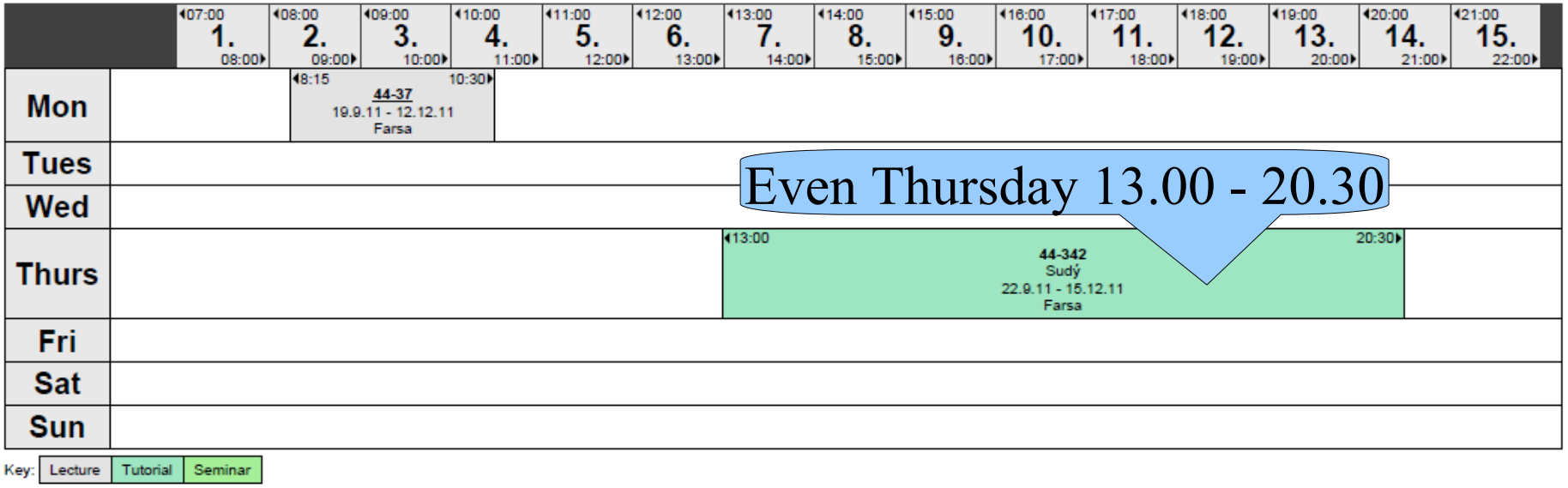
# Medicinal Chemistry II

## Course timetable

**Academic Year:** 2011/2012 **Semester:** ZS **Course:** 3150/FAFB2

**Name:** Medicinal Chemistry II




Key: Lecture | Tutorial | Seminar

# Antibacterial chemotherapeutics

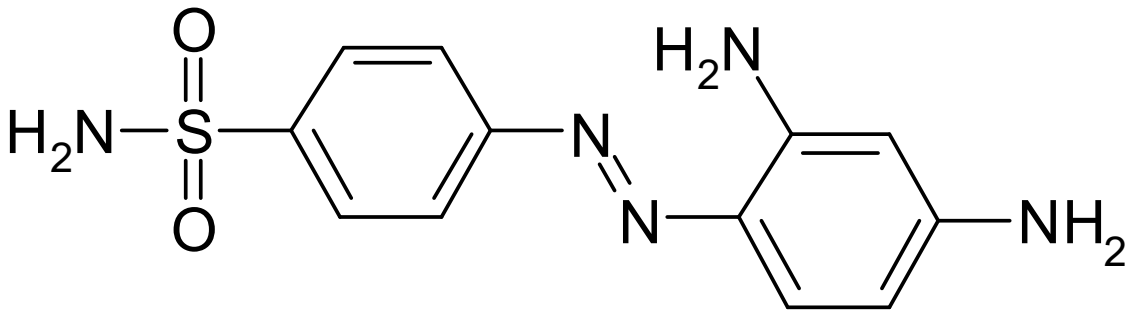
= compounds used for treatment of bacterial infections

Part 1

1. Antibacterial sulfonamides
2. Nitrofuranes
3. Quinolones
4. Tetracyclins

chapters 1.-3. contain.: chemotherapeutics in „narrower word meaning“, i.e. fully synthetic compounds

# Sulfonamides



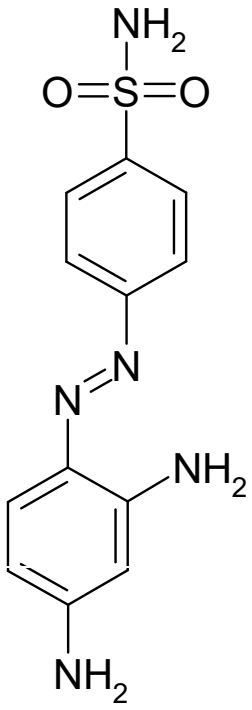
4-(2,4-diaminofenylazo)benzenesulfonamid

## Prontosil rubrum

1932 Mietsch & Klarer - synthesis
Gerhard Domagk - successful tests on activity against *Streptococci*

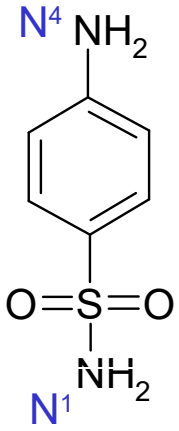
1935 Jacques & Therése Tréfoulé: sulfanilamide is the proper active compound

# Sulfonamides



reduction

by bacteria



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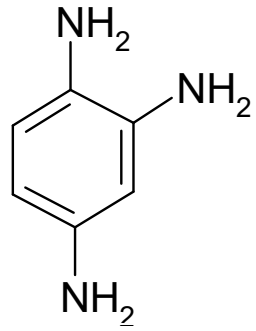


4-(2,4-diaminophenylazo)benzenesulfonamide

**Prontosil rubrum**

4-aminobenzensufonamide

**sulfanilamide**

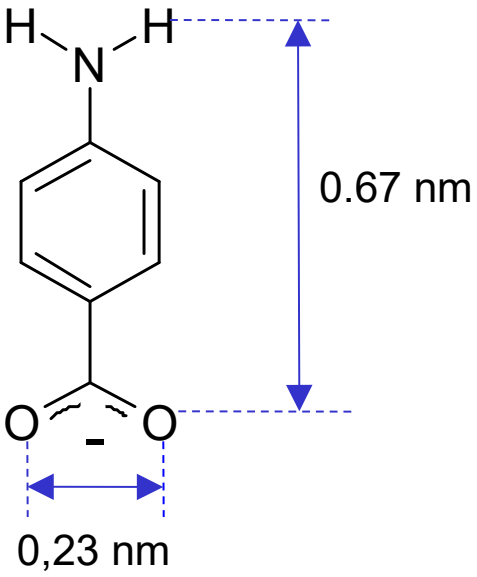
proper active compound

(Prontosil album)

