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Fluoroquinolone as antimicrobial agent: A Review

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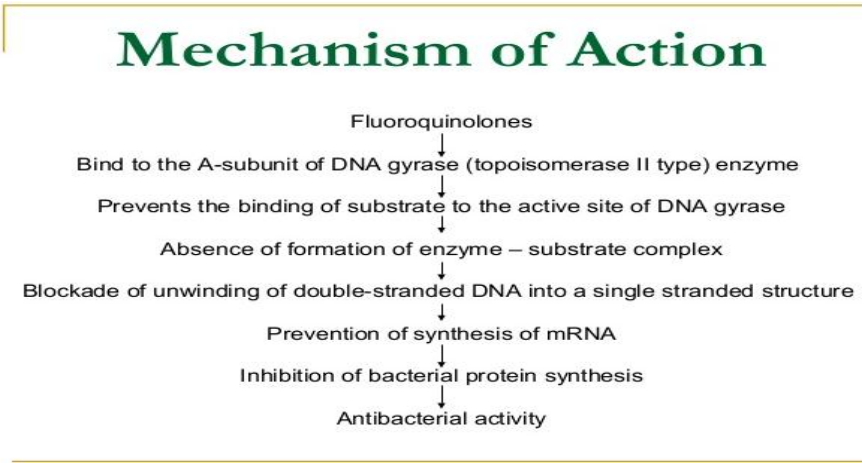
Abstract
The fluoroquinolones are used in the treatment of a variety of bacterial infections. These agents inhibit the DNA gyrase, abolishing its activity by interfering with the DNA rejoining reaction. The inhibition of the resealing leads to the liberation of fragments that are subsequently destroyed by the bacterial exonucleases. All fluoroquinolones accumulate within bacteria very rapidly, so that a steady-state intra bacterial concentration is obtained within a few minutes. Resistance develops slowly and is usually chromosomal and not plasmid mediated. However, development of resistance and transfer between animal and human pathogens has become a fervently argued issue among the microbiologists. Another concern regarding the use of new quinolones in the veterinary field is a possible detrimental effect on the environment. It still seems unlikely that the controlled use of veterinary quinolones will give rise to unfavourable effects on the environment.

Key words: fluoroquinolones, chemistry, antimicrobial activity

Introduction
Quinolones are one of the most commonly prescribed and wholly synthetic classes of antibacterial drugs all around the world and have been extensively used to combat with a number of bacterial infections, including gastrointestinal infections, respiratory and urinary tract diseases [1]. The first clinically useful quinolone was naldixic acid, discovered by Lesher and co-workers in 1962, which was generated from chloroquine, an antimalarial agent [2]. Quinolones and fluoroquinolones are a relatively new class of synthetic antibiotics with potent bactericidal, broad spectrum activity against many clinically important pathogens which are responsible for variety of infections including urinary tract infections (UTI), gastrointestinal infections, respiratory tract infections(RTI) [3], sexually transmitted diseases (STD) and skin infections [4, 5]. These fluoroquinolones has a prominent oral bioavailability in all monogastric species, a large volume of distribution and plasma proteins binding is low. So it allows them to cross membranes and reach the most remote parts of the body at concentrations above the minimum inhibitory concentrations (MIC's) of most pathogens. Tissues and sites demonstrating high concentrations following systemic administration include the kidney, liver and bile plus the prostate, female genital tract, bone and inflammatory fluids (Montay *et al*., 1984). They are eliminated mostly in the urine having the levels 100 to 300 times higher in the urine than in the serum (Montay*et al*., 1984). All the fluoroquinolones shows distributional and antimicrobial properties that make them potentially useful in veterinary medicine.

Mechanism of Action
Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death [6-8] As a general rule, gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive bacterial activity corresponds with inhibition of DNA type IV topoisomerase [6].



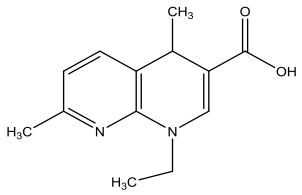
Classification

Two main classifications for fluoroquinolones based on chemical structure and biological properties respectively has been described by Bryskier & Chantot, which logically embraces the majority of active compounds known till date.

