Anti-Microbial Agents:

Anti-Bacterial Agents: Quinolones

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SECTION 7

Drugs Impacting Infectious and Neoplastic Disease Processes

CHAPTER 29

Drugs Used to Treat Bacterial Infections

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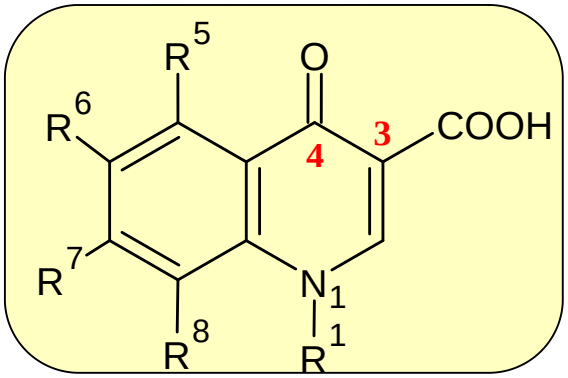
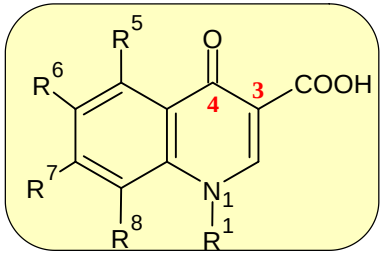
Quinolone class

- Besifloxacin
- Ciprofloxacin
- Delafloxacin
- Finafloxacin
- Gatifloxacin
- Gemifloxacin
- Levofloxacin, ofloxacin
- Moxifloxacin
- *Norfloxacin*



Quinolones



- New antibiotic: bacteriocidal
- Synthetic
- Chemistry: N1-alkylated-3-carboxy-pyrid-4-one fused to aromatic benzene
- First generation: nalidixic acid
- 2nd generation to 4th generation: fluoro-quinolones: FQs: broad spectrum
- MOA: consequence inhibition of topoisomerase II (G^-) & IV (G^+)

✓ key bacterial enzymes that dictate confomation of DNA

✓ + ATP: positive supercoil

✓ - ATP: negative relaxing

✓ selectivity to bacterial enzymes: at normally achievable doses

- SAR
- Pharmacokinetic (PK): absorption; distribution; Pr binding; half life
- Resistance: G^- more than G^+
- Clinical indications
- Side effects
- Contraindications