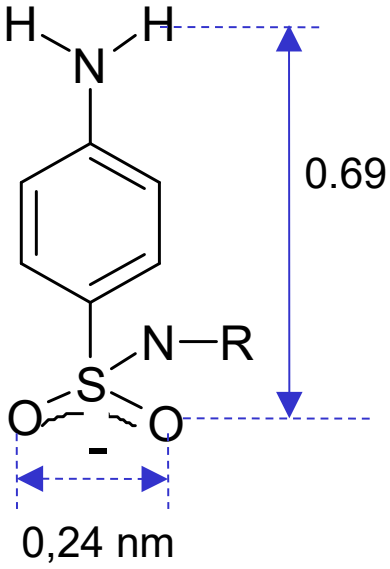
1,2,4-triaminobenzene

# Sulfonamides

## Structure-activity relationships (SAR)




4-aminobenzoate anion



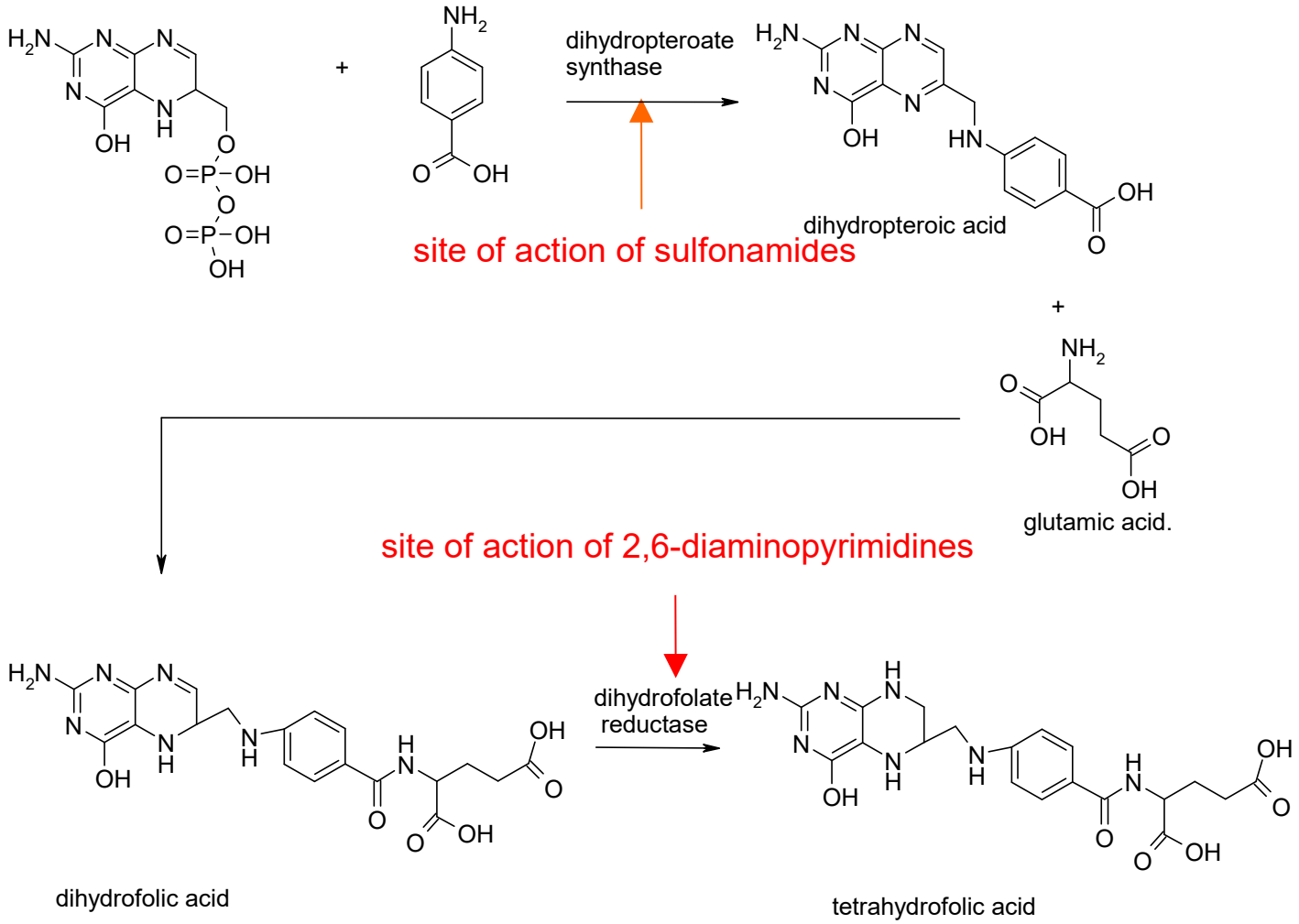

sulfonamide anion

- steric (spatial) similarity ⇒ competition for a binding site

# Sulfonamides

## Mechanism of action

## Scheme of synthesis of tetrahydrofolic acid in bacteria



# Sulfonamides

- effect is **bacteriostatic**, only in combination with 2,6-diaminopyrimidines (trimetoprim) **bactericidal**

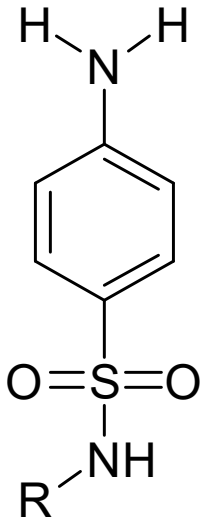
Spectrum of effect:

broad, $G^+$ as well as $G^-$

# Sulfonamides

- the most of used compounds are sulfonamides substituted with a nitrogenous heterocycle on N[1]

Overwiev of structures of commonly used compounds



| R | INN name/official name | Notice | Preparation authorized in the CR |
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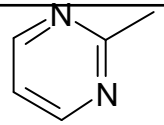
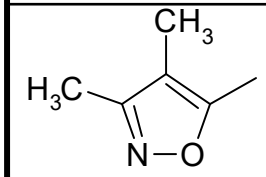
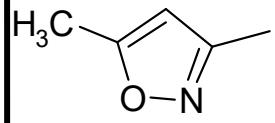
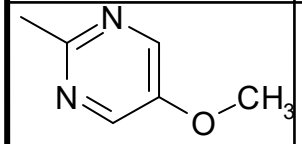
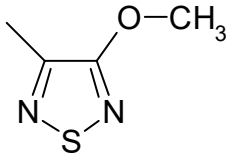
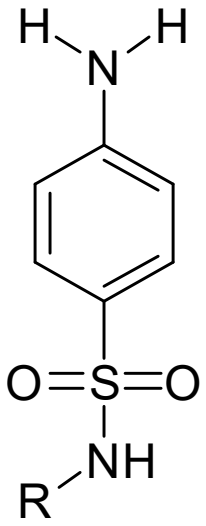
|  | sulfadiazine *Sulfadiazinum PhEur* | a.u.v. | Norodine® 24 a.u.v. inj. |
|  | sulfafurazol (syn. sulfizoxazole [USAN]) | | Sulfisoxazol® tbl. |
|  | sulfamethoxazole | in combination with trimetoprim - cotrimoxazol | Biseptol®, Co-trimoxazol AL®… |
|  | **sulfamethoxydiazine (syn. sulfameter [USAN)** | also leprostatic | |
|  | sulfametrole | in combination with trimetoprim - lidaprim | |

# Sulfonamides

Overwiev of structures of commonly used compounds - continued



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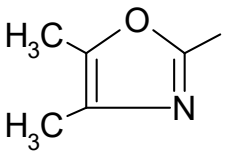
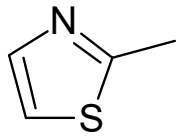
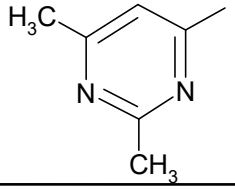
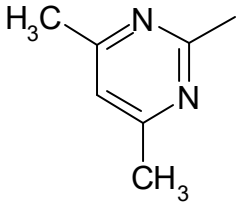
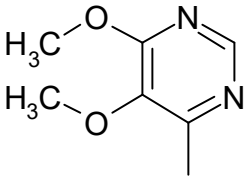
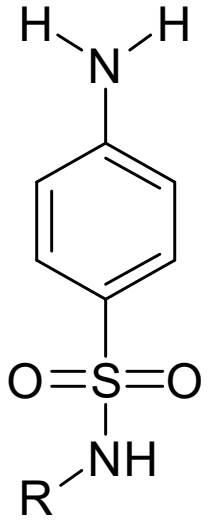
|  | sulfamoxole | in combination with trimethoprim - supristol | |
|  | sulfathiazole *Sulfathiazolum PhEur* | | Sulfathiazol Neo® ung. Argosulfan®2% (Ag salt) |
|  | sulfisomidine | | Aristamid® gel |
|  | sulfadimidine *Sulfadimidinum PhEur* | a.u.v. treatment of coccidiosis | Sulfadimidin Bioveta® a.u.v. plv. sol. |
|  | sulfadoxine *Sulfadoxinum PhEur* | | . |

# Sulfonamides

Overwiev of structures of commonly used compounds - continued



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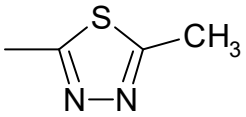
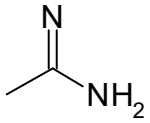
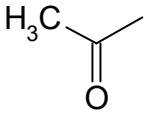
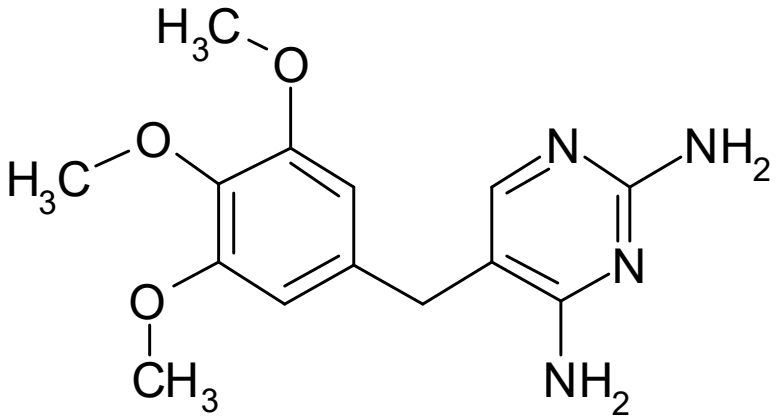
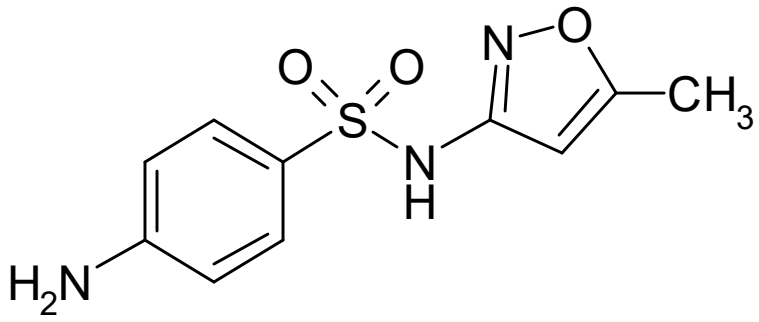
|  | sulfamethizole *Sulfamethizolum PhEur* | | |
|  | sulfaguanidine *Sulfaguanidinum PhEur* | a.u.v. | |
|  | sulfacetamide *Sulfacetamidum natricum monohydricum PhEur* | | |

