



# Studies and synthesis of new drugs formed with fluoroquinolones and metal ions

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## ABSTRACT

The present article is focused on studies carried on fluoroquinolone metal complexes, their generalized procedures for synthesis of novel fluoroquinolones metal complexes and their anti-microbial properties. Fluoroquinolones, which are categorized as antibacterial agents are a class of type-II topoisomerase (DNA gyrase) inhibitors. These have been successfully used as antibiotics from the past several decades and the foremost drug being used is the nalidixic acid, which has its major role in cure of urinary tract infections. Typically, these fluoroquinolones are termed as 4-quinolones having fluorine atom at position 6 and a piperazine ring at position 7 of quinolone -3- carboxylic acid. Also, the presence of fluorine atom attached to quinolone ring helps to increase pharmacological properties, increases the bioavailability of the drug and enhanced membrane penetration. The synthesis procedure involves the addition and elimination reactions between aniline or aniline derivatives and ethyl ethoxymethylenemalonate. The obtained intermediate product undergoes thermal cyclization to yield 4-quinolone system. However, the use of these fluoroquinolones faced an obstacle that is the development of resistant bacteria towards quinolones. The resistance towards drug is due to amino acid substitution on the binding sites of DNA gyrase where the drug molecule interacts and inhibits the formation of bacteria DNA. This factor led to the emergence of novel drugs by formation of co-ordination complexes with various transition metals and earth metals to curb infections by these resistant bacterial strains. Quinolones form metal complexes due their binding capacity with metals. 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. The antimicrobial or antibacterial activity of the synthesized fluoroquinolone compounds are tested by disk diffusion method also known commonly as agar diffusion method.

**Key words:** Anti-microbial, bidentate ligands, Fluoroquinolones, metal complexes

## INTRODUCTION

The history of quinolones begins with the discovery of 3-carboxy substituted quinolones. In further years this lead to the development of nalidixic acid, the first quinolone antibiotic to treat urinary tract infections. Later a large variants of derivatives were synthesized classifies as first generation quinolones with quinolone structure. These possess narrow antibacterial spectrum and can be used only for urinary antiseptics. Norfloxacin is the first fluoroquinolone of second generation developed from 3-carboxy substituted quinolone (Pintilie, 2012). 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. Due to the introduction of fluorine into the quinolone moiety broadened activity is observed against additional gram-negative bacteria and gram-positive bacteria. Since then, structural modifications of norfloxacin have resulted in second-, third-, and fourth-generation fluoroquinolones, which have improved coverage of gram-positive organisms. The fluoroquinolones have been a popular class of antibiotics for their usage in a variety of infections. Their large antibacterial spectrum includes anaerobes, Chlamydia and Mycoplasma.

The basic synthetic method for synthesizing of 4-quinolones is cycloacylation of aniline derivatives in the presence of Eaton's reagent. This reaction requires high temperatures.

Apart from treating urinary tract infections quinolones also has additional pharmacological activity in the treatment of upper and lower respiratory infections, gastrointestinal infections, gynecologic infections, sexually transmitted diseases, skin and soft tissue infections (Hooper, 2000). Almost all the quinolones possess excellent oral bioavailability, showing serum drug concentrations equivalent to intravenous administration.

Resistant bacteria are observed against fluoroquinolones due to amino acid substitutions on the type -II topoisomerase (DNA gyrase and topoisomerase -IV which are the binding sites for fluoroquinolones to cause bacterial cell death. The amino acid substitutions occur on Helix-4 of these enzymes which are the crucial binding sites of the drug molecule. Mg- Water Bridge, which is an essential binding site for fluoroquinolones, is present at Helix-4 of the enzyme. As a result of substitutions this bridge is no longer available for

getting affixed on to the ternary complex of DNA comprising topoisomerase II and topoisomerase IV. To overcome this bacterial resistant factor novel drugs are being developed in combination with metal ions because they play a pivotal role in interactions of drug molecules with proteins, nucleic acids, and other bio-molecules. One such type of metal ions includes transition metal ions which when bonded to drug molecules increase their efficiency due to the formation of co-ordination complexes. The drug molecules act as ligands and interact with metal ions forming metal complexes.

