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# QUINOLONES ANTIBACTERIAL AGENT WITH BROAD SPECTRUM ACTIVITY: A REVIEW

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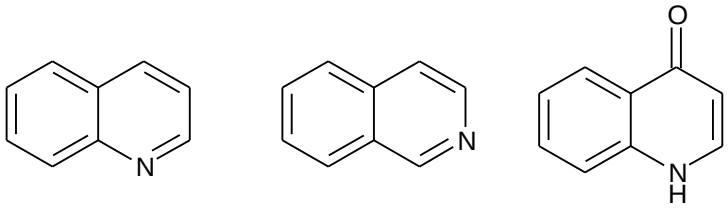
## ABSTRACT

Quinolones are broad-spectrum antibiotics (effective for both gram-negative and gram-positive bacteria) that play an important role in treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected. It was recognized as pyretic degradation product of cinchonamine. They are colourless liquid and miscible with organic solvent and dissolve in water and also they are slightly weaker bases. This review considers the quinolones that are available currently and used widely in India (norfoxacin, ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin) within their historical perspective, while trying to position them in the context of recent and possible future advances based on an understanding of their chemical structures and how these impact on activity and toxicity; resistance mechanisms (mutations in target genes, efflux pumps).

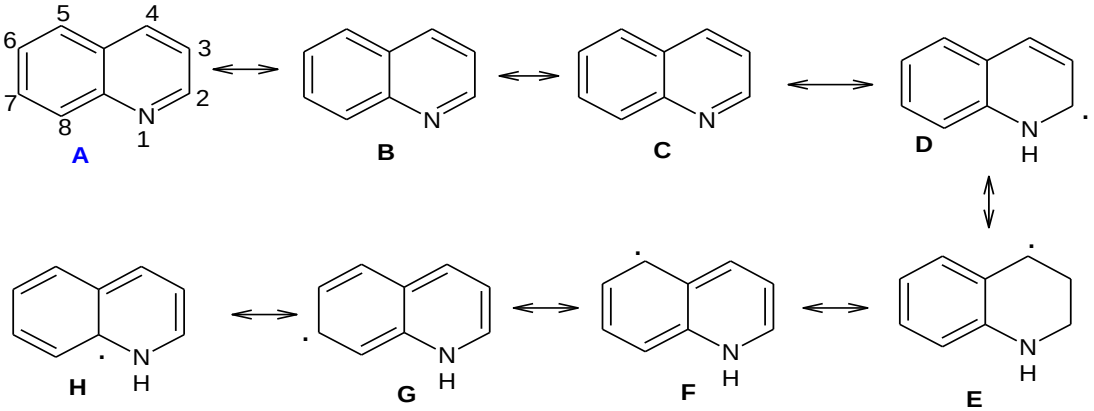
## INTRODUCTION

Quinoline was first isolated from coal tar in 1834, it was also recognized as pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine.The name quinoline was derived from *quina*, a Spanish version of a local South American name for the bark of quinine-containing *cinchona* Species.Several Synthetic anti-malarial drugs are based on the quinoline nucleus, Chloroquine is an example. Several antibiotics like fluro-quinolones now in clinical use were 4-quinolone-based antibiotics.




**Molecular structure:**

Quinolone is a base since, as for pyridine, the lone pair of electrons on the aromatic nitrogen atom is not utilized in its internal resonance. Although it is an aromatic compound the valance bond description of quinoline shows two of the neutral contributors, A and C to the resonance hybrid as quinonoid in character, where as in B either the carbocycle or the heterocycle must exist in the form of a 1,3-diene. The presence of pyridine nucleus is reflected by the inclusion of doubly charged colonical forms.




However the representations F to H involve disruption of both monocyclic π systems simultaneously. It fallows that these are of higher energy and they contribute very much less to the overall descriptions of the molecule than to the alternatives D and E that effect only the pyridine system. [1]

All the ring atoms in quinoline are $sp^2$ hybridized. The lone pair of electrons on the nitrogen is not involved in the formation of delocalized π molecular orbital. It shows aromatic properties because its π orbital contains ten electrons and satisfies the Huckle rule (n=2 in 4n + 2)-electrons.

