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Review Paper

Synthesis and Biological Activities of Selected Quinolone-Metal Complexes

Singh R.[1],* Debnath A.[2], Masram D.T.[2] and Rathore D.[1]
[1]Department of Applied Chemistry and Polymer Technology, Delhi Technological University, Delhi – 110 042, INDIA
[2]Department of Chemistry, University of Delhi, Delhi-110007, INDIA

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Abstract

4-Quinolones are the synthetic antibacterial agent structurally related to nalidixic acid. The coordination chemistry of these drugs with metal ions of biological and pharmaceutical importance is an active research area. In this review article, synthesis and biological activity of metal complexes of selected 4-quinolones such as norfloxacin, ciprofloxacin, enrofloxacin, gatifloxacin, and sparfloxacin are presented and discussed.

Keywords: Quinolone-metal complexes, norfloxacin, ciprofloxacin, enrofloxacin, gatifloxacin, sparfloxacin.

Introduction

Nalidixic acid [1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**1**)] and related 4-quinolones are a group of synthetic anti-bacterial agents[1,2]. A large number of structural modifications of **1** have been done based on structure activity relationships (SARS)[1,3]. It was found that the presence of fluorine atom at position 6 and a piperazine ring at position 7 without the presence of N at position 8 enhances the biological activity spectrum. The quinolones with these modifications are grouped together as fluoroquinolones[4]. They have broad spectrum antimicrobial activity and are very active against aerobic Gram-negative microorganisms but less active against Gram-positive microorganisms[5,6]. They are extremely useful for the treatment of a variety of infectious diseases[6,7] and also introduced as antitumor agents[8]. The coordination of these molecules with metal ions is of considerable interest from biological and pharmaceutical point of view. The metal ions like alkaline earth and transition metal ions have been found to complex with 4-quinolones[4,5]. The chelation between the metal ion and 4-quinolone has been mainly observed with the 4-oxo and 3-carboxy groups of 4-quinolones[5]. Since, these functional groups are also required for antibacterial activity; this has been thought that all 4-quinolone based antibacterial molecules interact with metal ions. There has been a tremendous growth in the publication about the interactions of metal ions with 4-quinolones after an initial study in 1978 by Nakauo[9]. More than 1000 publications have been published in the last 10 years on metal-complexes with different generations of 4-quinolones. This review article gives comprehensive coverage of literature on synthesis and biological activity of selected metal-quinolone complexes.

Synthesis and Biological Activities of Quinolone-Metal Complexes

Metal-drug interaction is very important from pharmacological point of view. For quinolones, the zwitterionic and uncharged molecules are responsible for diffusion through cytoplasmic membranes[10]. The presence of metal ions result in a higher uptake of these molecules by the bacterial cells compared to that of the free drugs[11]. Therefore, proper understanding of biological activities of quinolone metal complexes becomes important. Alkaline earth metal and transition metal complexes with quinolones play an important role during the biological process of drug utilization in the body[12,13]. In most of the quinolone-metal complexes, due to the ring carbonyl group at position 4 and one of the oxygen atoms of carboxylato group at position 3, the quinolones act as bidentate ligand[14]. They can also act as a bridging ligand and hence they are capable of forming polynuclear complexes also[14]. The functional group involved for complexation is also required for antibacterial activity and hence their interaction with metal ions is quite obvious and important[15].

Norfloxacin (norf) Metal Complexes: Norfloxacin [1-ethyl-6-fluoro-4-oxo-7-(1-piperazinyl)-l,4-dihydroquinoline-3-carboxylic acid (norf)(**2a**)] is a quinolone antibacterial agent which is active against a wide variety of aerobic Gram-negative and Gram-positive bacteria but specifically, active against aminoglycoside-resistant *Pseudomonas aeroginosa* and betalactamase producing organisms[16]. Presence of metal ion considerably alters the activity of quinolones against potentially susceptible bacteria[5].

A bismuth complex of norfloxacin was prepared by reacting bismuth citrate and norfloxacin[16]. Norfloxacin was added to the acidic solution of bismuth citrate which was further basified with strong ammonia solution and heated on steam bath for 5 h to get the bismuth-norfloxacin complex $Bi(norf)_4(H_2O)_2$(**3**)[16]. pH 7 has been the appropriate condition for maximum complexation between bismuth ion and norfloxacin. Antimicrobial studies of **3** were carried out using agar diffusion method against *B. pumilis* (NTCC 8241), *E. coli* (ATCC 25922), *K. pneumonia* (NTCC 10320), *S. aureus* (ATCC 29213)

and *S. epidermidis* (ATCC 12228)[16]. The result showed significant increase in antibacterial activity of the complex as compared with norfloxacin and physical mixture of norfloxacin and bismuth citrate[16]. This increase in activity is may be due to increased bioavailability of the metal quinolone complex[16].

The reaction of norfloxacin with Mg(II), Ca(II) and Ba(II) perchlorates having formula $Mg(ClO_4)_2.6H_2O$, $Ca(ClO_4)_2.4H_2O$ and $Ba(ClO_4)_2.3H_2O$ was performed in methanol at room temperature for 24 hours to get the metal complex with general formula $[M(norf)_2](ClO_4)_2.4H_2O$(**4a**)[17]. The reaction of norfloxacin with $AgNO_3$ in aqueous ammonia under reflux for eight hours yields an unusual mononuclear complex $[Ag(norf)_2]NO_3$(**5**)[18]. Its structural feature helped in fast release of Ag^+ ion and leads to better antibacterial action in topical burn treatments. Norfloxacin showed affinity towards coinage metals like Cu(II), Ag(I) and Au(III) and formed complex with formula $[Ag_2(norf)_2](NO_3)_2$(**6**), $[Au(norf)_2(H_2O)_2]Cl_3$(**7**) and $[Cu(norf)_2(H_2O)_2]SO_4.5H_2O$(**8**)[19]. The coordination of Ag(I) and Au(III) were found to take place through the N atom of the piperidyl ring. The metal complexes have shown moderate activity against the gram positive and gram negative bacteria as well as against fungi[19].