# Sulfonamides
# Combinations




**trimethoprim**

•originally antimalaric

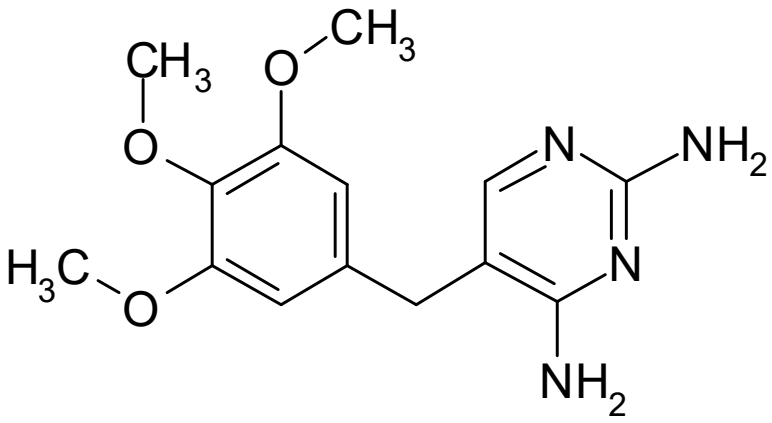



**sulfamethoxazole**

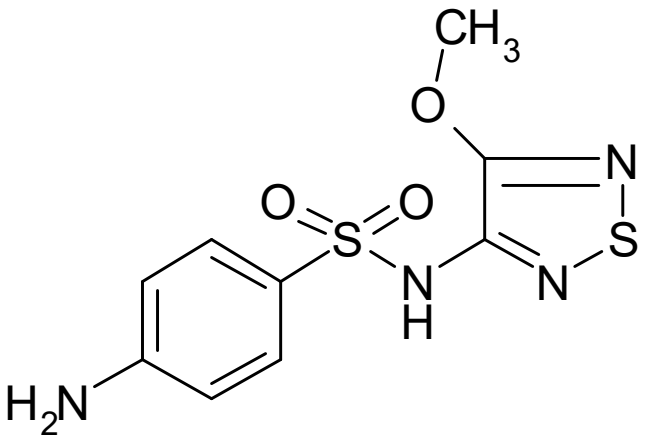
**Cotrimoxazol (co-trimoxazol)**

- baktericidal effect
- used since early 1970$^{th}$

# Sulfonamides
# Combinations



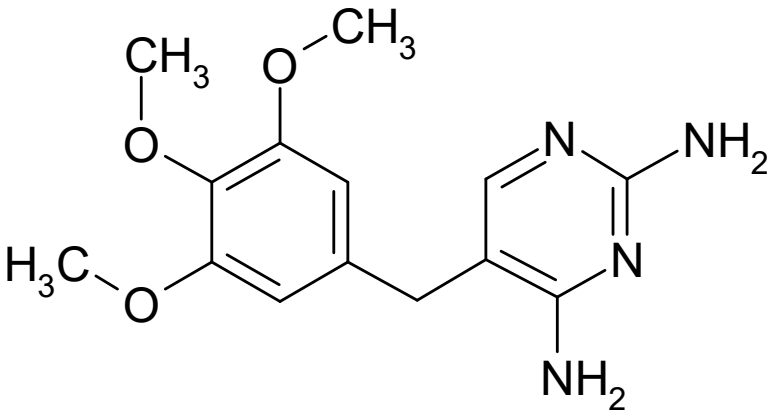

**trimethoprim**



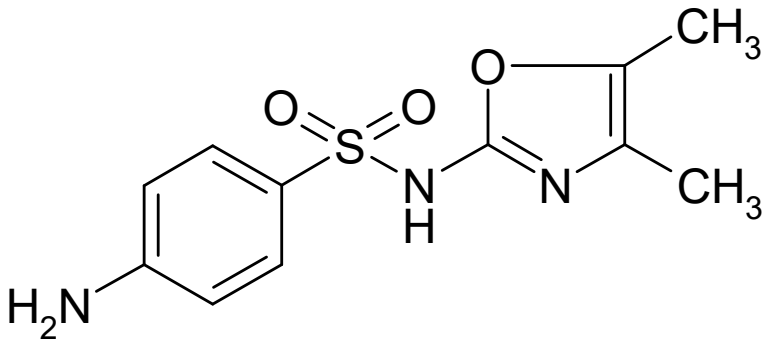

**sulfametrole**

**lidaprim**

# Sulfonamides
# Combinations



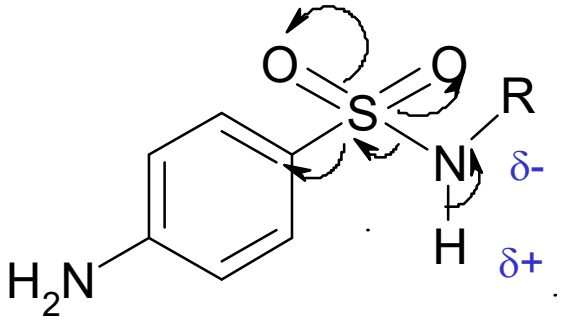

**trimethoprim**

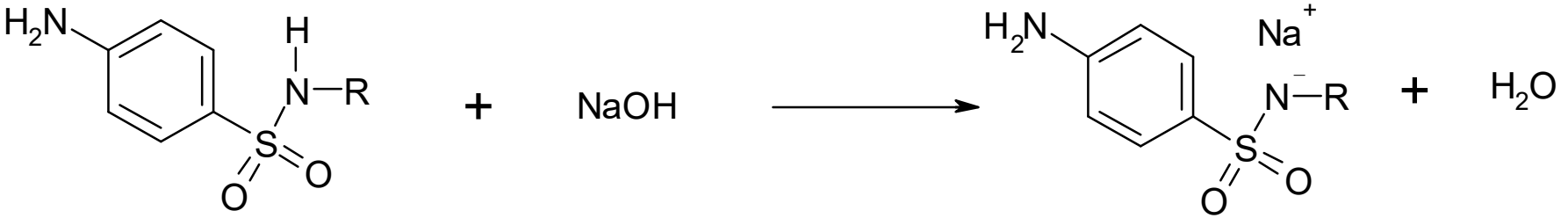


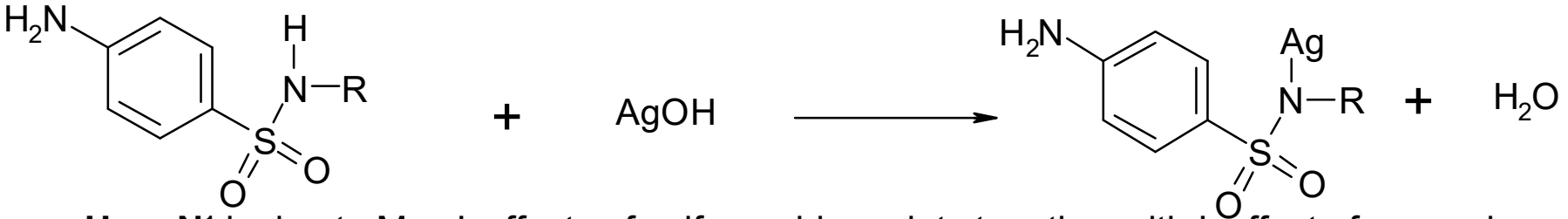

**sulfamoxole**

**supristol**

# Sulfonamides
# Chemical properties

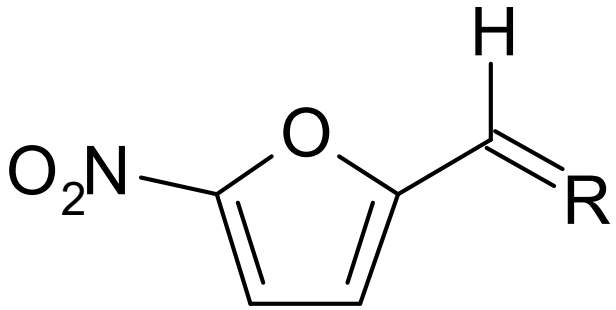


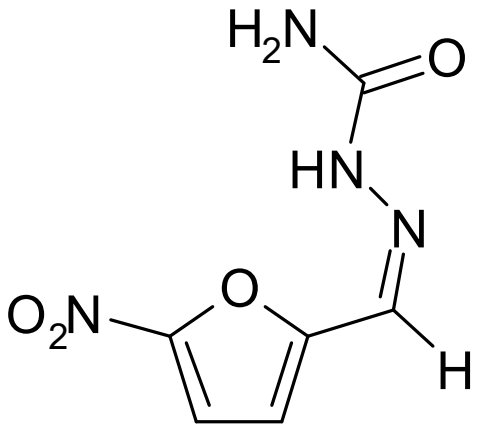

- **H on N$^1$** is due to M$^-$ a I$^-$ effects of sulfonamide moiety together with I$^-$ effect of arom. ring relatively strongly **acidic** ⇒ forming of salts with bases; salts are used in topical preparations (eye drops, oitments)
- **N$^4$** is **very slightly basic** (aniline nitrogen), some **heterocycles** attached to N$^1$ are much **stronger bases** ⇒ forming of therapeutically useful salts with strong acids (hydrochlorides, idy, mesylates etc.).

# Nitrofurans

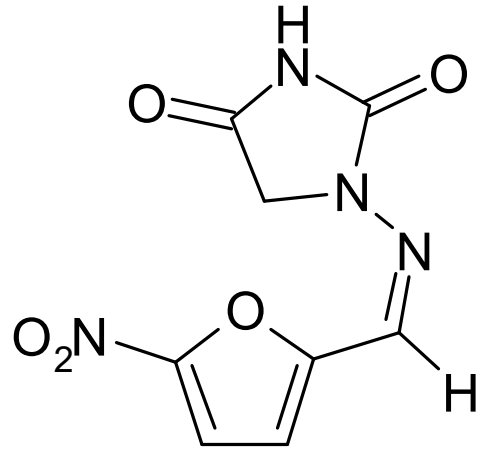



- 5-nitrofurancarbaldehyde derovatives, in most Schiff bases (azomethines)
- -$NO_2$ moiety in position 5 is necessary for their effect
- spectrum: both $G^+$ and $G^-$ bacteria, some protozoa (*Trichomonas vaginalis*)
- infections of urinary tract, topically in infections of skin and genital tract
- mode of action: related to reduction of -$NO_2$ moiety to –$NH_2$ group by bacteria; 2 hypotheses:
- either formed amino compound reacts with bacterial DNA by electrophilic mechanism
- or it is bound to ribosomes and obstruct proteosyntheis
- mutagenic, contraindiacation in the 1th trimester of gravidity (relative exception: nifuratel)

# Nitrofurans

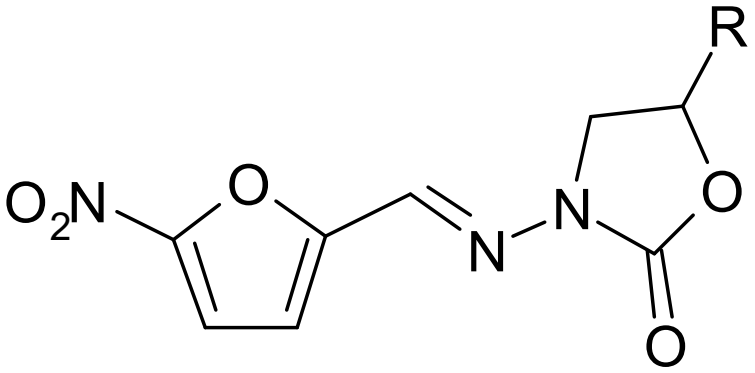



5-nitro-2-furancarbalehyde semicarbazone
**nitrofural**
syn. nitrofurazone [USP, BAN]




1-[(5-nitrofurfurylidene)amino]hydantoin
**nitrofurantoin**
Furantoin®
Urofur® forte/mite a.u.v.

