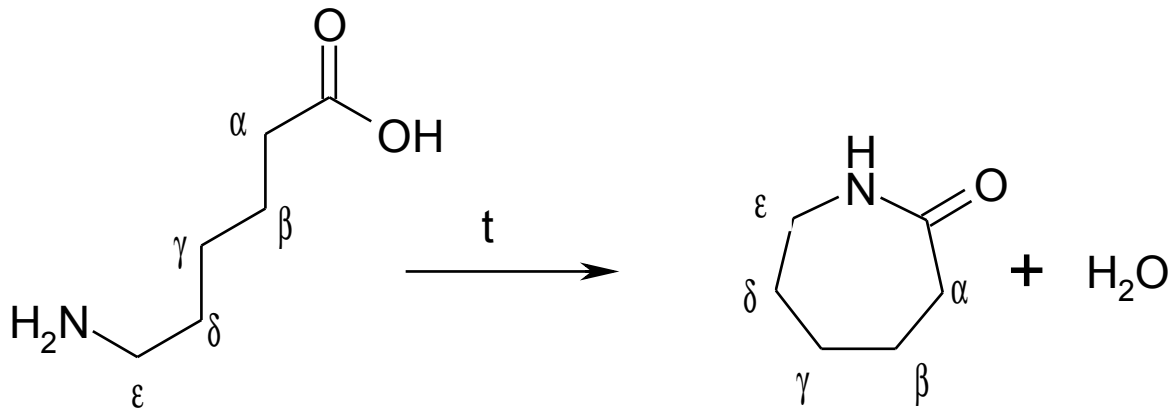
Antibacterial chemoterapeutics 2

1. β-lactame antibiotics
   1.1 Penicillins
   1.2 Cephalosporins
2. Macrolide antibiotics
3. (Poly)peptide antibiotics
4. Aminoglycoside antibiotics

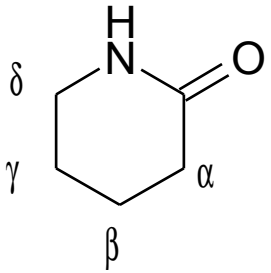
β-lactame antibiotics

Lactams = internal amides of amino acids

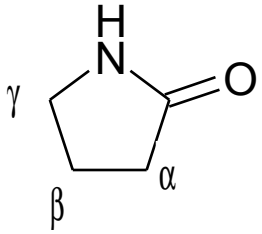


6-aminohexanoic acid
ε-aminocaproic acid

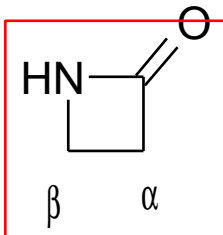
azepan-2-on
ε-caprolactam
6-hexanlactam



piperidin-2-on
δ-valerolactam
5-pentanlactam

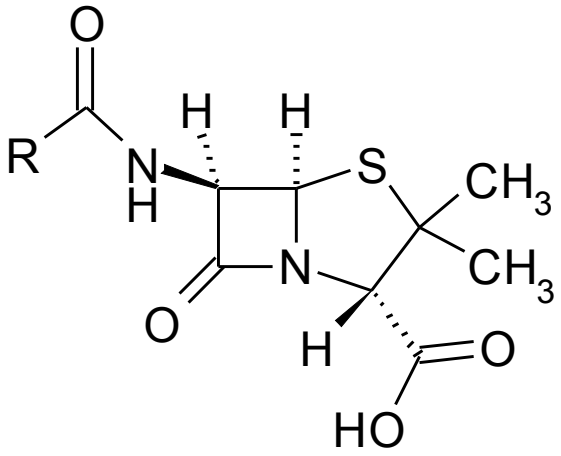


pyrrolidin-2-on
γ-butyrolactam
4-butanlactam

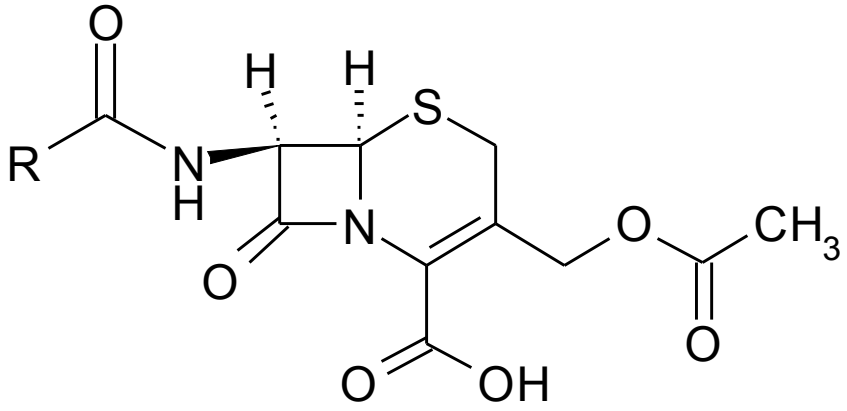


azetidin-2-on
β-propiolactam
3-propanlactam

β-lactame antibiotics



Penicillins
N-acyl-6-aminopenicillanic acids



Cephalosporins
N-acyl-7-aminocephalosporanic acids

Mechanism of action

- inhibition of cell wall synthesis by binding to specific proteins

Penicilins
History

World

1928(9) – **Alexander Fleming** – isolated a liquid concentrate inhibiting growth of bacteria from a mould of *Penicillium* species

1939 - 1943 Fleming, Florey, Chain & Johnson – isolation and constitution of penicillins

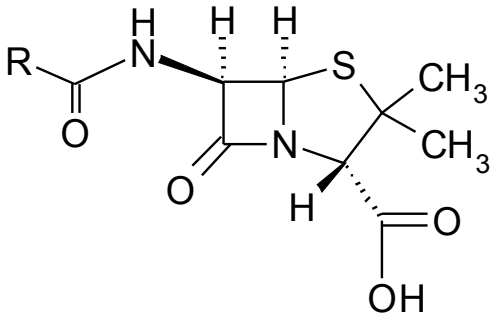
1945-Nobel prize for Fleming, Florey and Chain

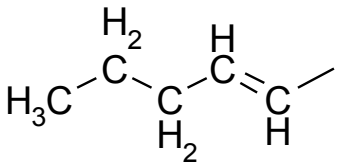
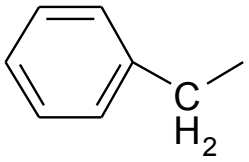
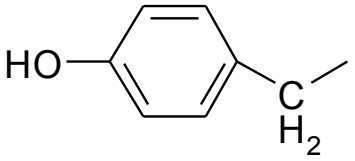
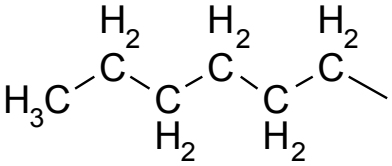
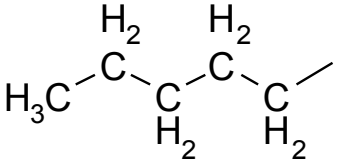
Czech territory

1943 – Málek, Fragner, Herold, Hais etc**. –** Mykoin BF 510

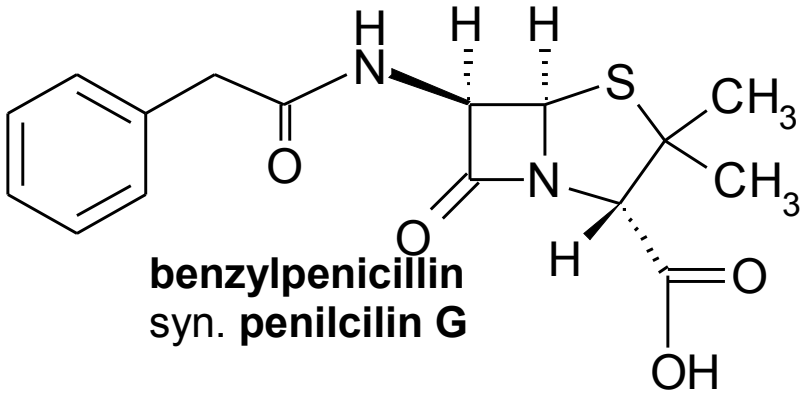
Penicillins

The initial „amorphous penicillin“ was a mixture of several compounds:



R	Penicillin	
	pentenyl-	F
	benzyl-	G
	*p*-hydroxybenzyl-	X
	heptyl-	K
	amyl-	dihydro-F

Penicillins
Benzylpenicillin and its problems

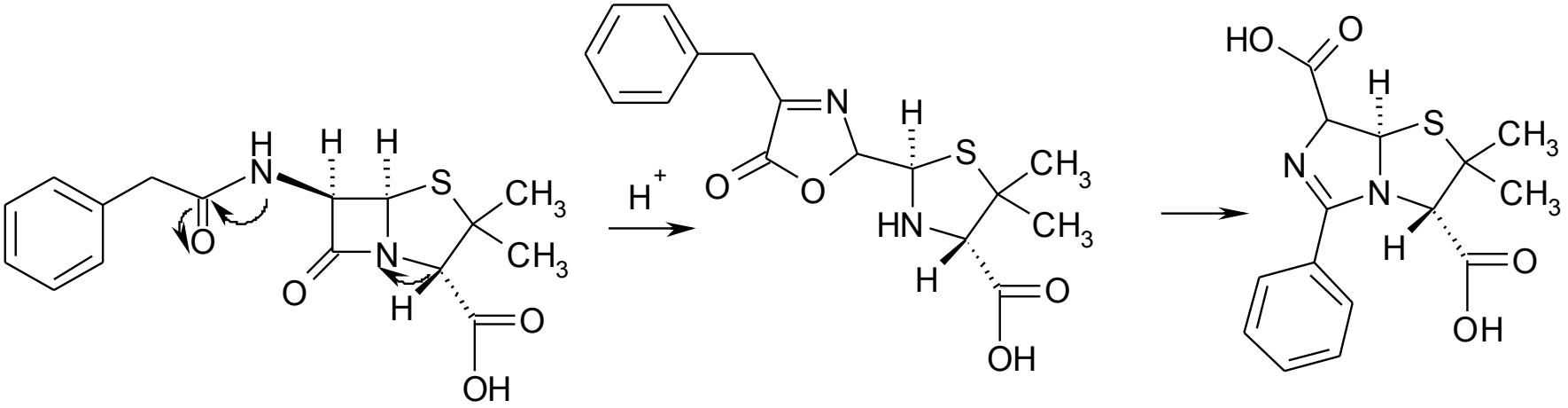


benzylpenicillin
syn. **penilcilin G**

- production of benzylpenicillin by the mould ↑ by addition of phenylacetic acid into its broth

Problems:

- weak binding to plasmatic proteins ⇒ fast excretion ⇒ frequent administration is necessary
- instability in acid media of stomach (see reaction scheme) ⇒ impossibility of p.o. application

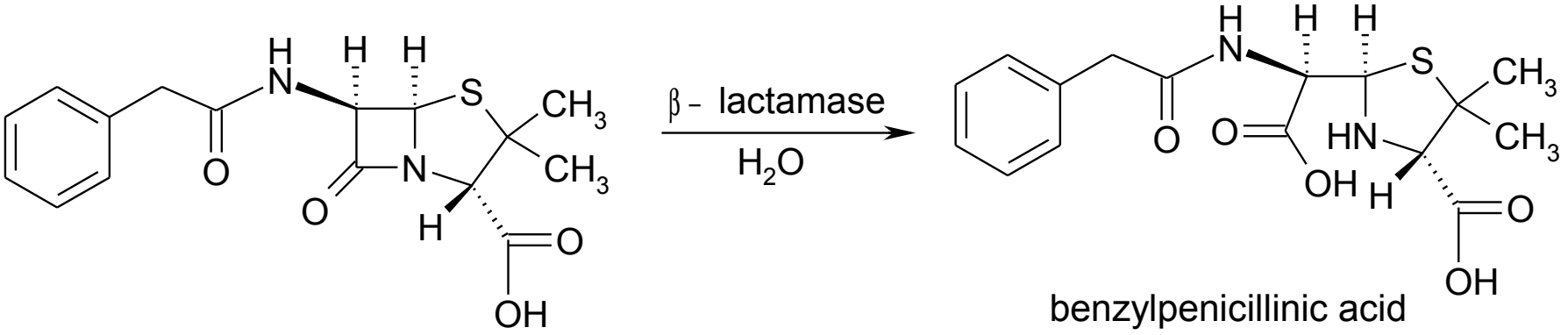


benzylpenicillin

penillic acid

Penicillins
Benzylpenicillin and its problems

3. Sensitivity to penicillinases (β-lactamases – enzymes catalysing hydrolytic cleavage of the β-lactame ring) – see the scheme

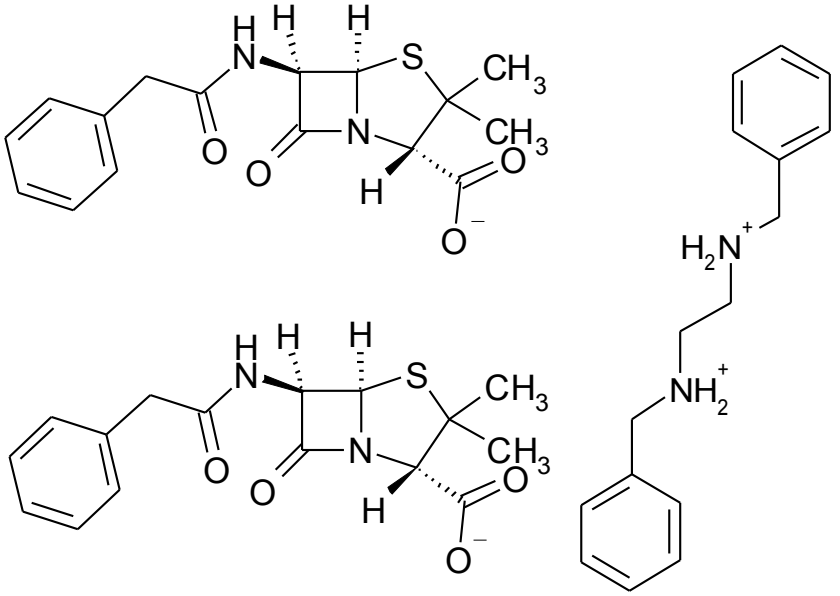


4. Rel. narrow spectrum – only G^+ strains (*Streptococcus, Staphylococcus, Clostridium, Neisseria, Corynebacteriun, Bacilus anthracis …)*

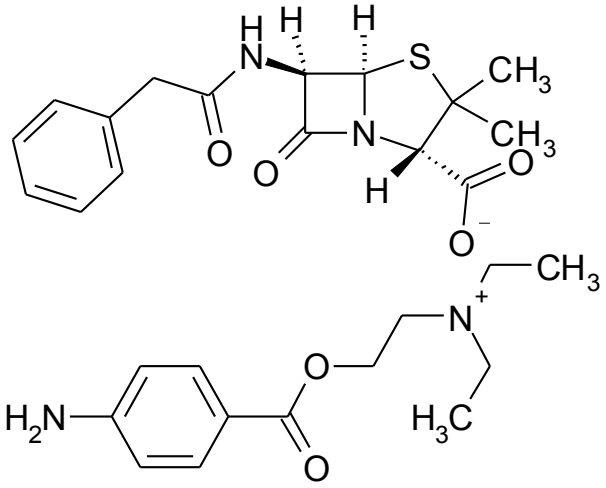
5. Inducing allergies – anaphylactic shock – caused by 6-aminopenicillanic acid as the impurity – resolved by better purification (chromatography)

Penicillins
Resolving of benzylpenicillin problems

Ad 1. (necessity of frequent application) – poorly soluble salts with organic bases



benzathine benzylpenicillin
Pendepon® inj. sic.

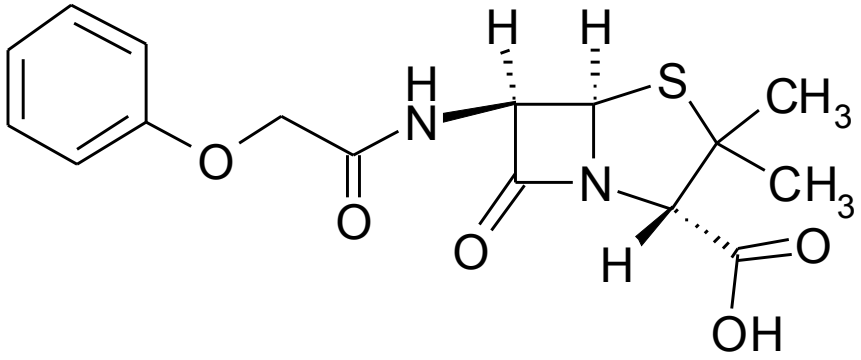


procaine benzylpenicillin
Prokain Penicilin G® Biotika inj. sic.