Classification : By Generation

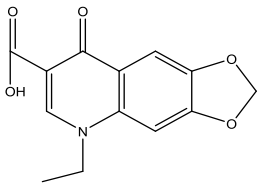
Generation	Drug names	Spectrum
1st	Nalidixic acid Cinoxacin	Gram negative; but, not pseudomonas species.
2nd	Norfloxacin Ciprofloxacin Enoxacin Ofloxacin	Gram negative (including, pseudomonas species) Some Gram positive & some atypicals.
3rd	Levofloxacin Sparfloxacin Moxifloxacin Gemifloxacin	Same as 2nd generation with extended Gram positive & atypical coverage.
4th	Trovafloxacin	Same as 3rd generation with broad anaerobic coverage.

General Chemical Structure of Fluoroquinolone



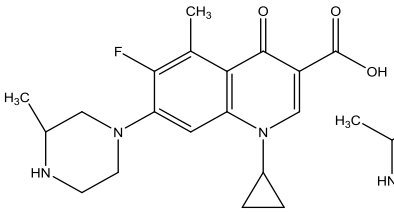
Nalidixic acid

Fig 1



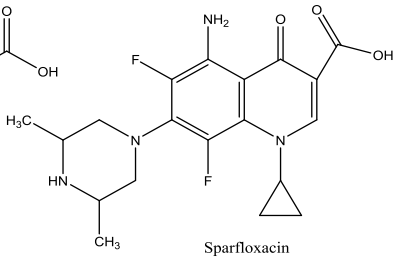
Oxolinic acid

Fig 2



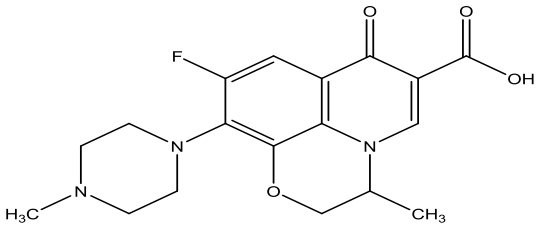
Grepafloxacin

Fig 3



Sparfloxacin

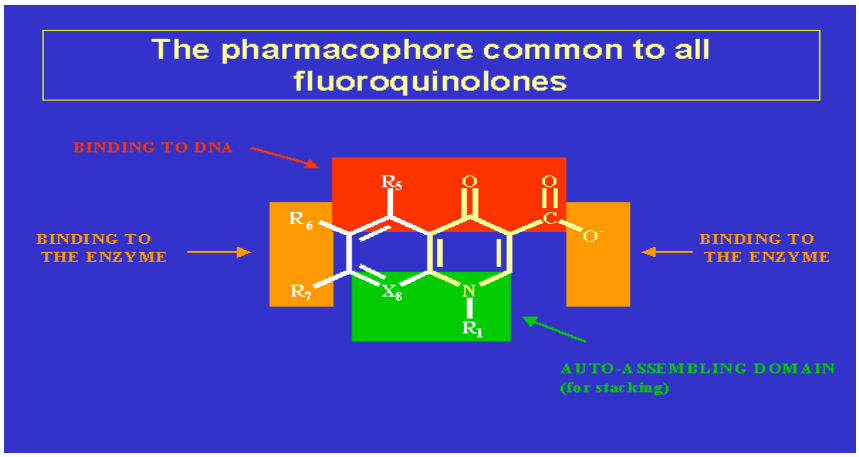
Fig 4



Ofloxacin

Fig 5

Structural Activity Relationship of Fluoroquinolone



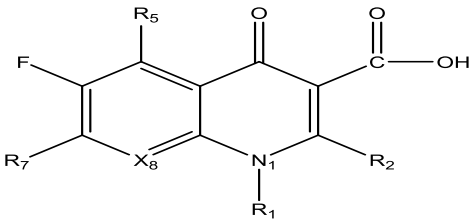


Fig 6: Pharmacophore

Fig 6 shows the core molecule and the positions at which key changes are engineered. There are 2, 3 and 4 positions, a hydrogen moiety is optimal in 2 Position and if any larger molecule added to 2 position may create a steric hindrance at the adjacent positions 3 and 4 which is carboxyl group and oxygen molecule, respectively.