# Nitrofurans




R = H- **furazolidone**

R= $CH_3SCH_2$-

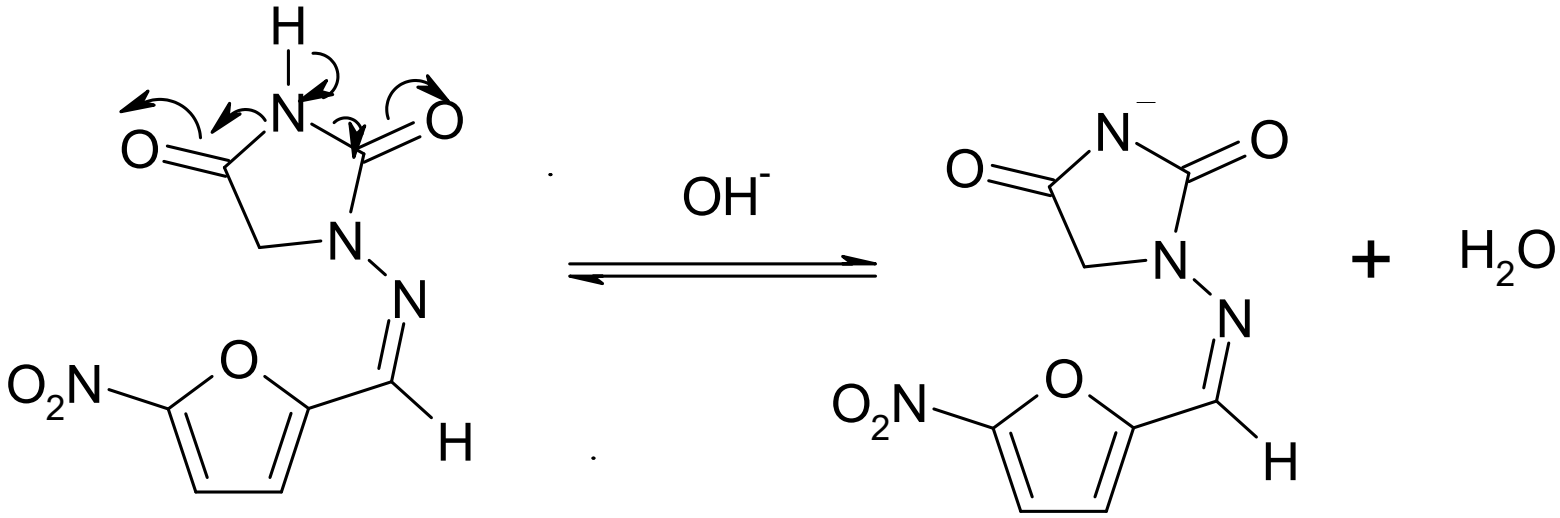
**nifuratel**

Macmiror® tbl., Macmiror complex® ung., sup. vag. (+ nystatin)

# Nitrofurans: physical & chemical properties

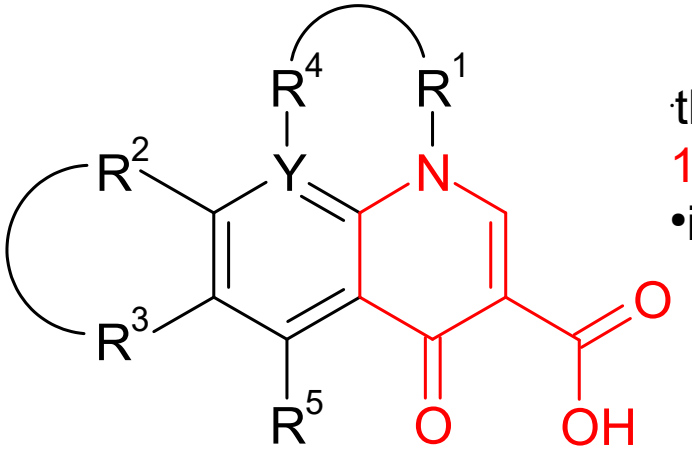
- double bonds of -$NO_2$ and azomethine -CH=N- moieties are conjugated with the $\pi$-electrons system of the furane ring $\Rightarrow$ chromophore $\Rightarrow$ yellow – orange crystallinic compounds
- unstable at the light
- other properties depend on a particular structure

Example: nitrofurantoin




- like other hydantoines, nitrofurantoin is weakly acidic due to $M^-$ effect of both imide carbonyls $\Rightarrow$ forming of salts with bases; $pK_a$ = 7.2

# Quinolones




- the fragment necessary for the effect:
  1-alkyl-1,4-dihydro-4-oxopyridine-3-carboxylic acid
- it must be fused to an other ring (benzene, pyridine)

Y = -N= (1,8-naphthyridine derivatives ) or **–C= (quinoline derivatives)**

$R^1$= alkyl, cykloalkyl, or a part of a heterocycle R1+R4

$R^2$= alkyl, saturated N-heterocycle, $R^1$ + $R^2$ can together form a heterocycle (dioxomethylene moiety)

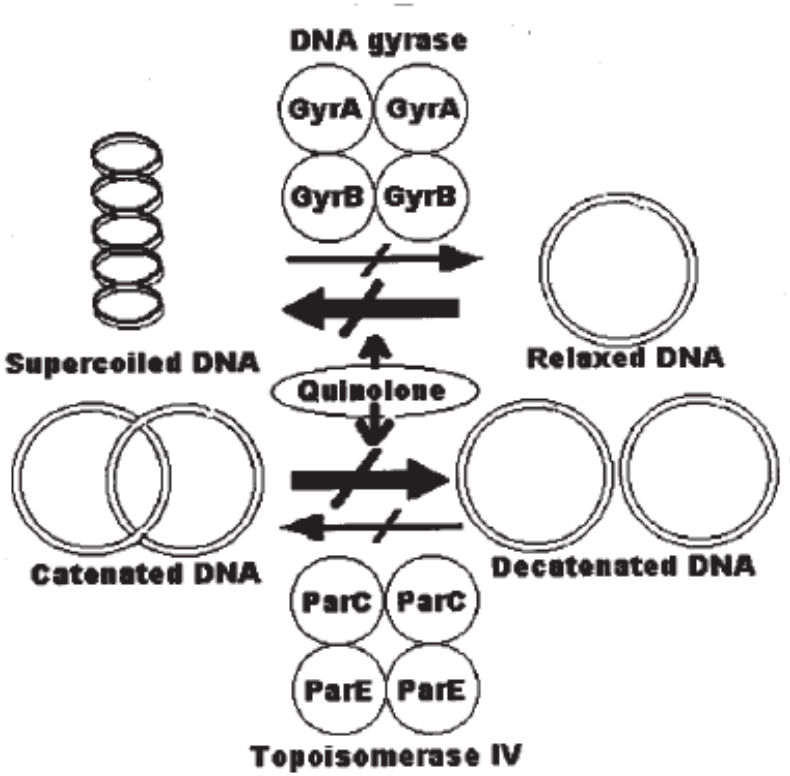
$R^3$= -H, halogen

$R^4$ = -H, -F, or a part of a heterocycle $R^1$+ $R^4$

$R^5$ = -H, $-NH_2$

# Quinolones

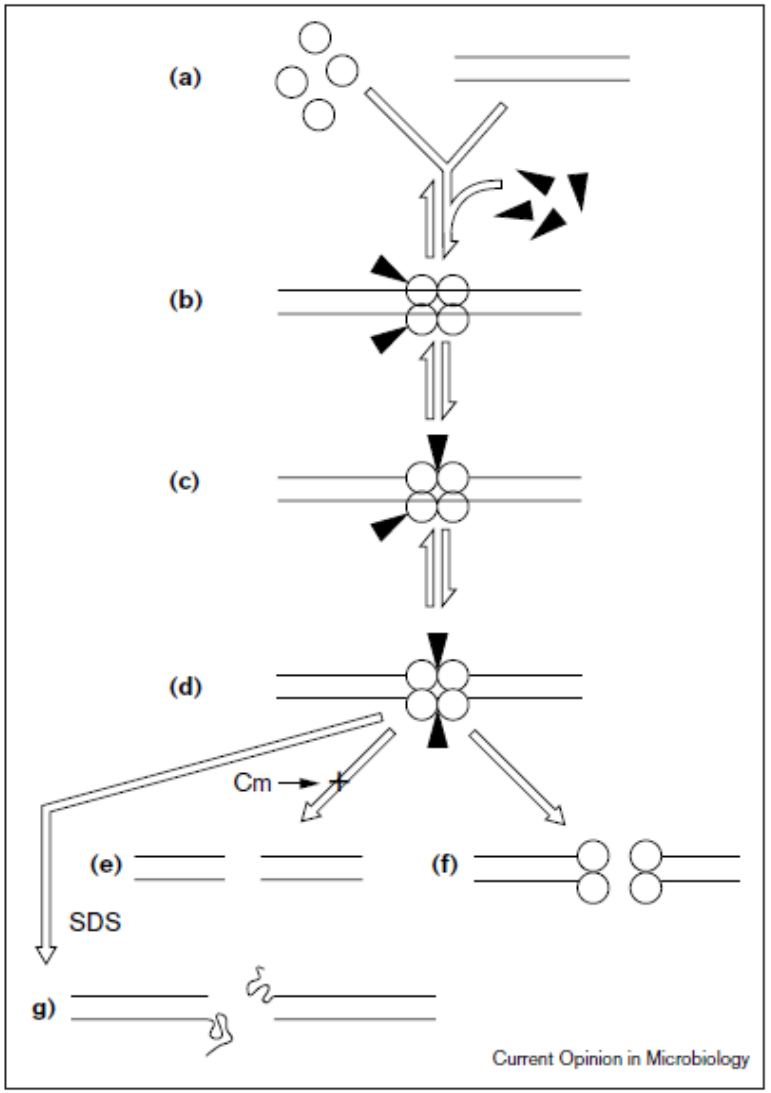
- **mode of action:** interference with the replication of bacteria by inhibition of bacterial gyrase (topoisomerase II) and topoisomerase IV; both enzymes are essential for bacterial DNA replication
- **bactericidal,** acts on both dividing and quiescent-state bacteria
- effect is inhibited by chloramphenicol: completely in the 1st generation, partially in fluoroquinolones



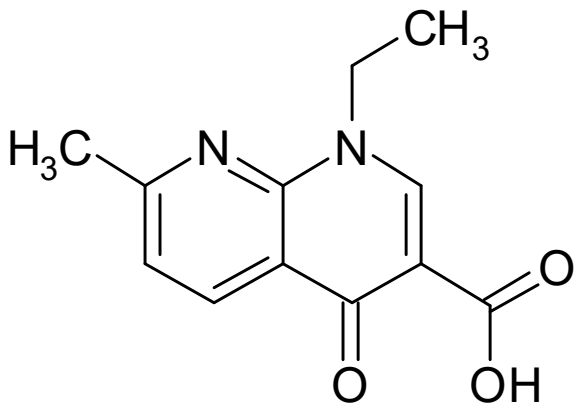

Major activities of DNA gyrase and topoisomerase IV. According to older hypotheses, quinolones simply block these activities by stabilizing a enzyme-DNA complex, which also functions as a barrier to the movement of other proteins such as DNA polymerase and RNA polymerase along the DNA.

