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Review Article

A Snapshot on the Development of Quinolones and Fluoroquinolones - An Origin of Nalidixic Acid

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Abstract

Quinolone antibacterial molecules are the most impactful types of anti-infective, active pharmaceutical ingredients in our never-ending battle against pathogens. Additionally, in contrast to many anti-infective classes, the discoverers published a startlingly small amount of information regarding the origin of the class or the justification for this significant group's first FDA-approved agent, nalidixic acid. With an emphasis on the Quantitative Structure-Activity Relationship (QSAR), chemistry, development, adverse effect, and future aspects of this class of antibiotics, this article discusses the discovery, total synthetic methods, pharmacology, clinical applications, and further lead to the new pipeline that produced various large selling and widely used antibiotics.
Keywords: Nalidixic Acid, Synthesis, Development, Quinolones, Fluoroquinolones

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Introduction

The history of anti-malarial drugs began with the use of Cinchona (Fever tree) family-Rubiaceae, which was used centuries ago due to the cure of the countess of Chinchona in 1638. The bark's effectiveness in treating intermittent fevers became widely known (1). It was officially reported as an infusion in London Pharmacopoeia in 1677. Various species of Cinchona were used because its bark contains Quinoline alkaloids mainly - Quinine. World War II and the global epidemic of malaria increased the demand for antimalarial drugs to balance supply and demand, resulting in reduction of quinine side effects. Various laboratories around the world have worked to develop semi-synthetic or synthetic derivatives of quinine. Hans Andersag discovered chloroquine in 1934 in the laboratories of Bayer IG, Farbenindustrie AG in Eberfeld, Germany. While searching for new chemical entities based on quinine's structure to increase treatment options for malaria, scientists at Sterling Company, New York, discovered derivatives of the molecule 1,8-naphthyridine exhibit antibacterial activity. In 1962, George Lesher discovered nalidixic acid in a distillate of chloroquine (2). Consequently,

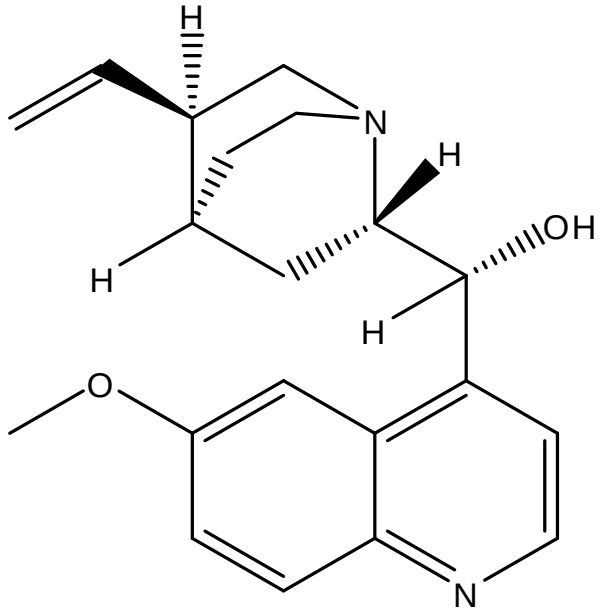

Figure 1. Chemical Structure of Quinine.

nalidixic acid, the precursor of all topoisomerase inhibitors, is a byproduct of antimalarial research**.** It was the first of the synthetic quinolone antibiotics. A great story began with the mysterious discovery of NA that generated more potent antibacterial drug molecules with little change in chemical functional groups and substituents (Figure 1 and 2).

Although NA was synthesized accidentally**,** we are currently aware that a number of naturally occurring drug molecules have a quinoline pharmacophore**.** Camptothecin (Topoisomerase I Inhibitor), Pteleatine, Cusparin**,** Kolbisine, Cinchonidin and Chinine (Anti-protozoal) itself became an inspiring factor for scientists to test its pharmacological action**,** which later turned out to be a promising antibacterial agent and thus began the quinolones to be developed in large quantities in 1962. Due to its frequent prevalence in bioactive chemicals, the quinoline scaffold might be considered a favoured structure (3). The quinoline motif is widely used in synthetic medicinal chemistry and exhibits a wide range of activities**,** including anticancer, antifungal, antibacterial, and anti-protozoic properties (3). In fact, the introduction of chloroquine in the treatment of malaria more than 60 years ago ushered in a new era of rapidly growing antimicrobial agents through nalidixic acid and fluoroquinolones, and its clinical use in 1967 marked the beginning of 50 years' research and development of quinolones. Naturally occurring quinoline in different plant families exhibits a wide range of biological activities (Figure 3) (3).