At Position 1

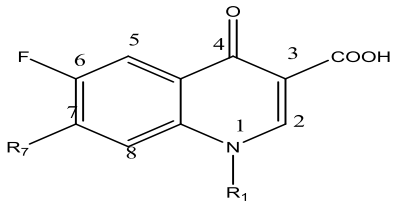


Fig 7

1. Earlier study indicated that substitution at N-1 position is important for Anti-bacterial activity Addition of a cyclopropyl moiety at N-1 position shows significant activity against gram-negative bacteria as seen in Ciprofloxacin and sparfloxacin.
2. Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against gram positive bacteria with minor reduction of activity against gram negative bacteria.

At position 2

1. Position 3 having carboxylic acid group and position 4 having the keto is the site necessary for binding of quinolones to DNA gyrase.
2. Carboxylic acid at position 3 is required for antimicrobial activity, similarly like a keto group at position 4
3. Replacement of 3-carboxyl group with isothiazole group produces the most potent isothiazquinolone [9], which is having 4 to 10 times greater *in vitro* antibacterial activity than ciprofloxacin, but it appeared to suffer from some undesirable properties such as insolubility and mam-malian toxicity [10].

Position 3

1. Compounds with small substituents such as nitro, amino, halo, alkyl groups have been synthesized. Among them, C-5 amino group enhances absorption and / or tissue distribution e.g Sparfloxacin, grepafloxacin.
2. The incidence of photo toxicity of Sparfloxacin is the lowest of the fluoroquinolones, because of the presence of the 5amino group, which counteracts the effect of the 8- fluoro substituent.

Position 4

1. Fluorine atom seems to be essential because it helps in binding with DNA topoisomerase enzyme of bacteria [9].

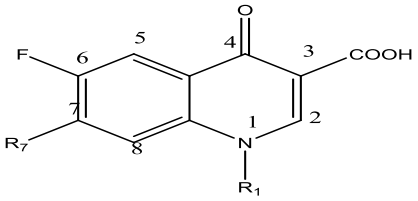


Fig 8

Position 5

1. The substitution of a piperazinyl ring at position 7 makes the molecule active against *Pseudomonas* and in the presence of a fluorine atom at position 6 extends the activity of the molecule to some but not all gram positive bacteria (Neer, *et al*. 1988). Additions of alkyl chains to the para position of the piperazinyl ring, and to the nitrogen at position 1, increase the lipid solubility and the volume of distribution of the compounds

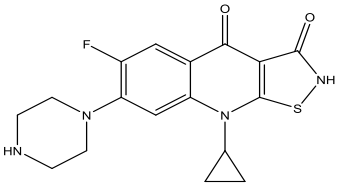


Fig 9

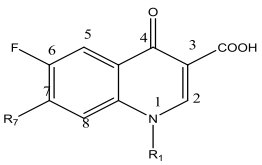


Fig 10

2. In general, quinolones with small or linear C-7 substituents (H, Cl, CH_3, NH_2-CH_2-CH_2- NH_2, NH- CH_3, NH-NH_2) possess moderate to weak anti-bacterial activities.

Position 6

1. A fluorine or chlorine substituents at position-8 leads to the formation of potentially active compounds.

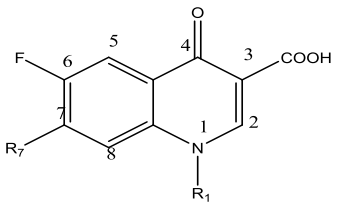


Fig 11

2. Methoxy group at position-8 provides good anaerobic activity, for example gatifloxacin and moxifloxacin. Oxygen substituent at C-8 position, where substituent is part of ring system has been shown to have better in vivo efficacy.

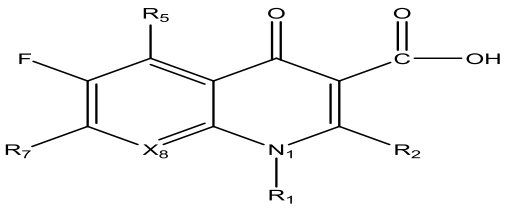
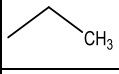
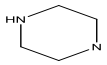
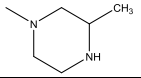
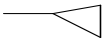
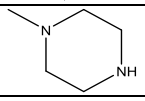
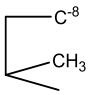
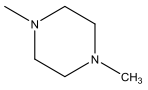
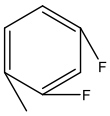
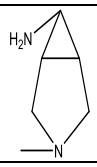
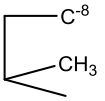
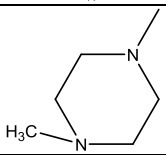
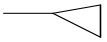
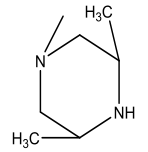
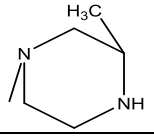
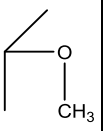