Quinolones and their derivatives like 4-quinolones are such type of ligands also termed as monoanionic bidentate ligands due to the presence of carbonyl group in position 3 and oxygen of carboxyl group on position 4 of the aromatic rings. These functional groups contribute for formation of co-ordination complexes with alkaline earth metals and transition metals. These metal complexes will make the drugs to act as a broad spectrum antimicrobial agent. However, transition metals have varying utility and interesting chemistry, as these metals when bonded to appropriate ligands the drug absorption, pharmacological actions were more significant and specific than the individual drug molecule and metal ion.

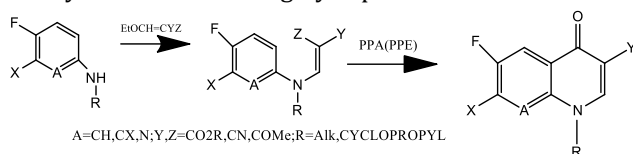
Our study is focused on the studies and synthesis of novel drugs developed on co-ordination of fluoroquinolones with metals like Ba (II), Fe (II), Cu (II), Zn (II) & Sn (II) (Akinremi et al., 2012). Quinolones also has the capability for forming polymeric complexes with metals. Quinolones can form 1:1, 2:1, and 3:1 chelates depending on the particular metal ion, relative concentration of the quinolone and the pH.

## SYNTHESIS of FLUOROQUINOLONES & METAL COMPLEXES:

### Synthesis of fluoroquinolones

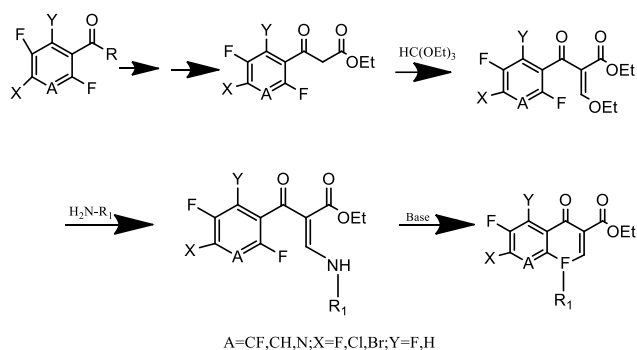
There are two fundamental approaches commonly used for the synthesis of fluoroquinolones. Common method used from past decades is the Gould Jacobs reaction. This reaction employs the use of fluorinated anilines or fluorinated 2-amino pyridines as the precursor molecules (Daniel et al, 2007). The first step is the condensation of starting chemicals with malonate ethoxymethylene and cyanoacetates resulting in the synthesis of enamine which is considered as an intermediate. Enamines undergo cyclization with the aid of polyphosphoric acid ending in the synthesis of the corresponding fluoroquinolones. The reaction

undergoes at high temperatures in the presence of diethyl ether which is highly expensive.



**Fig. 1:** Synthesis of fluoroquinolones

The second approach implies the use of fluorine containing benzoyl derivatives or their nicotinoyl analogues as backbone skeleton. The key intermediates in this reaction are benzoyl or pyridinoyl acrylates corresponding to the precursor molecule selected for synthesis. The intermediates are converted to enaminones with the use of alkylamines (Najma et al, 2013). The next step follows as the cyclization of aminoamines by heating in DMF (dimethyl formate) in the presence of base like potassium carbonate or heated in presence of ethylacetate with the help of sodium hydride (base).



**Fig. 2:** Synthesis of fluoroquinolones

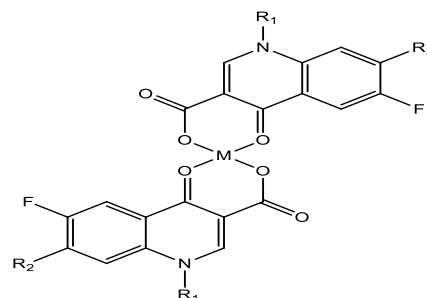
### Synthesis of metal complexes:

