Pharmaceutical chemistry
Antibacterial Antibiotics
Synthetic antibacterial agents quinolones, Aminoacridines, Rifamycins, Nitroimidazoles and nitrofurantoin

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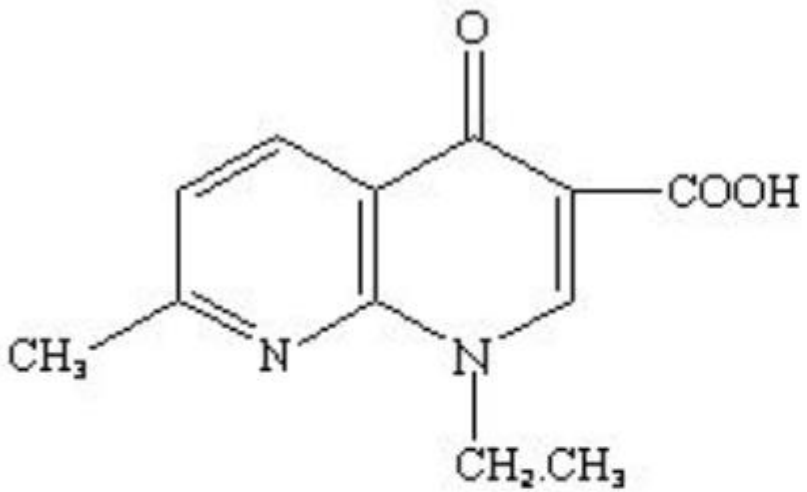
Quinolones

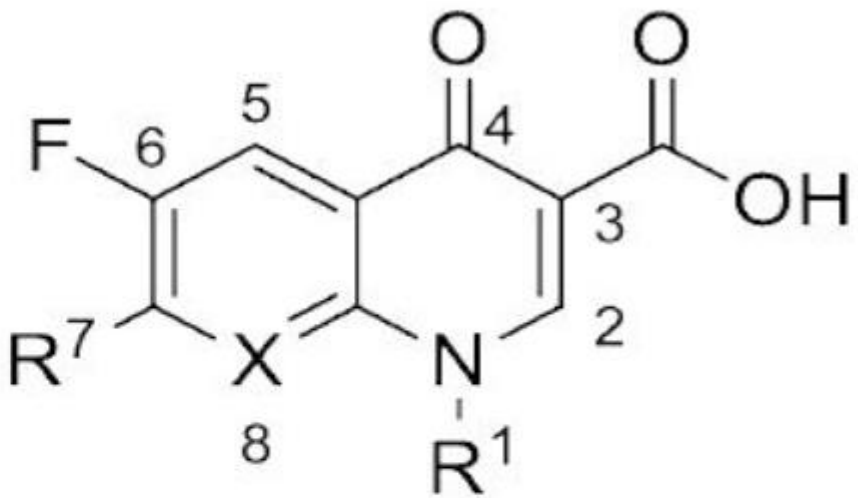
- The quinolones comprise a series of synthetic antibacterial agents patterned after nalidixic acid, a naphthyridine derivative introduced in 1963.
- Isosteric heterocyclic groupings in this class include the quinolones (e.g., norfloxacin, ciprofloxacin, lomefloxacin), the naphthyridines (e.g., nalidixic acid, enoxacin), and the cinnolines (e.g., cinoxacin).

Quinolones



Parent drug: nalidixic acid

Naphthyridine derivative



Quinolones

and fluoroquinolones

quinine derivative

Classification

- Quinolones (1st generation)

✓Highly protein bound

✓Mostly used in UTIs

- Fluoroquinolones (2nd, 3rd and 4th generation)

✓Modified 1st generation quinolones

✓Not highly protein bound

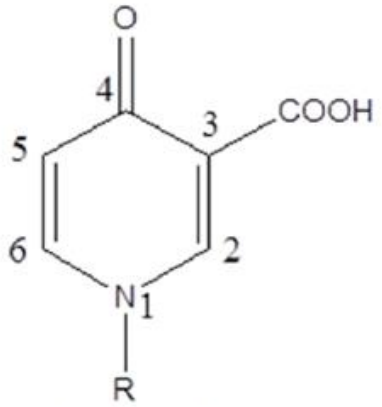
✓Wide distribution to urine and other tissues; limited CSF penetration.

Generation	Drug Names	Spectrum
1st	nalidixic acid cinoxacin	Gram- but not Pseudomonas species
2nd	norfloxacin ciprofloxacin enoxacin ofloxacin	Gram- (including Pseudomonas species), some Gram+ (S. aureus) and some atypicals
3rd	levofloxacin sparfloxacin moxifloxacin gemifloxacin	Same as 2nd generation with extended Gram+ and atypical coverage
4th	*trovafloxacin	Same as 3rd generation with broad anaerobic coverage

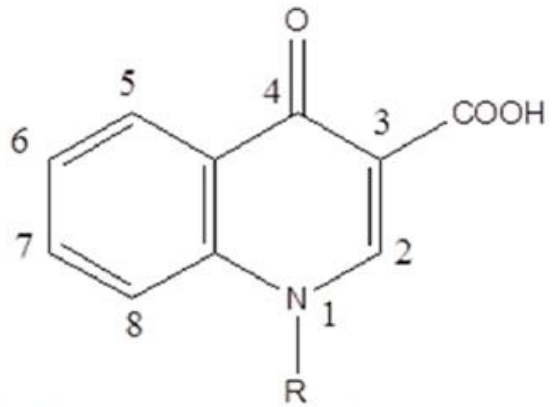
Structure–activity studies

- Structure–activity studies have shown that :

1. The 1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety is essential for antibacterial activity. The pyridone system must be annulated with an aromatic ring.

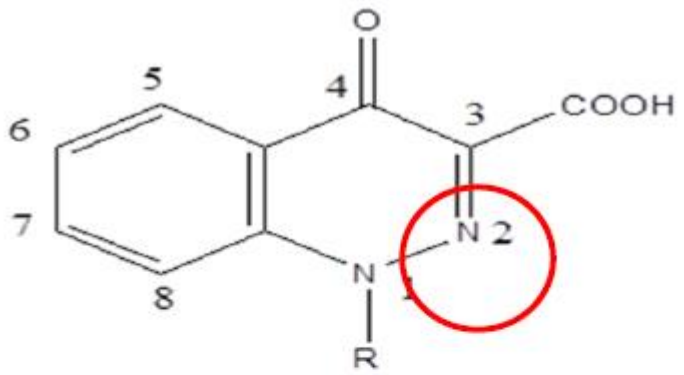


Substituted 1,4-dihydro-4-oxo-3-pyridinecarboxylic acid

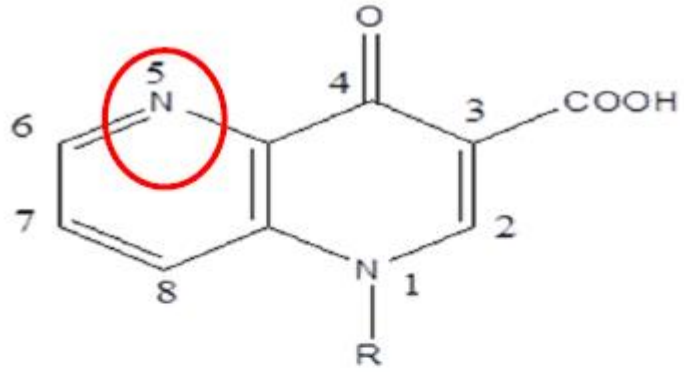


Substituted quinolone 3-carboxylic acid

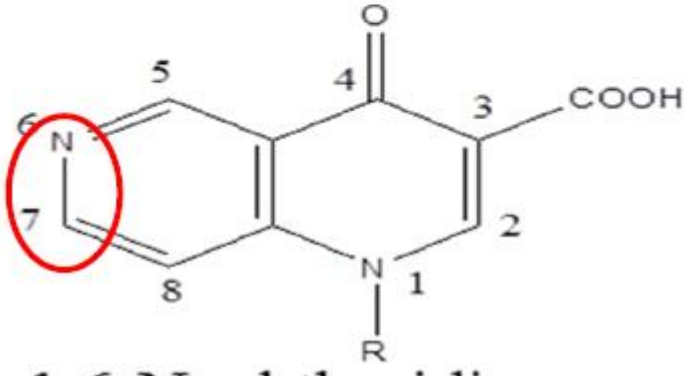
2. Isosteric replacements of nitrogen for carbon atoms at positions 2 (cinnolines), 5 (1,5-napthyridines), 6 (1,6-naphthyridines), and 8 (1,8-naphthyridines) are consistent with retention of antibacterial activity.