Fig 12

Table 1: Structure, and important clinical indications of fluoroquinolones:

Compound		Structure				Clinical indication	References
No.	Name	R1	R_5	R_7	X		
1	Norfloxacin					Uncomplicated urinary tract infections.	[11-18]
2	Enoxacin	do	do	do		Uncomplicated urinary tract infections	[11, 19, 20, 16]
3	Lomefloxacin	do	do			Uncomplicated urinary tract infections	[11, 20, 21, 22]
4	Ciprofloxacin		do			Complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections, sexually transmitted diseases, anthrax.	[23, 20, 24, 25]
5	Ofloxacin		do		do	Complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections, sexually transmitted diseases, anthrax.	[11, 20, 26-30]
6	Trovafloxacin		do			Intra abdominal infections, acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	[31, 11, 32-34]
7	Levofloxacin		do			Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	[31, 11, 24, 35, 36]
8	Sparfloxacin					Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	[31, 11, 20, 37-40]
9	Gatifloxacin	do				Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	[11, 20, 61, 41-45]
10	Grepafloxacin	do		do		Acute exacerbation of chronic bronchitis, community acquiredpneumonia, uncomplicated gonorrhea, urethritis, cervicities.	[31, 46, 47, 24, 48, 49]

Antimicrobial activity

(A)

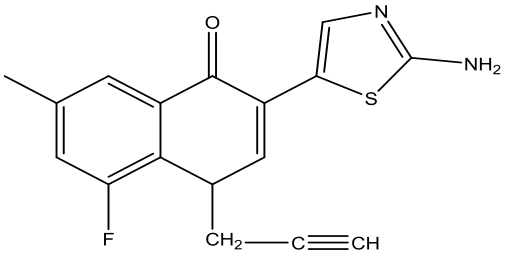


Fig 13

Yu Cheng *et al*. 2016 synthesized N-1 propargyl modified 2aminothiazolyl quinolone 10f which shows good broadspectrum and efficient antibacterial activitywhen compared to other compounds. The anti-B. typhi potency of compound 10f (MIC ¼ 1 mg/mL) was the strongest among the target compounds, which was 32-fold and 4-fold more potent than reference drugs Chloromycin and Norfloxacin, respectively. Furthermore, MRSA was also quite sensitive to compound 10f (MIC ¼ 8 mg/mL) comparable to Norfloxacin. Moreover, this compound also exhibited equal or better activity in contrast to the two reference drugs against *S. dysenteriae* and P. aeruginosa. These indicated that 2aminothiazolyl quinolone 10f had the potency to be a lead compound in the development of more effective board-spectrum antimicrobial agents.

(B)

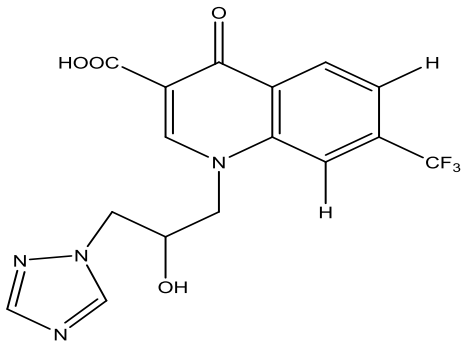


Fig 14

Sheng-Feng Cui *et al*. 2013 synthesized quinolone triazoles quinolone triazoles were evaluated in vitro for their antimicrobial activities against three Gram-positive bacteria (Micrococcus luteus ATCC 4698, MRSA and Staphylococcus aureus ATCC25923), four Gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli DH52, Shigella dysenteriae, and Eberthella typhosa) and four fungi (Candida utilis, Aspergillus flavus, Beer yeast, and Candida albicans) by two folds serial dilution technique recommended by National Committee for Clinical Laboratory Standards (NCCLS) with the positive control of clinically antimicrobial drugs Norfloxacin, Chloromycin and Fluconazole.The compound 6d having trifluoromethyl group at the 7-position of quinolone gives stronger antibacterial efficacies and broader bioactive spectrum than Norfloxacin and Chloromycin with quite low MIC values.

