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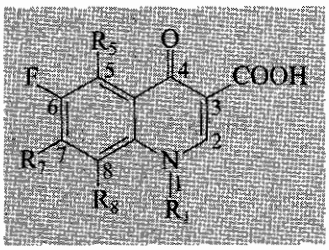
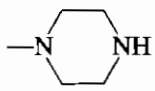
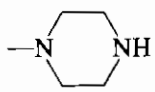
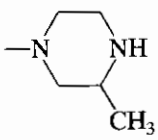
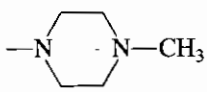
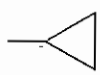
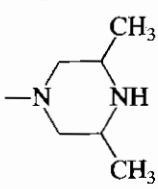
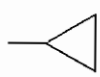
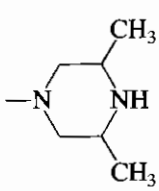
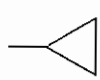
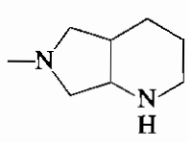
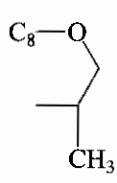
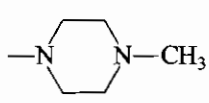
QUINOLONE ANTIBACTERIALS

INTRODUCTION

Quinolones constitute a large class of synthetic antimicrobial agents that are highly effective in the treatment of many types of infectious diseases, particularly those caused by bacteria. Quinolones are potent, broad spectrum antibacterial agents. The early congeners (non-fluorinated at C-6 like nalidixic acid) were limited to certain gram negative infections such as urinary tract infections. However, the modern generation of fluoroquinolones containing C-6 fluoro substituent and a cyclic basic amine moiety at C-7 surpass their predecessors in terms of spectrum of activity and potency. This has allowed for their use against a variety of gram-negative as well as some gram-positive pathogens. Quinolones are relatively easily prepared and administered via parenteral and oral routes and are well tolerated.

Structural Formula of Fluoroquinolones



	R_1	R_7	R_5	R_8
Norfloxacin	$-C_2H_5$		H	H
Ciprofloxacin			H	H
Lomefloxacin	$-C_2H_5$		H	F
Pefloxacin	$-C_2H_5$		H	H
Gatifloxacin			H	$-OCH_3$
Sparfloxacin			$-NH_2$	F
Moxifloxacin			H	OCH_3
Ofloxacin			H	1,8 bridge

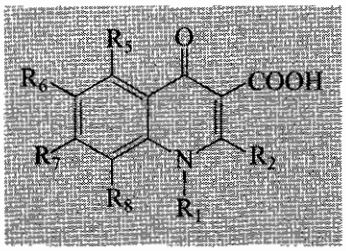
Mechanism of action

Quinolones inhibit the action of bacterial DNA gyrase enzyme. This enzyme is responsible for supercoiling and compacting bacterial DNA molecules into the bacterial cell during replication. This action is accomplished by modifying the topology of DNA via supercoiling and twisting of these macromolecules to permit DNA replication or transcription.

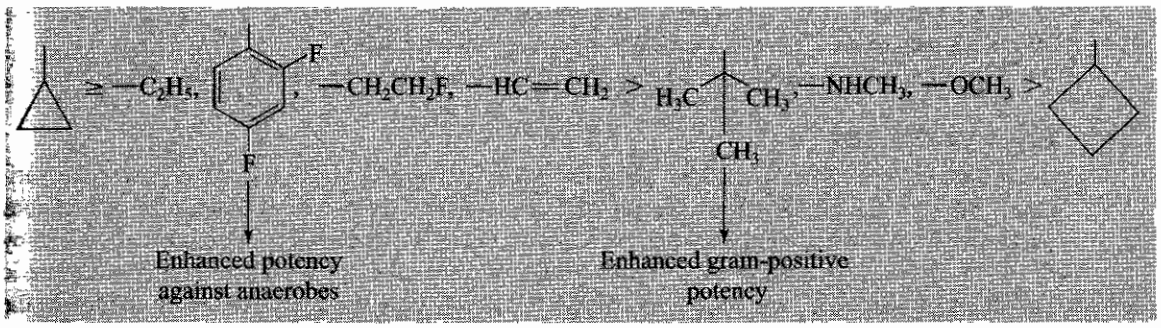
Uses

Fluoroquinolones are used to treat upper and lower respiratory infections, gonorrhea, bacterial gastroenteritis, skin and soft tissue infections, urinary tract infections, bone and joint infections and against tuberculosis.