The bond lengths of quinoline, which are irregular, support the resonance description; thus the 1-2, 5-6, and 7-8 linkage are shorter than that of the carbon-carbon bond benzene there is also a dipole of 2.19D directed towards the nitrogen atom. [2]

**Properties:**

1. Quinoline is a colorless liquid of bp. $237^0$C. It turns yellow on standing and has pyridine like smell.
2. Miscible with most organic solvents and dissolves in water to about 0.7 % at room temperature.
3. Slightly weaker base ($pK_a$= 4.94) than pyridine ($pK_a$= 5.2). It reacts with acid to yield salts which are sparing soluble in water.

**Reactions with Electrophilic Reagents:** [1]

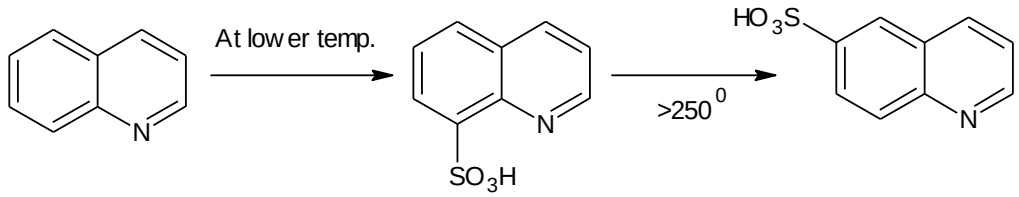
**Addition to nitrogen:**

It involves donation of the nitrogen lone pair of electrophiles, $pK_a$ values of quinoline and isoquinoline was 4.94 and 5.4 shown them to have similar basicity of pyridine.

**Substitution reactions:**

Nitration the position selectivity for proton exchange is partly mirrored in nitrations; quinoline gives approximately equal amount of 5- and 8-nitro-isomers.

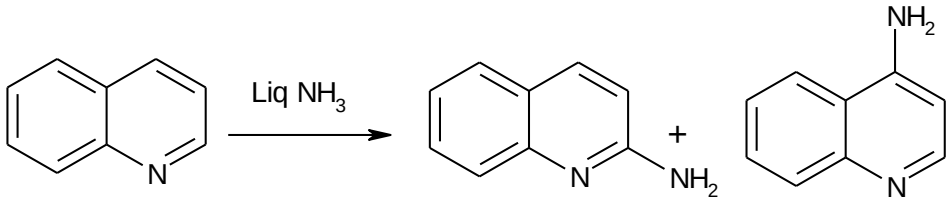
Sulphonation of quinoline gives largely the 8-sulfonic acid where as isoquinoline affords the 5-acids. Reactions at higher temperature produce other isomers under thermodynamic control, for example both quinoline 8-sulfonic acid and quinoline 5- sulfonic acids are isomerizes to the 6-acids.



**B] Reactions with Nucleophilic reagents:** [1,2]

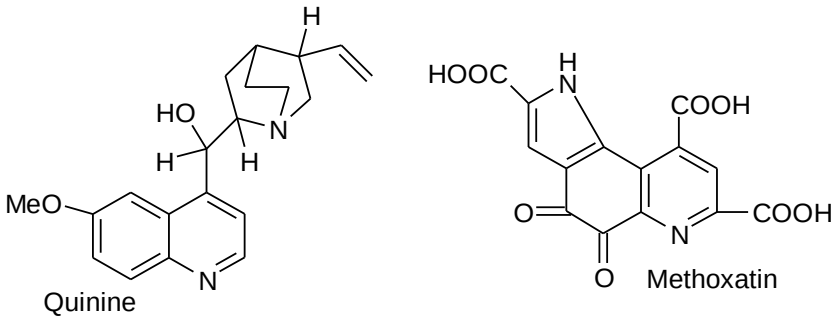
**Amination:**

Sodium amide reacts rapidly and completely with quinoline even at -45°C, to give Dihydro adducts at initial amide attack at C-2 (main) and C-4 (minor). The quinoline 2-adduct rearranges to give more stable 4-aminated adduct at higher temperatures.

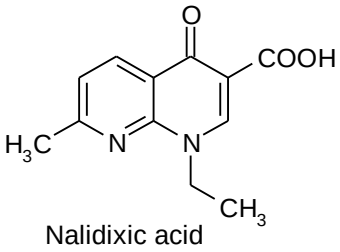



**History:**

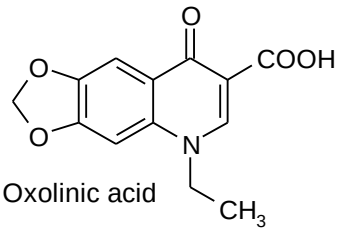
Quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. It was also recognized as pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine. They play a relative minor role in fundamental metabolism, methoxatin, an enzyme cofactor of methylotropic bacteria, being one of the examples. There are also comparatively few quinoline-containing secondary metabolites, in contrast to isoquinoline, which occurs mainly at the 1, 2, 3, 4-tetrahydro level, in a large no of alkaloids like the opium poppy alkaloids papaverine and in more elaborated form morphine and emetine. [3]




