

# The Complexes of Metal Ions with Fluoroquinolones<sup>1</sup>

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Received February 11, 2008

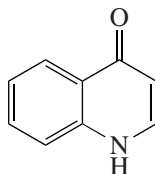
**Abstract**—Fluoroquinolones are defined as an important group of synthetic antibacterial compounds, having a fluorine atom at position 6 and a piperazine ring at position 7 of quinolone-3-carboxylic acid. It was proved that the activity of quinolones was decreased in the environment of certain metal ions by the formation of sparingly soluble metal complexes. The proposed reason for such maintenance might be the chelate bonding of the quinolone to the metal. Again, it was proposed that metal ions, especially magnesium ions, were engaged in the mode of action of quinolones. In this review article, selected structures of fluoroquinolones metal complexes were performed and discussed in terms of their therapeutic application. The nuclease activity and antibacterial activity tests were presented and the effects of metal complexes were compared to free fluoroquinolones. Finally, the results were introduced.

DOI: 10.1134/S1070328409020018

## INTRODUCTION

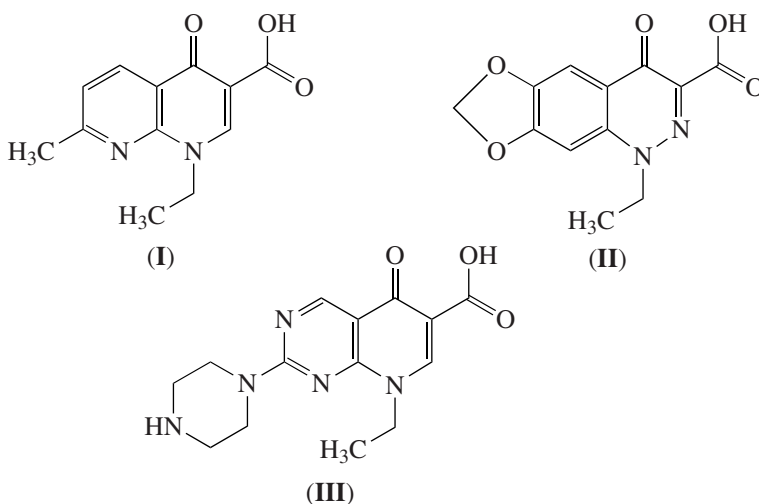
**Characteristic of fluoroquinolones.** The term “quinolones” is usually reserved for the quinolone car-

boxylic acids or 4-quinolones, which are the group of synthetic antibiotics with bactericidal action containing a 4-oxo-1,4-dihydroquinolone skeleton [1, 2]:



Nalidixic acid (**I**) [3–6] and cinoxacin (**II**) [7] belong to the first generation of quinolones, and the second generation of quinolones is piperimide acid

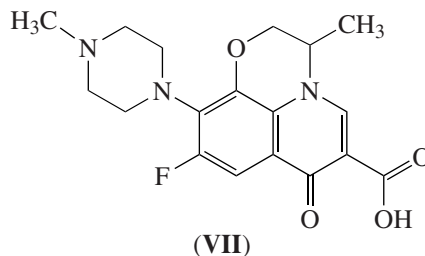
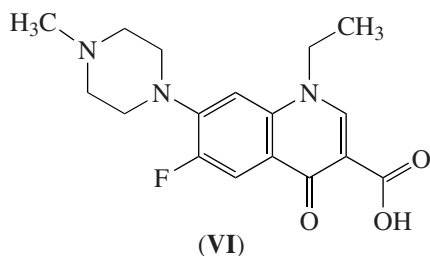
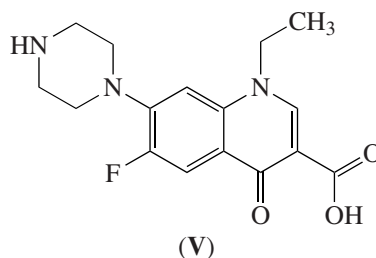
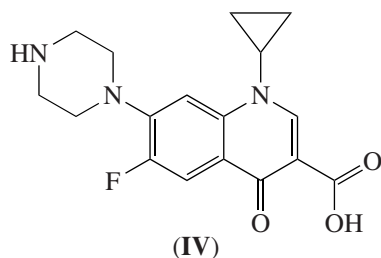
(**III**). All of them are active only against gram-negative bacteria (*Escherichia coli*, *Proteus*, *Shigella*, and *Klebsiella*) [8]:



<sup>1</sup> The article is published in the original.

The third generation of quinolones are fluoroquinolone antibiotics, such as ciprofloxacin (1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid (**Cf**, **IV**)), norfloxacin (1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1H-quinoline-3-carboxylic acid (**Nf**, **V**)), pe-

floxacin (1-ethyl-6-fluoro-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-3-quinolone carboxylic acid (**Pf**, **VI**)), and ofloxacin (+/-)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (**Oflo**, **VII**):



They were chemically modified to become more efficient antibacterial agents, which exhibit a broad spectrum of high activity against gram-negative bacteria (*Pseudomonas aeruginosa*, *Neisseria gonorrhoea*, *Haemophilus influenzae*) and lower activity against gram-positive bacteria (*Enterobacteriaceae*, *Staphylococcus aureus*) and also show significant activity against anaerobic bacteria [9].

Fluoroquinolones were discovered and presented as broad-spectrum antibacterial agents, which were derivatives of quinolone carboxylic acid [10]. Most of fluoroquinolones have a carboxylic group at position 3 and a carbonyl group at position 4: therefore they are usually referred to 4-quinolones. Then, it was discovered that the addition of the fluorine atom at position 6 and the piperazine ring or methyl piperazinyl group at position 7 greatly enhanced the spectrum of their activity. Differences at the moiety present at N(1) and at C(7) position have a strong impact on the microbiological activity and the pharmacokinetic properties of drugs [11].

Fluoroquinolones are specific inhibitors of the bacterial DNA gyrase (**topoisomerase II**) and prohibit DNA relegation activity and distort DNA in the complex **topoisomerase IV** [12], and inactivation of these enzymes is lethal to the bacteria. Due to their specific mode of action, they are considered to be the broad-spectrum antibiotics active against gram-positive and gram-negative pathogens. Additionally, they combat infections caused by microorganism that are resistant or multi-resistant to other antimicrobials, such as amino glycosides and tetracycline's of  $\beta$ -lactams [13].

Fluoroquinolones are extremely useful for the treatment of a variety of infections, especially urinary track infections, but also soft tissue infections, respiratory infections, bone-joint infections, typhoid fever, sexually transmitted diseases, prostatitis, community-acquired pneumonia, conjunctivitis, acute bronchitis, and sinusitis [14].

**Mechanism of fluoroquinolone action.** The fluoroquinolones' mode of action consists of interactions with both enzymes topoisomerase IV and topoisomerase II. These interactions are recognized as drug targets. The two enzymes frequently vary in their sensitivities to many quinolones, and predominantly topoisomerase II is more sensitive to gram-negative bacteria and topoisomerase IV is more sensitive to gram-positive bacteria [15].

The development of the ternary complex of fluoroquinolone, DNA, and also topoisomerase II or topoisomerase IV supervene through the interactions in which quinolone binding appears to infer transitions in DNA and the topoisomerase respectively, that occur separately from the DNA cleavage, which is the general mark of quinolones action [16]. Inhibition of DNA synthesis by fluoroquinolones requires the targeted topoisomerase to possess DNA cleavage capability, and failures of the replication fork with reversible fluoroquinolones—DNA—topoisomerase complexes transform them into an irreversible molecule [17–19].

