

FLUOROQUINOLONES: from structure to activity and toxicity

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www.sbimc.org - www.bvikm.org

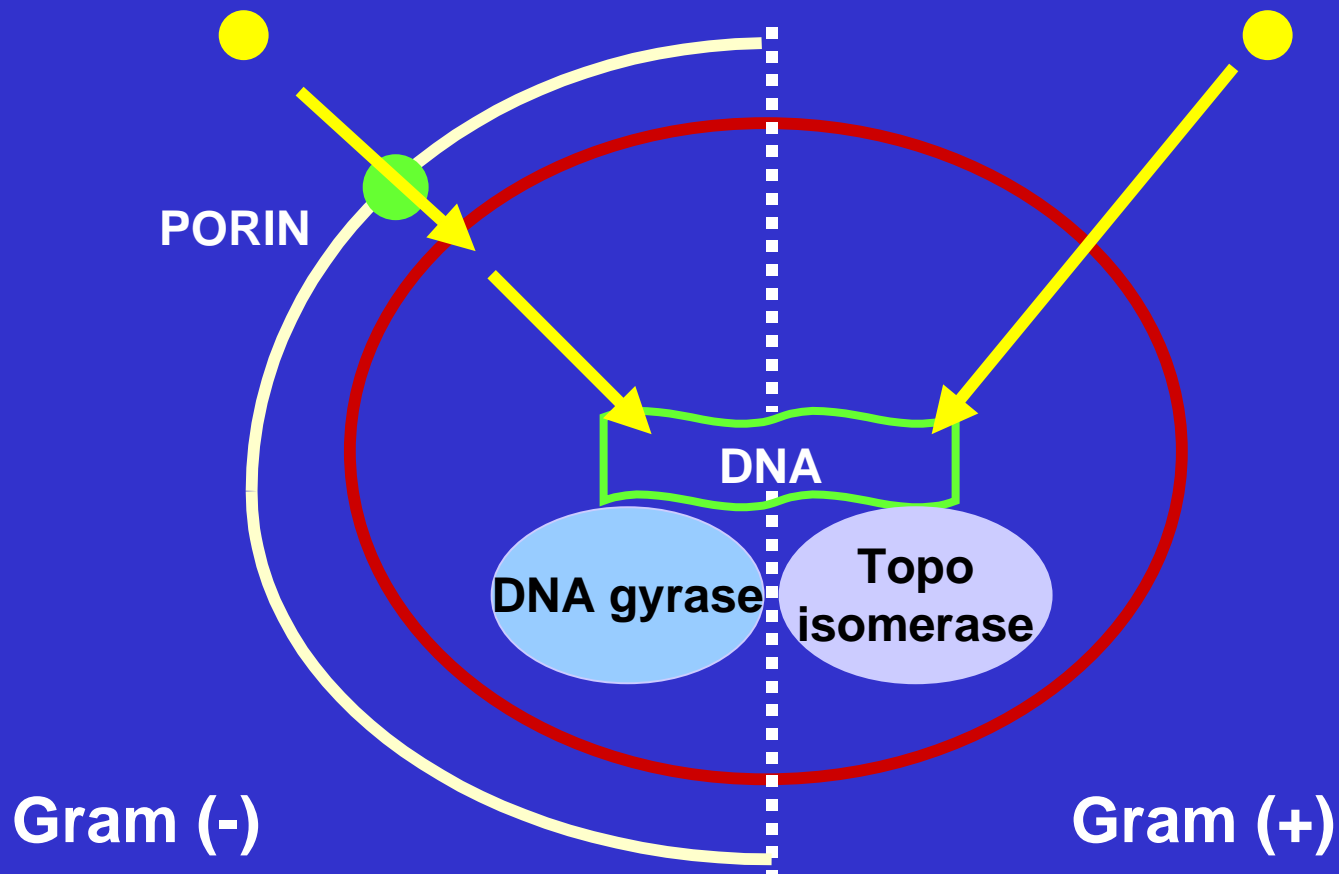
soon...



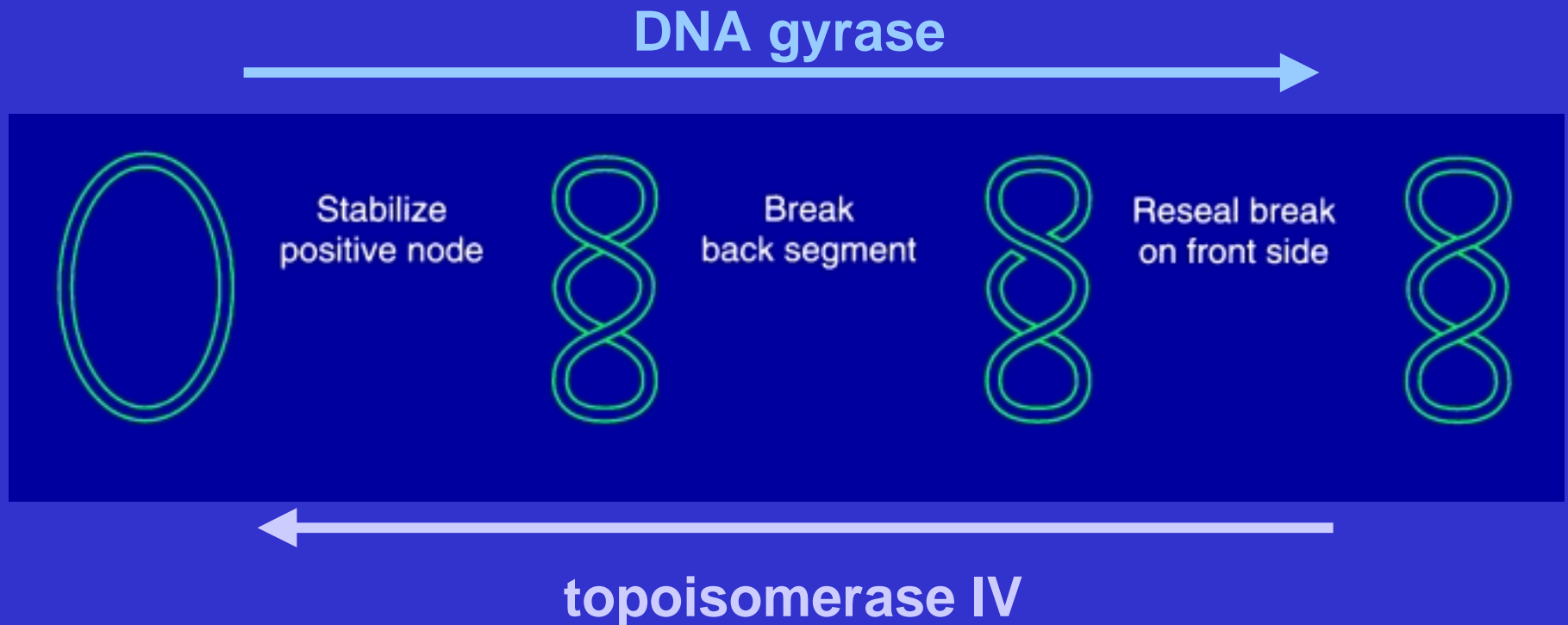
www.isap.org

www.md.ucl.ac.be/facm

Mechanism of action of fluoroquinolones: the basics...

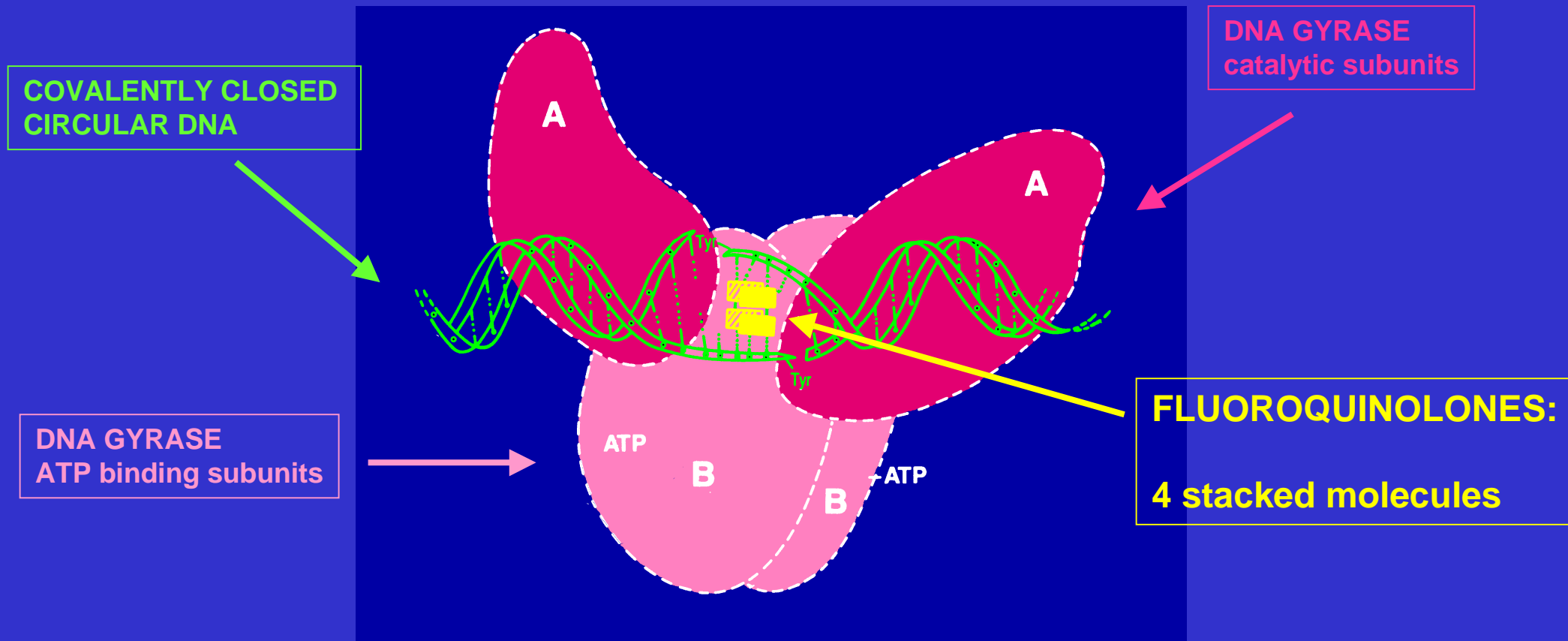


2 key enzymes in DNA replication:



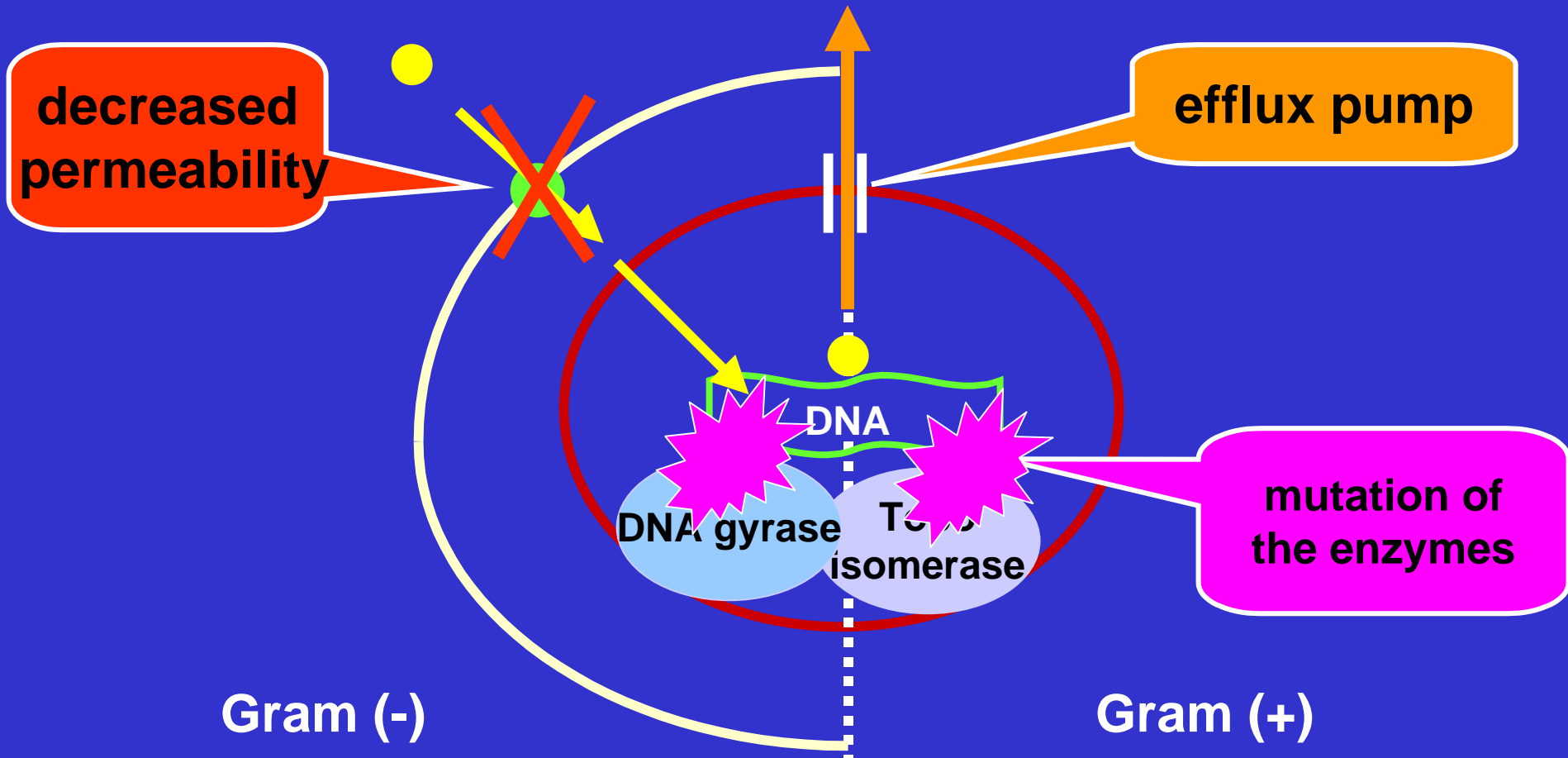
bacterial DNA is supercoiled

Ternary complex DNA - enzyme - fluoroquinolone



(Shen, *in* Quinolone Antimicrobial Agents, 1993)

