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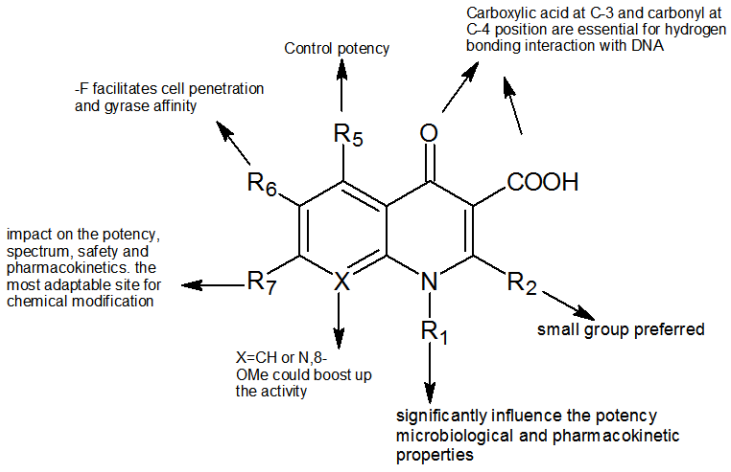
A review on recent development on fluoroquinolones

Umesh Kumar, Sandeep Kumar and Himangini

Abstract
The fluoroquinolones are used in the treatment of vast number of bacterial infection. these agents have excellent properties such as excellent bioavailability, good tissue penetrability and a relatively low incidence of adverse and toxic effects. They have been found effective in the treatment of various infection disease. This paper is an attempt to review the introduction of fluoroquinolone therapeutic prospects of fluoroquinolone, generational classification, synthesis, and there resistant with an updated account on their development and usage.

Keywords: classification, synthesis, uses, and resistance of fluoroquinolone quinolone, mechanism

Introduction
Nalidixic acid is a first synthetic quinolone which was discovered in 1962 [1] And first time marketed in 1965 [2]. Presence of exocyclic oxygen and a carboxyl group at the naphthyridine nucleus is characteristic of quinolone [1]. One fluoro substituted quinolone was introduced in 1990 and called first generation fluoroquinolones [3]. Fluoroquinolones are the organic compounds which are derived from the earlier analogs of quinolone (nalidixic acid, oxolinic acid, pipemidic acid, and cinoxacin) [4]. Fluoroquinolone is major or wide spectrum antibiotics with increasing use in community, hospitals, household and veterinary application. Fluoroquinolone is the third largest group of antibiotics [5], in the last decade, a huge number of antibacterial agents are developed and marketed. One of the most significant group is a class of synthetic antibacterial drugs called fluoroquinolone [6], they are broad-spectrum antibiotic which isused in a wide range of bacterial infection gram-positive as well as gram-negative [7]. These drugs have excellent bioavailability and high intracellular and tissue penetration, as a result, they are the 4th most prescribed drugs in the world [8]. Ciprofloxacin is the first fluoroquinolone which was launched in 1981 by bayer, followed by second-generation drug moxifloxacin [1]. These antibiotics inhibit *DNA gyrase* (Subunits encoded by *gyrA* and *gyrB*) and *topoisomerase IV* (Subunits encoded by *grlA* and *grlB* for *streptococcus aureus*) which interferes with the supercoiling of bacterial DNA, this binding induces permanent double-stranded DNA break and ultimately leads to cell death [6, 9, 10, 11]. Previous generation fluoroquinolones were selective towards gram-positive and gram-negative bacteria whereas fourth-generation fluoroquinolones having dual action acts both on *DNA gyrase* and *topoisomerase IV*. Which lead to slow development of resistance [12].



The structure-activity relationship (SAR) of fluoroquinolones antibacterial showed that the fluorine atom and the 1-alkyl, 1, 4-dihydro-4-oxoquinoline-3-carboxylic acid skeleton of fluoroquinolones are responsible for the potency of binding of *type-II topoisomerase enzyme, DNA gyrase* and *topoisomerase IV*. Substitution of 6-fluoro and 7-piprazinyle groups are responsible for the broad spectrum and anti-pseudomonal activity of fluoro quinolone [13]. SAR study shows that the chemical modification at the C-7 position is good for controlling pharmacokinetics modification and significantly influence their potency and safety [11, 12]. Five and six-member nitrogen heterocycles such as piperidinyl, pyrrolidinyl, and piperazinyl type side are proven to have the optimal activity at the C-7 position of fluoroquinolones [12].

Classification

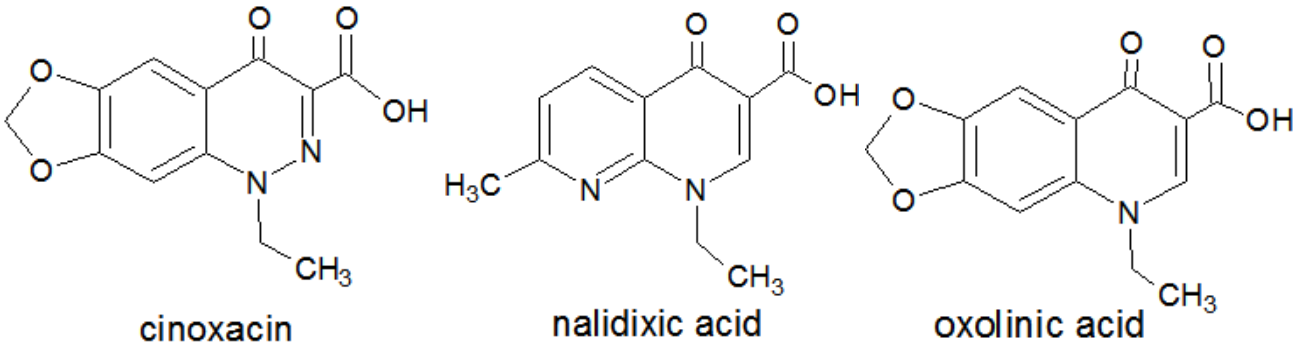
There Are various classification system (like approval date, generation, chemical structure, antibacterial spectrum, pharmacokinetics, indications, tolerability, administration forms, etc.) are available in the literature to describe the evaluation of Fluoroquinolone class of Antibacterial [14, 15, 16]. Here, we outline the classification of Fluoroquinolone antibacterial spectrum and activity (table-1) [17] and Generational classification system of quinolones with correlate with clinical utility.

