Chemotherapeutic Agents, chapter 38-43

- Antibacterial compounds (procaryotes)
- Antifungal compounds (eucarytotes)
- Antiparasitic agents (eucarytotes)

- Antiviral compounds

- Anticancer compounds

Different living organisms

Eucaryotes

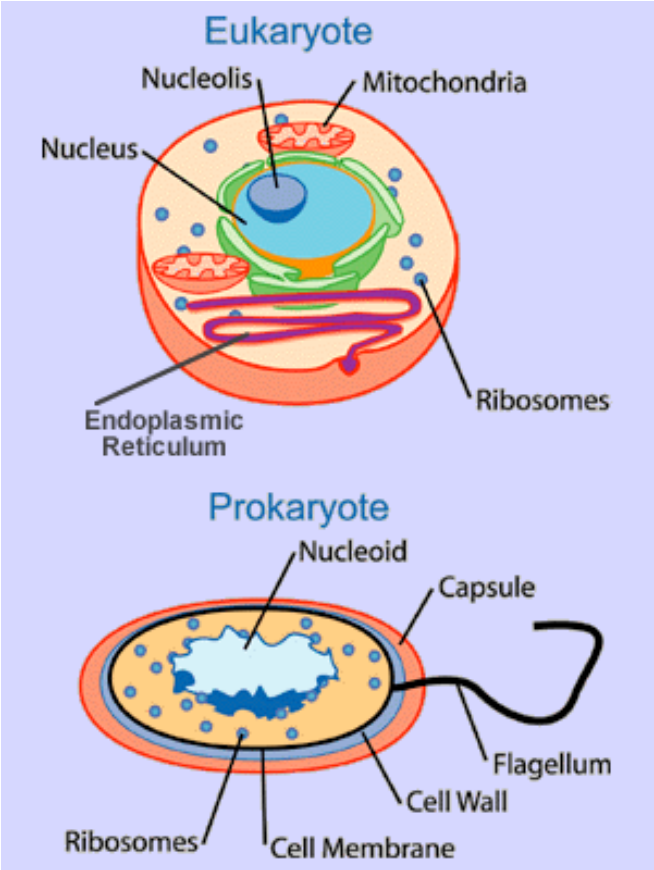
Mono or polycellular
Cell nucleus; DNA
May have cell wall
sexual and / or asexual replication

Animals

Plants

Fungi

Protocista: - Protozoea
- Algea



Procaryotes

Bakteriea:
Monocellular, no nucleus - DNA single strand, cell wall, asex. replic.

Virus

RNA or DNA + protein coating (not really a cell)
Use other oramisms ribosomes for protein synth

Antibacterial compounds, chapter 38(- antimycobacterials)

- **Synthetic antibacterials (chemotherapeutica)**
- **Antibiotics**

Antibiotics

Product from metabolism (natural product)
(also applies if compd is prepared synthetically,
or is a synthetic analog of a naturally occuring antibiotic/ semisynthetic compd)

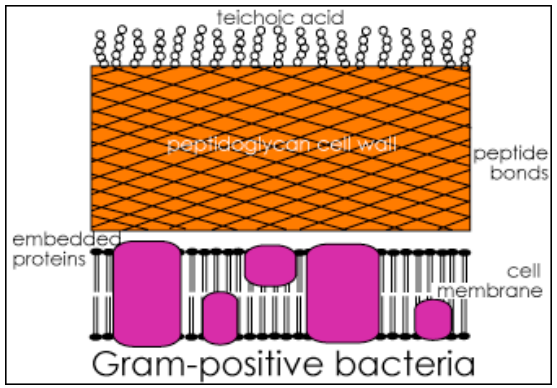
Inhibit growth (bacteriostatic) or kill (bacteriocide) microorg.

Effective in low conc.

Antimicrobial chemotherapeutics: Antimicrobial comp ≠ Antibiotics

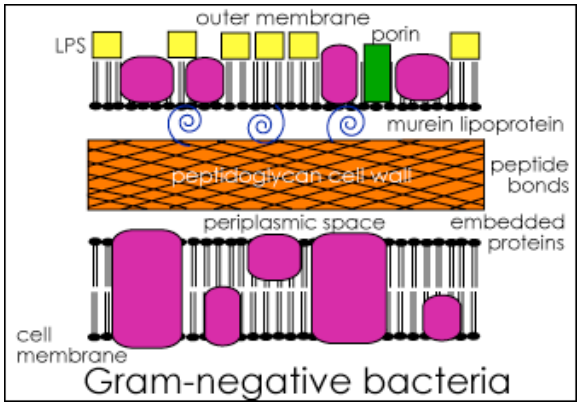
G+ and G- bacteria

Grampositive bakterier:
F. eks.
Streptococcus
Staphylococcus
Bacillus - causes anthrax and gastroenteritis
Clostridium - causes botulism, tetanus, gas gangrene, and pseudomembranous colitis
Corynebacterium - causes diphtheria
Listeria - causes meningitis