Resistance to fluoroquinolones: the basics



**Fluoroquinolones are the first entirely
man-made antibiotics:
do we understand our molecule ?**



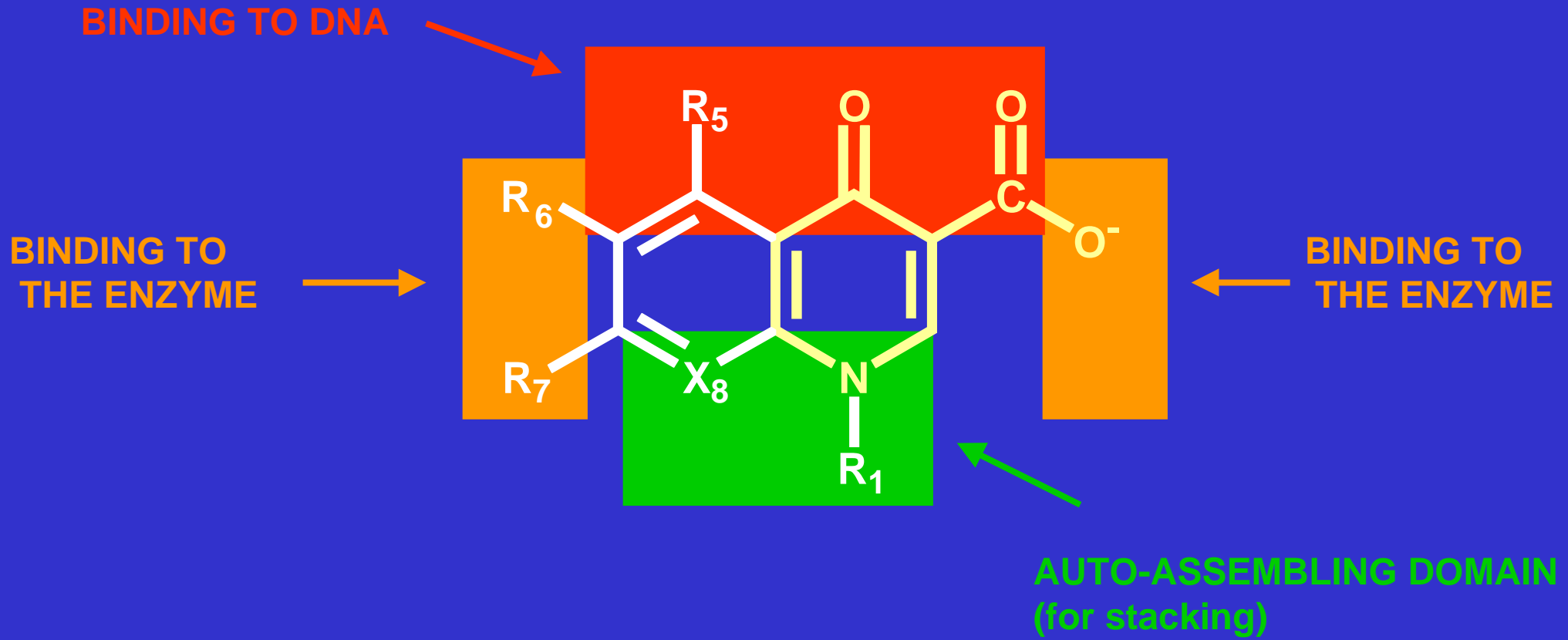
Don't panic, we will travel together....

Chemistry and Activity



This is where all begins...

The pharmacophore common to all fluoroquinolones



From chloroquine to nalidixic acid...



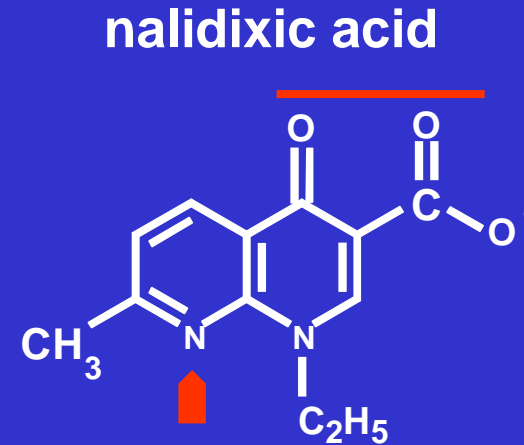
chloroquine

1939

1958



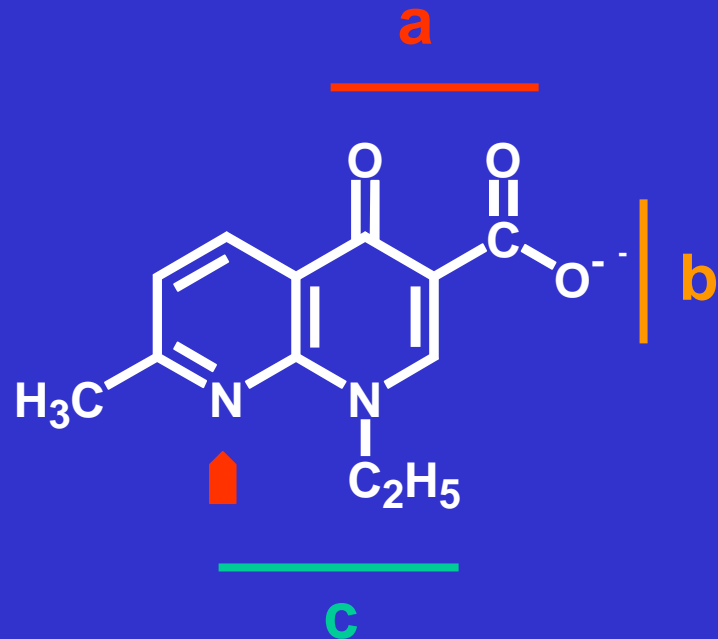
7-chloroquinoline
(synthesis intermediate
found to display
antibacterial activity)




nalidixic acid

1962

Nalidixic acid *

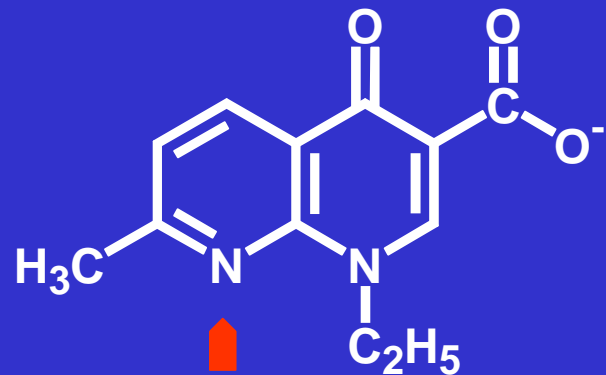


- typical chemical features of fluoroquinolones (a, b, c)
BUT a naphthridone
(N at position 8: )
- limited usefulness as drug
 - narrow antibacterial spectrum (*Enterobacteriaceae* only)
 - short half-life (1.5h)
 - high protein binding (90%)

* Belg. pat. 612,258 to Sterling Drugs, 1962

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

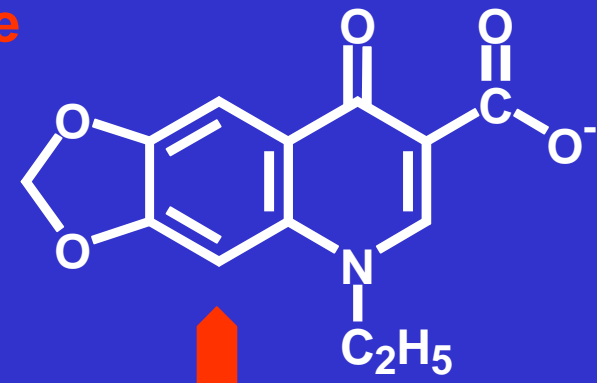
nalidixic acid



1. modify naphthyridone
into quinolone



oxolinic acid *



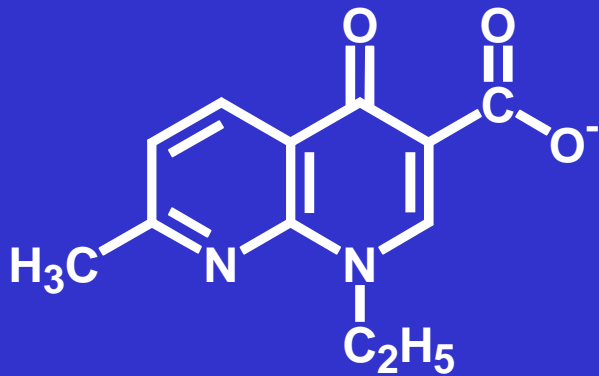
shows reduced protein binding...

* Ger. pat. to Warner Lambert, 1967

* quinoleine

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

nalidixic acid



2. discovery of
flumequine *



flumequine *



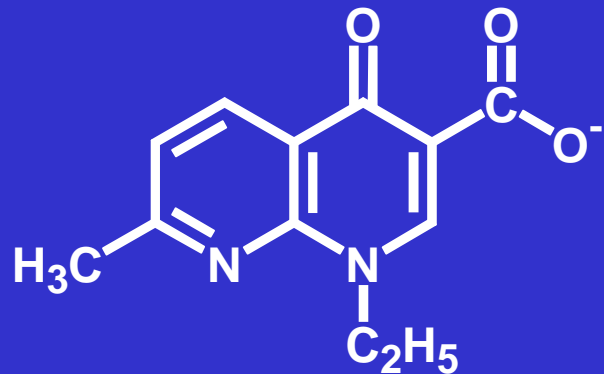
shows weak but broad
Gram(-) activity

* Ger pat. to Rikker Labs, 1973

* benzo-quinolizine

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

nalidixic acid



3. introduce a
piperazine *



pipemidic acid *

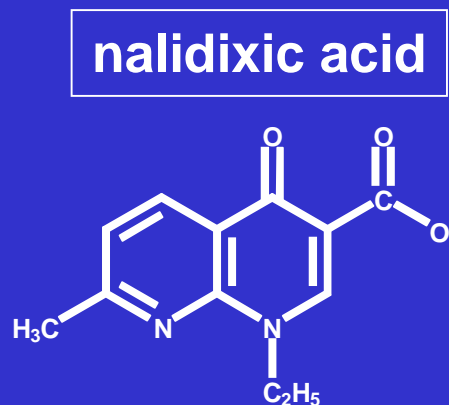


shows longer half-life...

* Ger. Pat. to Roger Bellon, 1974

* pyrido-2-3-pyrimidine

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

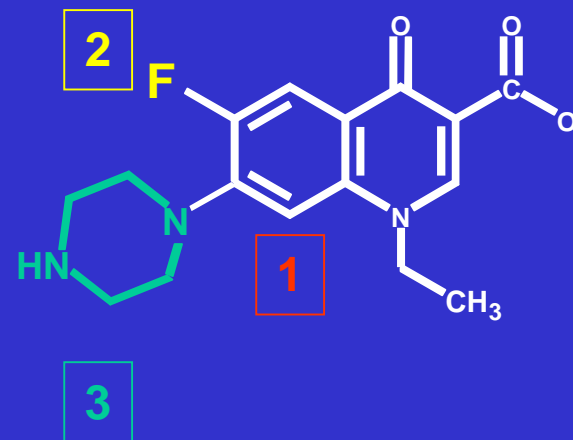


combine all 3
features * ...