(C)

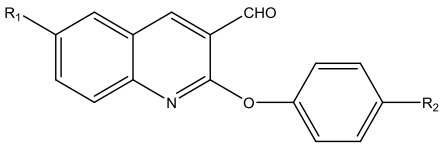


Fig 15

Compound	R_1	R_2
3c	H	Cl
3e	CH_3	CH_3
3g	OCH_3	H

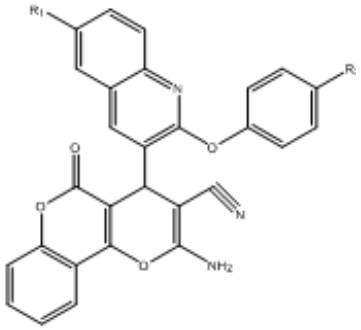


Fig 16

Compound	R_1	R_2	R_3
6F	CH_3	Cl	H
6I	OCH_3	Cl	H
6Q	OCH_3	CH_3	CH_3

Divyesh C *et al*. 2010 synthesized a new class of b-aryloxyquinolines 3a -i and their pyrano[3,2-c]chromene derivatives 6a-r via a nucleophilic displacement and a one-pot multicomponent reaction method. The antimicrobial activity is evaluated in invitro against pathogenic strains of specifically Bacillus subtilis, Clostridium tetani, Streptococcus pneumoniae, Escherichia coli, Salmonella typhi, Vibrio cholera, Aspergillus fumigatus and Candida albicans.The Compounds 3c, 3e, 3g, 6f, 6l and 6q shows excellent antibacterial activity. The compound 6p shows more potent antifungal activity than that of first line standard drugs.The compound 6f is emerged as the good antimicrobial member with better antitubercular activity.

(D)

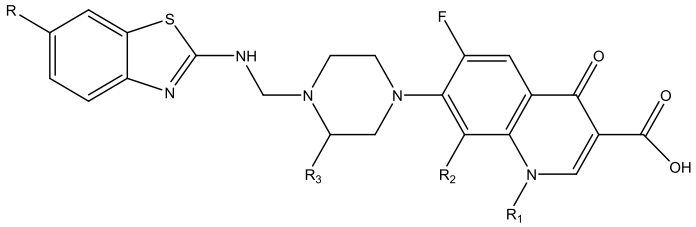
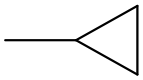
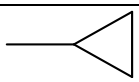
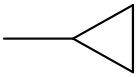
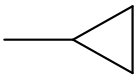
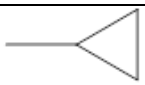
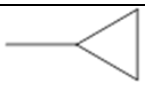


Fig 17

Table 2

Compound No.	R	R_1	R_3	R_4
4f	-OCH3		-H	- H
4d	-F	-C2H5	-H	-H
4g	-NO2		-H	-H
4h	-CH_3		-H	-H
4j	-Br		-H	-H
4k	-NO_2		-OCH_3	-CH_3
4i	-F		-OCH3	-CH3

Prabodh Chander Sharma *et al*. 2011 synthesized and evaluated against in vitro antibacterial activity of The compounds which exhibit more potent activities against Gram-positive organisms than those of ciprofloxacin, norfloxacin and gatifloxacin.The Compounds 4f, 4h, 4j and 4k shows good antibacterial activities against *Bacillus subtilis*.The Compound 4i i.e 1-cyclopropyl-6-fluoro-7-(4-(N-(6-fluoro-1,3-benzothiazol-2yl)aminomethyl)piperazin-1-yl)-1,4-dihydro-4-oxo-quinoline3-carboxylicacid(4i)and1-cyclopropyl-6-fluoro-7-(4-(N-(6-fluoro-1,3-benzothiazol-2-yl)aminomethyl)-3-methylpiperazin-1yl)-8-methoxy-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, which shows better antibacterial activity than the standard antibiotics norfloxacin and gatifloxacin when tested against *Escherichia coli*.The Compound 4f shows similar activity at higher concentration (50 lg/ml and 100 lg/ml). The Compounds 4d and 4g shows superior antibacterial activities as compared to the standard antibiotic norfloxacin when tested against *Pseudomonas aeruginosa*.The compound 4h having methyl group at 6-position of benzothiazole part of novel derivative shows better MIC (25 lg/ml) against *Bacillus subtilis* than standard antibiotic gatifloxacin (MIC value 100 lg/ml).The compound 4f having MIC of 08 lg/ ml, which is approximately eight times more potent than that of standard drug ciprofloxacin (MIC value 50 lg/ml).

