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Review Article

Biological activities of some Fluoroquinolones-metal complexes

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ABSTRACT

Background: Metal ions play a vital role in the design of more biologically active drugs. **Aim:** The paper reviewed the antimicrobial, toxicological and DNA cleavage studies of some synthesized metal complexes of fluoroquinolone antibiotics. **and Methods:** Literature searches were done using scientific databases. **Results:** Computer search was used to reveal relevant studies. Spectrophotometric and X-ray analyses of the metal complexes have revealed the bi-dentate coordination of fluoroquinolone ligand to the metal through the ring carbonyl and one of the carboxylic oxygen atoms. Most of the metal complexes showed comparable activities and in some cases greater activity against tested organisms. On the toxicological tests carried out, some of the metal complexes had less adverse effect on the body tissues studied compared to the parent drugs. The DNA cleavage studies revealed the possibility of the metal-fluoroquinolone complexes destabilizing linear double stranded DNA. **Conclusion:** The reviewed metal complexes of fluoroquinolones have the potential of being used as drugs.

Key words: Ciprofloxacin, fluoroquinolone, metal, antimicrobial, toxicology

INTRODUCTION

The chemistry of metal-drug coordination compounds is more popular now than before in importance particularly in the design of more biologically active drugs.[1] Metal ions are known to affect the action of many drugs. The efficacy of the drugs on coordination with a metal are enhanced in many cases.[2] Metal ions play a vital role in a vast number of widely differing biological processes and depending on their concentration, they may either contribute towards the health of the organism or cause toxicity.[3-6] Several metal chelates are known to possess antibacterial, antifungicidal, antiviral and anticancer activity. In several cases, the metal chelates have been found to be more antimicrobial than the chelating agents themselves.[7]

Recently, attention has been drawn to studies of the antitumor activities of inorganic especially metal complexes. From the initial discovery of the anticancer properties of the inorganic complex cis-diamminedichloroplatinum(II) [cis-$PtCl_2(NH_3)_2$] called CISPLATIN, many metal complexes have been tested for anticancer activities especially platinium(II) compounds,which has meant new advance in cancer medicine research.[8-11] The transfer of metal ion from the ligand to the viruses associated with cancer is a mechanism for releasing the anticancer drug in the locality of the tumor.[11]

MATERIALS AND METHODS

Computer search was used to reveal relevant studies. The metal complexes have been prepared by direct reaction between the ligands

(fluoroquinolones) and the corresponding metal ion (in the form of water-soluble salts) under different conditions. Various solvents were used ranging from distilled water, methanol to concentrated hydrochloric acid in preparing the solution of each reactant. The products were obtained majorly through filtration, washing and re-crystallization. The compounds that have been isolated were mainly amorphous, with fewer crystals.[12]

Various methods were utilized to determine the MIC; starting from the agar diffusion method, serial dilution in solid medium, broth dilution technique, to solid dilution technique. The pH, temperature and environment are factors affecting growth of bacteria. The majority of bacteria grow best at about pH 7.4(slightly alkaline) and incubation for most bacteria is at 37^{o}C.[12,13]

Toxicological studies were investigated in which therapeutic doses of the drugs, fluoroquinolones and the metal complexes were administered *in vivo* to albino rats and some enzyme activities were studied.[13] Binding of the metal complexes to DNA have been carried out on natural genomic DNA (Calf thymus DNA) at pH 7.0. Finally, absorbance versus temperature profile were measured at a particular wavelength in a UV-Vis spectrometer.[14]

FLUOROQUINOLONE ANTIBIOTICS: THEIR ANTIMICROBIAL ACTIVITIES AND TOXICITY

Antibiotics are chemical substances produced by microorganism which inhibit the growth of and/or destroy bacteria and other pathogens. The antibiotics are grouped into families such as penicillins, cephalosporin, tetracycline, polypeptides, erythromycins, fluoroquinolones, aminoglycosides, quinolones, streptogramins, and sulphonamides, with each family comprising many members.[15,16]

Fluoroquinolones (FQs) are new derivatives from the quinolone antibiotics, due to modification on the older quinolones based on structure- activity-relationship. It was discovered that the fluorine group at position 6 and the piperazine group at position 7 greatly enhanced the spectrum of activity.[15,16] Examples of this family are ciprofloxacin, norfloxacin, pefloxacin, ofloxacin, enoxacin, moxifloxacin and so on.[15,16]

Antimicrobial Activity

Fluoroquinolones have broad spectrum of antimicrobial activity, high bioavailability, good penetration into tissues, long serum half-life and safety. These have made the compounds very attractive agents for treating numerous infectious diseases.[15] The site of action of FQs has been pinpointed to a subunit of that remarkable enzyme, DNA gyrase which unwind the supercoiled DNA helix prior to replication and transcription.[16]