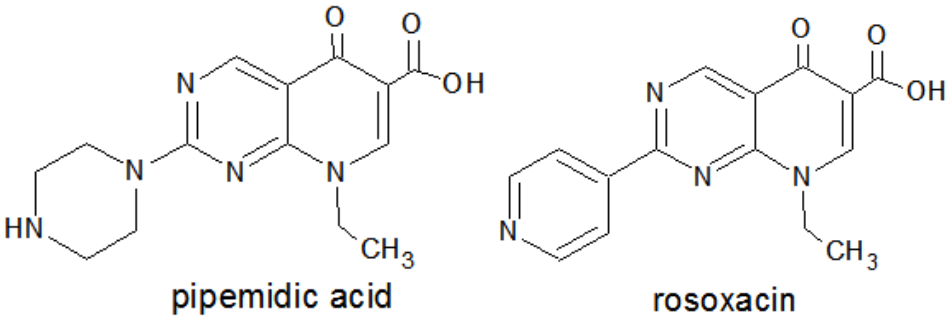
Table 1

I.	Oral fluoroquinolones with indications essentially limited to urinary tract Infections (in Germany)	Norfloxacin Pefloxacin
II.	Fluoroquinolones with broad indications for systemic use	Enoxacin Fleroxacin Ofloxacin Lomefloxacin Ciprofloxacin
III.	Fluoroquinolones of improved activity against Gram-positive and 'atypical' Pathogens	Levofloxacin Sparfloxacin
IV	Fluoroquinolones with improved activity against Gram-positive and 'atypical' pathogens, as well as anaerobes	Gatifloxacin Moxifloxacin Gemifloxacin

First generation

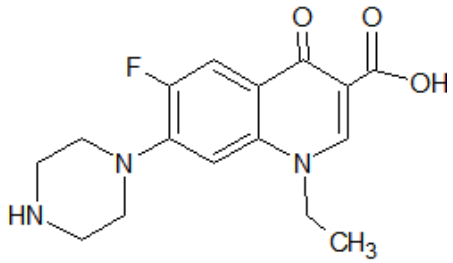
The First generations agent including nalidixic acid, cinoxacin, and oxolinic acid, which was found to have limited use. because of minimal serum level are achieve so require more Frequent dosing than the newer quinolone, Also their activity against Gram-negative bacteria are weak [18].

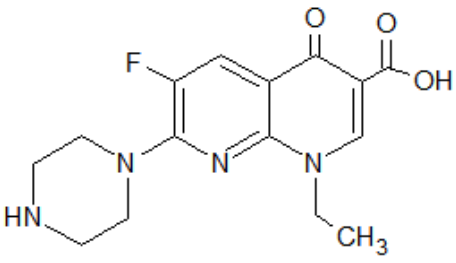


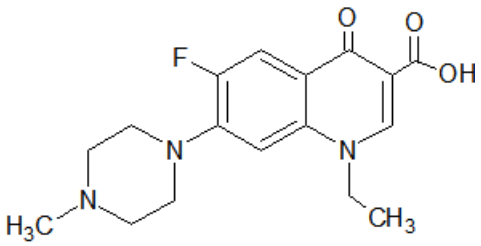


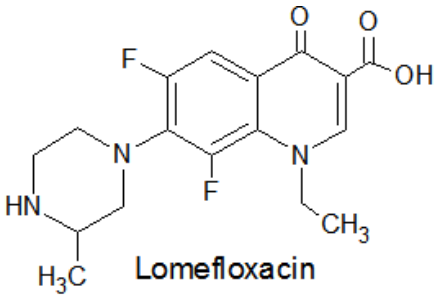
Second generation

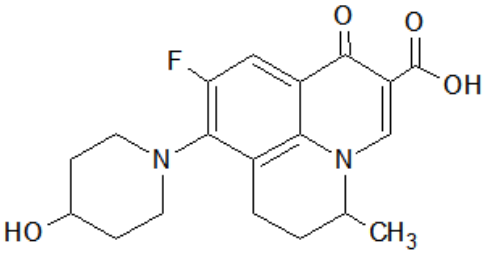
In the mid of 1980 the second-generation fluoroquinolone and were responsible for the huge change in the clinical treatment of important infection. The second generation is available is much effective than the first-generation drug because they have increased gram-negative activity as well as some gram-positive and atypical pathogen coverage. The main disadvantages of second-generation fluoro quinolones are limited activity against gram-positive pathogen including *S. pneumoniae* (because of low intrinsic activity against these species) and MRSA (due to developing resistance) [19]. Ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, and ofloxacin. Ciprofloxacin use in osteomyelitis caused by a susceptible organism, because of their availability in oral and i.v formulation ciprofloxacin and ofloxacin are most widely used second-generation fluoroquinolones [20].

