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Ciprofloxacin metal complexes and their biological activities: A review

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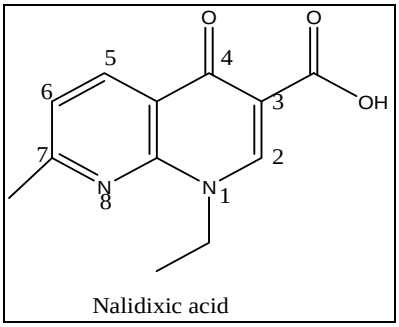
Abstract
Ciprofloxacin is a derivative of quinolone. Quinolones possesses antibacterial activity and they are structurally related to Nalidixic acid. Various modification has been done in quinolone moiety to enhance antibacterial activity and reduce resistance. On chelation, quinolones acts as unidentate, bidentate and bridging ligand. Metal ions play an important role in biological activity with quinolones. Various transition metals are used as chelating agent such as Ni^{2+}, Co^{2+}, Ca^{2+}, Zn^{2+}, Ag^{2+}, Au^{2+}, Mn^{2+}, Mg^{2+}, Fe^{2+} etc.

Keywords: Ciprofloxacin, metal complexes, antibacterial and antifungal activities

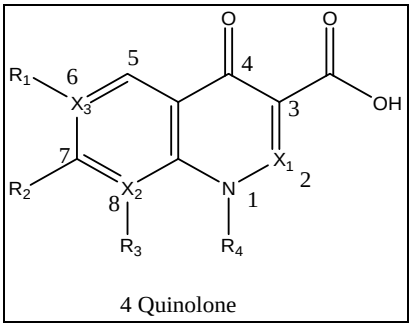
Introduction
Metal-drug complexed compounds are more popular nowadays due to their greater biological activity than uncomplexed ligands of some drugs [1]. In most of cases, it was found that Metal ions affects the action of drugs and in many cases enhance the efficacy of drugs on coordination [2]. Metal ions play an important role in different biological processes and they may act as site specific. Biological activity of metal ions depends on their concentration, they may either promotes the health of the organism or cause toxicity [3]. It was found that metal chelate possess Several biological activity viz., antibacterial, anti-fungicidal, antiviral and anticancer activity [4]. In many cases, it has also been found that the metal-drug complex possess more antimicrobial activity than the uncomplexed ligand themselves [5].
Antimicrobial resistance is fast becoming a global concern with rapid increases in multidrug-resistant bacteria. Some previously treatable pathogens are now becoming untreatable, for example methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). MRSA (resistant to methicillin, cephalosporins, all beta lactams, and occasionally gentamicin, erythromycin and trimethoprim/sulfamethoxazole) VRE (resistant to vancomycin, ampicillin, and gentamicin). To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency [6].
Among these novel metal complexes derivatives which show considerable biological activity may represent an interesting approach for designing new antibacterial drugs. This may be due to the dual possibility of both ligands plus metal ion interacting with different steps of the pathogen life cycle [7].
Compounds that contains an azomethine group (-CH=N-), are known as imines or Schiff bases and these are formed by the condensation of a primary amine with a carbonyl compound.

Chemistry of flouroquinolones
Quinolones are a group of synthetic anti-bacterial agents related to Nalidixic acid. Chemically, Nalidixic acid is (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) [8]. Various structural modifications in nalidixic acid have been done based on structure activity relationships [9]. 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 [1]. Fluoroquinolones was found to possess broad spectrum antimicrobial activity and these are cidal against aerobic Gram-negative microorganisms but less active against Gram-positive microorganisms [10]. They are extremely useful for the treatment of a variety of infectious diseases [11] and also introduced as antitumor agents [12]. 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 [1]. The chelation between the metal ion and 4-quinolone has been mainly observed with the 4-oxo and 3-carboxy groups of 4-quinolones [13]