The formed fluoroquinolones interact with bivalent or trivalent metallic ions to yield metal complexes. As an advanced research, recently metal complexes of third generation and fourth generation fluoroquinolones are being developed and tested for their crystalline properties and antimicrobial properties. The possible way of interaction between quinolones and metal ion is the chelation between the metal and the 4-oxo and adjoining carboxyl groups (Redha I et al, 2010). Quinolones can bind several divalent and trivalent metal ions including Mg<sup>2+</sup>, Ca<sup>2+</sup>, Mn<sup>2+</sup>, Fe<sup>2+/3+</sup>, Co<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup> (metal: ligand ratio is 1:2 molar ratio) and Al<sup>3+</sup> which may result in alteration of their activity (Jamil, 2002). For example metal complexes formed with Mg<sup>2+</sup> and Al<sup>3+</sup> tend to reduce the activity of drugs whereas metal complexes with Fe<sup>3+</sup> and Zn<sup>2+</sup> increases the activity of drug molecules (Serafin et al., 2009). Presence of divalent ions acts as a contribution factor for inhibition

of gyrase activity or as a neutralizing agent for the phosphate groups of DNA (Tillotson, 1996). Quinolone act as ligand in the deprotonated form in basic conditions and acts as zwitter ion in neutral conditions. They form ionic complexes in their cationic form in highly acidic medium.

In acidic conditions quinolones form ionic chelates due to presence of the N4 piperazinyl atom, generally obtained by slow evaporation of an acidic solution of complex and metal salt. Quinolones are co-ordinated as bidentate ligand through one of the oxygen atoms of the deprotonated carboxyl group and the ring carbonyl atom. Often, quinolones acts as bidentate ligands co-ordinated with two carboxyl oxygen atoms or through two nitrogen atoms of the piperazine ring. They also act as unidentate ligand through piperazinyl nitrogen and also form polymeric complexes through multiple coordination sites. Quinolones form stronger chelates with Fe<sup>3+</sup> in comparison to bivalent metal ions like Ba<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup> and Sn<sup>2+</sup> ions (Somia et al., 2013).

Quinolone metal complexes are formed by reaction of unimolar solution of metal salts (FeCl<sub>3</sub>, BaCl<sub>2</sub>, CuCl<sub>2</sub>, ZnCl<sub>2</sub>, and SnCl<sub>2</sub>) dissolved in methanol with bimolar solution of fluoroquinolone drug molecule. The solution will be refluxed for 4 hours at above 80° on a water bath with constant stirring. After completion of reflux the solution will be filtered, and the left over product will be exposed to evaporation and later crystallization at room temperature. After a few days, crystals deposited were washed with methanol and dried. The formed crystals were soluble in methanol and Dimethyl Sulfoxide. The formed metal complexes can be characterized by various studies like spectrophotometry, spectrofluorometry, Infrared spectra, magnetic susceptibility, conductivity measurements and X-ray diffraction techniques (Roudi El et al., 1989; Saeed et al., 2009, Megharbel et al., 2015).



**Fig 3:** Fluoroquinolone metal complex

M= Bivalent metal ions like Ba<sup>2+</sup>, Fe<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup> and Sn<sup>2+</sup> ions

The general structure of 1:2 (metal: ligand) quinolone chelates with divalent cations. The complexes were represented as  $[\text{BaCl}_2(\text{L})(\text{H}_2\text{O})_2]$ ,  $[\text{FeCl}_2(\text{L})(\text{H}_2\text{O})_6]$ ,  $[\text{ZnCl}_2(\text{L})(\text{H}_2\text{O})_4]$ .  $[\text{Ba}(\text{L})_2](\text{ClO}_4)_2 \cdot \text{X H}_2\text{O}$  L represents the ligand quinolone drug molecule (Anaconda et al, 2001).