1978

norfloxacin *



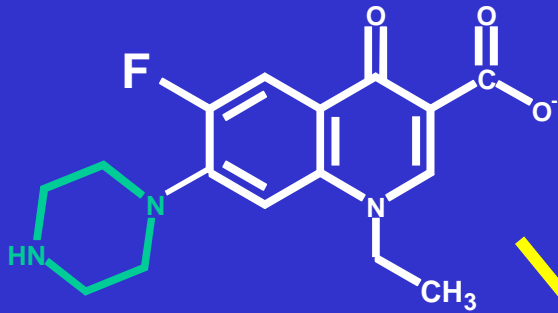
broader Gram(-) activity
less protein binding (50%)
longer half-life (3-4h)

* Belgian patent 863,429, 1978 to Kyorin

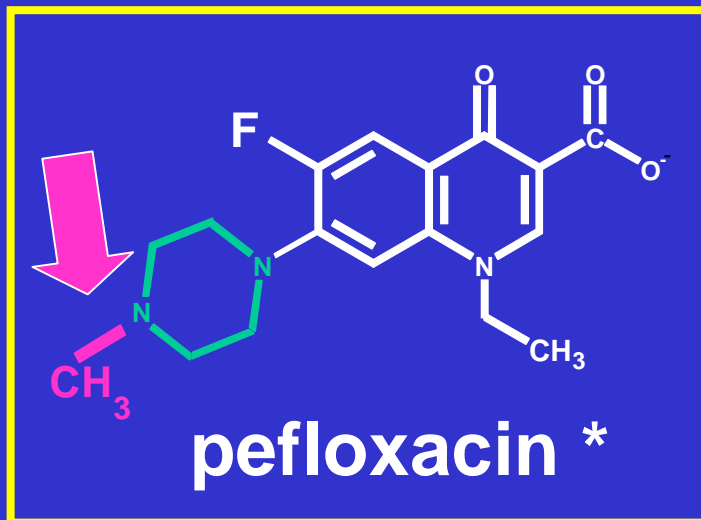
* 6-fluoro-7-pyrimidino-quinoleine

From norfloxacin to the other 1st generation fluoroquinolones: pefloxacin

norfloxacin



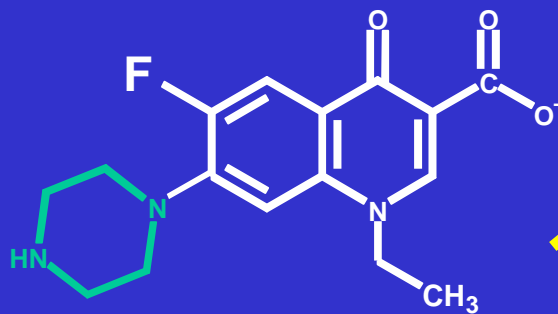
Add a methyl
to still increase
half-life



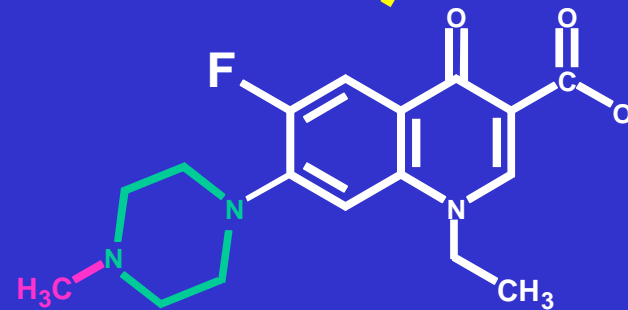
* Ger. pat. 2,840,910 to
Roger Bellon/Dainippon, 1979

From norfloxacin to the other 1st generation fluoroquinolones: ofloxacin

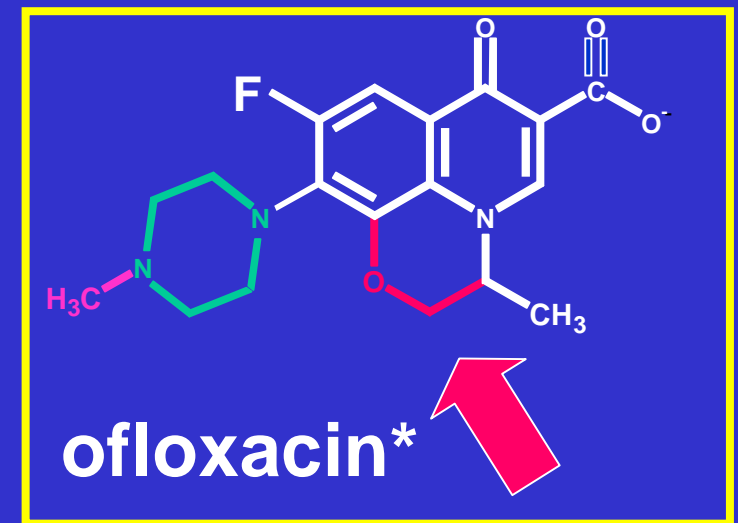
norfloxacin



tricyclic compound
(as in flumequine but
morpholine ring)



pefloxacin

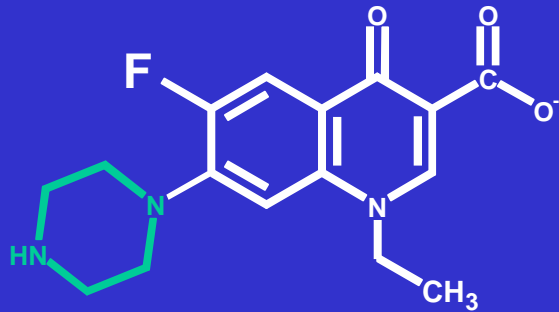


ofloxacin*

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

From norfloxacin to the other 1st generation fluoroquinolones: ciprofloxacin

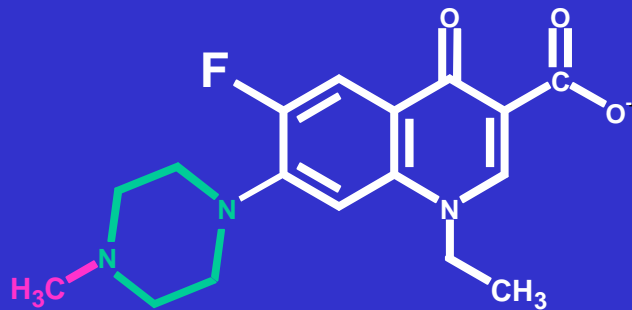
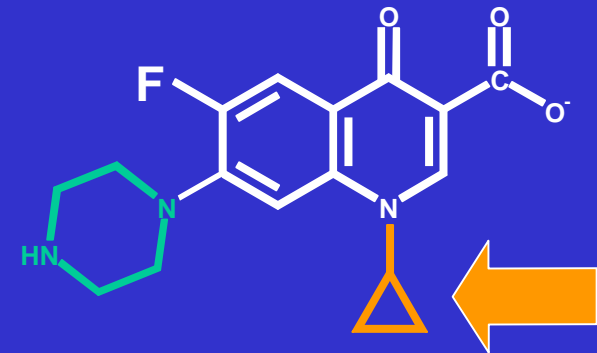
norfloxacin



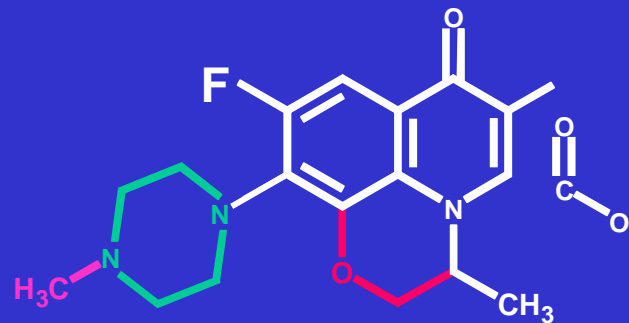
cyclopropyl to
increase potency



ciprofloxacin *



pefloxacin

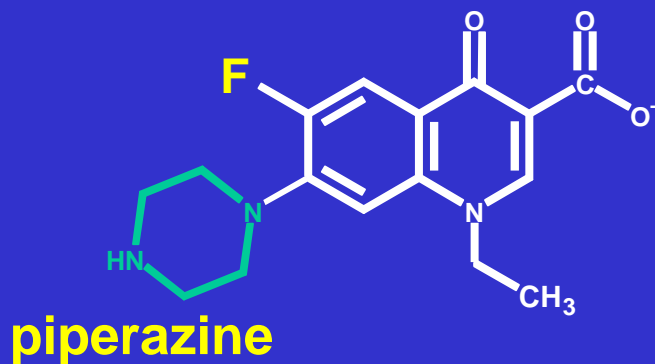


ofloxacin

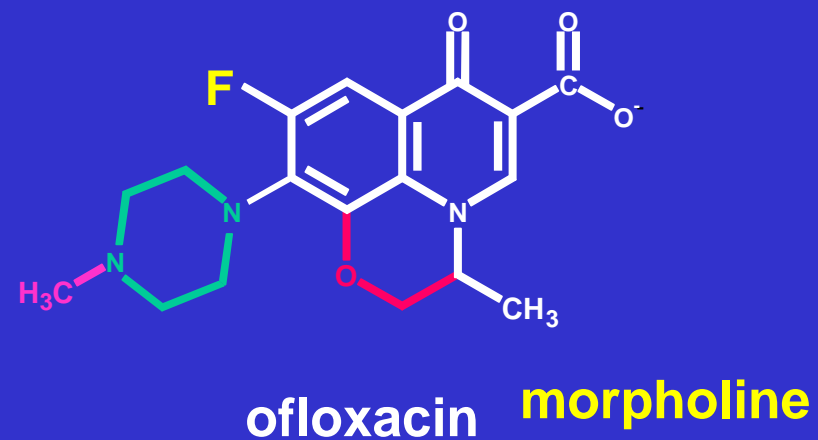
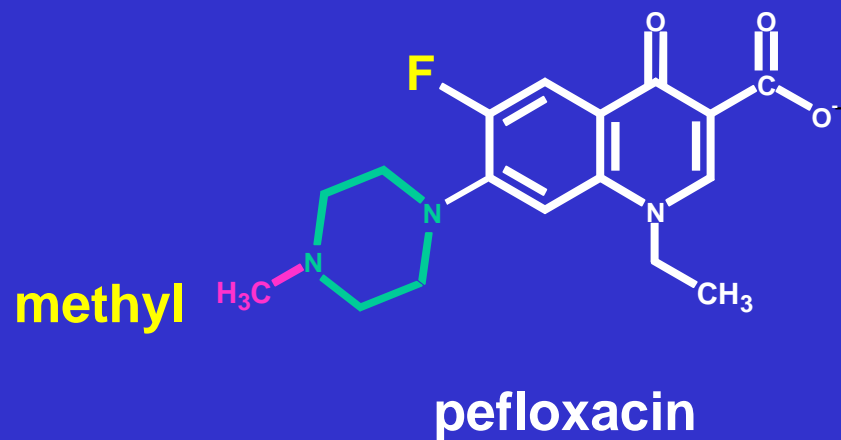
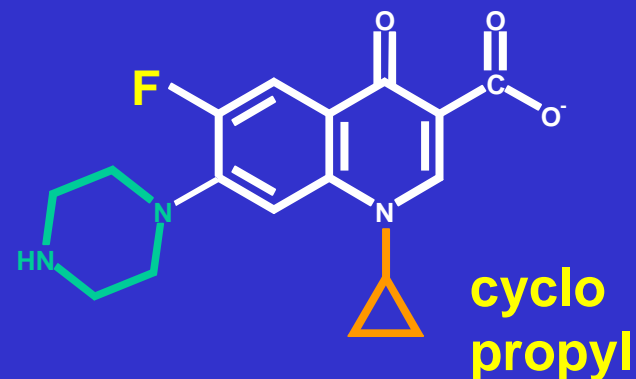
* Ger. pat. 3,142,854 to Bayer AG, 1983

"1st generation" fluoroquinolones

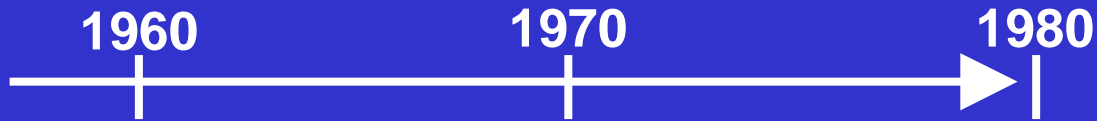
norfloxacin



ciprofloxacin



The "first generation" of fluoroquinolones



- Nalidixic acid
- Oxolinic acid
- Cinoxacin
- Pipemidic acid

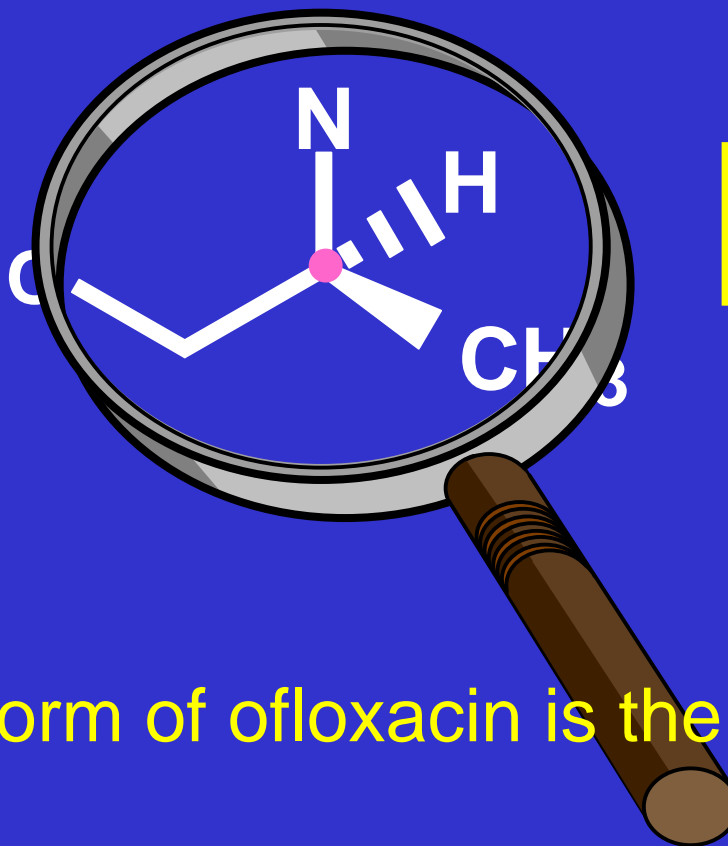
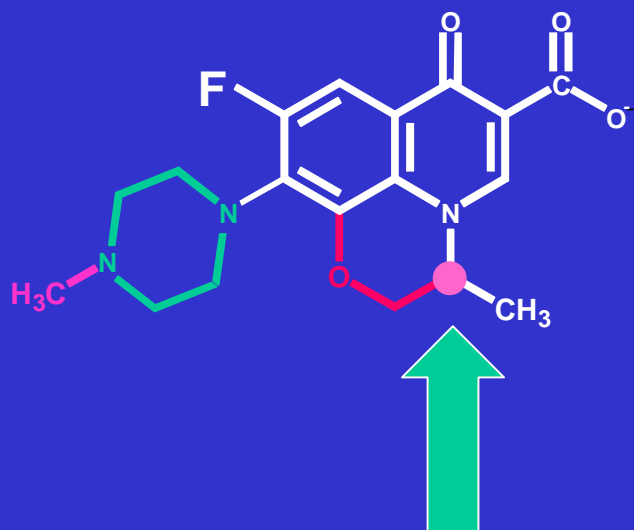
- **Norfloxacin**
- **Pefloxacin**
- **Ofloxacin**
- **Ciprofloxacin**
- Fleroxacin
- Rufloxacin

improved
anti Gram (-)
activity

$t_{1/2}$	activity
3-4 h	++
11 h	+
6 h	++
3-4 h	+++

From ofloxacin to levofloxacin...