Although the FQs are generally characterized by a broad antimicrobial spectrum, their activities against gram-positive organisms are limited with diminished potency especially against staphylococci, streptococci and enterococci.[16] Also majority of methicillin-resistant staphylococci especially *staphylococcus aureus* are now resistant to some currently available quinolones.[15] Therefore efforts have been directed toward the synthesis of compounds which have greater activities against organisms.[17,18] The potential for more structure modification of these synthetic organic compounds is now in existence. Based on these, it was suggested that amino group might have the appropriate steric and electronic requirement to replace the standard fluorine atom at C-6 which is one of the major factors indicated as responsible for the increased activities of the current fluoroquinolones.[17,18] On this basis, a wide series of 6- amino quinolone were synthesized and evaluated for *in vitro* bacteria activity; the result showed that while the C-6 fluorine atom was still the best substituent, good activity could be obtained by replacing it with an amino group while reoptimizing the other by substituents.[17]

Toxicity

In general, fluoroquinolones has been reported to be well tolerated.[19-21] In eukaryotic cells, there was a decrease in scheduled DNA synthesis by ciprofloxacin with minimum inhibitory concentration (MICs) of 270, 100, 1000 and 850 mgL^{-1} in rat thymic and splenic cells, respectively. Comparable value for inhibition of RNA synthesis gave MIC values of 82, 12.5 and 48mg.L^{-1} ciprofloxacin. It caused mechanical damage and elicited a foreign body reaction in the renal tubules. In mice, doses of 0.6, and 20mg.kg^{-1} body weight intraperitoneally caused a dose – dependent clastogenic effect.[21]

Ciprofloxacin is not a primary nephrotoxic substance but in high doses with restricted urine volume and alkaline, urine crystalluria occurs.Crystalluria (crystal containing dihydrate and

magnesium salt of norfloxacin) is said to cause urinary objection in rats and dogs at moderate or high doses when the urine pH is 6.0 and above when norfloxacin is administered. There was no observation of mutagenic effects in the dominant lethal test in mice. Similarly, there was no detection of carcinogenic effect on a 19-month study of chronic administration of norfloxacin to rat at 8-9 times the usual human dose. In mice, doses over 30 times the usual human dose have no effect on fertility.[21]