Different reports appeared in the literature that were connected with the molecular details of drug–DNA and drug–enzyme interactions. The first drug–DNA models were proposed by Shen and co workers and included hydrogen bond type interactions models between the

DNA unpaired bases and the quinolone, as well as stacked dimerization of the drug [20]. These models were modified and implied a possible interaction between the C(7) substituent quinolone and the B subunit of DNA gyrase.

There was also many theories about the mode of action of fluoroquinolones focused on the involvement of magnesium ions [21]. One of the more recent model suggested that ions  $Mg^{2+}$  played an important role in the drug binding to a DNA–gyrase complex. Certainly it is not yet known whether the magnesium ions influence is due to its stabilizing effect on the DNA topology or its ability to chelate with the keto and carboxylate groups of quinolones [22, 23].

It was also reported that a restrained strong interaction between quinolones and plasmid or single-stranded DNA appear only in the presence of a physiological concentration of  $Mg^{2+}$ . The satisfactory relationship between the binding constants for the ternary DNA–drug– $Mg^{2+}$  complex ( $K_T$ ) and gyrase poisoning activity was indicated. Nevertheless, the authors did not propose a structural model for the ternary complex, with the exception of reporting that the data did not enforce a mechanism of action based upon quinolone intercalation into B-DNA [24].

Nordén et al. using similar experimental methods (CD and LD measurements) discovered a near perpendicular orientation of the norfloxacin chromophore plane relative to the DNA axis that precluded classical surface binding. However, the possibility of classical intercalation was precluded based on DNA unwinding experiments [25].

**Correlation fluoroquinolones with metal ions.** In 1985, there was first information about concurrent administration of magnesium and aluminium containing antacid with ciprofloxacin resulted in a nearly complete loss of activity of the drug [26]. Antacids not only contain aluminium and magnesium, but also enclose other ions such as calcium and bismuth. Thereby, several authors began to observe the reasons for the decreased activity of fluoroquinolones in the presence of different ions (iron, zinc, calcium, aluminum, or magnesium), which were components of other antacids or the multivitamin mixtures [27–30]. Due to these studies, it was reported that patients who orally administered fluoroquinolones should avoid mixtures containing multivalent cations, because quinolones were chelate bonded to these metals, in consequence formed metal complex in the gastric system [31].

These studies were mainly addressed to identify the groups directly attached to the metal site and establish the structure of the coordination compounds thus formed [32–34].

It seems that the role of metal ions is imperative for the way of function of fluoroquinolones. The synthesis and characterization of new metal complexes with fluoroquinolones are a great importance for better understanding the drug–metal ion interactions. It was sug-

gested that the reactions of metal ions with fluoroquinolones were essential for the activity of these antimicrobial agents, and the metal ions (magnesium, copper, and iron) may bridge the binding of the quinolone to DNA gyrase or of bacterial DNA directly [35, 36].

The uptake of norfloxacin by *Escherichia coli* was analyzed under different pH conditions and by the monovalent / divalent metal ion concentrations. The simple diffusion mechanism for fluoroquinolones incorporation into cells was contributed by the result to the study. The uptake process declined under acidic conditions. The inherence of  $Na^+$  and  $K^+$  ions did not impact on the outcome to a prominent field, while divalent ions caused a dramatic inclination in drug incorporation. The antibacterial activity estimated under identical experimental conditions performed a straight relationship with the uptake data. It was suggested that the ability of the drug penetration into cells correlated to an action of its net charge. The zwitterionic form of a molecule represented the maximum permeation properties, while the uptake was intensely diminished when the drug bear a net charge as an effect of ionization or complex formation with divalent ions [37].

Metal ions play a pivotal role in the actions of some synthetic and natural antibiotics and are engaged in specific interactions of these molecules with proteins, nucleic acids, and other bio-molecules [38].

Magnesium as a very popular ion in biological fluids, being not only important for the activity of quinolones but also for other antibacterial agents, such as aureolic acid and its derivatives, various tetracyclines, and some others [39]. Due to the facts some of metal–quinolone complexes interact with DNA and impair its function, quinolones are also classified as “metalloantibiotics” [40].

The increasing incidences of bacterial drug resistance indicated an improvement of the existing antimicrobial drugs and development of new ones. The most important and characteristic target in pathogenic microorganisms is gyrase. As it was mentioned, quinolones are known as inhibitors of topoisomerase II. The molecular details of the inhibition of gyrase activity still remain unclear, but most models include divalent ions, either as a cofactor for the gyrase activity, or as a neutralizing agent of the negative phosphate groups of DNA [41]. The concern about the rational design of new transition metal complexes, which bind and cleave duplex DNA with high sequence or structure selectivity, is developing. According to these facts, the further aim of referred works was to determinate biological activity of the new complexes [42].

Several authors reported that the antibacterial activities of fluoroquinolones were altered in the presence of divalent cations [43]. The in vivo behavior of fluoroquinolones as antibacterial agents was strongly affected by their physicochemical properties, in particular, their

acid-base properties, as well as their capability to form complexes with metal ions [44].

Recent data reported a significant role of the  $\text{Cu}^{2+}$  ion in the mode of action of fluoroquinolones. It was suggested that the intercalation of the drug as a complex with metal ions would be an important step in this mechanism [45]. Additionally, quinolones impact on trace metal metabolism supposing to be potent inhibitors of copper- and zinc-dependent enzymes [46].

The suggested way of the interaction between quinolone and metal ions was chelation between the metal and the 4-oxo and contiguous carboxyl groups. Quinolones can bind several divalent metal ions, including  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{2+/3+}$ ,  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$ , and  $\text{Al}^{3+}$ , which may result in changes in their activity [47–49]. For example,  $\text{Mg}^{2+}$  and  $\text{Al}^{3+}$  were found to decrease the activity of the drugs, whereas the  $\text{Fe(III)}$  and  $\text{Zn(II)}$  complexes were thought to exhibit higher activity [50].

There are some data that present biological activity of some quinolone–metal complexes against various microorganisms and some other positive effects on the treatment of certain diseases. Certain bacterial infections now defy all known antibiotics, and antibiotic resistance is a growing problem. It is obvious that there is a great need for new antibacterial agents and metal complexes could be active against multi-resistant microorganisms [51].

**Chemical information.** The majority number of analytical methods were reported in the literature for the determination of quinolones in pure forms, dosage forms, and biological fluids [52]. The reported papers presented several free fluoroquinolone structures, such as pefloxacin methanesulfonate [53, 54], ciprofloxacin hexahydrate [55], and ciprofloxacin lactate [56].

The crystal structure of fluoroquinolone complexes evidence that the chemotherapeutic agents can take part in the formation of complexes in a great number of ways.

Low solubility of quinolones and their complexes in the pH range 5–10 presents a great difficulty in preparing single crystals of quinolone metal complexes. Only several crystal structures of coordinated quinolone to the metal ion have been already known. The optimum pH range for the formation of the metal complexes is 3.5–4.5 for all fluoroquinolones. At this pH quinolones mainly exist in their protonated form and complexation with a metal ion is accompanied by the liberation of a proton from the pyridine carboxylic group [57].

On the other hand, numerous crystal structures of mixed complexes with coordinated quinolones and N-, S-, or other O-donors were reported. In the like manner, metal–quinolone compounds in their ionic state can be easily achieved. In several analytical investigations it was presented that fluoroquinolone was coordinated to the metal in the pH range higher than 7.