•depot (= long acting) forms for i.m. injections

Penicillins
Resolving of benzylpenicillin problems

Ad 2. – ↑ of stability in acid media



phenoxymethylpenicillin

syn. **penicillin V**

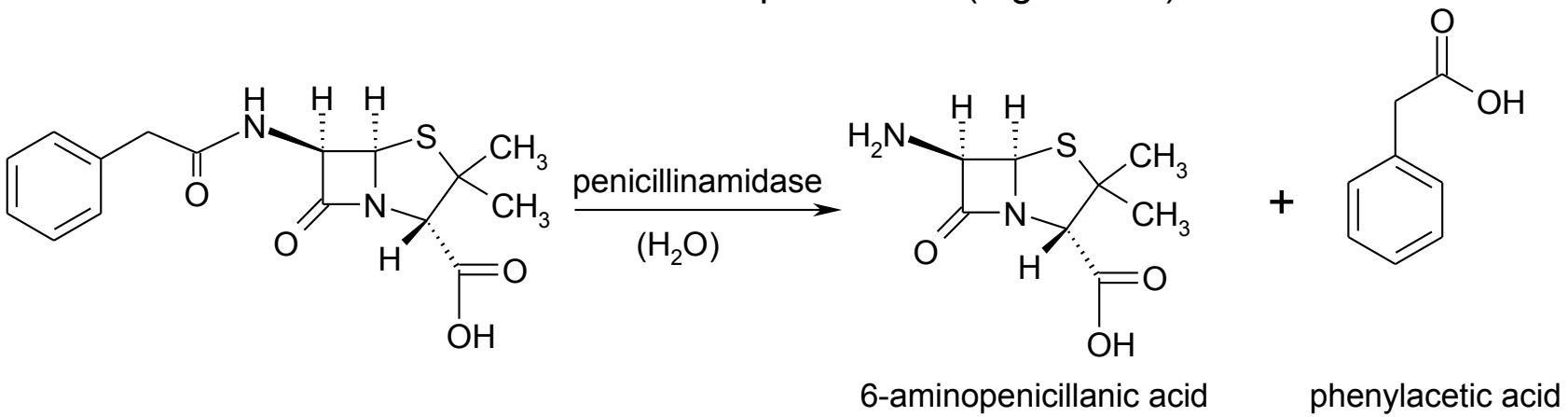
- acquired by addition of phenoxyacetic acid into the broth of the production strain
- suitable for p.o. administration

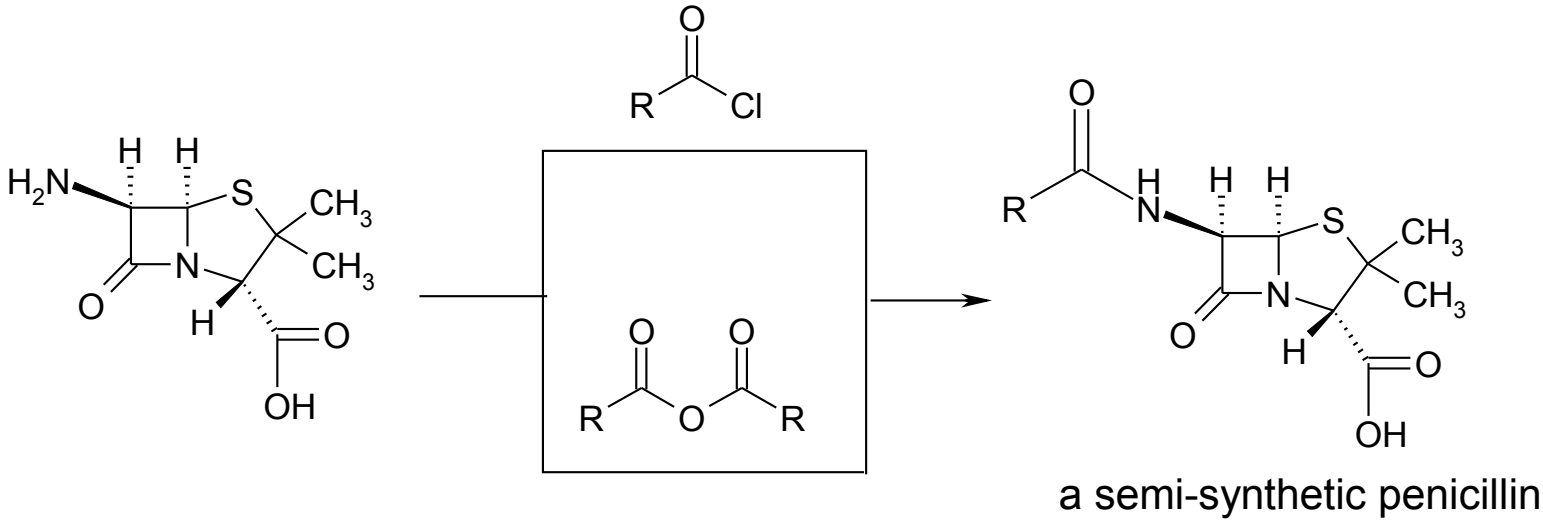
V-Penicilin®, Ospen®

Penicillins

Overall resolving of benzylpenicililn problems – **semi-synthetic penicillins**

- **penicillinamidase (penicillinacylase) –** hydrolyzes acyclic amide bond, not β-lactame ring
- used a microbe which produces it (e.g. *E. coli*)

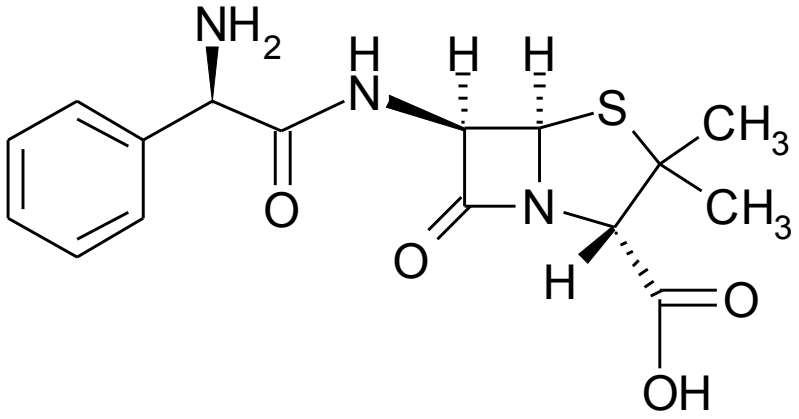




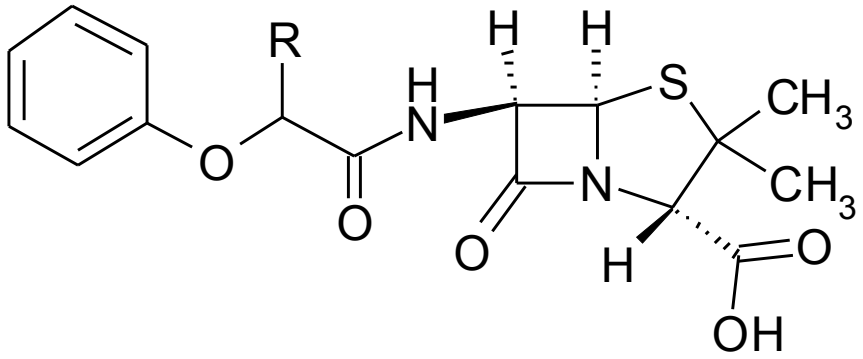
Penicillins

Mostly semi-synthetic penicillins stable in acid media

- stability against acids is increased by electron-donor substituents in N-acyl side chain (I+ or M+ efekt)



ampicillin
Ampicilin ® cps., inj sic.

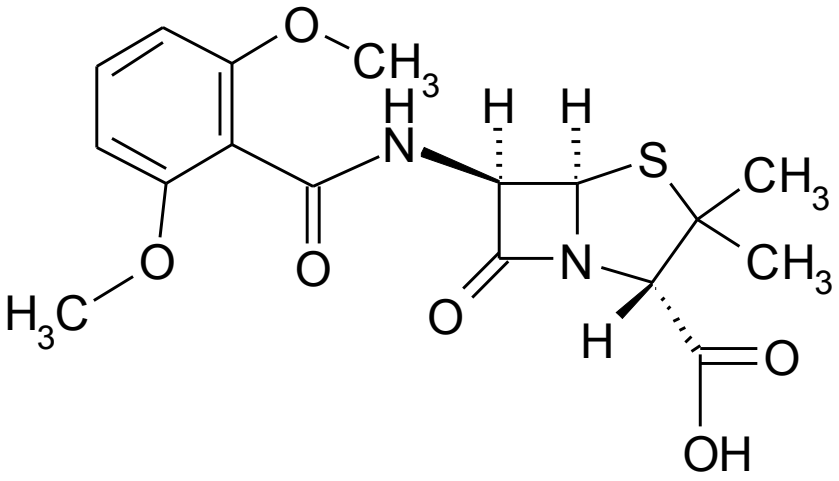


R = -H **phenoxymethylpenicillin**
V-Penicilin® tbl., Ospen tbl. obd.
R = -CH_3 **phenethicillin**
R = -CH_2CH_3 **propicillin**

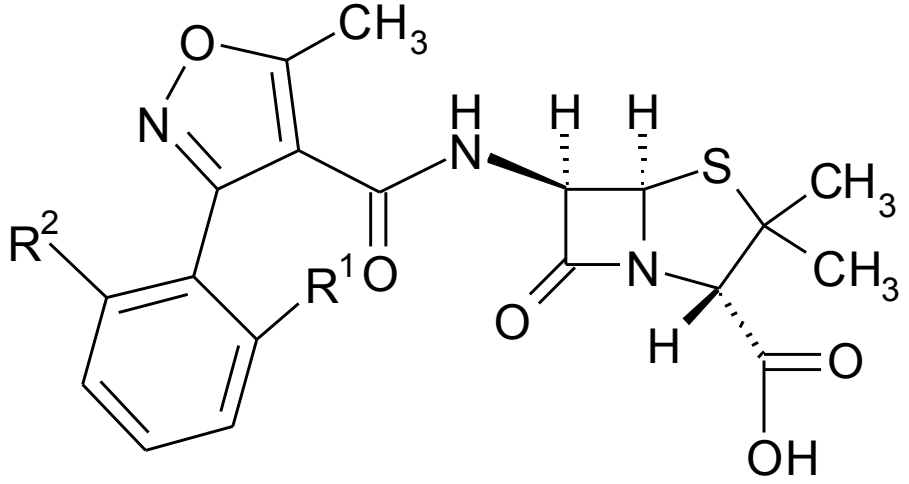
Penicillins

Semi-synthetic penicillins resistant to β-lactamases

•formed by acylation of amino group of 6-aminopenicillanic acid with bulky acyl rest; the lactame ring is then sterically hindered (⇒ protected)



meticillin



$R^1 = R^2 = -H$ **oxacillin**
Prostaphlin® ~~eps.~~, inj. sic.

$R^1 = -Cl$, $R^2 = -H$ **cloxacillin**

$R^1 = R^2 = -Cl$ **dicloxacillin**

$R^1 = -Cl$, $R^2 = -F$ **flucloxacillin**
syn. floxacillin [USAN]

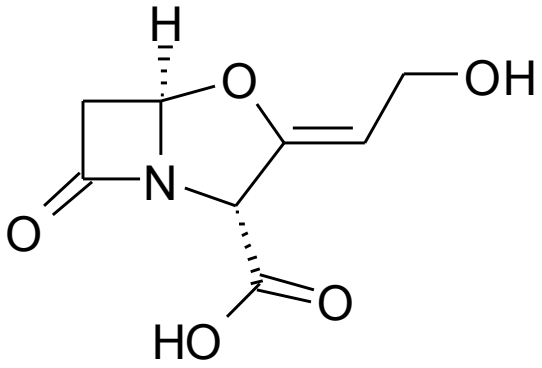
•resistant also to acid media; the resistance increases
oxacillin < cloxacillin < dicloxacillin = flucloxacillin

Penicillins

An alternative approach to ↑ of resistance to β-lactamases:

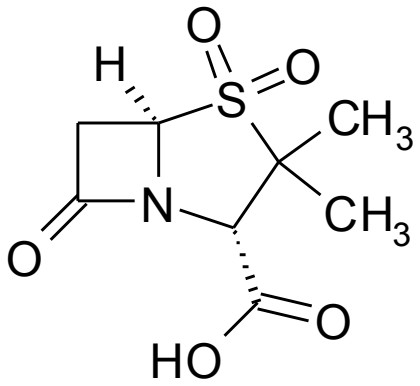
β-lactamases inhibitors

- compounds with β-lactam ring which binds to the enzyme active site with greater affinity and block this site
- used in combination with penicillins

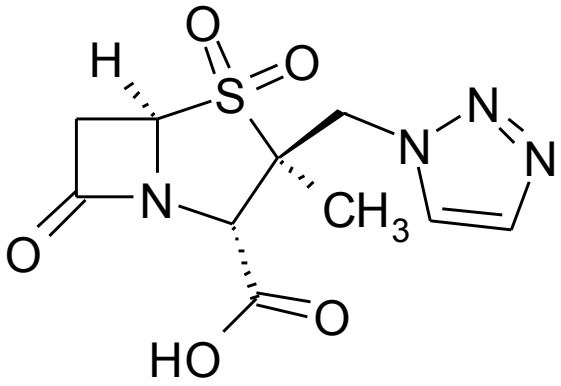


clavulanic acid
- isolated from *Streptomyces clavuligerus*

+ amoxicillin (= Amoxiklav®, Augmentin®)
+ ticarcillin (= Timentin® inj. sic.)



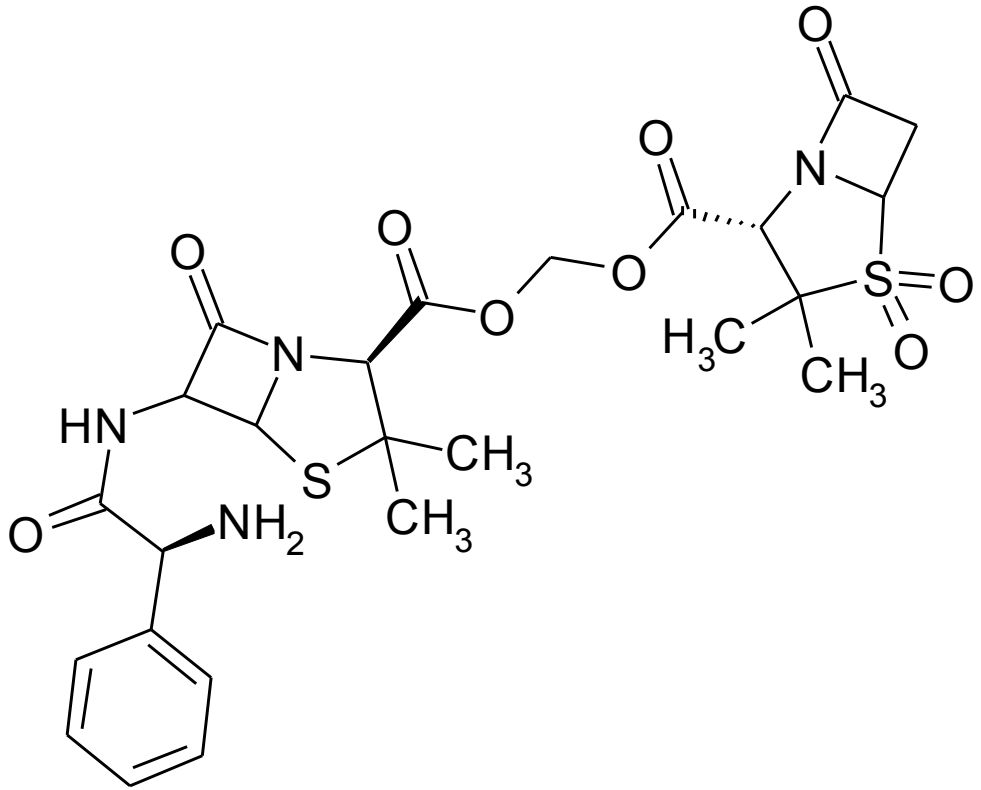
4,4-dioxopenicillanic acid
sulbactam
Betrion®
+ ampicillin (= Ampisucillin® inj. plv. sol.)



tazobactam
+ piperacillin (= Tazocin® inj. sic.)

Penicillins

A combination of a penicilline with a β-lactamase inhibitor in one molecule



•a mixed ester of ampicillin and sulbactam with methanediol

•a prodrug of both components

sultamicillin

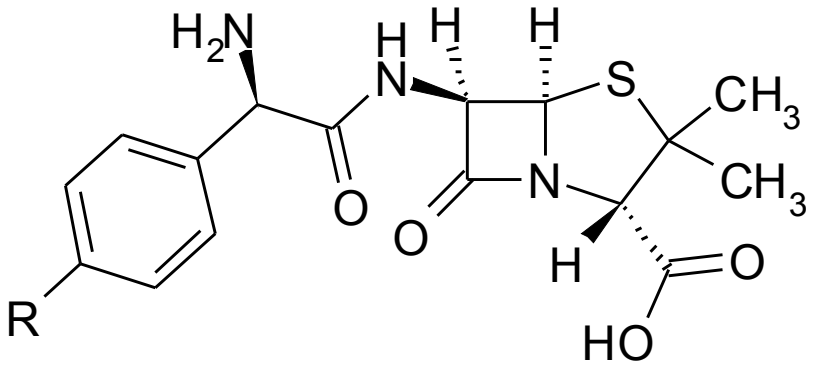
Bitamon® inj. sic., Unasyn® tbl. obd.