N-Protected norfloxacin such as N-propylnorfloxacin (pr-norf) was complexed with Cu(II) ion in the presence of nitrogen donor heterocyclic ligand 2,2'-bipyridine[20]. The reaction was performed in methanol to get the complex as [Cu(pr-norf)(bipy)Cl](**9**)[20]. The antimicrobial activity of the complex showed an enhanced biological activity in relation to the free N-propylnorfloxacin. The complex exhibits the best inhibition (MIC = 0.25 μgmL^{-1}) against *E. coli*[20]. Some other Cu(II) complexes of N-propylnorfloxacin were prepared using ligands such as 1,10-phenanthroline(**10**) and 2,2'-dipyridylamine(**11**)[21]. The synthesised Cu(II) complexes are [Cu(pr-norf)(phen)Cl], [Cu(pr-norf)(bipyam)Cl], $[Cu(pr\text{-}norf)_2(H_2O)]$ and [Cu(pr-norf)(bipy)Cl][21]. The antimicrobial activity of the complexes showed that the best inhibition among the compounds studied was provided by Cu(pr-norf)(bipy)Cl (MIC = 0.25 μgmL^{-1}) against *E. coli* and Cu(pr-norf)(phen)Cl (MIC = 0.25 μgmL^{-1}) against *P. aeruginosa*[21]. The interaction of N-propylnorfloxacin with other transition metal ions and transition metal oxide ions were also studied[22]. Nine metal complexes with the formula $VO(pr\text{-}norf)_2(H_2O)$(**12a**); $[M(pr\text{-}norf)_2(H_2O)_2]$ where M = Mn(II), Co(II), Ni(II), Zn(II) and Cd(II); $Fe(pr\text{-}norf)_3$ and $[M(pr\text{-}norf)_2]$ where M = UO_2(II) and MoO_2(II) were obtained by the reaction of methanolic solution of deprotonated N-propylnorfloxacin and methanolic solution of corresponding metal salts in 3:1 ratio for Fe^{3+} and 2:1 for other divalent metal ions[22]. The antibacterial activity of the ligands and complexes was studied against *S. aureus*, *E. coli* and *P. aeruginosa*. The complexes showed equal or decreased biological activity in comparison to the free pr-norfloxacin except $UO_2(pr\text{-}norf)_2$ which shows better inhibition against *S. aureus*[22].

Ciprofloxacin (cprf) Metal Complexes*:* Ciprofloxacin [1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (cprf)(**2b**)] is also a member of 4-quinolone family and is used for the treatment of diseases caused by various Gram negative and some Gram positive microorganisms[23]. The interactions of ciprofloxacin with different metal ions were studied by various methods. This quinolone reacted with oxovanadium(IV) in water to yield green crystals of a complex $[VO(cprf)_2(H_2O)]$(**12b**)[24]. The complex did not give better antibacterial activity in comparison to free ligand, cprf. The reaction of ciprofloxacin with Mg(II), Ca(II) and Ba(II) perchlorates having formula $Mg(ClO_4)_2.6H_2O$, $Ca(ClO_4)_2.4H_2O$ and $Ba(ClO_4)_2.3H_2O$ was performed in methanol at room temperature for 24 hours to get the metal complexes $[Mg(cprf)_2](ClO_4)_2.6H_2O$, $[Ca(cprf)_2](ClO_4)_2.4H_2O$ and $[Ba(cprf)_2](ClO_4)_2.2H_2O$ respectively(**4b**)[17].

The aqueous solution of ciprofloxacin hydrochloride reacted with aqueous solution of $K_2[PtCl_4]$ to give the complex $[PtCl_2(cprf)]$(**13**)[25]. This is an unusual complex formation where platinum (Pt) complexed with piperazine ring. The piperazine ring was supposed to achieve boat conformation which is stabilized by chelation to the platinum(II)[25]. The reaction of ciprofloxacin with metal(II) acetate in methanol at pH 8 under nitrogen atmosphere gave two types of complexes $[M(cprf)(OAc)(H_2O)_2].3H_2O$(**14**) where M = Mn(II), Co(II), Cu(II) or Cd(II) and $[M(cprf)(OAc)].6H_2O$(**15**) where M = Ni(II) or Zn(II)[26]. The copper(II) and zinc(II) complexes have shown higher activity than that of free ligand against *P. aeruginosa*. The copper(II) complex also showed higher activity against *S. typhimorium*[26]. Another study by Psomas showed that ciprofloxacin complexed with Mn(II), Ni(II), Fe(III) and MoO_2(II) ions having formula $[M(cprf)_2(H_2O)_2]$(**16**) for Mn(II) and Ni(II); $Fe(cprf)_3$(**17**) and $MoO_2(cprf)_2$(**18a**)[27]. In all these complexes, ciprofloxacin acts as a bidentate deprotonated ligand bound to the metal through the pyridone oxygen and one carboxylate oxygen. The biological studies showed that these compounds can bind to CT DNA (calf–thymus DNA)[27]. Perello et al. synthesised copper perchlorate complex of ciprofloxacin with formula $[Cu(cprf)_2(ClO_4)_2].6H_2O$ and $[Cu(cprf)_2(NO_3)_2].6H_2O$[28]. Not much improvement in the biological activity was achieved. Another ciprofloxacin complex **19** with UO_2^{2+} has been synthesized from the deprotonated mode of ligand[29]. The reaction was performed in methanol using the salt $UO_2(NO_3)_2.6H_2O$[29]. The reaction of $AgNO_3$ with ciprofloxacin gave a 1-D ladder-like silver(I) coordination polymer with formula $[Ag_4(protonated\text{-}cprf)_2(deprotonated\text{-}cprf)_2(NO_3)_2].4H_2O\}_n$ which consists of pseudo-tetra-nuclear silver building blocks constructed via monodentate protonated-crpf and tetradentate depronated-cprf ligands[30].

Enrofloxacin (erf) Metal Complexes: Enrofloxacin [1-cyclopropyl-7-(4-ethyl-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (erf)(**2c**)] is a broad spectrum antibiotic quinolone with activity against a wide range of Gram-negative and Gram-positive bacteria, including those resistant to β-lactam antibiotics and sulfonamides[31]. This has

been used in veterinary medicine for treatment of individual pets and domestic animals[32]. This is suspected to act by inhibiting bacterial DNA gyrase (a type-II topoisomerase), thereby preventing DNA supercoiling and synthesis[33]. This is also used for the treatment of uncomplicated and complicated urinary tract infections, pyelonephritis, sexually transmitted diseases, prostatitis, skin and tissue infections, urethral and cervical gonococcal infections[34,35]. However, the FDA withdrew approval of this drug for use in water to treat flocks of poultry, as this promoted the evolution of fluoroquinolone-resistant strains of the bacterium *Campylobacter*, a human pathogen[36].

