotics and are involved in specific interactions of these antibiotics with proteins, membranes, nucleic acids, and other biomolecules including DNA, RNA, proteins, receptors, and lipids, rendering their unique and specific bioactivities. [1] There are

a number of antibiotics called metalloantibiotics that require metal ions to function properly. This is due to the fact that metal ions can interact with many different kinds of biomolecules, including DNA, RNA, proteins, receptors, and lipids, rendering their unique and specific bioactivities. [3] The lipophilicity of the drug is increased through the formation of chelates and drug action is significantly increased due to effective permeability of the drug into the site of action. Interaction of various metal ions with antibiotics may enhance their antimicrobial activity as compared to that of free ligands. [4] The structural and functional roles of metal ions in metalloantibiotics is highly developed in recent years from extensive biological, biochemical, and physical studies, which are discussed herein to provide an overview of this important and unique group of antibiotics. [5]

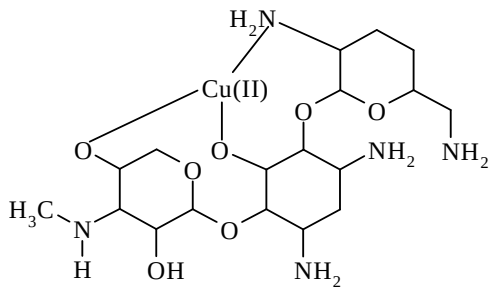
Complexes base on the antibiotics

1. Aminoglyosides
2. β-lactum antibiotics
3. Cepalosporine
4. Tetracycline
5. Chloramphenicol
6. Macrolide
7. Fluoroquinolones
8. Miscellaneous

1. Aminoglycosides

The ability of aminoglycosides to bind metal ions is primarily governed by sugar ring substitution on the 2-deoxy streptamine ring (Ring B). Vicinal amine and hydroxyl groups can form a potential metal chelating motif, as found within the 2-deoxy streptamine ring (1-amine and 6-hydroxyl). Gentamicins also possess metal chelate donor atoms in ring C(R [4]. Metal ions have been found to be involved in some unique activities of aminoglycosides. The binding of iron to gentamicin has been postulated to induce free radical formation which causes peroxidation of lipids. Intra- and extra-cellular low molecular weight oxidant scavengers are fascinating molecules with a high therapeutic potential. As ROS/RNS plays a pivotal role in ototoxicity ,these scavengers have been tested as otoprotective agents. The condition of oxidative stress generated after ototoxic drug administration or acoustic trauma is accompanied, to a varying degree, by a dyshomeostasis of metal ions, including the redox-active transition metals: iron and copper. Therefore, iron or copper chelation therapy could be a promising approach to prevent ototoxicity. Indeed, administration of the iron chelators, protects hearing function and cochlear hair cells of guinea pigs treated by aminoglycosides. [6,7]. The $Fe^{+2/+3}$ complexes of gentamicin have recently been investigated.

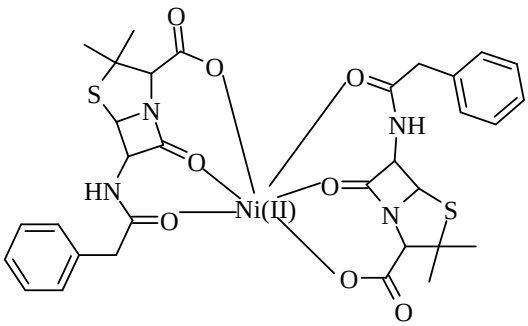
These redox-active iron complexes were implied for aminoglycoside toxicity. Several aminoglycoside antibiotics have been observed to bind Cu^{+2} gentamicin (**1**) and the semi-synthetic amikacin [8,9]. In addition, a few simple amino sugars have also been reported to bind Cu^{+2}, which serve as simple model for binding of aminoglycoside antibiotics to metals. The Cu^{+2} -aminoglycoside complexes are observed to exhibit oxidative activity, which can catalyze oxidation of nucleotides in the presence of H_2O_2. Aminoglycoside phosphotransferase (3')-IIIa (APH) has broadest substrate range among the phosphor transferases that cause resistance to aminoglycoside antibiotics. The presence of metalnucleotide increased the binding affinity of aminoglycosides to APH. Aminoglycosides can be considered as “metalmimics” because they bind to metal-ion binding sites of RNA molecules and interfere with the function of RNA by displacing functionally/structurally important metal (II) ions. Scientists showed that aminoglycosides also interfere with metalion binding sites of protein enzymes, showing that them “metal mimics” property of aminoglycosides is not only restricted to the interaction between aminoglycosides and RNA [10]



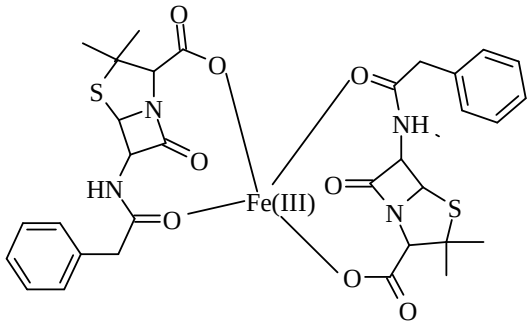
Gentamicin complex of copper (1)

2. β-lactum antibiotics

Metal complxese of Clavulinic acid, Penicillin and Ampicillin are reported. IR spectra of clavulanic acid, penicillin and ampicillin complexes showed strong modifications of the carbonyl group located on the lactamic ring, indicating that this oxygen participates in the coordination to the metal ions along with the carboxylate group. Penicillin behaves as bidentate (**3**) or tridentates ligand (**2**). In bidentate mode, coordination occurs through the carboxylate and lactamic oxygen atoms to the metal and in case of tridentate mode, coordination occurs through the carboxylate, lactamic oxygen and amide carbonyl group to the metal [11-13].