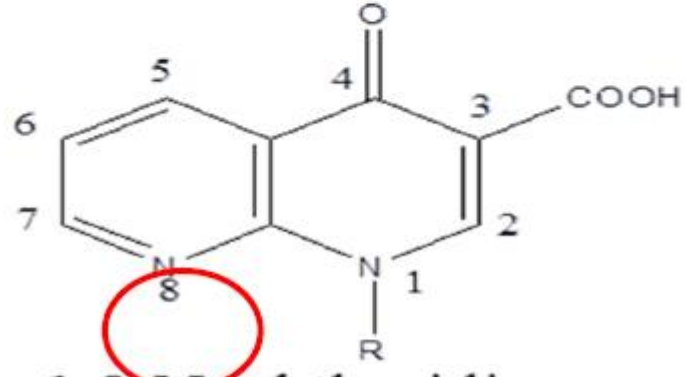
Cinnolines



1,5-Naphthyridines



1,6-Naphthyridines

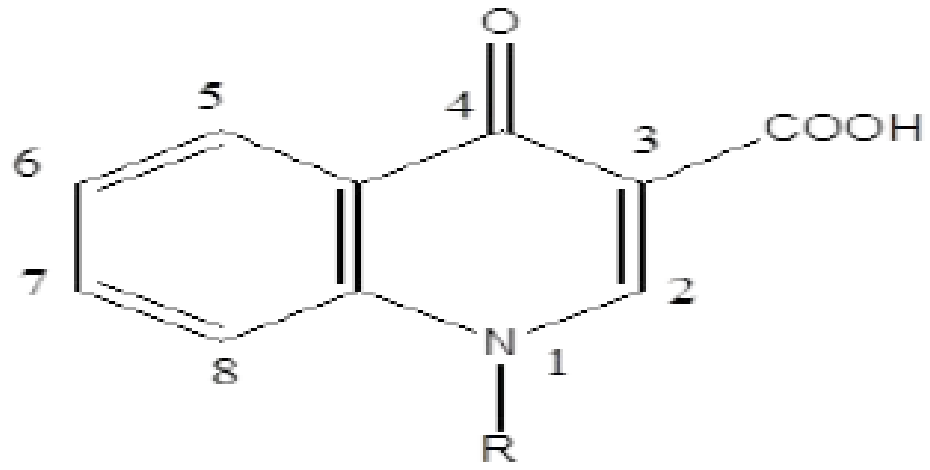


1,8-Naphthyridines

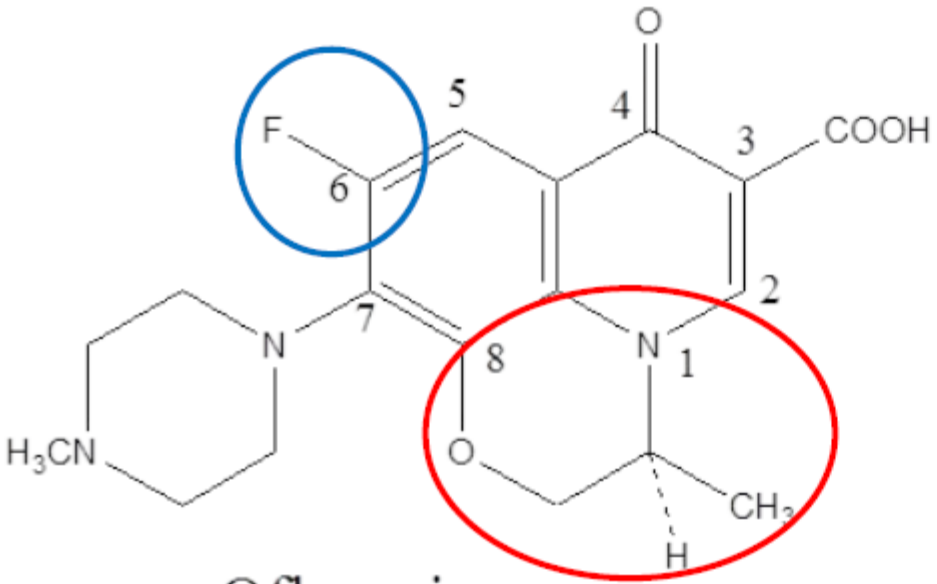
3. substituents at position 2 greatly reduces or abolishes activity,

4. Positions 5, 6, 7(especially), and 8 of the annulated ring may be substituted with good effects. For example, piperazinyl and 3-aminopyrrolidinyl

5. substitutions at position 7 have been shown to convey enhanced activity on members of the quinolone class against P. aeruginosa.



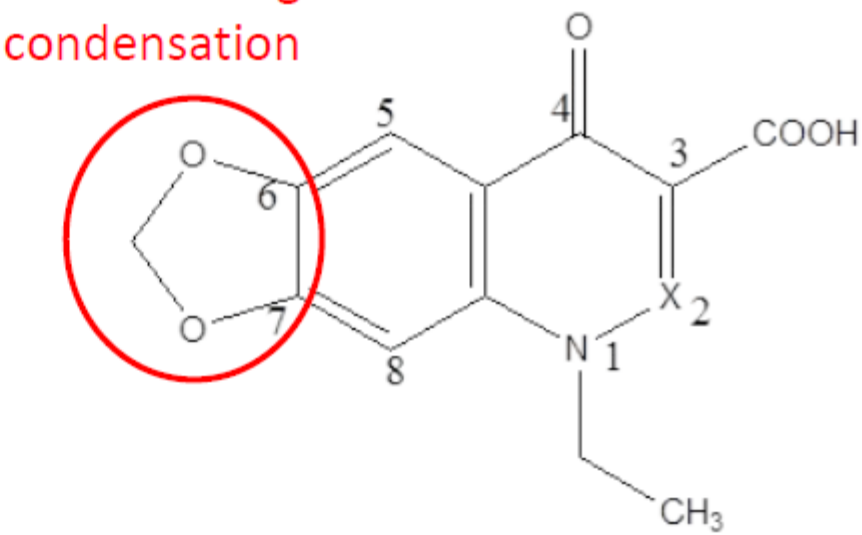
6. Fluorine atom substitution at position 6 is also associated with significantly enhanced antibacterial activity.



Ofloxacin
Levofloxacin (-)S

Ring condensation

Ring condensation



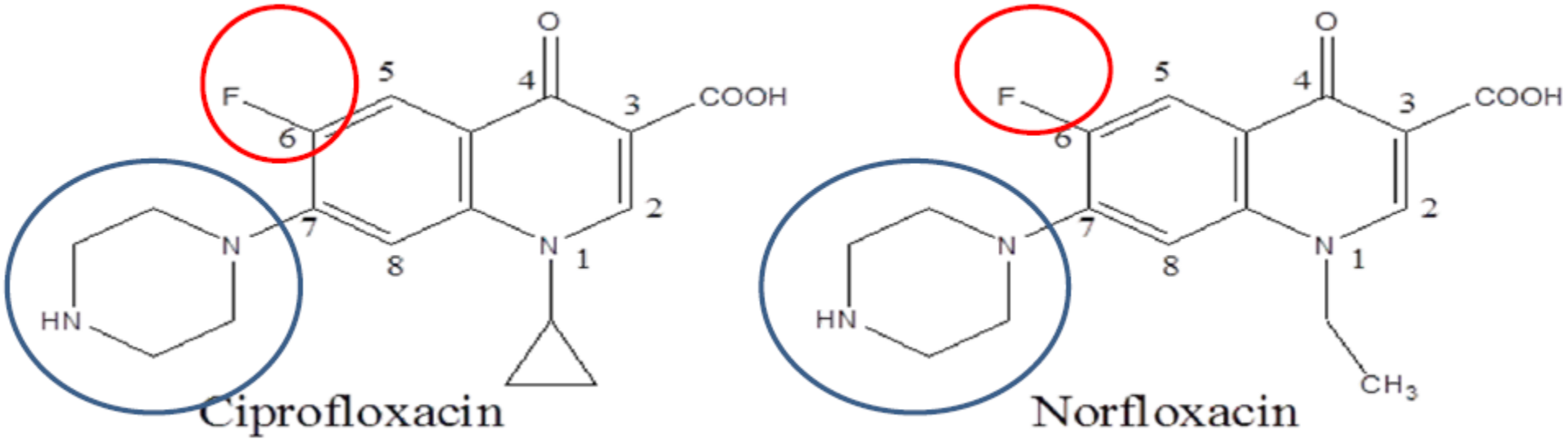
X: N = Cinoxacin
X: CH = Oxolinic acid

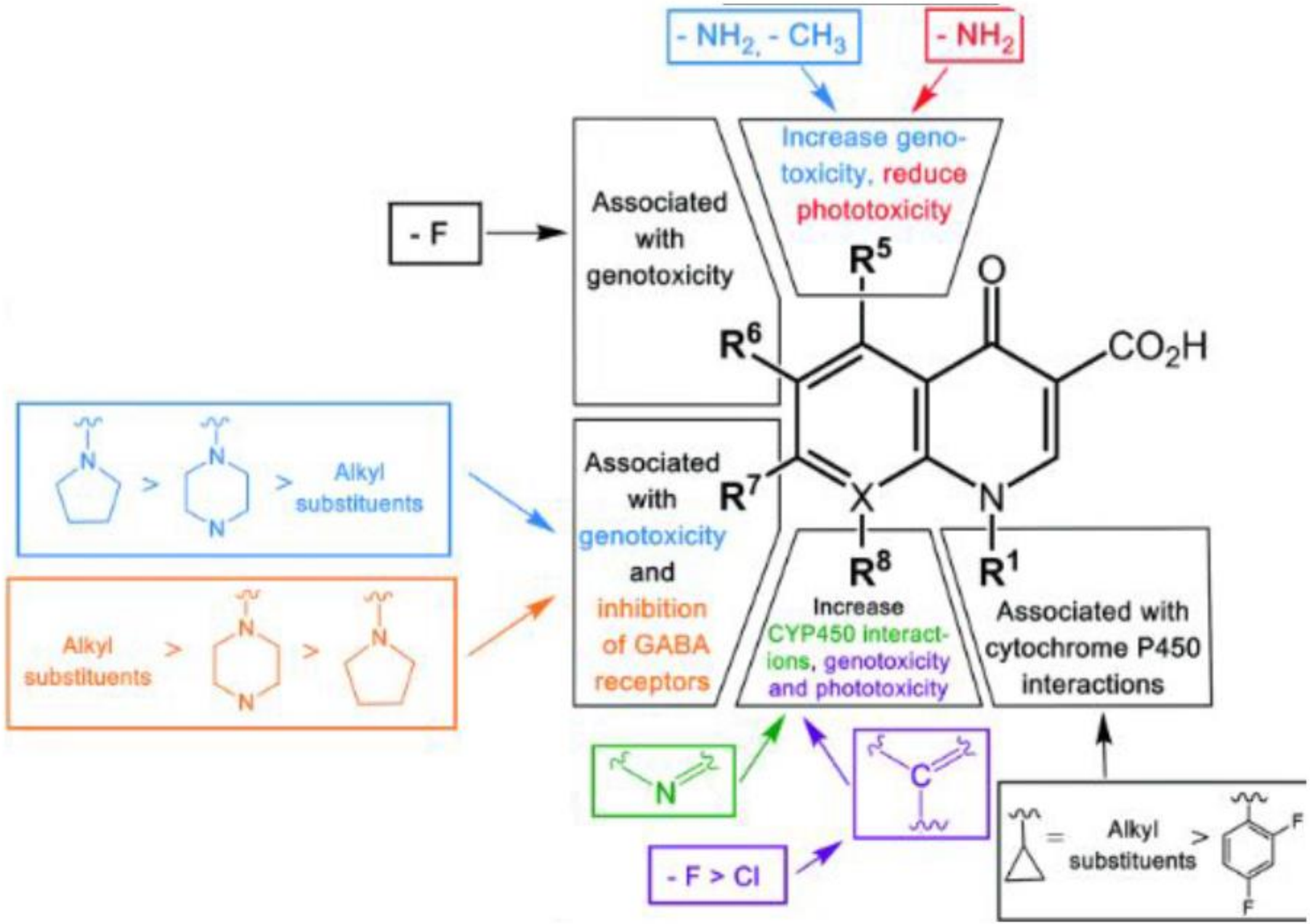
7. Alkyl substitution at the 1-position is essential for activity, with lower alkyl (methyl, ethyl, cyclopropyl) compounds generally having progressively greater potency.