The complexes isolated from acidic media usually contained single and / or doubly protonated quinolones that were unable to bind to the metal ion and, in these

cases, only the electrostatic interaction was observed between the drug and metal ions [58].

In other studies, it was found that neutral fluoroquinolones in the zwitterionic state were able to form simple complexes. In these complexes, the quinolone is coordinated through the ring carbonyl group at position 4 and through one of the oxygen atoms of the carboxylate group at position 3. Moreover, fluoroquinolones can act as bridging ligands and then be capable of forming polynuclear complexes [59].

It is important to mention that mostly the carboxylic group is not deprotonated and the hydrogen atom of this group is hydrogen-bonded to the adjacent 4-oxo atom. Sometimes the carboxylic group is ionized and the molecule presents in its zwitterionic form with protonated terminal nitrogen of the piperazine ring in the solid state [60, 131].

Most of fluoroquinolones are sparingly soluble in a wide range of pH [61]. Mixing of an aqueous solution of metal salts and a quinolone solution mostly results in precipitation, making it difficult in growing crystals of complexes.

A large number of chromatographic methods have been reported for the determination of fluoroquinolones. Ofloxacin [62], pefloxacin [63], norfloxacin [64], and ciprofloxacin [65] were determined by high-performance liquid chromatography (HPLC). Until presently, various spectrophotometric methods have been described for the determination of quinolone [66, 67] by charge-transfer complex formation with 2,3-dichloro-5,6-dicyano-*p*-benzo-quinone, chloranilic acid, and 7,7,8,8-tetracyanoquinodimethane [68]. Furthermore, there were a number of other methods presented for their determination, such as fluorimetry [69, 70], polarography [71], voltammetric [72], and capillary electrophoresis [73].

## CHARACTERISTIC OF METAL COMPLEXES WITH FLUOROQUINOLONES

### *Ciprofloxacin*

Ciprofloxacin (Cf) is one of two fluoroquinolones with the widest clinical application. In 1986, it received Food and Drug Administration approval [74].

The ability of ciprofloxacin to form metal complexes and transport of ciprofloxacin through bacterial membranes is extremely pH-dependent with peaking at neutral pH [75, 76].

It was suggested that the zwitterionic and uncharged structure of quinolone was responsible for passive transport through cytoplasmic membranes. In stomach pH is low, whilst in the intestine is rather higher, so transport of ciprofloxacin here would be best. Additionally, the intestine is the place where the metal–quinolone complexation occurs, decreasing absorption of the drug [77].

**Bismuth complex.** Ciprofloxacin was described as the most active quinolone against *Helicobacter pylori*,



but it was inefficient in eradicating the bacteria from the stomach of patients with gastritis [78]. Additionally, it is worth mentioning that the use of bismuth for the treatment of gastric diseases is very popular [79, 80].

Turel et al. [81] explored the bismuth (III) complex of ciprofloxacin  $(\text{Cf}_2)(\text{Cf})[\text{BiCl}_6] \cdot 2\text{H}_2\text{O}$  to find new and better activities against *Helicobacter pylori*. In this work, the crystal structure of this complex was presented, where  $\text{Cf}_2$  was a doubly protonated and  $\text{Cf}$  was once protonated molecule of ciprofloxacin. One of the ciprofloxacin molecule was protonated at the carbonyl oxygen and nitrogen of the piperazine ring, and another at nitrogen only. Two water molecules participated in the hydrogen bond network.

**Cerium complex.** The crystal structure of the cerium (III) complex with ciprofloxacin  $[\text{Ce}(\text{Cf})_2(\text{H}_2\text{O})_4]\text{Cl}(\text{H}_2\text{O})_{3.25}(\text{C}_2\text{H}_5\text{OH})_{0.25}$  was published. The quinolone was bonded to the metal through 3-carboxyl and 4-keto oxygen and the coordination number of the ligand was eight [82].

**Cobalt complexes.** The synthesis of the complex  $[\text{Co}(\text{Cf})_2] \cdot 3\text{H}_2\text{O}$  as single crystals was possible only when it was isolated from a saturated solution of fluoroquinolone under the basic conditions ( $\text{pH} \sim 8$ ). It was proved that at higher pH, where the solubility of ciprofloxacin was considerably higher, the coprecipitation of metal hydroxide baffled the synthesis of the pure metal complex.

This achieved that the complex was insoluble in water and organic solvents. It decomposed in dilute solutions of all strong acids. It was described by elemental analysis, FAB-MS, TG analysis, IR spectroscopy, and magnetic measurements. Mass spectrometry of the compound marked bonding of the  $\text{Co}^{2+}$  ion to quinolone, forming a  $[\text{Co}(\text{Cf})_2]$  molecule. The IR spectrum of the compound was similar to that of  $[\text{Cu}(\text{Cf})_2]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ . The cobalt ion was coordinated to the two pyridine and two carboxylic oxygen atoms of two quinolone molecules. Thermal analysis indicated that water molecules were included as lattice water in the crystal structure of  $[\text{Co}(\text{Cf})_2] \cdot 3\text{H}_2\text{O}$  [83].

**Copper complexes.** Jimenez-Garrido et al. [84] prepared three mixed complexes of ciprofloxacin with Cu (II), namely  $[\text{Cu}(\text{Cf})_2(\text{ClO}_4)_2] \cdot 6\text{H}_2\text{O}$ ,  $[\text{Cu}(\text{Cf})_2(\text{NO}_3)_2] \cdot 6\text{H}_2\text{O}$  and  $[\text{Cu}(\text{Cf})_2(\text{C}_2\text{O}_4)_2] \cdot 2\text{H}_2\text{O}$ . The single-crystal structure of  $[\text{Cu}(\text{Cf})_2(\text{ClO}_4)_2] \cdot 6\text{H}_2\text{O}$  was determined [85] and characterized. The complex composed of the  $[\text{Cu}(\text{Cf})_2(\text{ClO}_4)_2]$  unit with two semi-coordinated  $\text{ClO}_4^-$  anions, and one uncoordinated water molecule. The metal ion was in a tetragonally distorted octahedral environment [84, 86].

It was suggested that the binding of copper(II) depended on the features of other ligands (phenantroline) presented in the solution [87]. For the copper(II) complex with nalidixic acid, in the absence of the extra ligand, chelation occurred through the 3-carboxylate group, while in the presence of the ligand, chelation

was through the 3-carboxylate and also 4-keto groups [89]. The ciprofloxacin complexes in the absence of the ligand,  $[\text{Cu}(\text{Cf})_2\text{Cl}_2] \cdot 6\text{H}_2\text{O}$ , and in the presence of added ligands,  $([\text{Cu}(\text{Cf})(\text{Bipy})(\text{Cl})_{0.7}(\text{NO}_3)_{0.3}](\text{NO}_3) \cdot 2\text{H}_2\text{O})$ , where Bipy—2,2'-bipyridine, were explored. In both complexes, copper (II) was coordinated to the carbonyl group at position 4 and the oxygen of the carboxylate group at position 3 of ciprofloxacin to form a six-membered ring [88]. The second complex included the  $[\text{Cu}(\text{Cf})(\text{Bipy})(\text{Cl})_{0.7}(\text{NO}_3)_{0.3}]^+$  cation, nitrate anion, and two uncoordinated water molecules. It was a five-coordinate complex with the central metal ion coordinated with two nitrogen groups from Bipy, the keto and 3-carboxylate oxygen groups, and the disordered  $\text{Cl}^-/\text{NO}_3^-$  ions occupying the fifth site [89].