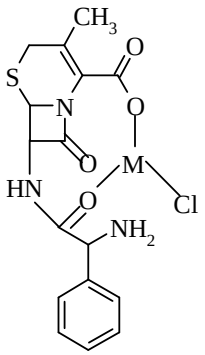
Nickel complex of Benzylpenicillin (Tridentate mode) (2)



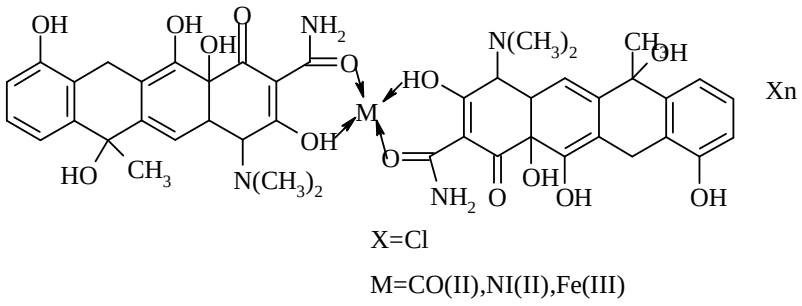
Iron complex of Benzylpenicillin (Bidentate mode) (3)

3. Cephalosporin

The cephalosporins antibiotics are semisynthetic antibacterials derived from cephalosporin C. Cephalosporin antibiotics are very closely related to penicillins. S. H. Auda *et al* concluded that Cephalosporins contain electron donor groups that can bind naturally occurring metal ions in vivo. Cephalosporin antibiotics exhibited a change in their toxicological properties and biological performance when they were tested as metal complexes. The proposed reason for such a behavior is the capability of chelate binding of the cephalosporins to the metals. Cephalosporins are acting as multidentate chelating agents, via the lactam carbonyl and carboxylate and N-azomoieties. The complexes are insoluble in water and common organic solvents but soluble in DMSO. Anacona *et al* reported synthesis and antibacterial activity of cephalexin (**4**) Metal Complexes with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II). The anti-bacterial study of Cu(II)-cefalexin and Zn(II)-cefalexin complexes sdemonstrated that the complexation of cefalexin with these metals enhances its activity significantly compared to cefalexin alone. The complex [Cu(cefotaxime)Cl] was found to have higher activity than that of cefotaxime against the bacteria strains studied under the test conditions, showing that it has a good activity as bactericide [14,15,].



Cefalexin metal complex (4)



Tetracycline metal complex (5)
[M= Cu(II), Zn(II), Ni(II)]

4. Tetracyclines

Tetracyclines inhibit binding of aminoacyl-tRNA to the mRNA-ribosome thereby inhibiting translation process which is an important step in protein synthesis. Their usage has been limited in recent years because of side effects.

The acidicoxy-groups at positions 1, 3, 10, 11, and 12 of Tetracycline are the potential metal binding/ chelating site. Recent studies of the mechanism for bacterial resistance of this drug has afforded new insight into rational design of analogues and searching for new analogues of this broad-spectrum antibiotic family. Antibiotics drugs of the tetracycline family are chelators of Ca^{+2} and Mg^{+2} ions. Tetracyclines coordinate metal (II) ions including Ca^{+2} and Mg^{+2} ions under physiological conditions forming chelate complexes with their ketoenolate moiety at rings B and C. These metal(II) complexes were the biologically relevant molecules conferring the antibiotic character of the drug by inhibiting ribosomal protein biosynthesis in prokaryotes. The beneficial effects of tetracyclines are attributed to their metal complex. Tetracyclines complex with copper acts as antioxidants and anti-inflammatory agents (electron scavengers) by neutralizing the damaging oxygen free radicals produced by the activated leucocytes [16,17].

Novel Co(Il),Ni(II) and Fe(IlI)complexes (**5**) of tetracycline have been synthesized and characterized by vibrational, electronic and HNMR spectroscopic Studies. The ligand was found to be bidentate, coordinating through the oxygen of alcoholic group and that of the carboxyl group. Antibacterial screening of the complexes has been made against Bacillus subtilis, Serratia species and Escherichia coli. All the novel complexes showed higher activity than the original tetracycline hydrochloride [18].

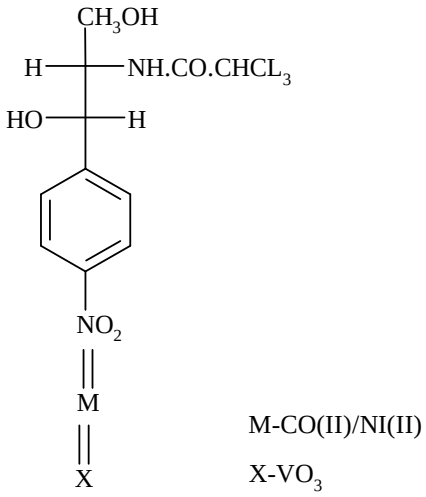
Anthracycline

Anthracycline (AC) antibiotics are produced by Streptomy cesspecies and exhibit wide spectrum of antineoplastic activity toward both solid and hematologic tumors and cancers. The redox activity of the AC ring plays a key role in the action of these drugs. In addition, the metal ion bound to the 11, 12-bketophenolate site is also thought to be involved in some actions of these antibiotics.ACs are known to bind various metal ions including transition metals, lanthanides, and uranyl ions. A number of articles have reported that some metal ions, e.g., $Fe^{+2/+3}$ $Cu^{+/+2}$, Pd^{+2} and Pt^{+2} play an important role in altering the biochemical properties of ACs. The binding of metal ions may cause a significant influence on the redox property of ACs, thus affecting their activities. The interaction and subsequent damage of DNA and other cell components with Fe/Cu–AC complexes have been previously studied with the help of various physical and biochemical methods. Doxorubicin is powerful chelators of other metal ions, including Cu^{+2} and Al^{+3}. Copper-complexation had no affect on the cytotoxicity of the doxorubicin drug suggesting thereby that extracellular as well as intracellular mechanisms may be involved in the development of its antitumor activity [19].

5. Chloramphenicol

Chloramphenicol was isolated from Streptomyces venezuelae in 1947. Chloramphenicol was found to be effective against typhus in 1948 and became the first antibiotic to undergo large-scale production. By 1950, the medical community was aware that the drug could cause serious and potentially fatal aplastic anemia, and it quickly fell into disfavor. Chloramphenicol currently is used in the United States only to combat serious infections where other antibiotics are either ineffective or contraindicated.

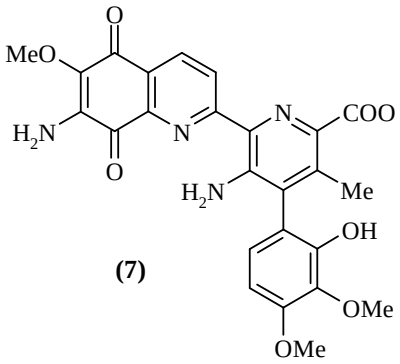
CO(III) and Ni(II)complexes(**6**) with chloramphenicol have been synthesized and characterized on the basis of element analysis and molar conductance formula $Co(C_{11}H_{12}CL_2N_2O_5)VO_3.2H_2O$ and $Ni(C_{11}H_{12}CL_2N_2O_5)VO_3.3H_2O$ [20].