Ofloxacin is a racemic mixture



Levofloxacin is the pure (-) S isomer *

The active form of ofloxacin is the (-) S isomer

* Eur. pat. 206,283 to Daiichi, 1987

The present "first generation" of fluoroquinolones ...



- Nalidixic acid
- Oxolinic acid
- Flumequine
- Pipemidic acid

- Norfloxacin
- Pefloxacin
- Ofloxacin
- Ciprofloxacin
- Fleroxacin
- Rufloxacin

improved
anti Gram (-)
activity

$t_{1/2}$	activity
3-4 h	++
11 h	+
6 h	++
3-4 h	+++

- Levofloxacin

6 h ++++

twice
as active as
ofloxacin per g

How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity

2. Improve Gram(+) activity

3. Acquire activity against anaerobes

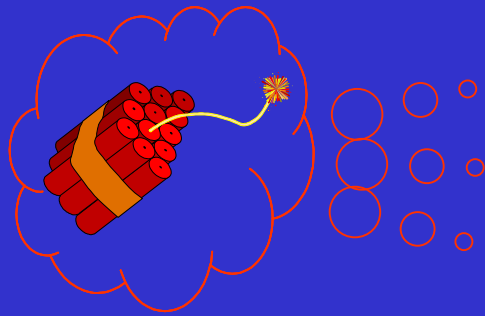


"2d generation"



"3d generation"

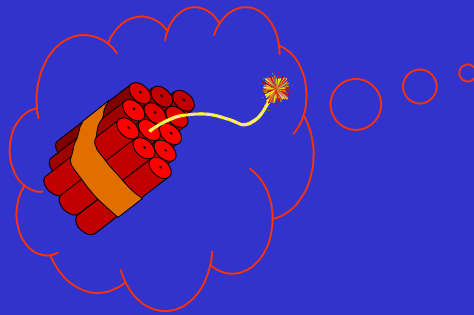
The “second generation” fluoroquinolones



- **Temafloxacin** ^a
 - **Sparfloxacin** ^b
 - **Grepafloxacin** ^c
 - **Gatifloxacin** ^d
- **Gram (-);**
- **improved Gram (+)**
- **anti-anaerobe**

a: Toyama, 1988 (?); b: Dainippon, 1985-1987; c: Otskuda, 1989; d: Kyorin, 1988

The “third generation” fluoroquinolones

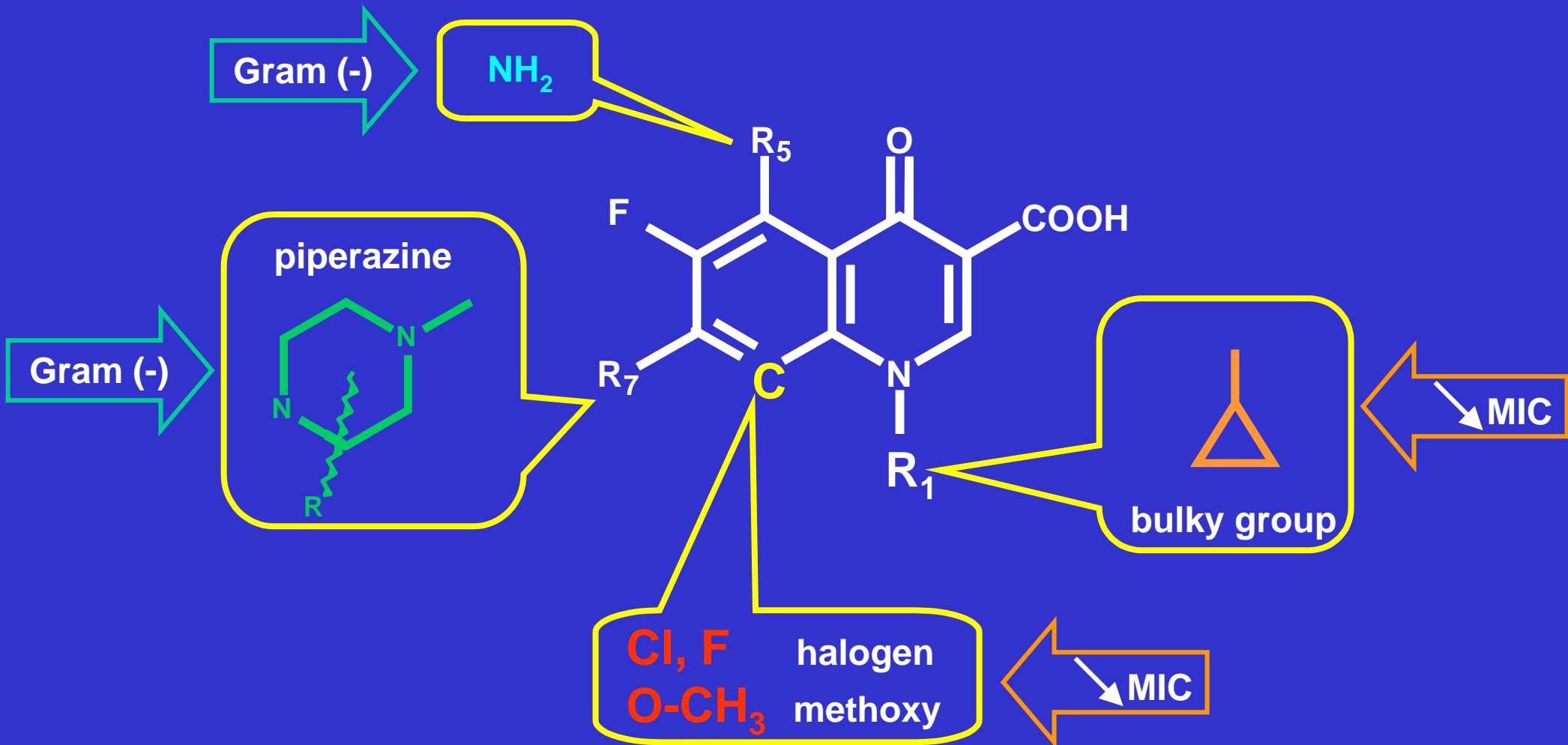


- Clinafloxacin ^a
- Trovafloxacin ^b
- Moxifloxacin ^c
- Gemifloxacin ^d

anti-Gram (-)
anti-Gram (+)
anti-anaerobe

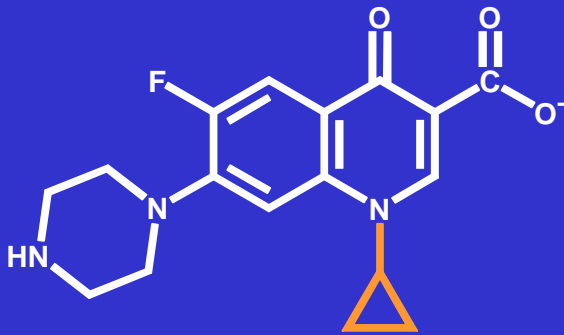
a:Kyorin, 1987; b: Pfizer, 1993; c: Bayer, 1994; d: LG Chemical Ltd., S. Korea, 1994-98

1. maintenance of anti - Gram (-) activity



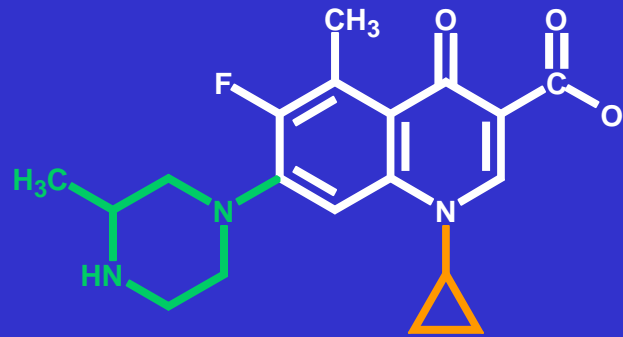
Gram (-) activity (*E. coli*)