An aqueous ethanol solution (v/v = 2/3) of $Cu(NO_3)_2.3H_2O$ was reacted with an aqueous solution of enrofloxain under alkaline condition for 2 hrs to get the complex $[Cu(erf)_2(H_2O)_2]$[33]. A neutral mononuclear dioxomolybdenum(VI) complexe of enrofloxacin have been prepared in high yield by the reaction of methanolic solution of the deprotonated quinolone to MoO_2 at a 2:1 ratio with formula $MoO_2(erf)_2$(**18b**)[37]. The antibacterial activity of **18b** have been tested against two Gram(-), *E. coli* and *P. aeruginosa*, and one Gram(+), *S. aureus*, microorganisms. The MIC for **18b** found to be 1–4 μgmL^{-1} [37]. A vanadyl complex of enrofloxacin with transition metal oxide, oxovanadium(IV) with the formula $[VO(erf)_2H_2O]$ (**12c**) have been synthesised[38]. The interaction of **12c** with calf-thymus DNA has also been investigated and the antimicrobial activity has been evaluated against three different microorganisms[38].

Psomas et. al. synthesised Ni(II) complexes in the absence and presence of the nitrogen-donor heterocyclic ligands such as phen(**10**), 2,2′-bipyridine (bipy)(**20**) or pyridine having molecular formula $[Ni(erf)_2(H_2O)_2]$, $[Ni(erf)_2(phen)]$, $[Ni(erf)_2(bipy)]$ and $[Ni(erf)_2(py)_2]$[39]. In all the complexes, enrofloxacin acts as bidentate ligand coordinated to Ni(II) ion through the ketone oxygen and a carboxylato oxygen. The complex bis(pyridine)bis(enrofloxacinato)- nickel(II) exhibits the highest binding constant to CT DNA[39]. A study by Psomas showed that enrofloxacin complexed with Mn(II), Co(II), Ni(II), Zn(II), Cd(II), Fe(III) and UO_2^{2+}(II) ions with formulas $[M(erf)_2(H_2O)_2]$ where M = Mn(II), Co(II), Ni(II), Zn(II), Cd(II) and $[M(erx)_n]$ where n=3 for Fe(III) and n= 2 for UO_2(II)[40]. In all these complexes, the ligand acts as a bidentate deprotonated ligand bound to the metal through the pyridone oxygen and one carboxylate oxygen. The antimicrobial activity of the complexes exhibited better or equal inhibition in comparison to free enrofloxacin. The biological studies showed that these compounds can bind to CT DNA (calf–thymus DNA)[40].

Gatifloxacin (gtf) Metal Complexes: Gatifloxacin [1-cyclopropyl-8-methoxy-7-(3-methyl-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (gtf)(**21**)] is also a synthetic broad-spectrum fourth-generation quinolone antibacterial agent[41]. This is also reported to have an inhibitory effect on the production of inflammatory cytokines by macrophages/monocytes and, particularly, suppresses bacterial infection-induced inflammation[42].

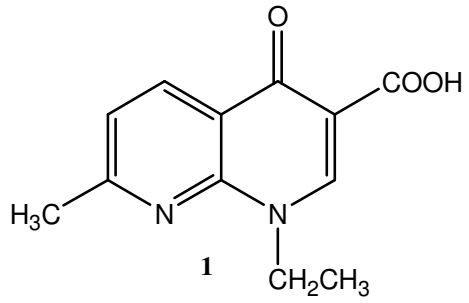
The complexes $[PdCl_2(gtf)]$ was obtained by reaction between gatifloxacin and the palladium salt $K_2[PdCl_4]$ in aqueous medium[43]. The platinum complexe was obtained when aqueous suspension of gatifloxacin reacted with aqueous solution of $K_2[PtCl_4]$ to give the complex $[PtCl_2(gtf)]$(**22**)[25,43]. The ligands coordinate to the palladium in the most common manner, i.e. in a bidentate fashion via the carboxylic and the carbonyl oxygens. Coordination to platinum occurs in a bidentate fashion *via* the piperazine nitrogen atoms, this type of coordination being considerably rare. Complexes with both metallic ions show good antitubercular activity[43]. Sadeek et al has synthesized Y(III), Zr(IV) and U(VI) complexes of gatifloxacin having formula $[Y(gtf)_2(H_2O)Cl]Cl_2.11H_2O$, $[ZrO(gtf)_2(H_2O)]Cl_2.14H_2O$ and $[UO_2(gtf)_2](NO_3)_2.6H_2O$ respectively[45]. In these complexes, gatifloxacin acts as a bidentate deprotonated ligand similar to other quinolones bound to the metal through the ketone oxygen and a carboxylato oxygen. The complexes are six-coordinated with distorted octahedral geometry[44]. The antimicrobial activity of the complexes has been tested against three bacterial species, such as *S. aureus*, *E. coli* and *P. aeruginosa* and two fungi species, *penicillium rotatum* and *trichoderma* sp., showing that they exhibit higher activity than free ligand[44]. The complexes of gatifloxacin with metal ions such as Mg(II), Ca(II),Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) have also been studied[45]. The complexes were found to have formula $[Mg(gtf)_2(H_2O)]Cl_2.2H_2O$, $[Ca(gtf)_2(H_2O)]Cl_2.2H_2O$, $[Cr(gtf)_2(H_2O)_2Cl]$ $Cl.2H_2O$, $[Mn(gtf)_2(H_2O)_2].6H_2O$, $[Fe(gtf)_2(H_2O)_2Cl]Cl.2H_2O$, $[Co(gtf)_2(H_2O)_2].4H_2O$, $[Ni(gtf)_2(H_2O)_2]Cl_2.2H_2O$, $[Cu(gtf)_2(H_2O)_2]$. H_2O, $[Zn(gtf)_2(H_2O)_2].2H_2O$ and $[Cd(gtf)_2(H_2O)_2]Cl_2.4H_2O$ respectively[45]. Hu et al has also studied the complexes with Co(II), Zn(II) and Ni(II) ions[46]. The Mg(II), Ni(II) and Zn(II) complex showed excellent activity against trouble shooting Methicillin-Resistant Staphylococcus Aureus (MRSA)[45]. The complexes of Ca(II), Mg(II) and Fe(III) showed good antibacterial activity. The results of anti-inflammatory activity showed that Cu(II) and Ni(II) complexes possessed excellent anti-inflammatory activity also[45].

Sparfloxacin Metal Complexes: Sparfloxacin [(5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (spf)(**23**)] is a third-generation quinolone antimicrobial drug. This is mainly used for the treatment of acute exacerbations of chronic bronchitis and community-acquired pneumonia[47-49].