The cell walls of gram-positive bacteria are made up of twenty times as much murein or peptidoglycan than gram-negative bacteria. These complex polymers of sugars and amino acids cross-link and layer the cell wall.
The thick outer matrix of peptidoglycan, teichoic acid, polysaccharides, and other proteins serve a number of purposes, including membrane transport regulation, cell expansion, and shape formation

Gramnegative bakterier:
F. eks.
Spirochetes - causes syphilis, lyme disease
Neisseria- causes meningococcus, gonorrhea

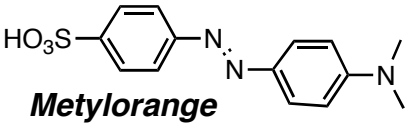


Gram-negative bacteria have a unique outer membrane, a thinner layer of peptidoglycan, and a periplasmic space between the cell wall and the membrane.
In the outer membrane, gram-negative bacteria have lipopolysaccharides (LPS), porin channels, and murein lipoprotein all of which gram-positive bacteria lack.
The gram-negative outer membrane which contains LPS, an endotoxin, blocks antibiotics, dyes, and detergents protecting the sensitive inner membrane and cell wall.

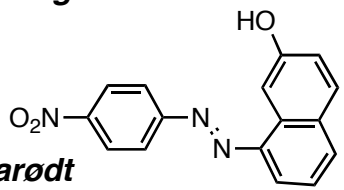
Synthetic antibacterials (chemotherapeutica)

Antibacterial sulfonamides

Azo dyes
Bayer etc
Late 1800-century, ex.

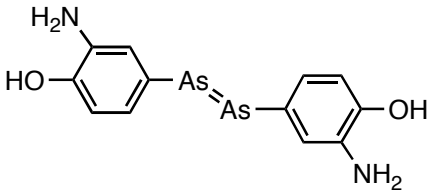


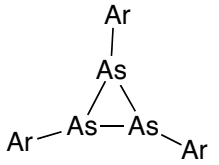
Metylorange

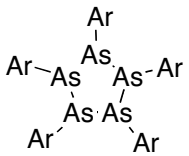


Pararødt

Salvarsan
1. antisyphilis drug 1912

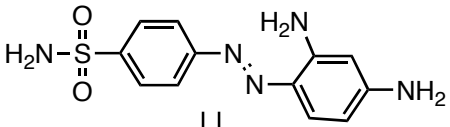




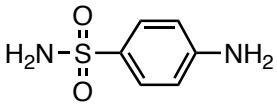


Screening of dyes as antibacterials

1932: ***Prontocil*** active against Streptoccocces infection
no activity on bacterial cultures

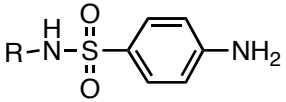


1935: Prontocil metabilized (azoreductase) to **Sulfanilamid** *in vivo*



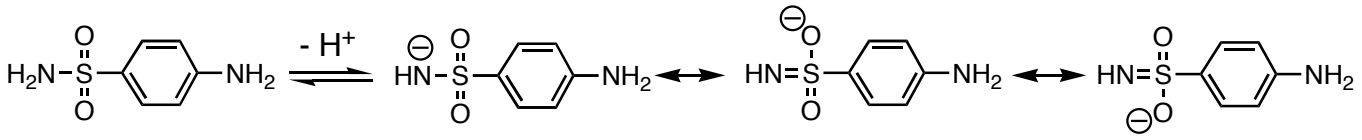
(rel. toxisk)

Modern sulfa drugsr



R: Aryl or hetroaryl

Sulfonamides are acidic

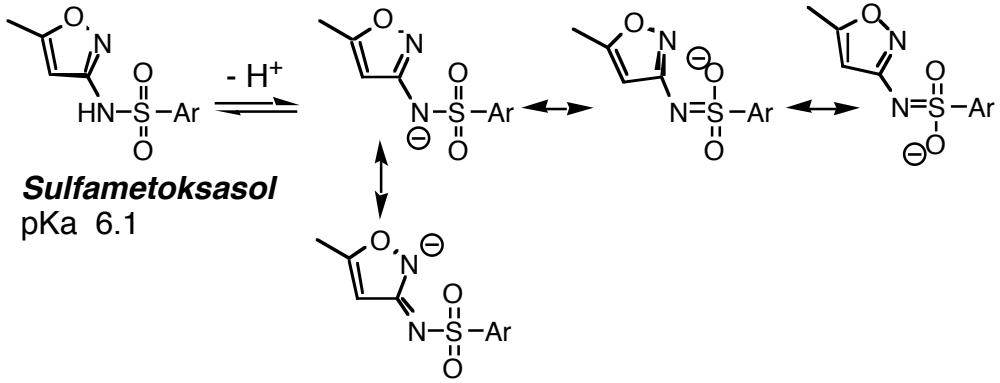


Sulfanilamid
pKa 10.4

Neutral sulfonilamid low water sol.