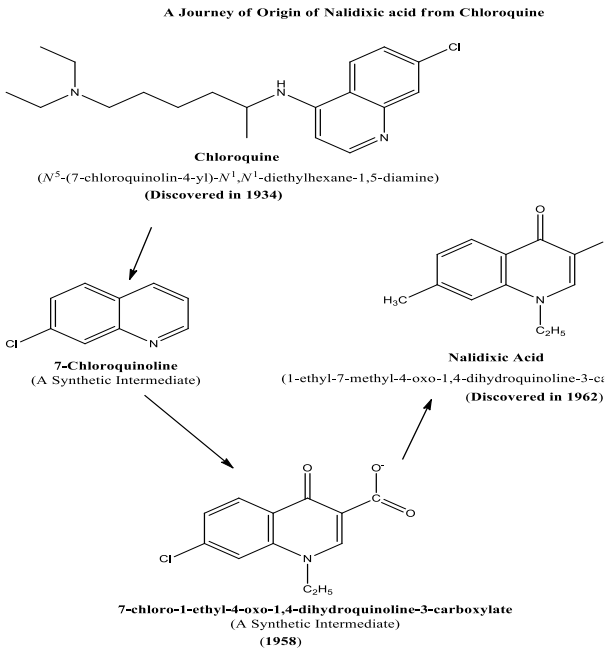

Figure 2. Reason for undergoing of Nalidixic acid (from chloroquine) for bioactivity studies.

The past of the quinolones may be traced back to NA, which was discovered in 1962. Furthermore, advances in drug design for the scaffold and basic side chains have enabled for enhancements to the first novel quinolone, norfloxacin, which was created in 1978. Although more than 10,000 molecules have been produced worldwide**,** merely 2% of them have been

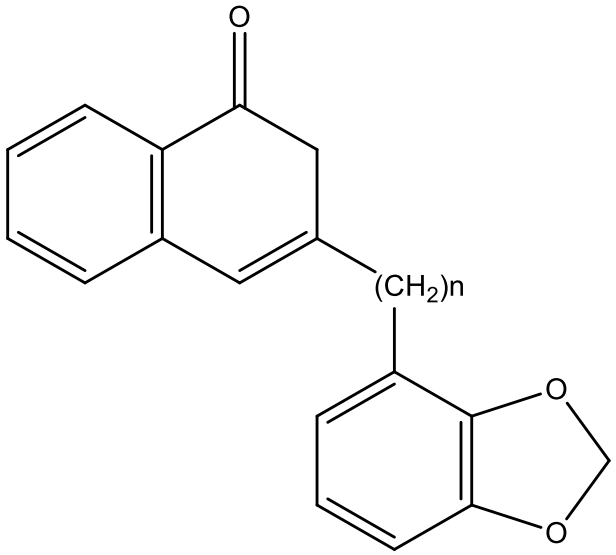

Figure 3. Structure of basic Quinolone moiety present in *Rutaceae* family (4).

established and verified in clinical trials. Moreover, just 20 of these molecules have been successfully introduced into the market (4).

Chemistry, synthesis and characterization of NA (5)

IUPAC Nomenclature is**:** 1-ethyl-7-methyl-4-oxo-[1,8]naphthyridine-3-carboxylic acid Molecular Formula: $C_{12}H_{12}N_2O_3$. Pharmacokinetic data: NA binds to proteins in the blood plasma at a rate of approximately 90%, much higher compared to its metabolite 7-hydroxymethylnalidixic acid; Half-life of NA is approximately 6-7 hours and primarily bio-transformed by hydroxylation (Figure 4 and 5).

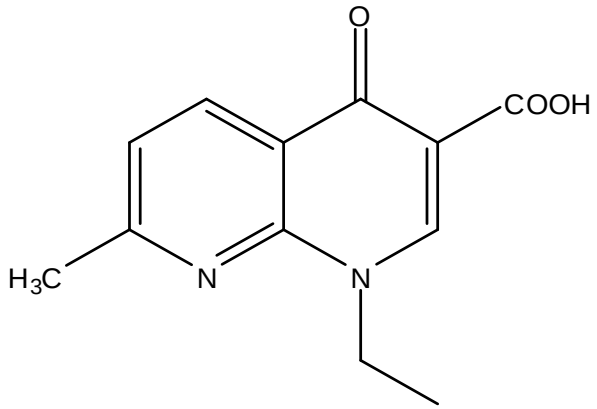

Figure 4. Structure of Nalidixic acid (6, 7).

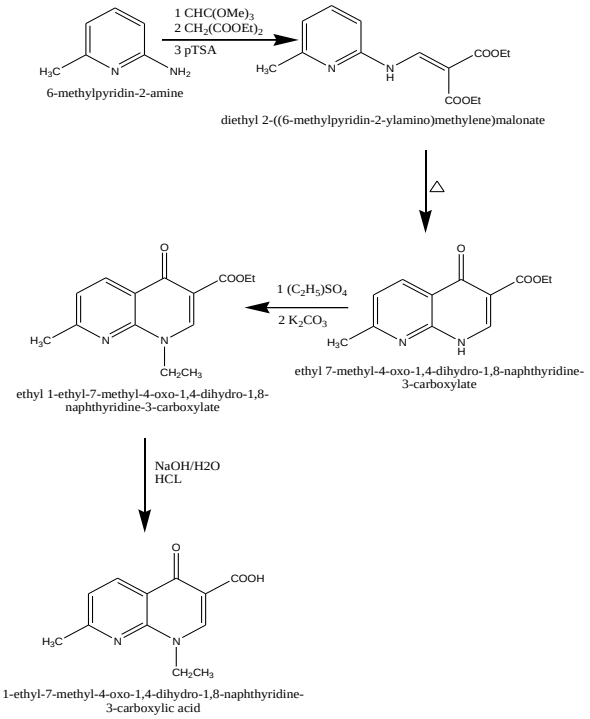

Figure 5. Total synthesis of Nalidixic acid (6).