I

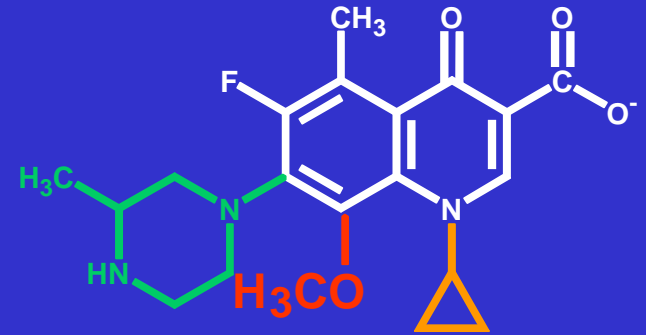


ciprofloxacin
0.125 - 0.5

II

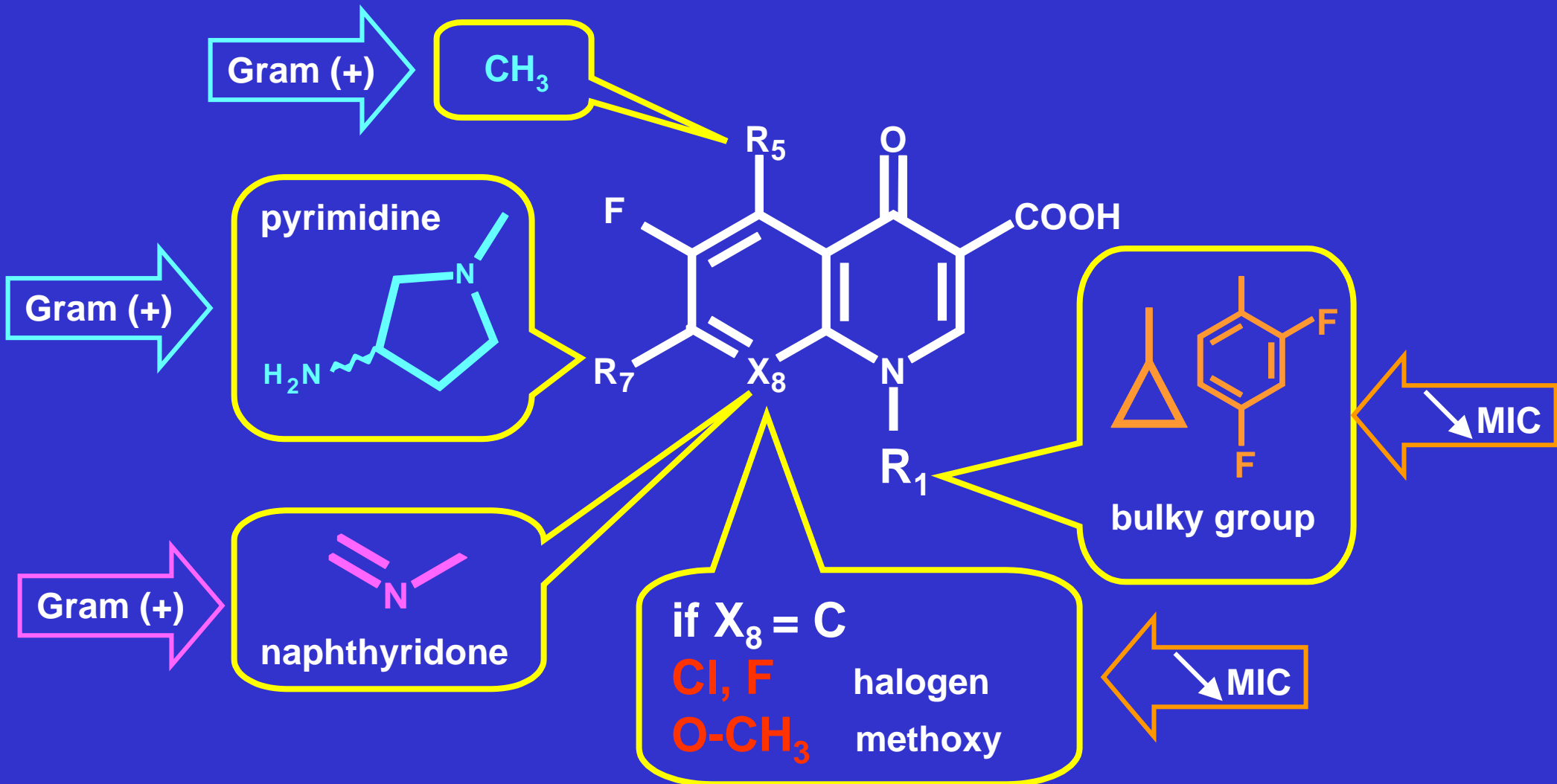


grepafloxacin
0.06 - 2



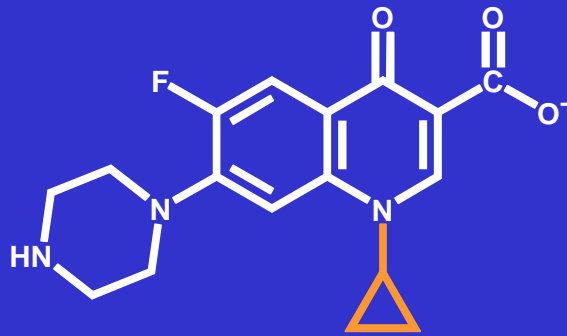
gatifloxacin
0.06

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



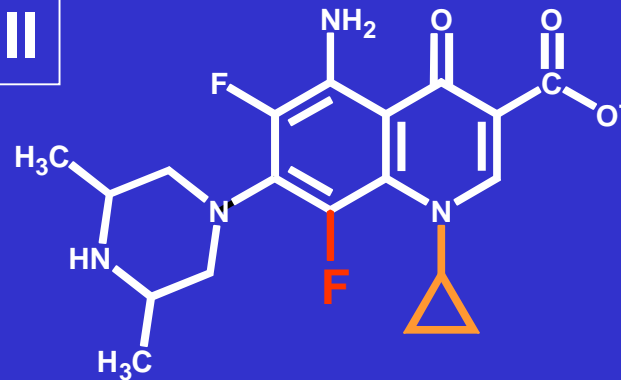
Activity against *S. pneumoniae*

I



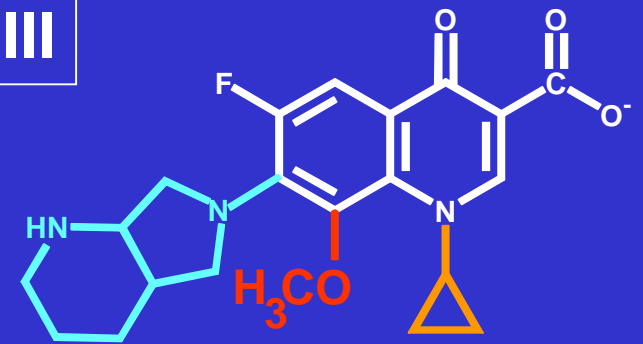
ciprofloxacin
0.5 - 2

II

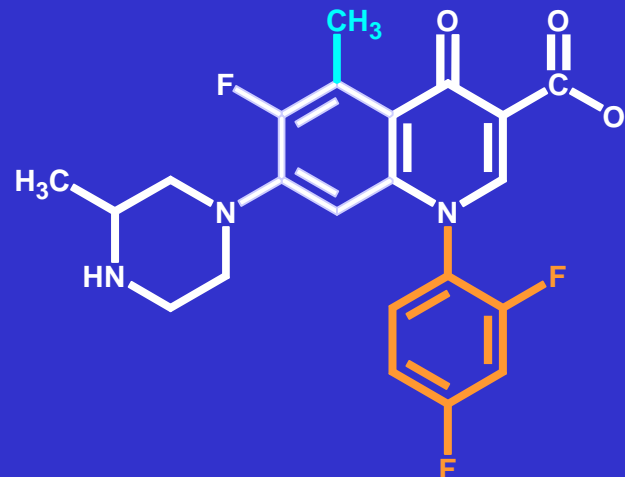


sparfloxacin
0.125 - 0.5

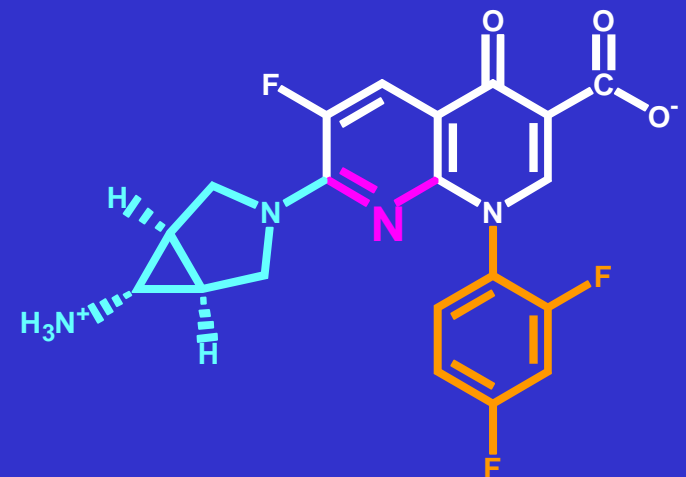
III



moxifloxacin
0.01 - 0.5

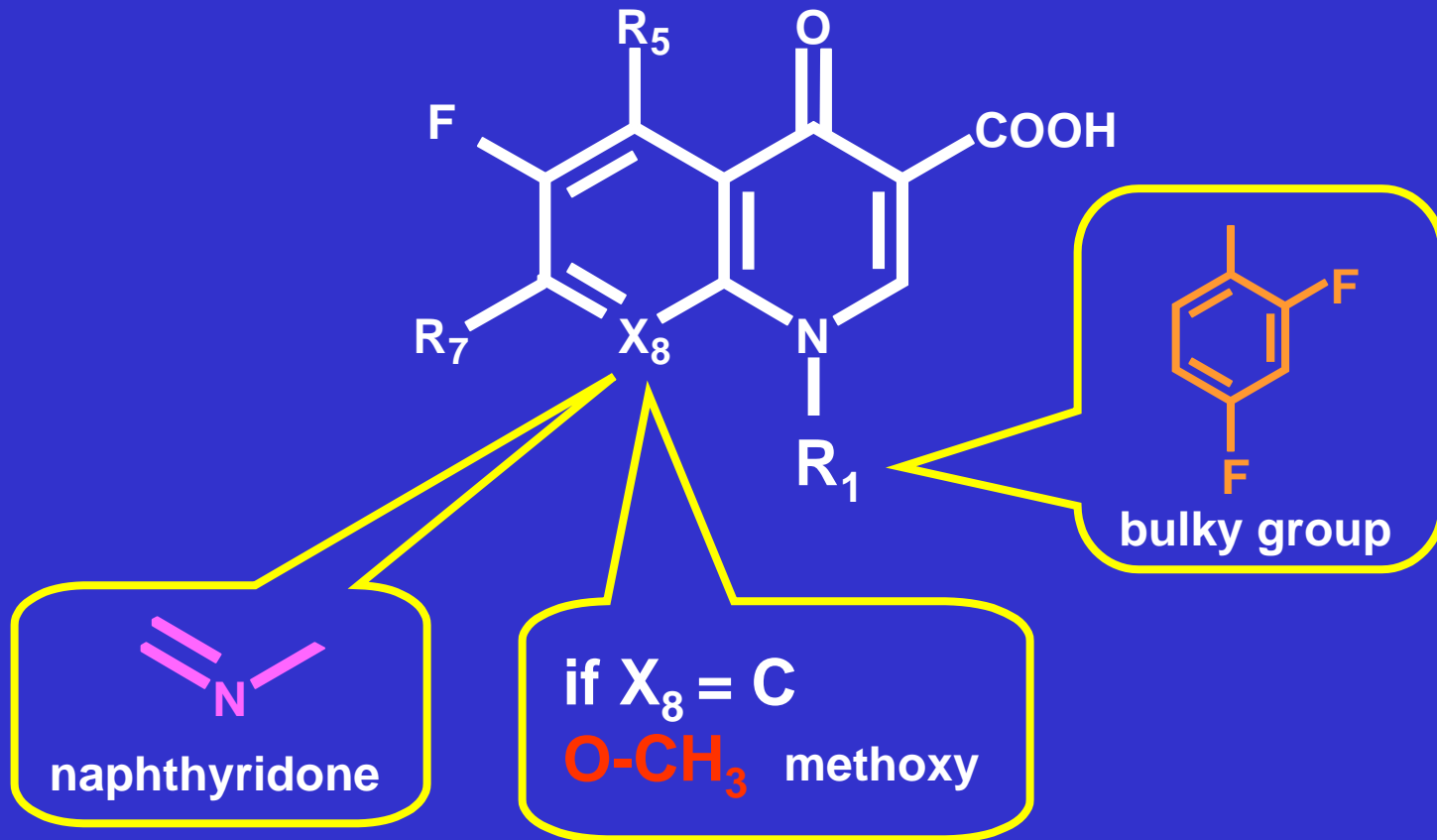


temafloxacin
0.5 - 1



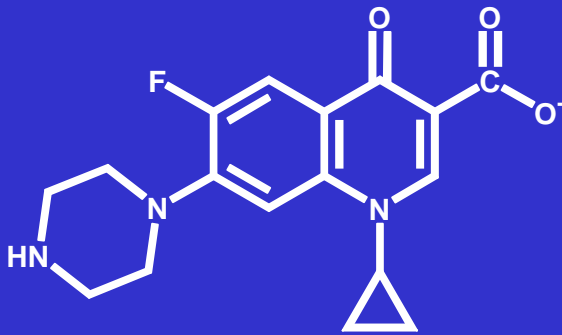
trovafloxacin
0.007 - 0.25

3. obtaining activity against anaerobes ...



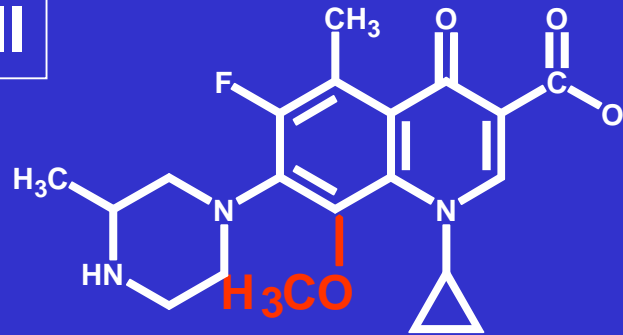
Activity against *B. fragilis*

I



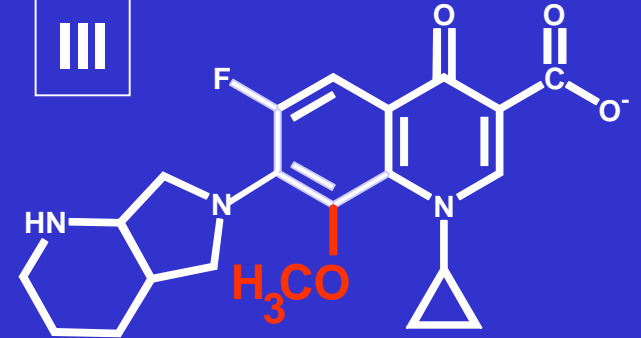
ciprofloxacin
2 - 128

II

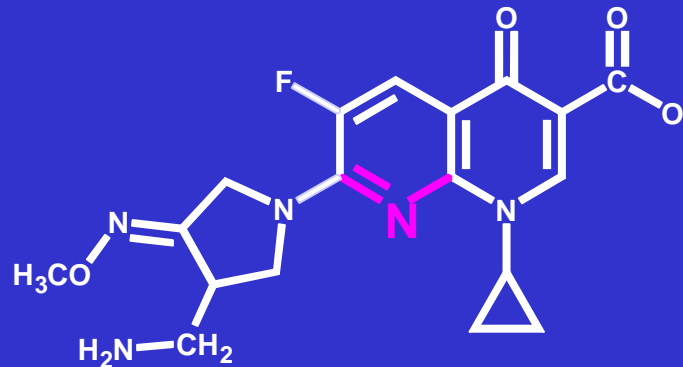


gatifloxacin
0.25 - 8

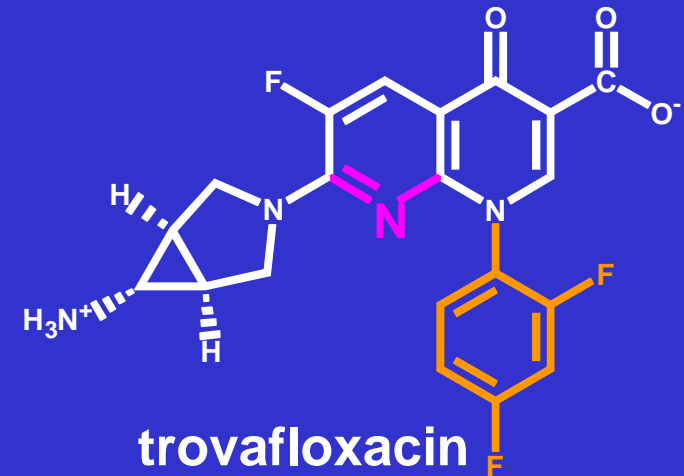
III



moxifloxacin
0.25 - 8



gemifloxacin
0.5 - 64



trovafloxacin
0.125 - 8

Is there a SAR for emergence of resistance ?