Urine pH ca 6: Crystallization neutral form, kidney damage

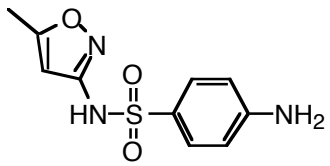
Modern sulfa drugs pKa 5 – 7; better solubility

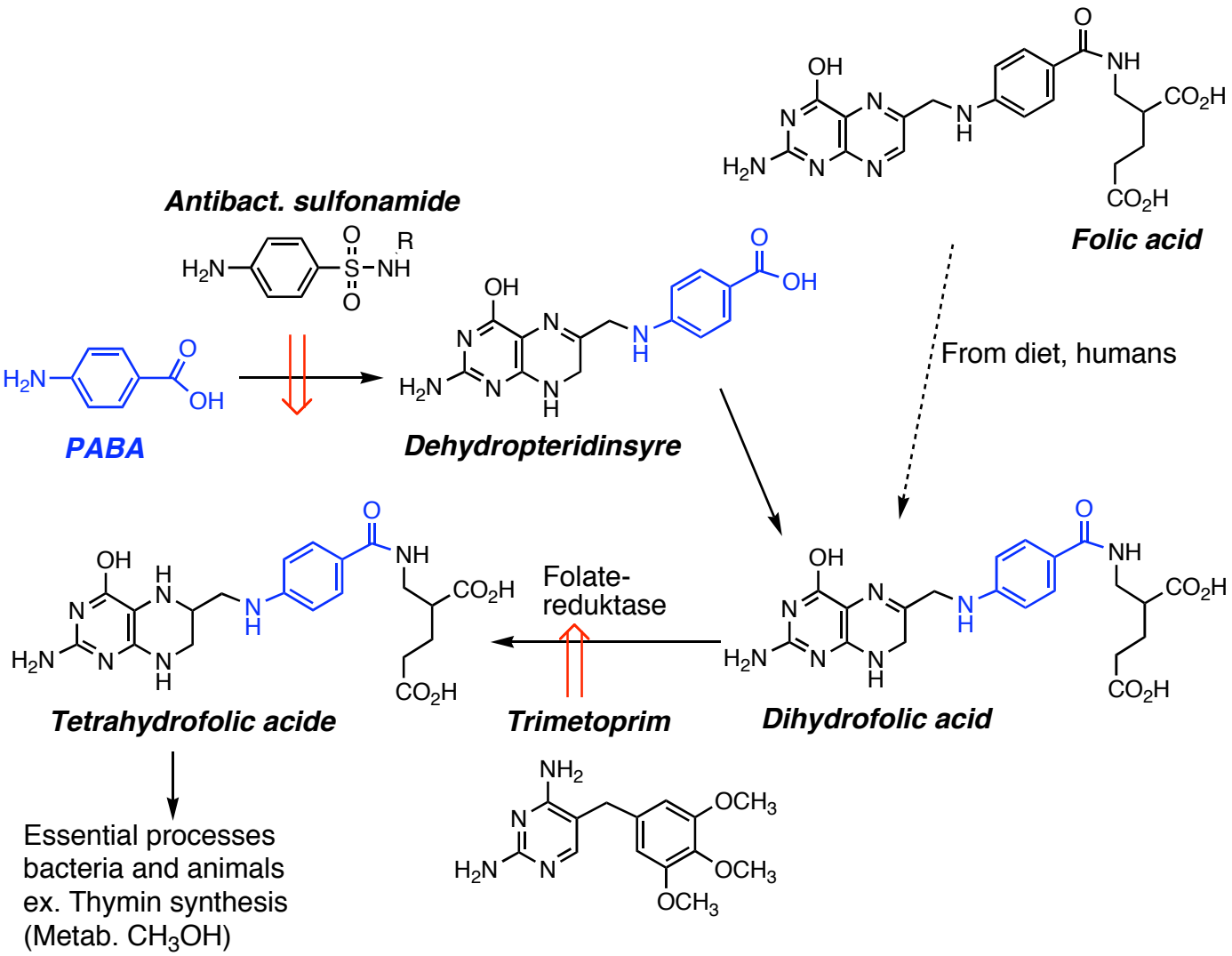


Sulfametoksasol
pKa 6.1

Sulfametoxazol

Bactrim®, Trimetoprim-Sulfa ® -
Urine infections
Combi. with trimethoprime





Inhib. of folate reductase

Quinolones

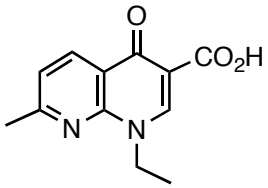
Inhib DNA-synthesis; DNA-gyrase (prokaryoter) uwounding DNA before replic.