Pharmacology and Mechanism of action

Deoxyribonucleic acid synthesis was stopped at the bactericidal concentration of NA, and not ribonucleic acid (RNA) or protein synthesis. Both RNA and protein formation were reduced at higher dosages, where the medication is less bactericidal. NA has narrow antibacterial range, therefore NA has limited clinical relevance. Bacterial resistance develops quickly, pharmacokinetics is poor, and the drug accumulates in the body and urine (26). The NA scaffold is an excellent starting point for the project and expansion, as it provides improved tissue diffusion and bioavailability for new quinolones. Antibacterial drugs are conjugated by adding peptides or carbohydrates as a vector for cell membrane penetration, can greatly improve their physicochemical characteristics, as well as intracellular and intercellular distribution**,** providing a way to increase antimicrobial activity.

Quinolones inhibit DNA synthesis and eliminate microorganisms. Quinolones block bacterial DNA gyrase production, preventing bacterial DNA from undergoing 3° (-) supercoiling. Topoisomerase IV, a gyrase homolog with substantial decatenating activity, was found in 1990, and it is obvious that topoisomerase IV, not gyrase, is accountable for decatenation of interconnected chromosomes. The antibacterial quinolones twin effect contrary to DNA gyrase and topoisomerase IV has since been established to be the equivalent principle (2, 9, 13). During replication and transcription, these amazing enzymes are answerable for upholding the authenticity of the supercoiled DNA helix. If they are prevented from acting, the bacterial chromosome remains unwinding and is too lengthy to get into the 2 offspring cells. Quinolones bind to bacterial topoisomerase type II enzymes through water–metal ions. At the concentrations used in clinical practice**,** quinolones did not have a similar effect on any mammalian enzyme (8) (Figure 6 and 7).

Development and QSAR of fluoroquinolones

Since the introduction of NA, the quinolone antibiotic, into clinical medicine, the issue of resistance has been a major concern**.** Pathogenic microorganisms' resistance to nalidixic acid has fueled the development of new versions, reviving the drug's prospective use. Fluoroquinolones have been shown to be more potent and effective than quinolones in QSAR studies

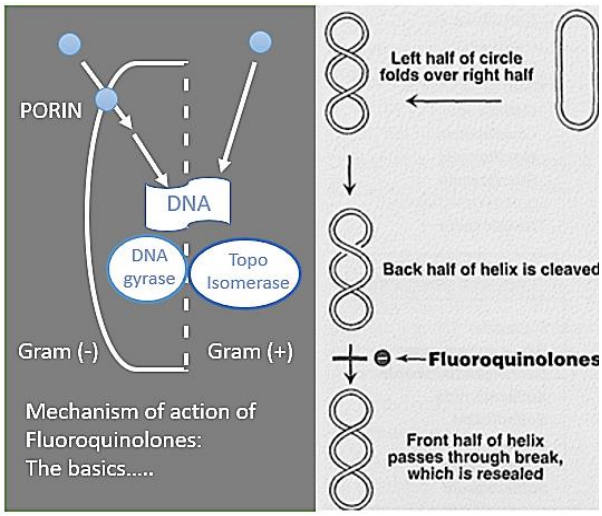

Figure 6. Mechanism of action of Fluoroquinolones and action of type-II topoisomerase.

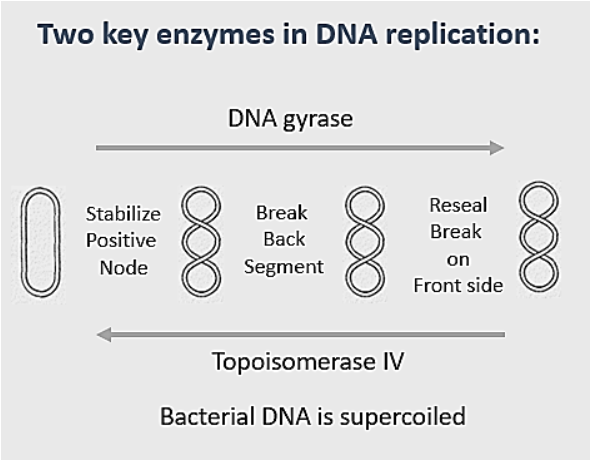

Figure 7. Functions of enzymes during replication in bacteria.

(Elaborated in Figure 10). For this reason, the quinolone content has been optimized in the future to achieve even better efficacy with less toxicity (Chart 1) (8, 9).

The growing thoughtful of fluoroquinolone structure-activity interactions has allowed for the synthesis of increasingly better molecules (9). The discovery of

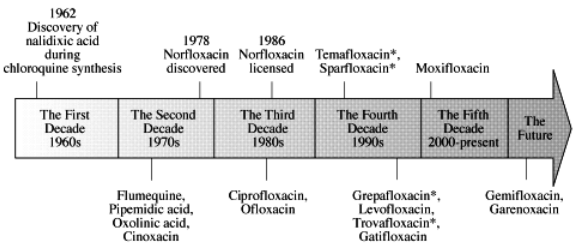

Chart 1. Chronological order in decades of discovery and use of Fluoro-quinolones.