Penicillins

Penicillins with broadened spectrum

Ad 4. – introduction of a hydrophilic substituent to α-position of the acyl attached to amino group of 6-aminopenicillanic acid ⇒ **broadening of the antibacterial spectrum of penicillins also to G⁻ strains**

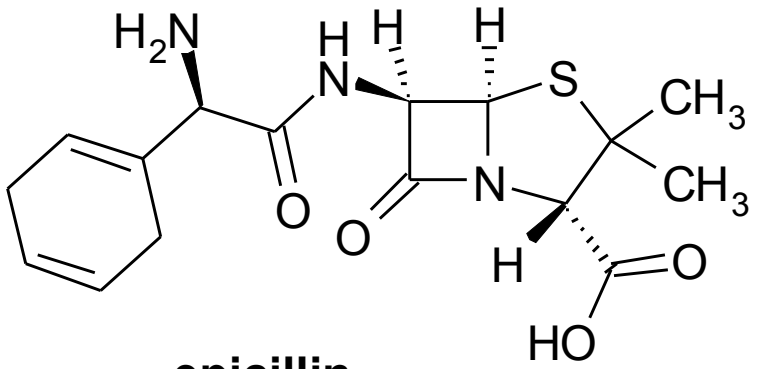
Compouns with free primary amino group



R = -H **ampicillin**

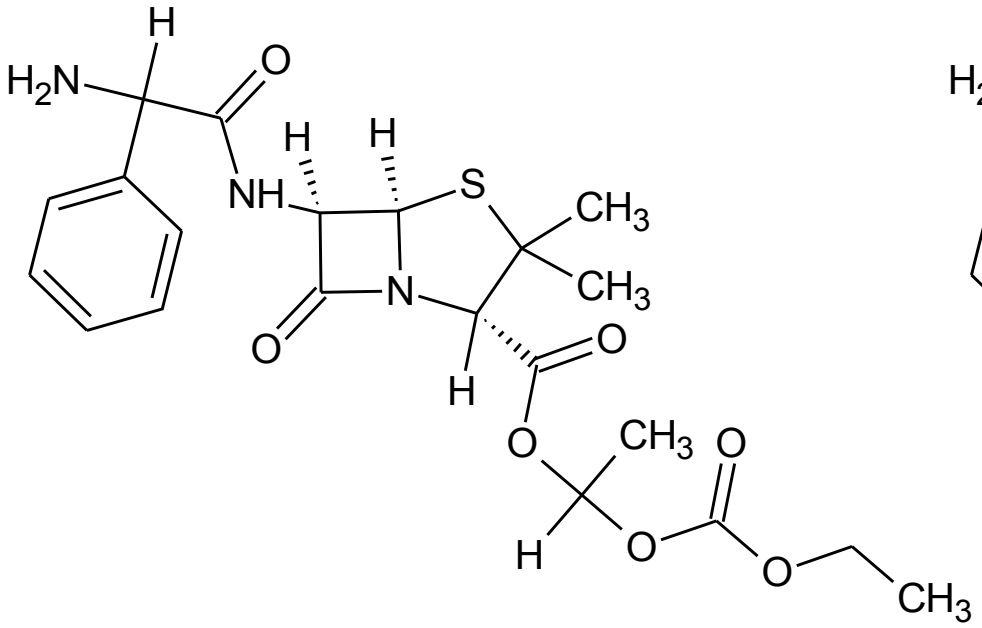
R= -OH **amoxycillin**

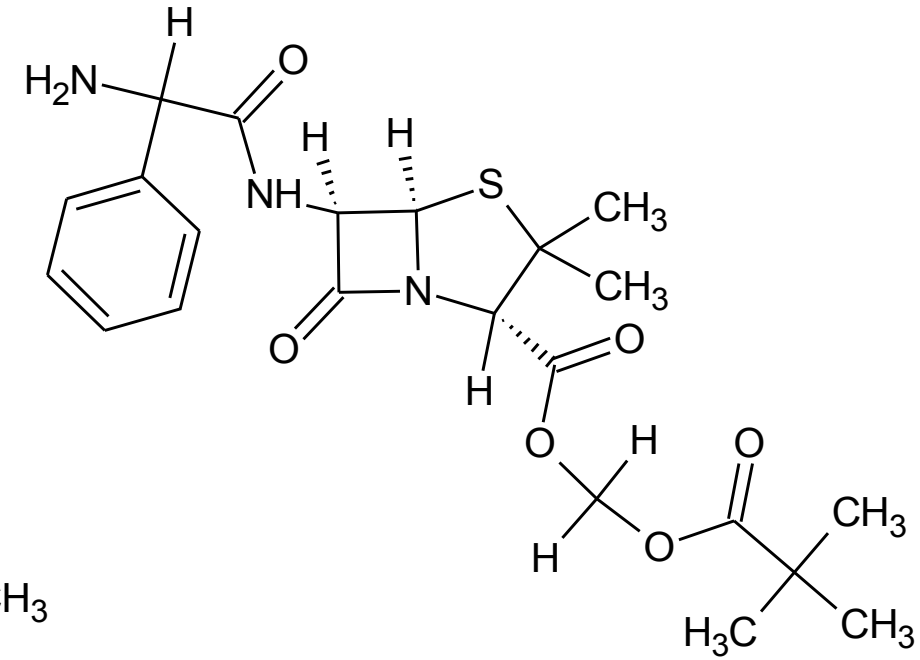
Amoclen®, Amopen®



epicillin

Penicillins with broadened spectrum
Ampicillin prodrugs





•hydrolyzed *in vivo* to ampicillin
•achieve significantly higher blood and tissue levels and attains peak blood levels more rapidly than equimolar doses of oral ampicillin
•more frequently used in veterinary (horses) than in human medicine
•models for design of prodrugs of cephalosporins

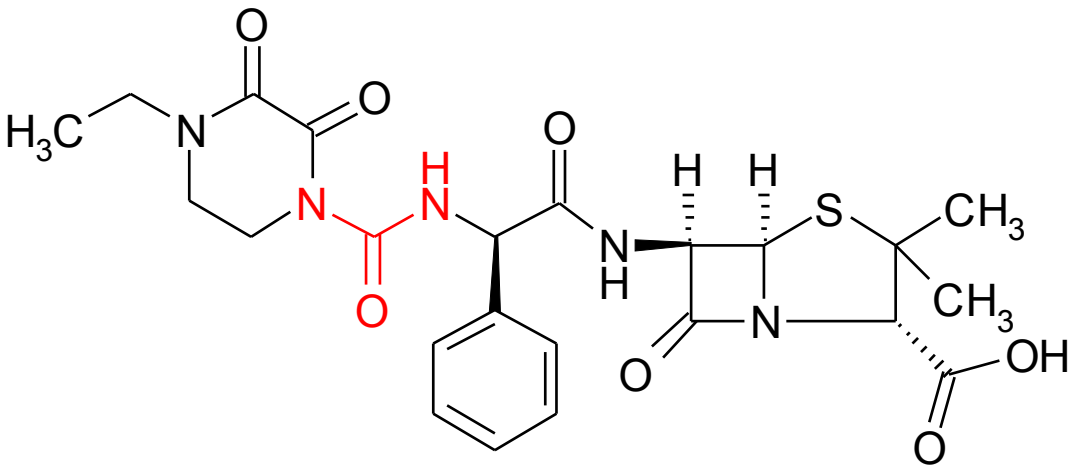
bacampicillin
ampicillin 1-(ethoxycarbonyloxy)ethylester

pivampicillin
ampicillin pivaloyloxymethylester
•successful in acute exacerbations of chronic bronchitis

Penicillins with broadened spectrum: ureidopenicillins

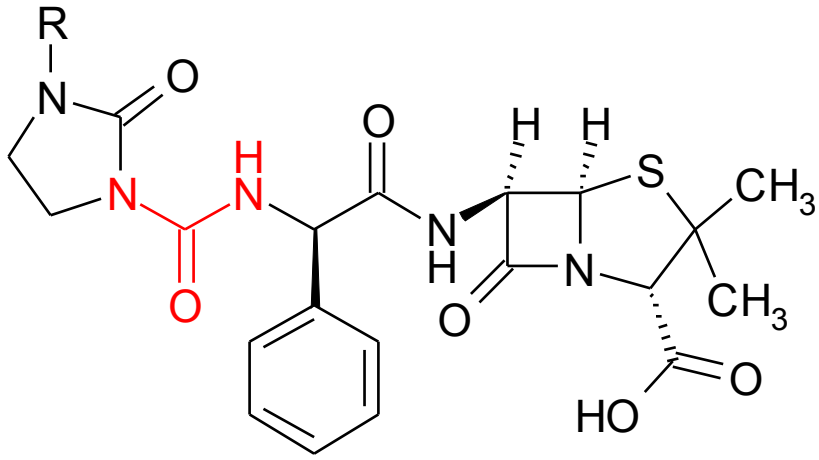
Compounds in which the amino group in α-position of the acyl is a part of urea moiety = **ureidopenicillins =** „anti-pseudomonas“ penicillins

•their spectrum includes *Pseudomonas aeruginosa*



piperacillin

Tazocin ® inj. plv. sol.(+ tazobactam)



R = H- **azlocillin**

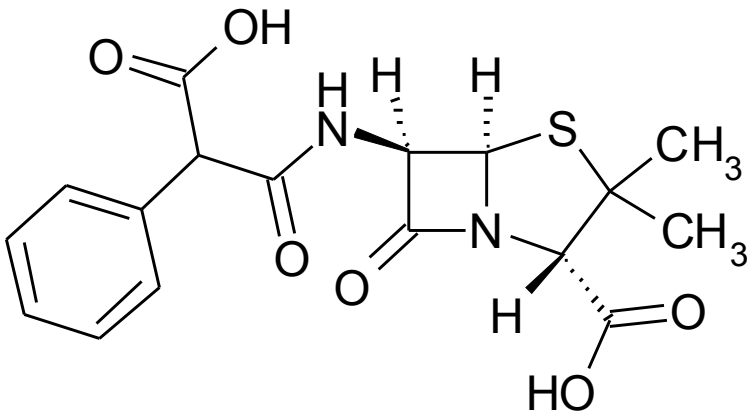
R= CH_3SO_2- **mezlocillin**

•serious infections including *otitis media,* CNS infections …

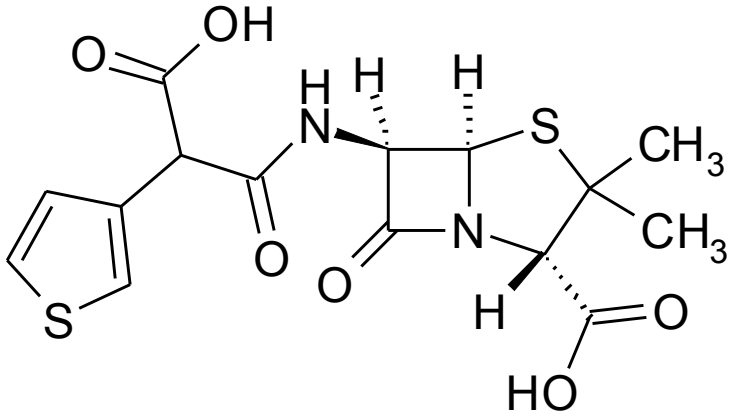
Penicillins with broadened spectrum:

•compounds with the additional carboxyl in α-position of the acyl attached to amino group in position 6

•in fact substituted malonic acids monoamides



carbenicillin



ticarcillin

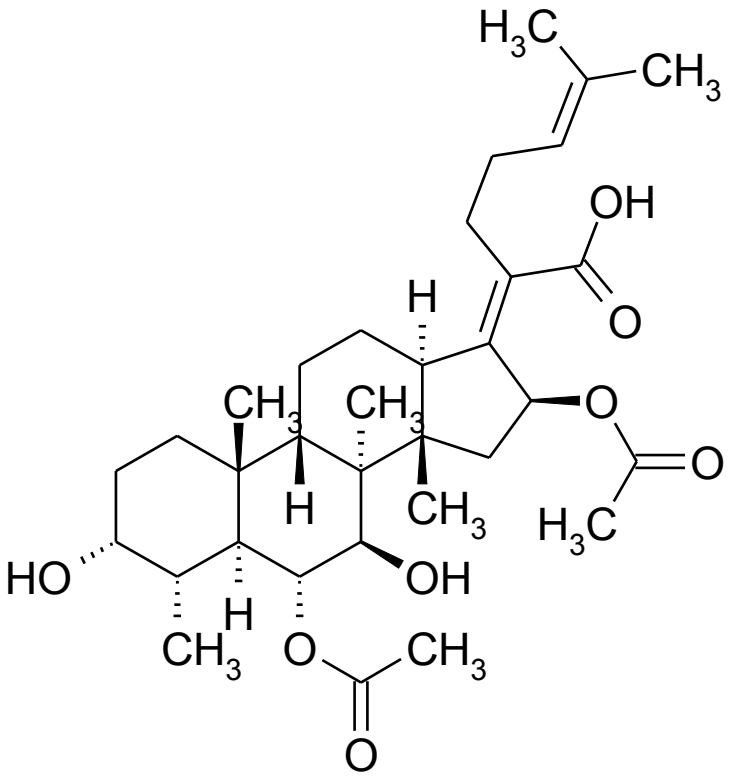
Timentin® inj. sic. (+ clavulanic acid)

•infections of bones and junctures (*Staphylococcus aureus*), gynecological & abdominal infections …

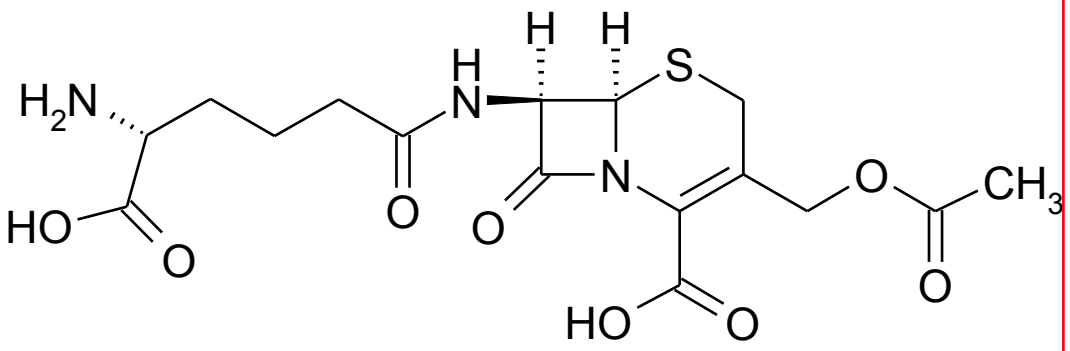
•ring analogy (benzene – thiophene)

Cephalosporins

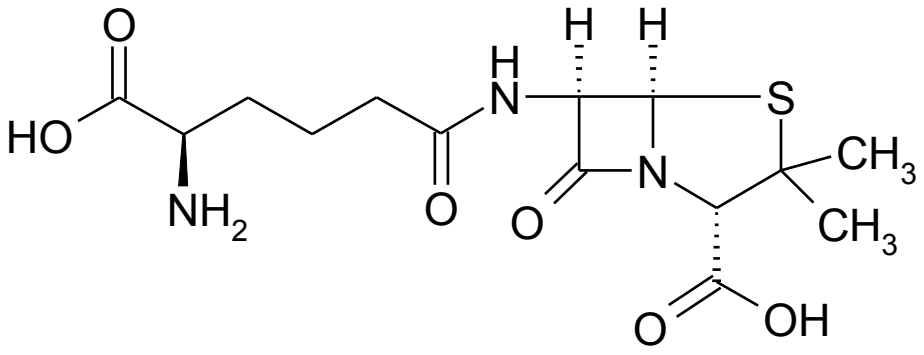
• fungi *Cephalosporium spp.* (1948)



cephalosporin P_1



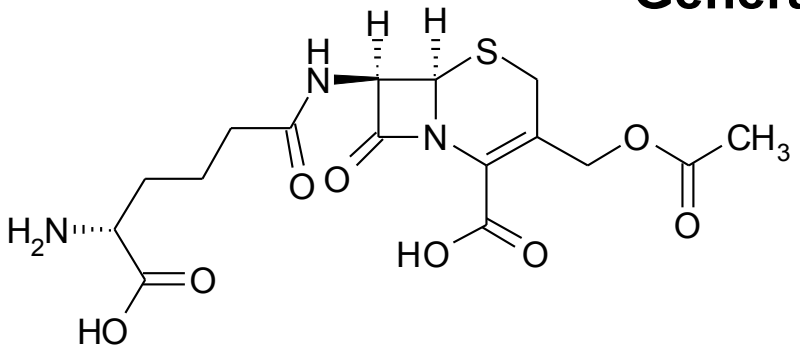
cephalosporin C



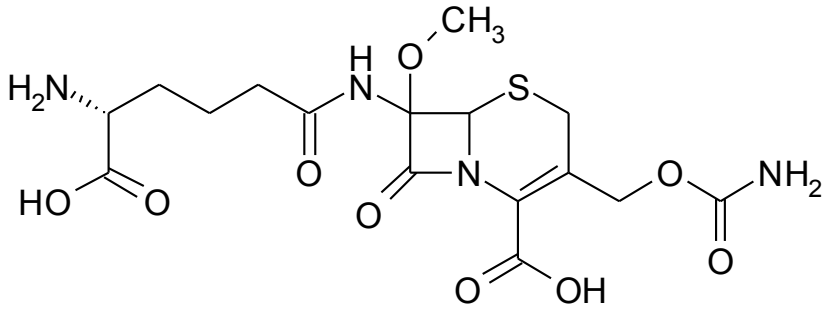
cephalosporin N

… and other various structures

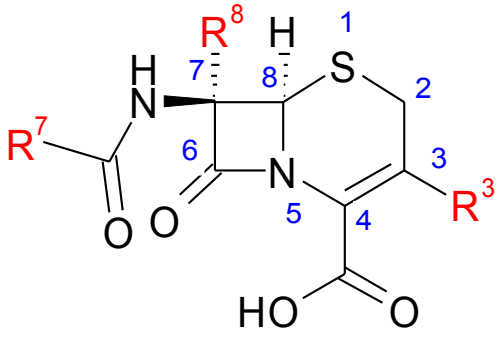
Cephalosporins
General structure



cephalosporin C
•isolated from *Cephalosporium spp.*

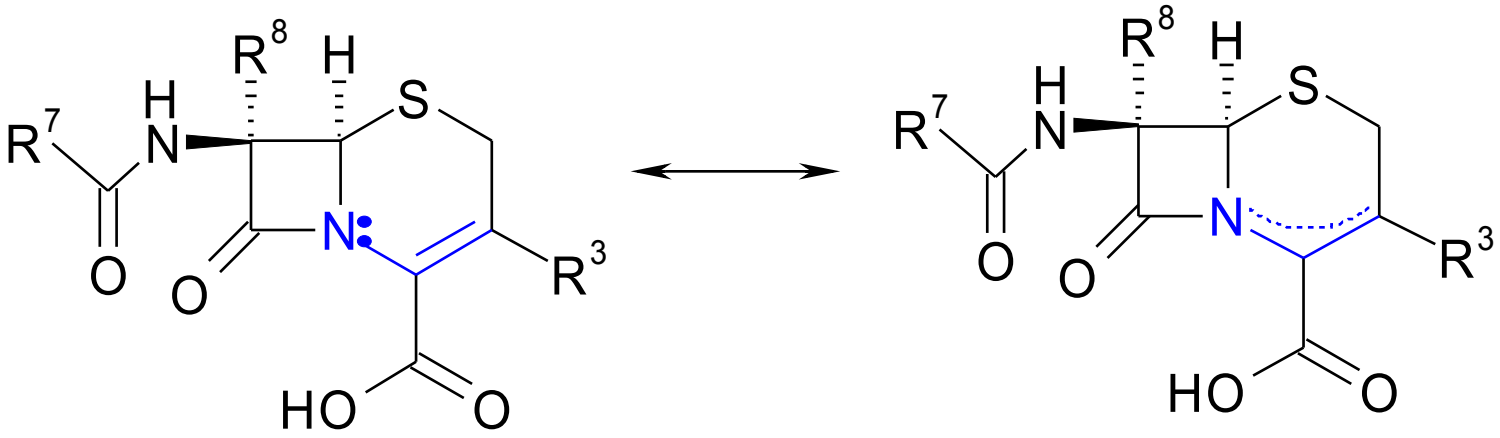


cephamycin C
•isolated from *Streptomyces lactadurans*



Cephalosporins

Properties

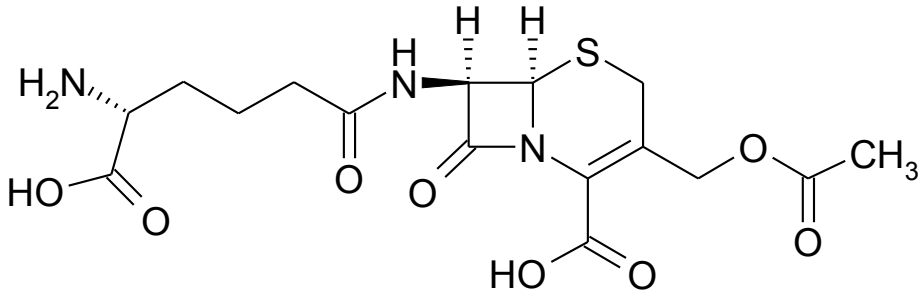


•electron pair on N5 is linked to conjugation with double bond ⇒ ↓ of electron density on N5 ⇒ ↓ of nucleophilicity of N5 ⇒ stability in acid media