# Quinolones: more recent and detailed view to mechanism of action

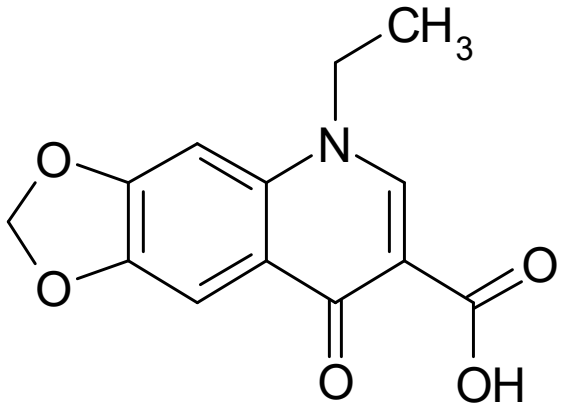
(a) Gyrase or topoisomerase IV (circles), DNA (parallel lines), and quinolones (triangles) form a ternary complex. (b) Quinolones bind to GyrA and ParC subunits of gyrase and topoisomerase IV, respectively. At this stage the DNA is intact. (c) One DNA strand is broken, forming a cleaved complex. Inhibition of DNA synthesis at substaturating concentrations of quinolone correlates with single-strand chromosome breaks. (d) Second DNA strand is broken. Inhibition of DNA synthesis correlates with the activity (MIC). (e) Release of doublestrand DNA breaks from cleaved complex leads to cell death. Inhibition of protein synthesis by chloramphenicol (Cm) completely blocks the lethal action of first-generation quinolone inhibitors of gyrase (nalidixic acid, oxolinic acid). (f) Release of lethal double-stranded DNA breaks via subunit dissociation. Fluoroquinolone lethality is incompletely blocked by chloramphenicol, requiring a second lethal pathway. (g) Release of double-strand DNA breaks by cell lysis in the presence of sodium dodecyl sulfate (SDS); single-strand breaks are released if cells are lysed at step (c).



# Quinolones
## „1st generation“ – treatment of urinary tract infections

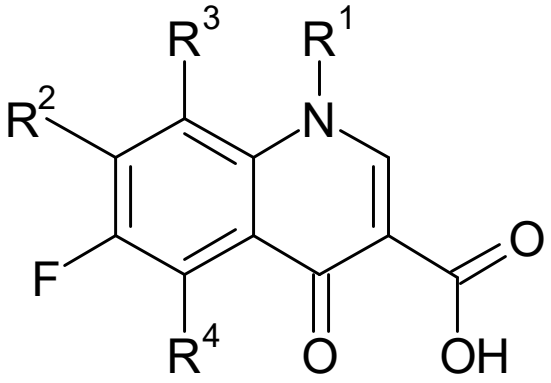



**nalidixic acid**
•mainly $G^-$




**oxolinic acid**
Desurol®
•mainly $G^-$, *E. coli, Proteus, St. aureus*

# Quinolones
## „2nd - 4th generation“ – fluorinated derivatives




$R^1$ = cycloalkyl, alkyl, sec. aminogroup, or a part of a heterocycle $R^1$+$R^3$

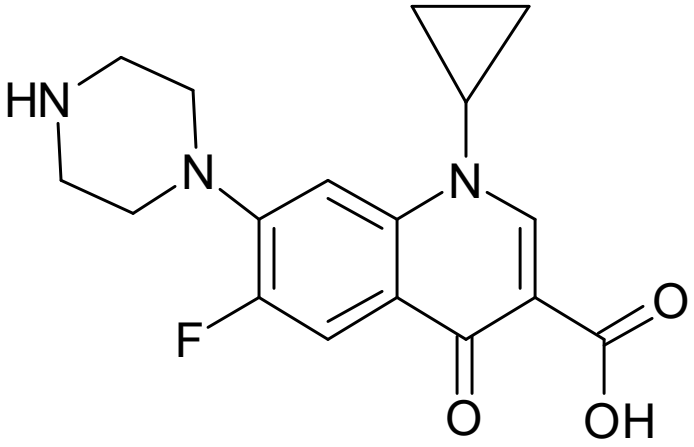
$R^2$ = saturated basic heterocycle attached through nitrogen

$R^3$ = -H, -F, or a part of a heterocycle $R^1$+ $R^3$

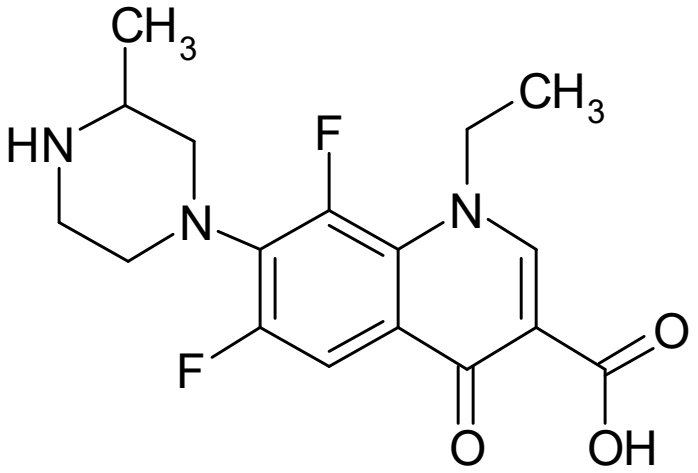
$R^4$ = -H, -$NH_2$

- 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids substituted in positions 1 and 7, less frequently also 8, exceptionally 5
- spectrum: broad, $G^+$ i $G^-$, e.g. *E. coli, Citrobacter, Klebsiella, Enterobacter, Yersinia, Serratia, Providencia, Vibrio, Pseudomonas aeruginosa, Proteus, Salmonella, Shigella, Legionela…*
- therapy of systhemic infections, urinary tract, eyes, GIT…

# Quinolones
## „2nd and 3rd generation“ – fluorinated derivatives
Overview of used compounds



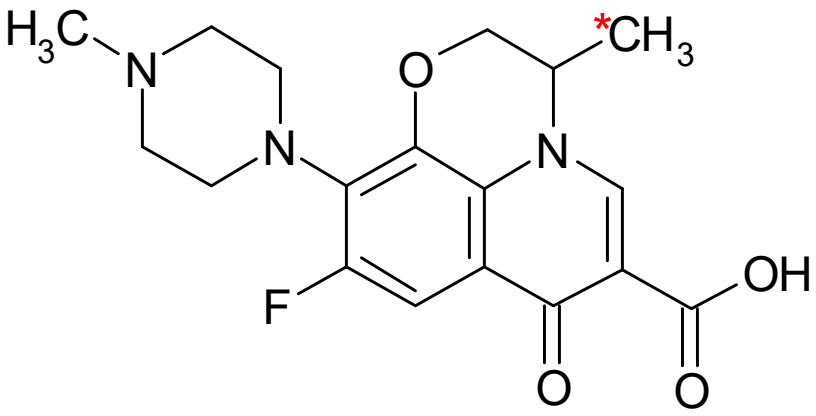

**ciprofloxacin**
Ciphin®



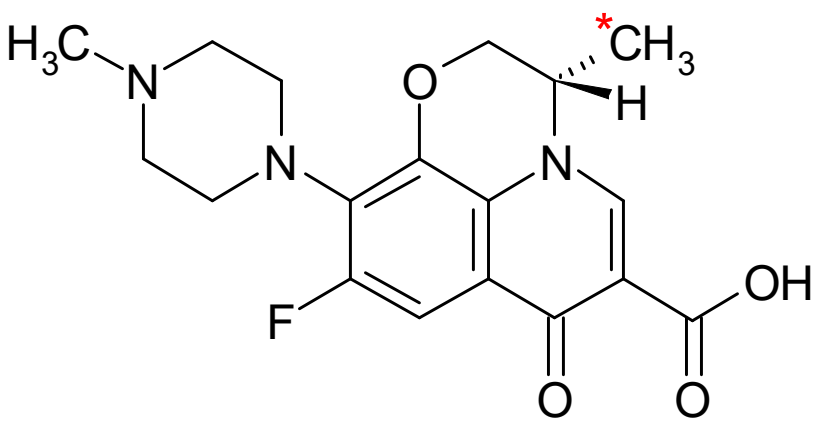

**lomefloxacin**
Maxaquin® tbl. obd.

- spectrum includes also some strains *M. tuberculosis*
- as bases or salts with acids