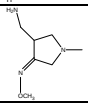
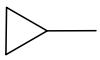
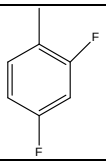
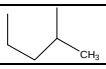
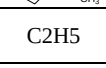
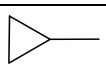
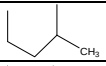
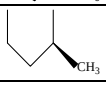


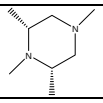
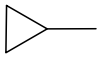
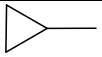
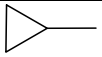
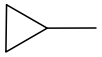
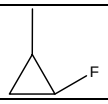
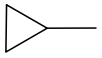
Nalidixic acid



4 Quinolone

Classes of quinolones based on chemical structure [14].

Quinolone Group/base Heterocycle	X1	X2	X3	R1	R2	R3	R4	Representatives	Generation
Naphthyridine (8-aza-4-quinolone)	CH	N	C	H	CH3	-	C2H5	Nalidixic acid	First
	CH	N	C	F		-	C2H5	Enoxacin	Second
	CH	N	C	F		-		Gemifloxacin	Third
	CH	N	C	F		-		Tosufloxacin	Third
Pyridopyrimidine (6,8-diaza-4-Quinolone)	CH	N	N	-		-	C2H5	Pipemidic acid	First
	CH	N	N	-		-	CH	Piromidic acid	First
Cinnoline (2-aza-4-quinolone)	N	C	C	-		H	C2H5	Cinoxacin	First
Quinoline (4-oxo-1,4-Dihydroquinoline, 4-quinolone)	CH	C	C	H		H	C2H5	Rosoxacin	First
	CH	C	C	-		H	C2H5	Oxolinic acid	First
	CH	C	C	F	H	-		Flumequine	First
	CH	C	C	F		H	C2H5	Norfloxacin	Second
	CH	C	C	F		H	C2H5	Pefloxacin	Second
	CH	C	C	F		H		Ciprofloxacin	Second
	CH	C	C	F		H		Enrofloxacin	Second
	CH	C	C	F		F	C2H5	Lomefloxacin	Second
	CH	C	C	F		-		Ofloxacin	Second
	CH	C	C	F				Levofloxacin	Third

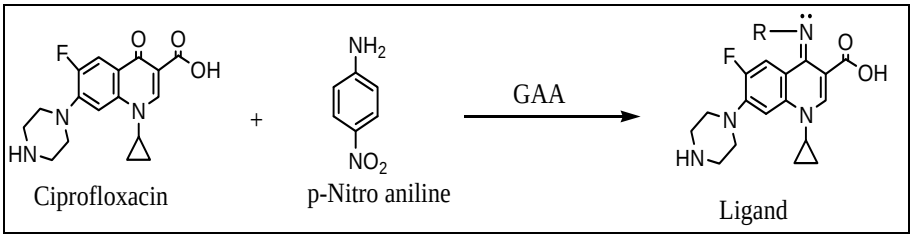
	CH	C	C	F		F		Sparfloxacin*	Third
	CH	C	C	F		OCH3		Gatifloxacin	Third
	CH	C	C	F		OCH3		Balofloxacin	Third
	CH	C	C	F		Cl		Clinafloxacin	Fourth
	CH	C	C	F		Cl		Sitafloxacin	Fourth
	CH	C	C	F		OCH3		Moxifloxacin	Fourth

Reactions

Metal complexes of ciprofloxacin:-

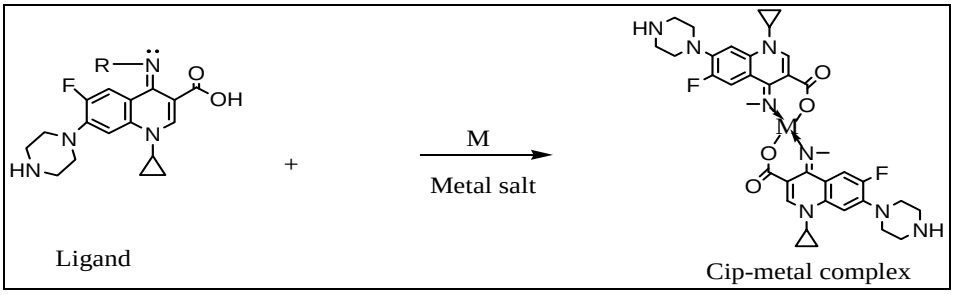
1. **Step I**

Synthesis of ciprofloxacin imines [15]