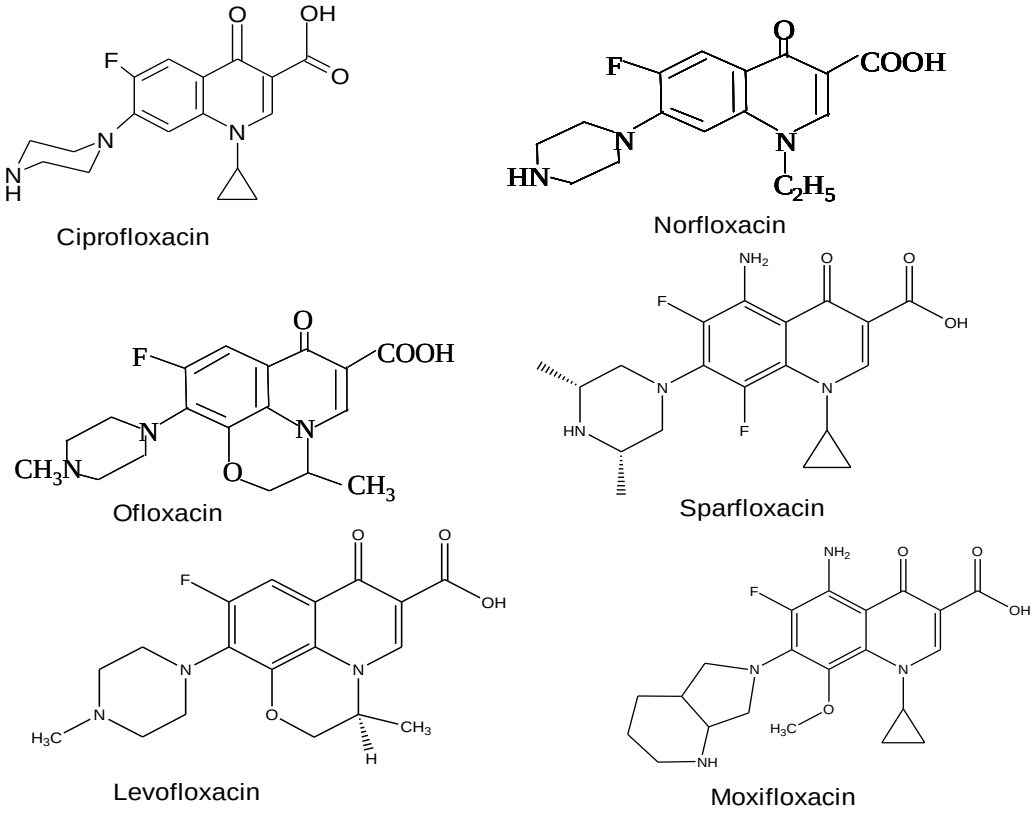


Figure 1: Structures of Some Fluoroquinolones

Acute toxicity has been evaluated on subcutaneous administration to mice and rats. Overt signs include but are not limited to hypo-activity, sedation, prostration, and convulsions. These studies suggested that acute toxicity of ofloxacin was minimal, within the safety margin of the proposed human dose. Chronic oral toxicity studies in rats provided estimates of no-effect dose at 20mgkg^{-1}. Toxicology studies in rats showed evidence of maternal and embryo toxicity, no teratogenicity was observed.[21]

THE INTERACTIONS OF FLUOROQUINOLONE WITH METAL IONS AND THEIR COMPLEXES

Studies with quinolones have revealed metal-drug interaction. Ciprofloxacin, for example, has been observed to exhibit decreased absorption when co-administered with magnesium- aluminum antacids.[21,22] Cations like calcium, iron, zinc also have similar interactions. The decreased bioavailability was presumed to be as a result of formation of poorly absorbed metal ion-ciprofloxacin complexes.[23-26] Kara *et.al.*[24] carried out a study on the bioavailability of ciprofloxacin using eight healthy humans on the effect ferrous sulphate gluconate and a combination table of iron, magnesium, zinc, calcium, copper, and manganese (cetrumforte) co-administered with ciprofloxacin. They found that when ferrous ions were mixed with ciprofloxacin, rapid spectral changes occurred in a manner consistent with oxidation of the ferrous form of iron to its ferric form, followed by rapid formation of a Fe^{3+}-Ciprofloxacin complex in a ratio of 3:1.[24] The close proximity of the carboxyl and keto group on the ciprofloxacin molecule would account for its good chelating properties.

The *in vitro* release of levofloxacin has been studied in presence of metal ions like magnesium, calcium, chromium, manganese, ferric, ferrous, cobalt, nickel, copper, zinc and cadmium in simulated gastric juice, simulated intestinal juice and at blood pH.[27] The availability of levofloxacin was found to be markedly retarded in the presence of all the metals studied.[27] The equilibria in moxifloxacin solution in the presence of gadolinium ion was quantitatively examined to gain better understanding of the identity, stability and speciation in gadolinium and fluoroquinolone family member, moxifloxacin, aqueous solutions.[28,29] Complexes of fluoroquinolones had been synthesized and extensive works were carried out in elucidating their structure. Depending on the medium of preparation of the complexes, different products can be obtained.[12,13,30] Fluoroquinolone antibiotics can take part in complex formation in several ways because they have the relevant ionisable functional groups, that is, the 3-carboxyl group and the N4 at the piperazine substituent. Therefore, they can exist as FQH^{2+}, an acidic cation; FQH, a neutral nonionised specie: $FQH^{\pm}$, an intermediate zwitterions and FQ^{-}, a basic anion, all depending on the pH.

Some metal complexes of ciprofloxacin have been prepared either as single ligand or in mixed ligand complexes.