# Quinolones
## „2nd and 3rd generation“ – fluorinated derivatives
Overview of used compounds - continued

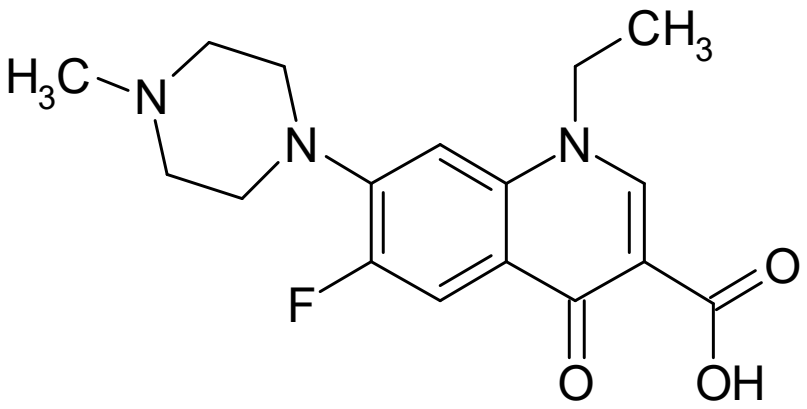



**ofloxacin**
-racemate
Ofloxin® tbl.

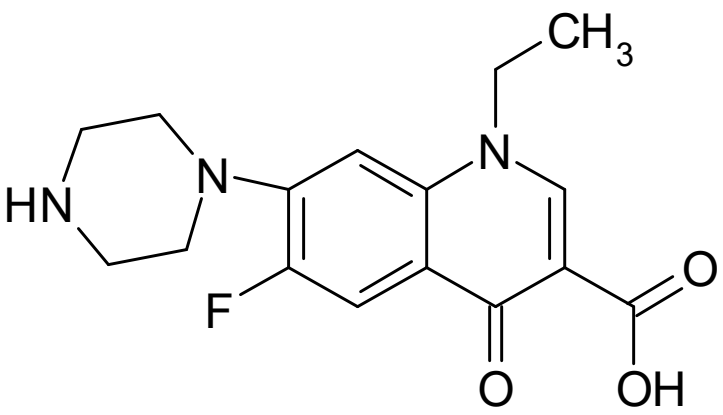



**levofloxacin**
- pure **S** – (**-**) -enantiomer
Tavanic® tbl. obd., inf. sol.

# Quinolones
## „2nd and 3rd generation“ – fluorinated derivatives
Overview of used compounds - continued

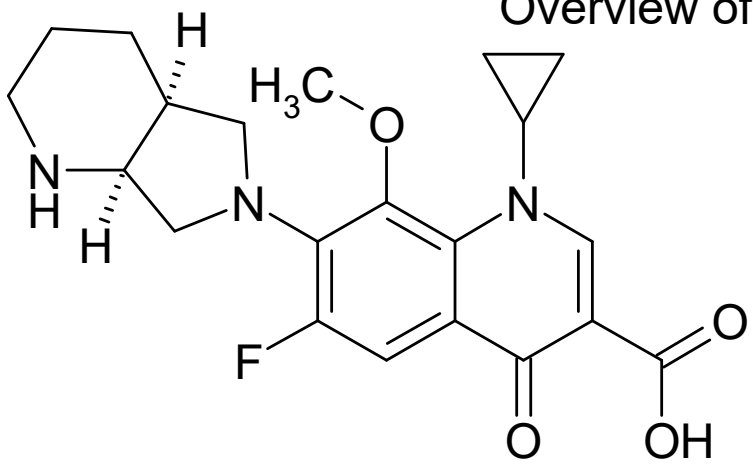



**pefloxacin**
Abaktal® tbl., inj.




**norfloxacin**
Nolicin® tbl. obd.

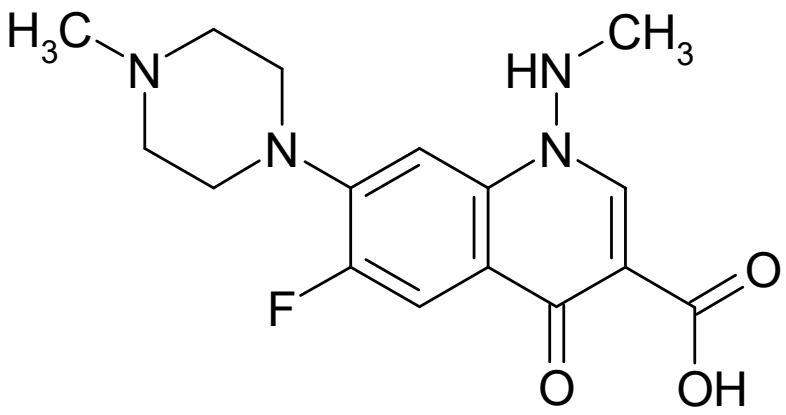
# Quinolones
## „2nd and 3rd generation“ – fluorinated derivatives
Overview of used compounds - continued




1-cyclopropyl-6-fluoro-8-methoxy-7-(octahydropyrrolo[3,4-b]pyridine-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

**moxifloxacin**

Avelox® tbl. obd.