Mechanism of Topoisomerases II (DNA-Gyrase) & IV

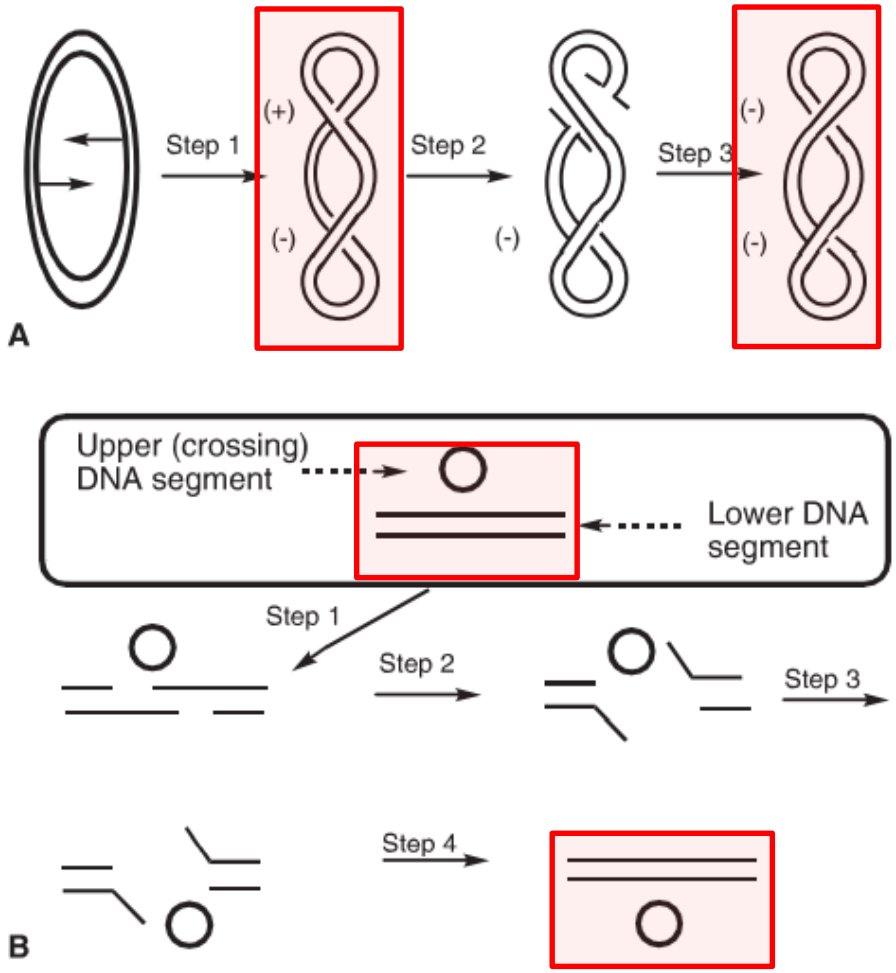
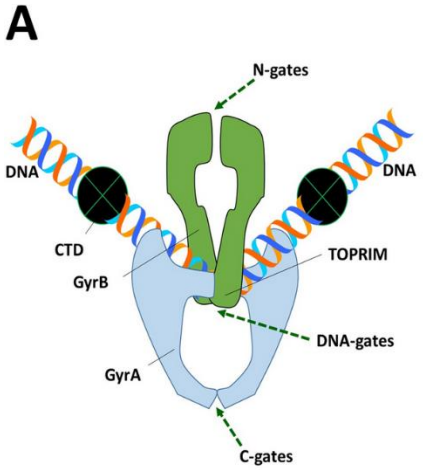
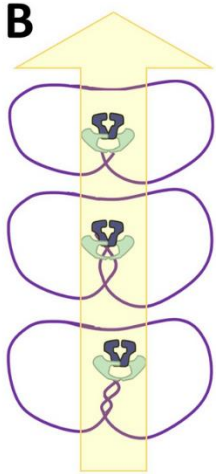
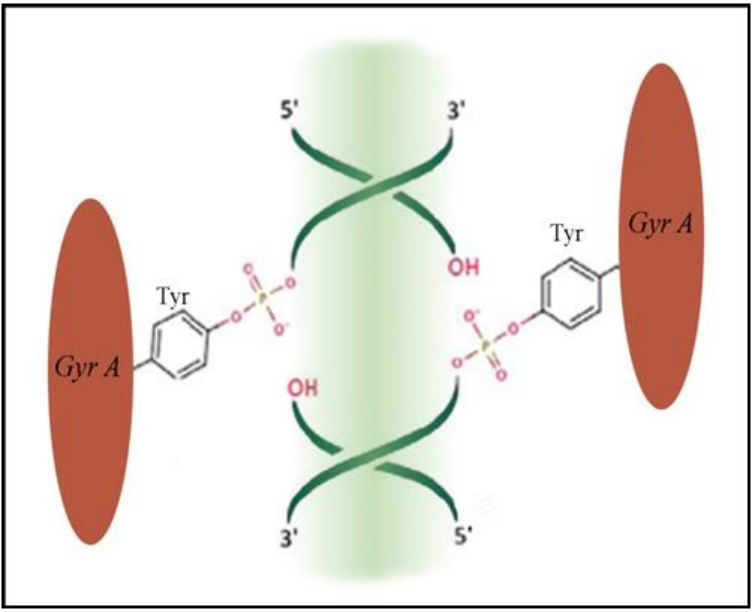


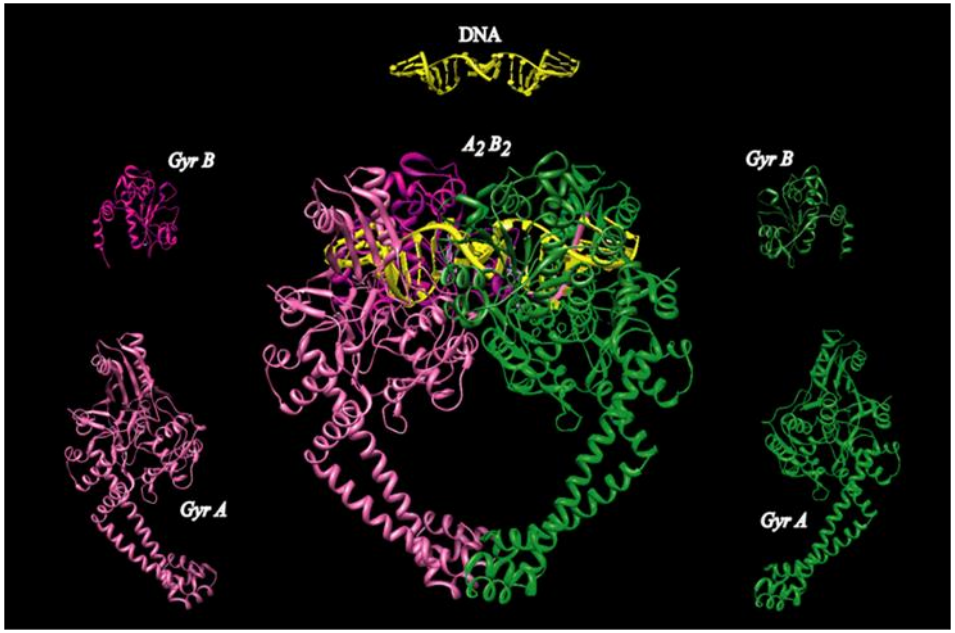
Figure 29.6 Schematic depicting supercoiling of circular DNA catalyzed by DNA gyrase. A, View from the top: Step 1, stabilize positive node. Step 2, break both strands of the back segment. Step 3, pass unbroken segment through the break and reseal on the front side. B, View from the side: Step 1, staggered cuts in each strand. Step 2, gate opens. Step 3, transverse segment passed through the break. Step 4, reseal cut segment.