Sparfloxacin also form metal sparfloxacinato complexes due to the presence of basic quinolone moiety. A neutral mononuclear nickel(II) complex in the presence of the nitrogen-donor heterocyclic ligand pyridine having formula $[Ni(spf)_2(py)_2]$(**24**) has been synthesized[50]. The complex has shown its ability to bind to CT DNA. Sparfloxacin has also been complexed with Fe(III), VO(II), Mn(II), Ni(II) and UO_2^{2+} having molecular formula $[Fe(spf)_3]$, $[VO(spf)_2(H_2O)]$(**25**), $[Mn(spf)_2(H_2O)_2]$(**26**), $[Ni(spf)_2(H_2O)_2]$(**26**), and $[UO_2(spf)_2]$(**27**)[51]. In these complexes, sparfloxacin acts as a bidentate deprotonated ligand bound to

the metal through the ketone oxygen and a carboxylate oxygen. The complexes exhibit good binding propensity to human and bovine serum albumin proteins having relatively high binding constant values[51]. The complexation of sparfloxacin has also been achieved with MoO_2^{2+} [37], and other divalent metal ions[52,53].

Mixed ligand complexation of sparfloxacin has also been achieved using N-donor heterocycles like **10**, **11** and **20**. 2,2'-bipyridine (bipy) and 2,2'-bipyridylamine (bipyam)[54,55]. The complexes [Cu(spf)(phen)Cl], [Cu(spf)(bipy)Cl] and [Cu(spf)(bipyam)Cl][54] and [Ni(bipy)(spf)$_2$], [Ni(phen)(spf)$_2$] and [Ni(spf)$_2$H$_2$O][55] were synthesised. The antimicrobial activity of the Ni-complexes revealed that the inhibition provided by the complexes is slightly decreased in comparison to free sparfloxacin. The complexes exhibit good binding propensity to human and bovine serum albumin proteins having relatively high binding constant values[55]. The Cu(sparfloxacinato)(N-donor)Cl complexes shown more activity against *E. coli*, *P. aeruginosa* and *S. aureus*, in comparison to the other corresponding copper–quinolone complexes and their antimicrobial activity is increased in the order bipyam < bipy = phen[54]. The studied have also shown that two of the Cu(sparfloxacinato)(N-donor)Cl complexes have decreased the viability of human leukemia cells HL-60 in a time-dependent manner[54].



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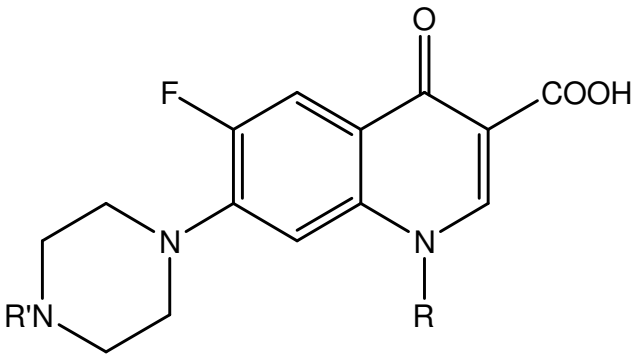

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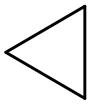
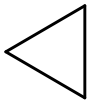
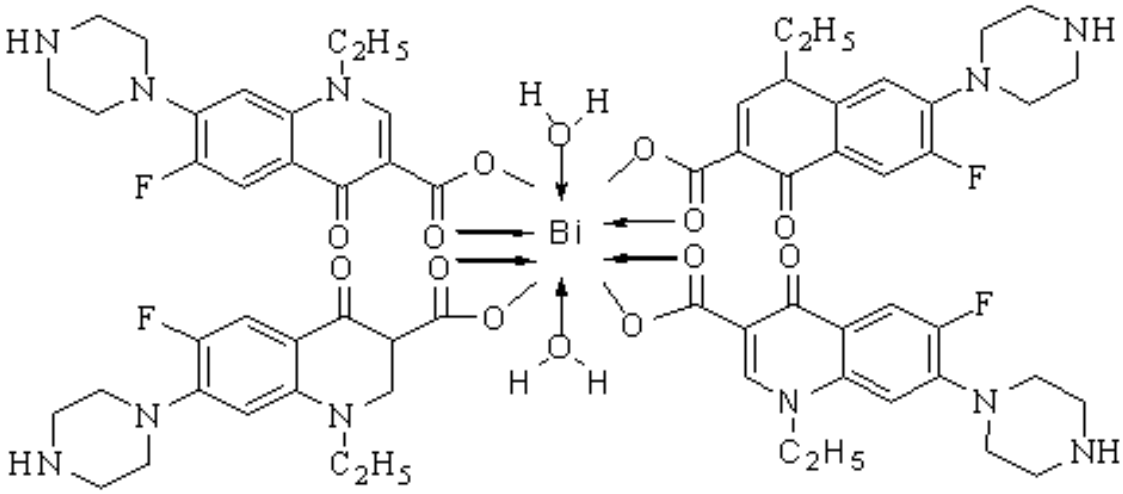
2b: R =  R' = H

2c: R =  R' = CH_2CH_3



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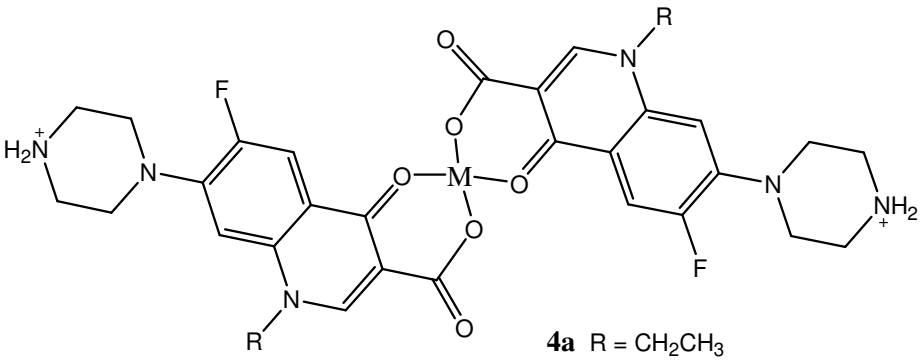

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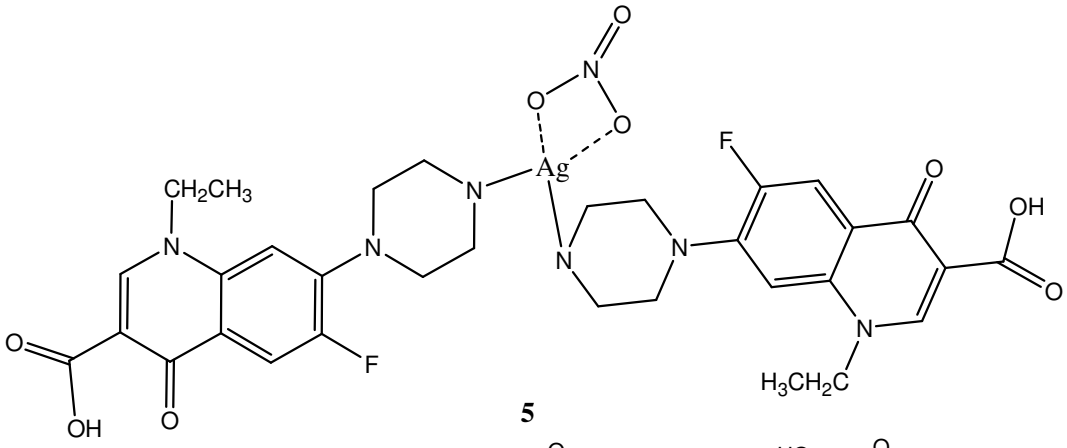