8. Aryl substitution at the 1-position is also consistent with antibacterial activity, with a 2,4-difluorophenyl group providing optimal potency.

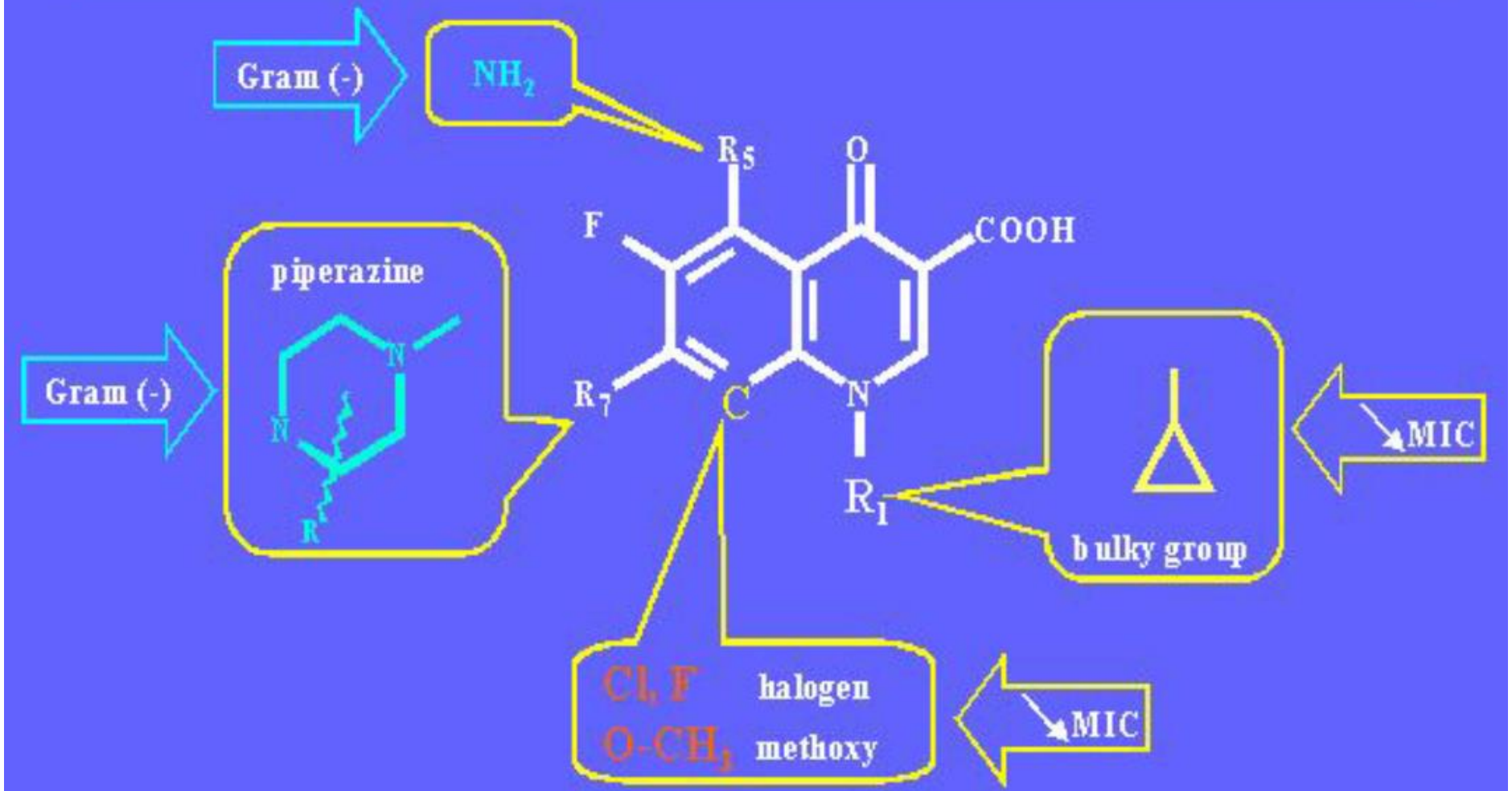
9. Ring condensations at the 1,8-, 5,6-, 6,7-, and 7,8-positions also lead to active compounds.

10. Newer members of the class possessing 6-fluoro and 7-piperazinyl substituents exhibit an extended spectrum of activity that includes effectiveness against additional Gram-negative pathogens

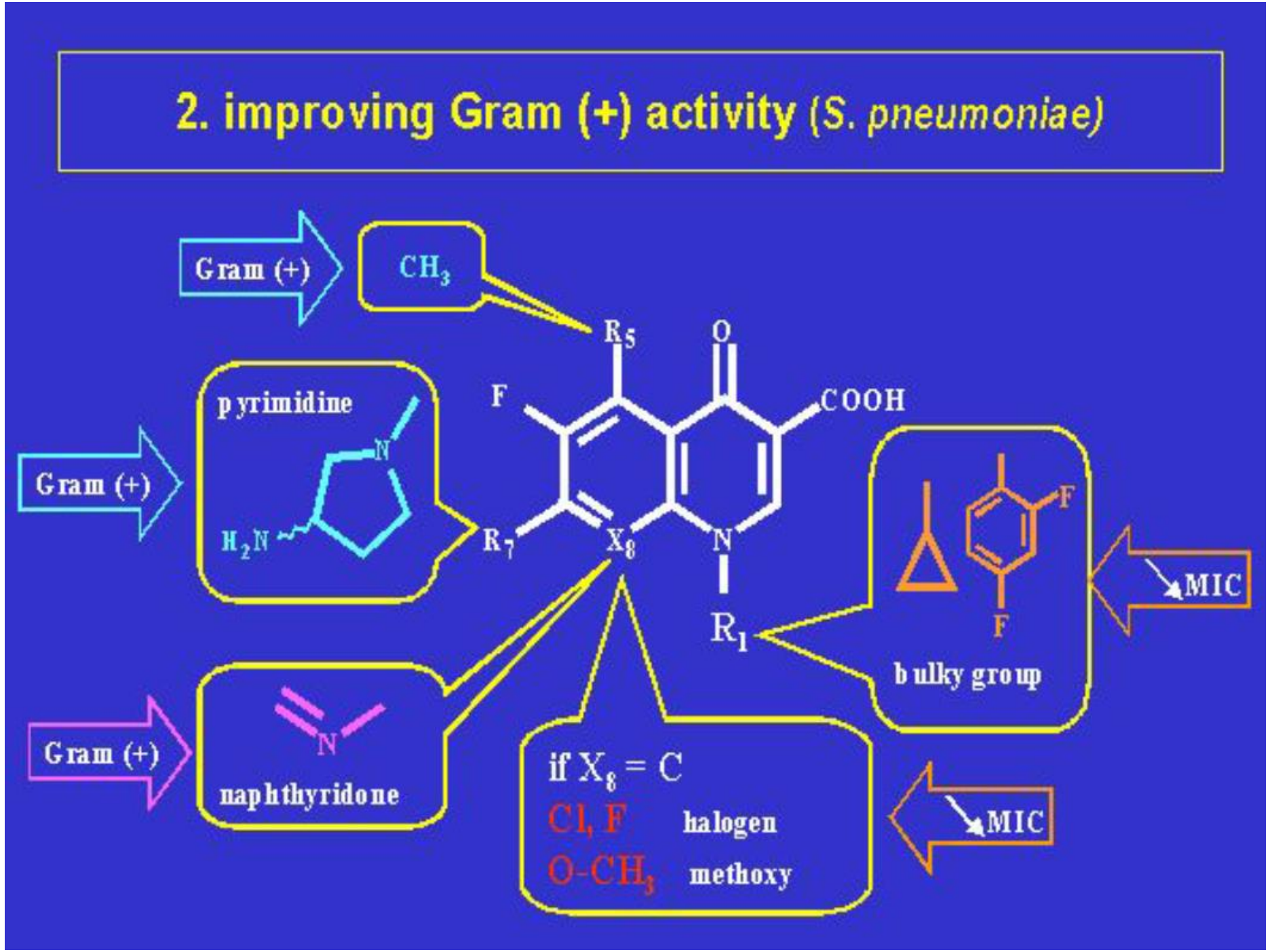



- NH2, - CH3
- NH2
Increase geno-toxicity, reduce phototoxicity
- F
Associated with genotoxicity
R5
R6
O
CO2H
R7
X
N
R8
R1
Alkyl substituents
Associated with genotoxicity and inhibition of GABA receptors
Increase CYP450 interact-ions, genotoxicity and phototoxicity
Associated with cytochrome P450 interactions
Alkyl substituents
- F > Cl
F
F