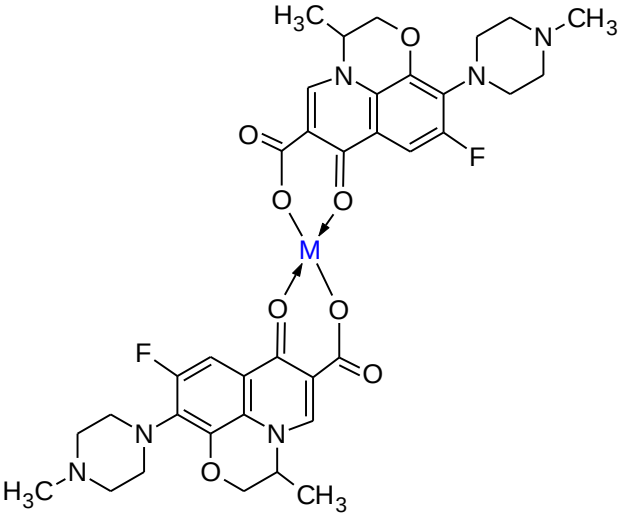


Figure 2: Binding Site for Ofloxacin

Turel *et al.*[31] prepared a copper(II) complex of ciprofloxacin $[Cu(cf)(H_2O)_3]SO_4.\ 2H_2O$ by direct reaction of copper(II) sulphate pentahydrate with ciprofloxacin in distilled water. The green crystals obtained were subjected to elemental analysis, infrared and X- ray crystallography which showed that the ciprofloxacin atom is bonded to the metal through carbonyl oxygen and carboxylic oxygen atom.[31] Water molecules are also coordinated to the copper.[31] Zupancic *et al.* have also reported the synthesis of two zinc (II) complexes with ciprofloxacin, $[cfH_2]_2[ZnCl_4].2H_2O$ and $[Zn(cf)_2]3H_2O$[32] and a cobalt complex, compound $[Co(cf)_2].3H_2O$.[33] The complex $[cfH_2]_2[ZnCl_4].2H_2O$ was shown to be ionic consisting of a tetrachlorozincate(II) dianion and two protonated monatomic ciprofloxacin molecules, while $[Zn(cf)_2]3H_2O$ and $[Co(cf)_2].3H_2O$ were shown to be molecular with the deprotonated ligand directly coordinated to the metal ion through the two oxygen of the 3-carboxyl and 4-keto groups.[32,33] Obaleye *et al.* have also extensively studied the complexation ability of fluoroquinolones with iron in which similar molecular and ionic complexes were prepared.[12]

Green crystals of the complex $[V^{IV}O(cf)_2(H_2O)]$[34] were isolated and its molecular connectivities established. The two-ciprofloxacinate anion bidentatively coordinated to vanadyl cations as in other ciprofloxacin complex (through the carboxylate and carbonyl oxygen atom) one water molecule is present in the coordination sphere. Drevensek *et. al.*[14] also reported on the synthesis of orange crystals ciprofloxacinium(1+) ciprofloxacinium(2+) tetrachlorocuprate(II) hydrate $(cfH_2)(cfH_3)[CuCl_4]Cl.H_2O$. The interaction of magnesium, calcium and barium perchlorate with Cip. and Nor. has been investigated.[35] The complex formed are $[M(Cip)_2](ClO_4)_2.\ H_2O$ and $[M(Nor)_2](ClO_4)_2.H_2O$ (where $M=Mg^{2+}, Ca^{2+}, Ba^{2}$).[35]

Turel and co-workers[37] studied the synthesis of norfloxacin(nf) metal complexes in acidic medium using $AlCl_3$, $CuCl_2.2H_2O$ and $ZnCl_2$ in conc. HCl. The first compound $(nfH_2)Cl_2.H_2O$ (nfH_2 -double protonated molecule of nf) was found to contain no metal.[37] The compound $(nfH_2)(nfH)(CuCl_4)Cl.H_2O$ and $(nfH_2)(nfH)[ZnCl_4]Cl.H_2O$ (nfH=monopronated molecule of nf) are ionic consisting of a tetrachlorometalate(II) anion and two non equivalent, protonated nf molecules.[37] From the analysis, it was revealed that in strong acidic media, proton is bonded between oxygen, which prevents the coordination of the metal ions to this position; therefore, the metal ion is not directly coordinated to the ligand.[37]

Chen *et. al.*[37-39] have carried out lots of work on the hydrothermal reactions of norfloxacin (H-Norf) with metal salts in which crystals of the samples were obtained. The products contained a direct coordinate bond between H-Norf and metal: $[Mg_2(H_2O)_6(H\text{-}Norf)_2]Cl_4.4H_2O$ and $[Ca_2(Cl)(H\text{-}Norf)_6]Cl_3.10H_2O$.[39] The Mg complex is a dimer in which the two Mg^{2+} ions are bridged by two oxygen atoms from carboxylate groups of the two-drug molecule to give rise to a four-member ring.[39] Each Mg^{2+} is coordinated in an octahedral environment, with the oxygen atom of the quinolone carbonyl and one of the two oxygen atom of the carboxylate chelating to Mg^{2+} ions, resulting in the formation of a stable six-membered ring.[39] The Ca complex was also a dimer, the bridging group is a chloride ion rather than the carboxylate oxygen atom.[39] The coordination geometry around each Ca^{2+} ion is best described as approximately pentagonal bipyramidal in which the H-Norf acts in a bidentate coordination as in Mg^{2+}, resulting in the formation of a stable six membered ring and the chloride ion completes the seven coordination around the Ca^{2+}ion.[37-39]

Metal complexes of Ofloxacin [Ni(II) and Cu(II)] have also been reported.[40-44] Crystals of Zinc-Ofloxacin complexes showed that the compound contains two molecules of ofloxacin per unit zinc atom and each molecule was directly coordinated to the Zn^{2+} ion along with two water molecules giving an octahedral complex $[Zn(Oflo)_2(H_2O)_2].2H_2O$, similar to the molecular structures of the complexes of the other fluoroquinolone.[41]