•also ↑ resistance to β-lactamases (cefalosporinases)

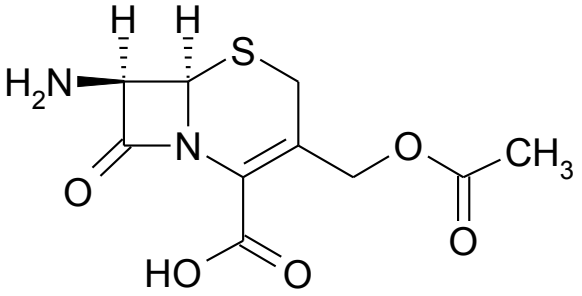
Cephalosporins

Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid.

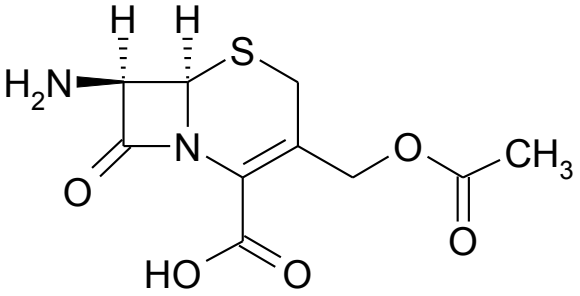


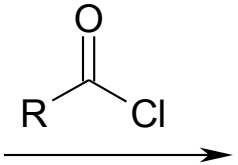
cephalosporin C

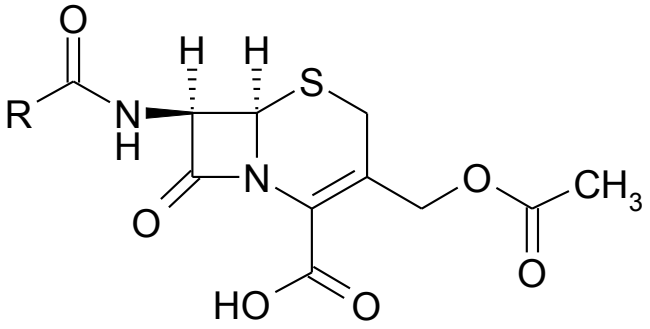
NOCl
or enzymes*



7-aminocefalosporanic acid







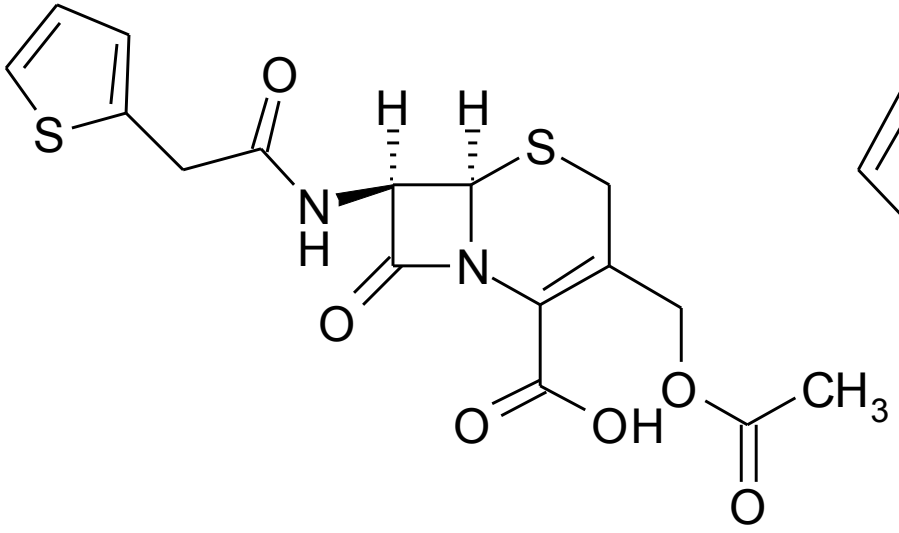
a semi-synthetic cephalosporin, or an intermediate

*glutarylacylase + D-amino acid oxidase

Cephalosporins

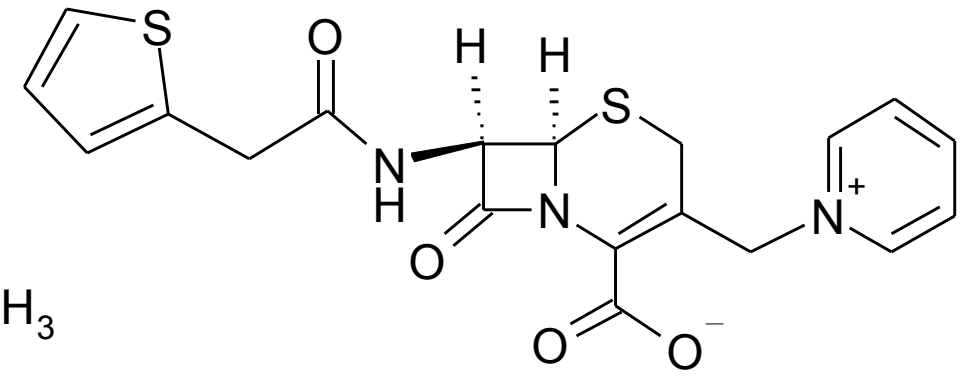
Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid

1st generation: for parenteral administration only (not absorbed from GIT)



cephalotin

Cefalotin® Biotika inj. sic.

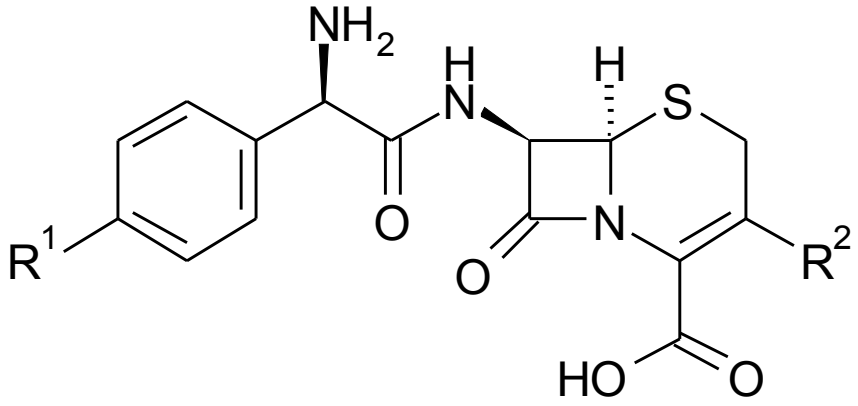


cefaloridin

Cephalosporins

Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid

2nd generation: for oral administration

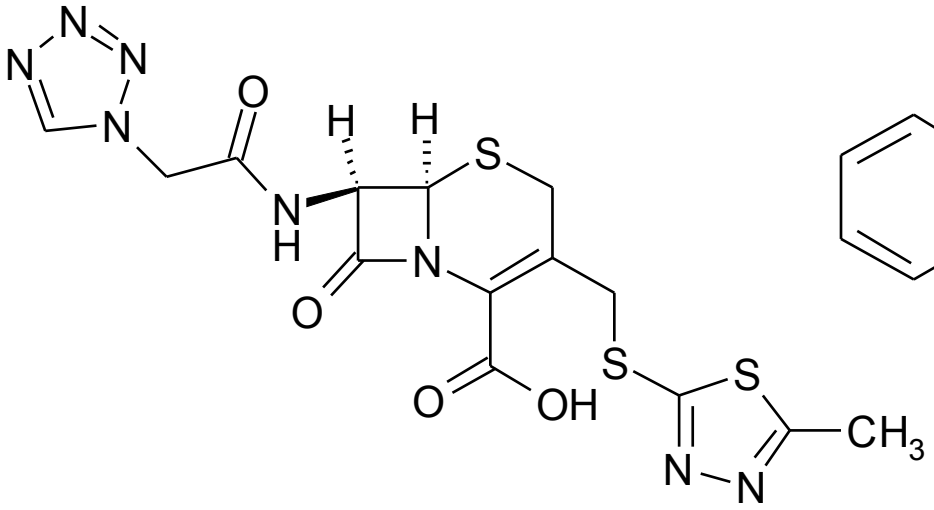


R^1= -H, R^2= $-CH_3$	**cefalexin**	Cefaclen® cps.
R^1= -OH, R^2= $-CH_3$	**cefadroxil**	Biodroxil® tbl. obd.
R^1= -H, R^2=Cl	**cefaklor**	Ceclor® cps.

Cephalosporins

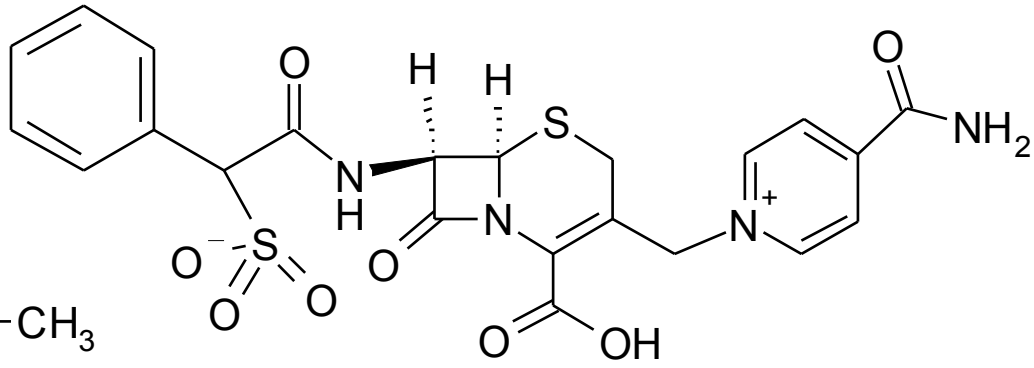
Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid

2nd generation: for parenteral use but with ↑ effect to G^-, ↑ resistance to β-lactamases



cefazolin

Kefzol® inj. sic.



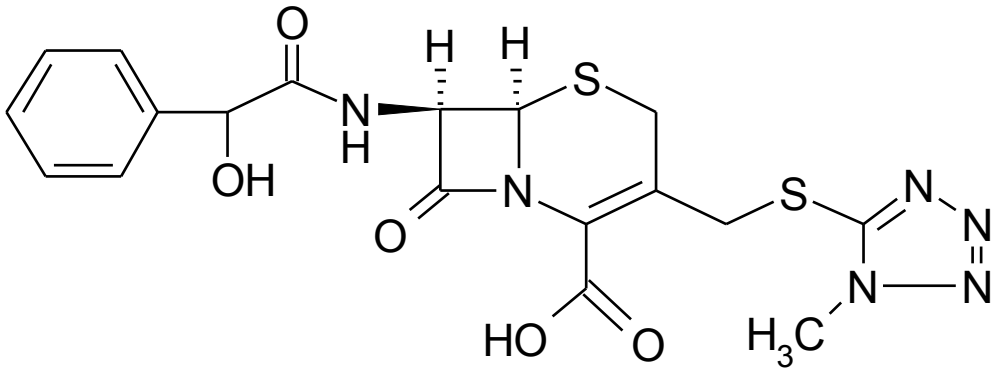
cefsulodin

·*Pseudomonas*

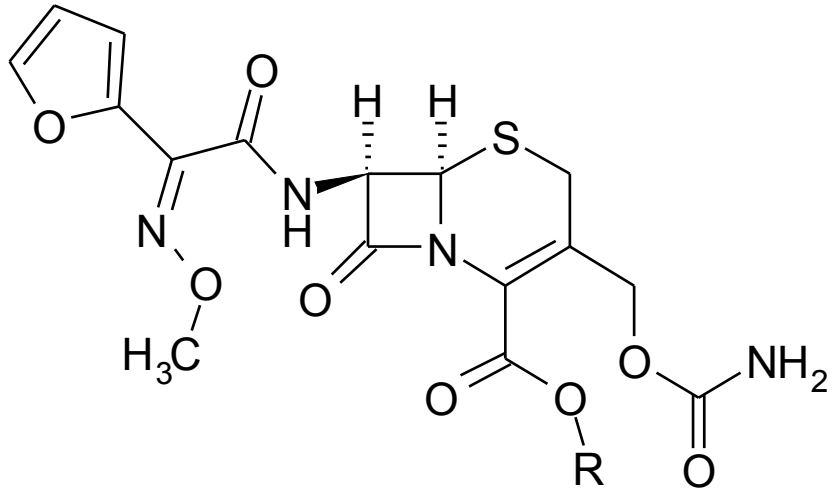
Cephalosporins

Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid

2nd generation: for both parenteral and p.o. administration, very resistant to β-lactamase

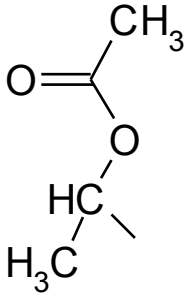


cefamandole



R = H- **cefuroxime**

Ceroxim® tbl.

R = 

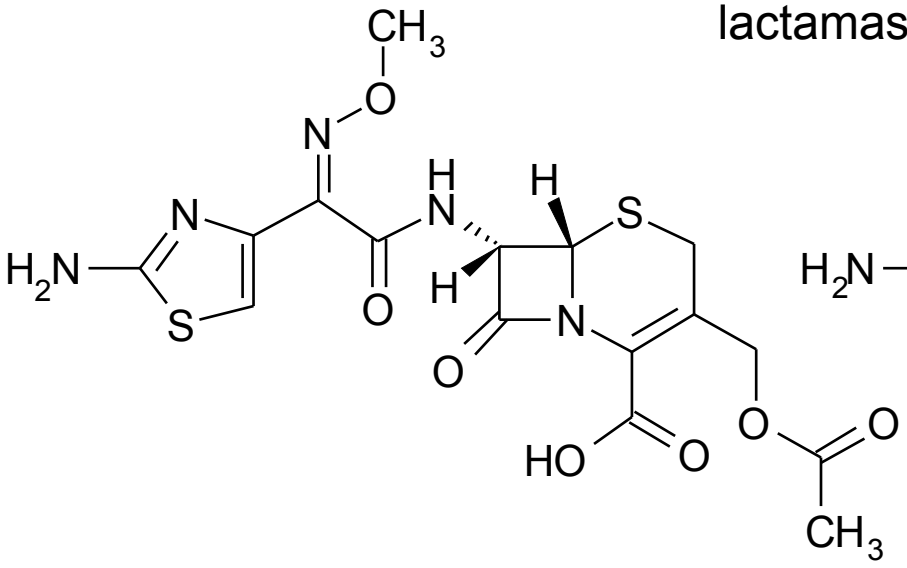
cefuroxime axetil

Zinnat® tbl. obd.

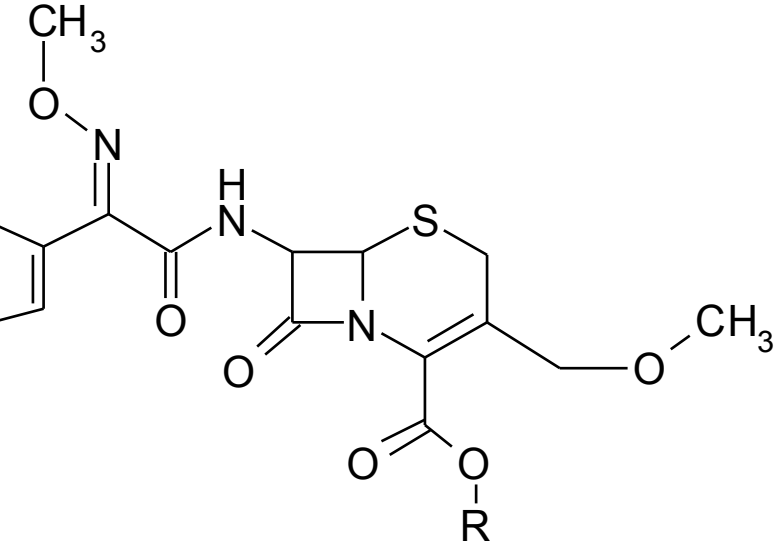
Cephalosporins

Compounds related to cephalosporin C, i.e. N-acylderivatives of 7-aminocephalosporanic acid

3rd generation: for both parenteral and p.o. administration, very resistant to β-lactamase

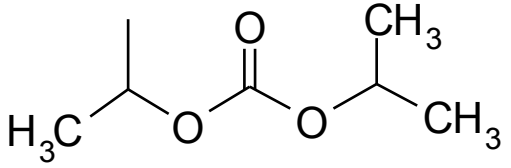


cefotaxime
Claforan® inj. sic.