The "*Mutant Prevention Concentration*" *



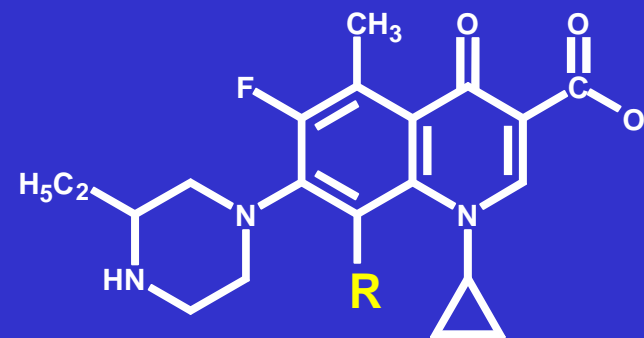
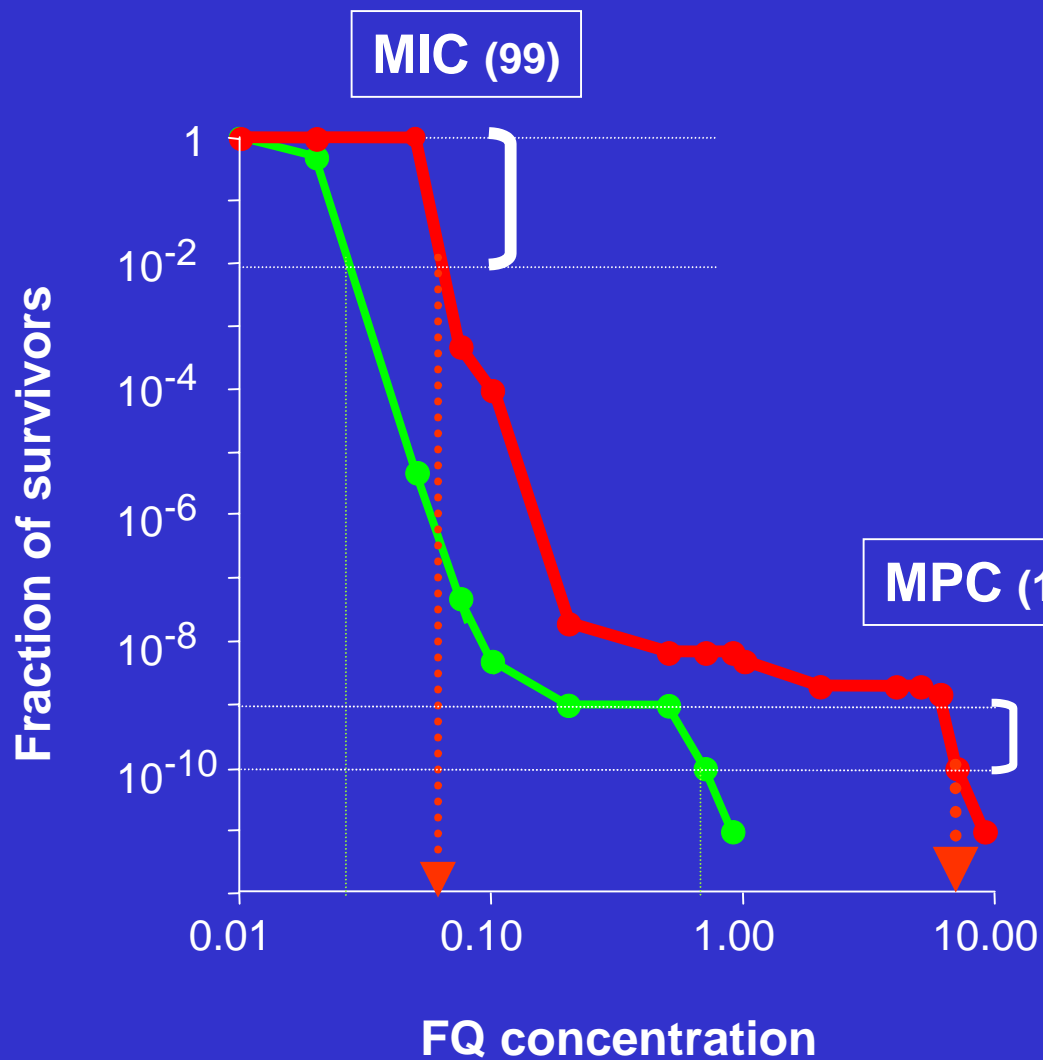
"When *Mycobacterium bovis* BCG and *Staphylococcus aureus* were plated on agar containing increasing concentrations of fluoroquinolone, colony numbers exhibited a sharp drop, followed by a plateau and a second sharp drop.

The plateau region correlated, with the presence of first-step resistant mutants. Mutants were not recovered at concentrations above those required for the second sharp drop, thereby defining a **mutant prevention concentration (MPC)**.

A **C8-methoxy group** lowered the MPC for an N-1-cyclopropyl fluoroquinolone"

Is there a SAR for emergence of resistance ?

Bactericidal activity of FQs against *Mycobacterium bovis*



PD160793

PD161148

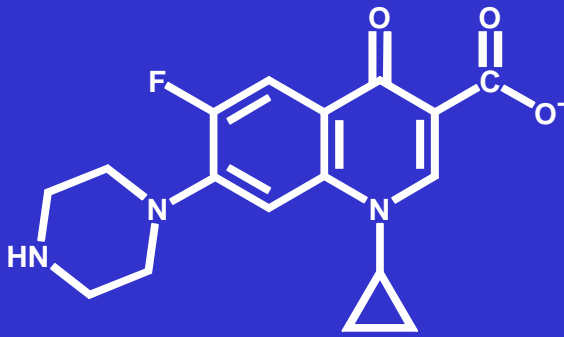
R = OCH₃

R = H

MIC 99	0.25	0.8
MPC 10	0.9	9
MPC/MIC	3.6	12

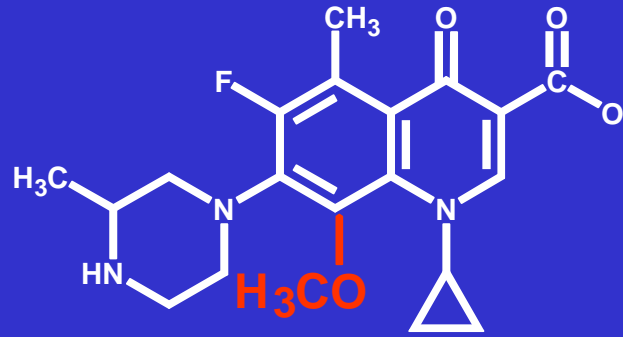
Fluoroquinolones with a C8-methoxy

I



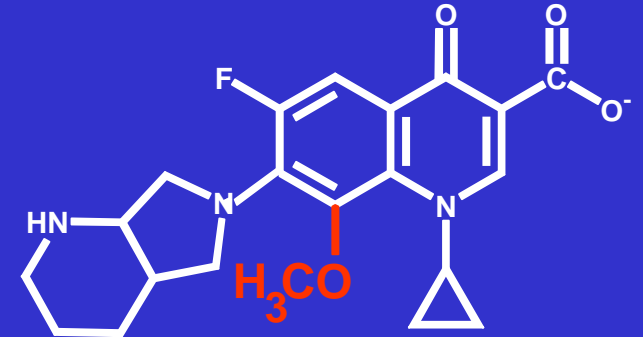
ciprofloxacin

II



gatifloxacin

III



moxifloxacin

Toxicity



This is where all may fail...

Frequent side effects of fluoroquinolones: is there a SAR ?



COMPLEXATION WITH METALLIC IONS (Fe, Al, Mg, Ca)



PHOTOTOXICITY



DRUG INTERACTIONS: INHIBITION OF cyt P450 (1A2)



CNS TOXICITY (BINDING TO GABA RECEPTOR)

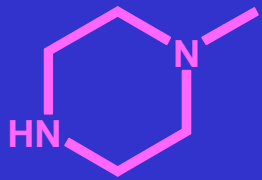


GASTRO-INTESTINAL DISCOMFORT



CARTILAGE and MUSCULOSQUELETAL TOXICITY

SAR of frequent side effects



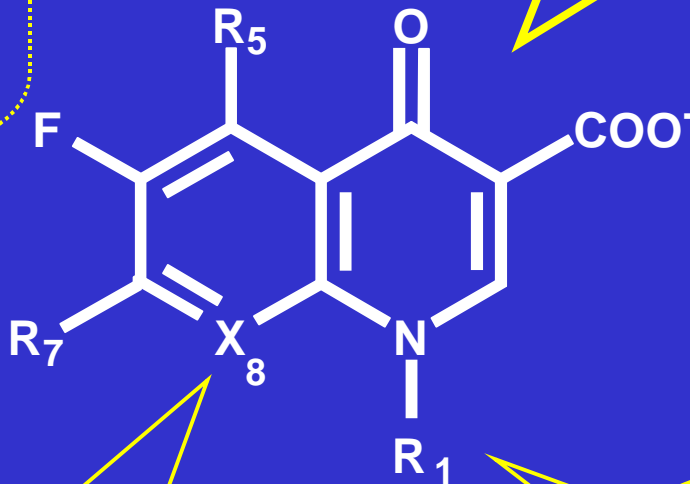
Binding to
GABA receptor



Penetration
in CNS

Ca⁺⁺, Al⁺⁺⁺, Fe⁺⁺
complexation

All FQs



cipro,
grepa ...

Inhibition of P450

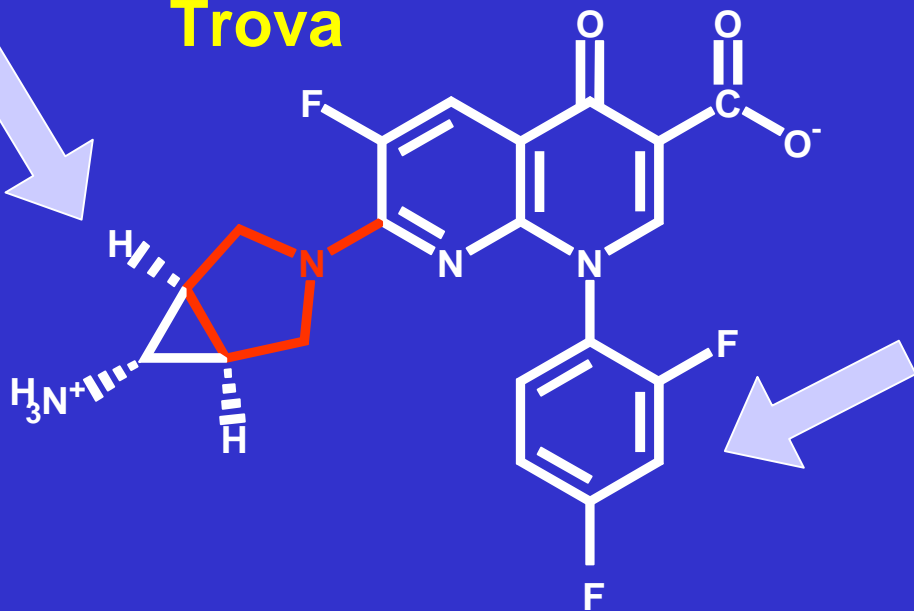
sparflo,
flero,
lomeflo

Phototoxicity

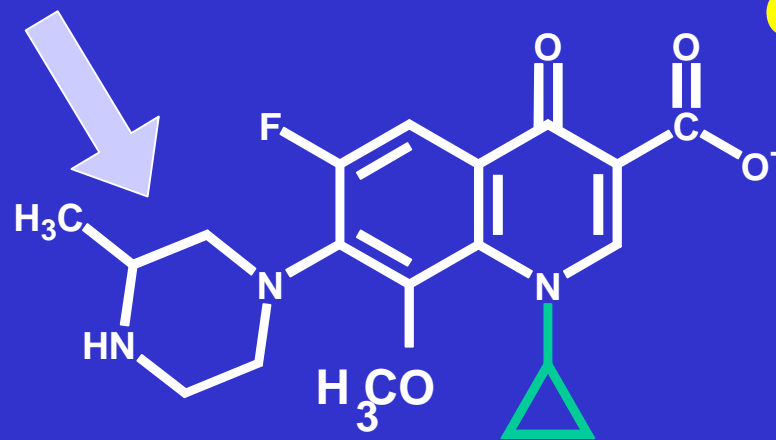
Inhibition of P450

Fluoroquinolones with low or no drug interactions..

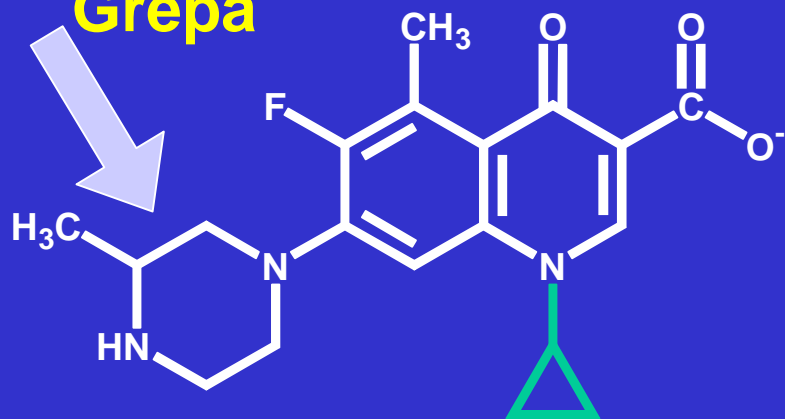
Trova



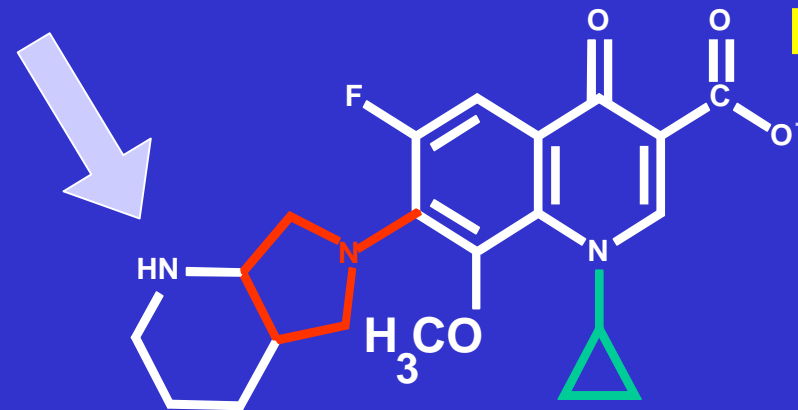
Gati



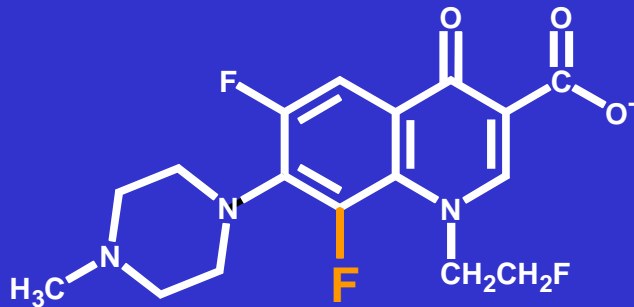
Grepa



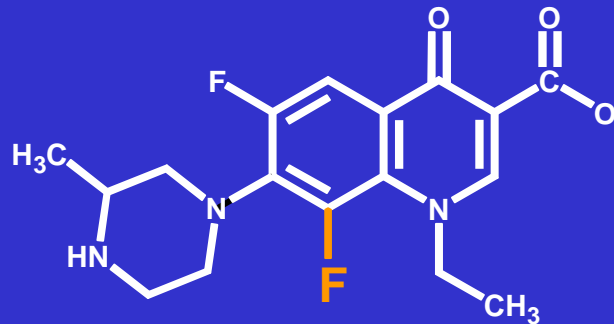
Moxi



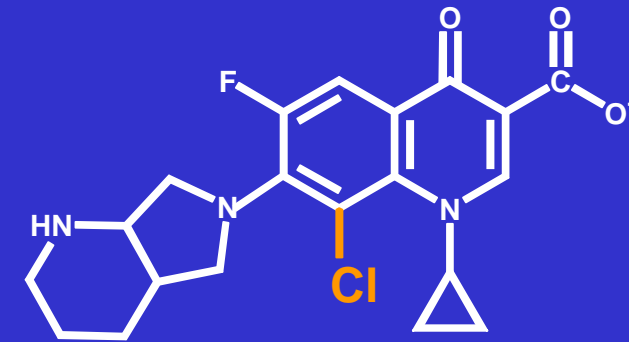
Fluoroquinolones with high phototoxicity ...