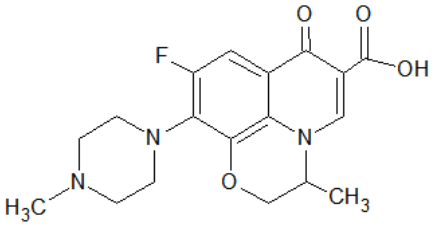

Norfloxacin

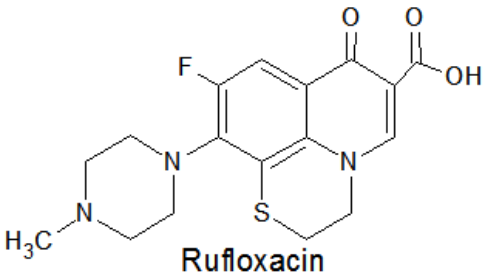

Enoxacin

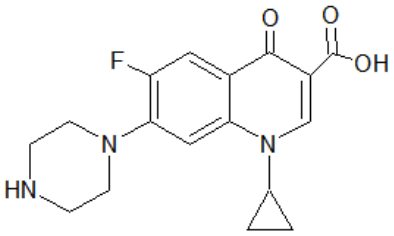

Pefloxacin

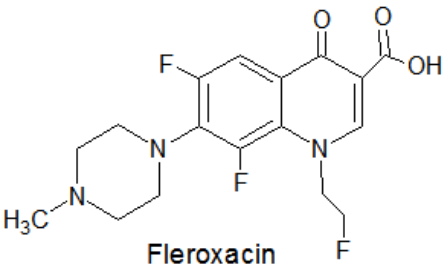

Lomefloxacin


Nadifloxacin


Ofloxacin

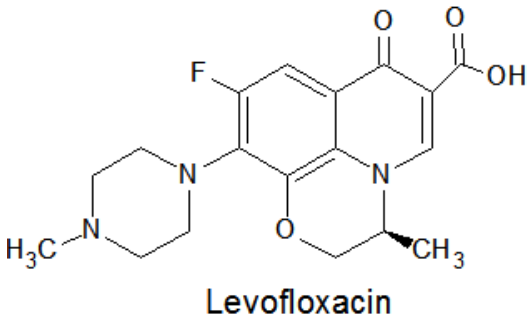

Rufloxacin

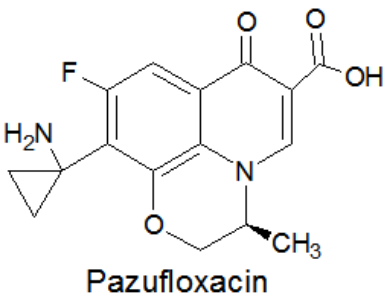

Ciprofloxacin

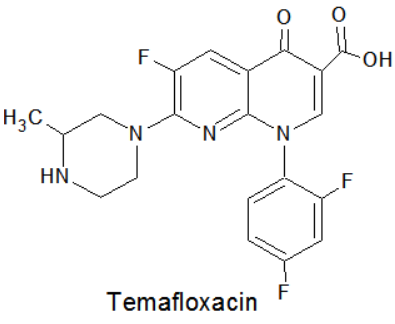

Fleroxacin

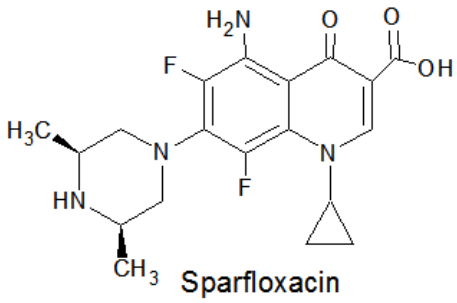
Third generation

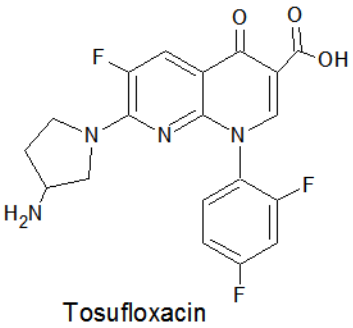
The third-generation fluoro quinolone has Improve their gram-positive activity, pharmacokinetic, tissue distribution and longer half-life which is permit once daily dosing. levofloxacin was Introducein 2000, which is pure L-enantiomer of a mixture of ofloxacin and show more water soluble then ofloxacin at neutral pH (because of pure L-enantiomer). Due to the severe side effect (allergic reaction and hemolyticanemia) temafloxacin were removed from the market, grepafloxacin is not quite as potent against S. pneumoniae compare with other third generation fluoroquinolones [15, 21].

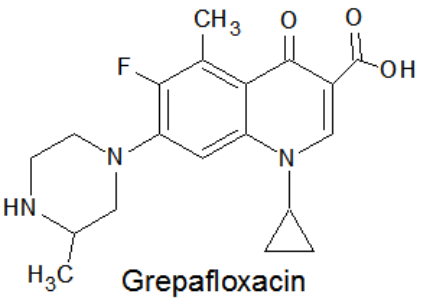

Levofloxacin

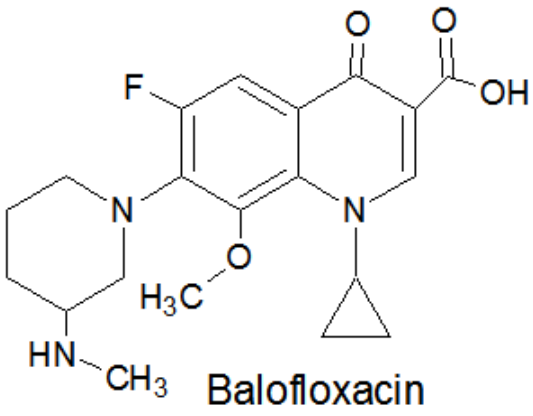

Pazufloxacin


Temafloxacin


Sparfloxacin

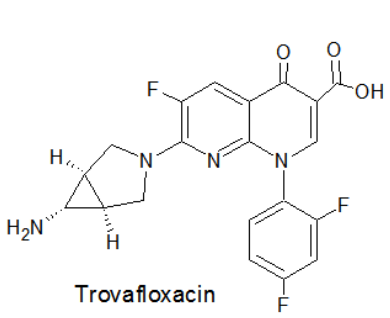

Tosufloxacin

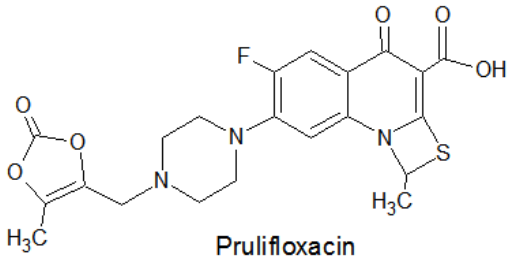

Grepafloxacin

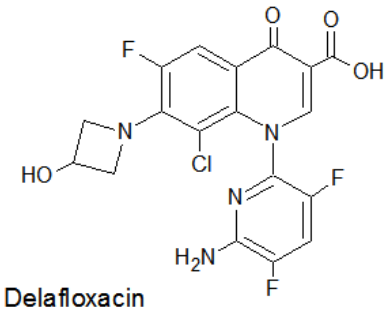


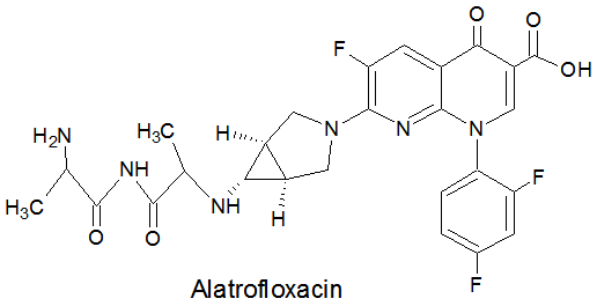
Fourth generation

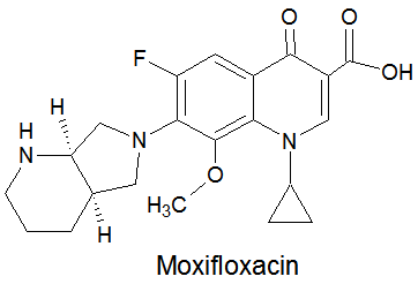
A structural modification is done to generate the new generation fluoroquinolone like gatifloxacin and moxifloxacin, specifically to improve broader spectrum activity, better minimum inhibitory concentration less side effect, good ocular penetration, and most important less resistance. Fourth generation fluoroquinolone shows dual mechanism they inhibit *both DNA gyrase* as well as *topoisomerase IV* in gram-positive bacteria, not only shows dual targeting but also reduce the risk of resistance. The dual mechanism is obtained by substitution of a methoxy group at position 8 in the quinolone ring, another advantage of a methoxy group at position 8 is a reduced the susceptible to efflux from the bacterial cell and further improve the bacterial resistance [22, 21].