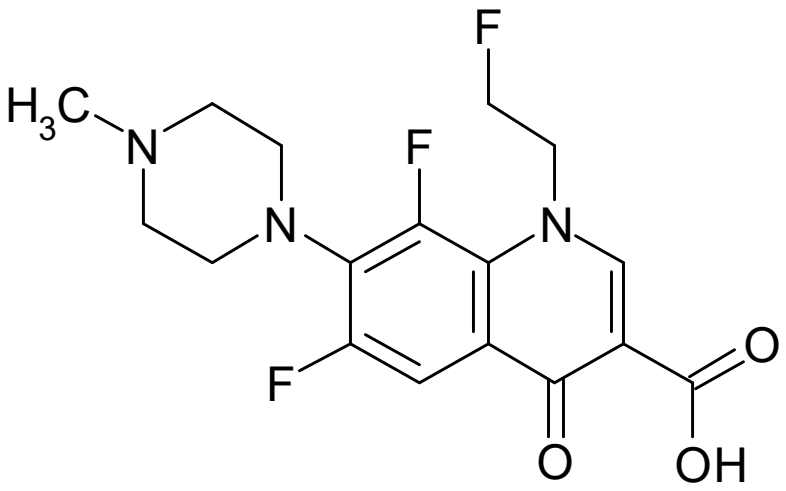



**amifloxacin**

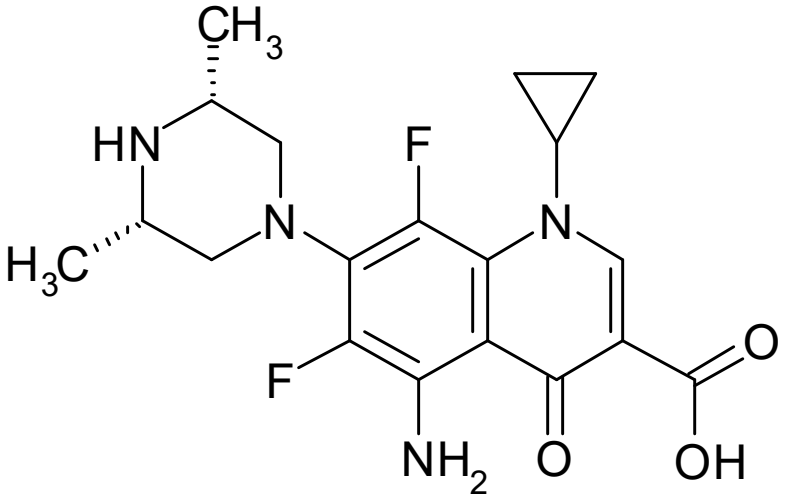
# Quinolones

## „3rd and 4th generation“ – fluorinated derivatives

Overview of used compounds



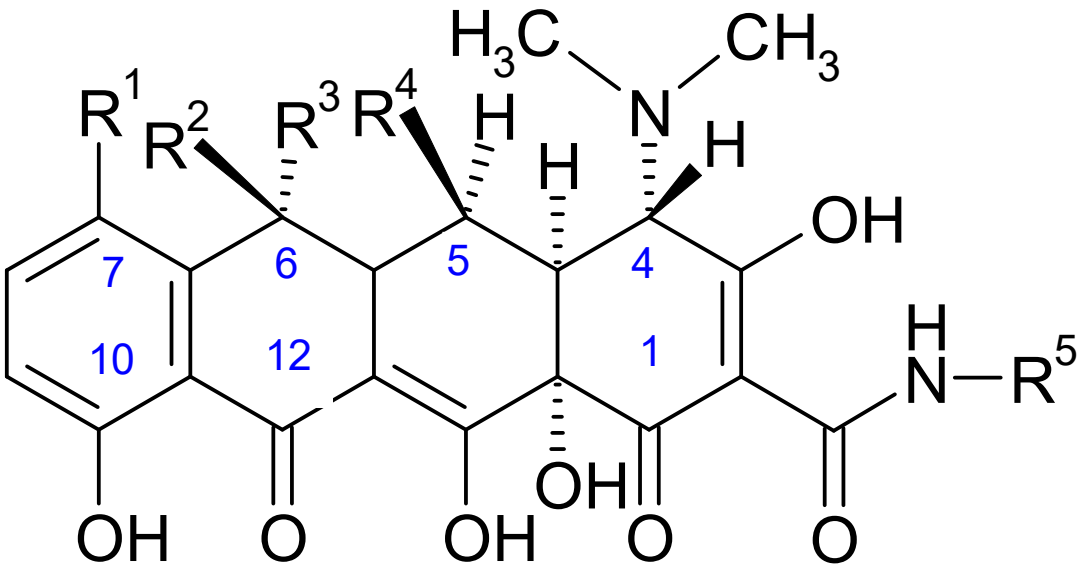

**fleroxacin**
3rd generation
Quinodis Roche® tbl. obd.




**sparfloxacin**
4th generation
Zagam® tbl. obd.
- also *Mycobacterium sp.*
- serious systemic infections

# Tetracyclines

- „true“ antibiotics: initial compounds produced by microorganisms




$R^1$ = -H, halogen, $-NHCH_3$

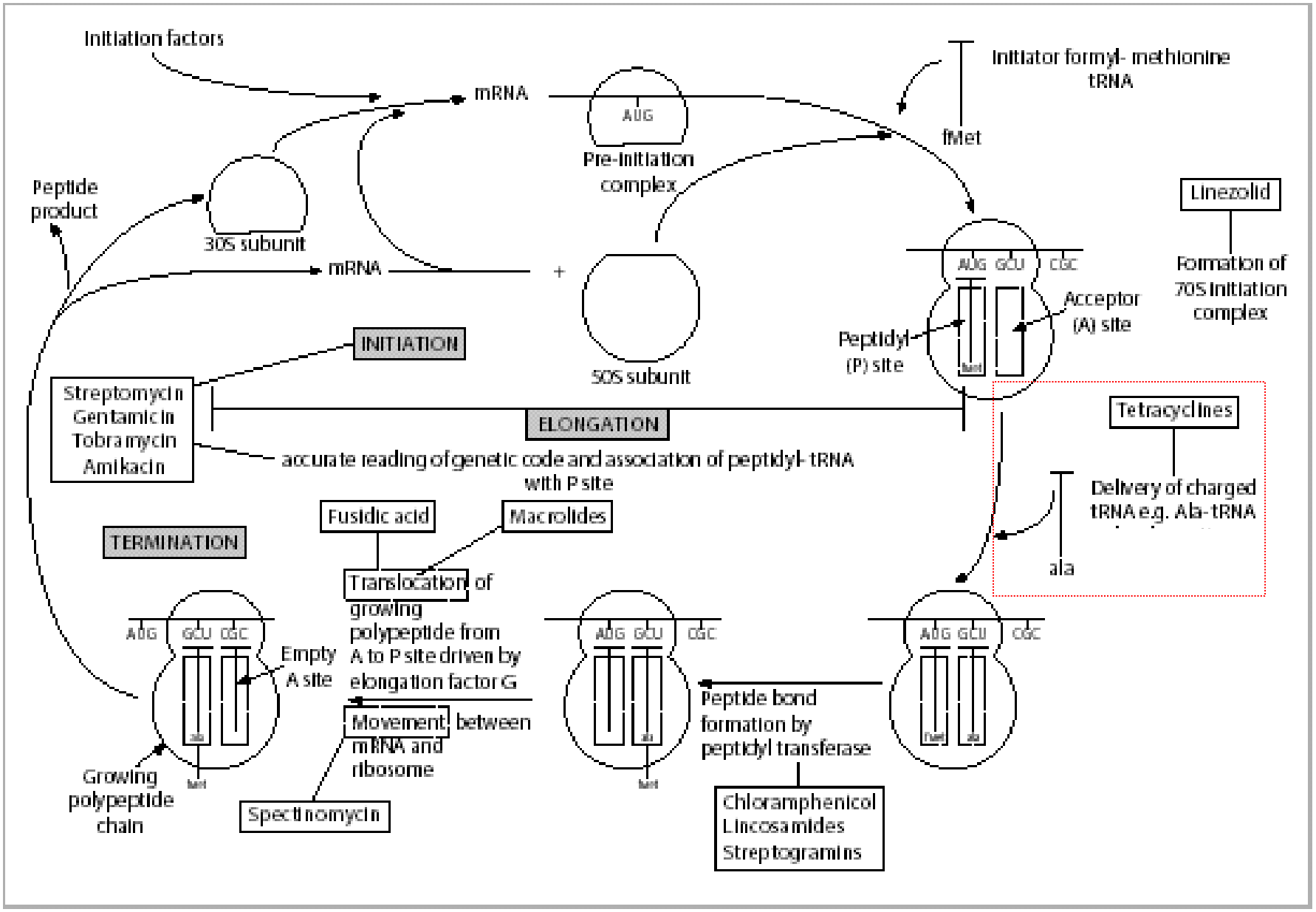
$R^2$ = -OH, -H

$R^3$ = $-CH_3$, -H

$R^4$ = -H, -OH

$R^5$ = H, heterocyclic aminoalkyl, carboxyaminoalkyl

# Tetracyclines
# Mechanism of action



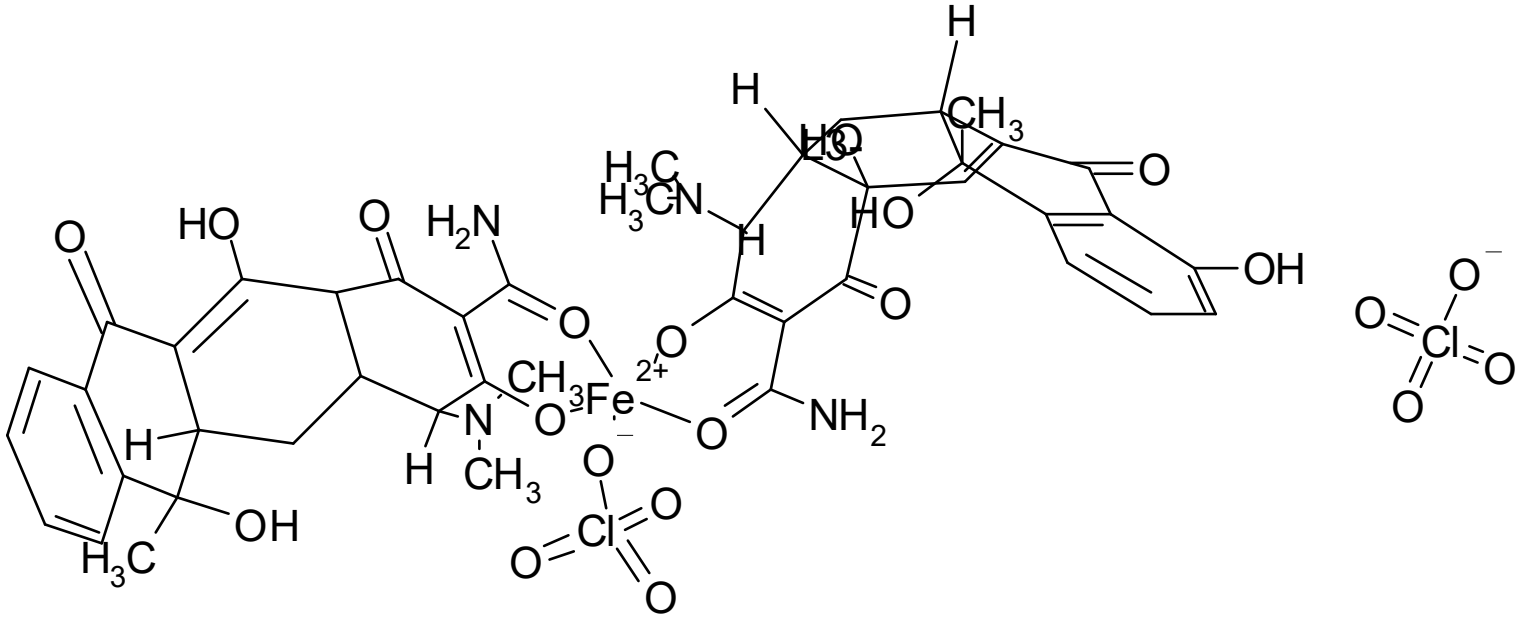
## Tetracyclines
## Mechanism of action

- inhibition of proteosynthesis: inhibit transfer of amino acids attached to tRNA („charged tRNA“) to acceptor site of mRNA
- effect **bacteriostatic** (exception: rolitetracycline)

## Tetracyclines

## Chemical properties

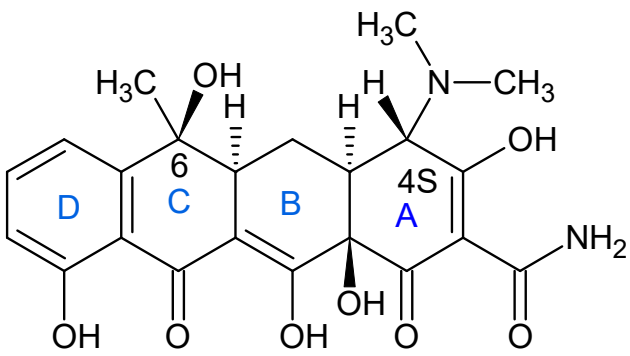
- ability to form coordination compounds bivalent ($Ca^{2+}$, $Mg^{2+}$, $Cu^{2+}$, $Fe^{2+}$, $Zn^{2+}$…), trivalent ($Fe^{3+}$, $Al^{3+}$…) and polyvalent cations
- complexes are water-soluble and non-absorbable $\Rightarrow$ salts of metals $\downarrow$ effect of tetracyclines
- doxycycline has the lowest affinity to metal ions
- chelates form deposits in teeth and bones, namely growing ones $\Rightarrow$ relative contraindication in childern