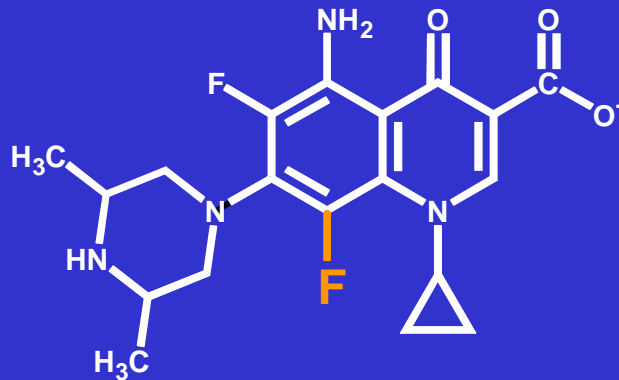
Fleroxacin^a



Lomefloxacin^b



Bay 3118^c



Sparfloxacin

a: Kyorin, 1981; b: Hokuriku, 1985; c: Bayer, 1994

Rare side effects of fluoroquinolones:



RENAL TOXICITY

crystalluria, hematuria, interstitial nephritis, acute renal failure



CARDIAC TOXICITY (QT prolongation, *Torsades de pointe*)

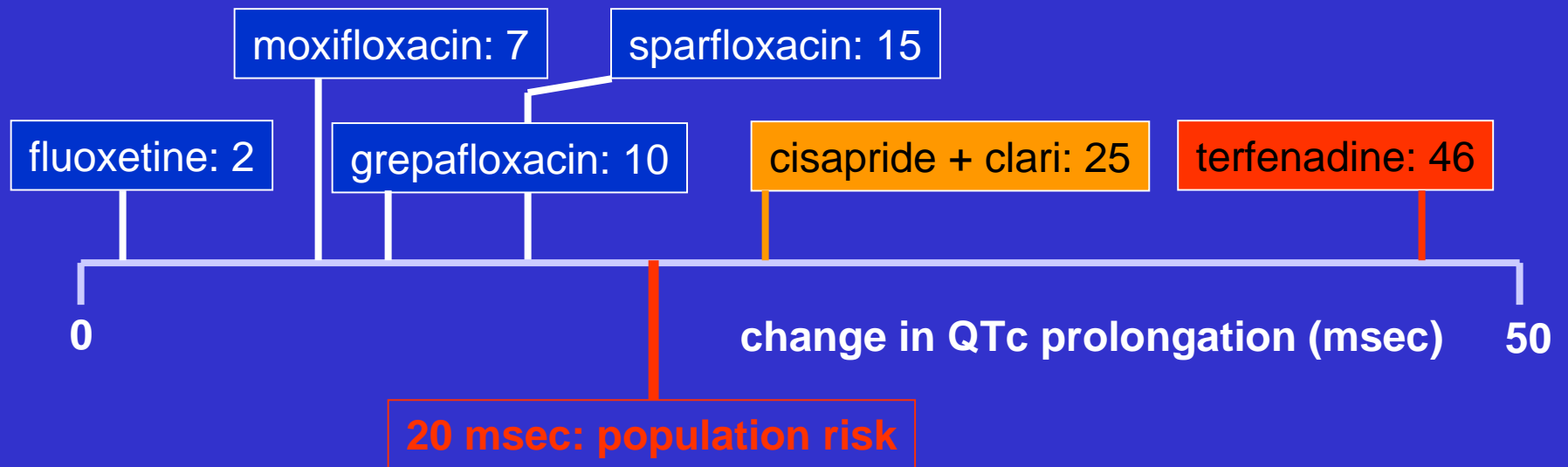


HEPATOTOXICITY

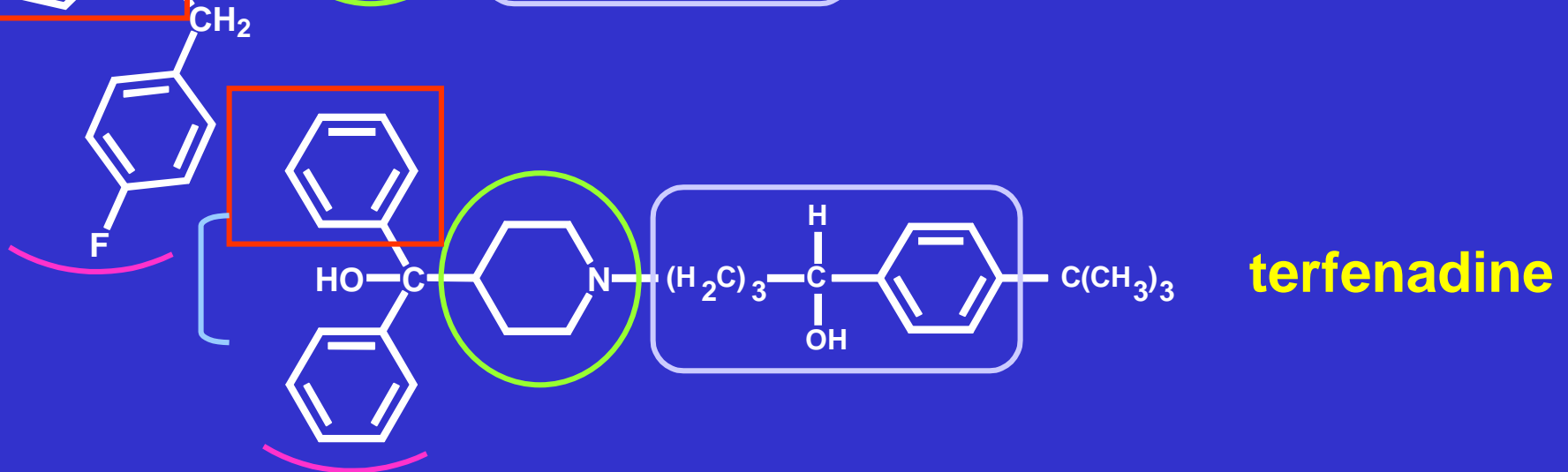
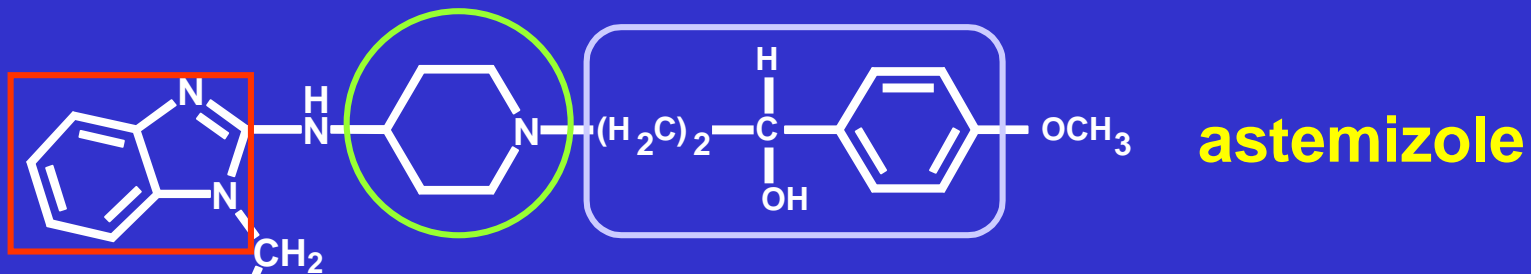
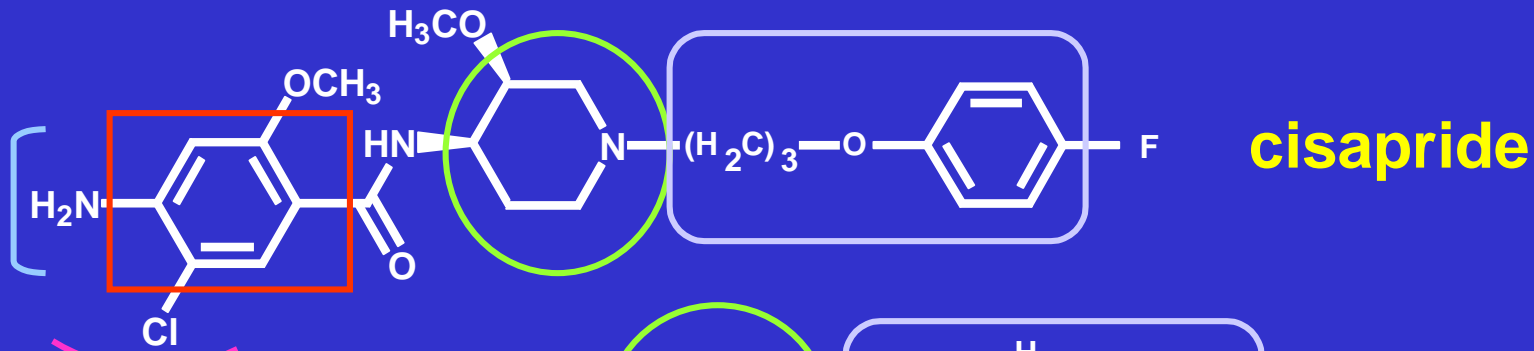
temafloxacin syndrome / trovafloxacin syndrome

Rare side effects of fluoroquinolones: cardiac toxicity

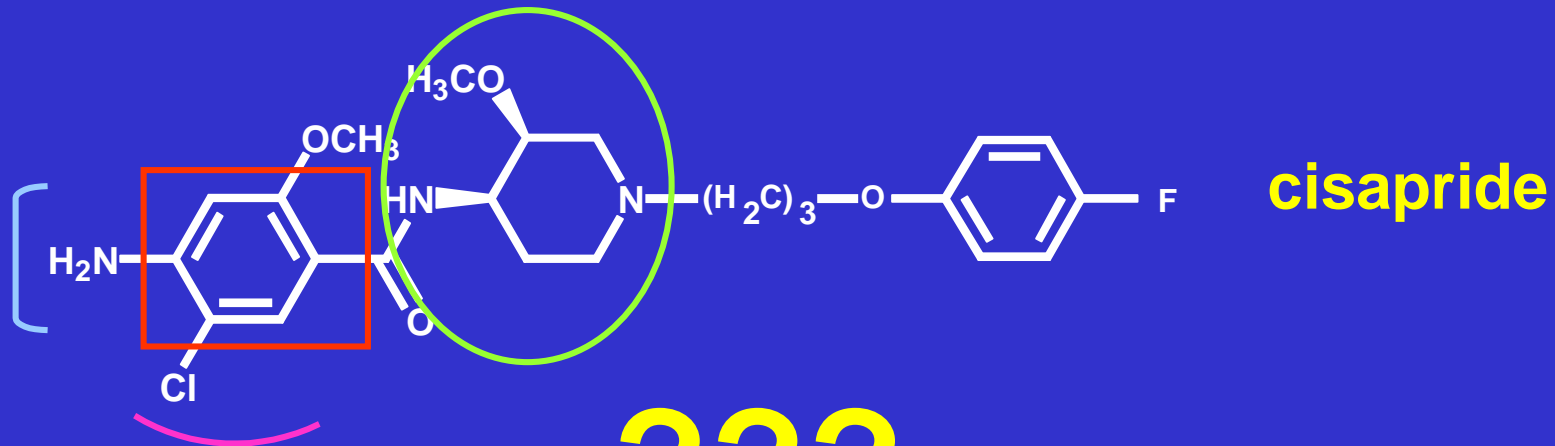
Torsade de pointes: paroxysm of ventricular tachycardia in which the electrocardiogram shows a steady undulation in the QRS axis in runs of 5 to 20 beats with progressive changes in direction. It is a most severe type of arrhythmia which may cause death. It is most often associated with and preceded by a prolongation of the QT interval.



