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A Review on Structural and Antibacterial Activities of Quinolones

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Abstract

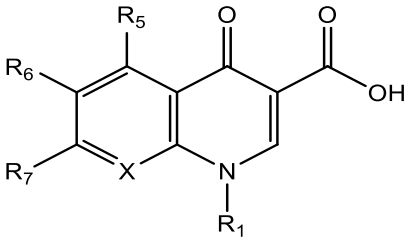
The aim of this paper to discuss about the quinolones. Quinolones shows amphoteric character due to the presence of both acidic and basic groups and having a great effect on antimicrobial field. It plays a crucial role in antibacterial drugs because most of the synthetic antibiotic contains quinolones and fluoroquinolones. The history of quinolones generated through the scientific and clinical awareness in 1960s. In this paper the structural activity relationship of antibacterial drugs containing quinolones and fluoroquinolone moieties has been discussed. The effect of different subsituients on different position of quinolones are also described. Along with this the antibacterial activity also considered by the various substitution on quinolones in this paper.

Keywords:- Quinolones, Fluoroquinolones, Structural activity, Antibacterial activity

1. Quinolones

In 1960, the scientific and clinical interest have been generated by the quinolone group of antibacterial.

Quinolone is a bicyclic ring in which N-1 position is substituted by different types of moieties as shown in Figure 1. It is a most interesting group in antibacterial drugs which have great effect on antimicrobial field. The modern field of antibiotic drug is covered by quinolones [1]. The behavior of quinolone is amphoteric because it has both basic and acidic groups [2, 3, 4].



Quinolones:X=CH or R

Naphthyridones:X=N

Figure 1. Basic Structure of 4-Quinolones

Quinolones are broadly classified into four generations on the basis of spectrum of activity. In 1962, **Lesher and co-workers** discovered the first quinolone which was generated from the chloroquine (antimalarial agent) i.e. Nalidixic acid based on 4-oxo-1,8-naphthyridin-3-carboxylic acid shown in Figure 1[1, 2]. Nalidixic acid was active against gram (-) bacteria shown in Figure 2 [2].

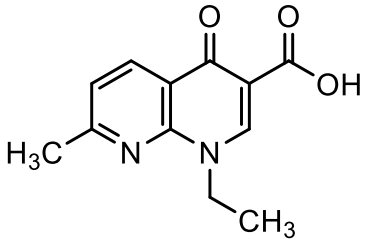


Figure 2. Nalidixic acid

In human body it metabolized fastly and lead to poor tissue distribution [5]. Due to narrow spectrum of activity the use of nalidixic acid was limited [6]. The activity of quinolone is removed by the reduction of 2,3-double bond [2].

2. *Fluoroquinolones*

In 1970s and 1980s the fluoroquinolones have comprehensive spectrum of activity as shown in Figure 5. Flumequine, the second generation antibiotic initiated with fluorine substituted at position-6 as shown in Figure 3 [1]. This brought a revolution in the field of synthetic antibiotics as fluoroquinolones which proves better activity against gram (-) bacteria [7].

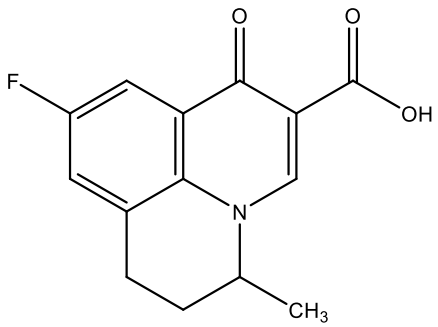


Figure 3. Structure of Flumequine

In 2002, F. V. Bankeke et. al. reviewed the history of the quinolone family and attempted to reposition the drugs on the resistance mechanism, pharmacodynamics(PD) and advantages and drawbacks of the compound used for their main therapeutic [6].

These scientists have extended their studies in explaining the utility of particular drugs and restriction for the usage of other type of drugs like norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin (shown in Figure 4).