DNA & DNA-Gyrase (A_2B_2)

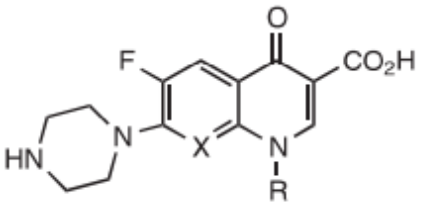






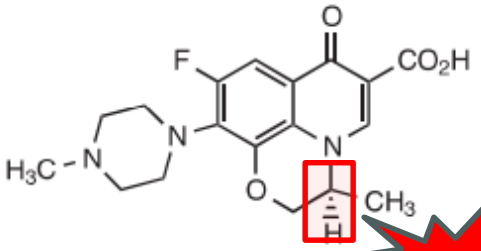


Docking of Fluoroquinolones to DNA-Gyrase



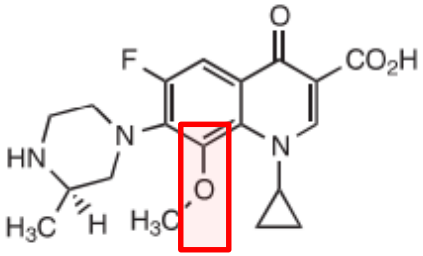
[a]Norfloxacin, R = ethyl; X = CH

Ciprofloxacin (Cipro), R = cyclopropyl; X = CH

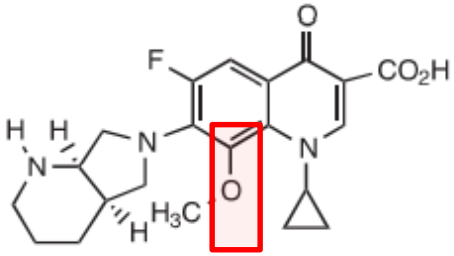


Ofloxacin (racemic) (Floxin)

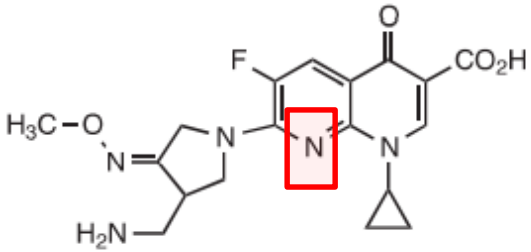
Levofloxacin (1-*S*) (Levaquin)



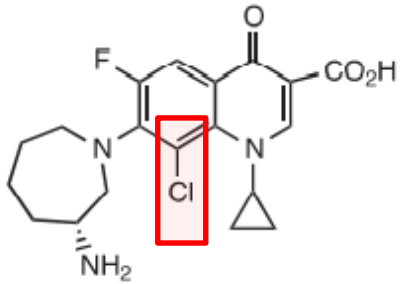
Gatifloxacin (Tequin)



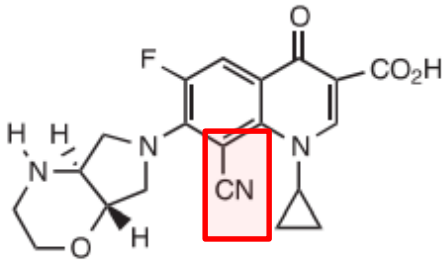
Moxifloxacin (Avelox)



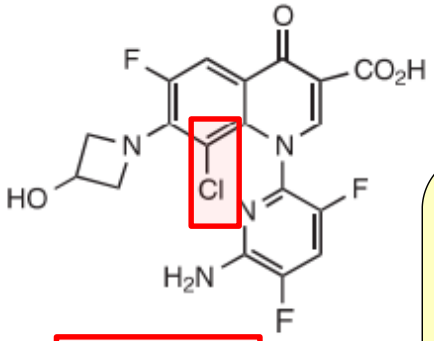
Gemifloxacin (Factive)