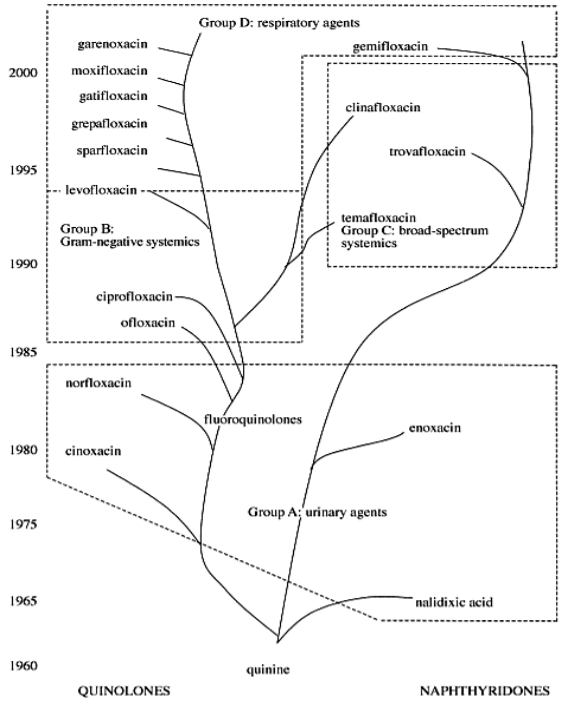

Figure 8. Development of Quinolones.

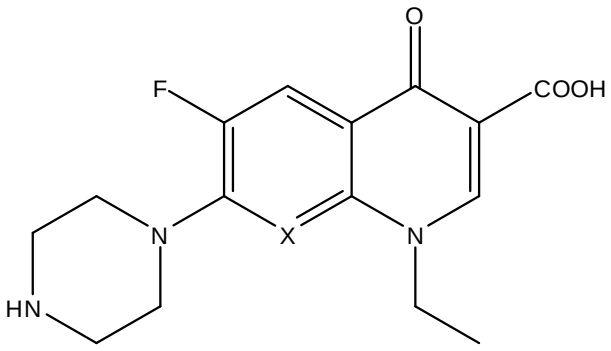

Figure 9. Scheme for different isosteres synthesis. X= N Enoxacin X= CH Norfloxacin.

substituents with a high affinity for binding to two target enzymes, DNA gyrase and topoisomerase IV, was made possible by studying structure-activity relationships. Substitutes and combinations of substituents on the Quinolone nucleus were used to create new Fluoroquinolones with an acceptable safety profile that outperformed earlier drugs' potential side effects. The wide-ranging breadth of activity of these novel fluoroquinolones was noted, counting action against anaerobic bacteria (except nemonoxacin). These novel fluoroquinolones are sensitive to many resistant bacteria. Delafloxacin and finafloxacin have the benefit of being particularly active in an acidic pH

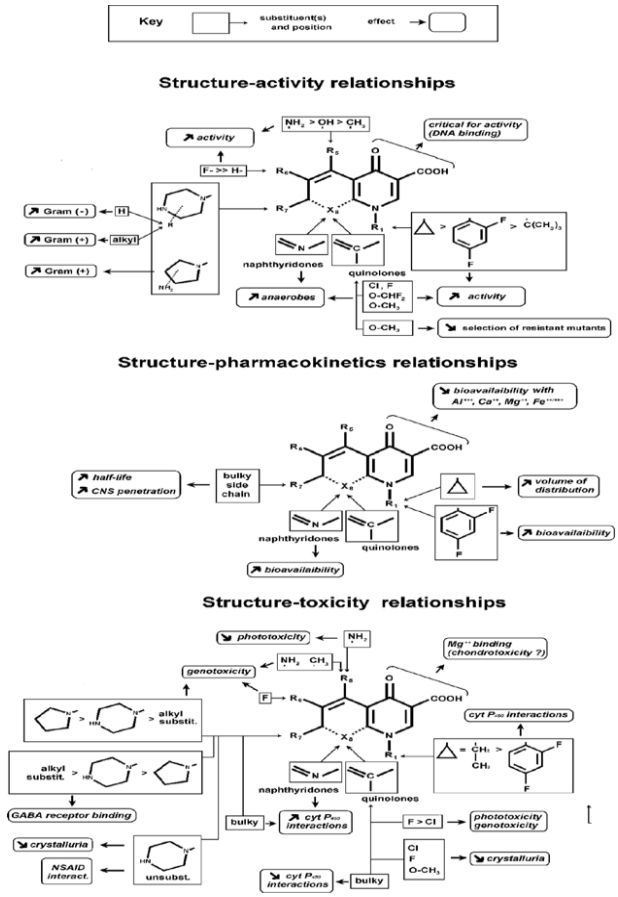

Figure 10. SAR, SPR and STR of Fluoroquinolones (9)

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environment. Due to its strong phosphatidylserine binding capacity, lascufloxacin has better tissue penetration. Besifloxacin and finafloxacin have only been licenced for topical use (10).