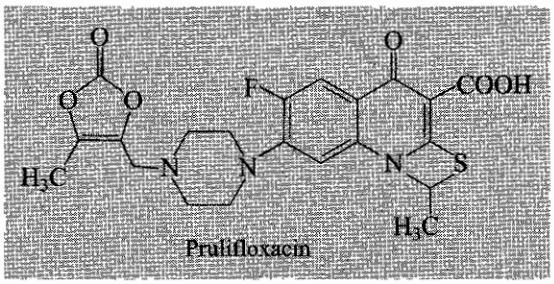
SAR of quinolones



1. Substituent at N-1 position: A compilation of active N-1 quinolone substituents is shown below with an emphasis on overall *in vitro* potency.

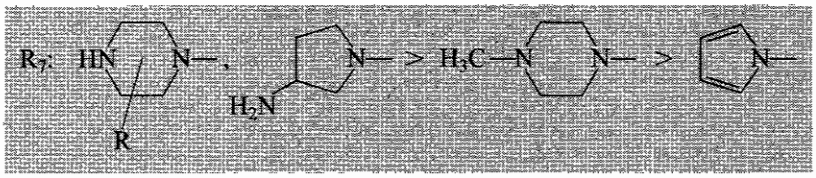


2. The simple replacement of C-2 hydrogen has generally to be disadvantageous, e.g. C-2 methyl or hydroxyl groups. However, some derivatives containing a suitable C-1, C-2 ring have been shown to possess notable activity.



3. Without doubt, the C-3 carboxylic acid moiety is most commonly encountered. Other acidic groups such as sulphonic acid, phosphonic acid, tetrazole as well as derivatisation as an ester results in a loss of antibacterial activity.
4. The C-4-oxo group of the quinolone nucleus appears to be essential for antibacterial activity. Replacement with 4-thioxo or sulphonyl group leads to a loss of activity.

5. The incorporation of an amino group at the C-5 position has proven beneficial in terms of antibacterial activity. The order of activity at R_5: NH_2, CH_3 > F, H > OH, OR, SH, SR.
6. The incorporation of a fluorine atom at the C-6 position of the quinolone is monumental. The order of activity at R_6: F > Cl, Br, CH_3 > CN.
7. The introduction of a piperazine moiety at C-7 was a landmark development. Other aminopyrrolidines also are compatible for activity.