R = H- **cefpodoxime**

R =

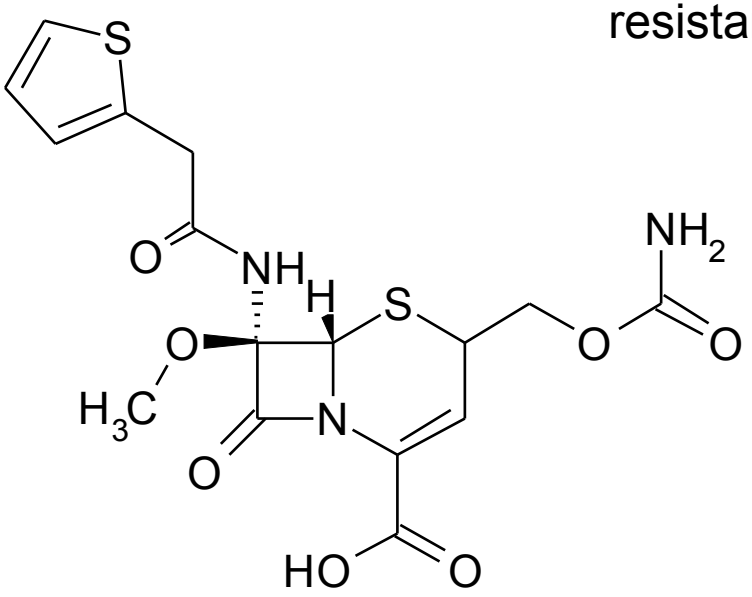


cefpodoxime proxetil
Orelox® tbl. obd.

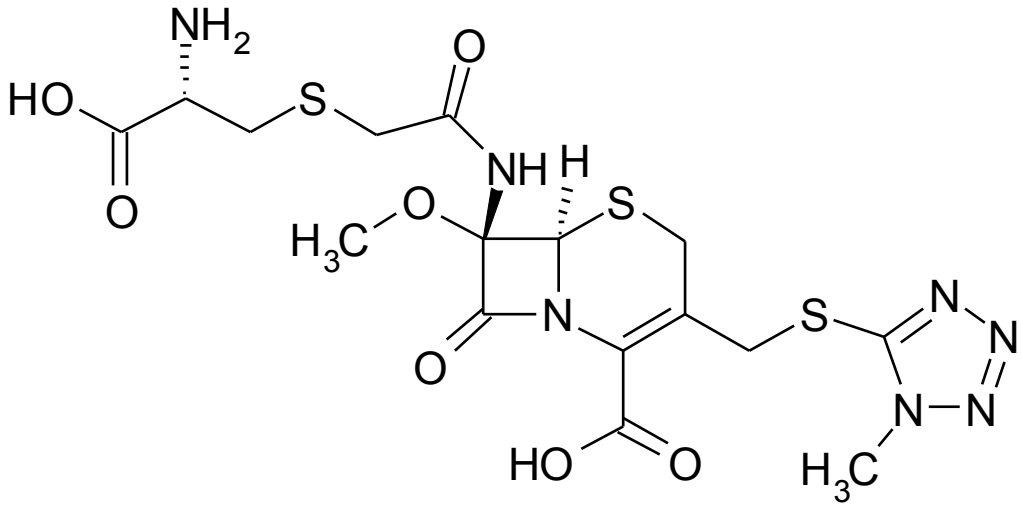
Cephalosporins

Compounds related to cephamycin C, i.e. N-acylderivatives of 7-methoxy-7-aminocephalosporanic acid

„New class = 4th generation“ – for both parenteral and p.o administration – resistant to β-lactamase

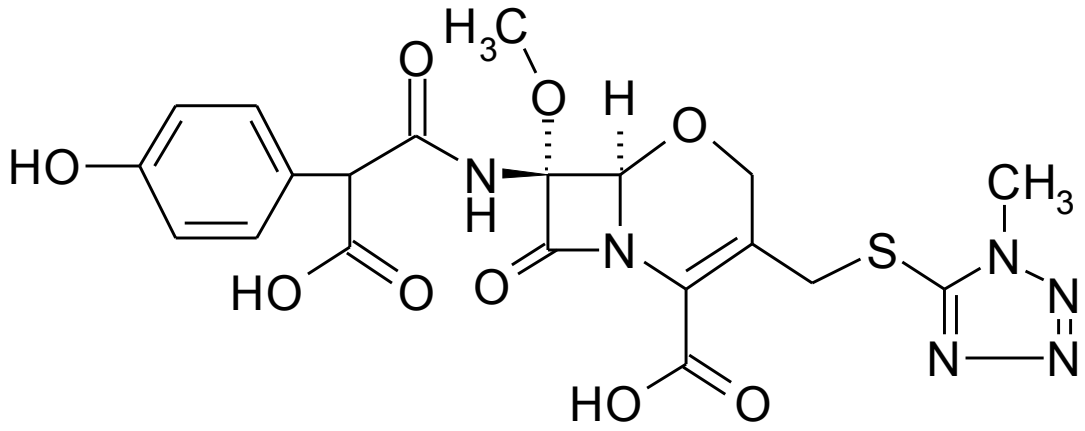


cefoxitin
Mefoxin® inj. sic.



cefminox

Cephalosporin analogues



moxalactam

•dihydrooxazine derivative related to 4th generation of cephalosporins

•developed especially for treatment of meningitis (crosses the blood-brain barrier) and anaerobic infections

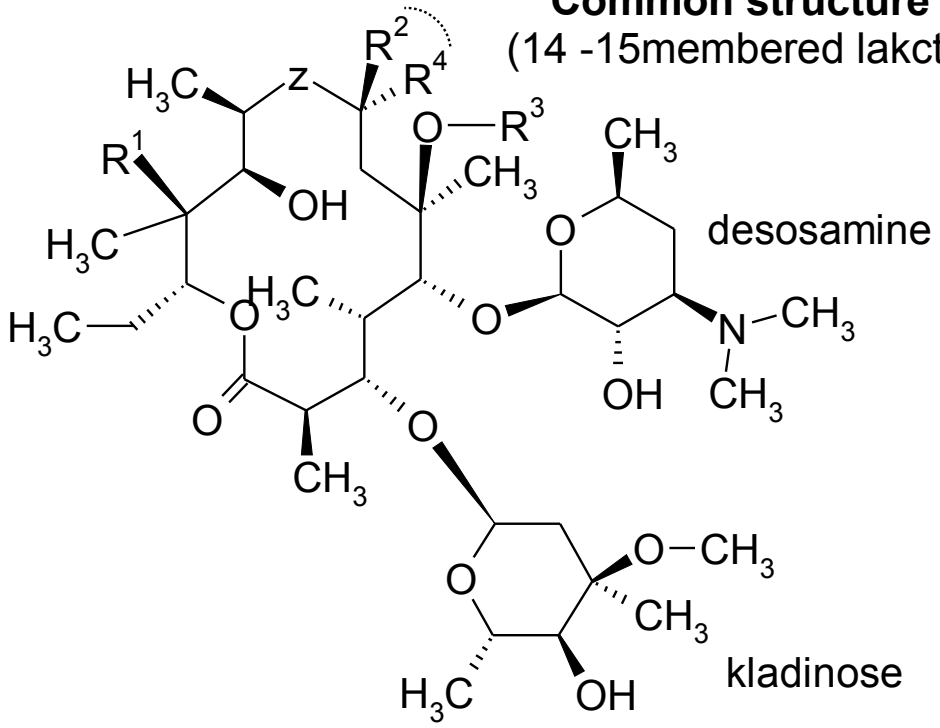
Macrolides

·makrocyclic lactones with 10 – 40membered ring with 1 aminomonosaccharide and 1 „neutral“ monosacharide which can have an additional aminosaccharide attached

·1st group (with larger ring)- natamycine, nystatine, amphothericine B – see antimycotics

·2nd group – **erythromycine group** (erythromycine and its analogues, spiramycine, tylosine)

Common structure of narrower group of erythromycine
(14 -15membered lakctone ring - erythromycine and analogues)



R^1= -OH, -H

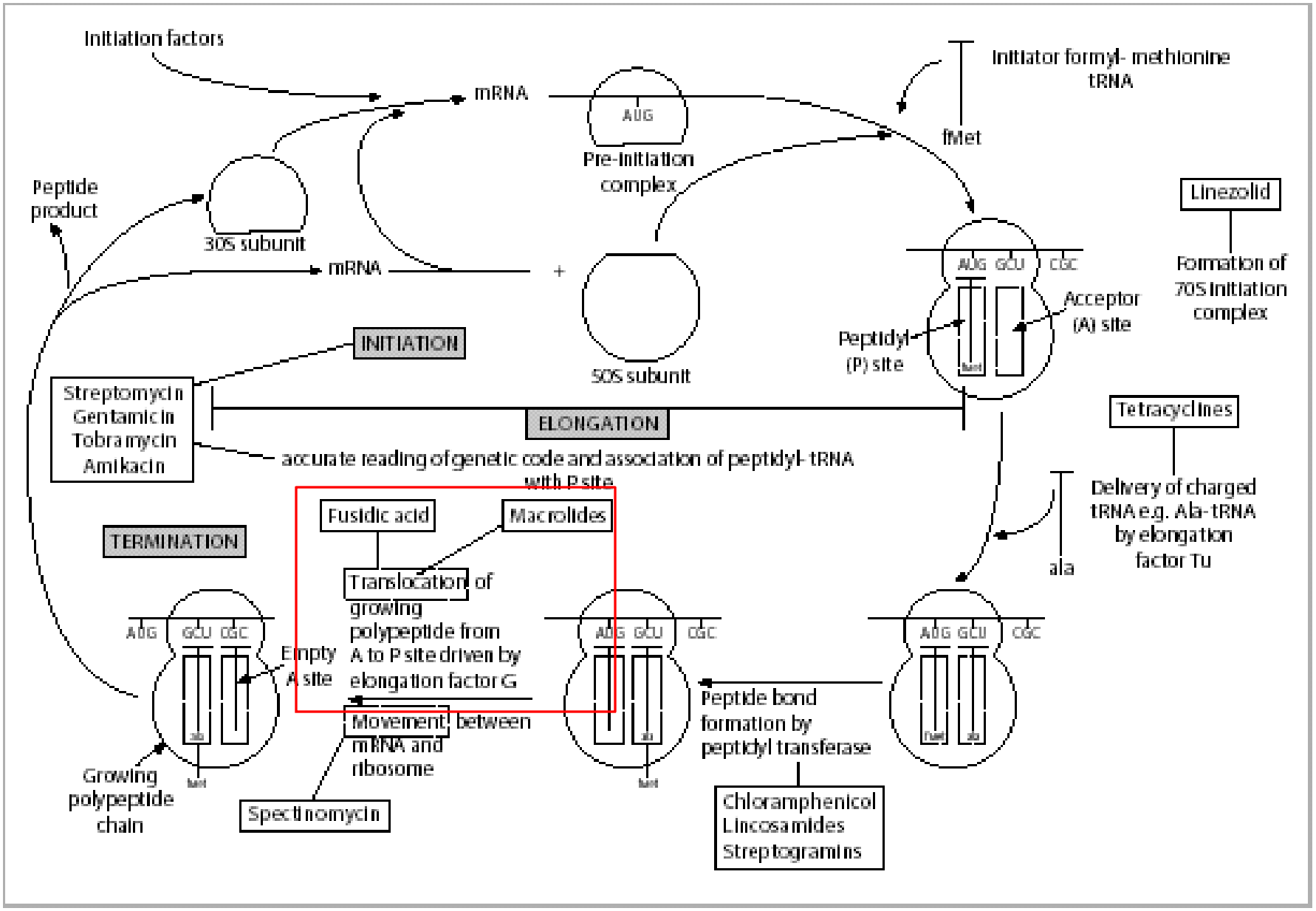
Z = ⟩C=O, $-CH_2N(CH_3)-$,⟩C=N-O-CH_3, ⟩C=N$OCH_2OCH_2CH_2OCH_3$

R^2= -H, -F

R^3= -H, -CH_3

R^4= -CH_3 or R^2 + R^4= oxirane

Macrolides
Site & mechanism of action



Macrolides

Site and mechanism of action

- **Proteosynthesis inhibition**
- act at 50S ribosome subunit
- inhibit the translocation of growing peptide from acceptor (A) to peptide (P) site
- **bacteriostatic effect**

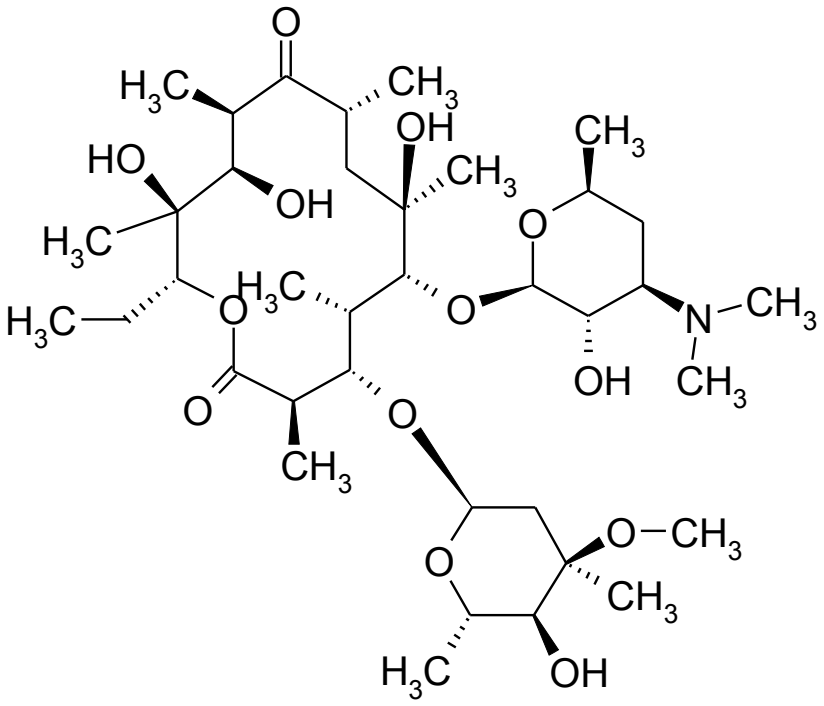
Spectrum:

- both G^+ and G^-

Neisseria, Haemophillus, Brahmanella, Legionella …

Macrolides

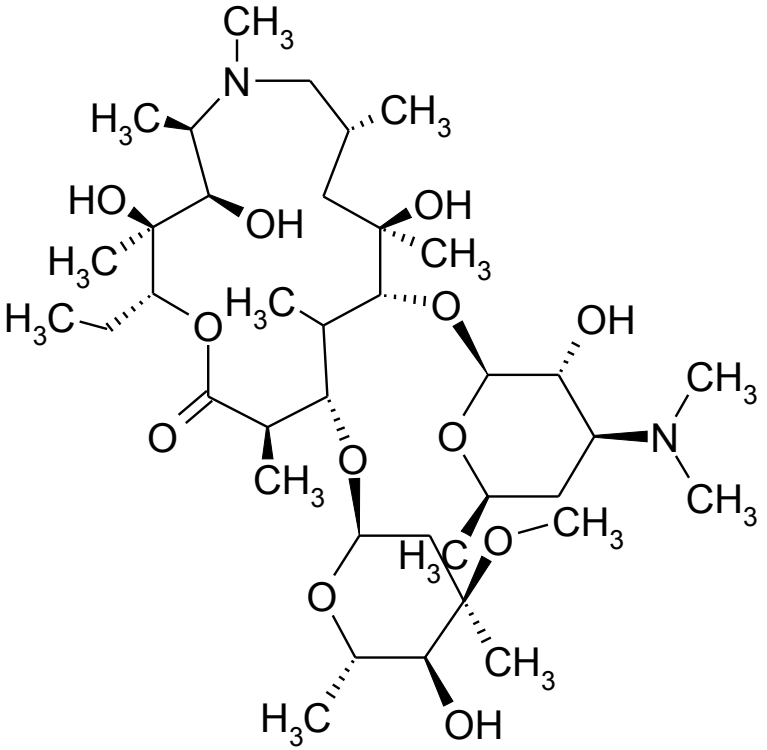
Erythromycine and its analogues



erythromycine

- isolated 1952 from *Streptomyces erythreus*
- poor biological availability ⇒ lipophilic salts (stearate, ethylsuccinate …)
- external form (lotions …) – treatment of *acne vulgaris*

Porphyrocin® tbl.