Limitations of NA and 1st generation of fluoroquinolones

- Minimal efficacy against Gram-positive bacteria and anaerobes such as *P. aeruginosa.*
- Toxicity, particularly in the areas of the central nervous system and the gastrointestinal tract.
- The establishment of resistance quickly.
- The therapeutic use of nalidixic was limited to the treatment of urinary tract infections due to its poor pharmacokinetics (8).
- High minimum inhibitory concentration [4–16 mg/L is the minimal inhibitory concentration (MIC)] (14).
- Due to weak antibacterial activity, moderate serum and tissue kinetics caused by significant protein binding, the benefits of NA treatment were limited to Gram-negative urinary tract infections in humans.
- A narrower spectrum of activities
- Benefit is limited to urinary tract and gastrointestinal infections due to lower efficacy

Newer fluoroquinolones have increased their activity

■ Enhanced resistance against Gram-positive bacteria (15)

- Clinafloxacin
- Gatifloxacin
- Sparfloxacin

■ Activity against Gram positive Anaerobes

- Moxifloxacin
- Trovafloxacin

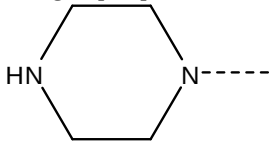
■ Norfloxacin and ciprofloxacin have serum half-lives of 3 to 5 hours, while sparfloxacin has a half-life of 20 hours (4).

■ Newer fluoroquinolone medicines, such as trovafloxacin, moxifloxacin, Gemifloxacin, Gemifloxacin, and grepafloxacin, are active against the microorganisms that cause typical respiratory disease once again.,

e.g., *M. catarrhalis, S. pneumoniae* and *H. influenzae*

When compared to earlier compounds, fluoroquinolones have a wider spectrum of activity and better pharmacokinetics (16).

Table 1: SAR of Quinolones (11).

Change in Substituents and Position	Effects
At position C-6, there is one fluorine atom	Inhibitory action against DNA gyrase has increased
At position C-8, there is a second fluorine atom	Phototoxicity was increased due to higher absorption and a prolonged elimination half-life
At position C-7, the piperazine group is present. 	Aerobic Gram-negative bacteria have the most activity; *Staphylococci* and *Pseudomonas* species have the most activity.
The C-7 ring is alkylated.	Gram-positive bacteria that are aerobic have increased their activity.

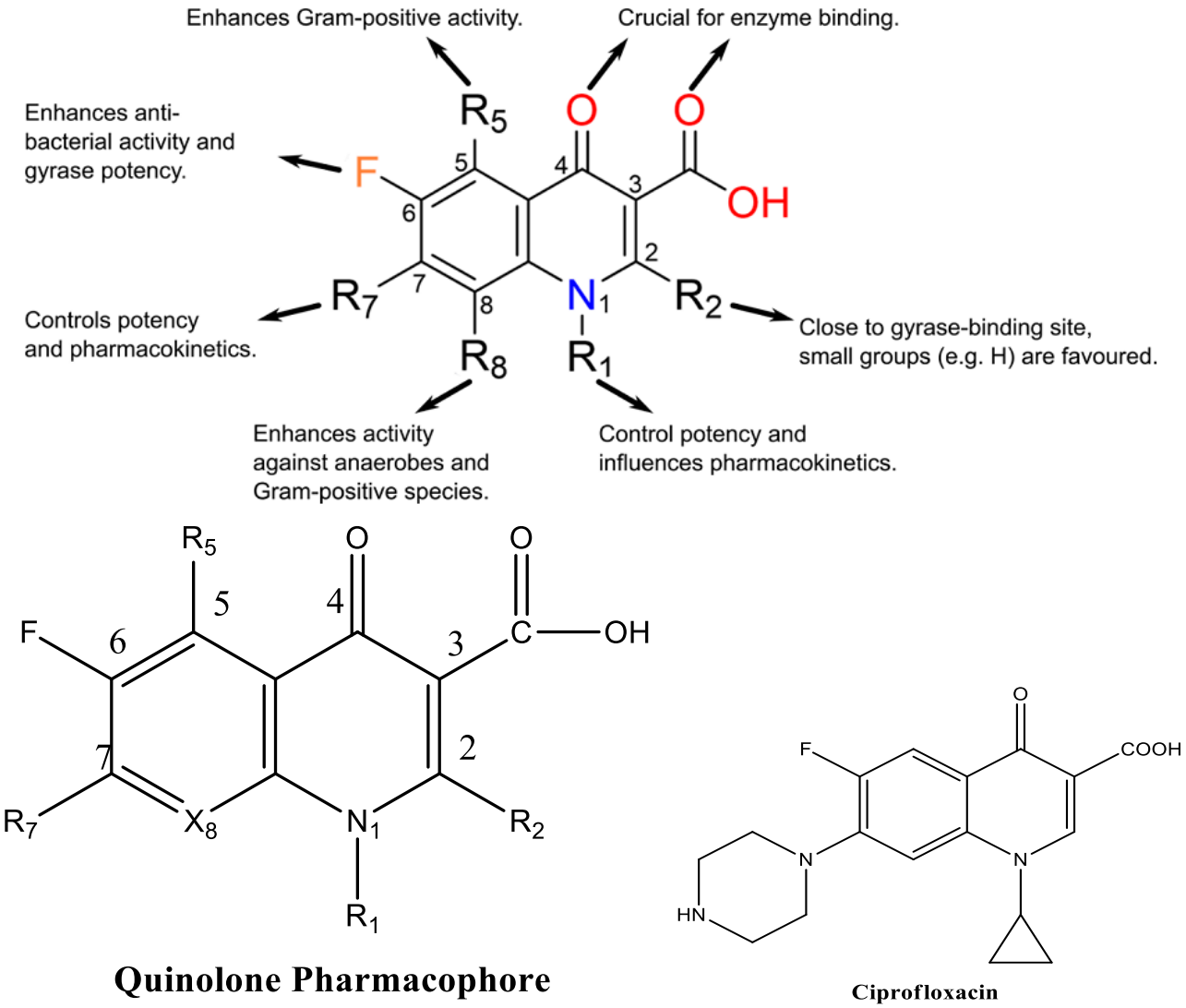


Figure 11. SAR of Fluoroquinolones (12, 13).