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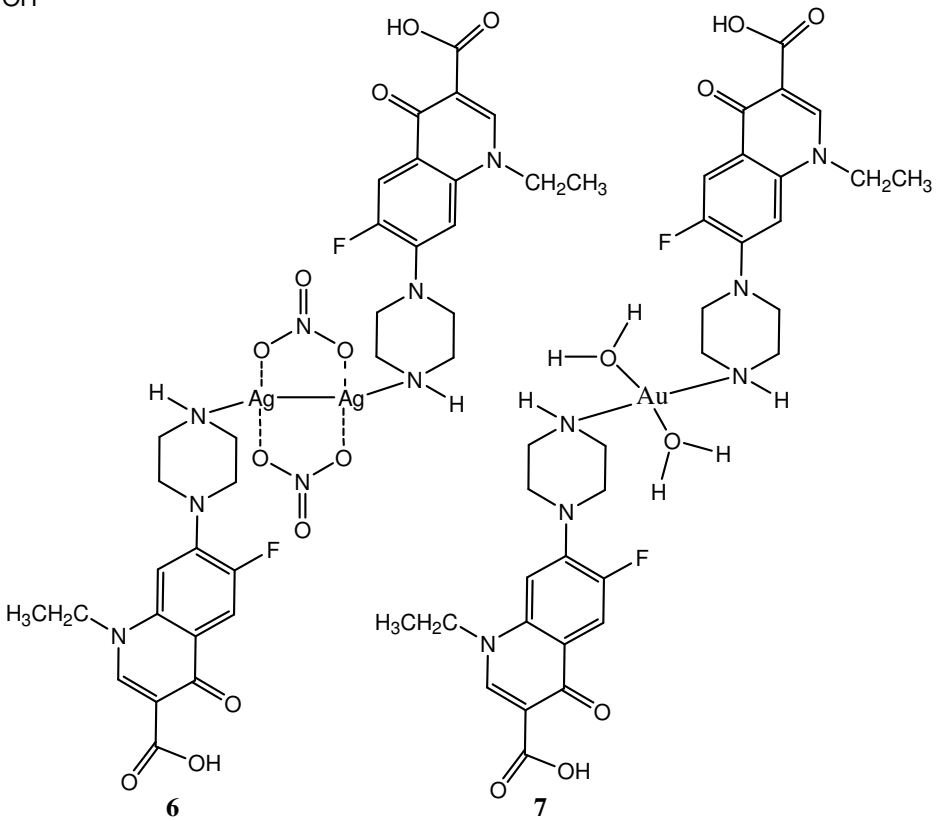

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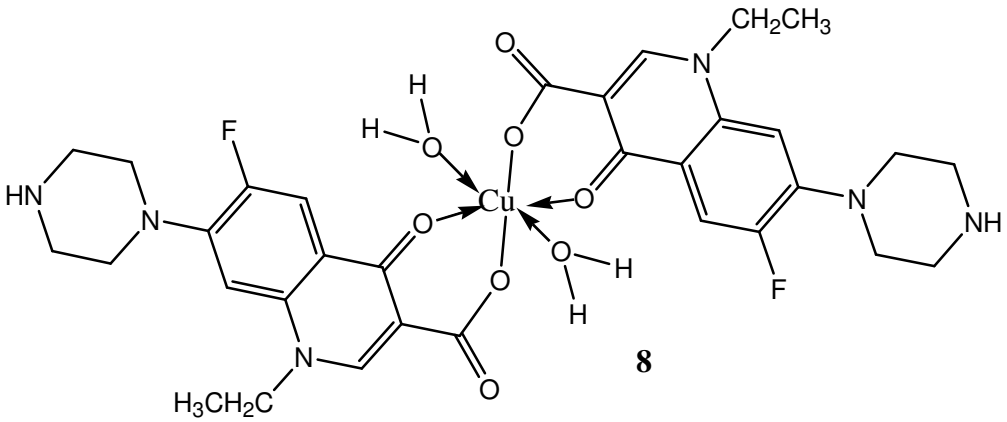

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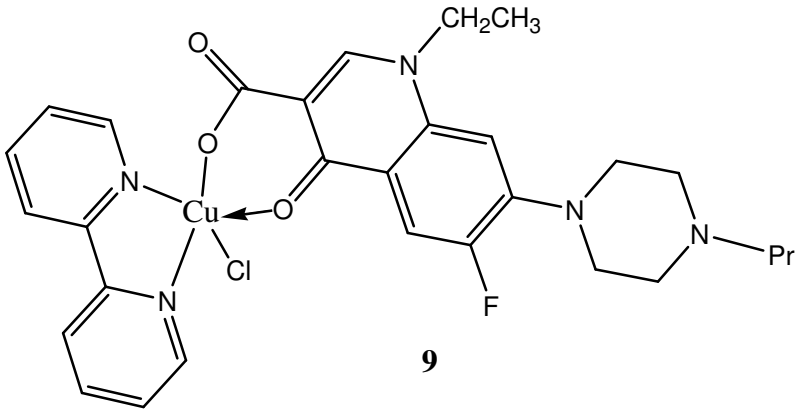

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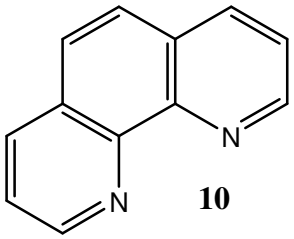

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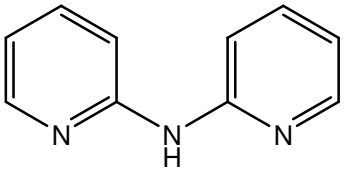