A complex of tetracycline with ferrous perchlorate

# Tetracyclines

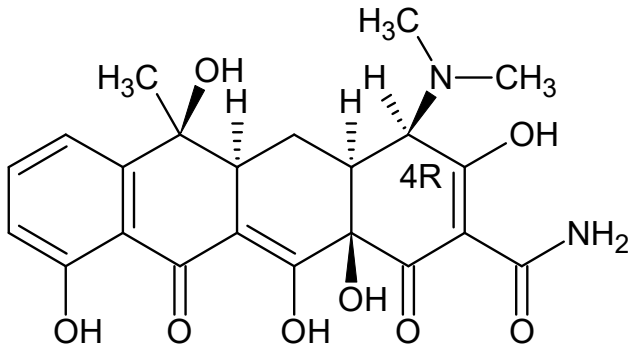
## Chemical properties - continued




tetracycline

$H_2O$

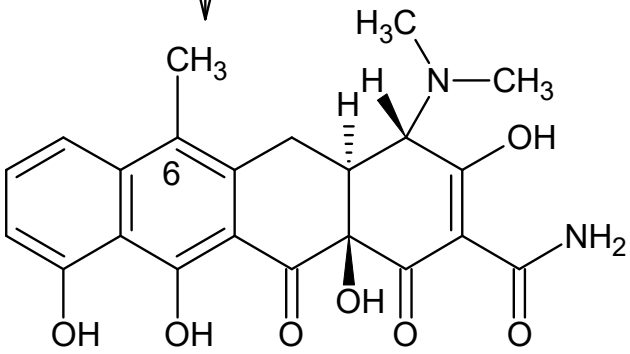
pH 2 - 6




4-epitetracycline

< 10 % activity, nephrotoxic

pH < 2 | - $H_2O$

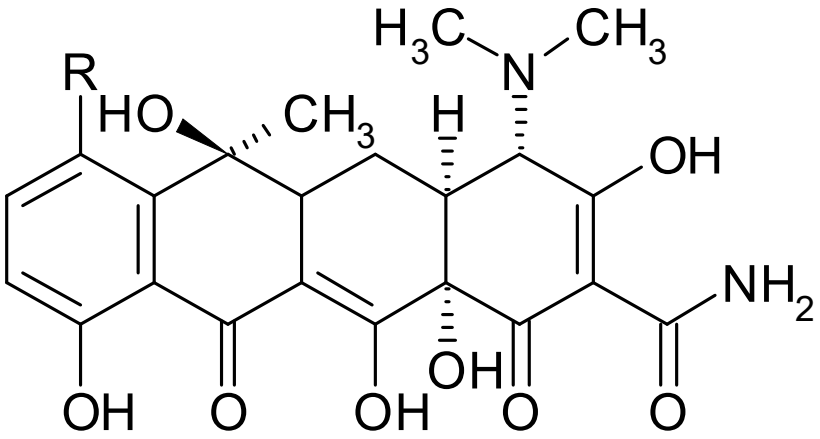



anhydrotetracycline

less active, nephrotoxic

# Tetracyclines

Overview of compounds




R = H **tetracycline**

- isolated from *Streptomyces viridifaciens*

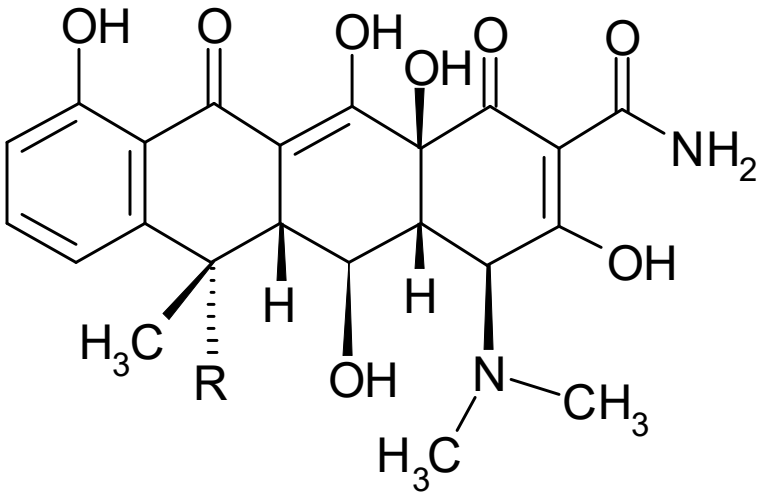
Rimatet® cps.

R = Cl **chlortetracycline**

- isolated from *Streptomyces aureofaciens*
- also antiprotozoal activity
- today a.u.v.
- start material for production of other tetacyclines
- Tetramutin Bio® a.u.v.

# Tetracyclines

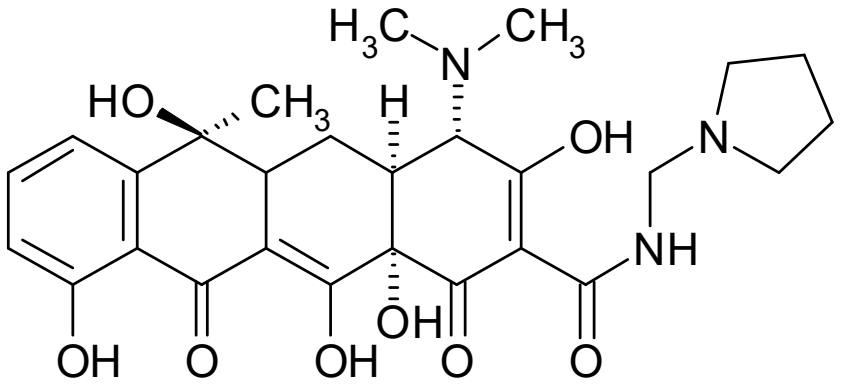
Overview of compounds - continued




R = OH **oxytetracycline**
Oxytetracycline® cps.
R = H **doxycycline**
Deoxymykoin® tbl.

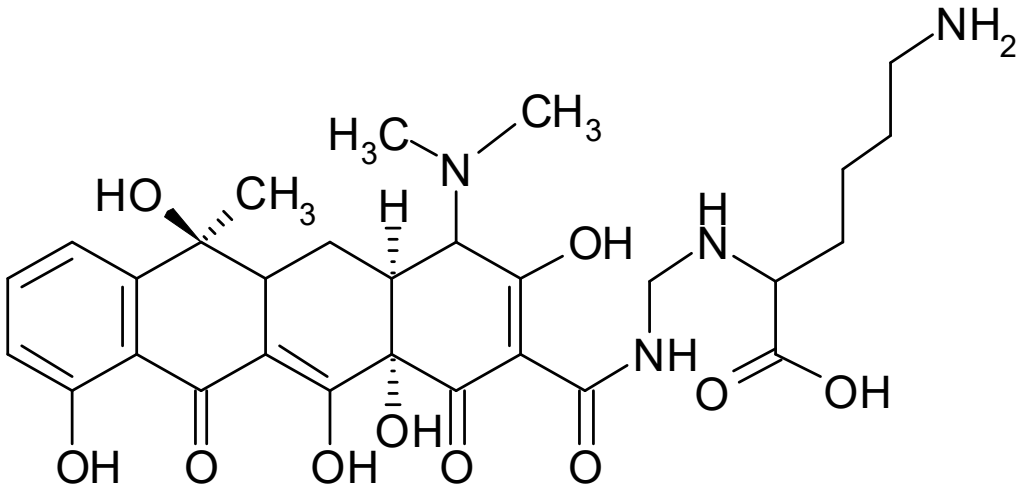
# Tetracyclines

Overview of compounds - continued




**rolitetracycline**

- bactericidal
- injection administration only

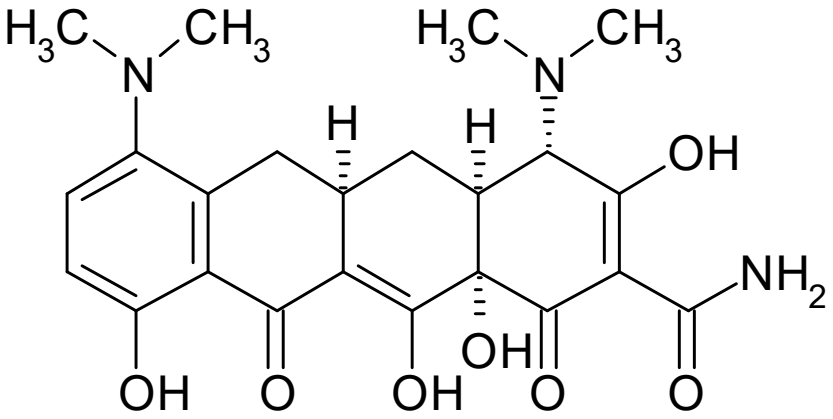



**lymecycline**

Tetralysal® cps.

# Tetracyclines

Overview of compounds - continued

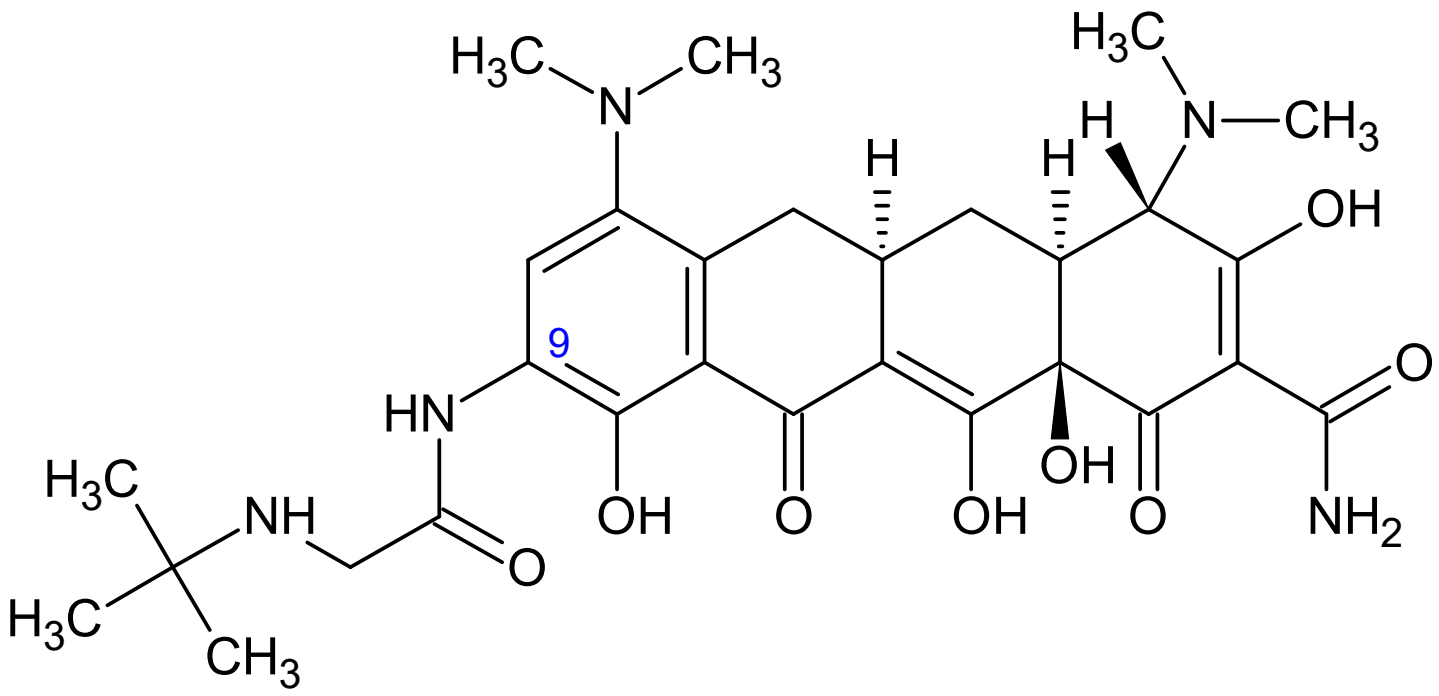



**minocycline**

Skid® tbl.

# Tetracyclines

Overview of compounds: newer subgroup of **glycylcyclines**




**tigecycline**

•complicated infections of the skin and soft tissue (the tissue below the skin), but not foot infections in people with diabetes

• infections in the abdomen

•only in hospitals

Tygacil ® inf. plv. sol.