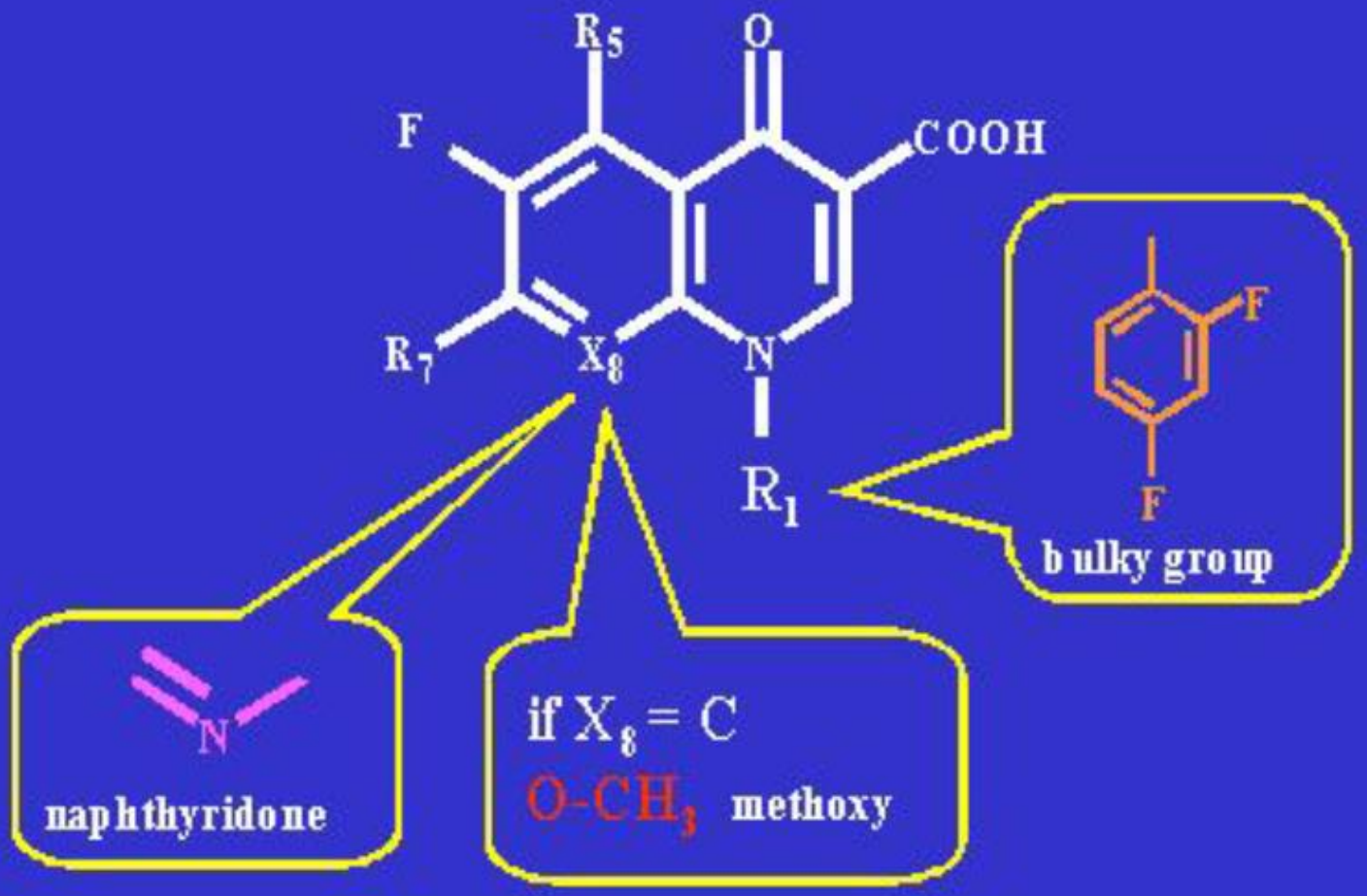
1. maintenance of anti - Gram (-) activity

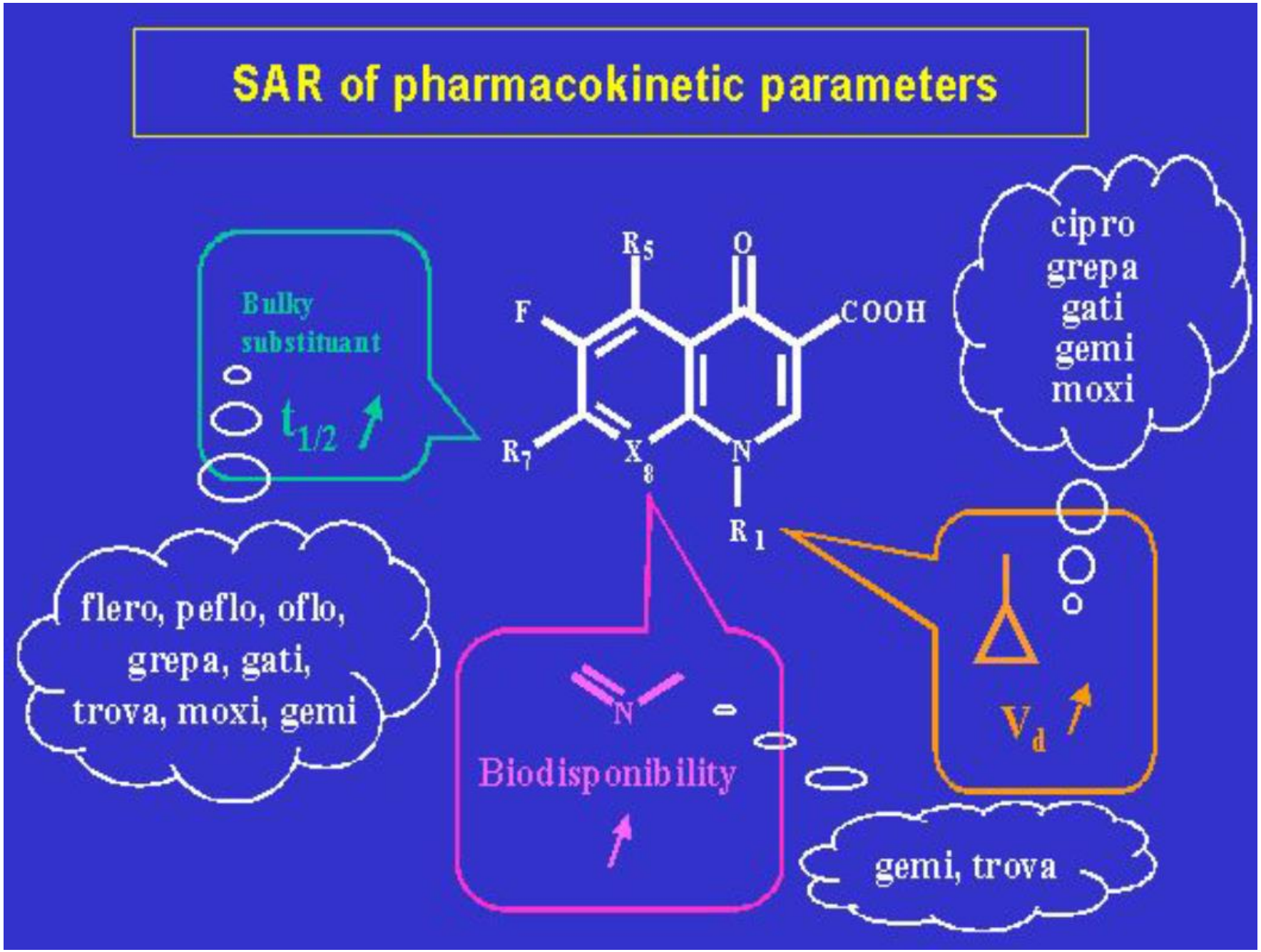


2. improving Gram (+) activity (*S. pneumoniae*)

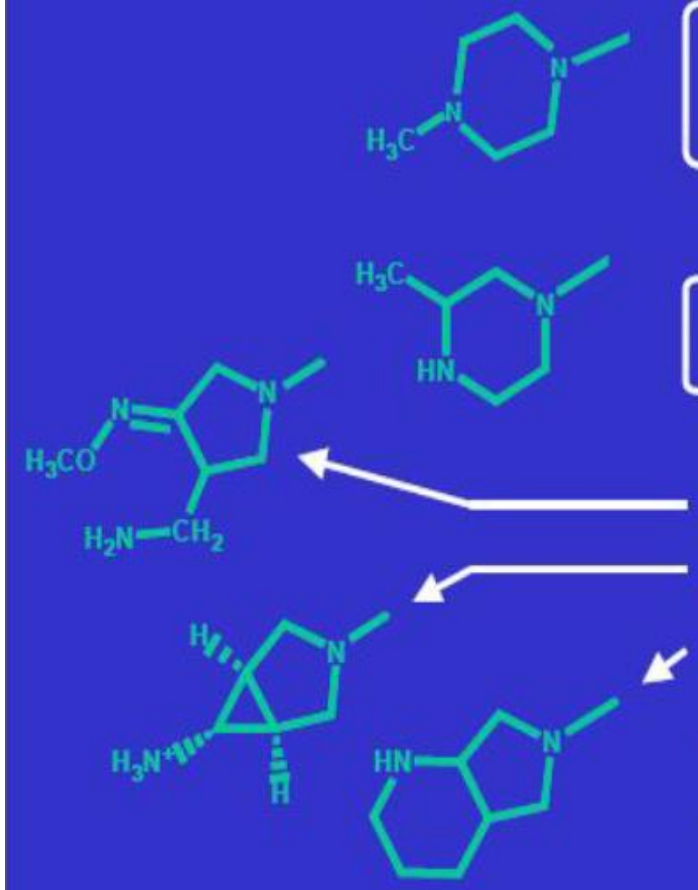


3. obtaining activity against anaerobes ...