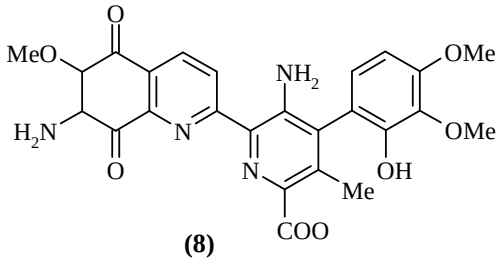
Chloramphenicol complex (6)

Streptonigrin

Streptonigrin (SN) is a metal-binding quinone-containing antibiotic produced by Streptomyces flocculus. A redox active metal ion such as Fe and Cu is required for this antibiotic to exhibit full antibiotic and anti-tumor activities. The implication for the formation of metal complexes of the antitumor antibiotic streptonigrin, which cleaves DNA in the presence of metal ions, has been reported. In vivo, metal ions such as Zn(II), Cu(II) and Mn(II) facilitated the initial reduction of streptonigrin to the semiquinone by capturing the semiquinone after streptonigrin reduction by biological reductants. Structure (**7**) has been determined for metal-free drug by means of crystallography, whereas the structure (**8**) represents the conformation upon metal binding as determined by means of NMR relaxation. Formation of structure (**8**) requires a twist of the C_2-C_2' bond in structure (**7**) [21].



(7)



(8)

The metal–SN complexes can be reduced to their semiquinone forms by NADH, which then can induce cleavage of DNA. Zinc ions bind SN to afford complexes with varying metal to ligand ratios at various temperatures, in which 1:1 metal–drug complex is the predominant one. The interaction of Zn^{+2}–SN with DNA and oligonucleotides has been investigated with ^{1}H- and P-NMR spectroscopy. This study concluded the requirement of metal ions for SN binding to DNA SN can bind to several different paramagnetic metal ions, including Co^{+2} and Fe^{+2} with large formation constants to form 1:1 metal-SN complexes. The study of Fe^{+2}–SN complex is particularly important since it is considered an active form exhibiting enhanced activity towards DNA destruction, both in vitro and in vivo [22].

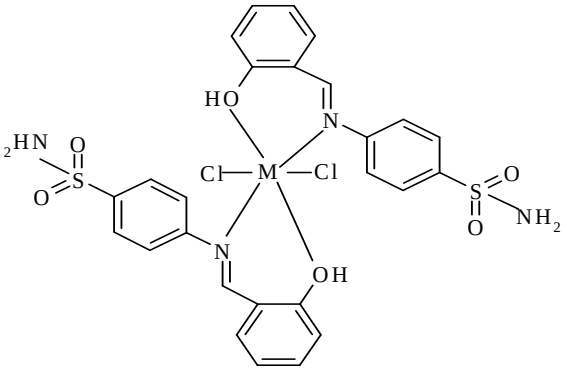
Bleomycin

Bleomycin (BLM) is a glycosylated linear nonribosomal peptide antibiotic produced by the bacterium Streptomyces verticillus. Bleomycin was first isolated as a Cu^{+2}-containing glycooligopeptide antibiotic from the culture medium of Streptomyces verticullus, and was later found to be the most widely used anticancer drugs. BLM contains a few uncommon amino acids, such as β-aminoalanine, β-hydroxyhistidine, and methylvalerate, two sugars (gulose and mannose), a few potential metal-binding functionalities such as imidazole, pyrimidine, amido, and amino groups, and a peptidyl bithiazole chain considered to be the DNA recognition site. DNA cleavage by bleomycin depends on

oxygen and metal ions, at least in vitro. It is believed that bleomycin chelates metal ions (primarily iron) producing a pseudoenzyme that reacts with oxygen to produce superoxide and hydroxide free radicals that cleave DNA. The bleomycin-iron complex was the well-studied example of site-specific, metal-mediated damage to DNA. The bleomycin- mediated cleavage of DNA occurred via formation of a ternary complex, DNA-bleomycin-iron. Further, oxidation of the complexed Fe(II) resulted in a site-specific oxidation of DNA, most probably by the hydroxyl radical. Antitumor properties of bleomycin and its several metal complexes as well as nucleic acid recognition by metal complexes of bleomycin has been reported [23, 24].

6. Sulphonamide

They are competitive inhibitiors of bacterial enzyme dihydropteroate synthetase, and microbial nucleic acids synthesis was also inhibited along with microbial folic acid synthesis. Sulphonamide posses free or substituted amino group, binding site for metal complexes. Subudhi *et al* [25] report the synthesis of Cu(II), Zn(II), Co(II), Ni(II) and Pb(II) complexes of 4-(2'-hydroxy phenylimino) phenyl sulphonamide (**9**). The Complexes were evaluated for their antibacterial activity using two gram positive bacteria (*S. aureus, E. faecalis*) and two gram-negative bacteria (*E. coli, P. aeruginosa*) by disc diffusion method. The results show that metal complexes were found to enhance the antimicrobial potental of the ligand. Quinolinyl sulfonamides, such as N-(quinolin-8-yl) methanesulfonamide and N-(5-chloroquinolin-8-yl) methanesulfonamide [potent methionine aminopeptidase (MetAP)] inhibitors showed different inhibitory potencies on Co(II)-, Ni(II)-, Fe(II)-, Mn(II)-, and Zn(II)-forms of E. coli MetAP, and their inhibition was dependent on metal concentration and form metal complex with residue at the enzyme active site [26].



4-(2'-hydroxy phenylimino) phenyl sulphonamide.
M= Cu(II), Zn(II), Co(II), Ni(II) and Pb(II) (9)

7. Microlide

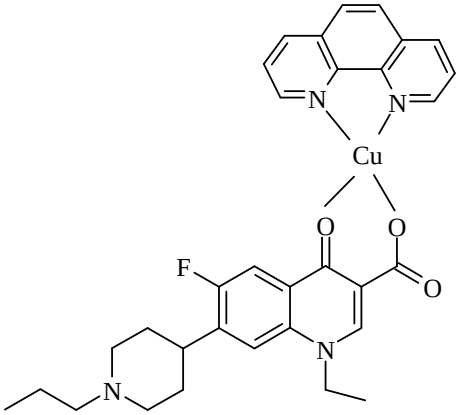
There are a couple of new relatives of erythromycin (azithromycin, erythromycin and clarithromycin) that work the same way, but kill more bugs and have slightly fewer side effects. The erythromycin-like antibiotics are also known as macrolides. Macrolides belong to the polyketide class of natural products. Macrolide antibiotics are used to treat respiratory tract infections, genital, gastrointestinal tract, soft tissue infections caused by susceptible strains of specific bacteria. Macrolides bind with ribosomes from susceptible bacteria to prevent protein production. This action is mainly bacteriostatic, but can also be bactericidal in high concentrations. Macrolide antibiotics contain a 14-membered lactone ring to which are attached one or more deoxy sugars. In order to establish the role of various essential and trace element complexation on the antibacterial activity of various macrolide antibiotics, the synergistic or antagonistic behavior of erythromycin metal complexes have been studied and compared with the parent drug. Metal complexes of erythromycin with magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc and cadmium have been investigated for their antibacterial activity and compared with erythromycin by observing the changes in minimum inhibitory concentration (MIC) and by measuring the zone of inhibition of complexes against both Gram-negative and Gram-positive microorganisms. Various microorganisms used were *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Salmonella typhi, Proteus vulgaris, Shigella dysentary, Klebsiella pneumoniae and Staphylococcus epidermidi* [27].