DNA-topoisomerase (humans), anticancer compds. ex. doxorubicin

Unique mecanism, no cross resistance

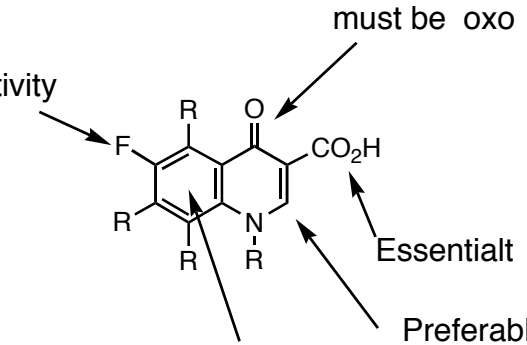
Broad spectrum: G+ and G- ; also mycobactria, clamydia

Parent comp.
Nalidixic acid



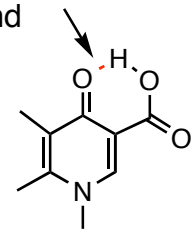
Urinary tract infect. earlier
effect on Gram-negative bacteria (ex. *E. coli*)

Moderne quinolones



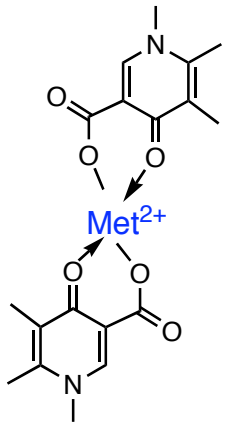
Must have aromatic ring
condenced with the pyridine

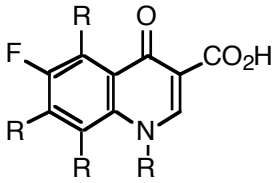
Intramolek.
H-bond



pKa ca 5.5 - 6.5
(Benzoic acid pKa 4.2)

Chelater with
Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, Bi^{3+}

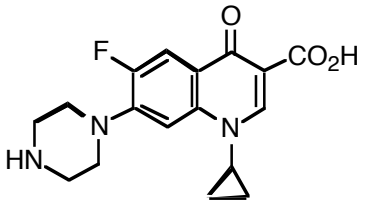




Ciprofloksacin

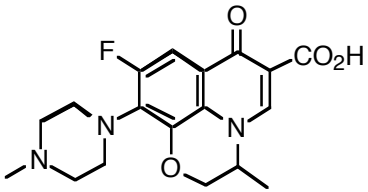
Ciprox®, Ciprofloxacin®

Cilox®



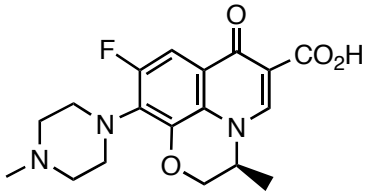
Ofloksacin

Tarivid®

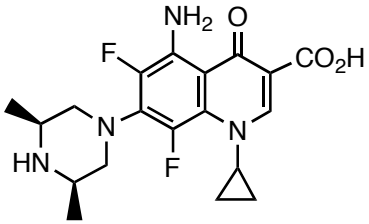


(±)