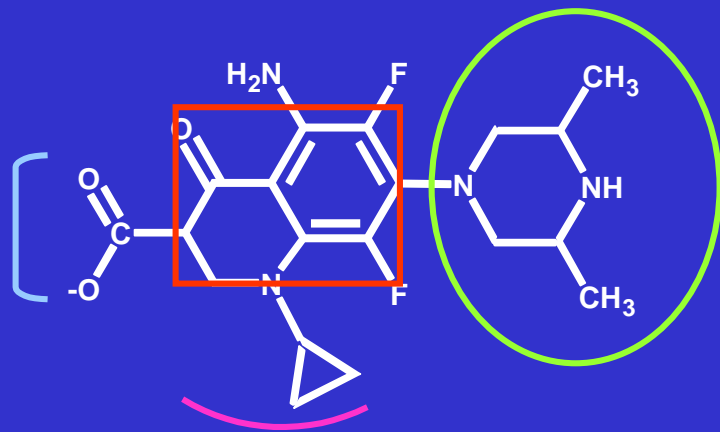
Cardiac toxicity QT prolongation: is there any SAR ?



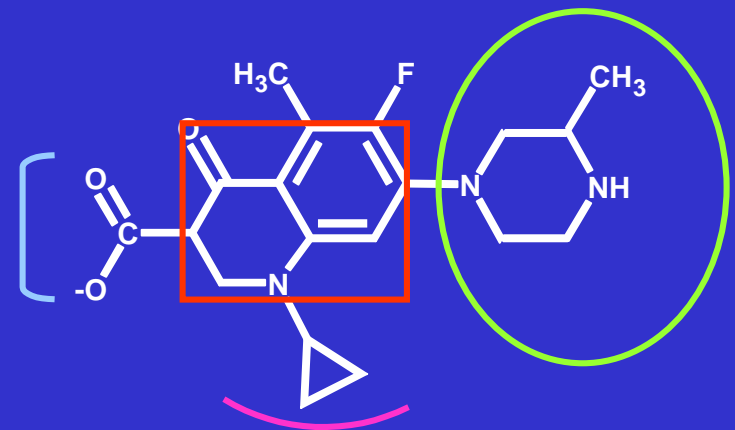
Cardiac toxicity QT prolongation: is there any SAR ?



???



sparfloxacin



grepafloxacin

Other severe toxicities

1992:

The temafloxacin syndrome:

hemolytic uraemic anemia

- discoloured urine, fever
- jaundice, nausea, vomiting
- abdominal pain
- coagulopathy
- hepatic and renal dysfunction

- 0.056% incidence
- 2 deaths

withdrawn in June 1992

1999:

The trovafloxacin syndrome:

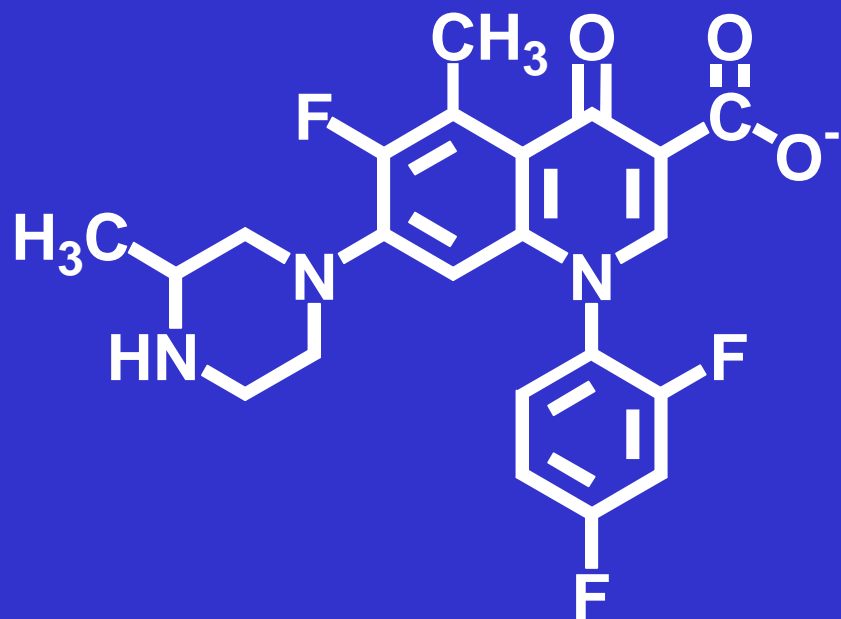
serious hepatic events

- laboratory abnormalities
 - ALT, bilirubin, encephalopathies
 - necrotic inflammation

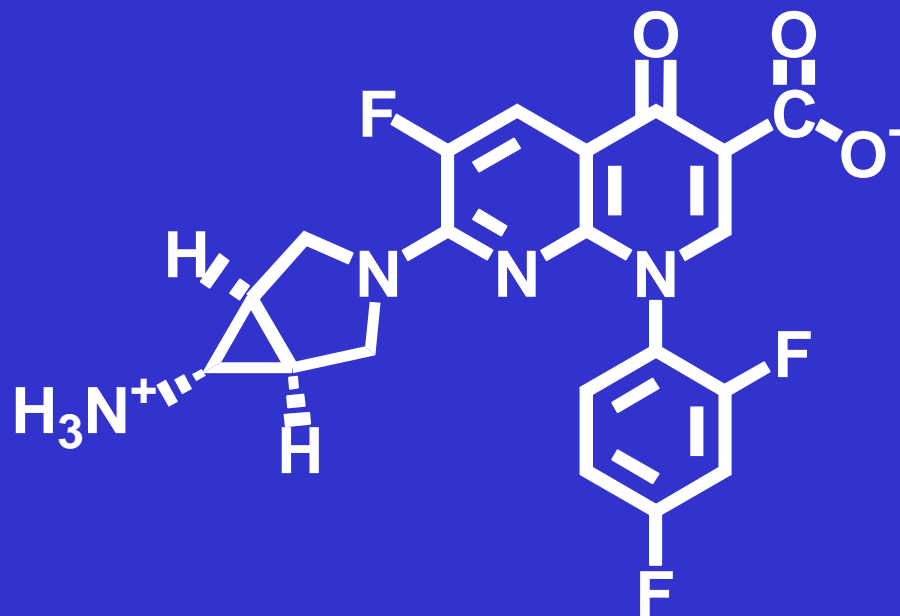
- 0.0056% incidence
- 5 transplants
- 6 deaths (multifactorial)

withdrawn / limited in June 1999

Which part of the molecule is the culprit ?

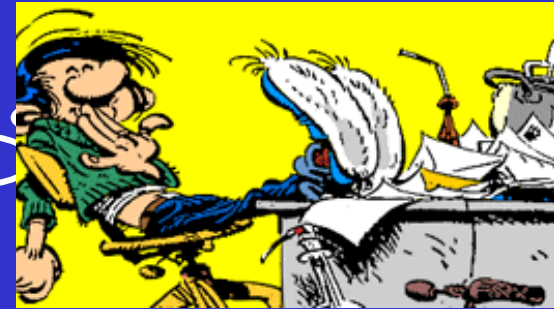


withdrawn in June 1992



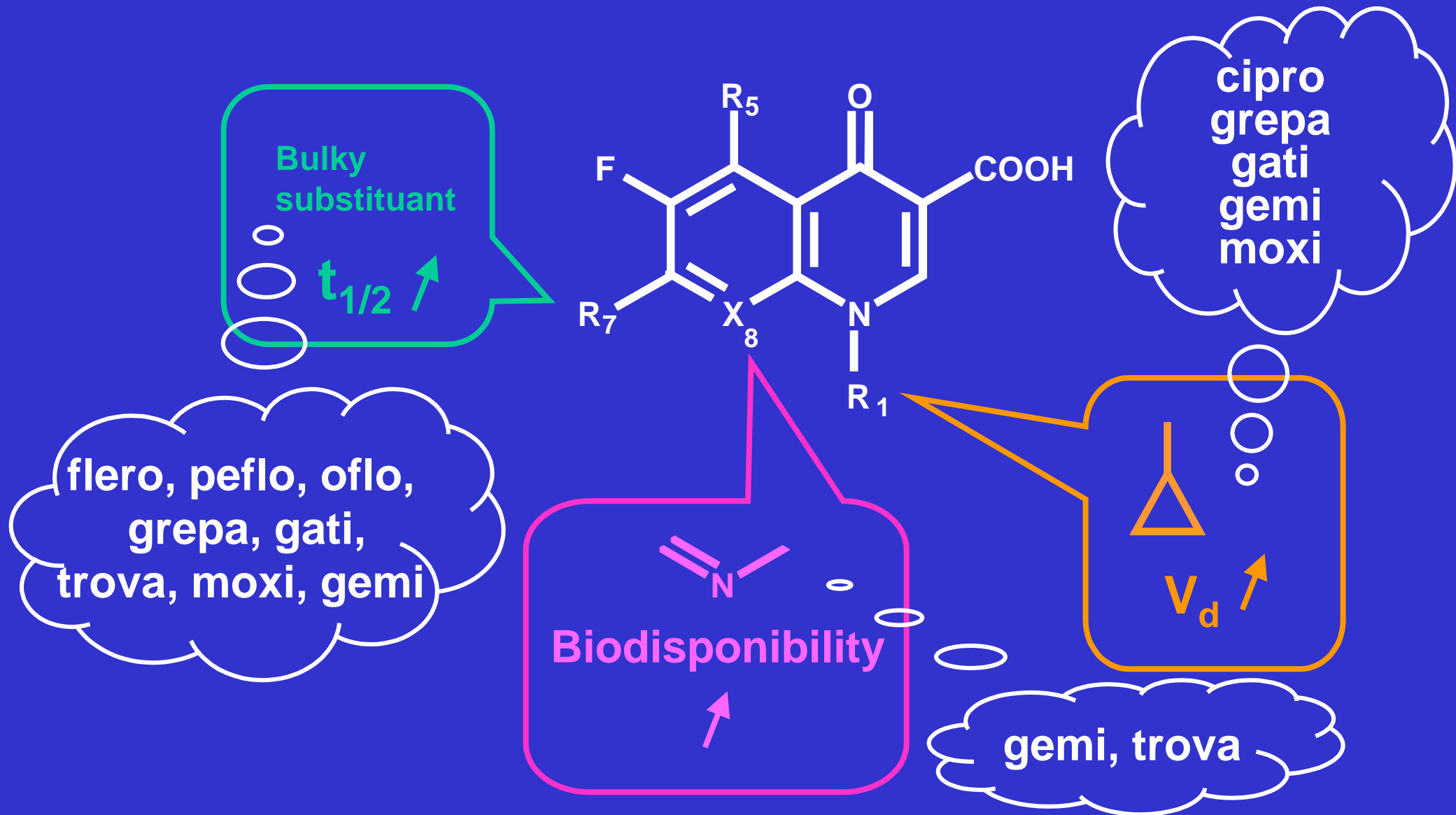
withdrawn / limited in June 1999

Pharmacokinetics

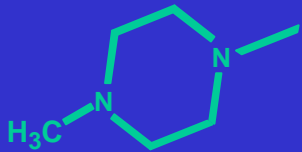
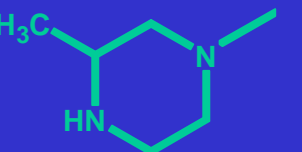
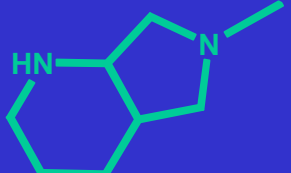


This is where people start sleeping..

SAR of pharmacokinetic parameters



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...

SAR of main pharmacokinetic parameters: biodisponibility



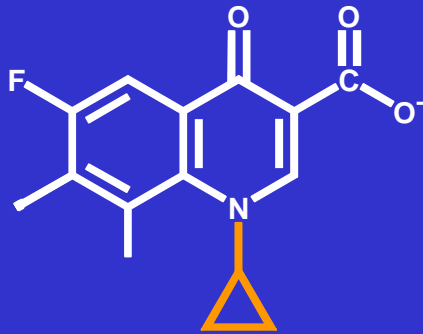
biodisponibility

trovafloxacin **90 %**

no data available for gemifloxacin

other FQ **60-90 %**

SAR of main pharmacokinetic parameters: volume of distribution



	V_d (L/Kg)
ciprofloxacin	3
gatifloxacin	1.8
grepafloxacin	8
gemifloxacin	1.5
moxifloxacin	2
other FQ	1- 1.5

?

Resistance: do not forget the correct dosing...

“Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance. A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy. The possibility to produce such a dose recommendation based on **pharmacokinetic** and **pharmacodynamic** considerations will be further investigated in one of the CPMP working parties...”

European Agency of the Evaluation of Medicinal Products (London)

*EMEA discussion paper
on Antimicrobial resistance
3 January 1999 EMEA/9880/99*



Pharmacokinetic parameters in relation with efficacy

	Dose (mg)	Cmax (mg/l)	MIC for pk/MIC=10	AUC (mg.h/l)	MIC for AUIC=125
norflo	400 (X2)	1.6	0.2	14	0.1
peflo	400 (X2)	4.6	0.4	108	1.0
cipro	500 (X2)	1.5	0.2	17	0.1
oflo	200 (X2)	3.1	0.4	66	0.4
levoflo	500	8.7	0.8	73	0.4
grepa	600	1.4	0.1	20	0.2
gati	400	4.5	0.4	28	0.2
trova	200	2.3	0.2	25	0.2
moxi	400	2.5	0.2	30	0.2
gemi	600	4	0.4	24	0.2

Indications of new fluoroquinolones

Consider local epidemiology, and do not believe it is always a first choice...

The use of the FQ should focus on infections in which

- there is a differential benefit over conventional agents in terms of efficacy, safety, or cost;**
- in infections for which few alternative treatments exist, or**
- against organisms towards which they are sufficiently active to prevent the rapid emergence of resistance.**

Shall we have a very bright future ?



**or some
problems ?**