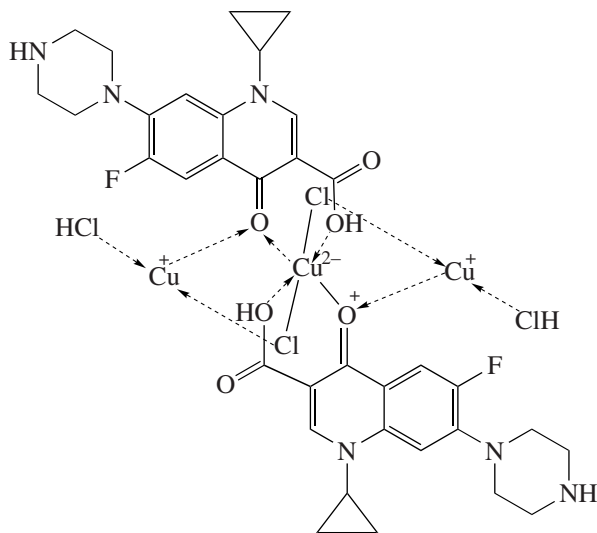
The  $[\text{Cu}(\text{Cf})_2\text{Cl}_2] \cdot 6\text{H}_2\text{O}$  complex of ciprofloxacin with copper(II) was prepared by mixing an aqueous solutions of ciprofloxacin and copper salts (chloride sulfate). The copper ion was surrounded by four oxygen atoms of the ciprofloxacin carbonyl groups and positioned at the center of inversion [90].

Another complex of copper with ciprofloxacin,  $[\text{Cu}(\text{Cf})(\text{H}_2\text{O})_3]\text{SO}_4 \cdot 2\text{H}_2\text{O}$ , was described, where only one molecule of quinolone was coordinated to the metal. The  $\text{Cu}^{2+}$  ion was a slightly distorted square pyramidal with the coordination environment around the central atom in the structure. Ciprofloxacin was coordinated to copper through the carbonyl atom and carboxylic atom. Two water molecules were coordinated at a longer distance [91].

The first known mixed-valence Cu(II)–Cu(I) complex with  $\text{Cf}[\text{Cu}^{\text{II}}(\text{Cf})_2(\text{Cu}^{\text{I}}\text{Cl}_2)_2]$  was achieved by Drevensek et al. [92]. The complex was isolated due to the reaction from a mixture of ciprofloxacin, copper(II) chloride dehydrate, and L-histidine in a molar ratio of 1 : 1 : 1. The unit included two zwitterionic molecules of the ligand,  $\text{Cu}^{2+}$  ion, and two dichlorocuprate(I) anions. In this complex, the copper(II) atom was distorted and surrounded by four oxygen atoms in the equatorial positions and two chloride ions of the dichlorocuprate(I) groups occupying the vacant apical positions. The chloride ion of the  $\text{CuCl}_2$  moiety served as the first bridging ligand between the Cu(II) and Cu(I) centers. The second bonding between two copper atoms, Cu(I) and Cu(II), indicated the quinolone oxygen O(1) that is engaged in a weak interaction with the Cu(2) atom.

It is necessary to mention that the absence of L-histidine resulted in the isolation of  $[\text{Cu}(\text{Cf})_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$ . Certainly, the added ligand played a role of a reducing factor in the reaction and was not able to coordinate. The interaction of copper and histidine is extremely important in biological fluids. Metal-catalyzed oxidation of proteins is a strongly selective reaction that appears principally at protein sites with transition metal binding capacity. Several sites including histidine have affinity for Cu(II). It was realized that copper binding to prior protein at a histidine-rich region resulted in a fac-

ile oxidation of the protein molecule, the reaction that was characterized by the vast aggregation and precipitation of prion protein [93]. Mixed-valence copper complexes were of great interest, because they display interesting properties, provide information on electron-transfer, and could serve as models for copper-containing enzymes [94, 95]. Structure of the mixed-valence complex Cu(II)/Cu(I) of ciprofloxacin is the following:

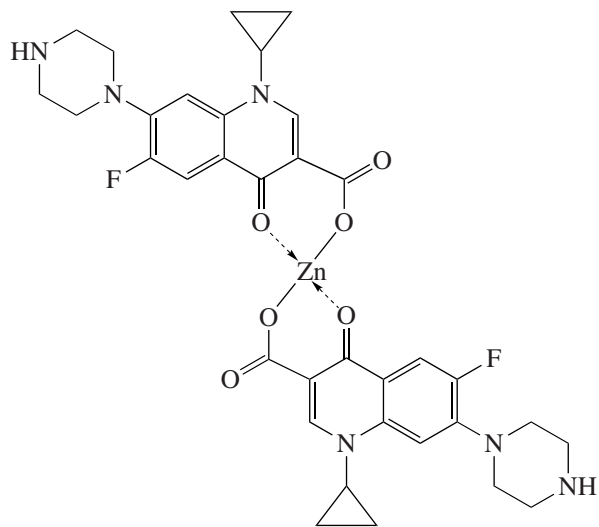


**Iron complex.** Wallis et al. [96] prepared from an aqueous solutions the iron (III) complex with ciprofloxacin and nitriloacetate (Nta) as an additional ligand,  $[\text{Fe}(\text{Cf})(\text{Nta})] \cdot 3.5\text{H}_2\text{O}$ . It was important to use a dilute ammonia solution to adjust the pH to 7. The compound folded of a neutral  $[\text{Fe}(\text{Cf})(\text{Nta})]$  complex and 3.5 water molecules. The iron was bonded to the keto and carboxylic oxygen of Cf, and the coordination number of ligand was six. The piperazinyl ring had a positive charge on the external nitrogen.

**Vanadium complex.** The vanadium complex was isolated from an aqueous solution of  $\text{VO}_2\text{SO}_4$  and Cf. The crystals were very unstable and contained a large amount of disordered water molecules, so the exact solution of the structure was not possible to be achieved. The complex  $[\text{VO}(\text{Cf})_2]\text{SO}_4 \cdot 10\text{H}_2\text{O}$  was characterized by chelate bonding of vanadium to 4-oxo and carboxylic oxygen of quinolone [97].

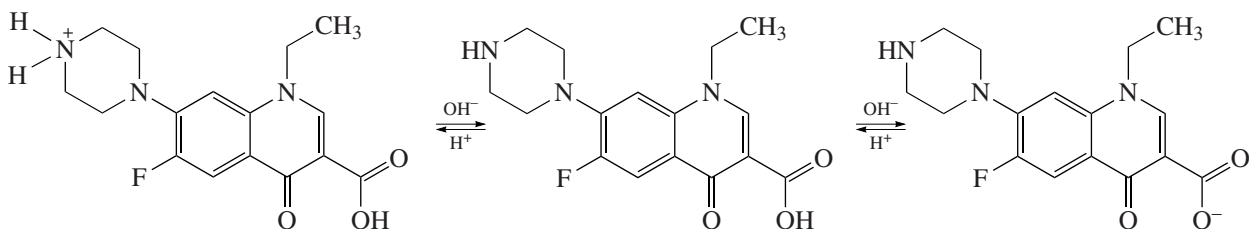
**Zinc complexes.** The pH dependence of the making complexes between Zn(II) and Cf was studied in [98]. Two compounds of ciprofloxacin with Zn(II),  $[\text{Cf}]_2 \cdot [\text{ZnCl}_4] \cdot 2\text{H}_2\text{O}$  and  $[\text{Zn}(\text{Cf})_2] \cdot 3\text{H}_2\text{O}$ , were gained. X-ray diffraction indicated that the structure of the first compound was ionic, consisting of the tetrachlorozin-

cate(II) dianion and two protonated monocationic ciprofloxacin molecules. The second compounds was achieved as crystals from an aqueous solution of ciprofloxacin hydrochloride and the salt of zinc in a range of pH 8 by the addition of sodium hydroxide. On the basis of the analysis of these two compounds, it was suggested that the second compound was coordinated with Zn(II). This complex of Cf with Zn(II) was insoluble in water, methanol, ethanol, chloroform, acetone, ether, ethylene glycol, 2-propanol, carbon tetrachloride, cyclohexanone, DMF, and DMSO. It decomposed in dilute solutions of all strong acids. Complex ciprofloxacin with Zn(II) is shown below.