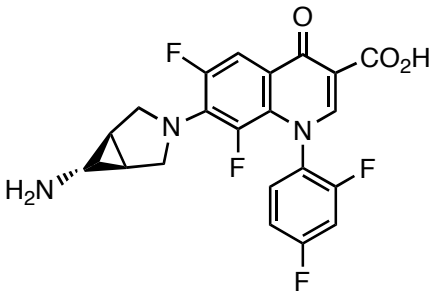
Levofloxacin, 2x active



Sparfloxacin



Trovafloxacin

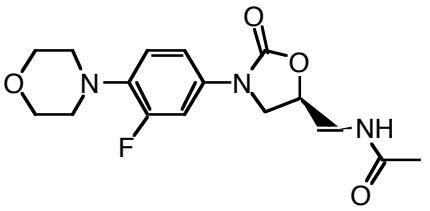


Better effect on G+

Oxazolidones

Linesolid

Zyvoxid®



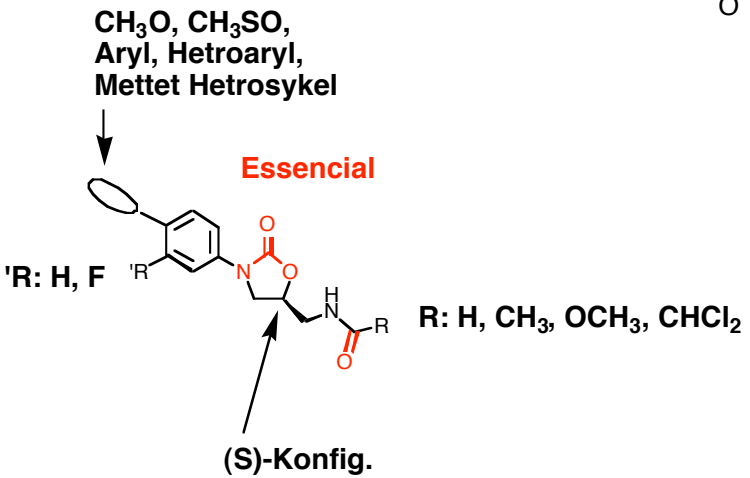
Reg. Norge 2002,

1. antibact. drug with new mechaanism of action in 35 years

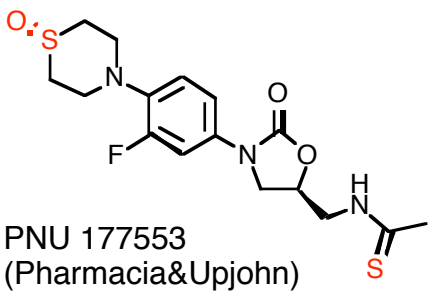
Inhib. protein synthesis early

No cross resist.. G+ and some G-.

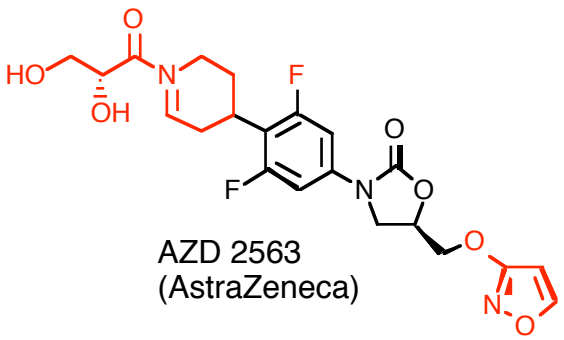
Resistant strains



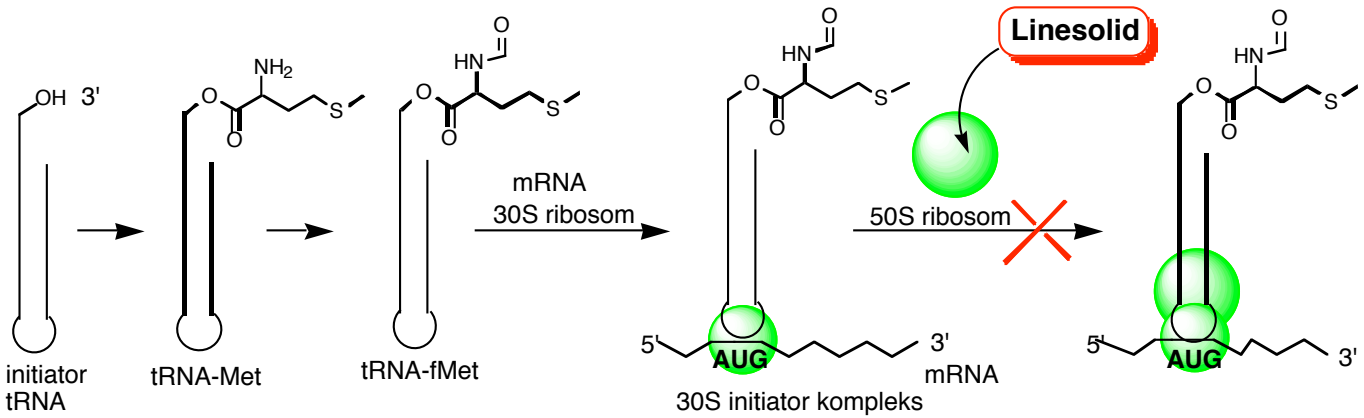
New drugs?