8. Fluoroquinolones

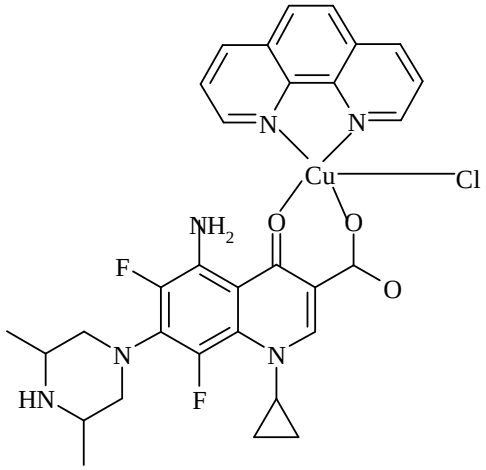
Numerous metal complexes of fluoroquinolones have been synthesised and tested for their antibacterial activity.In addition some mixed ligand complexes have been reported in the literature. There are different types of ligands used

for metal complexes formation, but Nitogen donor heterocyclic ligands have great interest in formation of metal complexes. 1,10- phenanthroline, 2,2'- bipyridine and 2,2'-dipyridylamine are reported in literature for metal complex.

Metal complexes of fluoroquinolones (Single and Mixed ligands approch)
The isolation of quinolone-metal complexes was achieved by the group of Xiao-Zeng You. They have prepared complexes with quinolones coordinated to magnesium, calcium, copper and zinc. In some of these crystal structures the bonding modes are significantly different from those reported before.The other complexes of Silver, Cobalt, Cadmium, Boron, Vanadium, Iron, Nickel and Bismuth with quinolones are reported. It has been found that metal complexes of quinolones enhanced biological activity in realation to the free quinolones.



Cu(pr-norf)(phen)Cl (10)

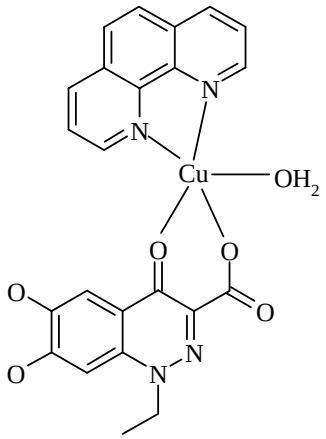


Cu(sf)(phen)Cl (11)

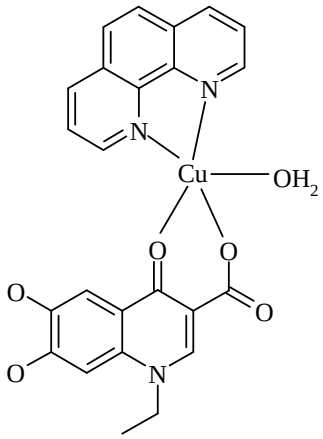
George Psomas *et al* reported the synthesis of copper (II) complex (**10**) with the quinolone antibacterial drug N-propyl-norfloxacin and nitrogen donor 1, 10-phenanthroline had been prepared and characterized spectroscopically. The antimicrobial activity of the complex has been tested on three different microorganisms and the best inhibition(MIC = 0.25 µg $mL7^{-1}$) has been exhibited against Escherichia coli. The interaction study of the complex with calf-thymus DNA also performed with various spectroscopic techniques and revealed that complex (10) is bound to calf-thymus DNA by the intercalative mode. Complex (10) showed an increased antiproliferative and necrotic effect on both HL-60 and K562 human leukemia cells in comparison to the free pr-norfloxacin. [28].

George Psomas *et al* reported the synthesis of copper (II) complexes (**11**) of the third-generation quinolone antibacterial drug sparfloxacin in the presence of a nitrogen donor heterocyclic ligand 1,10-phenanthroline have been prepared and characterized spectroscopically. The antifungal and antibacterial properties of many Cu (II) complexes have been evaluated against several pathogenic fungi and bacteria. Copper (II) complexes with drugs are much more active in the presence of a nitrogen-donor heterocyclic ligand [29].

G. Mendoza-Diaz also *et al* reported some mixed-ligand complexes (**12, 13**) of Copper (II) with drugs of the Quinolone family and (N-N) donors. They used cinoxacin (Cnx) or oxolinic acid (oxo) drugs of the quinolone family. The complexes were characterised by X-ray crystallography [30].

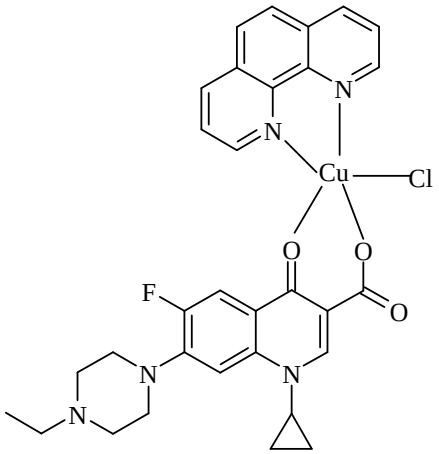


Cu(cnx)(phen)H2O (12)

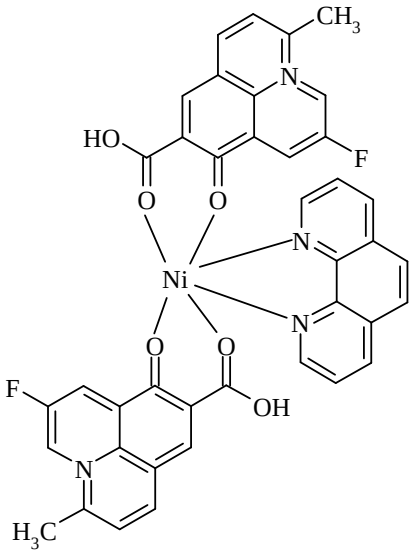


Cu(oxo)(phen)H_2O (13)

Efthimiadou *et al* also carried out the synthesis of the mononuclear copper complexes(**14**) with the quinolone antibacterial drug enrofloxacin in the presence of a nitrogen donor heterocyclic ligand 1,10-phenanthroline (=phen) and had been prepared and characterized. The antimicrobial efficiency of the complexes has been tested on three different microorganisms and the available evidence supports that the best inhibition is provided by MIC against *Escherichia coli and Pseudomonas aeruginosa* [31].