Palladium(II) and platinum(II) complexes of fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin) $[PdCl_2(L)]$ have also been synthesized.[45] The ligands were coordinated to palladium in the most common manner, a bidentate fashion via the carboxylic and the carbonyl oxygens.[45] Similar complexes have also been reported using bismuth.[46]

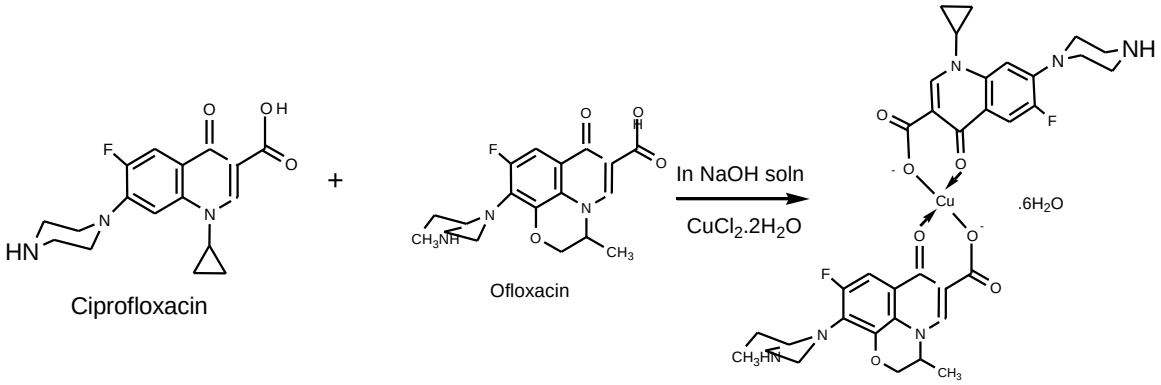
Structural modification of ciprofloxacin and subsequent preparation of the metal complexes has also been reported.[47] Schiff bases of ciprofloxacin has been prepared with a structural formula of $[ML_2]$ with L been ciprofloxacin imine.[47]

Mixed ligand complexes of some fluoroquinolones have also been prepared. Wallis and Gahan studied the reaction of ciprofloxacin (CIP) with iron(III) in the presence of nitriloacetate(NTA) which resulted in the isolation of yellow crystals of complex $[Fe(CIP)(NTA].3.5H_2O$.[48] The coordination of the Fe (III) occurred through the keto and the carboxylic acid oxygen of the Cip ligand formed a six – membered, ring with the four oxygen atoms of the NTA.[48] Copper (II) complex of Ciprofloxacin with 1,10-Phenanthroline and 2,2-bipyridine has also been reported.[49-52] From the result of the analysis, $[Cu_2(cip)_2(bpy)_2(pip)].6H_2O$[49] (bpy=2,2-bipyridyl, cip=ciprofloxacin, pip=piperazinyl anion), showed that the Cu(II) ion displayed a five coordinated square pyramidal coordination with two nitrogen donors from bipy, the 4-keto and 3-carboxylate oxygen of Cip and the third nitrogen atom of the pip anion occupying the fifth site.[49-52]

Chen *et al*. prepared a mixed ligand copper (I) complex $[Cu(PPh)_3)_2$ (H-Norf)].$C1O_4$ of norfloxacin using the solvothermal method.[53] The copper ion displayed a rather distorted tetrahdron being linked to two P atoms of PPh_3 ligand, two O-atoms of the H-Norf ligand as in other norfloxacin complexes.[53] Mixed fluoroquinolone metal complexes have also been reported as illustrated in scheme 1.[54]

ACTIVITY STUDIES OF METAL COMPLEXES OF FLUOROQUINOLONE ANTIBIOTICS

It is of great importance that the relative resistance of microorganism to each therapeutic agent is known since there is no point in administering an antibiotic or its derivatives that has reduced or no effect on the invading pathogens. As an index of antimicrobial activity, the MIC is used.[54-57]



Scheme 1: Illustration of mixed FQs-metal complex formation

Wise and co-workers,[59] determined the MIC of ciprofloxacin and norfloxacin, in comparison with those of other antimicrobial agents using the agar plate dilution method. All the plates were incubated in air at 37^{O}C for 24hrs. The MIC was taken as the concentration (in μg/ml of medium) at which there was an estimated 99% reduction (by counting) in the original inoculum.[59] The MIC of Ciprofloxacin for 90% of *Enterobacteriacea, Pseudomonas aeruginosa, Haemophilus influenzae*, *Neisseria gonorrhoeae, Streptococci, Staphylococcus aureus* and *Bacteriodes fragilis* strains were between 0.008 and 2 μg / ml.[59]

Fass[60] also carried out *in vitro* activity studies on ciprofloxacin, norfloxacin, and other antimicrobial agents. The MICs were determined by a standardized micro dilution method of cation-supplement Mueller-Hinton broth. MICs of the antimicrobial agent were simultaneously determined with the standard inoculum and with inocular containing 100-fold higher and 100-fold lower bacterial concentration.[60] This enhanced the determination of the effects of various inoculums sizes.