Norfloxacin

The molecule of norfloxacin (Nf) in its zwitterionic form possesses a favorable solubility in acidic or basic solvents, whereas its solubility in water, methanol, ethanol, and chloroform is very poor [61]. On the other hand, the metal complexes of norfloxacin can be better solved in water, methanol, and ethanol. This increase in solubility can improve the ability of drug in transport through the membrane of a cell and then enhance the biological utilization ratio and activity of the drug [99]. It is worth to accent that the hydrothermal reaction of norfloxacin (with non methylated piperazine) with different metal ions at pH between 7 and 8 resulted in a 2D squared grid of complexes, where also N-piperazine is coordinated to the metal [100]. Zwitterionic structure of norfloxacin is shown below:



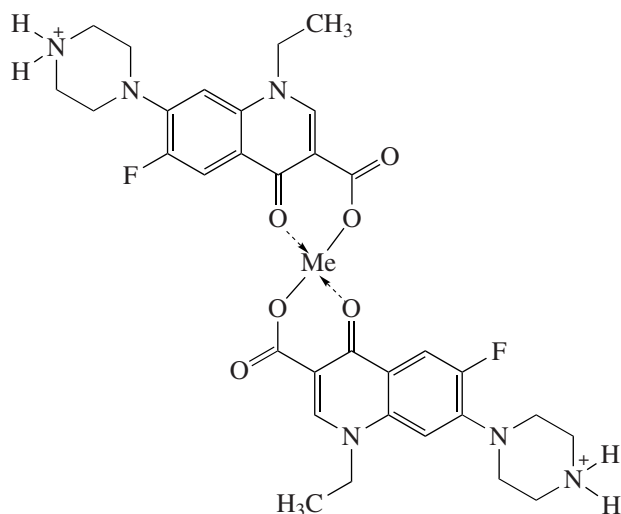
*Transitional Metal Complexes*

In vivo there are slightly low concentrations of transitional metals, and their ligand environment can be considerably altered when a therapeutically effective dose of drug is administered. This change in the balance between the metal ion and ligand may have a intensive impact on the antimicrobial activity of the complex against potentially susceptible bacteria [101].

The coordination compounds with transition metal ions have not been completely examined. Especially, the studies on the crystal structures of norfloxacin directly chelated to transition metal ions are very rare.

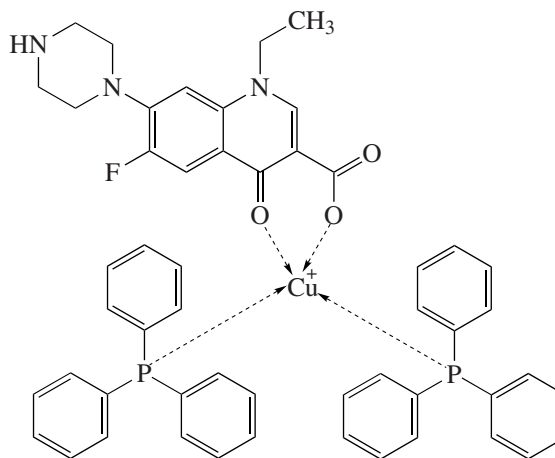
**Magnesium, calcium, and barium metal complexes.** Chen was the first one who described the synthesis of two dimeric complexes of norfloxacin with  $\text{MgCl}_2$  and  $\text{CaCl}_2$  [102]. The crystallographic study of these complexes proved that the carbonyl oxygen and one of the oxygen atoms of the carboxylate group of norfloxacin were directly coordinated to magnesium or calcium ions.

In 2001, Al-Mustafa isolated and introduced the characterization of the complexes formed from the interaction of norfloxacin and ciprofloxacin with magnesium, calcium, and barium perchlorate in methanol [103]. All of the isolated complexes were synthesized by the reaction of the metal salt with drug in a 1 : 2 molar ratio. The complexes were white air-stable solids at room temperature. The thermogravimetric analysis (TGA) [104] and differential scanning calorimetry (DSC) data indicated that all of the complexes were unstable and decomposed in two steps at temperatures above 270°C, which is characteristic of the quinolone complexes. These achieved complexes were insoluble in benzene, chloroform, and dichloromethane, and other nonpolar solvents are slightly soluble in water, methanol, and ethanol and are soluble in DMF and DMSO [103]. Proposed structures of the Nf complexes with  $\text{Ca(II)}$ ,  $\text{Mg(II)}$ , and  $\text{Ba(II)}$  are shown below:



**Copper complexes.** In 2001, Chen et al. prepared the mixed-ligand copper(I) complex  $[\text{Cu}(\text{PPh}_3)_2(\text{Nf})] \cdot$

$\text{ClO}_4$  [105]. The crystal structure of this compound consisted of the  $[\text{Cu}(\text{PPh}_3)_2(\text{Nf})]^+$  cation and  $\text{ClO}_4^-$  anion. There was no appreciable cation–anion interaction in the structure but the static interaction one. The copper ion in this complex displayed a rather distorted tetrahedron, and was linked to two phosphorus atoms of the triphenylphosphine ( $\text{PPh}_3$ ) ligands, and two oxygen atoms of the ligand. Structure of the mixed-ligand complex of Nf with  $\text{Cu(II)/Cu(I)}$  is shown below:



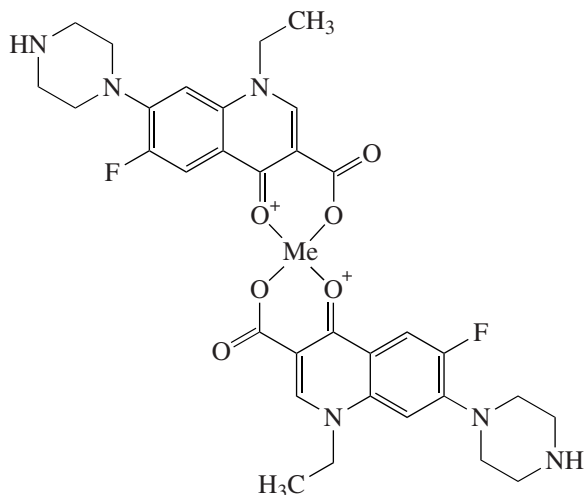
The most part of Nf complexes were known to behave in a similar way, where the norfloxacin ligand was chelated to the copper ion through the  $\text{O}_{\text{keto}}$  and  $\text{O}_{\text{carbox}}$  atoms displaying a stable six-membered chelating ring [106]. Consequently, the coordinate mode around  $\text{Cu(I)}$  in this complex was quite different from those found in the  $\text{Fe(III)}$ ,  $\text{Co(II)}$ , and  $\text{Zn(II)}$  complexes with Nf proposed by Gao et al. [107]. The quinolone ring system was almost planar, and the ethyl group stuck out of the plane. The piperazine ring was in the chair conformation, where the terminal nitrogen atom was protonated, which probably explained why it failed to coordinate to the  $\text{Cu}^+$  ion. The charge of the quinolone molecule was neutralized by the positive charge of the piperazinyl ring on the external nitrogen; and because of this norfloxacin behaved as a neutral ligand in this complex.