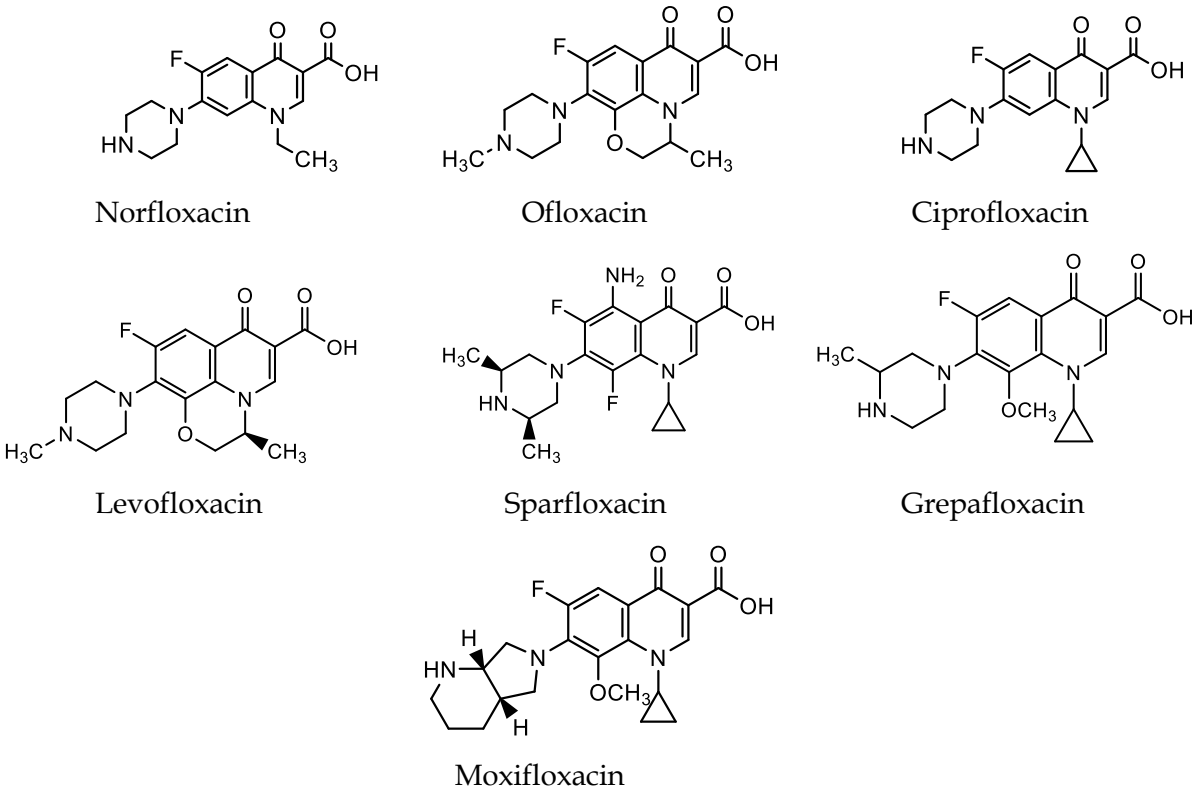


Figure 4. Structures of antibiotics containing fluoroquinolone moiety

2.1 Structure Activity Relationship

Fluoroquinolones have created a major impact in the field of chemotherapy and generated interesting antibacterial properties in the last few decades.

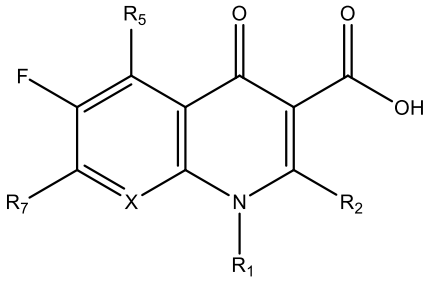


Figure 5. The basic structure of fluoroquinolones

The basic skeleton of majority of antibiotics comprised of quinolone moiety. The potency of antibacterial activity is influenced by the basic structure of quinolone. Over a decade structural modifications important at positions 1, 5, 7 and 8 only [8].

At Position C-1

For antibacterial activity, the substitution at N-1position is very important [5]. The steric bulk of N-1 group influences the antibacterial activity [1]. Except Levofloxacin as shown in

Figure 4 and Trovafloxacin (shown in Figure 6), all of fluoroquinolones have cyclopropyl group at position-1[8].