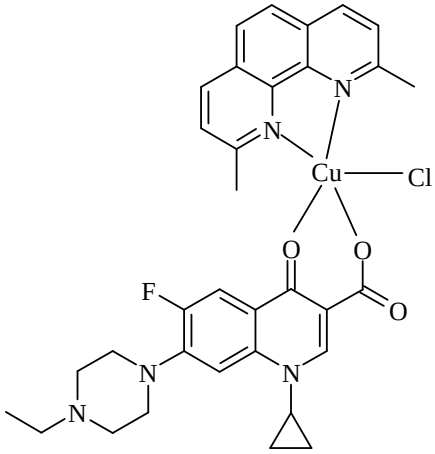
Cu(erx)(phen)Cl (14)



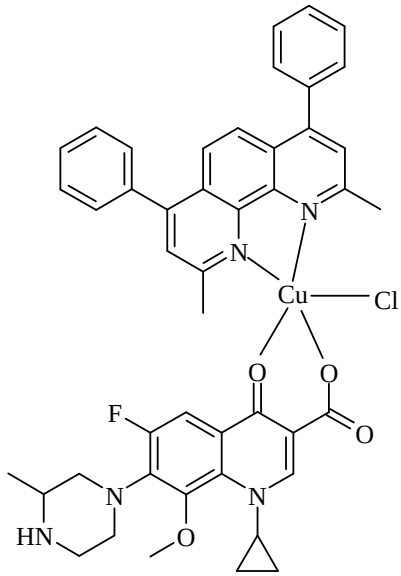
[Ni(flmq)$_2$(phen)] (15)complex

George Psomas *et al* reported the synthesis of Nickel (II) complexes (**15**)with the first-generation quinolone antibacterial agent flumequine in the presence of nitrogen donor heterocyclic ligands 1, 10-phenanthroline characterized by physicochemical and spectroscopic techniques [32].

Patel *et al* reported the synthesis of Copper (II) complexes (**16**) of Enrofloxacin in presence of neutral bidentate ligands. The complexes have been characterised by elemental analysis, IR and mass spectroscopy. Complexes have been screened for their in-vitro antibacterial activity agaianst two Gram (+ve) *Staphylococcus aureus, Bacillus subtilis*, and three Gram (−ve) *Serratia marcescens, Escherichia coli* and *Pseudomonas aeruginosa* organisms using the double dilution technique [34].



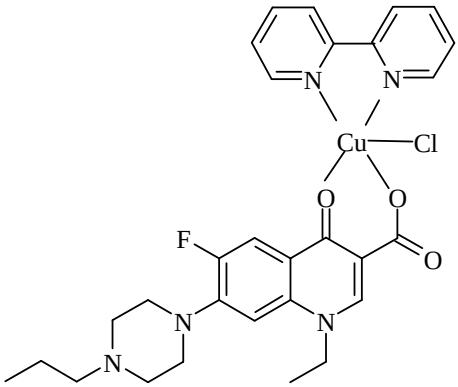
Cu(Enrofloxacin)(2, 9-dimethyl-1,10-Phenanthroline)Cl (16)



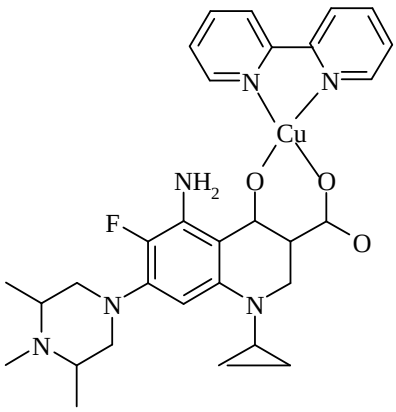
Cu(Gatifloxacin)(2, 9-Dimethyl-4,7 -diphenyl-1, 10-phenanthrolin (17)

Patel *et al* synthesis the square pyramidal copper (II) complexes (**17**) with fourth generation fluoroquinolone and neutral bidentate ligand. They focused the coordination of different neutral bidentate ligand to copper ion in combination with gatifloxacin. They used 1, 10-Phenanthroline derivatives as neutral bidentate ligands in complex formation [34].

Alexandra Karaliota *et al* reported the synthesis of mononuclear copper complex (**18**) with the quinolone antibacterial drug N-propyl-protected norfloxacin, N-pr-norfloxacin, in the presence of the nitrogen donor heterocyclic ligand 2, 2'-bipyridine.The crystal structure has been determined and refined with X-ray crystallography. X-band electron paramagnetic resonance (=EPR) spectroscopy at the antimicrobial activity of the complex has been tested on three different microorganisms and the best inhibition (MIC = 0.25 lg mL_1) has been exhibited against Escherichia coli [35].



Cu(N-propyl-norfloxacin) (2, 2'-bipyridine)Cl (18)

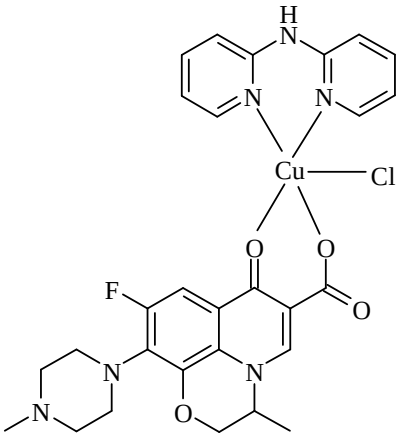


Cu (sparfloxacin) (2, 2'-bipyridine)Cl (19)

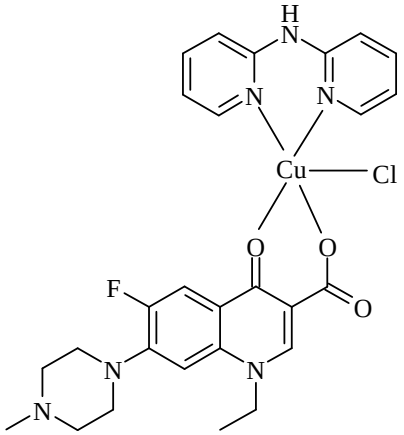
George Psomas *et al* reported the synthesis of neutral mononuclear copper(II) complex(**19**) of the third-generation quinolone antibacterial drug sparfloxacin in the presence of a nitrogen donor heterocyclic ligand 2,2'-bipyridine characterized by physicochemically and spectroscopically. The antimicrobial activity of the complexes has been

tested on three different microorganisms. The complex most active ones against Escherichia coli, Pseudomonas aeruginosa and *staphylococcus aureus*, when compared to the other corresponding copper–quinolone complex [36]. Patel *et al* studied the Superoxide dismutase SOD mimic activity, DNA binding and in-vitro antibacterial studies of drug based copper(II) complex(**20**) with levofloxacin(levo) in presence of 2,2'bipyridylamine(bpd) Compounds were checked for their in-vitro antimicrobial activity against two Gram(+ve) and three Gram(–ve) bacterial species.