The evolution of quinolones actually emanated from the discovery of nalidixic acid by Lesher who followed chemistry developed previously for the synthesis of esentative of the quinolones which was found effective against some G-ve microorganisms and possessed pharmacokinetic properties for treating urinary tract infections (UTIs). However, following the introduction of nalidixic acid for the treatment of uncomplicated UTIs caused by enteric bacteria, the quinolones became a neglected group of antimicrobials until the development of the fluoroquinolones in the1970s and 1980s. [4]




Nalidixic acid




Oxolinic acid

The fluoroquinolones have an extended spectrum of activity and improved pharmacokinetics compared with the earlier compounds. In two decades, the quinolones moved from a relatively small and unimportant group of drugs used predominantly for the treatment of UTI, two molecules with potent activity against a wide spectrum of significant bacterial pathogens.

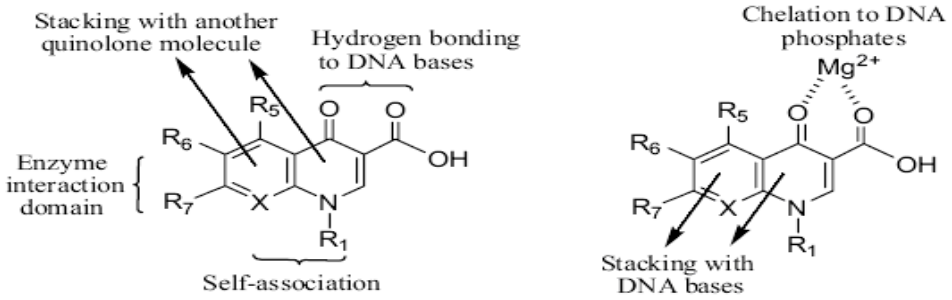
**Generation and development of quinolones:**

Based on the 4-quinolone nucleus the quinolones comprise a relatively large and expanding group of synthetic compounds. An alkaloid having quinolone structure was first prepared by Price but it possessed no biological activity. In 1960, Barton *et al.* isolated 6-chloro-1*H*-ethyl-4-oxo-quinoline-3-carboxilic acid during antimalerial research, which showed antibacterial activity. In 1962 during the process of synthesis and purification of Chloroquine (an antimalerial agent), a naphthyridine derivative, nalidixic acid, was discovered which possessed bactericidal activity. However, its clinical use was limited to the treatment of UTIs caused by the majority of G-ve bacteria, with the exception of *Pseudomonas aeruginosa.* Thereafter, novel compounds of this family, such as oxolinic acid, pipemidic acid and cinoxacin were synthesized and introduced. The quinolone carboxylic acids are a class of highly potent and orally active broad spectrum antibacterial agents. The products represent a development of the earlier analogues (nalidixic acid, oxalinic acid, pipimedic acid and cinoxacin) is been more potent in invitro and is having broader antibacterial spectrum, which induces gram positive and gram negative organisms. Structurally members of the class are defined generally as 1-substituted-1,4 dihydropyridine-3 carboxylic acids with a fused ring at the 5 and 6- position, although very recently effective replacement for the carboxylic moiety have been reported. [5]

**Mechanism of action:**

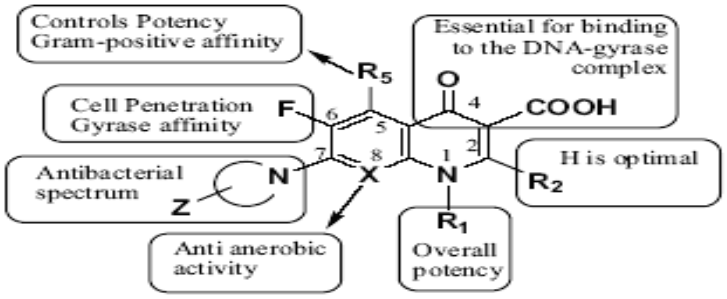
Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-Enzyme complexes of DNA gyrase and type II topoisomerase, resulting in rapid bacterial death. The molecular organization of the complex is presently unknown although several models have been suggested. According to one model, four quinolone molecules bound as two pairs of

noncovalently associated drug dimers in a single-stranded DNA bubble opened up by topoisomerase action. Based on another model, the affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA enzyme-complex via a magnesium ion as a general rule, G-ve bacterial activity correlates with inhibition of DNA gyrase, and G+ve bacterial activity corresponds with inhibition of DNA type II topoisomerase.