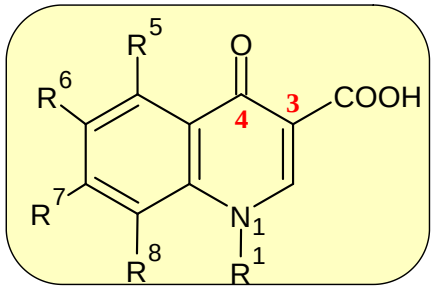
Besifloxacin (Besivance)



Finafloxacin (Xtoro)



Delafloxacin (Baxdela)



[a]Norfloxacin was discontinued in 2017, but a generic substitution may be available in the future

Figure 29.5 Second-, third-, and fourth-generation quinolones.

SAR for Quinolones

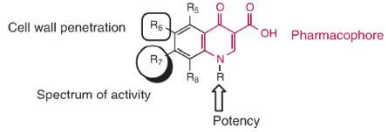


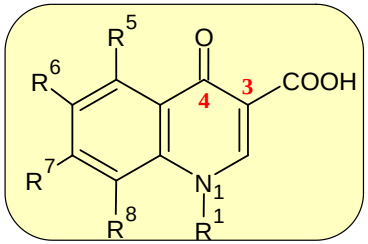
Figure 29.7 Major structure-activity relationship (SAR) features
4-quinolones.

1. N1: PD:

✓ R^1 = di-F-phenyl: SE; R^1 = Et & Cyclopropyl; di-F-pyridine

✓ cyclized with C8 to provide 6-membered oxazine

2. C2: = C-H; C2-C3: double bond
3. C3: -COOH; C3-C4 resembles double bond
4. C4: ketonic carbonyl
5. C5: R^5 = H; investigational substitutes
6. C6: R^6 = F: Fluoroquinolones: optimized PK & PD
7. C7: R^7 = saturated heterocycles: PD: spectrum of effect (G^-); CNS SE



✓ consider methoxyimino (oxime ether); amino; hydroxy as substitutes

2. C8: =C-H; =N: bio-isosteric replacement

✓ R^8 = H; R^8 = OCH_3: PK; R^8 = Cl; R^8 = CN;

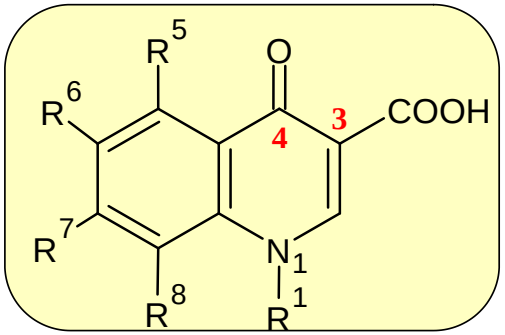
✓ R^8 = F: drug induced photosensitivity

✓ also cyclized with N1 to provide 6-membered oxazine

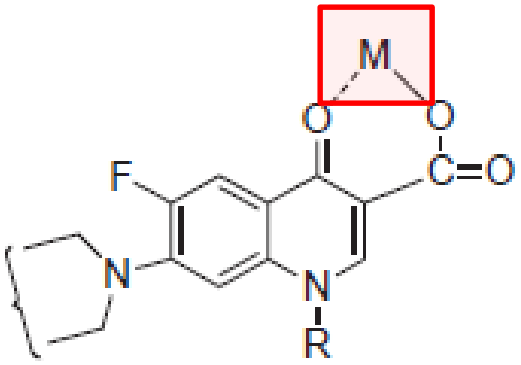
Therapeutic Classification of FQs

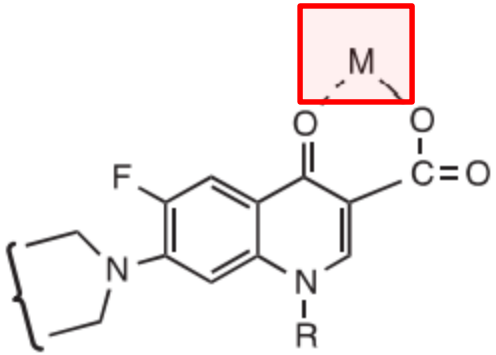
Table 29.3 Therapeutic Classification of Quinolones