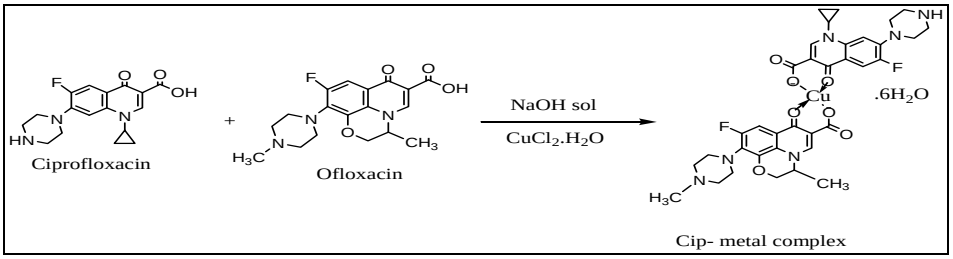


Step II

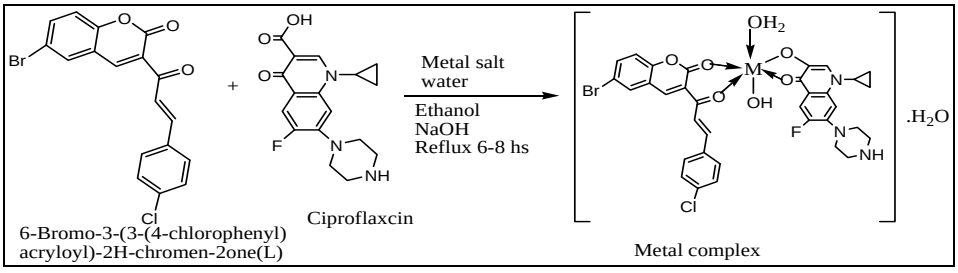
Synthesis of metal complexes



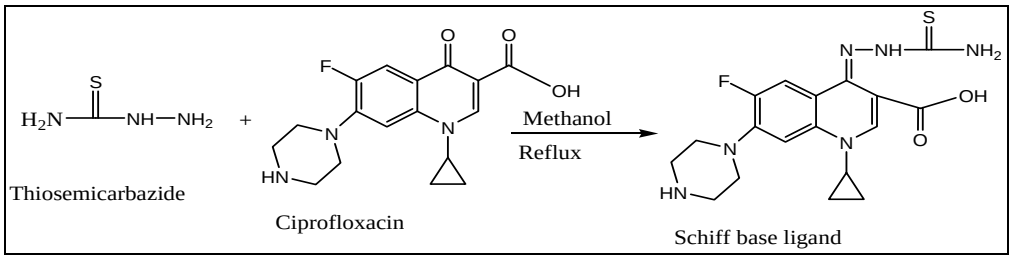
2. Mixed FQs-metal complex formation [1]