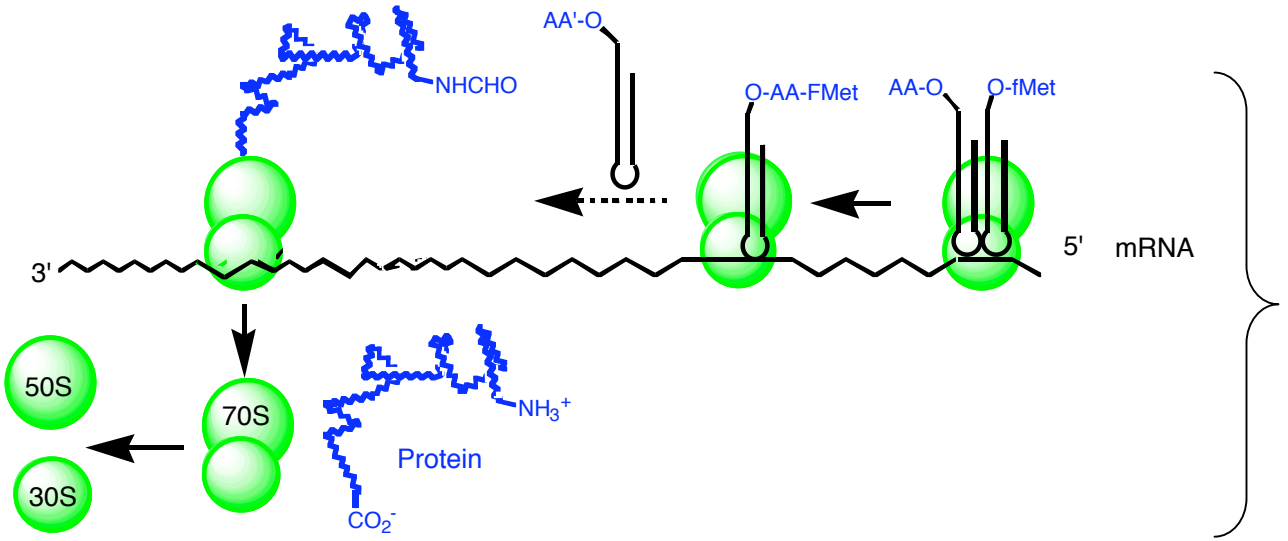


PNU 177553
(Pharmacia&Upjohn)



AZD 2563
(AstraZeneca)



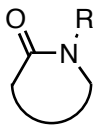


Other antibiotics

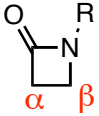
Antibiotics

β-Lactam-antibiotics

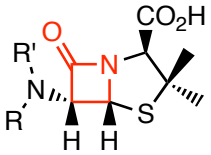
Lactam = cyclic amide



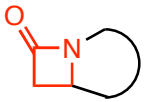
β-Laktam



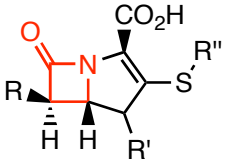
Penicillins



β-Laktamase-inhibitors

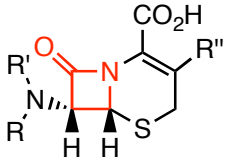


Karbapenems

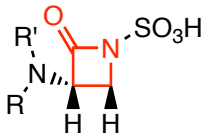


+ Cilastatin

Cefalosporines

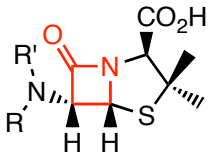


Monobaktames



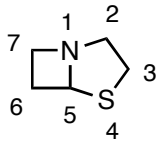
Penicillines

Gen. struct



β-lactam

(2S, 5R, 6R)