#### **PHARMACOLOGY and PHARMACOKINETIC PROPERTIES:**

Fluoroquinolones inhibit bacterial replication by blocking their DNA replication pathway. During protein synthesis and DNA replication the unwinding of DNA is the crucial step. Unwinding of DNA is done by DNA gyrase or topoisomerase II in gram positive bacteria and topoisomerase IV is responsible in gram negative bacteria. Fluoroquinolones act by inhibiting this topoisomerase enzyme which causes cell death (Lecomte S et al., 1984). But these drug molecules interact with enzyme only in the presence of DNA. In quinolone metal complexes divalent metal ions act as a bridge between the phosphate groups of the nucleic acid and the carboxyl & carbonyl moieties of fluoroquinolones. Also presence of metal ions stabilizes the quinolone-metal-DNA linkage in presence of stacking interactions between the condensed rings of the drug molecules and the DNA bases. Also the drug metal complexes reduce the stability of DNA protein thus increasing the structural flexibility so that drug molecules can easily binds to the respective sites. The divalent metal ions also possess the characteristic feature of enzyme poisoning. Presence of metal ions increases the efficiency and efficacy of the drug molecules (Alkaysi HN et al., 1992). The important feature of these fluoroquinolone metal complexes is to fight against resistant bacteria. The drawback of these quinolone metal complexes is that their bioavailability decreases when they are orally administered. Recent investigations concluded that among all the bivalent ions complexes, metal complex formed with  $\text{Fe}^{2+}$  shows lesser bioavailability when quinolones are administered orally (IztokTurel, 2002). The possible cause for lesser bioavailability is conversion of  $\text{Fe}^{2+}$  ion to  $\text{Fe}^{3+}$  ion in the gastro intestinal tract. Advanced studies on metal complexes proposed hypothetical conclusion stating that the lesser bioavailability is due to formation of insoluble and unabsorbable chelates in the gastrointestinal tract. Also there is increased solubility of the drug molecules due to the presence of metal ions. Experimental studies revealed that fluoroquinolone metal combinations resulted in a reduced intestinal permeability compared to that of the corresponding

fluoroquinolone, contributing to the lesser bioavailability of the drug.

#### **BIOLOGICAL ACTIVITY of FLUOROQUINOLONE METAL COMPLEXES:**

##### **Anti-bacterial property:**

Many chelate complexes of fluoroquinolones exhibited an equal or superior activity than that of the parent molecule. The increased biological activity or efficacy is due to more cell permeability in the presence of  $\text{Ba}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Sn}^{2+}$  metal ions. Observed increase in activity is based on the over tone concept and chelation theory (Sharma Ritu Gupta, 2013). As per overtone theory, of cell permeability, the lipid membrane surrounding the cell allows the passage of only lipid molecules; hence lipophilicity is the major factor for exhibiting anti microbial property. Upon formation of co-ordination complexes the polarity of metal ion is reduced due to partial sharing of cationic charge with the donor groups of the ligand (Carboxyl and carbonyl or piperazinyl groups). In addition to this, chelation also increases the delocalization of pi-electrons over the chelate ring and ensuing in increase of lipophilic nature of the central ion. The increased lipophilic feature of the drug enhances the easy penetration into the cell through the lipid membranes (Takacs Novak K et al., 1990).

But there also evidences and studies proving that these metal complexes reduce the anti microbial property of the quinolones. One such example is Ciprofloxacin in combination with metal ions has low permeability into the cell wall and also forms inactive chelate resulting in decrease of the antibiotic action (Benjamin Howard, 2015).

##### **Antifungal and ant parasitic activity:**

Quinolones are well known for their antibacterial property from their day of invention. Quinolones themselves do not possess antifungal properties but metal complexes of some newer fluoroquinolones exhibit this activity.  $\text{Fe}(\text{III})$ ,  $\text{Cu}(\text{II})$ , and  $\text{Zn}(\text{II})$  Complexes of levofloxacin proved to have higher antifungal effects than the standard drug against *Candida albicans* (Tumer M et al., 1999). Complexes of gatifloxacin with  $\text{Cu}(\text{II})$ ,  $\text{Zn}(\text{II})$ ,  $\text{Fe}(\text{III})$ , in 1:2 (metal: ligand) stoichiometry displayed excellent antifungal properties against fungi *Trichophyton rubrum*, *Candida albicans* and *Fusarium solani*. Research experimentation also revealed that some complexes of sparfloxacin show ant parasitic activity against parasite

*Trypanosoma cruzi*. Studies are ongoing in this area as some metal complexes tend to reduce the antiparasitic activity of the free molecule and some tend to increase the activity by three to four folds (Ma H et al., 1997; Valentina Uivarosi, 2013; Stevara Clinton, 2015;).

#### **ANTI TUMOR ACTIVITY:**

Numerous research studies confirmed that quinolone metal complexes had ability to interact with DNA, by blocking topoisomerase enzymes and thus inhibiting the DNA repair, which is a promising factor for anticancer treatment (Sanjay kumar Gajera et al., 2016).