SAR of pharmacokinetic parameters
Bulky substituant
$t_{1/2}$
cipro
grepa
gati
gemi
moxi
flero, peflo, oflo,
grepa, gati,
trova, moxi, gemi
Biodisponibility
V_d
gemi, trova

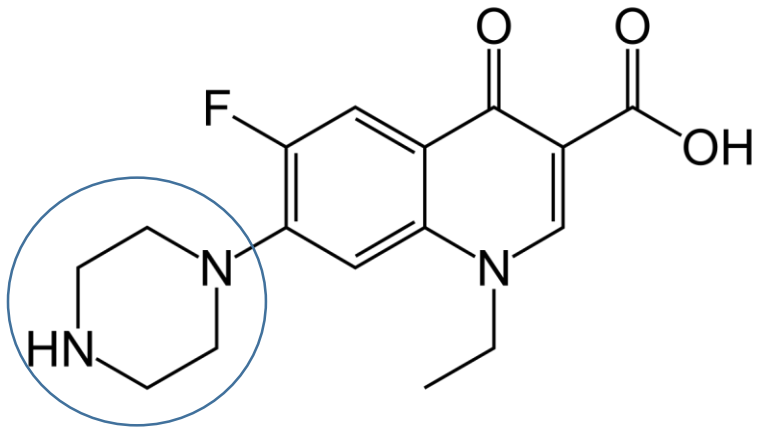
SAR of main pharmacokinetic parameters:
how to get a long half life



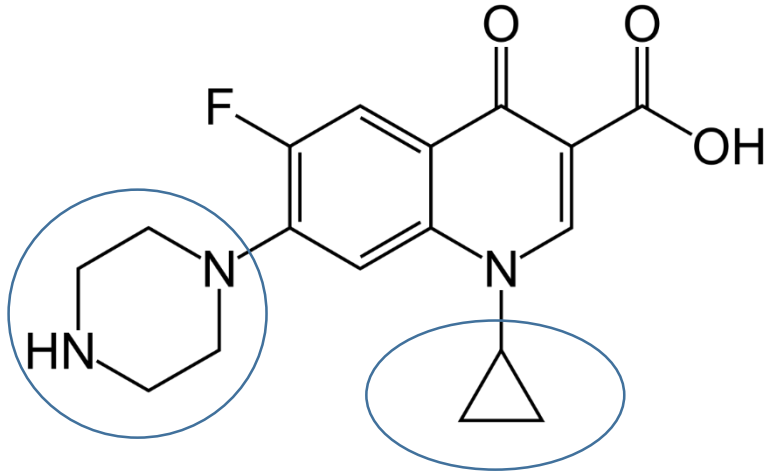
	$t_{1/2}$ (h)	no. of daily administrations
oflo	5 - 7	2 x*
peflo	10	2 x*
flero	9 - 13	1 x
grepa	10 - 12	1 x
gati	13	1 x
gemi	8	1 x
trova	10	1 x
moxi	12	1 x
other FQ	3 - 6	2 x

* higher MIC...

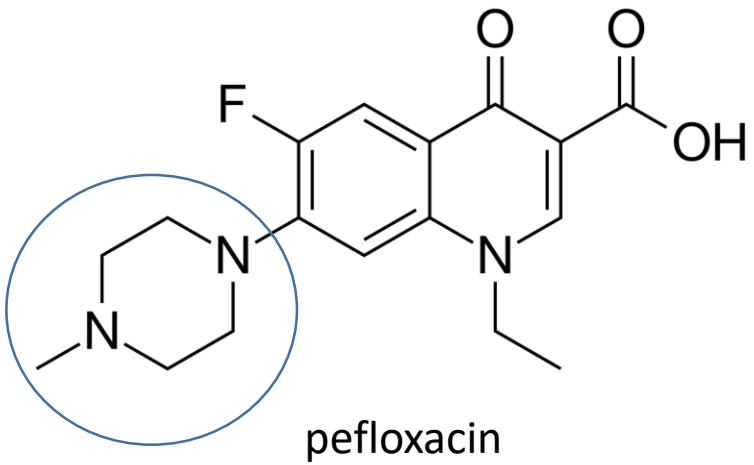
First Generation Fluoroquinolones



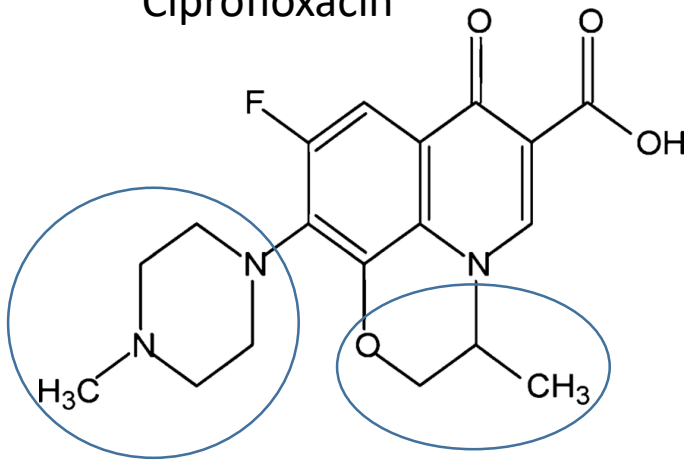
Norfloxacin



Ciprofloxacin



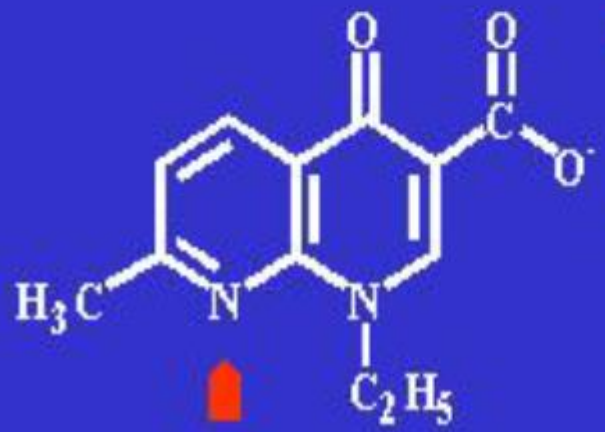
pefloxacin



Ofloxacin

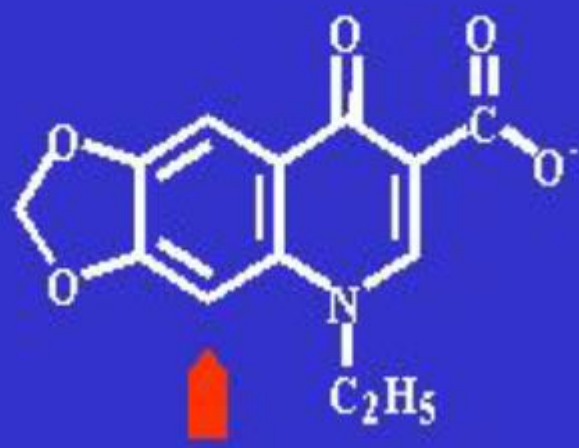
From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



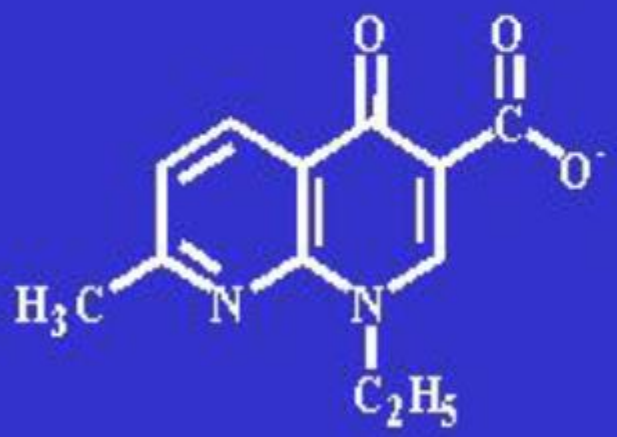
1. modify naphthyridone into quinolone

oxolinic acid *



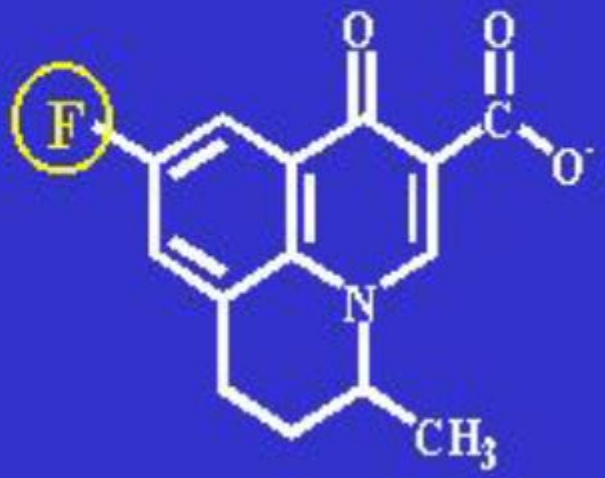
From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



2. discovery of flumequine *

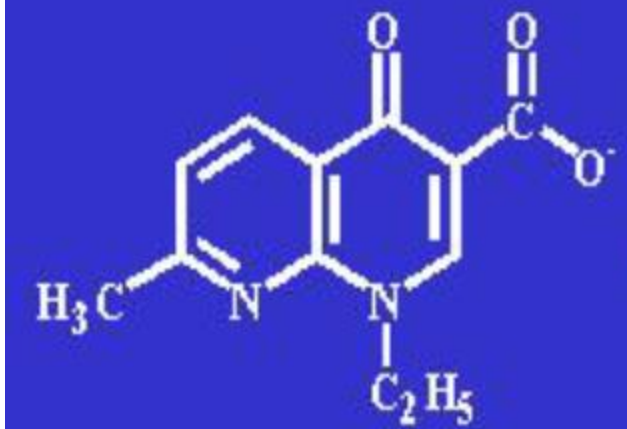
flumequine *



shows weak but broad Gram(-) activity

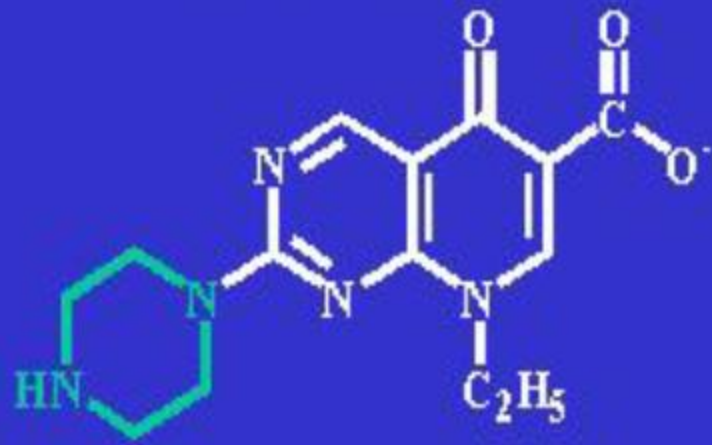
From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



3. introduce a piperazine *

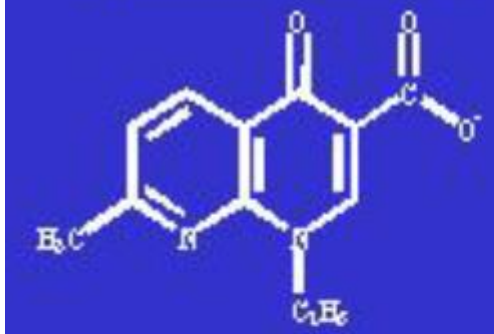
pipemidic acid *



shows longer half-life...