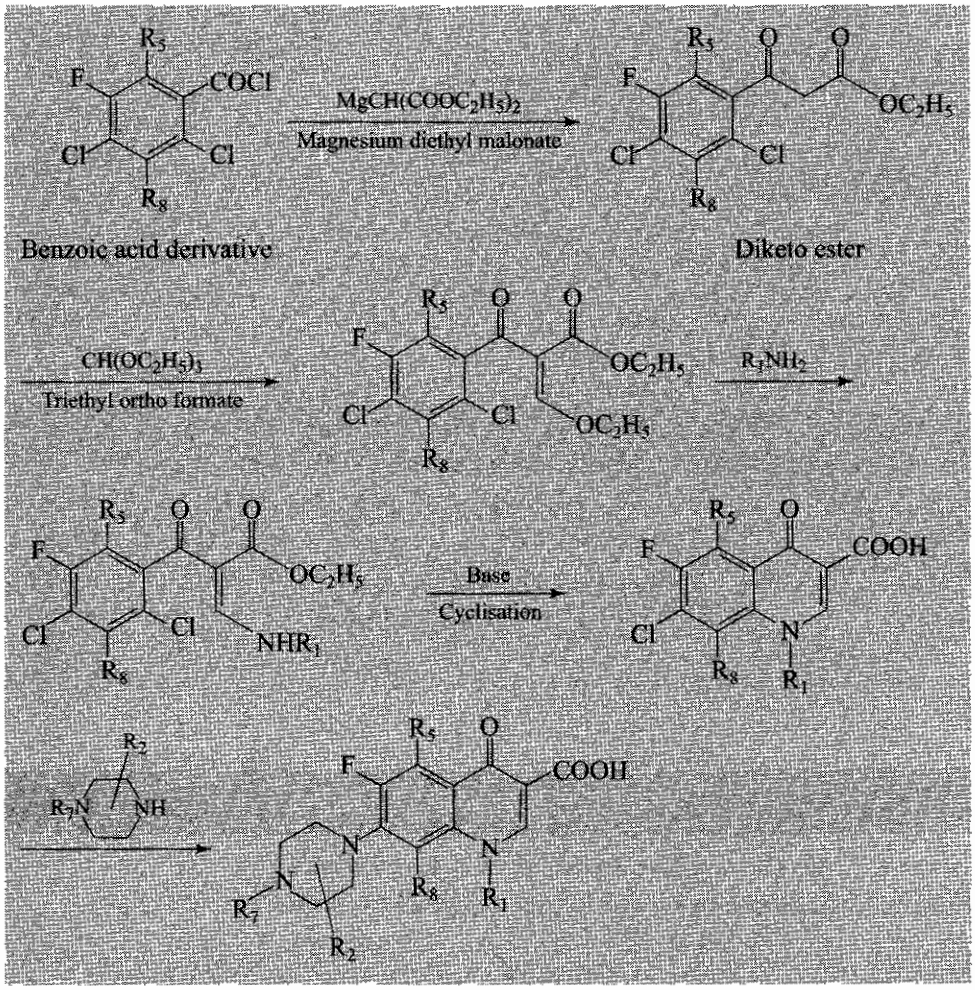
8. A hydrogen atom at the C-8 or a nitrogen atom (a naphthyridone) is the most common. In general, a C-8 fluoro substituent offers good potency against gram-negative pathogens, while a C-8 methoxy moiety is active against gram-positive bacteria. The order of activity at R_8: F, Cl, OCH_3 > H, CF_3 > methyl, vinyl, propargyl.
9. A halogen (F or Cl) at the 8-position improves oral absorption.
10. The joining of N-1 group to the C-8 position with oxazine ring leads to active ofloxacin.

Adverse effects

Some side-effects of the quinolones are class effects and cannot be modulated by molecular variation. Most of the fluoroquinolones produce photosensitivity reactions and cause convulsions particularly concurrent administration of NSAID Fenbufen. This effect is strongly influenced by the C-7 substituent with simple pyrrolidines and piperazines as the worst actors. Increasing steric bulk through alkylation ameliorates these effects. Phototoxicity is determined by the nature of the 8-position substituent with halogen causing the greatest photoreaction while hydrogen and methoxy show little light induced toxicity. Arthralgia and joint swelling have developed in children receiving fluoroquinolones; therefore, these drugs are not generally recommended for use in prepubertal children or pregnant women. Genetic toxicity is controlled in additive fashion by the choice of groups at the 1, 7 and 8 positions.