Some copper(II) ciprofloxacin complexes $(cfH_2)(cfH_3)[CuC_4]Cl.H_2O$, $[Cu(cf)(H_2O)_3]SO_4.2H_2O$ and $[Cu(cf)_2]Cl_2.6H_2O$ have been tested against the growth of various gram positive and gram negative microorganism.[14] Antimicrobial activities were evaluated using agar diffusion test against the growth of the following bacterial strains, *S. aureus, Streptococcus salvanus, Micrococus luteus, Bacillus cercus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurum.*[14] The complexes showed comparable antimicrobial activity with the free ligand.[14]

The antimicrobial study of $[Cu(cip)_2(bpy)_2(pip)]$ $6H_2O$ in comparison with ciprofloxacin HCl has also been reported.[48] The ligand and complex were tested against gram positive and gram negative bacteria (*Staphylococcus aureus, Micrococus luteus, E. coli* and *P. aeruginosa*).[48] The complexes showed the same MIC against *S. aureus* and *E. Coli* bacteria as the ligand and lower MIC against *M. Luteus* and *P. aeniginosa* than that of the ligand.[48] $[Fe(nfH)_2(H_2O)_2]Cl_3.6H_2O$ and $[Zn(nfH)_2]Cl_2.7H_2O$ have been tested against the gram negative microorganism *E. Coli* and *Bacillus dysentria* bacteria and the complexes were reported to show stronger activity than the ligand, nfH.[12]

The minimum inhibitory concentrations (bacteriostatic) (MIC) and the minimum bactericidal concentrations (MBC) of the ligands and iron(III) complexes of ciprofloxacin ($[Fe(Cip)_2Cl_2]Cl.6H_2O$ and $(H_3Cip)[FeCl_4]Cl.H_2O$) have been determined.[13] The ligand and iron complexes showed antimicrobial effect against the tested organism species except against the molds of *Penicillim* and *Aspergillus* as presented.[13] *Neissera gonorrhoea* was the most sensitive organism to the fluoroquinolones and their complexes.[13] The metal complexes showed comparable activity or greater activity against some of the microorganisms in comparison to the parent compounds and the MIC of the samples against the various isolates ranged from 20 to 450 g/ml of the antimicrobial dilutions, while that of the MBC ranged from 30 to 550 g/ml.[13] Similar observations were made for some metal complexes of norfloxacin and ofloxacin however, increasing the concentrations of the samples led initially to increased bactericidal effect to a certain point, after which the reverse effect occurred, that is increasing concentration leading to decreasing sensitivity.[43]

Antimicrobial studies of Copper (II) complexes of mixed fluoroquinolone (ciprofloxacin, norfloxacin and ofloxacin) ligands (Cip-Nor, Cip-Ofl and Nor-Ofl) have also been reported.[61] Clinical cultures of *Staph. aureus, Klebsiella sp, E.coli, Pseudomonas aeruginosa, N.gonorrhoea, S.typhi, Shigella, Penicillin sp, Aspergillus sp*. were used. *Neissera gonorrhoea* was the most sensitive organism to the fluoroquinolones and their complexes.[61] Some of the metal complexes showed comparable activity or greater activity against some of the microorganisms in comparison to the parent compounds.[61] These concentrations in comparison to previously reported MIC_{90} of the ligands are seemingly high this could be due to the different conditions under which the studies were carried out.[61] These are reflections of the fact of possible interference from the media broth and some other materials and chemicals used during the test, which are not absolutely compatible with conditions present in the cells.[61]

The ciprofloxacin-imines as well as their metal complexes were also evaluated for their antibacterial activity against several bacterial strains, such as Staphylococcus aureus, Bacillus subtilus, Salmonella typhae, and E. coli.[46] It was found that metal complexes are more antibacterial as compared to uncomplexed ligands.[46] A comparative study of ligands and their metal complexes showed that they exhibited higher antibacterial activity than uncomplexed ligands. [46] Such increased activity of metal chelate can be explained on the basis of the overtone concept and chelation theory.[47]