Patel *et al* studied the SOD mimic activity, DNA binding and in-vitro antibacterial studies of drug based copper(II) complexes (**21**) with pefloxacin(pef)in presence of 2,2'-bipyridylamine (bpd) Compounds were checked for their in-vitro antimicrobial activity against two Gram(+ve) and three Gram(–ve) bacterial species. Intrinsic binding constant (Kb) of complexes with CT DNA were determined using absorption titration. Viscosity measurement suggested that complexes bind with CT DNA through partial nonclassical intercalative mode. Superoxide dismutase (SOD) like activity of the complexes was also determined [37].



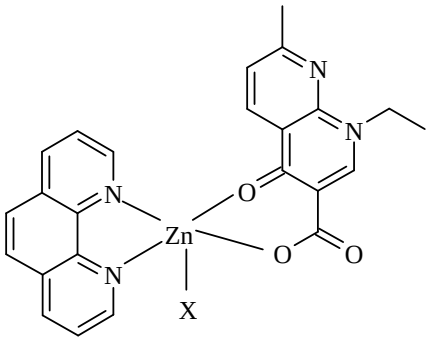
Cu (levo) (bpd)Cl (20)



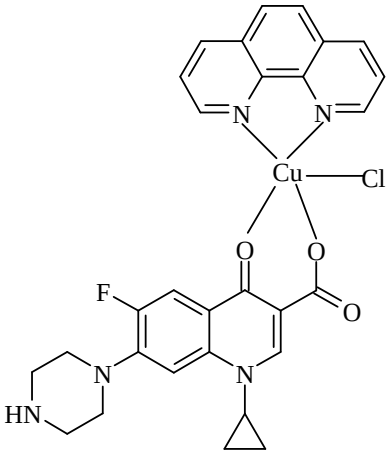
Cu(pef)(bpd)Cl (21)

G. Mendoza-Diaz *et al* reported the synthesis and characterization of Zinc mixed complexes with nalidixate anion and (N-N) donors 1, 10-phenanthroline as N-N donor. The complexes (**22**) have been characterised by 13C NMR studies [38].

Wallis et at studied the synthesis of Copper (II) Complexes (**23**) of the Fluoroquinolone antimicrobial ciprofloxacin and norfloxacin in presence of 2, 2'-bipyridine. The complex [Cu (cip)(phen)(Cl)(NO_3)]2H_2O (**23**) was characterized by ^{13}C NMR and potentiometric study. The selective broadening of resonances in the ^{13}C NMR spectrum of ciprofloxacin by the addition of Cu^{+2}(aq) was determined. The protonation constants of norfloxacin and ciprofloxacin were determined by potentiometric titrations at 25°C [39].



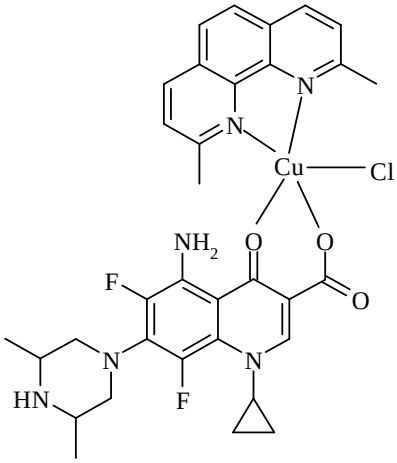
Zn(phen)(Nal)X (22)

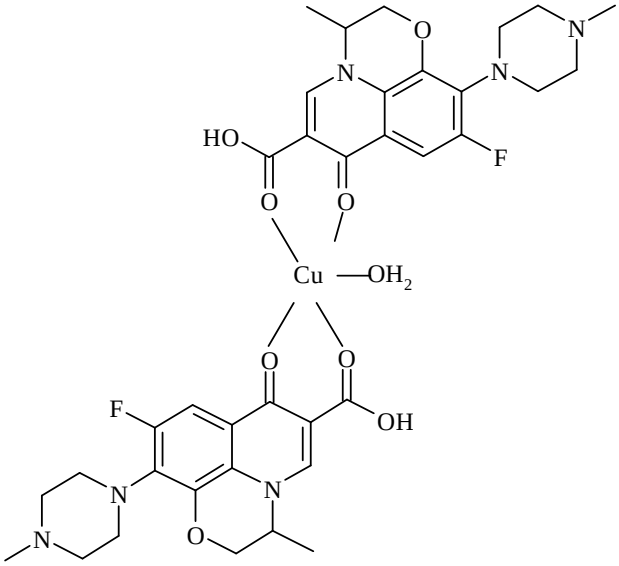


Cu(cipro) (1, 10-phen)Cl complex (23)

Patel *et al* carried out synthesis, biological aspects and SOD mimic activity of square pyramidal copper(II) complexes (**24**) with the 3rd generation quinolone drug sparfloxacin and phenanthroline derivatives An antimicrobial efficiency of the complexes was tested on five different microorganisms and exhibited diverse biological activity against two Gram (+ve), Staphylococcus aureus and Bacillus subtilis, and three Gram (−ve), Serratia marcescens, Pseudomonas aeruginosa and Escherichia coli, microorganisms by the broth dilution method [40].

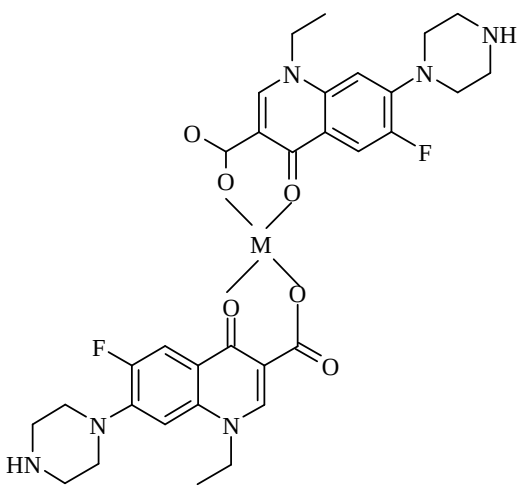
Benigno Macıas *et al* synthesis Cu(II) with ofloxacin and characterized. According to elemental chemical analysis and FT-IR spectroscopy data direct reaction of Cu(II) salts (**25**) with ofloxacin leads to formation of precipitates for which mass spectrometry demonstrates their polymeric nature [41].