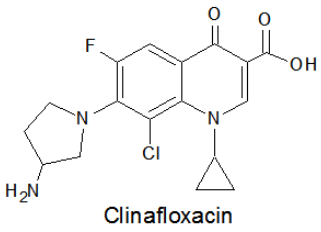


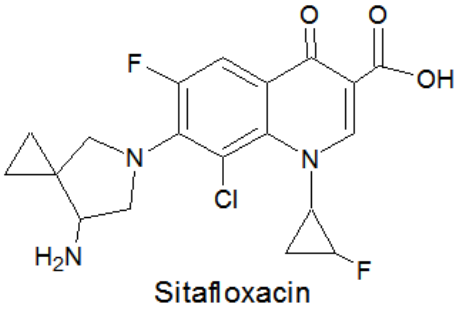


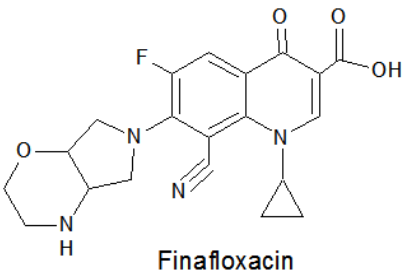


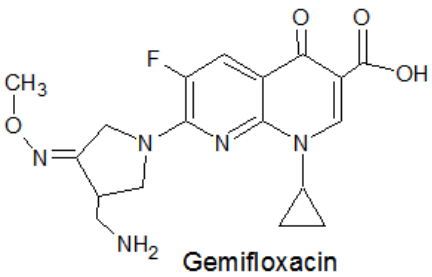


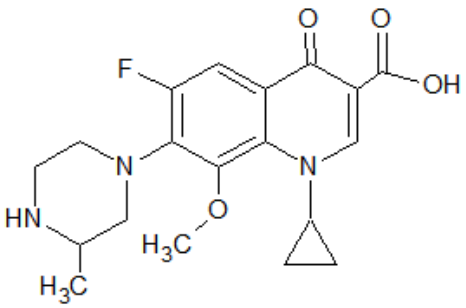




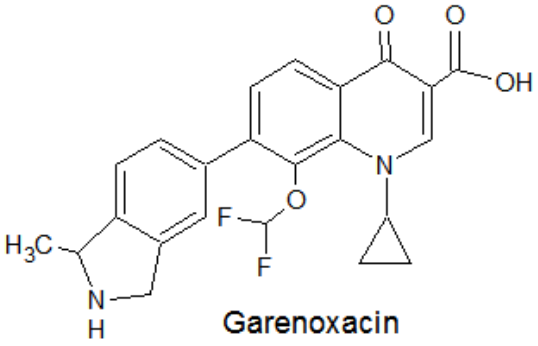








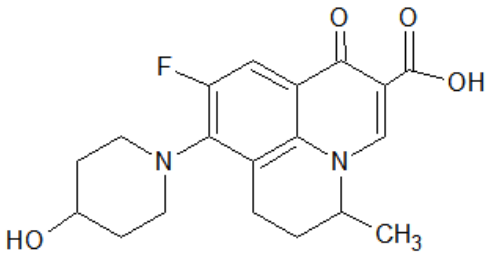
Gatifloxacin



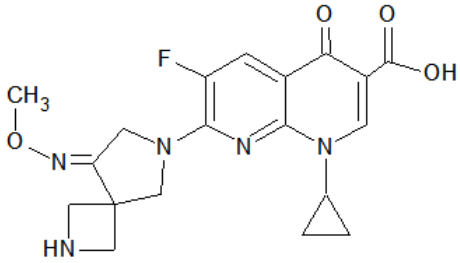
Garenoxacin

Under clinical trial

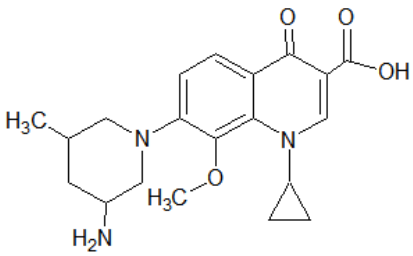
Apart from all four generation same of 4-quinolone drugs are under clinical trials such as levonadifloxacin, nemonoxcin (non-fluorinated quinolone antibiotic) and zabofloxacin, and may be used for the treatment of bacterial infection. It is believed that new later-generation agents are more broad-spectrum then the earlier one [23].



Livonadifloxacin



Zabofloxacin



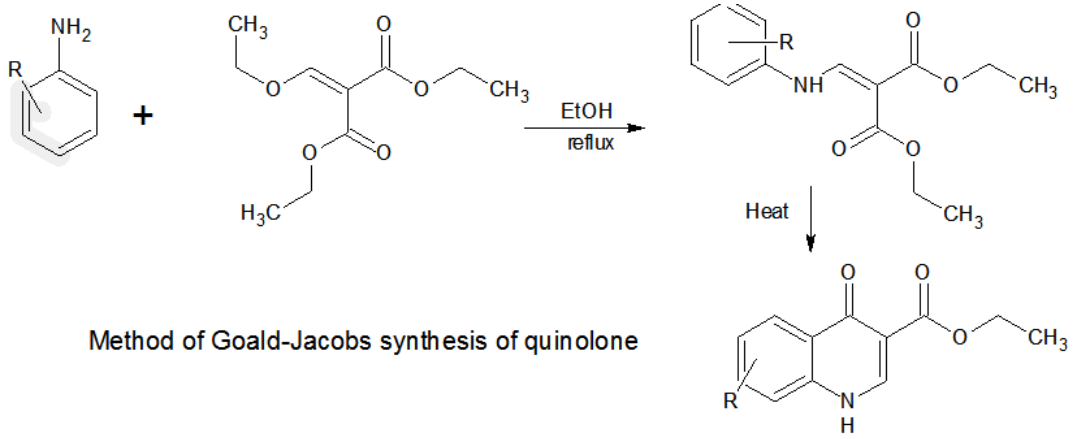
Nemonxacin

Method of synthesis of quinolones

There are a various method available for synthesis of quinolone moiety these are followings