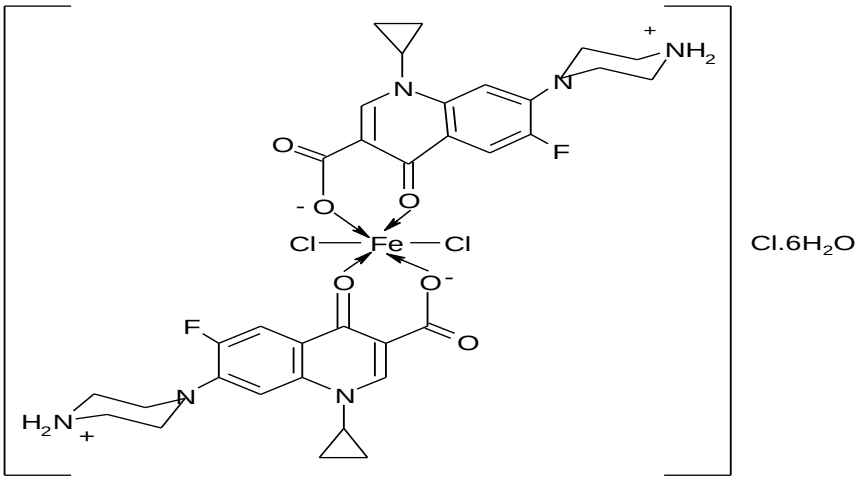


Figure 3: Proposed Structure of $[Fe(Cip)_2Cl_2]Cl.6H_2O$[28]

The antibacterial potential of the magnesium complexes of levofloxacin and ofloxacin -[Mg(R-oflo)(S-oflo)$(H_2O)_2$].$2H_2O$ and [Mg(S-oflo)$_2$(H_2O)$_2$]. $2H_2O$ was assayed using three Gram positive (*Staphylococcus epidermidis, Micrococcus luteus, Bacillus subtilis*) and five gram negative (*Salmonella enteritidis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus foecalis*) bacterial strains.[44] Free levofloxacin and ofloxacin, dissolved in the same buffer, were used as reference compounds.[44] Levofloxacin exerts higher antibacterial activity than ofloxacin and the same trend was observed with magnesium complexes of both antibiotics.[44] None of the tested compounds showed any special preference for gram positive or gram negative bacterial strains.[44]

The antibacterial potential against *Helicobacter pylori* and other microorganisms of the fluoroquinolones, norfloxacin, ofloxacin, ciprofloxacin, sparfloxacin, lomefloxacin, pefloxacin and gatifloxacin, with bismuth has been investigated.[46] These compounds were found to possess strong activity against *Helicobacter pylori* with a minimum inhibitory concentration of 0.5 mgL^{-1}.[46] They also exhibited moderate activity against *Escherichia coli, Staphylococcus aureus*, *Bacillus pumilus* and *Staphylococcus epidermidis.*[46] These bismuth-fluoroquinolone complexes have the potential to develop as drugs against *H. pylori* related ailments.[46] Bismuth-ciprofloxacin complex was found to be most potent against *E. coli* with *MIC* of 0.05 mgL^{-1}, bismuth-ofloxacin complex (against *S. aureus* with *MIC* of 0.125 mgL^{-1}, bismuth-sparfloxacin complex against *S. epidermidis* with *MIC* of 0.125 mgL^{-1} and bismuth-

ofloxacin complex against *B. pumilus* with *MIC* of 0.045 mgL^{-1}.[46]

The activity of the complexes against *Mycobacterium tuberculosis* virulent strain H37Rv was determined.[45] Both, Pd(II) and Pt(II) complexes with sparfloxacin were the most active within each series inhibiting bacterial growth at 0.31 mg/mL.[45] The same MIC was found for the Pt(II) complex with gatifloxacin.[45] On the other hand, the least active complexes of the series were the Pd(II) complex with ciprofloxacin and the Pt(II) complex with ofloxacin, which exhibited MIC¼ 1.25 mg/mL.[45] Although the complexes have not shown better antitubercular activity than free gatifloxacin, in general all of the complexes exhibited good activity and, all but one of them were more active than rifampicin.[45]

$[MnCl_2(NOR)(H_2O)_2]$, $[MnCl_2(SPAR)(H_2O)_2]$, $[CoCl_2(NOR)(H_2O)_2]$, $[CoCl_2(SPAR)(H_2O)_2]$, $[CuCl_2(phen)(NOR)]$ and $[CuCl_2(phen)(SPAR)]$ together with the corresponding ligands were evaluated for their *in vitro* trypanocidal effect, against both bloodstream trypomastigotes and intracellular forms of *Trypanosoma cruzi*.[62] Sparfloxacin and Norfloxacin were poorly effective upon *T. cruzi*. The cobalt complexes were active against intracellular forms of the parasite.[62] The copper complexes displayed a higher activity upon both bloodstream and intracellular forms.[62]