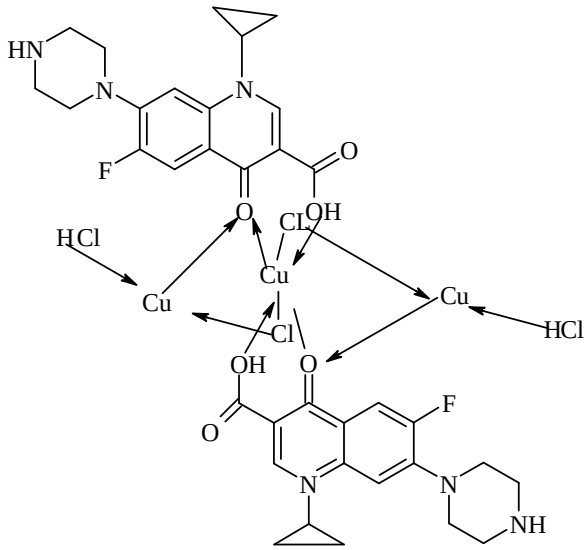




Cu(Sparfloxacin) (2, 9-dimethyl-1, 10-Phenanthroline) Cl complex (24) **M-(Ofloxacin)$_2$cu complex;(25)**

Sadeek *et al* reported the synthesis of Mn(II), Co(II) and Fe(III) norfloxacin complexes (**26**). The complexes were characterised by by elemental analysis, infrared, electronic, mass spectra and thermal analysis. It was found that the norfloxacin act as bidentate ligands through one of the oxygen atoms of the carboxylic group and the ring carbonyl oxygen atom [42].

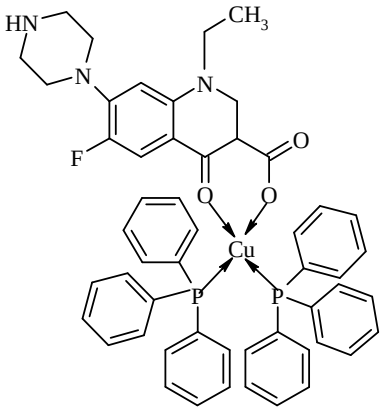




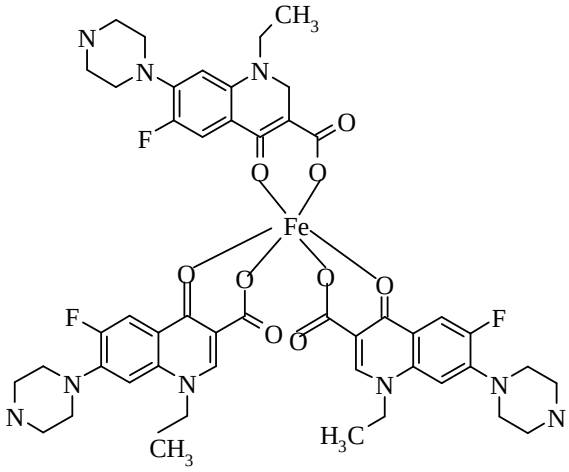
M-(Norfloxacin)$_2$ complex; where M= Mn or Co (26) [Cu (Cf)$_2$(ClO$_4$)$_2$] · 6H$_2$O (27)

Jimenez-Garrido et al. prepared three mixed complexes of ciprofloxacin with Cu (II), namely [Cu(Cf)$_2$(ClO$_4$)$_2$] 6H$_2$O,[Cu(Cf)$_2$(NO$_3$)$_2$] 6H$_2$O(**27**) and [Cu(Cf)$_2$(C$_2$O$_4$)$_2$] 2H$_2$O. The single crystal structure of [Cu(Cf)$_2$(ClO$_4$)$_2$] · 6H$_2$Owas determined and characterized [43].

Chen et al. prepared the mixed-ligand copper (I) complex (**28**) [Cu(PPh$_3$)$_2$(Nf)ClO$_4$]. The crystal structure of this compound consisted of the [Cu(PPh$_3$)$_2$(Nf)] cation and Cl anion. The antibacterial activities of the newly synthesis compounds were evaluated and correlated with their physicochemical properties [44].

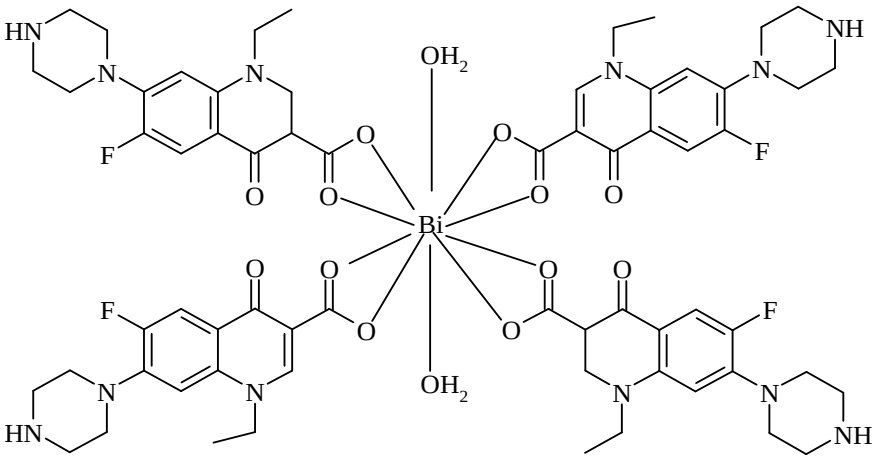


Cu(PPh$_3$)$_2$(Nf)] · ClO$_4$ (28)



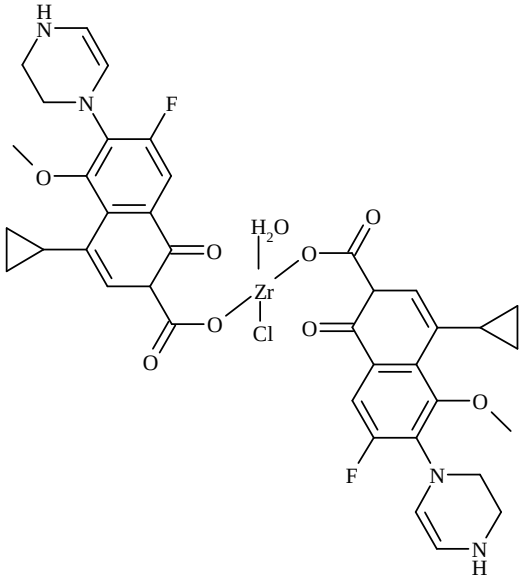
[Fe (Cf) (Nta)] · 3.5H$_2$O (29)

Wallis *et al* prepared from aqueous solutions the iron (III) complex (**29**) with ciprofloxacin and nitriloacetate (**Nta**) as an additional ligand, [Fe(Cf)(Nta)] ·3.5H$_2$O. The complexes have been characterized by elemental analysis, reflectance spectra, IR and mass spectroscopy [45].