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***In-vitro* studies**

Using the agar dilution method, the activity of ciprofloxacin was compared with norfloxacin, NA, ampicillin, mezlocillin, cefadroxil, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, latamoxef (moxalactam), and gentamicin on 365 clinical isolates. Ciprofloxacin was the most active agent against aerobic

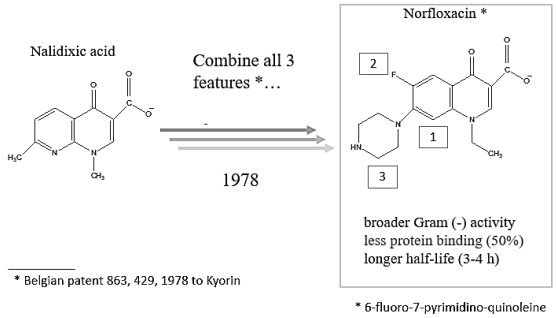

Figure 12. Creation of 1st fluoroquinolone antibacterial from NA.

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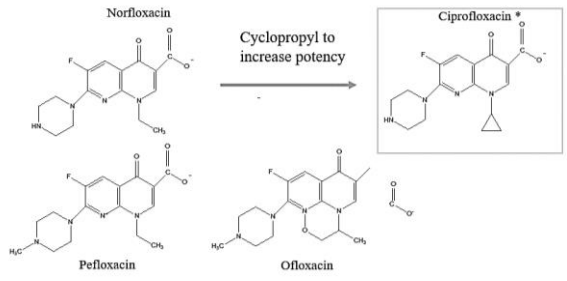

Figure 13. Development of newer generation of fluoroquinolones antibacterial.

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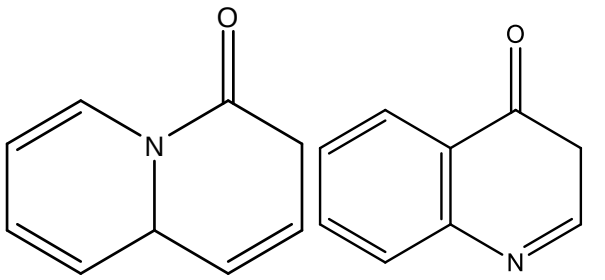

Figure 14. The similarity between 2-Pyridone and Quinolone structure (8).

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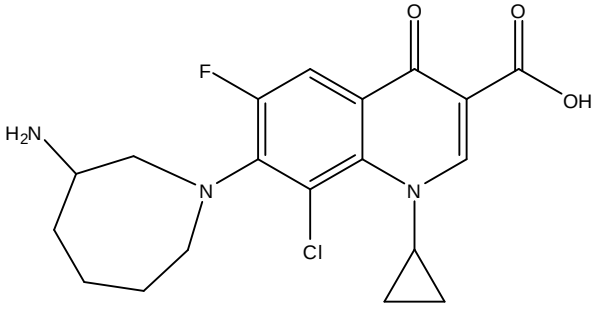

Figure 15. Structure of Besifloxacin.

Gram-negative bacteria, with MIC90 values for all species being less than 1 mg/l and the vast majority being less than 0.12 mg/L. Many of the strains were chosen because they were resistant to beta-lactam antibiotics or gentamicin, and ciprofloxacin was effective against both of these antibiotics. At the inoculums of 10^4 or 10^6 colony- forming- unit, there was little variation in ciprofloxacin activity (14). The action of ciprofloxacin in broth dilution experiments was unaffected by pH in the range of 6.0–8.0, human serum; however, the presence of urine lowered its activity. Human serum protein binding was 20–28 percent. At concentrations close to its MICs, ciprofloxacin was rapidly bacterial in broth. It was able to enhance ciprofloxacin's MIC for bacteria in daily subcultures by exposing it to subinhibitory concentrations. After 10 days, the MIC levels were frequently 16-times higher than the original values (17). *In-vitro* synergism occurs when fluoroquinolones were combined with β-lactam antibiotics, aminoglycosides, or Fosfomycin (18). They exhibit concentration-dependent killing.

Clinical status and future developments

Quinolones have evolved from a minor**,** unimportant class of drugs**,** with the first quinolone molecule NA, most commonly used to treat urinary tract infections, to a class with worldwide sales of US$3.04 billion in

Table 2: Differential activities of representative fluoroquinolones against *S. pneumonia* (16).