**Structure-activity relationships:** [6,7,8]

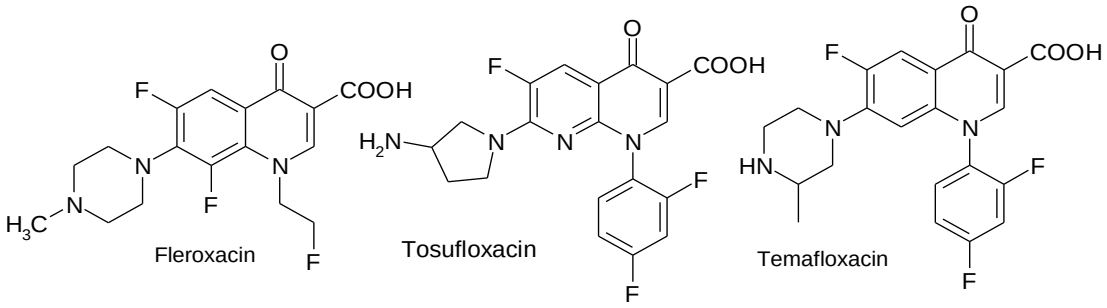
The minimum pharmacophore required for significant antibacterial activity consists of the 4-pyridone ring with a 3-carboxylic acid group. Indeed, quinolones consist of a bicyclic ring structure in which there is a substitution at position N-1, with various moieties. Most of the current agents have a fluorine atom at position 6 and a nitrogen heterocycle moiety at the C-7 position. In general, β-keto carboxylic acid moiety (positions 3 and 4) is essentially required for hydrogen bonding interactions with DNA bases in the single-stranded regions of dublex DNA created by the action of the enzyme. Thus, the 1-, 2-, 5-, 6-, 7-, and 8- positions are the major targets of chemical variation.




$R_1$= Et, cyclopropyl, halo substituted aromatic ring , etc.
$R_2$= H, -SMe, or $R_1$& $R_2$ may join to form a ring.
$R_5$= H, $-NH_2$ ,-OMe
X= N, CH, CF, C-OMe, or X & $R_1$ may join to form a ring.
Z= attached group to cycloalkylamine ring.

**Position-1:**

Antibacterial activity is greatly influenced by the steric bulk of N-1 substituent and optimal groups in order of activity being cyclopropyl, ethyl followed by fluorosubstituted phenyl and *t*-butyl. It is also found that substituent with more steric bulk e.g. fluoroethyl (fleroxacin), 2, 4-difluorophenyl (tosufloxacin and temafloxacin) group have also enhanced activity against anaerobes.

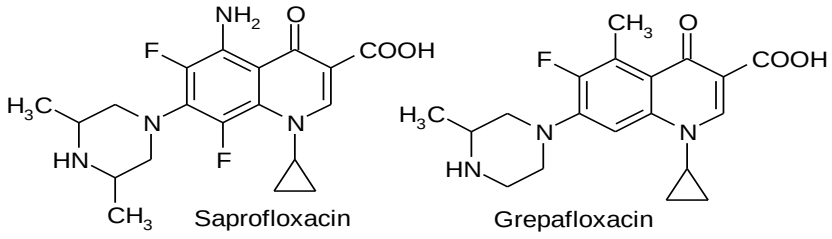



**Position-2:**

Very little is known about the SAR of quinolone having substituents at C-2 position; as loss of bioactivity has been found with methyl, hydroxyl or methylthio substituents. However a ring between C-1 and C-2 position was shown to have biological activity. The C-2 position is left unsubstituted because of its proximity to the enzyme binding site.

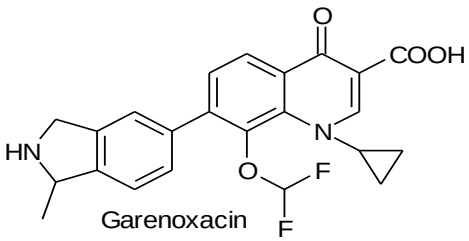
**Position-5:**

Introduction of some substituents such as halogen, nitro, amino, hydroxy and alkyl groups at C-5 were initially thought to reduce antibacterial activity of the quinolones. However, 5-amino substitution in the 6, 8-difluoroquinolone series having N-1 cyclopropyl group showed enhanced *in-vitro* activity, especially against G+ve organisms. Thus, substitutions at this position are thought to contribute to potency against G+ve organisms. The influence of 5-amino group depends on the substitution pattern at C-8 and N-1 and a few potent analogues in this series are Sparfloxacin and PD 124816; having improved G+ve activity as well as anaerobic activity. Moreover, Grepafloxacin with a methyl group at C-5 exhibits increased activity.