**Cobalt, iron, and manganese metal complexes.**

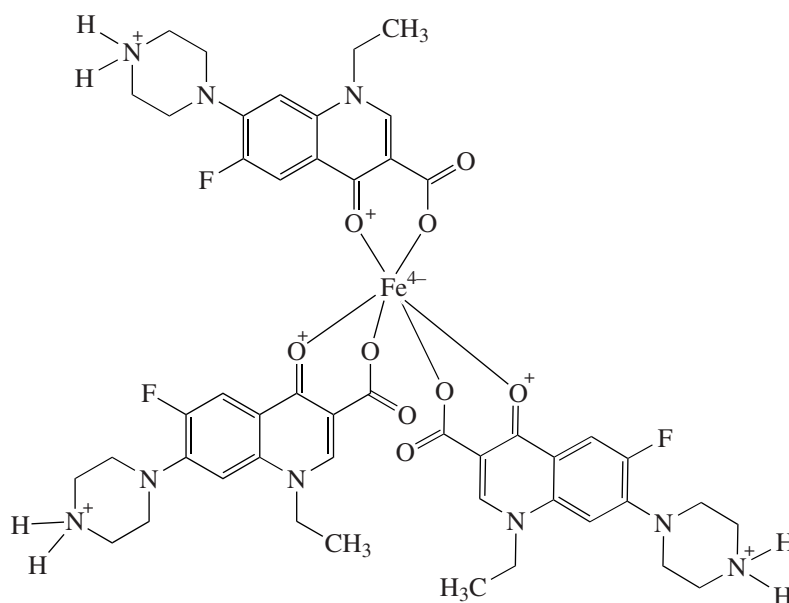
Norfloxacin reacted with  $\text{Mn(II)}$ ,  $\text{Fe(III)}$ , and  $\text{Co(II)}$  in acetone or methanol solutions at room temperature to form solid complexes with a characteristic color of the particular metal ions. The metal ( $\text{Mn(II)}$ ,  $\text{Co(II)}$ , and  $\text{Fe(III)}$ ) to ligand (norfloxacin) molar ratio for all complexes was established on the basis of the elemental analysis: 1 : 2 for  $\text{Mn(II)}$  and  $\text{Co(II)}$  and 1 : 3 for  $\text{Fe(III)}$  [108, 109]. All achieved complexes possessed different numbers of water molecules in particular compounds [110]. The complexes  $[\text{Mn}(\text{Nf})_2](\text{CH}_3\text{COO})_2 \cdot 8\text{H}_2\text{O}$ ,  $[\text{Fe}(\text{Nf})_3]\text{Cl}_3 \cdot 12\text{H}_2\text{O}$  and  $[\text{Co}(\text{Nf})_2]\text{SO}_4 \cdot 8\text{H}_2\text{O}$  were described by infrared spectra analysis. The Nf complexes indicated all the features of a neutral molecule in the zwitterionic form [111].

The novel complexes of norfloxacin with Co(II), Fe(III), and also with Zn(II) achieved by Gao et al. [107] presented better solubility in

water and ethanol than free norfloxacin. Complexes of norfloxacin with Mn(II), Co(II), and Fe(III) are shown below:



M = Mn(II), Co(II).



Al-Mustafa investigated the reaction of norfloxacin (also ciprofloxacin) with iron(II) and iron(III) perchlorate. The different colors of the solid complexes indicated that the composition of the product depended on the metal to ligand ratio (1 : 1, 1 : 2, 1 : 3). The complexes were soluble in DMF and DMSO, slightly soluble in methanol, ethanol, and water, and practically insoluble in dichloromethane and chloroform [112].

**Silver complex.** The silver complex of norfloxacin was investigated to prevent bacterial infections for humans during burn treatment and to utilize its antibacterial properties in topical applications, superior to those of silver and zinc sulfadiazine. In both examples, the characteristic structures of these complexes were

highly connected with the slow release of the metal ions  $\text{Ag}^+$  and  $\text{Zn}^+$  as well as to their biological activity [113]. Surprisingly, the reaction of Nf with  $\text{Ag}^+$  afforded monomeric  $\text{Ag}(\text{Nf})_2(\text{NO}_3)$  in which norfloxacin only acted as a monodentate ligand to bind to the  $\text{Ag}^+$  ion by the N atom of the piperidyl ring. To our knowledge, this complex was the first example of the Nf complex with the metal ion involving only the coordination of the N atom of the piperidyl ring, whereas the 4-oxo and 3-carboxylate oxygen atoms did not take part in coordination [114]. Due these facts, the new coordinate bonding of Nf in this complex yielded a new light on understanding of norfloxacin drug action mechanism.



The molecular structure of this complex consisted of cationic molecules of  $[\text{Ag}(\text{Nf})_2]^+$  and a slightly coordinated anion of  $\text{NO}_3^-$ . This mode of coordination was unexpected and unexampled in quinolone drug interactions toward metal ions. The silver atom might be considered to be 4-coordinated. Two neutral Nf ligands were in the *trans*-position around the axis of N(1)–Ag–N(4), and the Ag atom was in a symmetric center. The strong intermolecular hydrogen bonds were observed between O(1) and O(2) as well as between O(4) and O(5). The hydrogen bonds may prevent the carboxylate groups from coordinating to the  $\text{Ag}^+$  ion [115].

**Zinc complexes.** These norfloxacin complexes with zinc(II),  $[\text{Zn}(\text{Nf})_2] \cdot 4\text{H}_2\text{O}$  and  $[\text{Zn}(\text{H}_2\text{O})_2(\text{Nf})_2](\text{NO}_3)_2$ , were achieved by the hydrothermal reaction. In both cases, the crystal structure of these complexes presented that two ligands displayed coordination binding to the metal through the ring carbonyl and one of the carboxylate oxygen. Surprisingly, the apical positions were occupied by two nitrogen atoms of piperazine rings, whereas the apical positions in the second complex were occupied by two water molecules. The authors suggested that in a neutral or weakly basic solution the nitrogen atom of the piperazine ring could take part in the coordination, while in a weakly acidic solution this nitrogen was protonated and loose its coordination capacity. Authors also reported that both complexes expressed strong blue fluorescent emission and could be used in the future as materials for blue-light emitting diode devices [116].

### Ofloxacin

Ofloxacin (Oflo) is characterized by a tricyclic structure. The presence of a methyl group at position 3 at the oxazine ring provides an asymmetric center at this position [117]. The methyl group is attached to the ring and because of this can exist in two optically active forms, whereas the *S*-isomer is up to two orders of magnitude more active than the *R*-isomer [118]. Ofloxacin has two ionizable functional groups in position 4' and the carboxylic acid group in position 6 [119]. The quinolone molecule of ofloxacin is in the anionic form. The ofloxacin anion probably binds through: ring carbonyl oxygen and one oxygen of the carboxylate group; two oxygen atoms of carboxylate group; one oxygen atom of the carboxylate group.