(E)

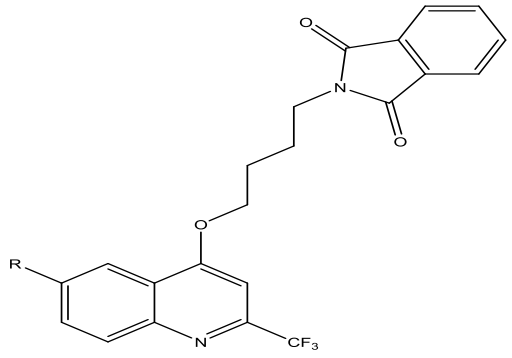


Fig 18: 6a-c

Compound	R
6a	-H
6b	-F
6c	-CH_3

Siva S. Panda *et al*. 2013 synthesized and evaluated against vitro
antimicrobial activities 100 lg/mL against two Gram-positive bacteria like *Staphylococcus aureus* MTCC 096 and *Bacillus subtilis*, three Gram-negative bacteria like *Escherichia coli* MTCC 443, *Salmonella typhi* MTCC 733, and *Klebsiella pneumoniae* MTCC 432 and four fungi like *Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus flavus* MTCC 277, and *Candida albicans* MTCC 227. All the derivatives showed good activity towards Gram-positive bacteria and less activity towards Gram-negative bacteria. The compounds 6a–c which is O-substituted shows significant antimicrobial activity against all the Gram-positive strains.

(F)

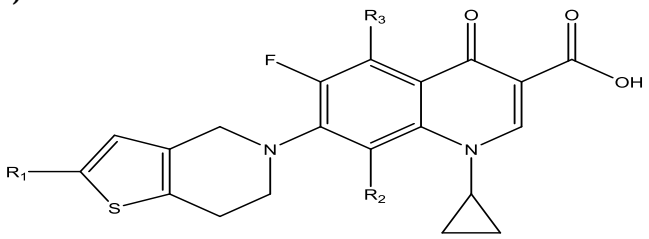


Fig 19

Compound	R_1	R_2	R_3
14	-H	-OCH_3	-NO_2
15	-H	-H	-H
16	-Br	-H	-H
17	-H	-F	-NH_2
18	-H	-F	-NHAc
19	-H	-F	-F
20	-Br	-F	-NH2

Brijesh Kumar Srivastava *et al*. 2007 Synthesized and evaluated against antibacterial activity in standard in vitro MIC assay method of a number of substituted 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine quinolones which is compared to standard Gatifloxacin, Ciprofloxacin, and Sparfloxacin. Compound 14,containing nitro group is present at C-5 position having less antibacterial activity Compared to compound 7.The Compound 19 have moderate antibacterial activity.The Compound 9 contain an electron withdrawing –NO2 group on the tetrahydrothienopyridine exhibit similar antibacterial activities with that of Gatifloxacin against the strains of *Bacillus subtilis* ATCC 6633; S.e., *Staphylococcus epidermidis* ATCC 12228; S.a., *Staphylococcus aureus* ATCC 33591; E.f., *Enterococcus faecalis* ATCC 29212; P.a., *Pseudomonas aeruginosa* ATCC 27853; K.p., *Klebsiella pneumoniae* ATCC 10031; E.c., *Escherichia coli* ATCC 25922. When modifications is done on quinolone nucleus, which results the formation of compounds 14–20, which shows significant loss of antibacterial activity.

Conclusion

The aim of writing the review to provide information, chemistry and its antimicrobial activity of Fluoroquinolone molecule. Fluoroquinolone is broad spectrum activity against Grampositive and Gramnegative bacteria. The new fluoroquinolones derivatives are potent which is used to treat urinary tract and gastrointestinal tract bacterial pathogens. The use of orally administered fluoroquinolones (when indicated) instead of intravenously administered antibiotics may provide significant advantages in terms of reduced hospitalization or home health care costs. Thus a judious and efficient use of these antibiotics is recommended.

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