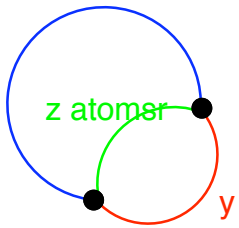


1-Aza-4-tiabicykco[3.2.0]heptane

N S

tot. 7atoms in ring

X atomsr



z atomsr

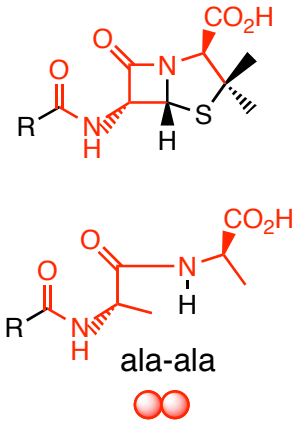
y atoms

[x.y.z]alkane

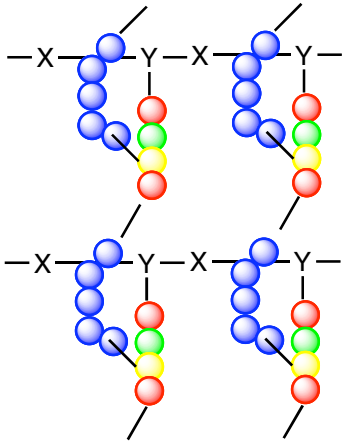
tot no. of atomes

Mechanism

HInhib. cell wall synth. - peptidoglycane
≈ ala-ala



Peptidoglycane detail

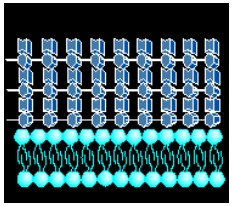


X: N-acetylglucosamin
Y: N-acetylmuraminsyre

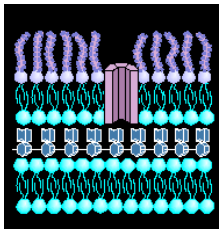
Pentapeptide:
gly-gly-gly-gly-gly

Tetrapeptide:
L-ala-
D-glu-
L-lys-
L-ala

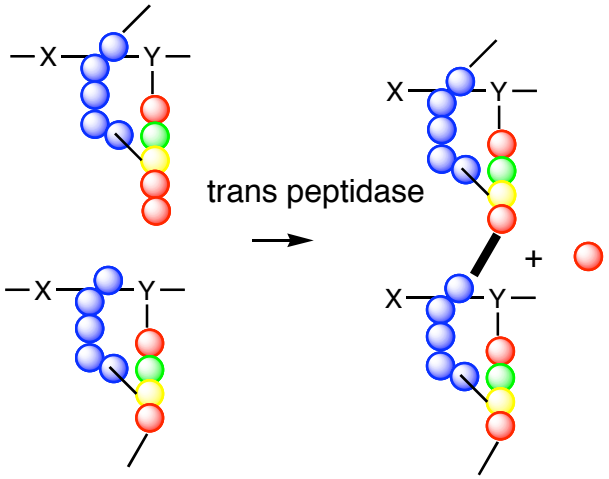
G+



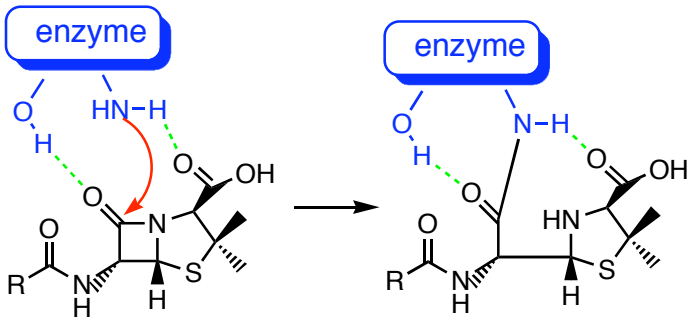
G-



Peptidoglycane synth. -cross linking

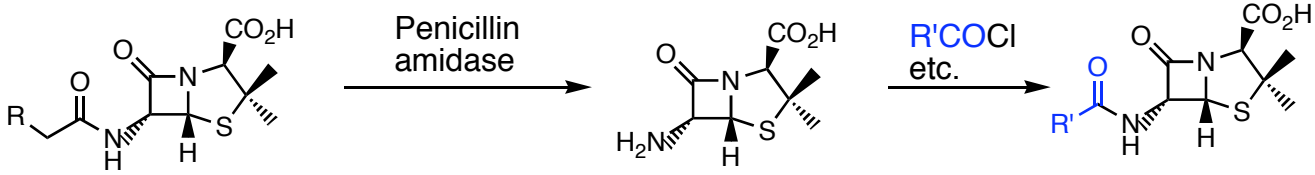


penicillin (≈ ala-ala)irreversible binding to trans peptidase
Cross linking inhibited