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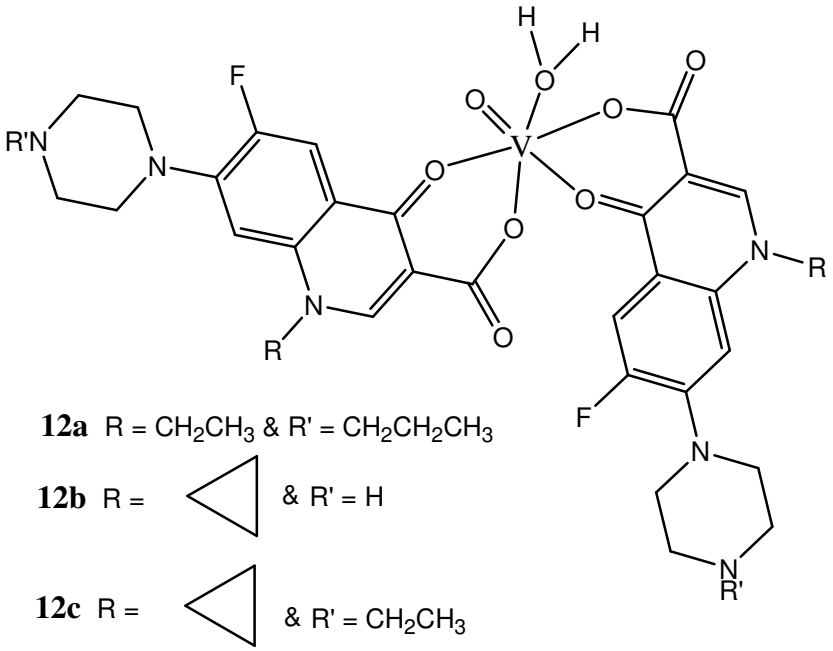

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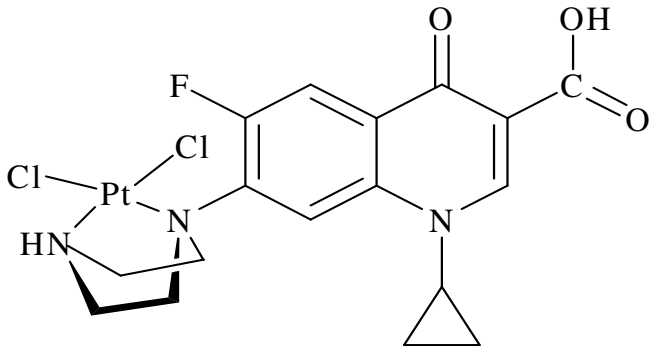
12b R = & R' = H

12c R = & R' = CH_2CH_3



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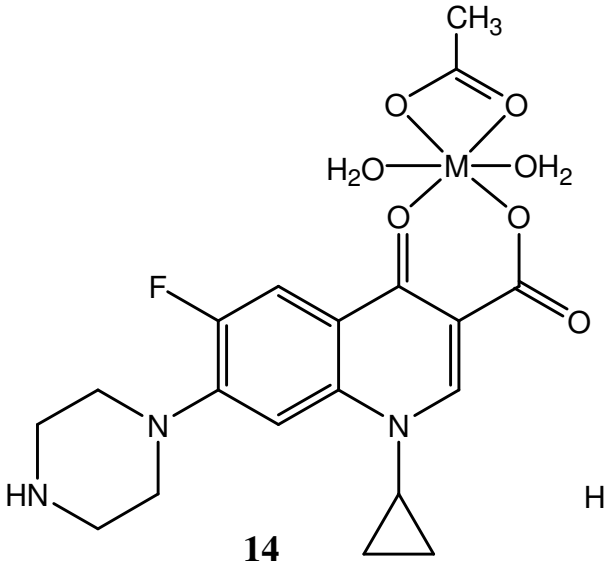

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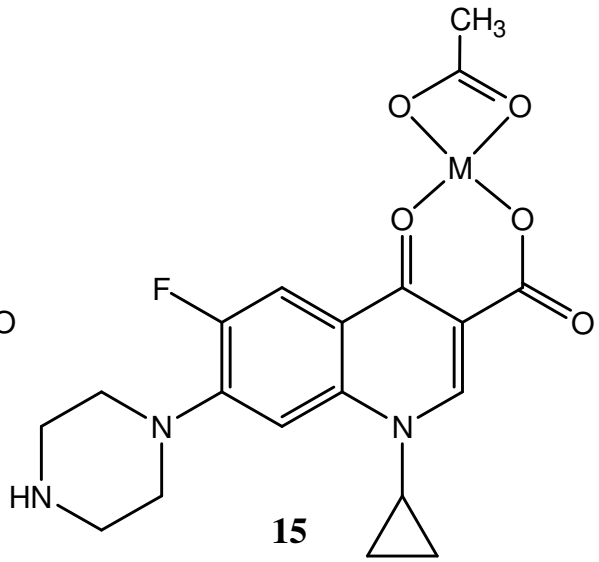

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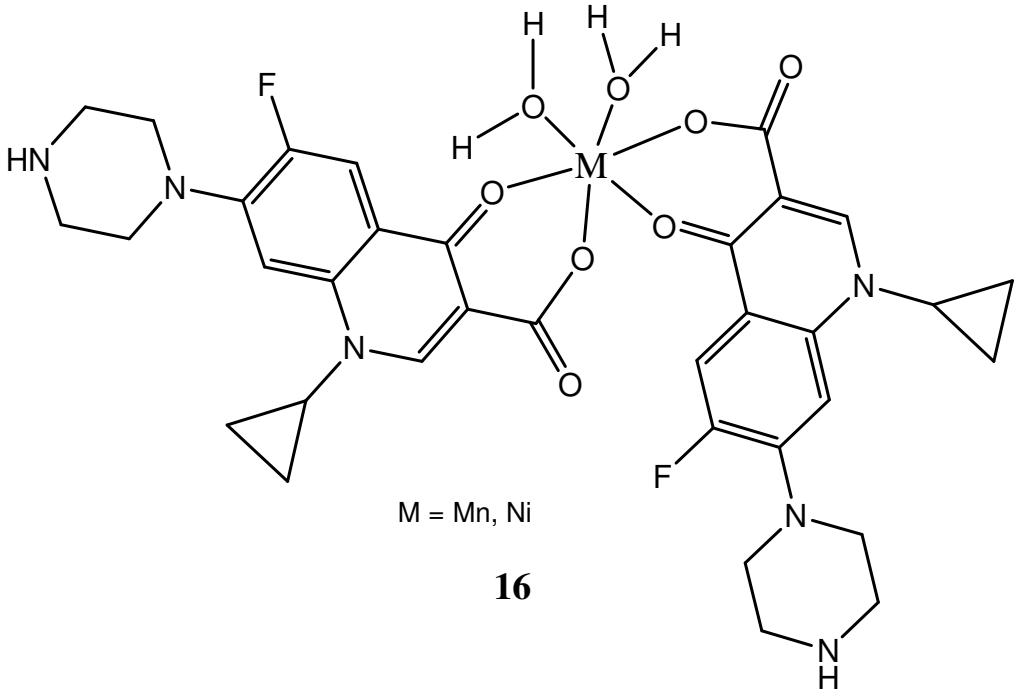
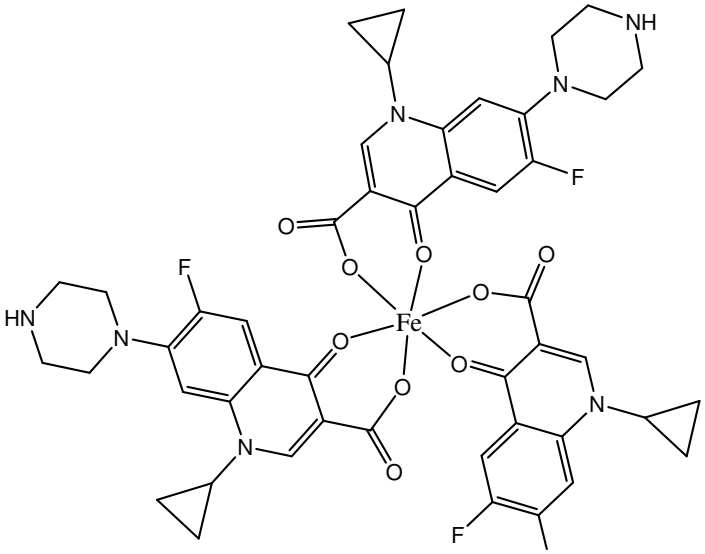