From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



combine all 3 features *...

1978

norfloxacin *

broader Gram(-) activity
less protein binding (50%)
longer half-life (3-4h)

From norfloxacin to the other 1st generation fluoroquinolones: pefloxacin

norfloxacin

Add a methyl to still increase half-life

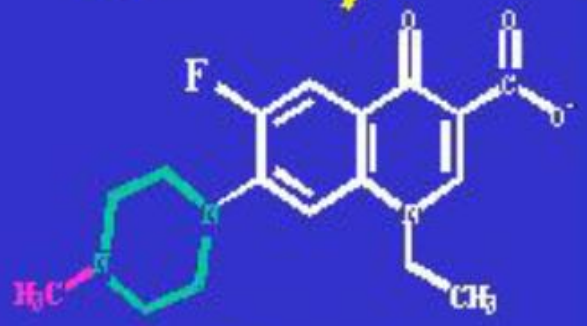
pefloxacin *

* Ger. pat. 2,840,910 to Roger Bellon/Dainippon, 1979

From norfloxacin to the other 1st generation fluoroquinolones: ofloxacin

norfloxacin

tricyclic compound
(as in flumequine but
morpholine ring)



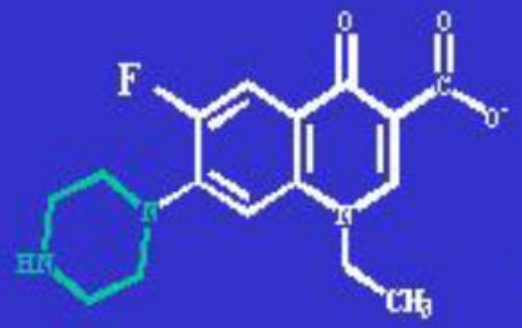
pefloxacin

ofloxacin *

* Eur. pat. App1. 47,005 to Daiichi, 1982

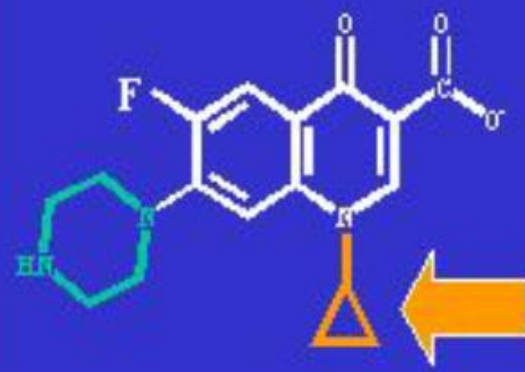
From norfloxacin to the other 1st generation fluoroquinolones: ciprofloxacin

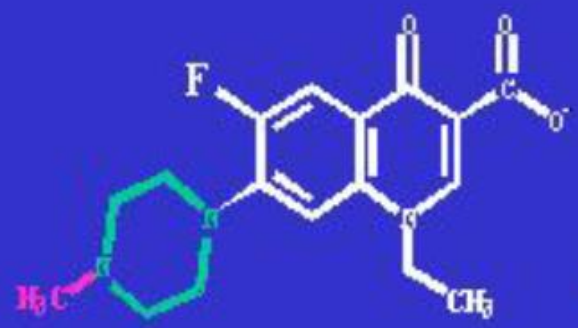
norfloxacin



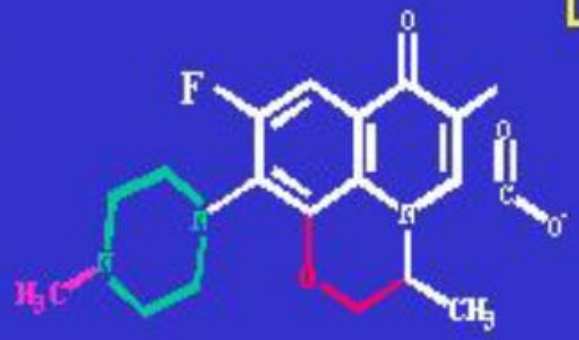
cyclopropyl to increase potency

ciprofloxacin *





pefloxacin

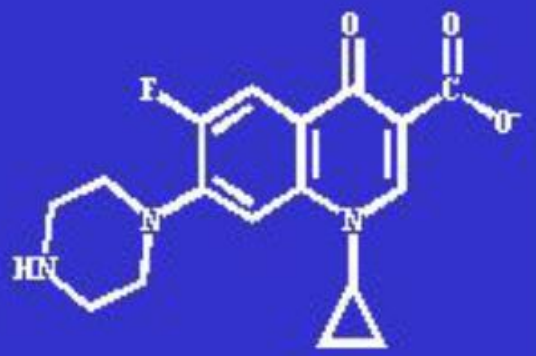


ofloxacin

* Ger. pat. 3,142,854 to Bayer AG, 1983

Fluoroquinolones with a C8-methoxy

I



ciprofloxacin

II

gatifloxacin

III

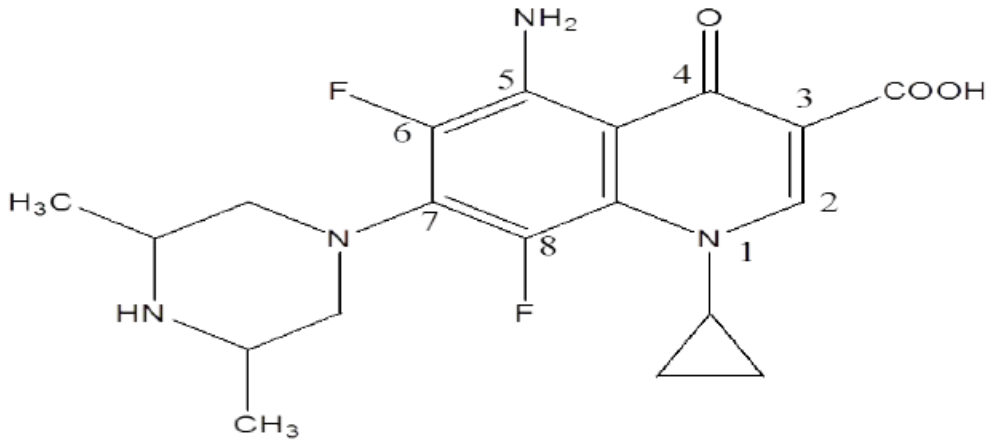
moxifloxacin

Second generation fluoroquinolone

- Ciprofloxacin is differentiated from the quinolone class of antibiotics by the fluorinated carbon atom located at C6 in the aromatic ring. This substitution helps increase the specificity of the drug for topoisomerase by a factor of ten.

Third Generation

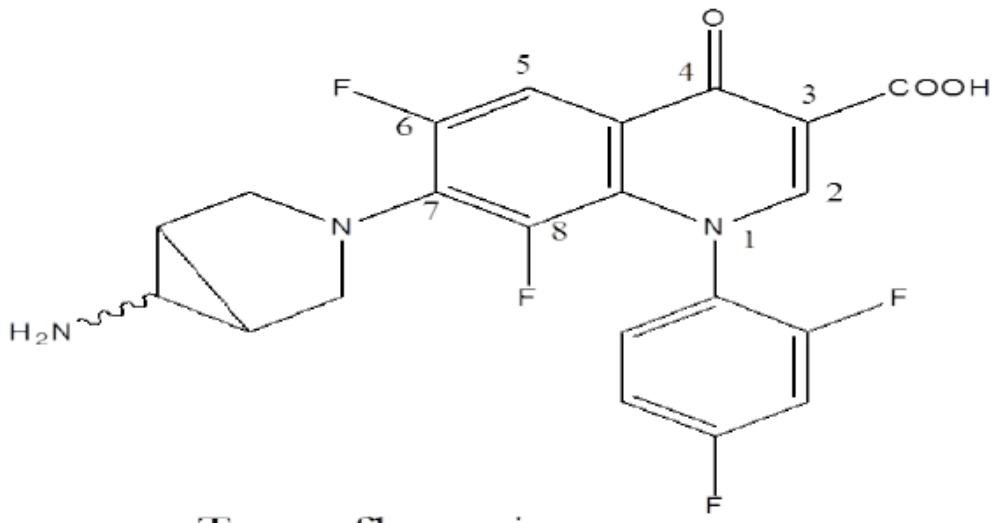
- Sparfloxacin is a fluoroquinolone antibiotic used in the treatment of bacterial infections.
- It has a controversial safety profile. It was patented in 1985 and approved for medical use in 1993. Zagam is no longer available in the United States.



Sparfloxacin

Fourth Generation

- Trovafloxacin is a broad spectrum antibiotic. It was withdrawn from the market due to the risk of hepatotoxicity. It had better Gram-positive bacterial coverage and less Gram-negative coverage than the previous fluoroquinolones.