The N atom in the piperazinyl group of ofloxacin may also participate in complexation with divalent cations. Steric barrier from the methyl substituent of N in the piperazinyl group of Oflo resulted in a weak interaction between the nitrogen atom and the metal ion [120]. It was found that there was a better agreement of the compound vibration on frequencies when metal was chelated to ring carbonyl oxygen and one oxygen of the carboxylate group of Oflo as compared to its bonding to other form. Metal–oxygen stretching bands for the fluoroquinolones' complexes are metal-sensitive

and are shifted to higher frequencies as the metal changes in the order  $\text{Co} < \text{Ni} < \text{Cu} > \text{Zn}$  and  $\text{Ca} < \text{Mg} < \text{Ba}$  (Irving–Williams series) [121].

### Transitional Metal Complexes

**Magnesium complexes.** The magnesium complexes of a racemic form of Oflo and its only *S*-form levofloxacin (**S-Oflo**) were achieved by Drevensek et al. [122]. Two compounds,  $[\text{Mg}(\text{R-Oflo})(\text{S-Oflo})(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$  and  $[\text{Mg}(\text{S-Oflo})_2(\text{H}_2\text{O})_2] \cdot 2\text{H}_2\text{O}$  were gained by hydrothermal reactions, respectively and their crystal structures were determined. In both examples, the ligands were bonded through the keto and carboxylate oxygens achieving a mole ratio of 1 : 2 for Mg : Oflo complexes. The two structures were almost the same with the exception of the orientation of one of the oxazine methyl groups at the chiral center of the second combination, which was found in the equatorial position, the other oxazine methyl groups in both complexes being axial. This dissimilarity influenced on the stacking pattern of quinolone molecules in the cell. The insignificantly distorted octahedral coordination of magnesium was completed by two water molecules that were located in axial positions. The piperazine nitrogen did not interact with magnesium, likely on account of steric crowding of the methyl group [123].

**Copper, cobalt, and zinc complexes.** The ofloxacin complexes with Cu(II), Co(II), and Zn(II) salts were also achieved with the presented formulas  $[\text{Cu}(\text{Oflo})_2] \cdot 2\text{H}_2\text{O}$  and  $[\text{M}(\text{Oflo})_2] \cdot 4\text{H}_2\text{O}$  ( $\text{M} = \text{Co}$  or  $\text{Zn}$ ). It was proved that from an acidic solution of quinolones and various metals ionic type compounds could be isolated as a complexes [124]. It was proved that the metal ion was coordinated to ofloxacin in the complexes through the ring carbonyl and one of the carboxylic oxygen atoms [125].

The complexes of Co(II) and Zn(II) with Oflo were insoluble in water but soluble in different organic solvents, such as dimethylformamide, methanol, or dimethyl sulfoxide. In addition, it was also possible to isolate from methanol the Co(II) complex in a crystalline form,  $[\text{Co}(\text{Oflo})_2(\text{MeOH})_2] \cdot 4\text{MeOH}$ . The structural data showed that the Co(II) ions were in an octahedral local geometry surrounded by six oxygen atoms. Equatorial positions belonged to the two coordinating ofloxacin molecules, and the axial (*trans*) positions were occupied by methanol molecules [126].

The copper complex with ofloxacin,  $[\text{Cu}(\text{Oflo})_2(\text{H}_2\text{O})] \cdot 2\text{H}_2\text{O}$ , was also isolated. The  $\text{Cu}^{2+}$  ion was chelate bonded to quinolone through ring carbonyl and one of the carboxylic oxygen atom. Furthermore, one water molecule was bonded to the copper and the next two water molecules provided additional crystalline stability through a network of hydrogen bond interaction [127].

*Pefloxacin*

**Calcium and magnesium complexes.** It was proved that magnesium and calcium ions [128] perform an affinity to pefloxacin mesylate at pH 7.4. At the beginning the carbonyl and carboxyl groups were the binding sites, then the N-4'-piperazinyl atom was investigated as another site to interact with magnesium and pefloxacin ethyl ester [129].

**Silver complex.** The complex of pefloxacin with silver metal,  $[\text{Ag}_2(\text{Pf})_2(\text{H}_2\text{O})_2] \cdot 6\text{H}_2\text{O}$ , was isolated by dissolving the silver complex in an aqueous ammonia solution. The nature of bonding in this compound was much different. Two silver atoms were coordinated by two carboxyl groups from two ligand molecules. The nitrogen atom of the piperazinyl moiety from the second pefloxacin molecule was also bonded to each silver atom. The silver coordination was completed by an oxygen atom from a water molecule [130, 131].

*Short Analysis  
of the Metal–Fluoroquinolone Structures*

According to Turel's [131] interpretation of the structural analysis presented that "in free fluoroquinolones the ring carbonyl carbon–oxygen distances were between 1.246 and 1.276 Å and the distances between carbon and oxygen in carboxylic groups were in the range from 1.205 to 1.327 Å". According to the facts, "the carboxylic group was not dissociated one of the later bonds was much shorter (double bond) whereas the other bearing the hydrogen was longer (single bond)" [132, p. 230; 133]. The distances and angles within the ligand moiety (quinolone) were nearly similar to their zwitterionic forms [134].

The bonding of the metal to the quinolone oxygen atoms had impact on a slight lengthening of both ring carbonyl and carboxylic carbon–oxygen bonds. Additionally, it was discovered that the bond distances in the chelate bonding of the metal to ring carbonyl and one of the carboxylic oxygen atoms had similar lengths [131, 135, 136]. Near the carboxylic group, the metal–bonded oxygen presented longer carbon–oxygen distance than the non bonded oxygen [132, 137, 138]. The coordination numbers of the metal is in the range from 4 to 8 and the most commonly appeared coordination polyhedron is octahedron. The metal : ligand (quinolones) mole ratios were between 1 : 1 and 1 : 3 [139].

We summed that the most popular bonding noted for metal–quinolone complexes was the chelate bonding of the metal to ring carbonyl and one of the carboxylic oxygen atoms. There were also some exceptions. In the complexes  $[\text{Ag}(\text{Pf})_2(\text{H}_2\text{O})_2] \cdot 6\text{H}_2\text{O}$ ,  $[\text{Zn}(\text{Nf})_2] \cdot 4\text{H}_2\text{O}$ , and  $\text{Ag}(\text{Nf})_2(\text{NO}_3)$ , the piperazine terminal nitrogen atom might also take part in the bonding to the metal. It was also discovered that several complexes with other ions (magnesium and calcium) were dimeric [140]. It is very probable that the different conditions of the syn-

thesis had strong impact on the differences in bonding of the reported complexes.

Only a few crystal structures of fluoroquinolones coordinated to the metal ions are known. On the other hand, in great number of crystal structures of mixed metal complexes with coordinated quinolones were reported.

*Antibacterial Activity of Metal Complexes  
with Fluoroquinolones*

It was proved that millimolar concentration of magnesium ion was required for tight binding of quinolones to DNA [141] and also the interaction between gyrase A and quinolones was improved in the presence of magnesium [142]. These facts suggested that the interactions between magnesium and quinolone were significant for the drug mode of action. It was estimated that the intracellular concentration of magnesium ions was much higher than that of quinolone [143]. According to the stability constants, it can be indicated that also in biological fluids a mixture of 1 : 1 and 1 : 2 magnesium–quinolone complexes, free quinolones, and hydrated magnesium ions were present. It was supposed that the magnesium–quinolone complexes interact with their target to create DNA–gyrase complex [144]. However, it was also established that a high concentration of extracellular magnesium could decrease the transport of fluoroquinolones into bacterial cells [145]. There were discovered some analogies between the magnesium complex with ofloxacin and the magnesium complex of aureolic family drug (chromomycin, anticancer antibiotics) and it was tempting to propose that the binding of the Oflo complex to DNA could be similar to the binding of the magnesium chromomycin complex [146].