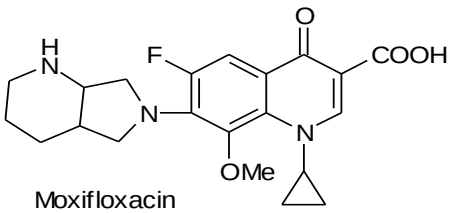


**Position-6:**

Several substituents besides fluorine have been introduced into position 6. All of the quinolones having those substituents were less active than 6-fluoroquinolones. The influence of fluorine at C-6 is essential for high activity as evidenced by its enhanced gyrase inhibition and cell penetration which has become the basis for generic name fluoroquinolones. However, there has been a recent interest in quinolones without fluorine at this position. The non-fluorinatedquinolones, for example Garenoxacin, show greater potency than the newer fluoroquinolones, Moxifloxacin against both sensitive and resistant G+ve organisms, thus casting doubt on the validity of the necessity of the C-6 fluorine. Garenoxacin does however have a difluoromethoxy at position 8; although an analog of this compound without the C-8 moiety is still as potent as moxifloxacin. Recently, fluorine at C-6 is replaced by $NO_2$ group to get highly potent nitroquinolones. They are potent inhibitor of *Streptococcus* and *Staphylococcus* species.[7]



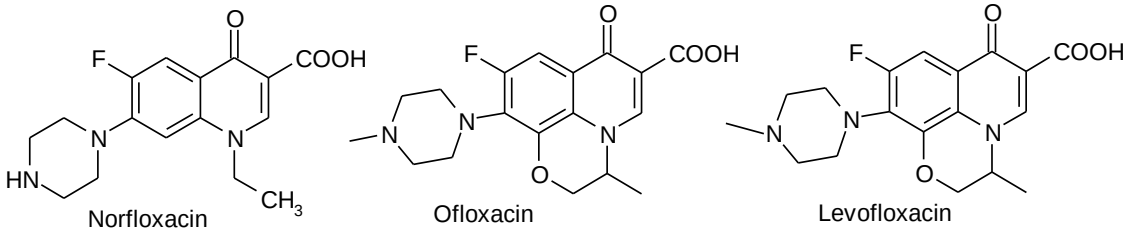
Garenoxacin



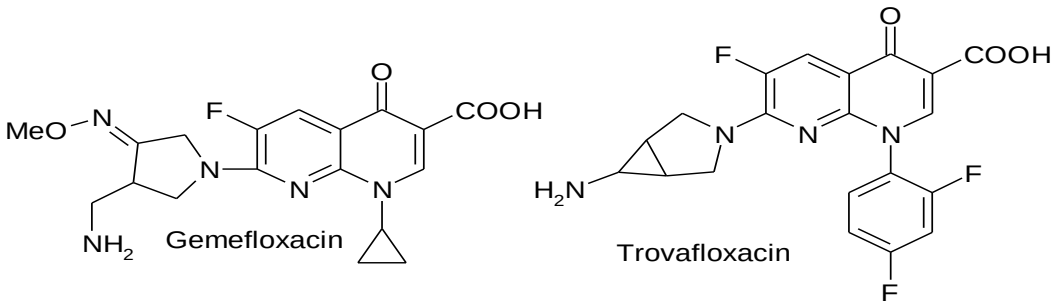
Moxifloxacin

**Position-7:**

Substituents at position 7 are closely associated with properties of the quinolones such as their antibacterial spectrum, bioavailability and side effects. Introduction of a basic group at C-7 of the quinolone ring was found to enhance antibacterial activity, as this substituent greatly influences antibacterial and pharmacokinetic properties. A five or six membered cycloamino moieties (e. g. pyrrolidine or piperazine rings) is the most commonly used substitutions at C-7 position. Piperazine rings are particularly common (e.g. norfloxacin, ciprofloxacin, pefloxacin, ofloxacin, sparfloxacin, lomefloxacin, levofloxacin, enoxacin and fleroxacin) and confer potency against G-ve bacteria. The addition of methyl groups can improve both oral absorption and *in-vivo* activity. However, the improved activity against G+ve bacteria can sometimes be at the expense of activity against *Pseudomonas aeruginosa*. The piperazine moieties of 7-piperazinyl quinolones possess enough structural flexibility to allow product optimization. In addition substitutions of bulky groups are permitted at the N-4 of piperazine ring of 7-piperazinyl quinolone molecule.