Trovafloxacin

Mechanism of action

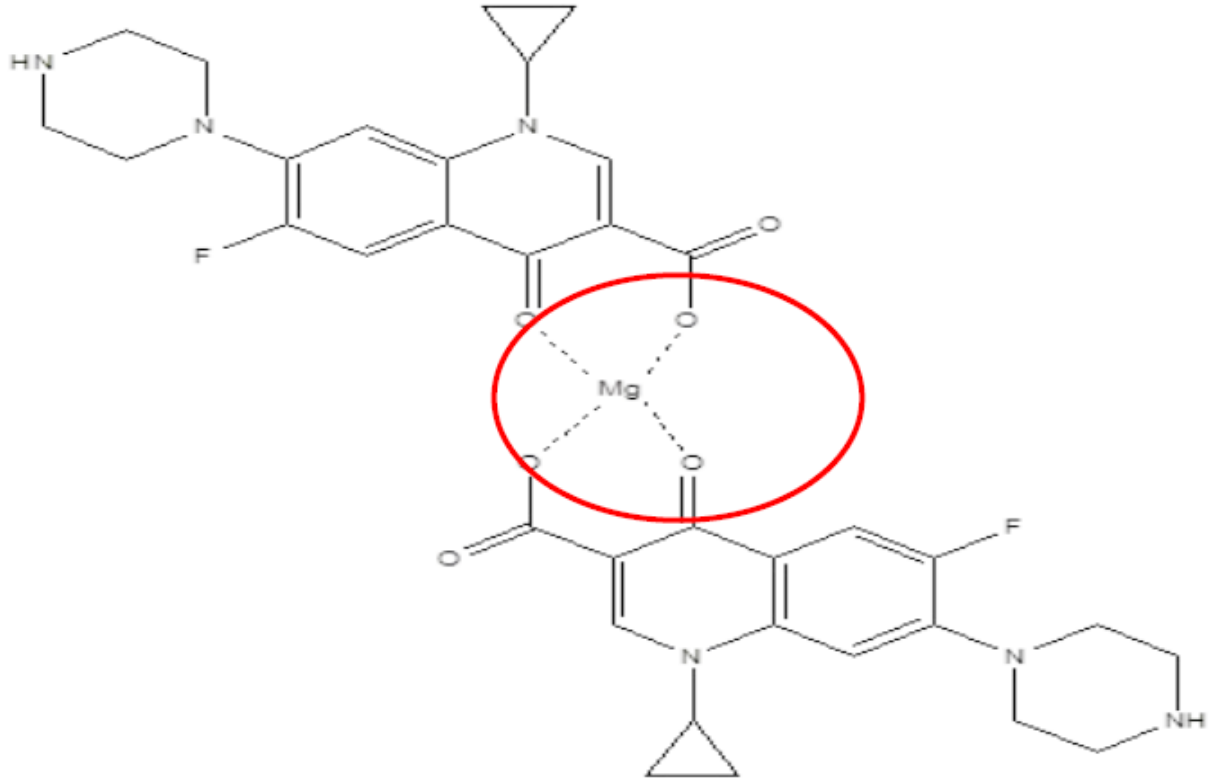
- The bactericidal action of nalidixic acid and its congeners is known to result from the inhibition of DNA synthesis. This effect is believed to be caused by the inhibition of bacterial DNA gyrase (topoisomerase II), an enzyme responsible for introducing negative supercoils into circular duplex DNA.
- The highly polar quinolones are believed to enter bacterial cells through densely charged porin channels in the outer bacterial membrane. Mutations leading to altered porin proteins can lead to decreased uptake of quinolones and cause resistance.

- The antibacterial quinolones can be divided into two classes on the basis of their dissociation properties in physiologically relevant conditions.
- The first class, represented by nalidixic acid, oxolinic acid and cinoxacin, possesses only the 3-carboxylic acid group as an ionizable functionality. The pKa values for the 3-carboxyl group in nalidixic acid and other quinolone antibacterial drugs fall in the range of 5.6 to 6.4
- These comparatively high pKa values relative to the pKa of 4.2 for benzoic acid are attributed to the acid weakening effect of hydrogen bonding of the 3-carboxyl group to the adjacent 4-carbonyl group.

- The second class of antibacterial quinolones embraces the broad-spectrum fluoroquinolones (namely, norfloxacin, enoxacin, ciprofloxacin, ofloxacin, lomefloxacin, and sparfloxacin), all of which possess, in addition to the 3-carboxylic acid group, a basic piperazino functionality at the 7- position and a 6-fluoro substituent. The pKa values for the more basic nitrogen atom of the piperazino group fall in the range of 8.1 to 9.3

- The excellent chelating properties of the quinolones provide the basis for their incompatibility with antacids, hematinics, and mineral supplements containing divalent or trivalent metals.
- The quinolones may form chelates with metal ions such as Ca2, Mg2, Zn2, Fe2, Fe3, and Bi3.

How fluoroquinolones cause metal complexation

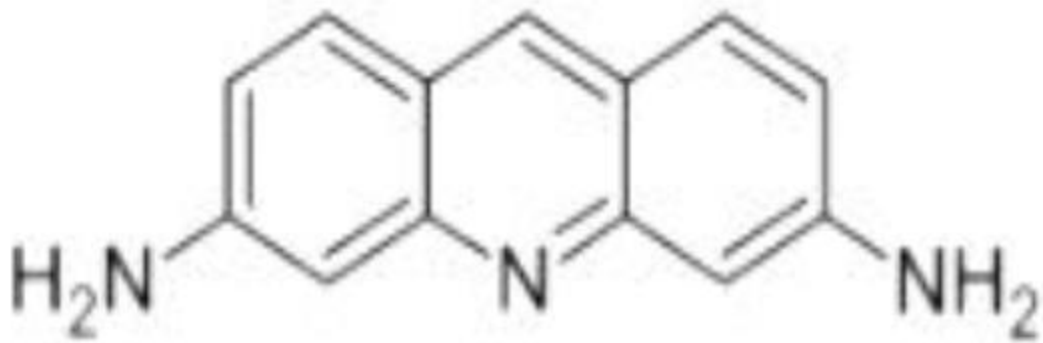


- This occurs with cations such as Ca2+, Zn2+, Fe2+, Fe3+, Bi3+. That's why there is an interaction between quinolones and mineral containing drugs.

Aminoacridines

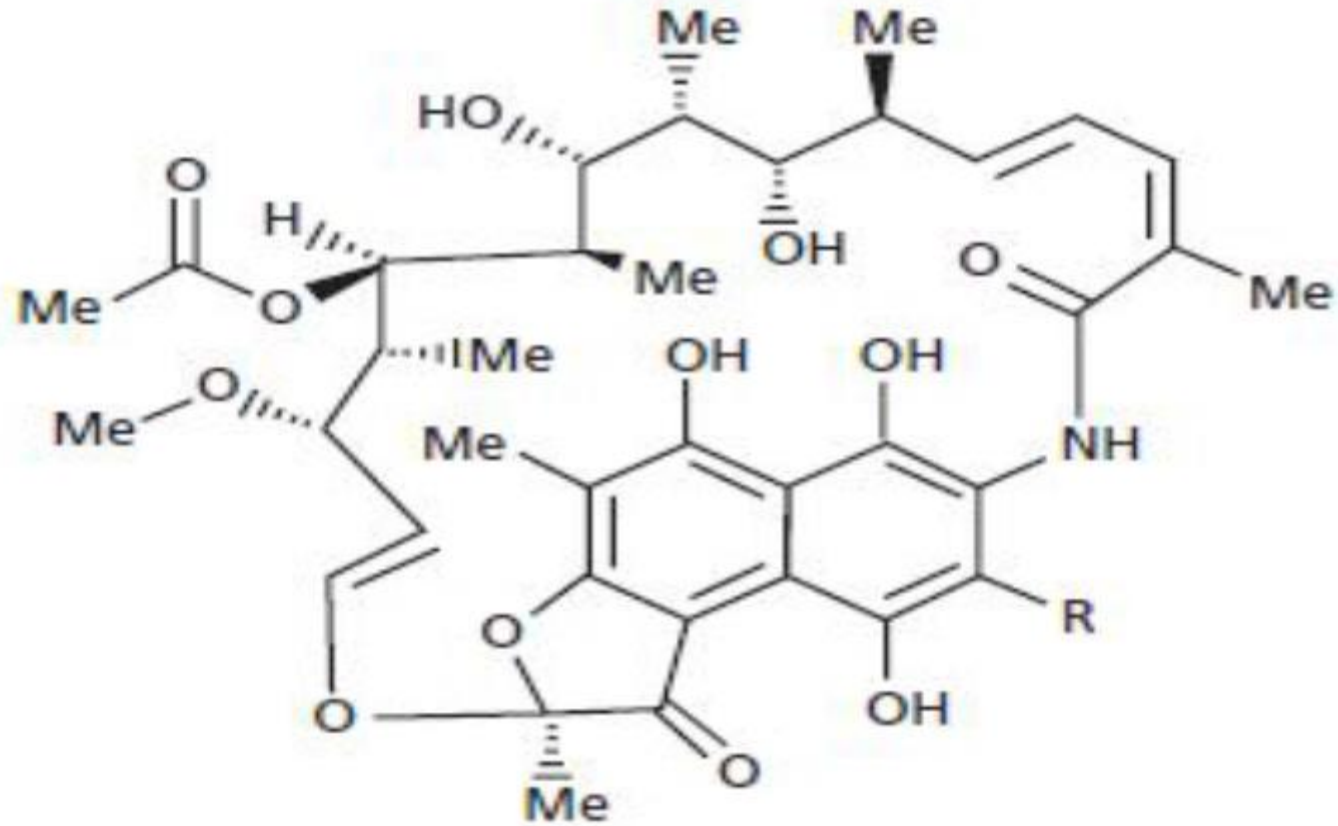
- Aminoacridine agents, such as the yellow-coloured proflavine , are topical antibacterial agents which were used particularly during World War II to treat deep surface wounds.
- The best agents are completely ionized at pH 7 and they interact directly with bacterial DNA by intercalation. Proflavine, also called diaminoacridine, a disinfectant bacteriostatic against many gram-positive bacteria.
- It has been used in the form of the dihydrochloride and hemisulfate salts as a topical antiseptic, and was formerly used as a urinary antiseptic.