1. Gould-Jacobs

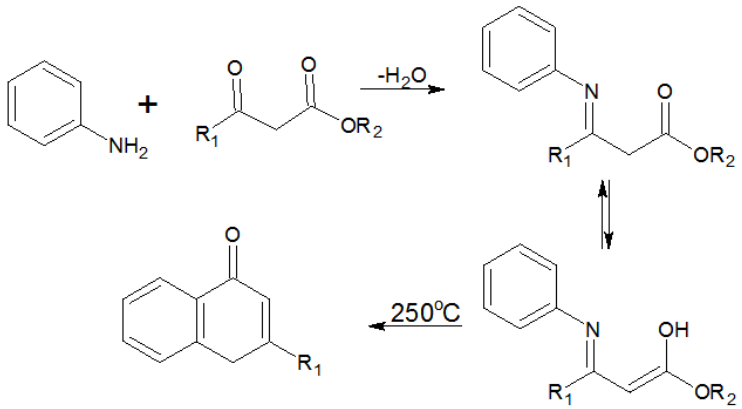
Gould-Jacobs method is the most used method for the synthesis for quinolone, which is based with the addition of Michael by the elimination of substituted aniline, using as reagent diethyl ethoxymethilenemalonate in the ethanol with agitation and reflux with high temperature [24, 30].



Method of Goald-Jacobs synthesis of quinolone

2. Conrad-Limpach

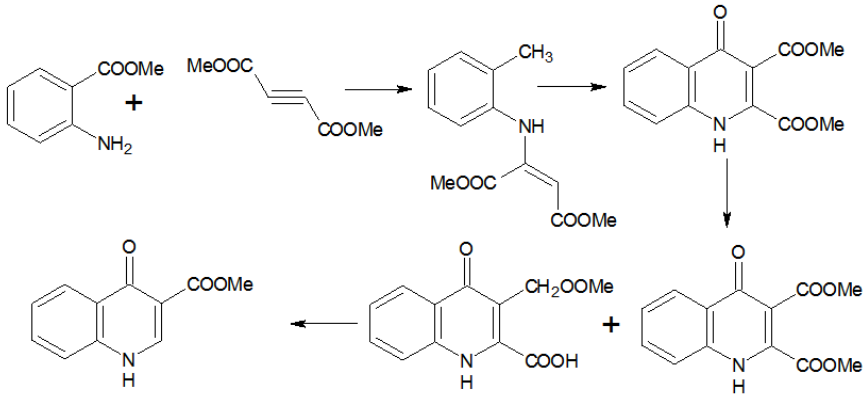
Conrad-limpach method is used for the synthesis of 4-quinolone in this method one substituted aniline and acetoacetic ester are used to form a Schiff base, after the obtaining Schiff base they are heated at a high temperature to obtain the quinolone [25].



Method of cornad-limpach synthesis of quinolone

3. Biere synthesis

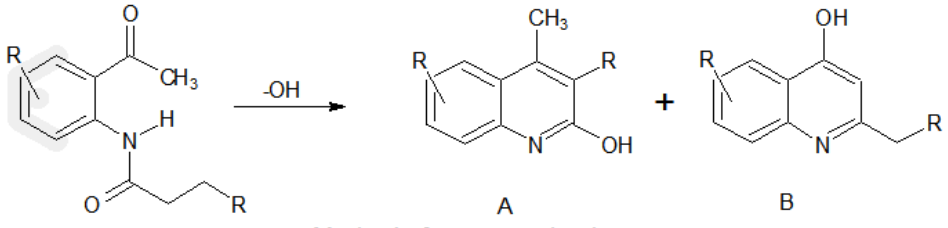
In 1977 Biere developed a new method for synthesis of a quinolone, in this method Biere using Michael mechanism to obtain one substituted ester enamine and then the addition of a strong base, followed by the hydrolysis to obtain one dicarboxylic acid and after the decarboxylation, we obtained quinolones [26].



Method of biere synthesis of carboxylated quinolones

4. Camps synthesis

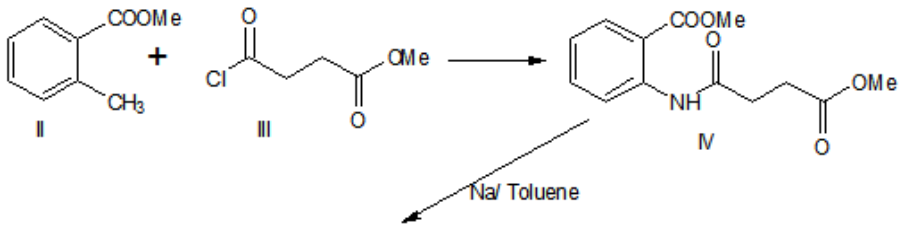
The method of Camps synthesis is based on the transformation of o-acylaminoacetophenone into two different hydroxyquinolines by using hydroxide ion. Formation of two different hydroxyquinolines is depended on the reaction condition and structure of starting material [27].