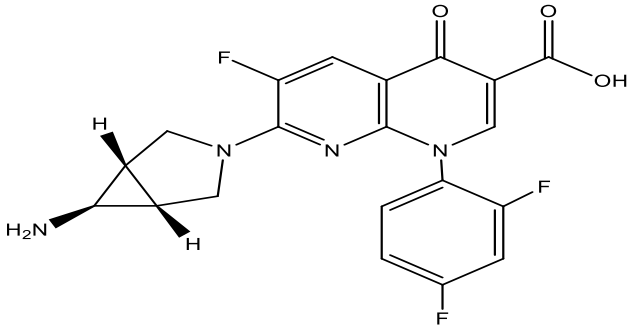
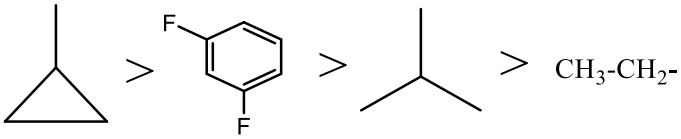


Figure 6. Trovafloxacin

A third ring which link the N-1 and C-8 position in the structure of levofloxacin increases the activity against gram (+) bacteria and a little decrease in activity against gram (-) bacteria (*Pseudomonas aeruginosa*) [8]. The potency of trovafloxacin has increased by 2,4-difluorophenyl group at position N-1[3]. The increase in activity against gram (+) bacteria and little decrease in activity against gram (-) bacteria is indicated by t-butyl group at N-1 position. Out of these cyclopropyl ring is known to be better and most active group [8]. The volume of distribution and lipid solubility of compound is increased by Nitrogen at position-1[3].



At Position C-2

In the chemical structure of all the antibiotics, C-2 position is deficit of substitution. It was explained by the researchers that this position is very close to DNA gyrase binding site of the fluoroquinolones, so hydrogen is most favorable at this position [8].

At Position C-3

For antimicrobial activity, the COOH group at position-3 is required, which is essential for binding to DNA gyrase [8]. This group is never been replaced by any presence of a keto group, at position-4 of the quinolones, is also the major need for antimicrobial activity [2]. It is the combined effect of carbonyl and that of carboxyl group which plays an important role during binding with the desired DNA gyrase binding site [8].

At Position C-5

Due to the presence of bulky groups at position-5, activity decreases. But the substitution of amine and methyl group at C-5 in sparfloxacin [2] and grepafloxacin shown in Figure 4 respectively increases the activity against gram (+) bacteria [8]. The presence of halogens, nitro, amino, hydroxyl and alkyl group at position-5 initially reduces the antibacterial activity [1].

At position C-6

Due to the addition of fluorine atom at position-6 antibacterial activity increases. The DNA gyrase complex binding is also increased by fluoro group at position-6 of quinolone as shown in Figure 1 [5].

At position C-7

At this position of quinolone five and six memebered rings are very common. The antibacterial activity is increased by the basic groups at C-7 of the ring [1]. The potency of fluoroquinolone against gram (-) bacteria is increased by piperazine moiety at this position like ciprofloxacin as shown in figure 4, gatifloxacin as shown in figure 8 etc. The activity of fluoroquinolone against gram (+) bacteria is increased by pyrolidine moiety at this position like moxifloxacin, trovafloxacin. The activity of fluoroquinolones against gram (+) bacteria is also increased by the alkyl substitution on piperazine ring like gatifloxacin as shown in Figure 7 and sparfloxacin as shown in Figure 4 [8].

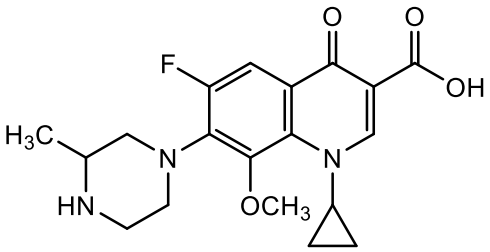


Figure 7. Gatifloxacin

At position-8

Presence of N atom at C-8 position also responsible for the activity [1]. The spectrum of antibacterial activity is expanded by the substitution of halogen group at this position like sparfloxacin and clinafloxacin (shown in Figure 2 and 8). There is increase in activity against anaerobes by the substitution of methoxy group at this position like moxifloxacin and gatifloxacin. The low incidence of phototoxity is caused by the methoxy group at this position in both cases moxifloxacin and gatifloxacin [8]. The antibacterial activity is also affected by the stereochemistry of methyl group on the third ring of ofloxacin. The activity of S-enantiomer is more than R-enantiomer [2, 6, 9].

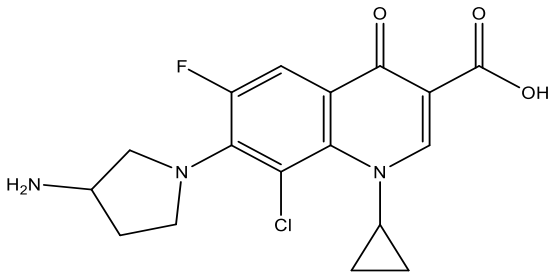


Figure 8. Structure of Clinafloxacin

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