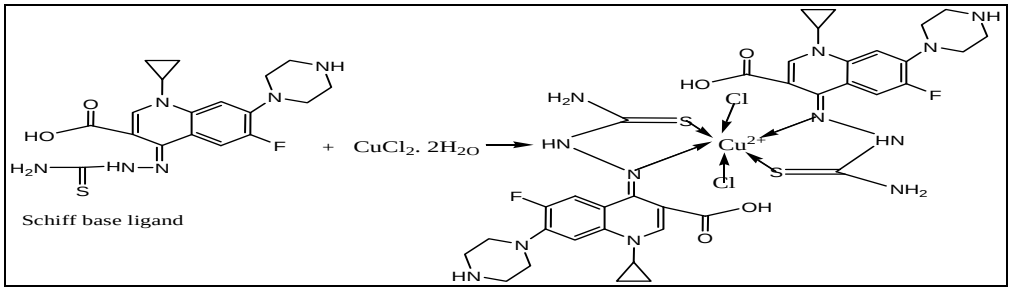
3. General procedure for synthesis of complexe [16]



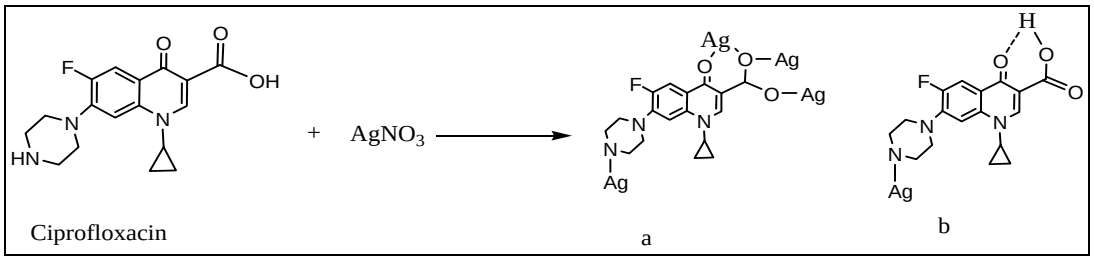
4. Step I [17]
Synthesis of Schiff base ligand



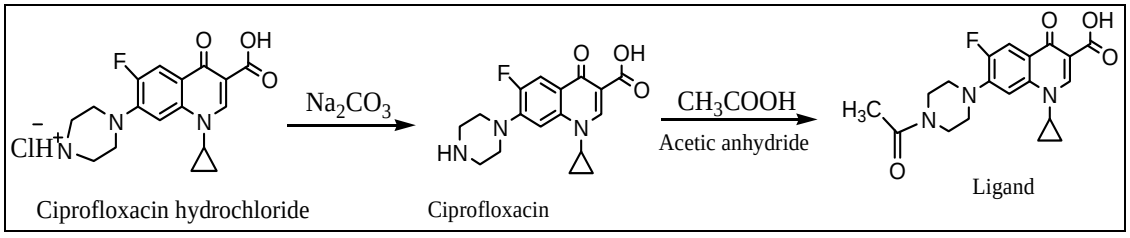
Step II
Synthesis of Copper (II) Complex



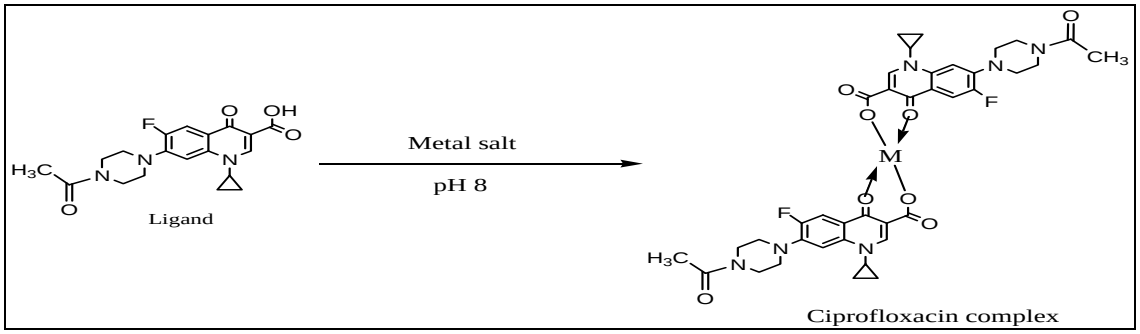
5. Two coordination modes of ciprofloxacin in polymer complex [18]