Pyrrolidine rings (five-membered) are also common substituents at position 7 and are associated with enhanced potency against G+ve bacteria. However, this group is associated with low water solubility and low oral bioavailability. Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties.




Gemifloxacin a naphthyridone derivative is a good example of the advantages and disadvantages associated with a pyrrolidine ring at position 7. In a series of compounds, it was shown that antibacterial activity against Gram-negative bacteria increased in the following order 4'- methyl piperazinyl < 3'- methyl piperazinyl < piperazinyl < 3'- amino pyrrolidinyl; whereas the Gram-positive activity follows the sequence piperazinyl < 3'- methyl piperazinyl < 4'- methyl piperazinyl < 3'-amino pyrrolidinyl. Alkyl amino and alkyl oximino substituent's in the ring further enhances bactericidal action and serum half life of the compounds. The addition of azabicyclo groups onto position 7 has resulted in agents (moxifloxacin and trovafloxacin) with significant anti-G+ve activity and marked lipophilicity.

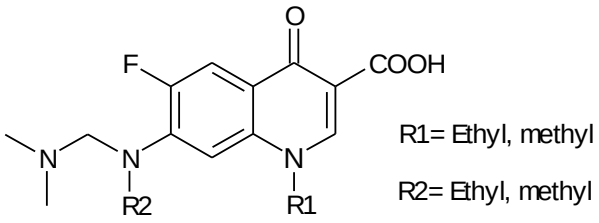
**Position 8:**

Manipulation of the group at position 8 has also been shown to play a role on oral pharmacokinetics and broadening the spectrum of activity. Among many modifications investigated in C-8 position, a few substituents such as fluoro, chloro methyl and methoxy group offered good antibacterial activity, especially against G+ve; as well as against anerobes. While other substituent's will decrease the activity. A number of naphthyridone in which C-8 of quinolone is replaced by a nitrogen atom showed excellent activity.

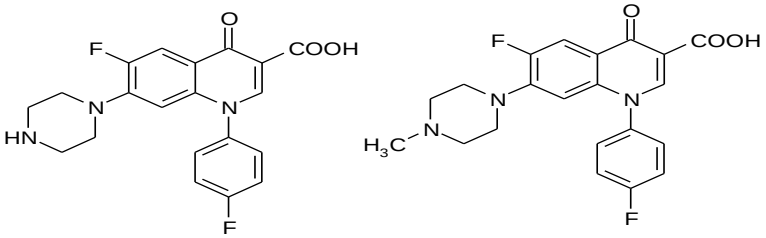
**Pharmacological and biological activities:**

Quinolones are very important family of antimicrobial agents that are widely prescribed for the treatment of infections in humans. Since their discovery in the early 1960s, the quinolone group of antibacterials has generated considerable clinical and scientific interest .Since from 1980's a lot of work was in progress for the development of various chemotherapeutic agents mainly on the fluoro-quinolones.

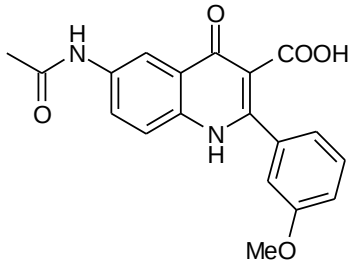
In 1980, a new series of 6,7- and 7,8-Disubstituted 1-Alkyl-1,4dihydro-4oxoquinoline-3-carboxylic Acids were prepared for their anti-bacterial activity by Hiroshi K et al. The compounds synthesized were tested against G+ve and G-ve bacteria among them 1-ethyl -6-fluro-1,4-dihydro-4-oxo-7-(1-piperizinyl) quinoline-3-carboxylic acid showed more potent than oxanillic acid.[10]



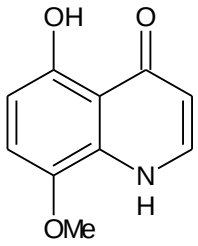

In 1985 Daniel et al carried out the synthesis and Structural-Activity Relationships of novel Arylfluroquinolone antibacterial agents. The below compounds showed excellent in vitro potency and in vivo efficiency. This confirmed that electronic and spatial properties of 1-substituted, as well as steric bulk play important role in antimicrobial potency in class of drugs.[11]