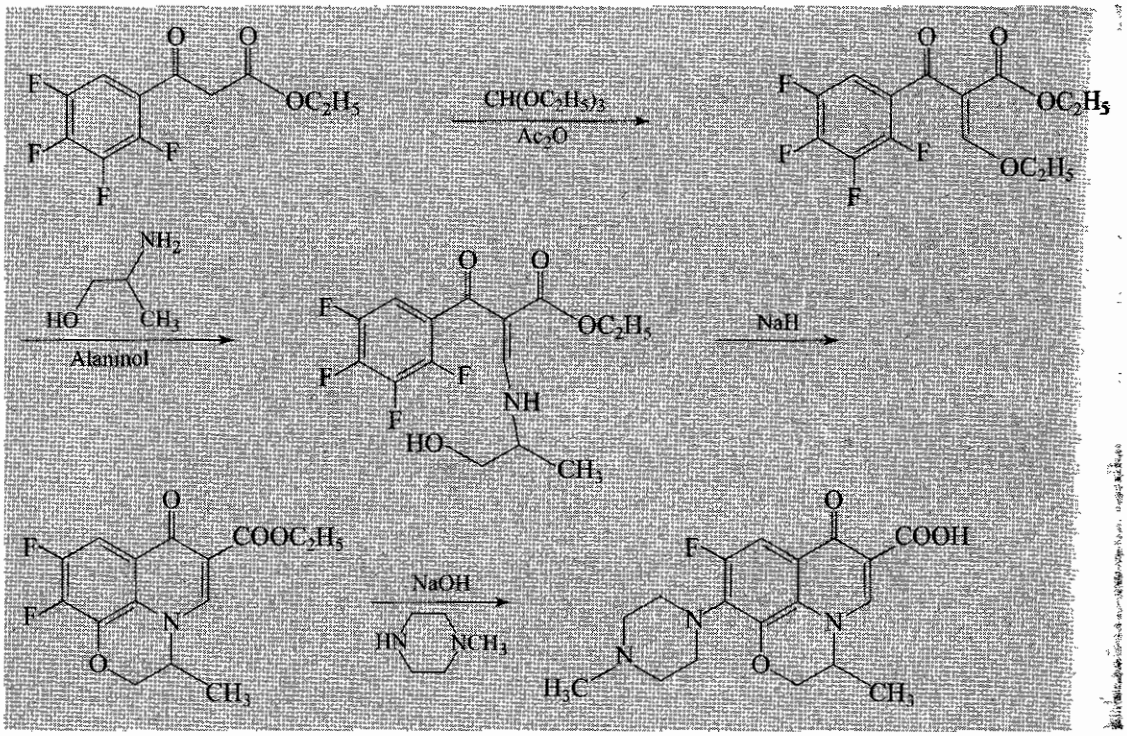
Synthesis

Fluoroquinolones



Norfloxacin, ciprofloxacin, lomefloxacin, gatifloxacin and sparfloxacin are prepared by this method using proper starting material, primary amine and piperazine derivatives.

Ofloxacin



FURTHER READINGS

1. Andriole, V. T., Ed., *The Quinolones*, 3rd edition, Academic Press, **2000**.
2. Domagala, J. M., *Antimicrob Chemotherapy*, vol. 33, pp. 685–706, **1994**.

MULTIPLE-CHOICE QUESTIONS

1. The N-1 position of pefloxacin contains
   a. Cyclopropyl
   b. Methyl
   c. Ethyl
   d. Piperazine
2. The C-7 position of gatifloxacin contains
   a. Piperazine
   b. 4-methylpiperazine
   c. 3,5-Dimethylpiperazine
   d. 3-Methylpiperazine

3. Fluoroquinolones are indicated for all of the following except:
   a. Urinary traet infection
   b. Tuberculosis
   c. Bone infection
   d. Bronehial asthma
4. The order of activity of (I) cyclopropyl, (II) methylamino, (III) cyelobutyl at N-1 position of quinolone is
   a. I > II > III
   b. I > III > II
   c. II > III > I
   d. III > I > II
5. One of the following is not a side effect of fluoroquinolones:
   a. Phototoxcity
   b. Ototoxicity
   c. Convulsion
   d. Arthralgia

GENERAL QUESTIONS

1. Write a short note on fluoroquinolone antibacterials with few structural examples.
2. Discuss SAR of fluoroquinolones and their effects on toxicity.
3. Give the synthetic protocol for eiprofloxaein, norfloxacin and ofloxacin.
4. How do quinolones exhibit their antibacterial activity?