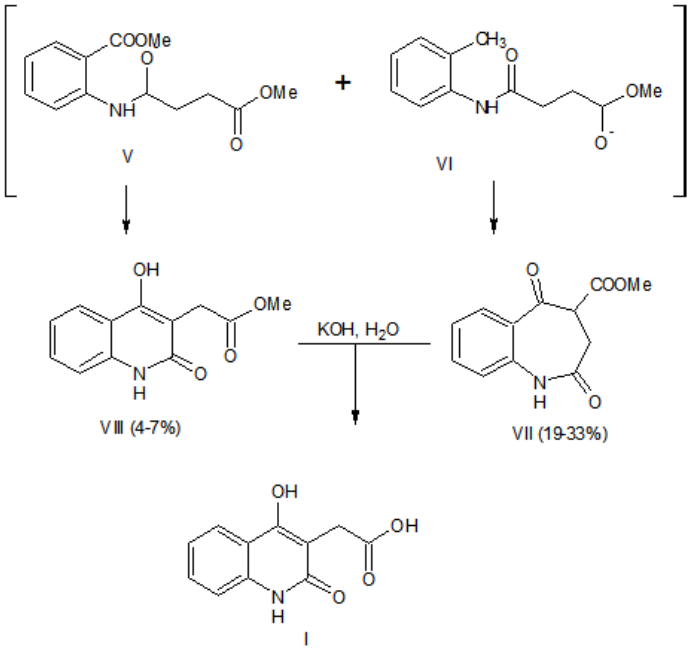


Method of camp synthesis

5. Dieckman synthesis

Dieckman method is used for the synthesis of hydroxyquinoline in this method Acylation of methyl anthranilate II is done with the help of β-carbomethoxypropionyl chloride III, followed by Dieckmann cyclization of the anilide IV formed by using base. The yield of the final product depends on the reactant [28].

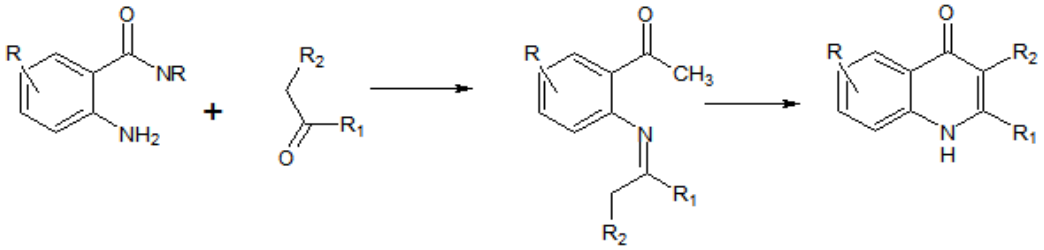




Method of dieckman synthesis of quinolone

6. Snieckus synthesis

The snieckus method is used for the synthesis of one quinolone by the denominated of one orthop aniline substituted with one acetone presence of strong base to execute the deprotonation and intermolecular cyclization to obtain the quinolone [29].



Method of sniekus synthesis of quinolone

Uses of fluoroquinolone

1. Urinary tract infection

Fluoroquinolones are the excellent agents for different type of urinary tract infection (UTI), also they are ideal agents for nosocomial UTIs, pyelonephritis (upper-track disease), and complicated UTIs, they inhibit *Enterobacteriaceae* and *P. aeruginosa*, including strain resistant to beta-lactams, aminoglycoside, and cotrimoxazole, also they have been used successful as single-dose therapy [31, 47], norfloxacin(800 or 1200 rag), ciprofloxacin (100 or 250 rang), ofloxacin (100 rag), fleroxacin (200, 400 or 600 rag) and pefloxacin (800 rag) are some of fluoroquinolones shown highly effective in women with uncomplicated lower urinary tract infection caused by *Enterobacteriaceae*, but may be less effective against *Staphylococcus saprophyticus*, although Fluoroquinolones are shown less activity when lower urinary pH is reduced (pH 5.5-6.0 vs pH 7.4) [32, 33, 47], ciprofloxacin has a broad antibacterial spectrum that include activity against many aerobic gram-negative rods, including those resistant to aminoglycoside and cephalosporin agents. If we compare ciprofloxacin with aminoglycoside, ciprofloxacin is slightly better clinical response in the treatment of UTIs [34]. and short-course ciprofloxacin treatment has a better safety profile than 7 days therapy with either co-trimoxazole or nitrofurantoin [35, 36] During the therapy, FQ may show some adverse effects and resistance, but they still prescribed due to their better spectrum of activity, affordability and improved compliance of the patients [37] levofloxacin has well-characterized tolerability profile and can be used in a once-daily regimen for the treatment of complicated urinary tract infection including pyelonephritis and uncomplicated SSTIs [38, 39, 40]. Sparfloxacin 400-mg regimen for 3 days is equivalent to 7 days, twice daily regimen of ciprofloxacin, its shows that's parfloxacin may be a suitable alternative to ciprofloxacin in the patient with acute uncomplicated UTI [41].

2. Chronic bacterial prostatitis

Aerobic gram-negative bacilli like *E. coli* is responsible for 50%-80% of bacterial prostatitis, other pathogen includes *Enterobacteriaceae* (10%-30%), *Enterococcus* species (5%-10%), *Pseudomonas* species (5%) [42] Chronic prostatitis syndrome are among the most common and frustrating challenges due to the insufficient penetration of drugs into the prostate, which leads to difficult to cure. Fluoroquinolone is the first choice of treatment therapy, like newer fluoroquinolone (levofloxacin, ciprofloxacin, ofloxacin) levofloxacin treatment is generally well tolerated and shows convincing efficacy in chronic bacterial prostatitis (CBP) and given once daily [43, 44, 45, 32]. fluoroquinolones are the are preferred drug in our therapeutic arsenal, but due to the

resistance to these agents will require that we find others that adequately penetrate the prostate [42], in the treatment of chronic bacterial prostatitis, the daily dose of fluoroquinolone is more important than the duration of therapy, as administration of cumulative dose of 21 g of ciprofloxacin at the rate of 750mg day 21 for four weeks, rather than 500mg day21 for six week [46].

3. Acute pyelonephritis

Acute pyelonephritis is a bacterial infection of the upper urinary tract infection, specially the renal parenchyma and pelvis, *Escherichia coli* is responsible for 80% of infection and sometimes include aerobic gram-negative bacteria, In the treatment of acute pyelonephritis fluoroquinolone, are preferable. Because of fluoroquinolones are excellent kidney penetration and well absorbed from gastrointestinal tract[48], in the treatment of acute pyelonephritis, fluoroquinolone is the most preferable antibacterial drug (26.7%), followed by cephalosporin(23.3%), aminoglycoside (14.1%), and penicillin (13.8%)[49].Unfortunately, there has been a recent trend of increasing resistance to fluoroquinolone among the uropathogens in many countries but still, fluoroquinolones are preferred empiricantimicrobial class in communities where the resistance of fluoroquinolone is less than 10%. And can be given with oral ciprofloxacin (Cipro; 500mg twice a day, for 7 days), or a once-daily oral fluoroquinolone, such as ciprofloxacin (1000 mg, extended- release for seven days) or levofloxacin (Levaquin, 750mg for five days) [50, 51, 52].