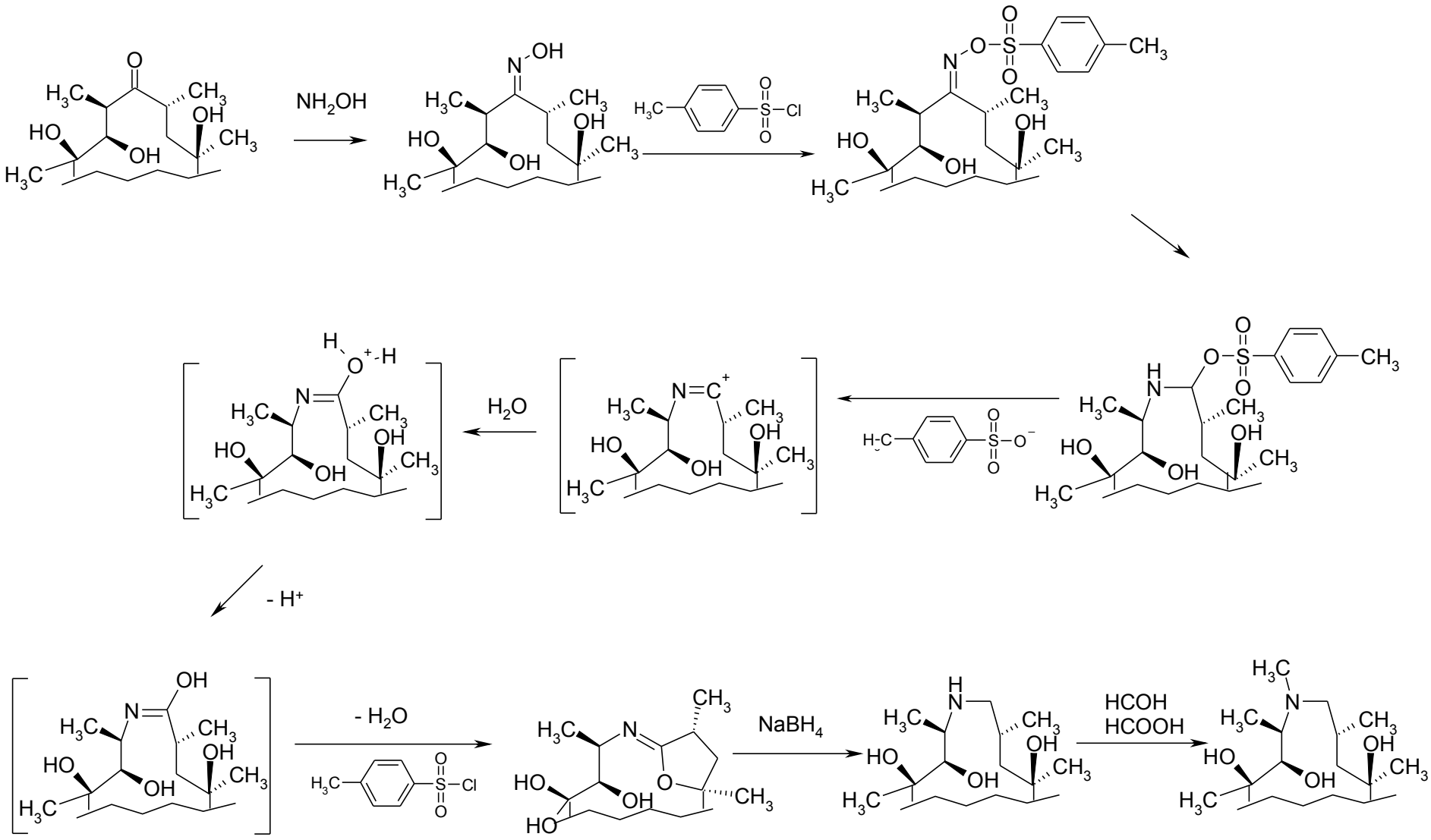
azithromycine

- semi-synthetic compound

Sumamed® tbl. obd.

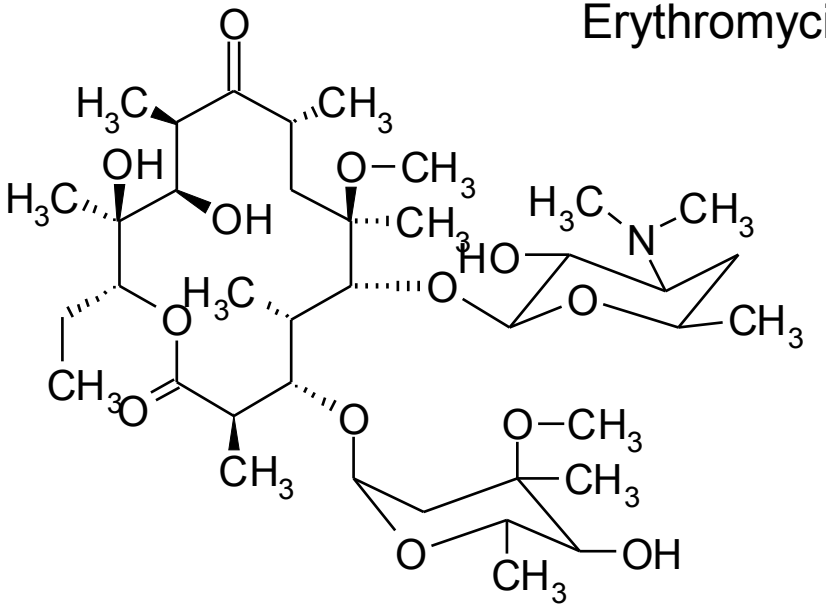
Macrolides

Synthesis of azithromycine from erythromycine



Macrolides

Erythromycine and its analogues

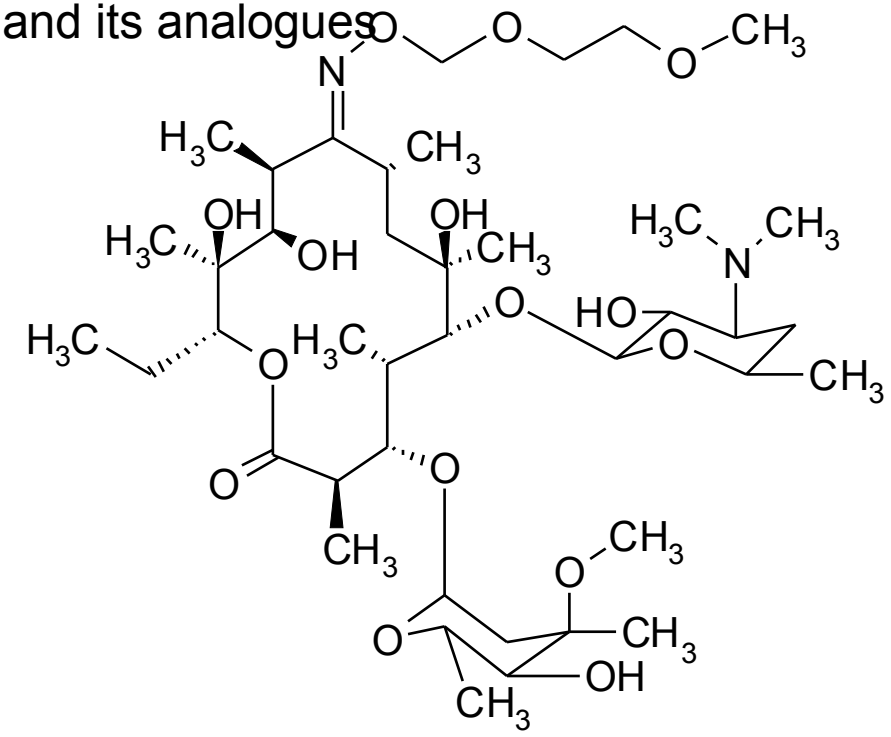


6-*O*-methylerythromycine

clarithromycine

·also some strains of *Mycobacterium avium*

Klacid® tbl. obd.

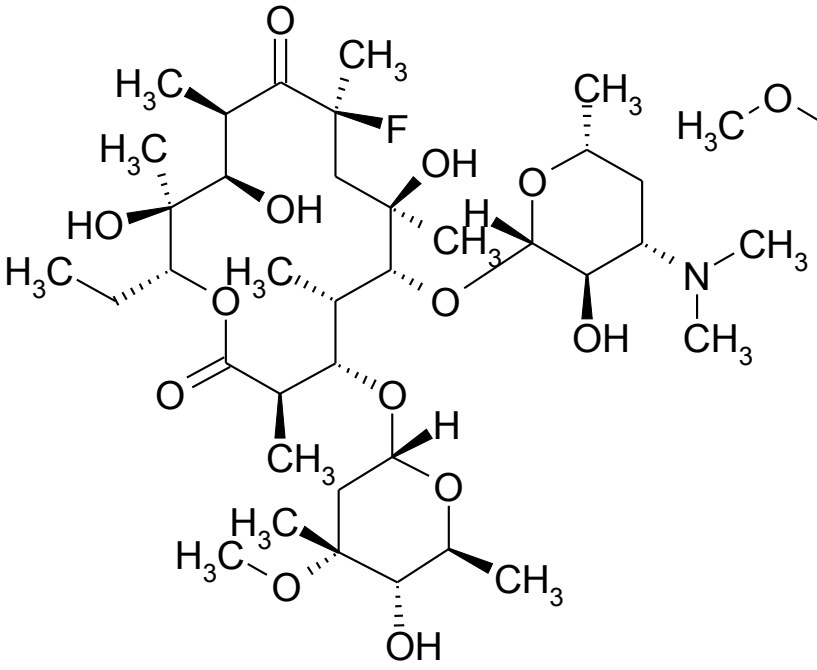


roxithromycine

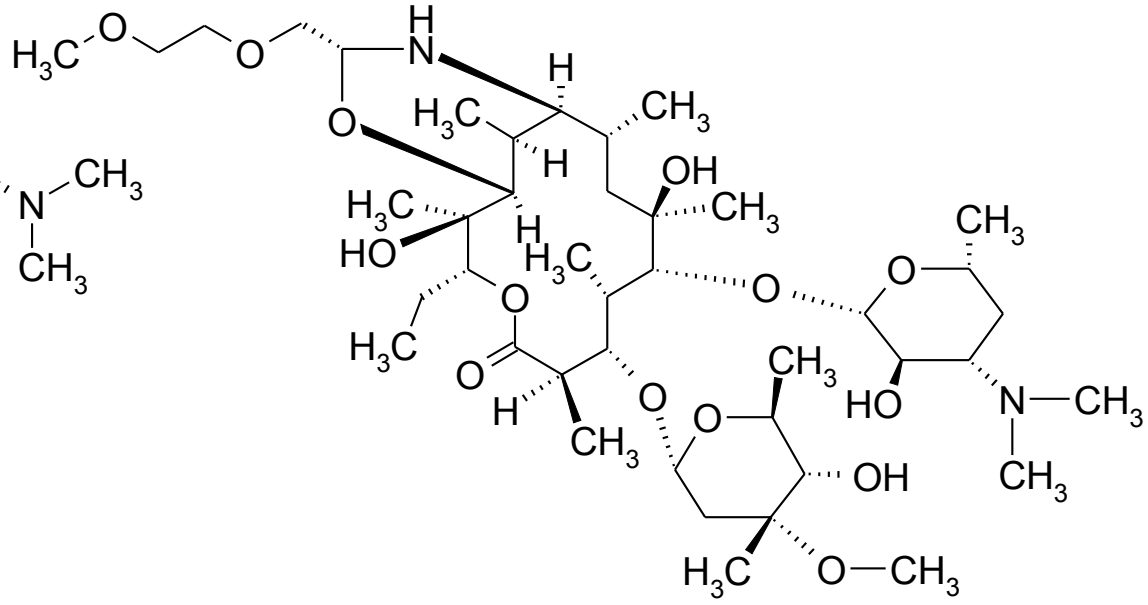
Rulid® tbl.

Macrolides

Erythromycine and its analogues



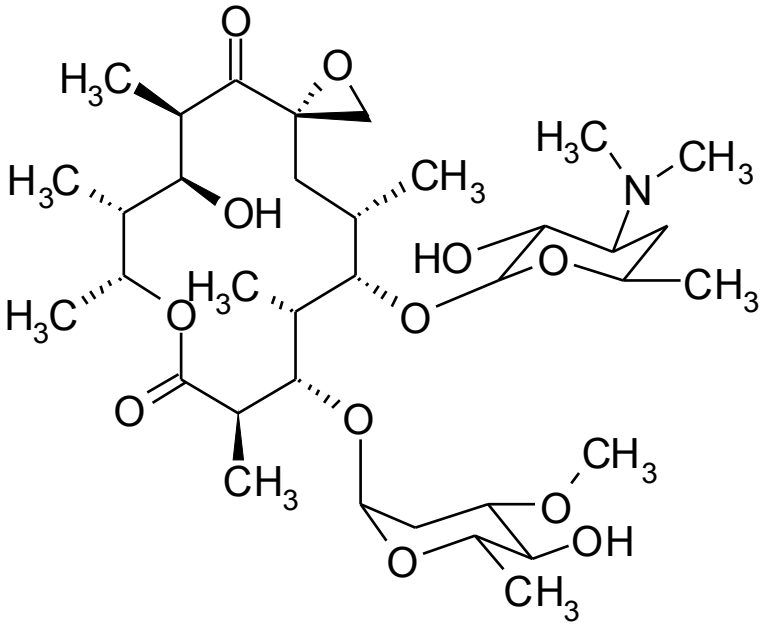
8-fluoroerythromycine
flurithromycine



dirithromycin

Macrolides

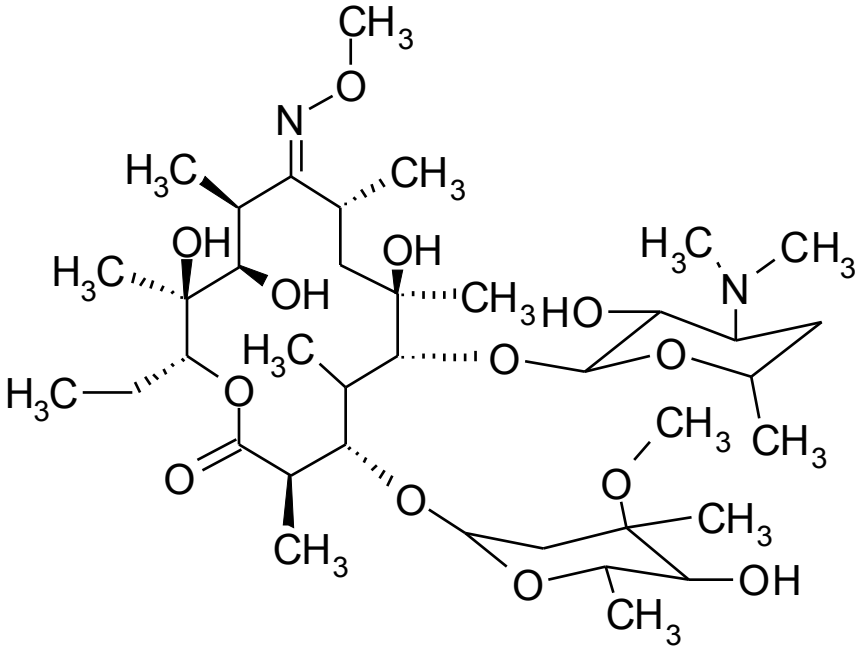
Erythromycine and its analogues



L-oleandrose

oleandomycine

- isolated 1954 from *Streptomyces antibioticus*

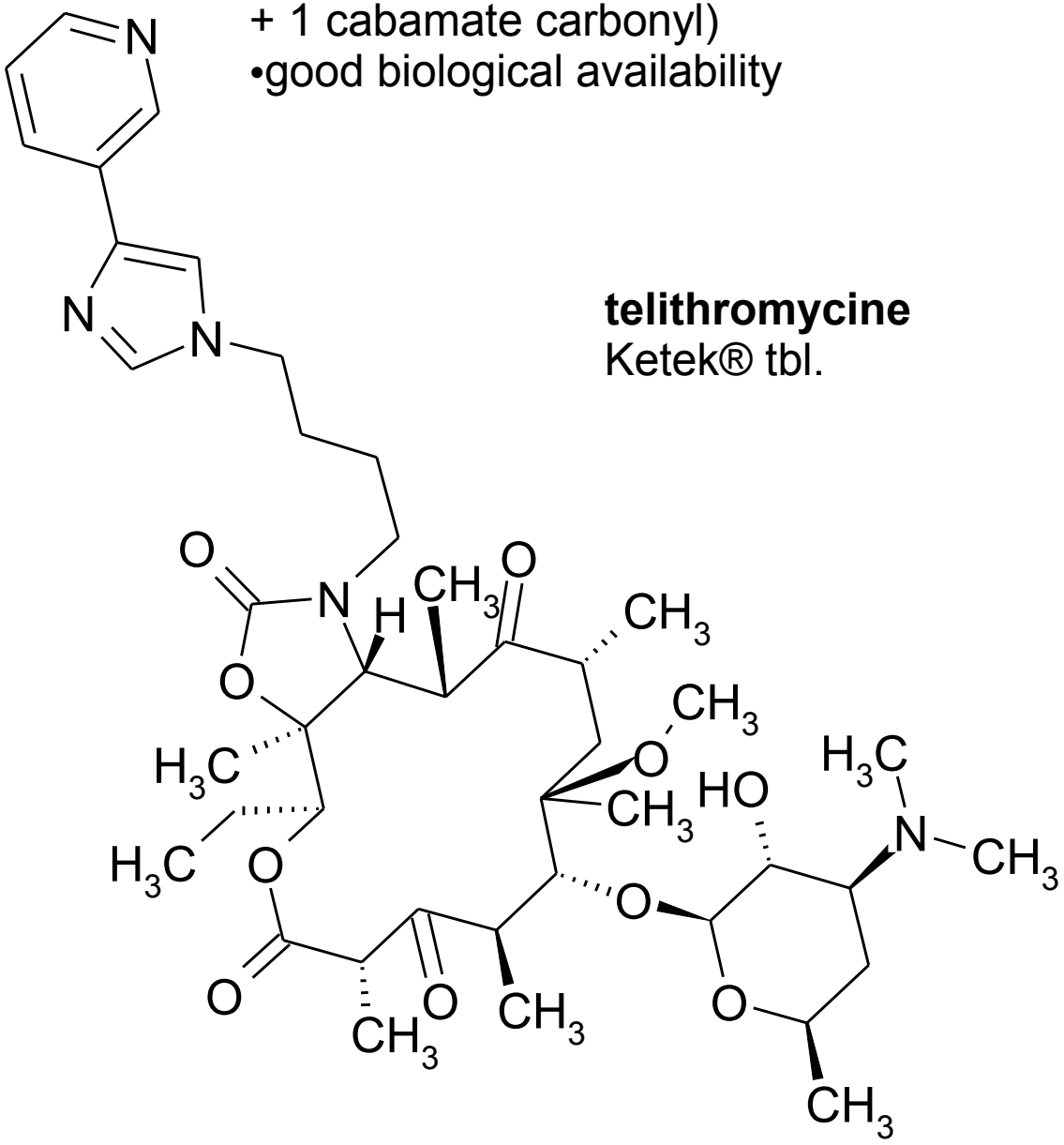


lexithromycine

„More free“ erythromycine analogues: **Ketolides**

•2 keto-moieties on lactone ring (+ 1 ester carbonyl + 1 cabamate carbonyl)