The antimicrobial activity of $[Ti(MOX)_2](SO_4)_2 \cdot 7H_2O$, $[Y(MOX)_2Cl_2]Cl \cdot 12H_2O$, $[Pd(MOX)_2(H_2O)_2]Cl_2 \cdot 6H_2O$ and $[Ce(MOX)_2](SO_4)_2 \cdot 2H_2O$ complexes had been evaluated against three gram-positive and three gram-negative bacteria and compared with the reference drug moxifloxacin.[63] The antibacterial activity of Ti(IV) complex was reported to be significant for *E. coli* K32 and highly significant for *S. aureus* K1, *B. subtilis* K22, *Br. otitidis* K76, *P. aeruginosa* SW1 and K. oxytoca K42 compared with free moxifloxacin.[63]

TOXICOLOGICAL STUDIES OF METAL COMPLEXES OF FLUOROQUINOLONE ANTIBIOTICS

The essential attribute sought in any chemotherapeutic agent is the efficacy of a safe dose.[64] This means that there is a wide range of dosage between the effective and the toxic dose. A simple procedure for a preliminary assessment of the toxicity of drug is the determination of lethal dosage in mice. The LD_{50} test has been criticized on both economic and ethical ground, leading to numerous alternatives been devised with the objective of providing more detailed information on the nature of the toxicity as well as reducing the number of the animals.[65]

Toxicological studies were carried out in which therapeutic doses of some fluoroquinolones (Ciprofloxacin, Norfloxacin and Ofloxacin) and the metal complexes were administered to albino rats *in vivo.*[13,43] The test solutions were also prepared based on therapeutic dose (Ciprofloxacin-500mg, Ofloxacin-250mg and Norfloxacin-400mg, all per 70kg body weight, twice daily for seven days).[13,43] The serum and homogenates of the heart, kidney, liver and small intestine were studied for enzyme activities (Alkaline Phosphatase, Aspartate Aminotransferase, Acid Phosphatase, Alanine Aminotransferase) and tissue-bodyweight ratio. All assays were carried out at 37^oC and optimal condition was employed. From the toxicological studies of ciprofloxacin and its iron complexes, $[Fe(Cip)_2Cl_2]Cl.6H_2O$ and $(H_3Cip)[FeCl_4]Cl.H_2O$, had less negative effect on the body tissues studied compared to their parent drug.[28] Consequently, the metal complexes were much better than the parent drug.[28] The norfloxacin metal complex $(H_2Nor)_2[NiCl_4]$, caused more adverse effects especially on the liver and heart – bodyweight ratio than the parent drug. The metal complexes of ofloxacin caused more adverse effect on some of the tissues than their parent drug. Ofloxacin, $[Cu(Ofl)_2(H_2O)].2H_2O$ and $(H_3Ofl)[CuCl_4].0.5H_2O$ adversely affected the liver/bodyweight ratio though the ofloxacin did at a lesser degree. In general, parent drugs and their metal complexes both have comparable effects on the rat organs studied. However, only the ciprofloxacin-metal complexes were found to be better than their parent drugs.

DNA CLEAVAGE STUDIES ON THE METAL COMPLEXES OF FLUOROQUINOLONES

Deoxyribonucleic acid (DNA) is an most important target molecule in anticancer and antiviral therapies. Studies have been carried out on the interaction of DNA with metal–quinolones complexes.[12] From a theoretical-experimental study on the structure and activity of certain quinolones and the interaction of their Cu (II) complexes on a DNA model, it was suggested that the interaction of the quinolone complexed to a metal is an important step in these processes.[12] Also, a Copper (II)- Ciprofloxacin ionic compound

has been reported to slightly thermally destabilize the linear double stranded DNA.[14] Turel *et al*. established that the electrostatic attraction between the ruthenium complex and DNA in a solution is important for binding because interactions were observed only in a solution with low ionic strengths.[66] The experiments revealed that binding of the organometallic ruthenium complex of ofloxacin ([(η(6)-p-cymene)RuCl(O,O-oflo)]·2.8H(2)O (1·2.8H(2)O), to DNA occurs also if guanine N7 is protonated. The complex was shown to provoke DNA shrinkage.[66]

CONCLUSION

This review has summarized the metal ion interaction with some fluoroquinolones, some synthesized metal-fluoroquinolone complexes, their biological activities and potential as safe antimicrobials. Since emergence of resistance to antimicrobial drugs has become an issue of public health concern, it is thus pertinent to develop new agents with antibacterial activities to curb infections by these resistant strains. Since some of these metal complexes showed better antimicrobial activity than the parent drugs, they have potential to be used as antibacterial and this should be explored.

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