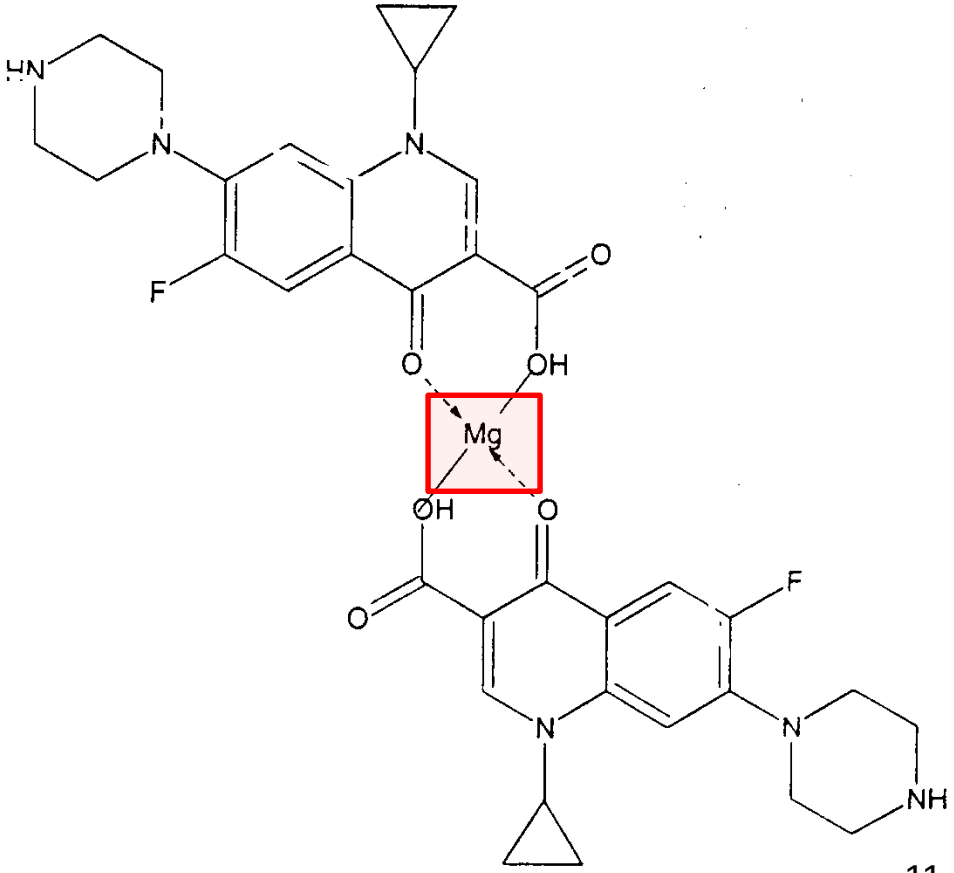
Generation	Characteristics
First generation	Poor serum and tissue concentration Not valuable for systemic infections Lack activity against *Pseudomonas aeruginosa*, gram-positive organisms, and anaerobes
Second generation	Adequate serum and tissue concentration Good for systemic infections Active against gram-negative organisms including *P. aeruginosa*; weak activity against *Streptococcus pneumoniae*; and no activity against anaerobes
Third generation	Once-daily dosing Active against *S. pneumoniae* and atypical bacteria; less active against *P. aeruginosa*
Fourth generation	Active against anaerobes and aerobic gram-positive and gram-negative organisms



Fluoroquinolone's Metal Conjugation







Figu
roflox

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FQ Ionization Considering pKa_1 & pKa_2