•good biological availability

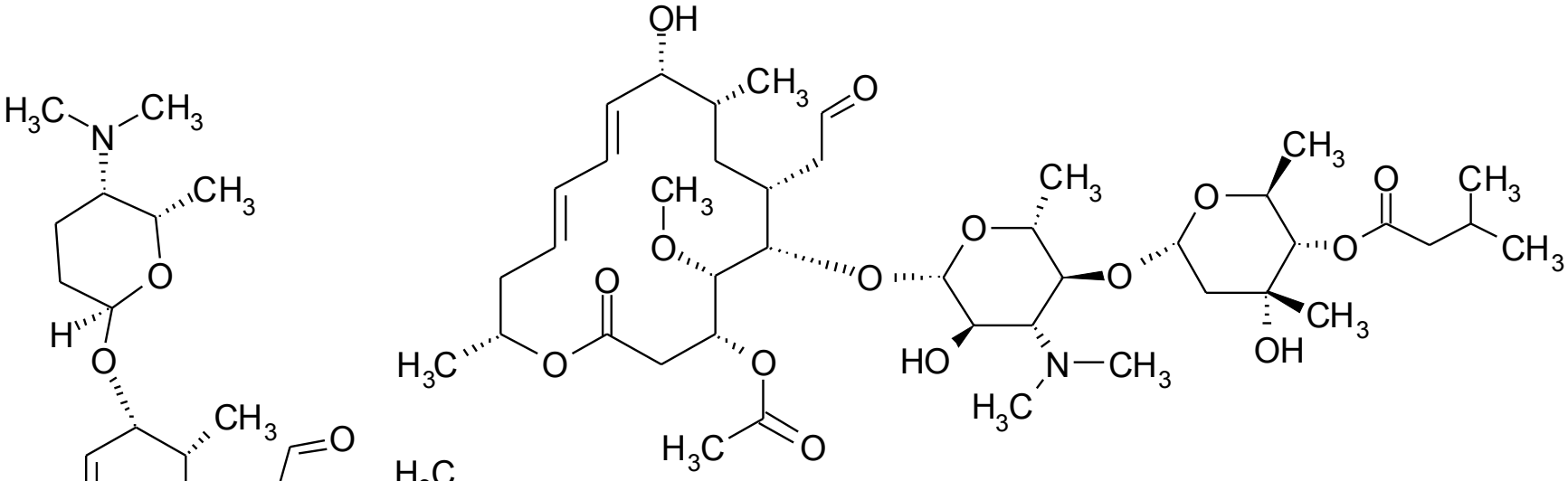


telithromycine

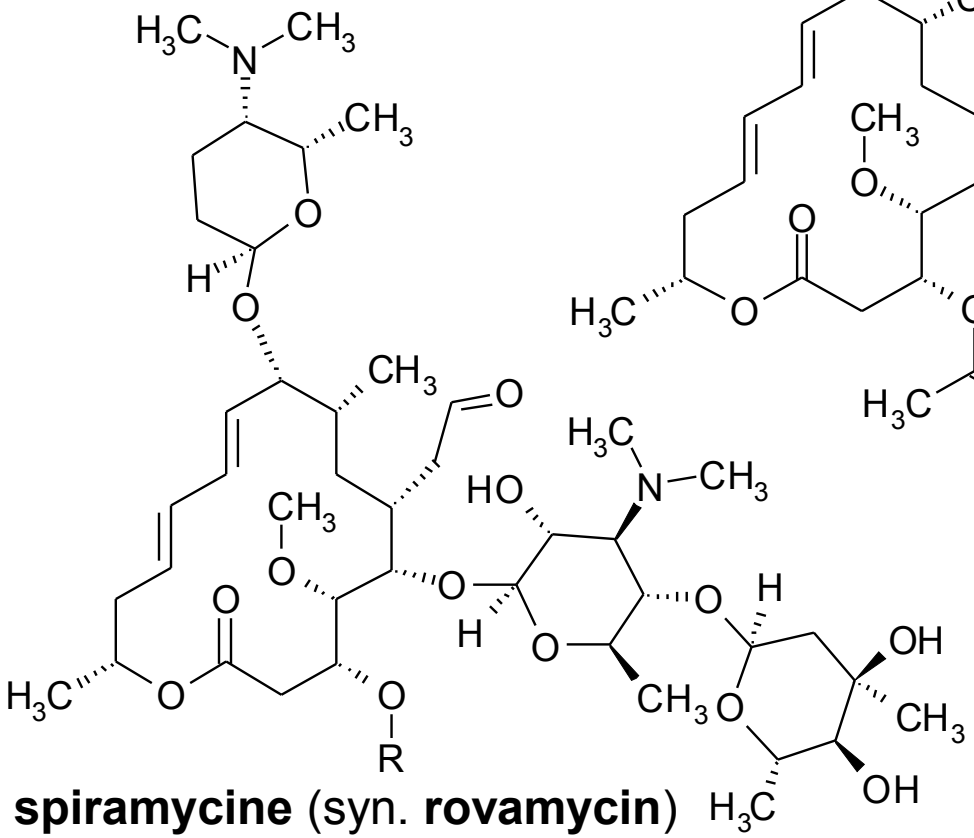
Ketek® tbl.

Macrolides

Compounds with 16membered lactone ring unsaturated in positions 10 and 12



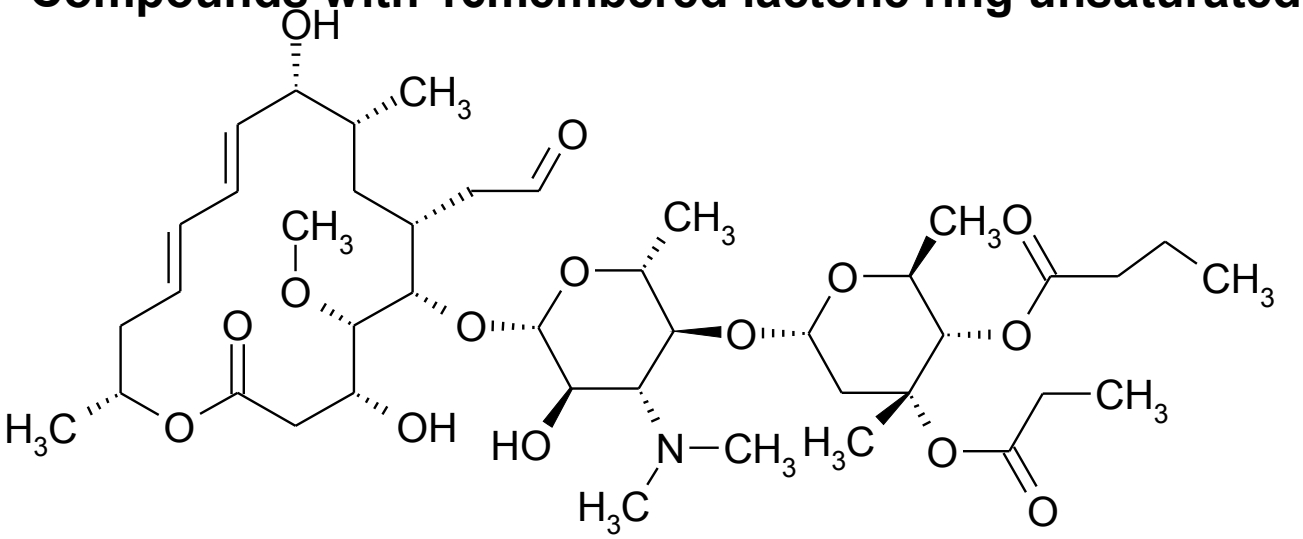
josamycin
·also *Mycoplasma*
Wilprafen® tbl. obd., Alpucine® premix a.u.v.



spiramycine (syn. **rovamycin**)
·isolated 1954 from *Streptomyces ambofaciens*
R = HCO- spiramycine A = spiramycine I
CH_3CO- spiramycine B = spiramycine II
CH_3CH_2CO- spiramycine C = spiramycine III
Rovamycine® tbl. obd.

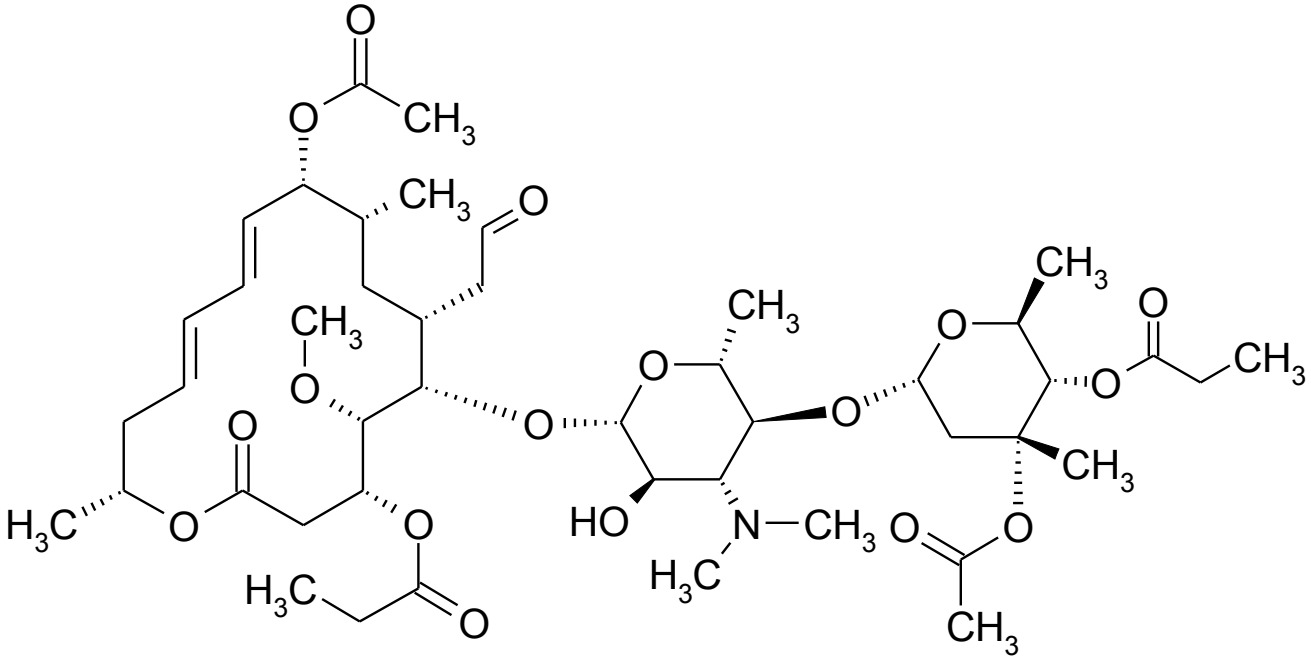
Macrolides

Compounds with 16membered lactone ring unsaturated in positions 11 and 13



rokitamycin

miokamycin

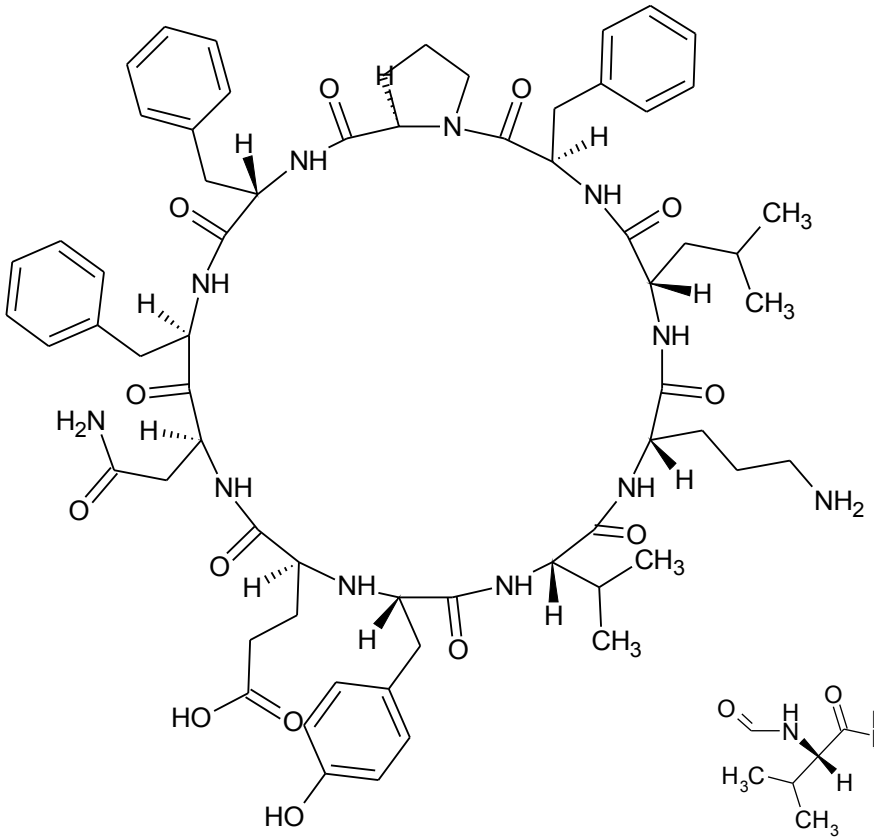


(Poly)peptide antibiotics

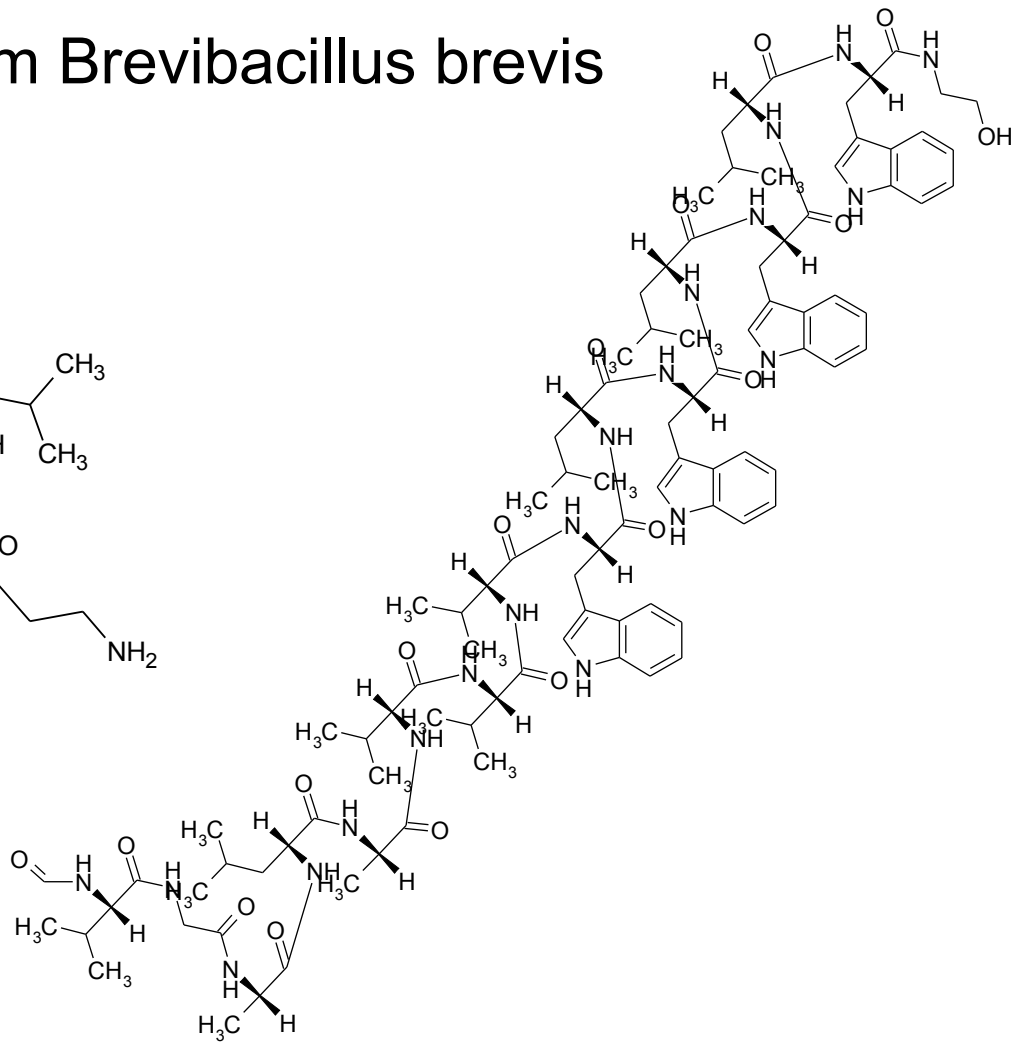
- site of action: cytoplasmic membrane
- mode of action: ionophores: cause uncontrolled exchange of ions between inside and outside media of a bacterial cell and thus ionic imbalance and cell death
- very toxic, external application
- totally known approx. 200 ATB of polypeptid structure
- homomeric peptides: contain amino acids only (often D-)
- heteromeric peptides: except amino acids also other carboxylic acids
- if they are cyclic, then homodets and heterodets