Proflavine

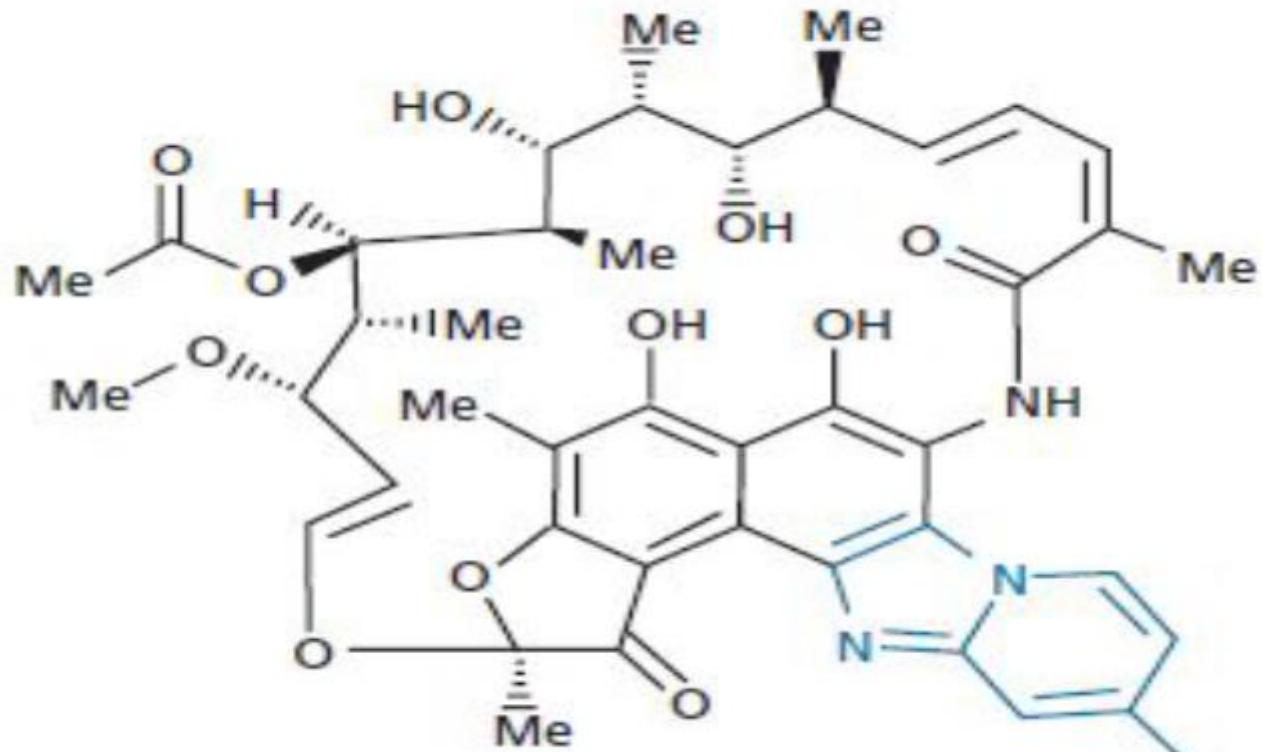


Rifamycins

- Rifampicin is a semi-synthetic rifamycin made from rifamycin B —an antibiotic which was isolated from Streptomyces in 1957.
- It inhibits Gram-positive bacteria and works by binding non-covalently to DNA-dependent RNA polymerase and inhibiting the start of RNA synthesis.
- The DNA-dependent RNA polymerases in eukaryotic cells are unaffected because the drug binds to a peptide chain not present in the mammalian RNA polymerase. It is, therefore, highly selective.
- The flat naphthalene ring and several of the hydroxyl groups are essential for activity and the molecule exists as a zwitterion, giving it good solubility both in lipids and aqueous acid.
- Rifaximin is another semisynthetic analogue that was approved in 2004 for the treatment of diarrhoea and E. coli infection.



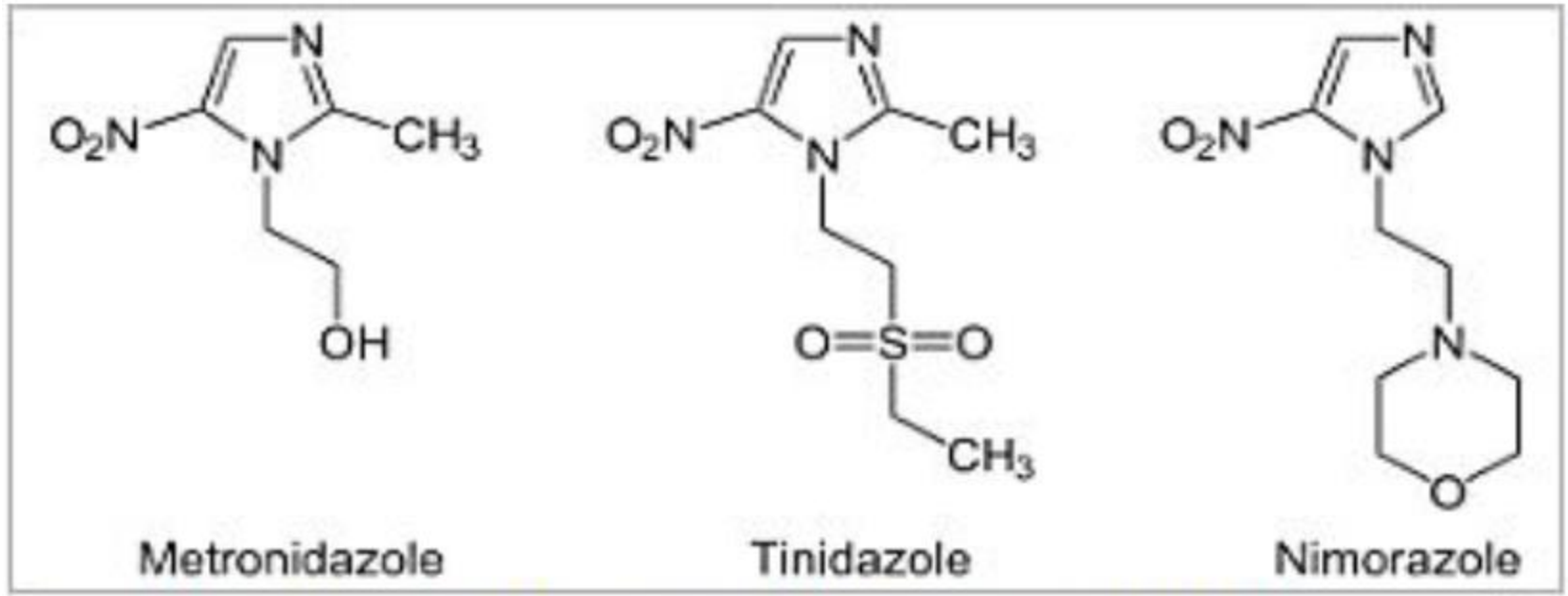
R =	H	Rifamycin B
R =	CH=N–N NH	Rifampicin



Rifaximin

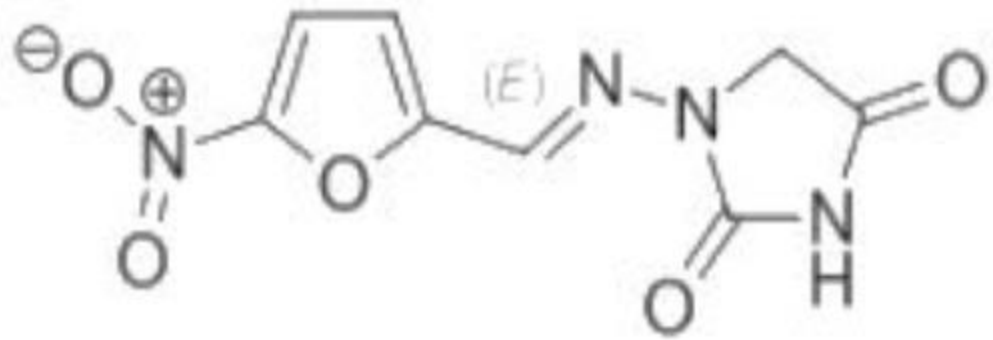
Nitroimidazoles and nitrofurantoin

- Metronidazole is a nitroimidazole structure which was introduced in 1959 as an anti-protozoal agent, but began to be used as an antibacterial agent in the 1970s.
- The nitro group is reduced when the drug enters the bacterial cell, which lowers the concentration of metronidazole within the cell and sets up a concentration gradient down which more drug can flow.
- The reduction mechanism also proves toxic to the cell as free radicals are formed which act on DNA.
- Nitrofurantoin also undergoes reduction within bacterial cells to form radical species that act on DNA.



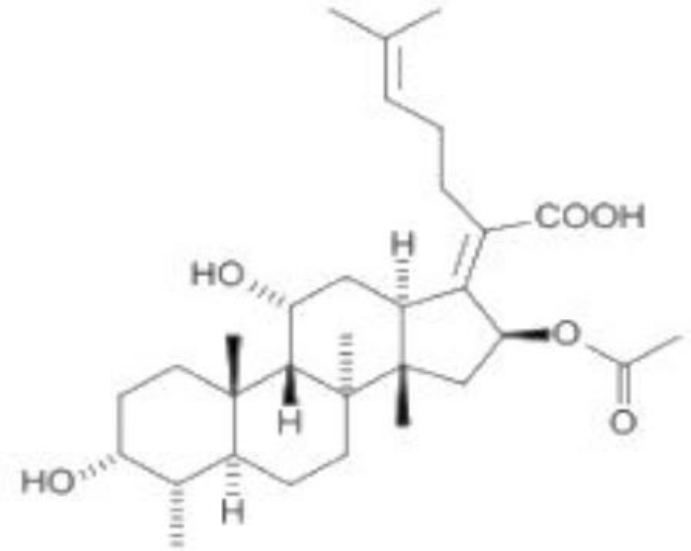
Three nitroimidazole antibiotics: metronidazole, tinidazole, and nimorazole

Nitrofurantoin

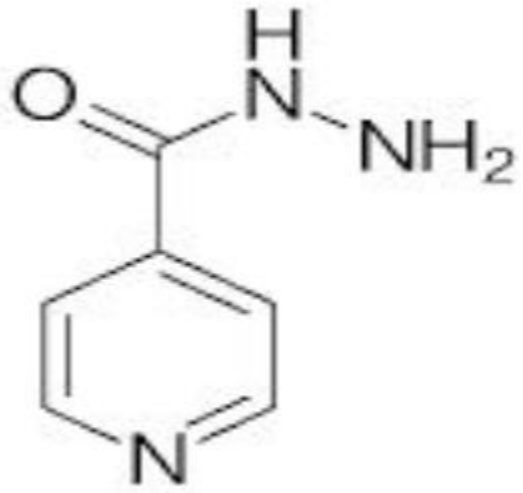


Miscellaneous agents

- Fusidic acid acts as a bacterial protein synthesis inhibitor
- It is a topical antibacterial agent that is used in eye drops and skin creams. It can penetrate intact and damaged skin, so it is useful for the treatment of boils.
- It has also been used to eradicate MRSA colonies carried in the nasal passages of hospital patients and health workers.



- Isoniazid is the most widely used drug for the treatment of tuberculosis and is part of a four-drug cocktail which is the first choice treatment for the initial phase of the disease.



THANK YOU

- ANY QUESTIONS??

Rest for 15 minutes