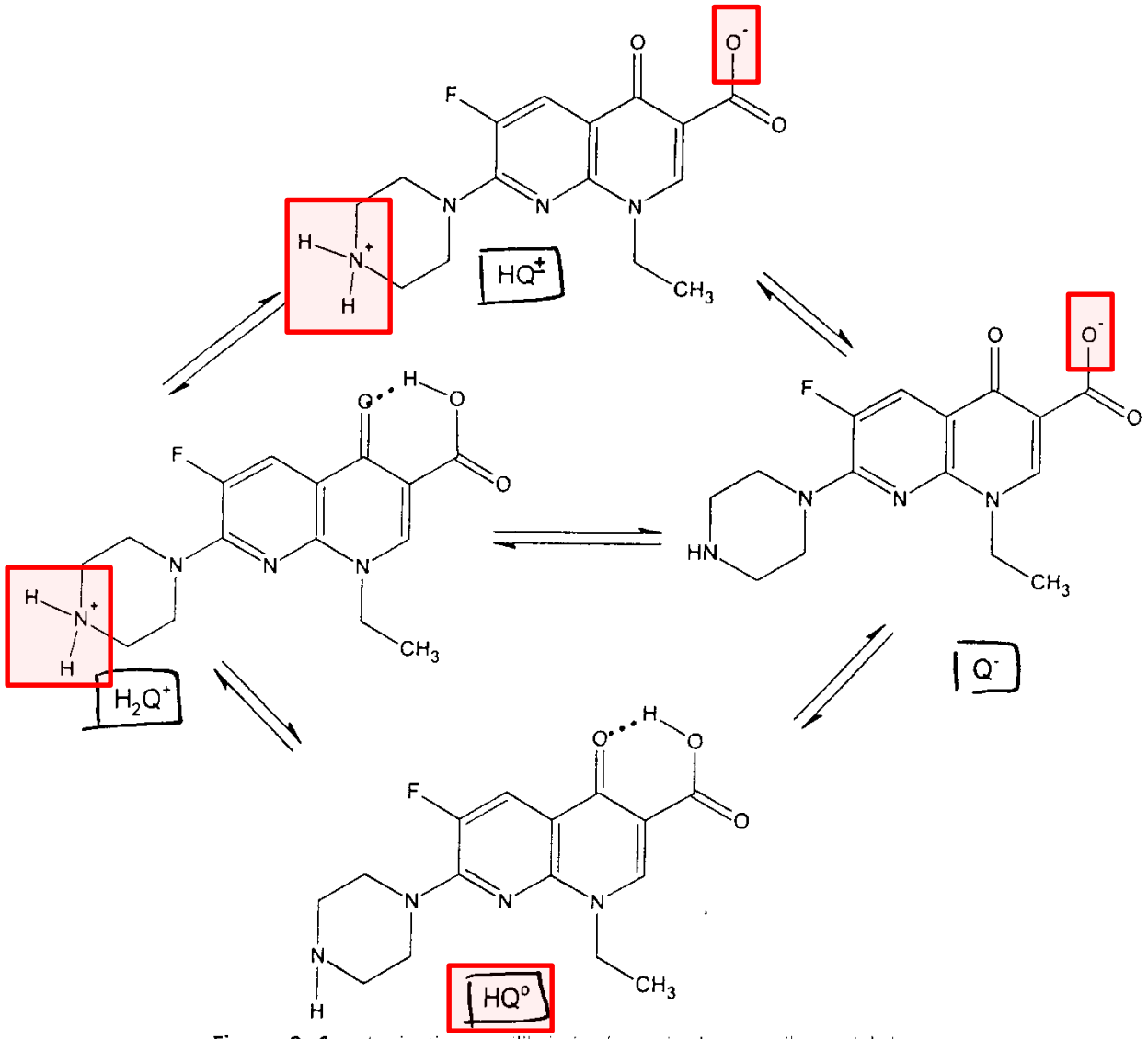


Figure 8–6 ■ Ionization equilibria in the quinolone antibacterial drugs.

Pka_1=5.6-6.4

pka_2=8.1-9.3

PK Properties of FQs

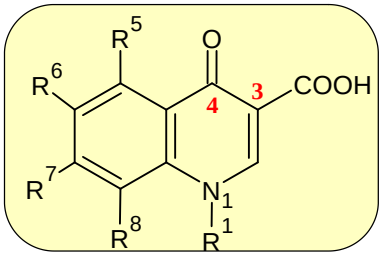


Table 29.2 Pharmacokinetic Properties for Select Quinolones

Drug	Bioavailability (%)	Protein Binding (%)	Half-Life (hr)
Ciprofloxacin	70	30	3.5
Norfloxacin	30-40	10-15	3-4
Enoxacin	90	40	3-6
Levofloxacin	99	31	6.9
Gatifloxacin	96	20	8.0
Gemifloxacin	71	60-70	8.0
Delafloxacin	59	84	8.0
Ofloxacin	98	32	9
Moxifloxacin	86	47	12.1

Generations of Flouroquinolones

- 1st: nalidixic acid; cinoxacin
- 2nd:ciprofloxacin; norfloxacin
- 3rd: ofloxacin; levofloxacin; gatifloxacin; gemifloxacin
-
- 4th: moxifloxacin; delafloxacin

Types of Fluoroquinolones in Clinic

- Systemic:

✓ Ciprofloxacin; ofloxacin; levofloxacin; gemifloxacin; moxifloxacin

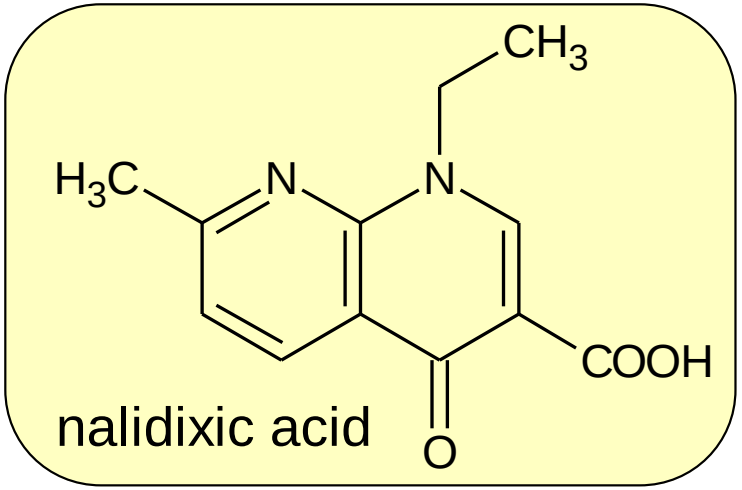
- Ophthalmic use:

✓ Ciprofolxacin; ofloxacin; levofloxacin; besifloxacin; gatifloxacin; moxifloxacin

- Topical otic: finafloxacin, ciprofloxacin, ofloxacin

Quinolones: 1st Generation

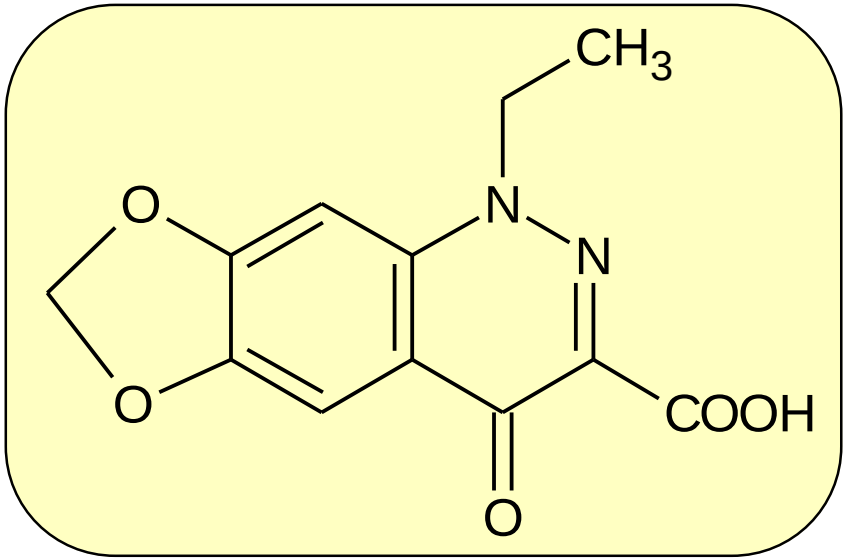
- Nalidixic acid: since 1965
- Chemistry: 1,8-Naphthyridine-3-carboxylic acid
- In UTI
- Active metabolite