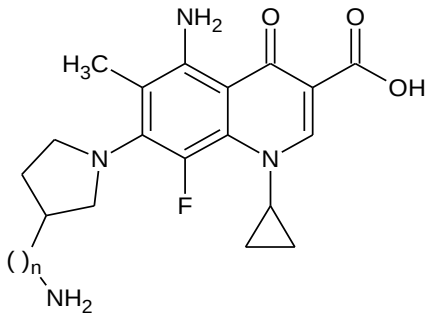

John MD et al studied the Quantitative structural activity relationships at $N_1$- substitute quinolones for their Antibacterial activities. They discussed the QSAR results along with the conformational analysis from molecular modeling studies.[12] Leping L and co-workers reported a new series of 3',6,7-Substituted 2-Phenyl-4-quinolones and tested against human tumour cell lines including those derived from ovary, Prostate, Lung, Colon and Breast cancers they found that the below compound inhibit tubilin polymerization.[13]



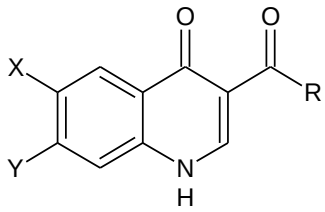

In 1997 Moon Woo Chun et al, synthesized a series of 8-hydroxy-4-quinolone and 5methoxy-4-quinolone derivatives were synthesized as truncated acridone analogues and evaluated for antitumor and antiherpes activities. Among them 8-hydroxy-smethoxy- quinolone showed potent antitumor activity (ICse = 17.7 KM for HL60) which was greater than that of acronycine.[14]



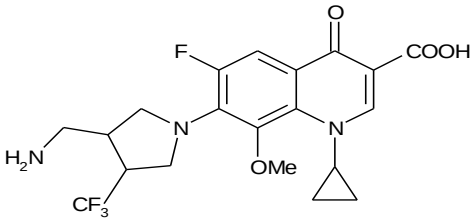

Chang Yong Hong,Se Ho Kim, and Young Kwan Kim in 1997 synthesized A novel 5-amino-6-methylquinoline carboxylic acid was synthesized from 2,3,4-trifluoro aniline in 12 steps and coupled with various types of amines to furnish new quinolone antibacterial agents. Depending on the strucaae of amine, some of quinolones showed comparable activity to ciprofloxacin or better Gram positive activity than ciprofloxacin, demonstrating that the C6 fluorine atom is not a necessary requirement for good antibacterial potency.[15]



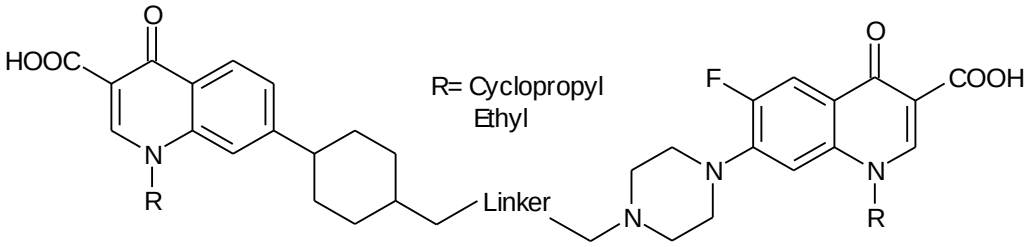

Sandhya Srivastava, Sanjay K. Srivastava in 1999 synthesized a series of 6/7-mono and disubstituted quinolone-3-carboxamide derivatives and their *in vitro* methemoglobin producing capacity have been delineated. The compounds showed minimum methemoglobin toxicity.[16]



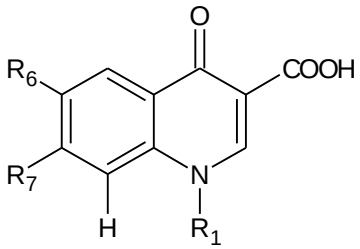

Masahiko H and coworkers studied the *in vitro* anti-bacterial activity of some novel 7-(3-Substituted-3 or 4-trifluoromethyl- 1-pyrrolidinyl)-8-methoxy fluoroquinolones among them (3R,4S)-3-aminomethyl-4-trifluoromethyl derivative (S-34109) was confirmed to be optimal because of its superior activity against quinolone and methicillin-resistant *Staphylococcus aureus* and low side effect potential.[17]