Drug	MIC_{90} (mg/L)
Sparfloxacin	0.5
Ciprofloxacin	2
Levofloxacin	1-2
Norfloxacin	16

1997, and this amount is expected to climb. Because of Trovafloxacin's high potential for causing serious and often fatal liver harm, its use is severely limited. The medication is currently in the United States, it has not been approved for usage in the European Union due to reports of acute liver failure and death. Gatifloxacin is available only as an ophthalmic solution in the United States and Canada, because of its adverse side effects, such as fluoroquinolone-associated dysglycemia and exacerbate QT prolongations, so oral formulations have been withdrawn from the market. We realised the need of solid background when we looked at quinoline alkaloids and the most potent group of antimicrobial medicines, quinolones. Such a background, in terms of drug design, is a molecular scaffold that is both flexible for development and strong enough for good activity. According to previous research on antimicrobial medications, quinoline may be appropriate as a scaffold for mefloquine and moxifloxacin, which resulted in action against *M. tuberculosis* resistant to isoniazid, rifampicin, and ethambutol. Norfloxacin was too used as a structure to create antibiotics with a broad spectrum of action, further modifying the fluoroquinolone part to find even better activity. Al-Trawnehetal investigated certain structures with fused aromatic rings. new group -2-pyridones alternative compounds that kill bacteria via DNA gyrase are also available. It is often used to treat urinary tract infections and other hospital-acquired conditions suspected of being sensitive to older antibiotic groups. Furthermore, they are widely used for veterinary purposes, which have been criticized by some as hastening the growth of resistance. Quinolone resistance can evolve quickly; in 2002, they were antibiotics that are most commonly administered in the USA, and their use for unrecommended conditions or viral infections is thought to be a major contributor to

resistance growth.

Garenoxacin from Astellas Pharma in year 2007, Sitafloxacin from Daiichi in 2008, and Besifloxacin from Bausch & Lomb in year 2009 were the three synthetic antibacterial available during this time period (20).

Various nano-formulations of nalidixic acid, a report on revitalizing NA by creating constant nano-formulations. Acid-based complexes had a high level of stability. On pathogenic bacteria such as against Bacteria that are Gram +ve bacteria, such as *S. aureus* and *Bacillus subtilis*, as well as Gram -ve bacteria *P. aeruginosa*, and *Acinetobacter. baumannii*, antibacterial assessment studies indicated promising outcomes when compared to non-nano derivatives. Biosafety studies using the mammalian model are also available. All nano-formulations showed no toxicity in *Galleria mellonella* larvae (27).

Clinical Uses

Quinolones are used to treat infections of the urinary and respiratory tracts, gastrointestinal (GI) and abdominal infections, sexually transmitted illnesses, and infections of soft tissues. Although NA is helpful for urinary tract infections, bacteria can become unaffected to it over time, especially if it is administered for long periods of time. In the treatment of urinary tract infections, all second-generation fluoroquinolones are equally effective. Fluoroquinolones are used to treat a variety of respiratory infections, although they aren't always the best option; these infections include acute and chronic bacterial sinusitis. In cases of acute sinusitis caused by *M. catarrhalis, H. influenzae, or S. pneumonia*, a second-generation cephalosporin, such as cefuroxime, is usually the treatment of choice. Due to their lack of efficacy against S. pneumoniae, second-generation quinolones are typically ineffective in