Tyrothricin

•mixture from Brevibacillus brevis

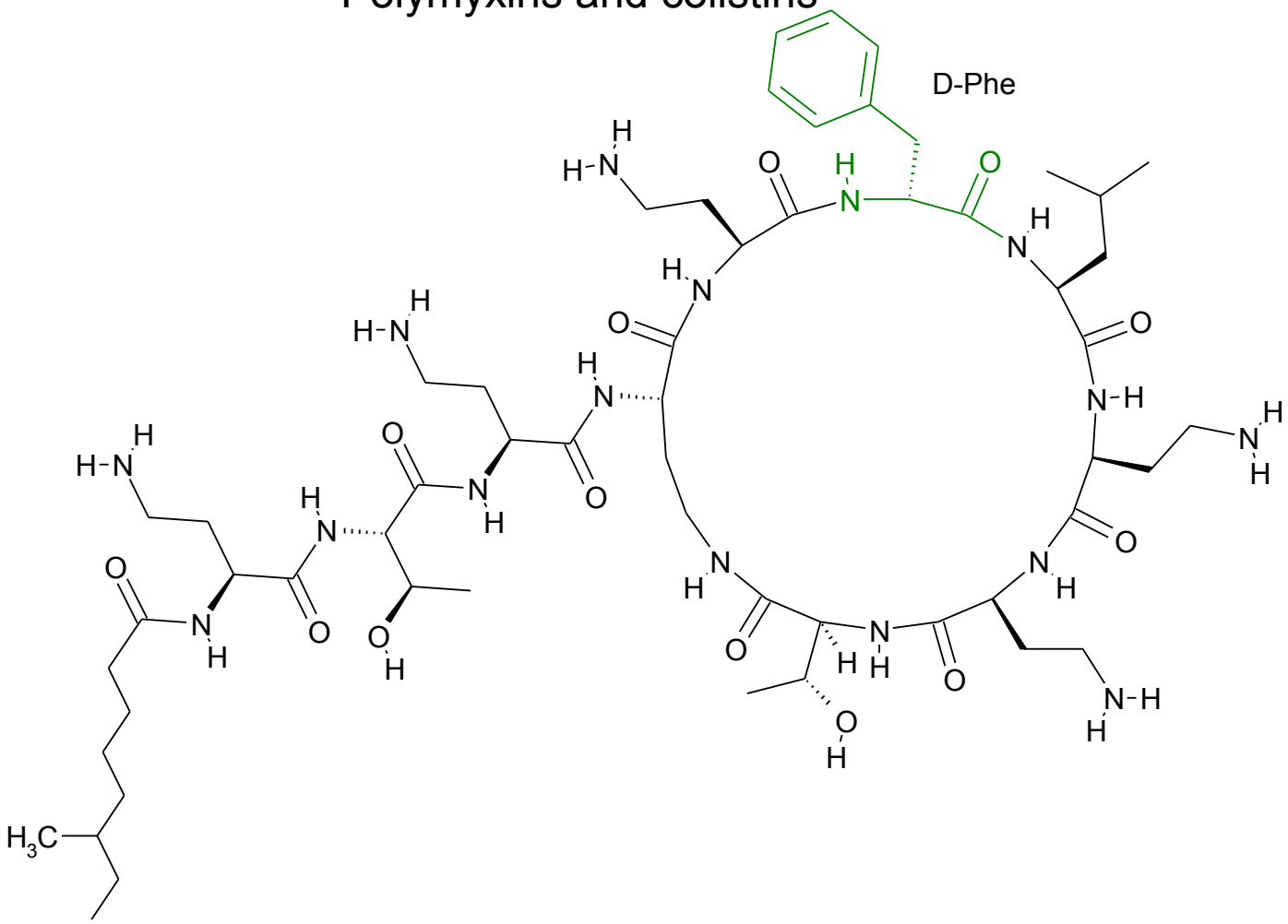


tyrocidin A
tyrocidins A – E total 80%
decapeptides



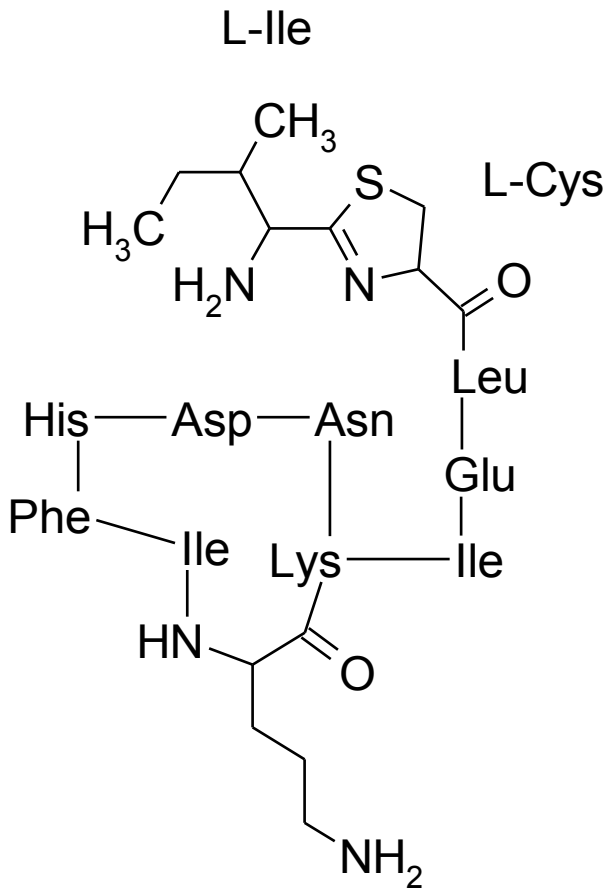
gramicidin A_1
20 % of gramicidines A_1, A_2, C_1 and C_2
pentadecapeptides

Polymyxins and colistins



polymyxin B
colistin A: D-Leu instead D-Phe

Bacitracin



bacitracin A

Framykoin® ung., Pamycon® plv. (+ neomycin B)

Aminoglycosides

- aminosaccharide glycosides produced by strains of *Streptomyces* genus
- Streptomycin group
- Neomycin group
- Kanamycin and gentamycin group

Mechanism of action

- **protheosynthesis inhibition**
- they avoid accurate reading of the genetic code and binding of peptidyl-tRNA to the peptide binding site
- **effect bacteriostatic – bactericidal**

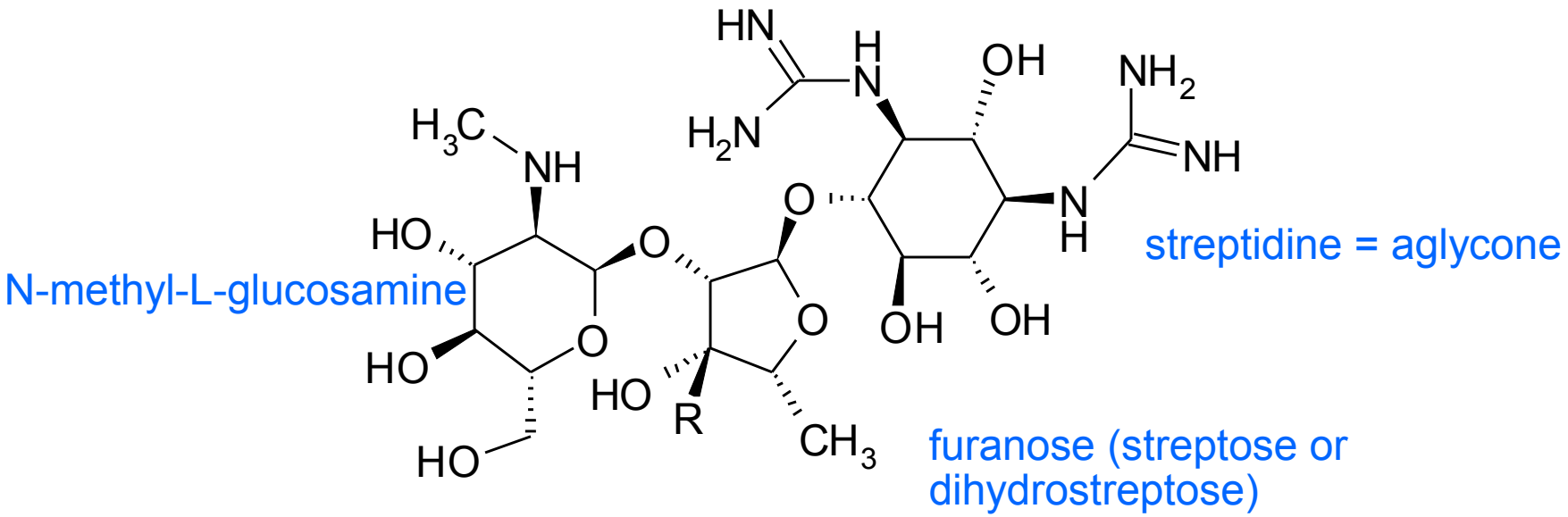
Spectrum

$G^+ < G^-$

Bacillus anthracis, Bordetella pertussis, Brucella, Corynebacterium diphteriae, E. coli, Enterobacter, Haemophillus, Mycobacterium tuberculosis…

Aminoglycosides

1. Streptomycin group



R = -CHO **streptomycin**

- isolated 1944 from *Streptomyces fradiae*
- used to *M. tuberculosis* in combination with other tuberculostatics
- bactericidal

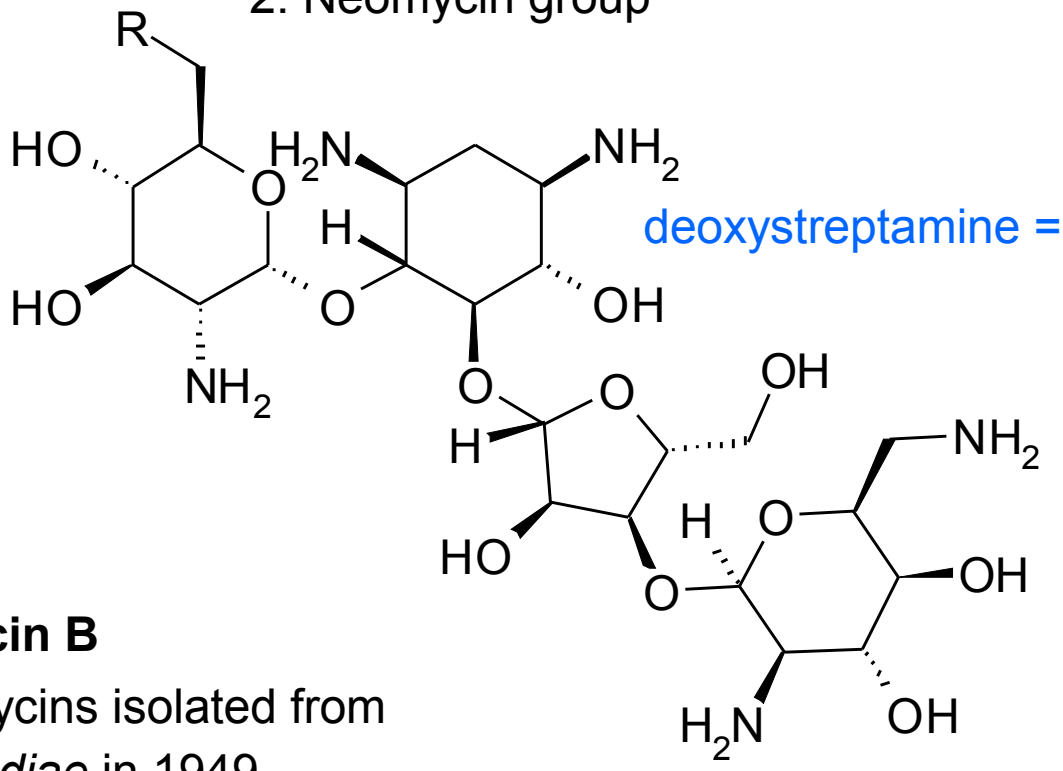
Streptomycin „Grünenthal“® inj. sic., Streptowerfft® a.u.v

R = -CH_2OH **dihydrostreptomycin**

Depomycine® a.u.v. inj. (+ benzylpenicillin)

Aminoglycosides

2. Neomycin group



deoxystreptamine = aglycon

R= -NH_2 **neomycin B**

- mixture of neomycins isolated from *Streptomyces fradiae* in 1949

Framykoin® ung., Pamycon® plv. (+ bacitracin)

R = -OH **paromomycin**

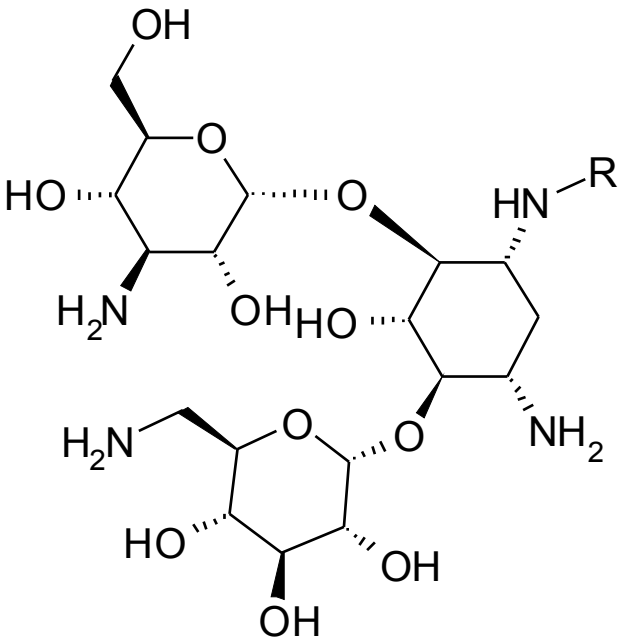
- not absorbed from GIT
- used for *Entamoeba histolytica*

Humatin® cps.

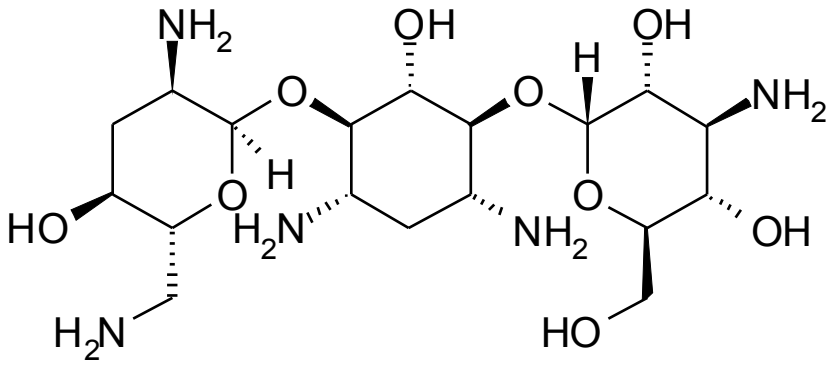
Aminoglycosides

3. Group of kanamycin and gemtamycin

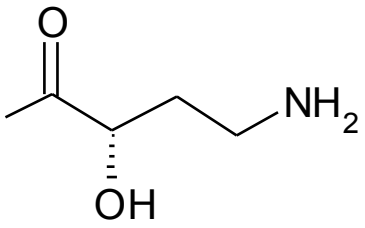
Kanamycin subgroup



R = -H **kanamycin**
Kanacol® a.u.v. inj.



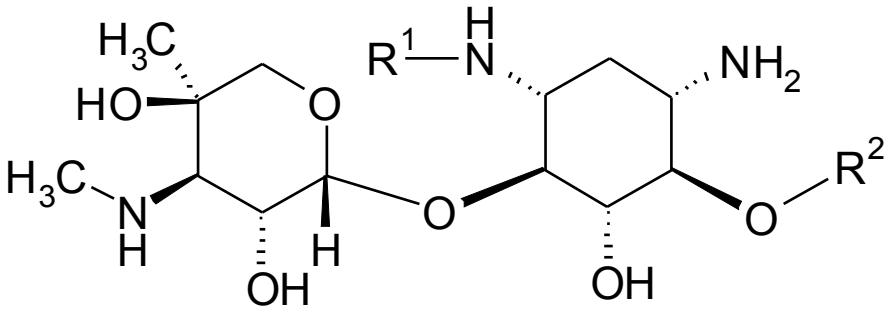
tobramycin
Tobi Nebuliser Solution® inh. sol.
•treatment of chronic pulmonary infection caused by *Pseudimonas* in patients with cystic fibrosis

R= 

amikacin
Amikin® inj.

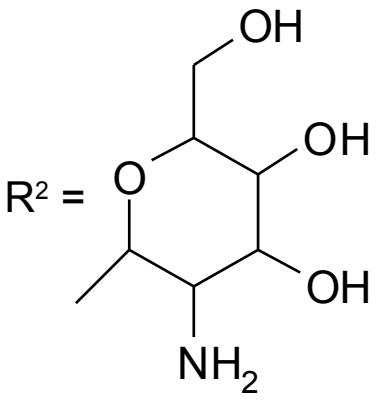
Aminoglycosides

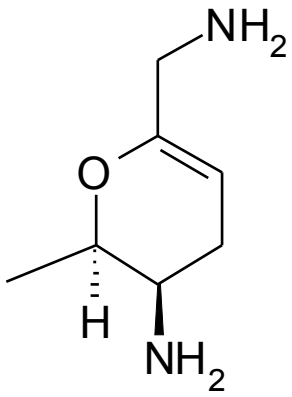
3. Group of kanamycin a gemtamycin
Subgroup of gentamycin

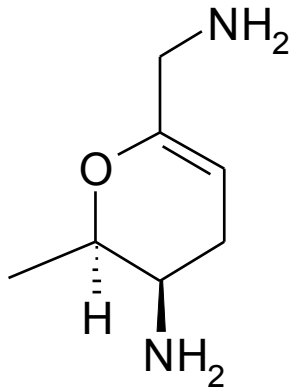


R^1= H- H- CH_3CH_2-

R^2 =







gentamycin
Garasone® gtt. opht.
(+betamethason)
Diagen® a.u.v.

sisomycin

netilmycin
Netromycine® inj.
•serious infections,
sepsis …