4. Uncomplicated cystitis

Uncomplicated acute cystitis is one of the common problem of the bacterial infection in adult, the organisms most often responsible for uncomplicated cystitis are gram-negative bacteria of a group of *Enterobacteriaceae*. *E. coli* (86%), *Staphylococcus saprophyticus* (4%), *Klebsiella species* (3%), *Proteus* species (3%), *Enterobacter* species (1.4), *Citrobacter* species (0.8%)[53,54].Quinolone have very good activity against *E. coli,* and also it has achieved high urinary concentration and have minimal effect on the natural vaginal protective flora, fluoroquinolone like ofloxacin, ciprofloxacin, and levofloxacin are consider as a second-tier antimicrobials drugs but some allergy were shown by the physicians[54].And also the resistant of fluoroquinolone were increases and due to this they are less prefer drugs[57,58]infectious diseases society of American (IDSA) guideline for acute uncomplicated cystitis recommend first-line treatment with an alternative agent such as nitro furantoin (NFT), Fosfomycin [55, 56, 59].

5. Complicated intrabdominal infection

Fluoroquinolones likegatifloxacinin combination with ciprofloxacin or levofloxacin plus metronidazole are used for the pathogens associated with intraabdominal infection. They show effective activity against infection due to their better oral bioavailability. For the treatment of mild to moderate infection fluoroquinolones like Ciprofloxacin, levofloxacin, moxifloxacin orgatifloxacin was used in combination with metronidazole for infection, because of its long half-life of 8 hours metronidazole can be administered on an every 12 hours basis. A dose of 500mg twice daily is the standard dose of metronidazole in combination with fluoroquinolones (Ciprofloxacin, levofloxacin, moxifloxacin, or gatifloxacin) were the choice for treatment of complicated intrabdominal infection [61, 60].

6. Skin and soft tissue infection

These are one of the most common infectious disease affecting skin and skin tissues [62]. SSTIs are also called acute bacterial skin and skin structure infections (ABSSSIs) [65]. These infections include impetigo, erysipelas, cellulitis, folliculitis, postoperative wound infections, and simple abscesses [64]. They effectively penetrate the skin and soft tissue and achieve the effective concentration at the site and against many organisms. The bacterial skin and soft tissue infection are caused by *Staphylococcus aureus* or *beta-hemolytic* (*streptococcus pyogens*) [63, 64]. Fluoroquinolones like ciprofloxacin were used to treat the infection due to *staphylococcal* and many gram-positive infections and considered the best for *P. aeruginosa* infection [63]. The main mechanism by which fluoroquinolones work, they mainly act on the DNA gyrase or topoisomerase IV, which is an important enzyme responsible for DNA replication [62, 63]. In a dose of 750mg OD for 7-10days levofloxacin is approved for the treatment of skin and skin tissue infection [63]. Ofloxacin has better activity against Staphylococcus aureus and streptococci as compared to ciprofloxacin [66].

7. Bone and joint infection

Quinolones are the drugs of choice for the treatment of bone and joint infection [67, 68] causative agents for BJIs are *staphylococci*, fluoroquinolones are used against these organisms, they are having high bone concentration[69]. they are having the activity against *staphylococcal* species and gram-negative bacteria. Pefloxacin and ciprofloxacin are the drug of choice for the treatment of bone and joint infection due to their long half-life of these agents, their availability and their antibacterial action [67]. Levofloxacin in a dose of 500mg single dose daily is the drug of choice for the treatment of bone and joint infection [68]. Lomefloxacin, levofloxacin, or ciprofloxacin are the drug effective against the infection and used orally in the therapy against gram-positive as well as gram-negative organism [71], fluoroquinolone in combination with cefepime are safe and effective in the treatment for bone and joint infections caused by GNB [70].

8. Infection diarrhoea

Fluoroquinolone is a drug of choice for treatment of the acute diarrhoea in adults because they have good bioavailability and excellent tissue and intracellular penetration, achieved high fecal concentration [72, 73]. The use of 500mg ciprofloxacin in the treatment of acute diarrhoea has been shown to decrease the infection in adults. according to the American academic of paediatrics as well as several experts have suggest the fluoroquinolone is not advisable in the small children due to high chances of resistance [75] and *Clostridium difficile-associated* (CDAD) were responsible for the cause of nosocomial diarrhoea in a different countries, the resistance was also shown by *C. difficile* towards levofloxacin, moxifloxacin, gatifloxacin [76, 74].

9. Typhoid fever

It is a systemic disease which is caused by the gram-negative bacterium *salmonella typhi* and *salmonella paratyphia,b,c*, in which there are sustained fever and gastrointestinal symptoms [77, 79, 80]. Typhoid fever may become fatal for adults and children's leads to bacteremia and inflammatory destruction of many organs like intestines and other organs[78].Quinolones are the drug of choice for the treatment of typhoid fever for

the period of one-two weeks rate 100% cure rate is achieved. They have shown great bactericidal activity against *Salmonella typhi*. They will show good tissue penetration and concentration. They are taken by orally as well as parenteral route as well. for the treatment of enteric fever ciprofloxacin 500mg twicedaily, ofloxacin 200mg twice daily, pefloxacin 400mg twice daily and fleroxacin 400mg four times daily ae very effective [77, 79].

10. Sexual transmitted disease

Fluoroquinolones are the group of antibiotics which are used in the management of the sexually transmitted diseases.fluoroquinolones antibiotics are not much effective for *post-gonococcal urethritis* in a single dose. These agents are effective against in the treatment of chancroid which are ciprofloxacin, flerofloxcin [83].

There is very less activity against *Treponema pallidum* but having highly effective against *Neisseria gonorrhoea*.The ideal chemotherapeutic agent would have activity against *gonococci*, *Chlamydia*, *Ureaplasma*, *Mycoplasma* species, *Treponema pallidum*, and anaerobes such as *Bacteroides fragile*Currently,there is no available monotherapy that will eradicate all of these pathogens, as well as gram-positive cocci and*Enterobacteriaceae* fragilis [85].

Gonorrhoea- these agents are highly effective in the management of uncomplicated gonorrhoea. Gonorrhoea is most commonly to occur in the adolescent females aged 15-19 [86, 87, 84]. Norfloxacin 800mg, ofloxacin 400mg, ciprofloxacin 250mg, and pefloxacin 400mg used single dose only due to their better effectiveness against *Neisseria gonorrhoeae*. For the treatment of *urogenital gonorrhoea* a single dose of norfloxacin 800mg used in men and woman [85].