nalidixic acid

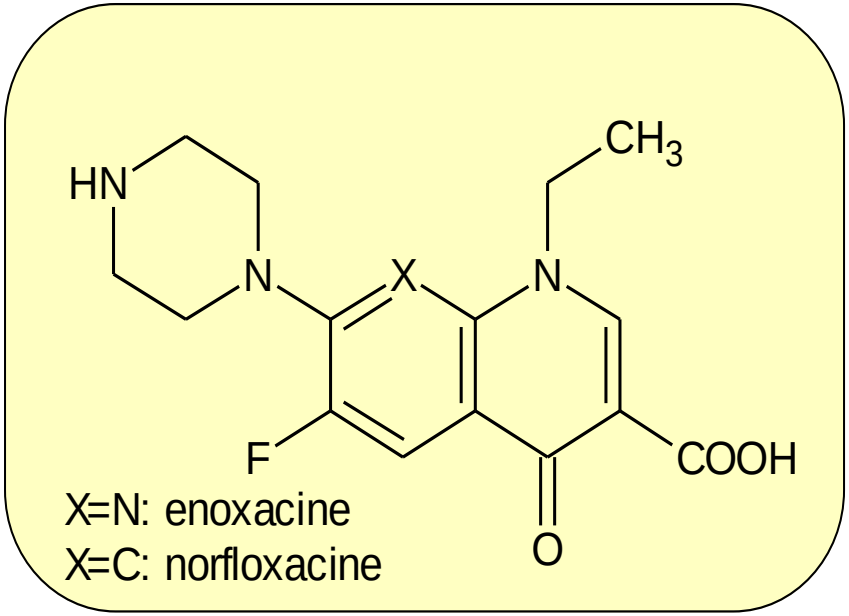
Quinolones: 1st Generation

- Cinoxacin
- Chemistry: cinnoline-3-carboxylic acid
- In UTI



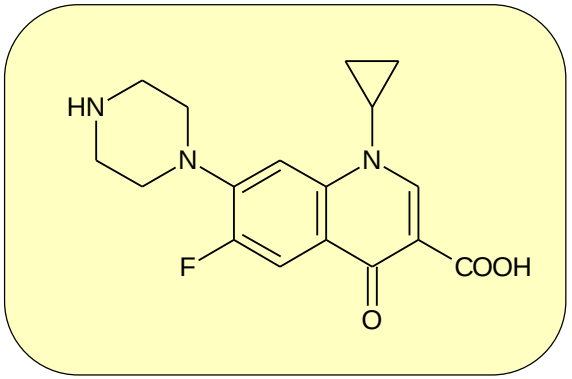
Fluoro-Quinolones: 2nd Generation

- Follow SAR in this generation of FQs.
- Broad spectrum



Fluoro-Quinolones: 2nd Generation

- Ciprofloxacin
- Follow SAR in this FQ.
- IUPAC name:



1-cyclopropyl-6-fluoro-1,4-dihydro-
4-oxo-7-(1-piperazinyl)-quinoline -3-caroboxylic acid

- Clinical applications:

✓ UTI

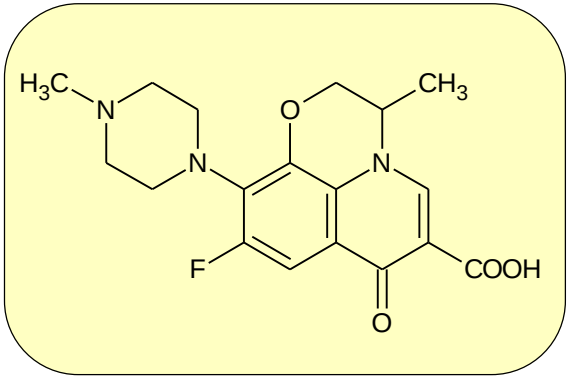
✓ agent of choice in gastroenteritis caused by *E. coli*; *salmonella* & *shigella* spp.

✓ widely used in respiratory tract infections

✓ in combination therapy

Fluoro-Quinolones: 2nd Generation

- Ofloxacin
- Follow SAR in this FQ.
- Chemistry: FQ possessing third ring
- Stereochemistry points: C3’:



✓ S isomer is 8-128 times more potent than R isomer: levofloxacin

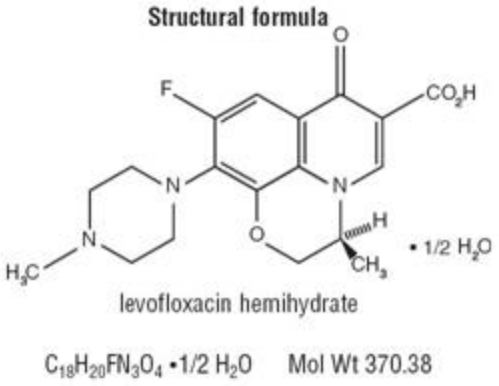
- Similar to ciprofloxacine in potency & spectrum of effect
- Distribution to CSF more than ciprofloxacine

- Clinical applications: in lower respiratory tract infections in pelvic inflammatory

OfloxacinFluoro-Quinolones: 3rd Generation: Levofloxacin

Follow SAR in this FQ.

- What is advantage to ofloxacin?



Fluoro-Quinolones: 3rd and 4th Generations: Newer Fluoroquinolones

- Increase potency and spectrum:

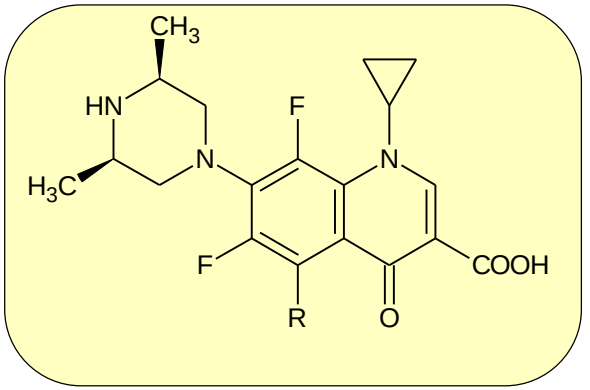
against anaerobic bacteria;

especially obligatory anaerobic: chlostridium and bactroides

- Increase half life
- alter moieties which are responsible for side effect

✓ alkyloxime group on C7-saturated heterocycle

Fluoro-Quinolones: Sparfloxacin



- Diflourinated quinolone
- Follow SAR in this FQ.

- Advantages & side effects: ?
- Clinical applications: against G^+ (strep. & staph.)

✓ in lower respiratory infections

✓ in pelvic inflammatory

✓ in bacterial gastroenteritis