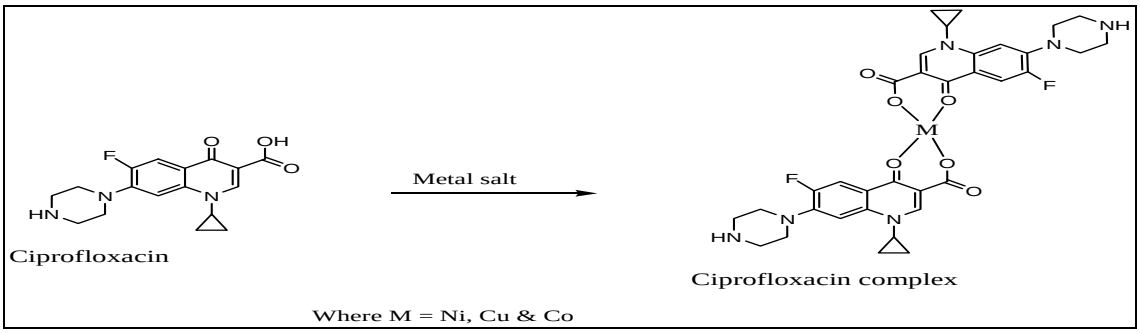
6. Step I [19]
Regeneration of ciprofloxacin and synthesis of ciprofloxacin ligand



Step II
Synthesis of metal complex of ciprofloxacin



6. Synthesis of ciprofloxacin metal complex [20]



Pharmacological Activities

S. No.	TITLE	Author	Pharmacological Activities
1.	*In vitro* antibacterial studies of ciprofloxacin-imines and their Complexes with Cu(ii),Ni(ii),Co(ii), and Zn(ii)	Muhammad imran	Antibacterial studies
2.	Synthesis, characterization and Antimicrobial evaluation of bismuth-fluoroquinolone Complexes against *helicobacter pylori*	Anwar R. Shaikh	Antibacterial activity
3.	Synthesis, characterization and antimicrobial Activity of cobalt metal complex against multi Drug resistant bacterial and fungal pathogens	Subhasish saha	Antibacterial activity Antifungal activity
4.	Synthesis, characterization and antimicrobial studies of Transition metal complexes of imidazole derivative	Saeed-ur-rehman	Antimicrobial activity
5.	Synthesis, characterization, and antibacterial activity of Some transition metals with the schiff base N-(2-furanylmethylene)-3-aminodibenzofuran	Aurora reiss	Antibacterial activity
6.	Preparation, characterization and microbiological Studies of cr+3, mn+2, co+2, ni+2, cu+2, zn+2 and cd+2 Chelates of schiffs base derived from vanillin and Anthranilic acid	M. S. Suresh	Antibacterial activity
7.	Synthesis and antibacterial activity of metal complexes of barbituric acid	Ikotun a. A.	Antibacterial activity
8.	Synthesis, characterization and bio- activity of metal complexes of Isatin derivative	G. Vall	Antibacterial activity
9.	Biological activities of some fluoroquinolones-metal complexes	Akinremi C.A.	antimicrobial, toxicology
10.	Metalloantibiotics in therapy: an overview	Prafulla m sabale	DNA interaction; Cytotoxicity.
11.	Synthesis, characterization and antimicrobial activity of metal chelates of 2-[(8-hydroxyquinolinyl)-5 aminomethyl]-3-(4-bromophenyl)-3(h)-Quinazolin-4-one	R. T. Vashi	Antifungal activity
12.	Synthesis, characterization and antimicrobial activities of some metal(ii) amino acids' complexes	Temitayo olufunmilayo aiyelabola	antimicrobial activity
13.	Synthesis, spectral and antimicrobial activity of mixed ligand complexes of Co(ii), Ni(ii), Cu(ii) and Zn(ii) with N,O and S donor ligands	R.c Sharma	Antimicrobial activity
14.	Antimicrobial activity of nikel ii coordinated compounds	Ajay kumar	Antibacterial activity
15.	Synthesis of Cu(ii), Ni(ii), Co(ii), and Mn(ii) complexes with ciprofloxacin and their evaluation of antimicrobial, antioxidant and anti-tubercular activity	ketan s. Patel	Antimicrobial activity Anti-tubercular activity Antioxidant studies
16.	Synthesis, characterization and antimicrobial screening mixed-ligand Cu(ii) and Zn(ii) complexes: dna binding studies on Cu(ii) complex	Omar h. Al-obaidi	DNA binding Antibacterial activity
17.	Synthesis, spectral and antimicrobial activity of mixed ligand complexes of Co(ii), Ni(ii), Cu(ii) and Zn(ii) with *anthranillic acid and tributylphosphine*	*Taghreed*	Antibacterial activities
18.	Synthesis and characterization of mixed ligand complexes of zinc and cadmium with phthalic Succinic cinnamic and anthranilic acid and their antimicrobial activities	G.d.rawate	Antimicrobial activities.
19.	Applications of copper – schiff's base complexes.	Rishu katwal	Antimicrobial activity, antitumor activity, catalytic properties
20.	Metal complexes of quinolone antibiotics and their applications.	Valentina uivarosi	Antimicrobial activity Antifungal and antiparasitic activity
21.	Microwave synthesis, spectral, thermal and antimicrobial studies of some Ni(ii) and Cu(ii) schiff base complexes	A. P. Mishra	Antimicrobial activities
22.	Preparation characterization, ^{1}H, ^{13}C NMR study and antibacterial studies of schiff bases and their Zn (ii) chelates	V. prakash	Antibacterial activity