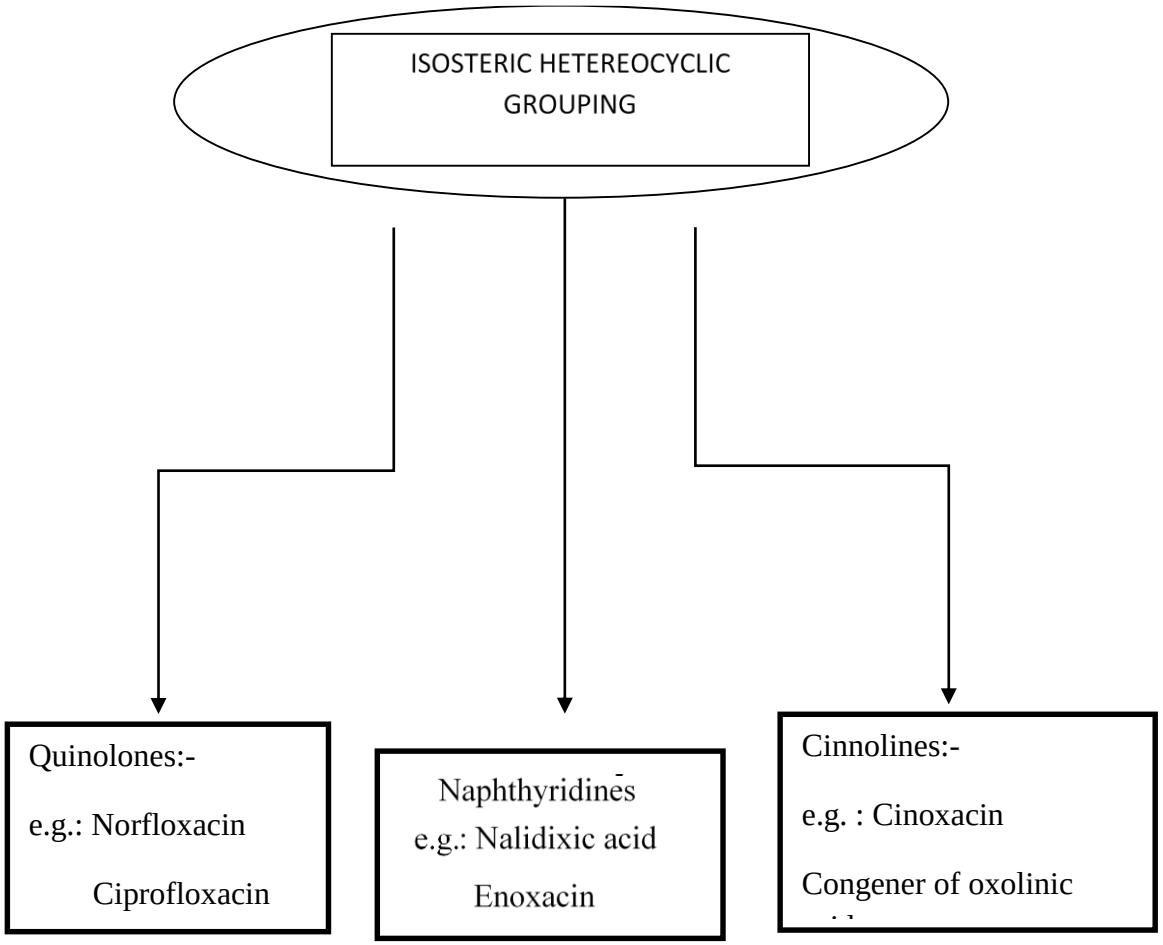

Figure 16. Development of different quinolones derivatives by isosteres synthesis.

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treating community-acquired pneumonia (CAP). Because of their efficacy against *S. pneumonia*, third- and fourth-generation fluoroquinolones are much more successful in treating CAP. Hospital-acquired pneumonia, chronic bronchitis (acute exacerbations), and chronic otitis media are among the conditions for which fluoroquinolones are prescribed. Traveler's diarrhea caused by *E. coli*, shigellosis, and typhoid fever are among the gastrointestinal diseases for which fluoroquinolones are prescribed (8).

Adverse effects and Contraindications

Tendinopathy has been the most common side effect of fluoroquinolone treatments, and it manifests as well as discomfort or inflammation throughout the tendon's length. This type of damage has been documented both during and after medication administration. Fluoroquinolones should be avoided by patients with quinolone-related hypersensitivity reactions, chronic autoimmune disorder, or a prolonged QTc interval. Fluoroquinolones are recognized to have a variety of adverse effects in humans and test animals. Possibly the most common adverse effects in humans include feeling of joint pain, tendonitis, photosensitivity, dizziness, and confusion as well as gastrointestinal symptoms such vomiting, stomach discomfort, and, on rare occasions, diarrhoea. Despite the temporary unpleasantness of these side effects, no specific structure has yet been identified as the primary cause, and hence no quinolone has yet been developed that is free of gastrointestinal side effects. In 0.5-3 percent of individuals, adverse dermatological symptoms such as skin rash or pruritis occur, and these symptoms may be caused by histamine. Utilizing an animal model (in vivo) constructed to determine the effect of alkylation of the piperazinyl at position 8 found that this alkylation was advantageous, and it suggests that such an animal model could be useful in studying future quinolones. Hypersensitivity reactions along with reported signs Seizures, cardiovascular collapse, shock, loss of consciousness, airway obstruction, dyspnea, itchy, angioedema, urticaria, skin burning, and other allergic skin appearances are just some of the symptoms.

Cohort study

Newton *et al.* (20) have reported an increased rate of aortic aneurysms was observed within 90 days after fluoroquinolone use compared to alternative antibiotic use in a cohort study of 47 596 545 antibiotic prescription fills among US grown-ups aged 18 to 64 years, and when stratified by age, an increased incidence of aneurysms was observed in adults 35 years or older. When stratified by sex and common comorbidities (e.g., hypertension and hyperlipidemia), no changes were seen; rather, the link between fluoroquinolone usage and aneurysm rate was reliable, signifying a risk of drug class across both well and unwell people.

Mechanism of Resistance

In microorganisms, resistance to fluoroquinolones is usually caused by changes in the target enzymes DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. Another option to reduce fluoroquinolone build-up is to use an efflux mechanism. Resistance is caused by increased expression of a chromosomal gene, which results in greater fluoroquinolone efflux (21-24). The Boinett C & *et. al.* (25) reported that their experimental evolution showed, resistant *S. sonnei* develops under fluoroquinolone exposure *in vitro* additional antimicrobial intolerance, whereas the susceptible counterpart does not achieve total resistance.

Conclusion

Based on our interest in pharmaceutical sciences (28-35), we summarized a review on “how a class of total synthetic antibiotics came not only its existence but very rapidly became a significantly used and prescribed medicine”. Without a doubt, our battle with harmful microorganisms resembles a fight. Despite the fact that millions of dollars invested on investigate and expansion of new advance treatments may be quickly wasted due to resistance, the oldest drugs are still used in many regions where neglected diseases – largely of bacterial source – constitute a major threat. With time, original patterns may emerge. Natural medications are intriguing once more, but this time as sources of inspiration rather as pure ointment or decoction. The development of quinolones and then fluoroquinolones is the best example of how nature and its products can lead to ignition to work on an idea for better drug molecules. In the medical dimension, the discovery of NA**,** and then the discovery of a completely innovative

line of antibacterial fluoroquinolones, ushered in an era of new logical thinking and the uniquely broadened perspectives of body safety and work on various research predictions.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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