M = Mn, Ni

16



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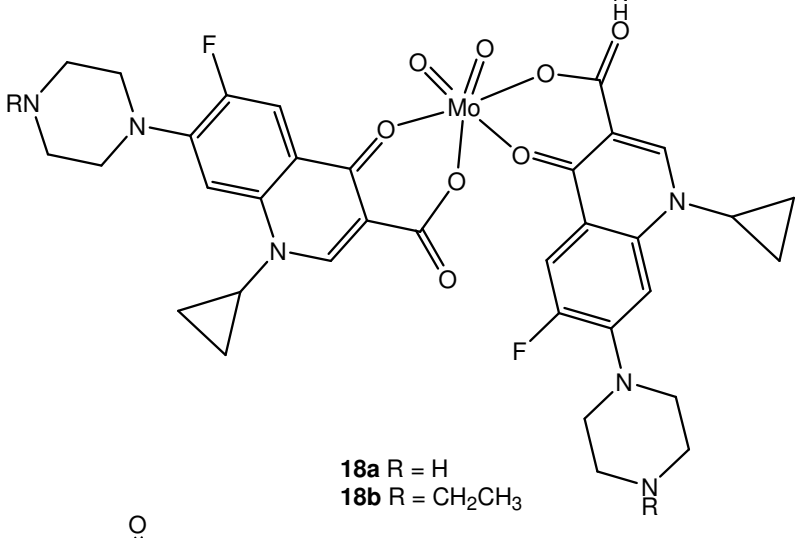
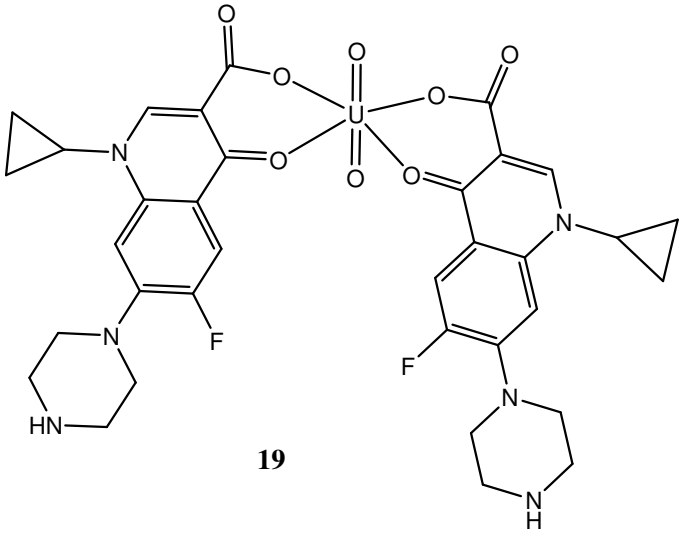


18a R = H
18b R = CH_2CH_3



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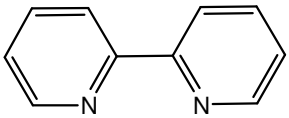

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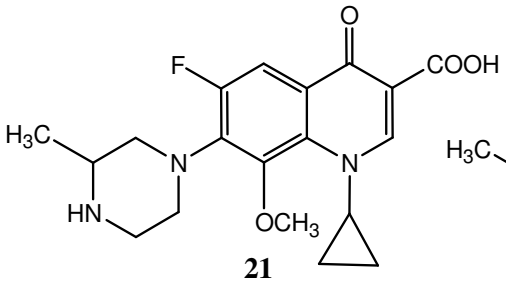

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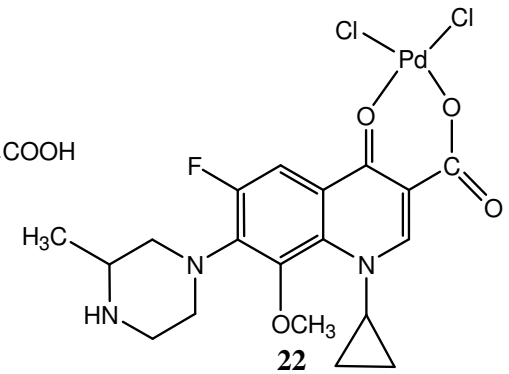

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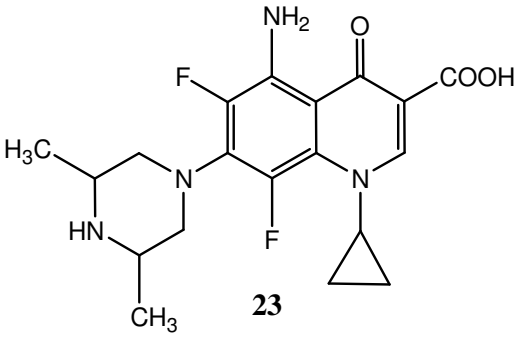