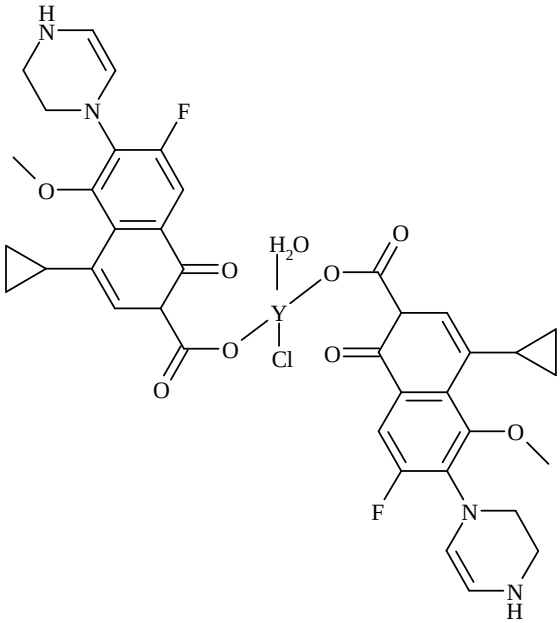


Structure of Bi (Norfloxacin) $_2$(H_2O) $_2$ complex (30)

Shaikh *et al* studied the Synthesis, physicochemical and antimicrobial evaluation of Bismuth-Norfloxacin complex (**30**). The complex was prepared by reacting bismuth citrate with aqueous solution of norfloxacin. The structure of the bismuth-norfloxacin complex (BNC) was confirmed by spectral, chemical and elemental analysis. Antimicrobial studies were carried out using agar diffusion method against *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Bacillus pumilis* and *Staphylococcus epidermidis*. The results showed significant increase ($p < 0.05$, Tukeys test) in antibacterial activity of BNC as compared with norfloxacin and physical mixture of norfloxacin and bismuth citrate. This increase in activity is being considered due to increased bioavailability of the metal drug complex. [46]



[Zarconium(gatifloxacin)$_2$Cl].H_2O complex(31)

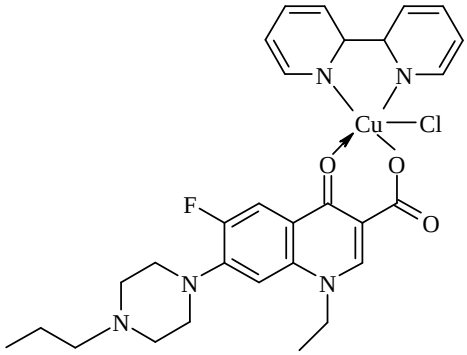


[Yattrium(gatifloxacin)$_2$Cl].H_2O complex(32)

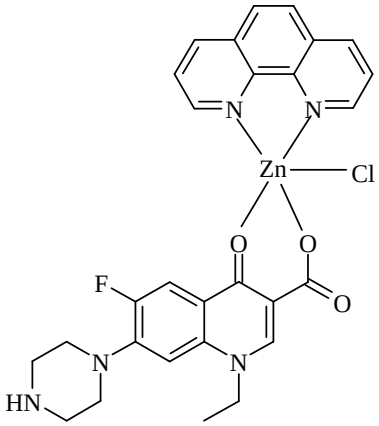
Sadeek A *et al* were reported three metal complexes of the fourth generation quinolone antimicrobial agent gatifloxacin (GFLX) with [Y(III)]**(31),** Zr(IV)**(32)** and U(VI) and characterized with physicochemical and spectroscopic techniques. In these complexes, gatifloxacin acts as a bidentate deprotonated ligand bound to the metal through the ketone oxygen and a carboxylato oxygen. The complexes are six-coordinated with distorted

octahedral geometry. The antimicrobial activity of the complexes has been tested against microorganisms, three bacterial species, such as *Staphylococcus aureus (S. aureus), Escherichia coli (E. coli) and Pseudomonas aeruginosa (P. aeruginosa)* and two fungi species, penicillium (*P. notatum*) and trichoderma (T. sp.), showing that they exhibit higher activity than free ligand.[47]

Patel *et al* reported the antibacterial and DNA interaction studies of zinc (II) complexes with ciprofloxacin. Six binuclear Zn (II) complexes using ciprofloxacin and neutral bidentate ligands were synthesized and characterized using absorption spectra, viscosity measurements, as well as gel electrophoresis studies. Absorption spectral study indicate that the Zn(II) complexes intercalate between the base pairs of the DNA tightly with intrinsic binding constant in the range. Antibacterial study indicates that all the metal complexes were more active compared to metal salts and Schiff bases. The antimicrobial activity of all the ligands and metal complexes has been examined by minimum inhibitory concentration method All the complexes were found to be more potent than all standard drugs against *S. aureus* and *B. subtilis*. Gel electrophoresis data suggested that presence of H_2O_2 enhances the DNA cleavage to a significant extent. [48]



Cu(N-propyl norfloxacin)(2,2'-bipyridine)cl complex(33)



Zn(norfloxacin)(1,10-phen) Complex (34)

Our research group had synthesized zinc metal complexes with fluoroquinolone antibacterial drugs like Sparfloxacin, Ofloxacin, Levofloxacin, Pefloxacin, Norfloxacin and Gatifloxacin in the presence of a nitrogen donor heterocyclic ligand 1,10-phenanthroline. The antimicrobial activity of the complexes had been tested on two different microorganisms and the results shown a diverse biological activity in comparison to the free fluoroquinolone. The mixed fluoroquinolone and N-donor ligands zinc complexes were found among the most active ones against *E. coli* compared to *S. aureus*. Especially, the zinc-norfloxacin-N-donor complex (**34**) was found the most active one against *E. coli* and *S. aureus* when compared to other corresponding zinc–quinolone complexes.

CONCLUSION

In this review, overviews of the metal complexes of antibiotics with have been discussed. Metal complexes offer a platform for the design of novel therapeutic compounds. Activity of the compound can be increased by the formation of complex with different metal ion. It seems that opportunities exist to develop metalloantibiotics for better and improved activity of parent antibiotics molecule due to altered properties. The encouraging results of preclinical and clinical studies with metal compounds form the basis for further investigations towards the development of metalloantibiotics for better therapeutic profile. Although, metalloantibiotics have some side effects, they are successfully being used in cancer therapy and several other therapies. Therefore there is a need for new approaches that are required to circumvent these drawbacks and cover a way for potent drug treatment.

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