Investigations also proved that zinc complexes of lomefloxacin, a second generation quinolone is found to be very active against breast cancer cell line MCF7 (Cozzarelli NR, 1980). Also the gold complexes of levofloxacin and sparfloxacin, the fourth generation fluoroquinolones were tested against various cancer cell lines like A20 (murine lymphoma), B16-F10 (murine melanoma) and K562 (human myeloid leukemia). Results concluded that the metal complexes have more significant activity against cancer cells than the free ligand drug molecules (Abd El-Halim HF et al., 2011). Recent studies also revealed that the introduction of quinolone ligands onto the surface of polyoxometalates exhibited higher anti tumor activity than the free drug molecules (Mitscher, 2005). One study proved that introduction of pipemedic acid (quinolone) Zn (II) complexes onto SiW<sub>12</sub> polyoxoanion showed more anti tumor activity than the parent compound without metal complex against MCF-7 cell lines. Similarly Cu (II) complexes of enrofloxacin in combination with polyoxoanions have more anti cancer activity against SGC7901 lines (Patitungkho S et al., 2011).

#### **EVALUATION of ANTIBACTERIAL ACTIVITY:**

The efficacy of fluoroquinolones metal complexes towards inhibition of bacteria can be tested by disc diffusion method or agar diffusion method. This method employs the principle of measuring minimum inhibitory concentration (MIC) with respect to bacterial strains. This procedure involves the testing of new drug metal complexes against various strains of gram positive bacteria like *Staphylococcus aureus* and gram negative bacteria like *E.coli* and *Pseudomonas aeruginosa*. Different concentrations of drug are prepared by dissolving measured quantities in dimethyl formamide. An appropriate quantity of prepared

nutrient agar media was poured in each petri plates. After solidification of agar medium, the bacterial suspension of known concentration will be streaked on the surface of agar media with spreader. Four paper discs were placed at four corners of the plate and drug solutions were added drop wise on to the disc (Sha JQ et al., 2011). The paper disc treated with dimethyl Sulfoxide serves as control and the paper disc with standard drug concentration acts as standard. These petri plates shall be maintained at 5°C for 24 hours to allow prediffusion. Later petri plates will be incubated at 30°C for 24 hours. The zone of inhibition will be measured and the minimum concentration required by the drug complex to acquire the zone of inhibition is the minimal inhibitory concentration which is calculated for each drug complex.

#### **TOXICOLOGY:**

Metal complexes of fluoroquinolones were synthesized to fight against broad spectrum bacteria. These chelates help to increase the activity, efficacy, solubility of the drug and also help to increase the cell permeability by improving its lipophilicity. The efficacy and activity of the parent molecules might increase with formation of metal complexes or remain the same for most of the fluoroquinolones (Breda SA, 2009). But on the other hand due to the formation of metal complexes with certain type of metals like Fe(II) and Fe (III) there is lesser bioavailability of the drug in the gastrointestinal tract and reduced intestinal permeability due to formation of insoluble chelates. Although introduction of metal complexes do not induce major toxicities but exhibit the common adverse effects seen with the parent drug (Polk RE et al., 1989). These adverse effects were related to gastrointestinal system which includes nausea, vomiting, gastric irritation and occasionally diarrhea (Deepa Singh Thakur et al., 2014). Some metal complexes produce longer post- antibiotic effect compared to that of free drug ligand. This is observed by introduction Al (III) metal into ciprofloxacin. Also case studies depicted that complexation with metals like Bi (III) reduces the solubility of the drug than its original form.

#### **CONCLUSION**

Most of the present day bacterial infections exhibit resistance to the well known antibiotics and this antibiotic resistance is the rising problem in the field of drugs. Hence there is an emergency for the development of Fluoroquinolone novel drugs with metal complexes.



This article presents the need for metal complexes, their synthesis, pharmacological actions and their biological activities.

Fluoroquinolone antibiotics are strong complexing agents with divalent metal ions and the formation of complexes involves direct interaction of the quinolone moiety with the metal ion. This metal chelates helps to increase the solubility of the drug molecules in polar solvents. The mode of action of fluoroquinolones metal chelates is the increase in lipophilicity of the drug moiety for easy penetration into the bacterial cell wall. Also the presence of divalent metal ions increases the efficacy of the drug by poisoning topoisomerase enzyme responsible for bacterial DNA replication. Quinolone metal complexes also profoundly act as antibacterial, antifungal, ant parasitic and anti tumor agents.

Furthermore studies need to be carried out to investigate on potential drug resistance of fluoroquinolones metal complexes because some bacterial strains are insensitive to pure fluoroquinolones and are sensitive to their metal complexes. Indeed, 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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