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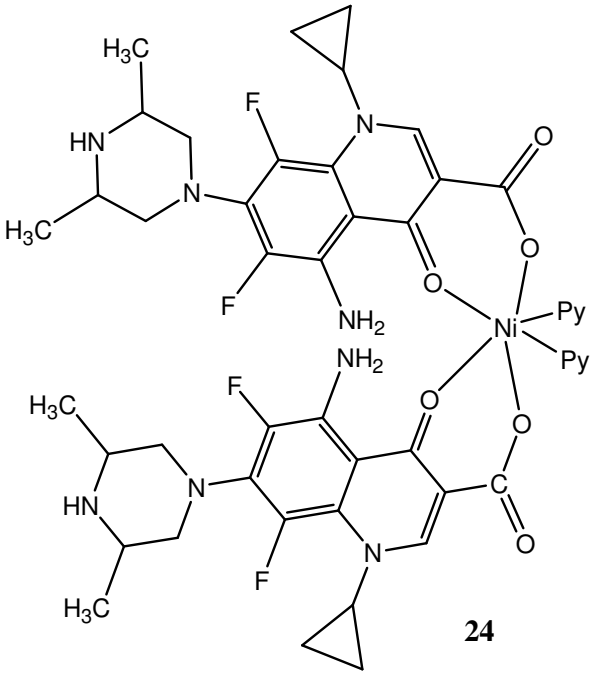

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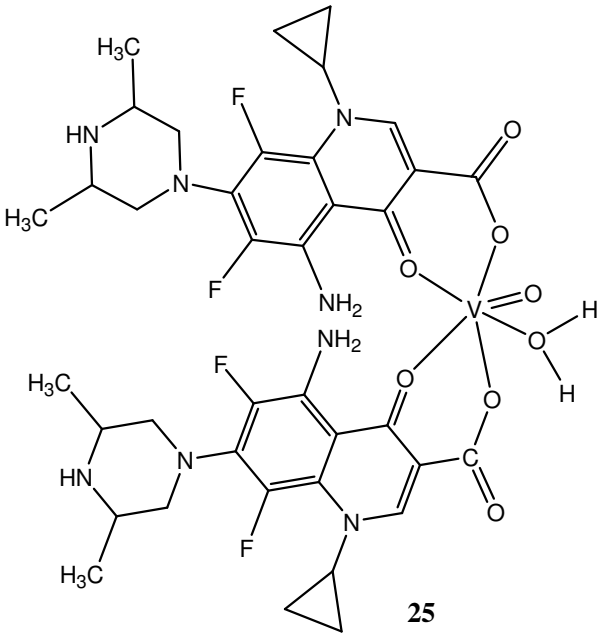

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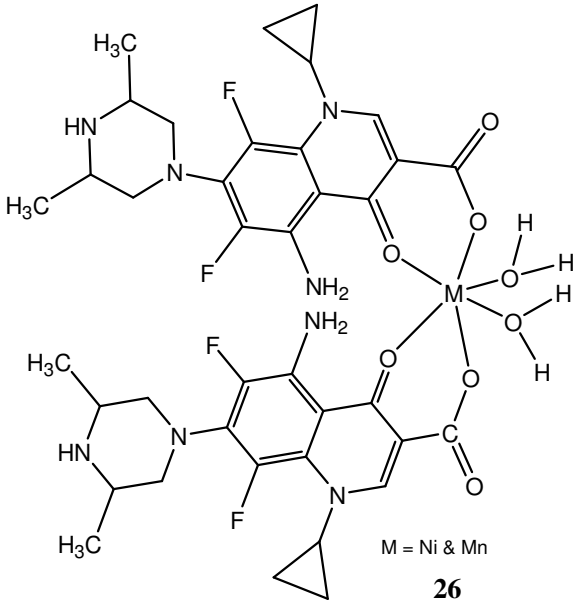

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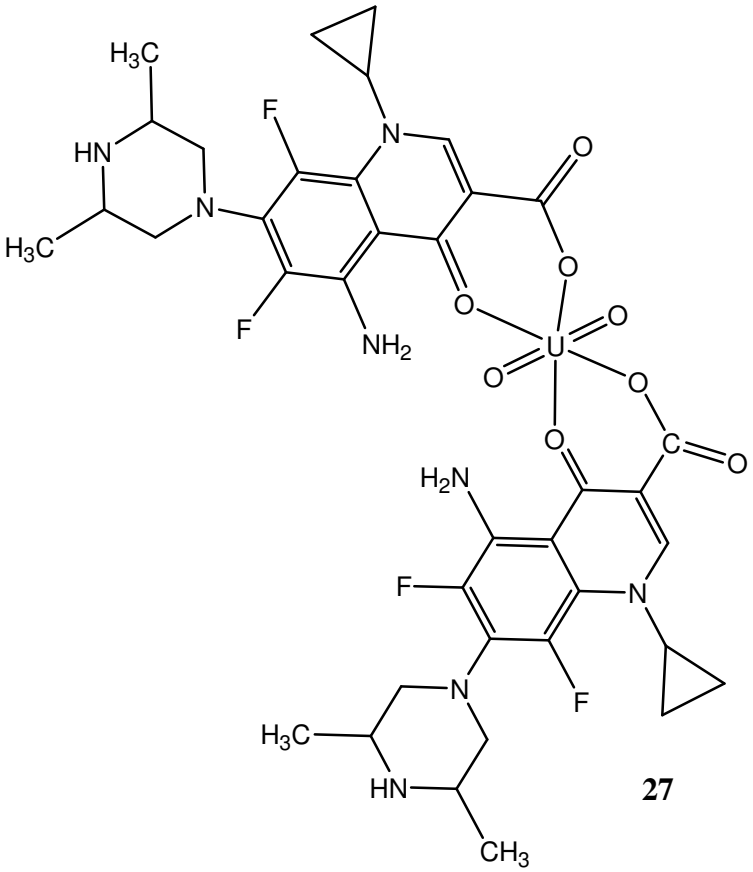

27

Conclusion

The chemistry of metal-drug interaction is significant and becoming popular. The efficacy of the drugs on complexation with metal ion is enhanced in many cases. This review article covered some of the recent literature of the metal-ion interaction with selected quinolones and their comparative biological activities with respect to free quinolones. The quinolones represent a diverse class of bactericidal agents with multiple applications in ocular infectious diseases. Their mechanism of action particularly targets to stop bacterial DNA synthesis and structural modification in different generations of these compounds have led to improved bioactivity against wide coverage of resistant species. Transport of organic ligands into bacterial cells can be facilitated by the formation of metal complexes. In most of the quinolone-metal complexes, due to the ring carbonyl group at position 4 and one of the oxygen atoms of carboxylato group at position 3, the quinolones act as bidentate ligands. The synthesis of the complexes does not require any extreme reaction conditions rather most of the complexes have been formed by simple stirring with corresponding salts at room temperature. We can conclude that the mode of action of these drugs and their metal complexes were extensively studied in the past, but there are still several questions to be answered hence effective research in the field is still the need of the hour.

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