23.	Synthesis of anthranilic acid and phthalic anhydride ligand and their Metal complexes	Saleem raza	Antimicrobial activity
24.	Antimicrobial studies of *n*-heterocyclic carbene silver Complexes containing benzimidazol-2-ylidene ligand	Yetkin gök	*Antimicrobial activity*
25.	Synthesis, characterization and antimicrobial studies of salicylic acid complexes of some transition metals	S. G. Yiase	*Antimicrobial*
26.	Synthesis, characterization and antimicrobial activity of Co(ii), Ni(ii), Cu (ii) and Zn(ii) complexes N- O –S donor ligands.	Vinita gupta	Antimicrobial activity
27.	Synthesis, characterization and antimicrobial studies of metal (ii) Complexes of ciprofloxacin	Mustapha a. N.	Antimicrobial, antibiotics
28.	Antibacterial, antifungal and cytotoxicity studies of ciprofloxacin-acetylated and its metal complexes with mn(ii), Fe(ii), Cu(ii), Ni(ii), Co(ii) and Zn(ii) inorganic salts	Mohammad golam rabbani	Antibacterial, antifungal, cytotoxicity

Conclusion

The chemistry of metal-drug interaction is important and turning into standard. The effectiveness of the medication on complexation with metal particle is increased in several cases. The metal particle - quinolone complexation represents a look field of accelerating progress, having in sight the results and applications of this method. several metal ion—quinolone complexes obtained within the solid state have shown numerous biological effects: antimicrobial activity (sometimes equal or higher than that of the parent quinolone), antineoplastic activity, and, in some cases, antifungal and antiparasitic activity. Their mechanism of action notably targets to prevent microorganism DNA synthesis and structural modification in numerous generations of those compounds have crystal rectifier to improved bioactivity against wide coverage of resistant species. Transport of organic ligands into microorganism cells is expedited by the formation of metal complexes. we will conclude that the mode of action of those medication and their metal complexes were extensively studied within the past, however there area unit still many inquiries to be answered thence effective analysis within the field continues to be the necessity of the hour.

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