Chlamydial Genital- ofloxacin demonstrate the efficacy of a single daily dose for 7 days for chlamydial genital infection in men and women. In the treatment of a *chlamydial genital* single daily dose of ofloxacin up-to 7 days for both male and female [81].

Syphilis- There are few data on the activity of the quinolones against *Treponema pallidum*. Of loxacin has been reported as ineffective in an animal model There are no reports of therapeutic trials with quinolones in the treatment of syphilis [81].

Bacterial Vaginosis- Gardnerella vaginalis is associated with bacterial vaginosis, but is probably not causative. Anaerobic organisms (*Bacteroides spp. and Mobiluncus spp.*) are consistently found. Ciprofloxacin and ofloxacin show moderate activity and clinafloxacin against anaerobic offspring [81, 82].

Chancroid- is caused by the microorganism Haemophilus ducreyi, which is highly susceptible to quinolones. Ciprofloxacin. Excellent cure rates have been reported for single-dose therapy with ciprofloxacin 500mg and fleroxacin 200 to 400mg. a single dose of ciprofloxacin 500mg and fleroxacin 200-400mg have very cure rate against chancroid [81, 82].

Pelvic Inflammatory Disease- One area where the quinolones may have an important role in the future is in the treatment of pelvic inflammatory disease [81, 82].

Non-Gonococcal Infection- The major pathogen is undoubtedly *C. trachomatis*. 9 days with ofloxacin (200mg twice daily or 400mg once daily) were microbiologically cured at the end oftherapy. Other studies with ofloxacin 200mg twice daily for 7 days have also produced high microbiological cure rates [81, 82].

11. Acute sinusitis

Acute sinusitis is the most common infection of the upper respiratory tract. In this the paranasal sinus mucosa is inflamed, *S. pneumonia-influenza* and *M.catarrhalis*, these are some microorganisms which are most commonly causing the acute sinusitis other which are less commonly associated with it are *S. pyogens*, and *S. aureus* [98]. It is found that amoxicillin/clavulanate and moxifloxacin along with gatifloxacin and levofloxacin provide better treatment for acute sinusitis against *H. influenza* and *S. pneumonia* [99]. While on the other hand few other newer fluoroquinolones like levofloxacin, grepafloxacin, and gatifloxacin active against all causative agents for acute sinusitis. Moxifloxacin has the better sinus tissue penetration against the pathogens without causing inflammation and better patient acceptance due to its dosage regimen once a daily and best choice for the treatment of acute sinusitis and have lower chances to development of resistance [99].

12. Lower respiratory tract infection

Lower respiratory tract infection also called as *pneumonia*, it can also be applied to other types of infections including lung abscess and acute bronchitis. The most common symptoms associated with LRTIs are coughing, shortness of breath, weakness, fatigue, and fever. Fluoroquinolones against the *H.influenza* used are gatifloxacin, levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, and ciprofloxacin. Fluoroquinolones also active against gram-negative *bacilli* and highly active against *S.pneumoniae* and *b-hemolytic* or *viridans*group of streptococci [100]. Gatifloxacin is anew 8-methoxy fluoroquinolone has activity against *S. pneumoniae* few newer fluoroquinolones having in vitro activity against *staphylococci*. The use of older agents and incorrect dosing are the main causes for the development of resistance [101].

Resistance of fluoroquinolone

Fluoroquinolones introduced into clinical use in the mid-1980 were largely developed for the treatment of infection due to Gram-negative bacteria, although ciprofloxacin had limited activity against some gram-positive bacteria. Subsequently developed and marketed fluoroquinolone- including levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, gatifloxacin, and moxifloxacin- have had increased activity against Gram-positive *cocc*i and have received regulatory approvals for treatment of patient with various infection with these organisms shortly after introduction of these agents into clinical use the emergence of fluoroquinolone-resistant *S. aureus* was noted, especially among methicillin-resistance strains [88, 89, 90]. There are three ways by which resistance to these agents is accomplished

1. Several point mutation in *gyA* have been describing
2. *Cf-ofx* locus (this locus confers lower-level resistance)
3. Efflux of fluoroquinolone from the cell

Fluoroquinolone efflux mediated by *norA* is an active process that is sensitive to protonophores, such as dinitrophenol and carbonyl cyanide m-chlorophenylhydrazone (CCCP),

suggesting that the proton motive force is important in the efflux process [91] *M. tuberculosis* strain and evaluated the possible correlation between gene mutation and resistance to ofloxacin, moxifloxacin, and gatifloxacin based on their MICs. In the present study, moxifloxacin and gatifloxacin were more active than ofloxacin, showing strong cross-resistance with the latter [92, 93]. Twenty-four of the 26 moxifloxacin and gatifloxacin-resistance strain had a mutation in *gyrA*, mostly at position Ala-90 and Asp-94 [94]. The result from a number of longitudinal studies of a trend in fluoroquinolone susceptibility. Examples include methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Streptococcus Pneumonia*. Chromosomally mediated resistance may occur through alteration in the genes coding for both subunits of *DNA gyrase* (*gyrA* and *gyrB*) and *topoisomerase IV* (*parC* and *parE*) [95, 96] duringthe 1997 through 1998 SENTRY-programme four (0.13%) fluoroquinolone-resistance *H. influenza* strain were identified. The strain genetically distinct and had different *gyA* mutation. *Enterobacteriaceae* and non-fermenter are variably fluoroquinolone-resistance [97].

Conclusion

The older quinolone class of antibacterial was limited use, they restricted mostly to gram-negative and used only for UTIs. The newest group of the compound has a remarkably broad spectrum activity against a various gram-negative member of the *Enterobacteriaceae*, *streptococci* (*including pneumococci*), *staphylococci*, and other species. Activity against ciprofloxacin and ofloxacin-resistance strain of staphylococci and non-fermentative Gram-negative is an area that should need to improve. Clinafloxacin, Gemifloxacin, and sitafloxacinare overall the better active compound. The fluoroquinolones are bactericidal and penetrate into mammalian cell and tissues well so that they are valuable agents for treating infections caused by intracellular bacteria, they are an indication that these newer agents are less resistance, this could prove an asset in the clinic. The newer fluoroquinolones have better pharmacokinetics properties than older compounds, and they may be given once dailydose.

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