The bismuth complex with ciprofloxacin showed the same antimicrobial activity against gram-positive and gram-negative bacteria as ciprofloxacin itself. No antifungal effect was observed. The antibacterial effects were similar to those reported for the copper(II) and iron(III) quinolone compounds. There were no microbiological test against *Helicobacter pylori* [147].

It has been already known that free fluoroquinolones (levofloxacin) exerts higher antibacterial activity than ofloxacin [148–150]. The same situation was noticed with the magnesium complexes with both chemotherapeutic agents. The minimum inhibitory concentration (MIC) values of both complexes did not significantly differ from free fluoroquinolones, presenting a general slight decrease in their antibacterial activity. Congenial antibacterial activities of metal complexes and free quinolones was reported in the majority of studies of metal–quinolone complexes. It was not a surprise because it was probably a result of the intracellular biological conversion of the complexes.

From all results that were described by authors it can be assumed that the antimicrobial activity of metal–

ciprofloxacin compounds was similar to the free ligand with one exception: the magnesium complexes have often been significantly less active than the parent quinolone drugs, suggesting that the role of this ion could be different from the other metal ions studied. It was also found that the activity of fluoroquinolones were reduced when the solutions of fluoroquinolones were titrated with magnesium ions [151]. "In addition, the bactericidal studies against *Staphylococcus aureus* ATCC 25923 revealed that the quinolone ligand parent exhibited the "paradoxical effect" (diminution in the number of bacteria killed at a high drug concentration), which was described and related to the mechanism of action of quinolones, but the complexes did not suggest different mechanisms of bactericidal action." [84].

Most antimicrobial activities of the copper complexes with fluoroquinolones were comparable of those of free ciprofloxacin. No essential differences in the antimicrobial activity among the tested ciprofloxacin-copper complexes was presented. It could be due to intercellular biological inversion complexes to free quinolones [92].

It should be mentioned that the zinc complex with norfloxacin possesses considerably better activity against gram-negative bacteria than free norfloxacin. As an essential element for life zinc has multiple biological functions in many physiological processes, and its abundance is relatively high. So, the zinc complexes achieved from coordination with drug molecules may be important in the development of new chemotherapy agents [153].

The complexes of iron Fe(III),  $[\text{Fe}(\text{Nf})_2(\text{H}_2\text{O})_2]\text{Cl}_3 \cdot 6\text{H}_2\text{O}$ , and zinc(II),  $[\text{Zn}(\text{Nf})_2]\text{Cl}_2 \cdot 7\text{H}_2\text{O}$ , were tested in vitro against gram-negative microorganisms *E. coli* and *Bacillus dysenteria* bacteria. The complexes showed stronger activity than norfloxacin itself [110].

The silver salt of norfloxacin having better antibacterial action in topical burn treatments may be the result of unique bonding between the ligand and  $\text{Ag}^+$  and its mononuclear structure. Such bonding may result in a larger concentration and the fast release of  $\text{Ag}^+$  [130].

#### Nuclease Activity

The compound  $\text{Cu}(\text{Cf})_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  was the first complex of ciprofloxacin able to behave as an efficient chemical nuclease. Previously, Mendoza et al. determined the nuclease activity of the ternary copper(II) compound of nalidixate acid and phenanthroline [154]. They found that it acted as a powerful nuclease in the presence of MPA (mercaptopyropionic acid) through a mechanism involving hydroxyl radicals. Several authors investigated the interaction of ciprofloxacin with DNA [155].

Ulrich et al. [156] studied the influence of Cu(II) and Mg(II) on the binding of ciprofloxacin to DNA. Their results revealed different modes of action of ciprofloxacin in the presence of Cu(II) and Mg(II). The

authors found that the  $\text{Mg}^{2+}$  ions were directly involved in ciprofloxacin binding to DNA via phosphate oxygen was observed, and the Cu(II) interaction with the N(7) position of purine bases was proposed.

Tabassum et al. [157] investigated the binding of the bisciprofloxacin borate copper(II) complex with calf thymus DNA. From these studies they proposed intercalative binding of this compound with DNA.

Jimenez-Garrido [158] proposed that in compound  $[\text{Cu}(\text{Cf})_2(\text{ClO}_4)_2] \cdot 6\text{H}_2\text{O}$  the positively charged piperazine group of the ligand bonded with the negative charge of the phosphate backbone in DNA via electrostatic interactions and / or hydrogen bonds and that Cu(II) could interact with the N(7) positions of the purine bases, strengthening the binding with DNA. However, intercalation of the complex with DNA, as has been proposed for the bisciprofloxacin borate copper (II) compound could not be excluded. It was noted that the positive charge of ciprofloxacin in this complex can be ponded a key agent responsible for its high nucleolytic activity, since the previously reported  $\text{Cu}(\text{Cf})_2 \cdot 6\text{H}_2\text{O}$  compound, where ciprofloxacin was in the anionic form, did not show nuclease activity [84].

The first analyzing compound that possessed some nuclease activity in the absence of peroxide was the Cu(II)/Cu(I) complex of ciprofloxacin [159, 160]. This DNA cleavage activity was so important, because the main compound did not contain phen or other similar ligand, which has previously been defined to cause DNA cleavage [161, 162]. These facts suggested that the main action of the complex may be different from that of the copper-phenantroline complexes [163, 164]. Several alternative ways of action were possible, for example, copper could directly coordinate to purine bases and its mater activated by peroxide as proposed Kawanishi and Yamamoto [165]. Another solution was that the piperazine nitrogen of the quinolone might be involved in the activity. This atom either coordinate the copper ion under basic pH conditions or it might also bind to DNA through positive charges in a like aminoglycosides, which were also well-known class of chemical nucleases [166].

Lecomte [167] proved that, in the absence of magnesium, pefloxacin binds poorly to DNA and preferentially to single-stranded rather than to double-stranded DNA.

It is obvious that more test are required to determine more details of this activity and additionally the possible sequence selectivity of this reaction.

#### CONCLUSIONS

The most of bacterial infections now defy all known antibiotics and the antibiotic resistance is a growing problem in our environment. There is a great need for new antibacterial agents and metal complexes as novel derivatives of fluoroquinolones can play an important role in this field.



This review article presents physicochemical and pharmacokinetic information and also antibacterial properties of fluoroquinolone complexes with different metal ions.

The most of the described metal complexes with fluoroquinolones and metal–quinolone compounds were tested for the activity against diversity of microorganisms. In most cases, it was evidenced that the antimicrobial activity of the complexes was comparable to free fluoroquinolones. In certain examples the activities were also increased, for example, the norfloxacin complexes with zinc, iron, and silver. On the other hand, it was proved that the magnesium complex with ciprofloxacin is characterized by a slight decrease in its antibacterial activity. It was also discovered that the vanadium–ciprofloxacin complex is promising with the respect to its insulin-mimetic behavior and to its concomitant low toxicity in the physiological concentration range [168].

The mode of action of quinolones involves interactions with topoisomerase IV and topoisomerase II (DNA gyrase). Due to this fact, it is interesting to investigate the mode of action of fluoroquinolones as complexes with other metal ions (palladium, platinum, ruthenium, titanium) against cancer cell lines (cytotoxicity).

Additionally, fluoroquinolones as metal complexes ought to be examined in the respect of their potential drug resistance. There is a chance that bacterial strains that are insensitive to pure fluoroquinolones are sensitive to metal complexes of fluoroquinolones.

Certainly, there is a need to continue research in this area and more results are expected to be published in the future.

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