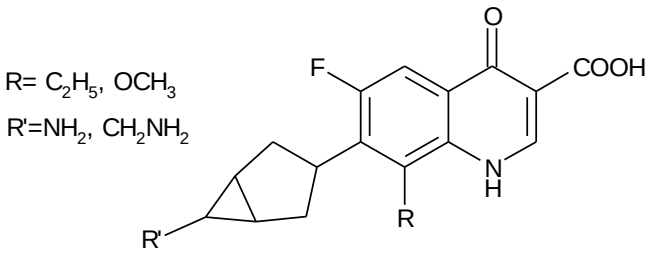

In 2003 Robert JK and coworkers Synthesized Piperazinyl-Linked Fluoro quinolone Dimers and evaluate the anti-bacterial activity against Drug resistance strains of *Staphylococcus aureus*.[18]




Sara N. Richter, Barbara Gatto in 2005 introduced Structural modifications in 6-amino-quinolones to increase antiviral activity can strongly affect cytotoxicity to host cells. By competition to Tat–TAR complex and binding experiments to viral and cellular DNA and RNA structures, they shown that the nature of the substituent at position 7 modifies drug affinity and specificity for the nucleic acid.[19]



The new 6-fluoroquinolones were designed and synthesized by Guillaume A and coworkers and evaluated their biological evaluation against *T. gondii and Plasmodium (P.) spp*., and their effect on *Mycobacterium (M.) tuberculosis* DNA gyrase. From QSAR analysis they rationally desigened the activity against *Toxoplasma (T.) gondii.*[20]




The fluoroquinolones are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory and urinary tract infections. Fluoroquinolones are active against a wide range of aerobic gram-positive and gram-negative organisms. Gram-positive coverage includes penicillinase- and non-penicillinase producing Staphylococci, Streptococcus pneumoniae and viridans, Enterococcus faecalis, Listeria monocytogenes, and Nocardia species. Gram negative coverage includes Neisseria meningitides and gonorrhoeae, Haemophilus influenzae, and most clinically important Enterobacteriaceae species, Pseudomonas aeruginosa and Vibrio species. The fluoroquinolones are believed to act by inhibition of type II DNA toposiomerases (gyrases) that are required for synthesis of bacterial mRNAs (transcription) and DNA replication. They demonstrate little inhibition of human, host enzymes and have had an excellent safety record. The fluoroquinolones are indicated for treatment of several bacterial infections, including bacterial bronchitis, pneumonia, sinusitis, urinary tract infections, septicemia and intraabdominal infections, joint and bone infections, soft tissue and skin infections, typhoid fever, bacterial gastroenteritis, urethral and gynecological infections, and pelvic inflammatory disease and several other infectious conditions.

The fluoroquinolones currently available in the United States include ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. These agents are well absorbed orally and well tolerated with a low rate of adverse effects. Several quinolones and fluoroquinolones were introduced, but were subsequently withdrawn after spontaneous reports of severe adverse events including hepatotoxicity: temafloxacin (1992), gatifloxacin (2006), and trovafloxacin (1999). The currently available fluoroquinolones appear to cause idiosyncratic liver injury rarely, at an estimated rate of 1:100,000 persons-exposed. Idiosyncratic liver injury

due to fluoroquinolones may be a "class" effect; the pattern of injury is similar, marked by acute and often severe hepatocellular pattern of injury arising within 1 to 4 weeks of starting therapy.

**CONCLUSION**

Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue. When taken for four to six weeks, norfloxacin, ciprofloxacin, levofloxacin, and ofloxacin have eradication rates of 67 to 91 percent. Treatment failures have been associated with shorter treatment courses and less susceptible bacteria, specifically P. aeruginosa and Enterococcus species. Levofloxacin is an excellent first-line agent in the treatment of prostatitis. Ciprofloxacin should be reserved for use in patients with resistant gram-negative, pseudomonal, and enterococcal prostatitis, because of its superior activity against P. aeruginosa and enterococci.

As long as these agents are used to treat the appropriate types of patients, and are not regarded by prescribers as the magic bullet, the effectiveness of the class will survive long into the present century. However, if they are dispensed with a lack of concern, then their day will conclude prematurely. As always, bacteria are smarter than humans, and both fundamental and very practical approaches are required to conserve antibiotics as useful agents and not as discoveries of the past. Quinolones are no exception to this rule, which makes it essential that they are used in an educated fashion.

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