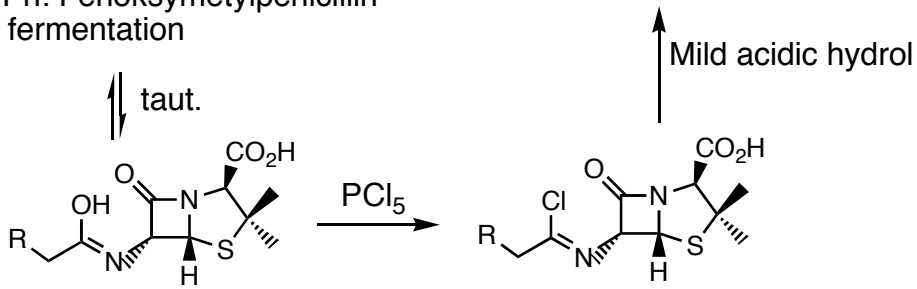
Semi synthesis

two amide func.
Hydrolysis



R=Ph: Benzylpenicillin
R=OPh: Fenoksymetylpenicillin
from fermentation

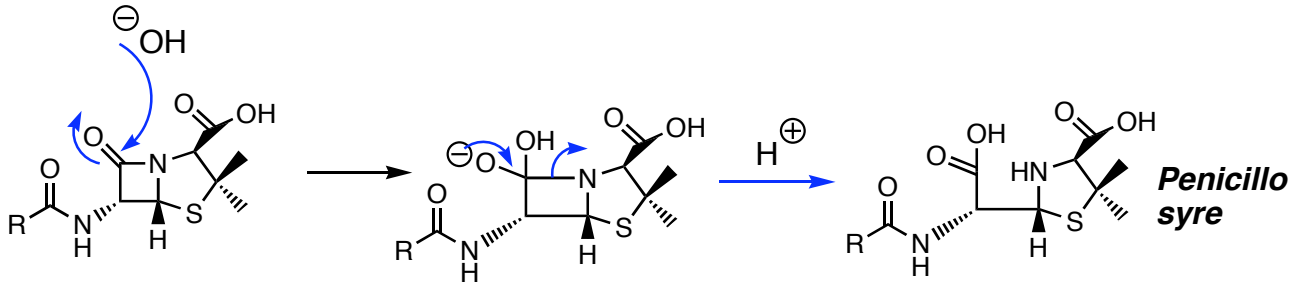
6-aminopenicillansyre



iminochloride

Stability

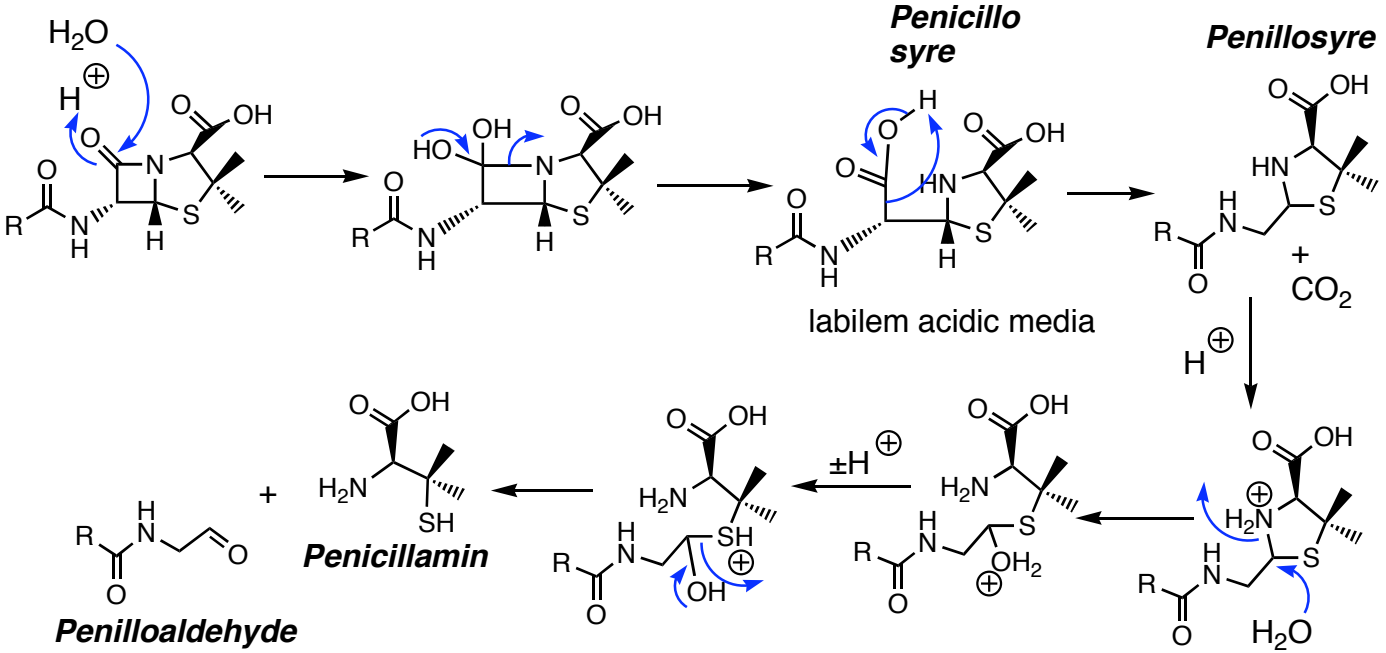
Basic amide hydrol. - ring strain in β-lactame



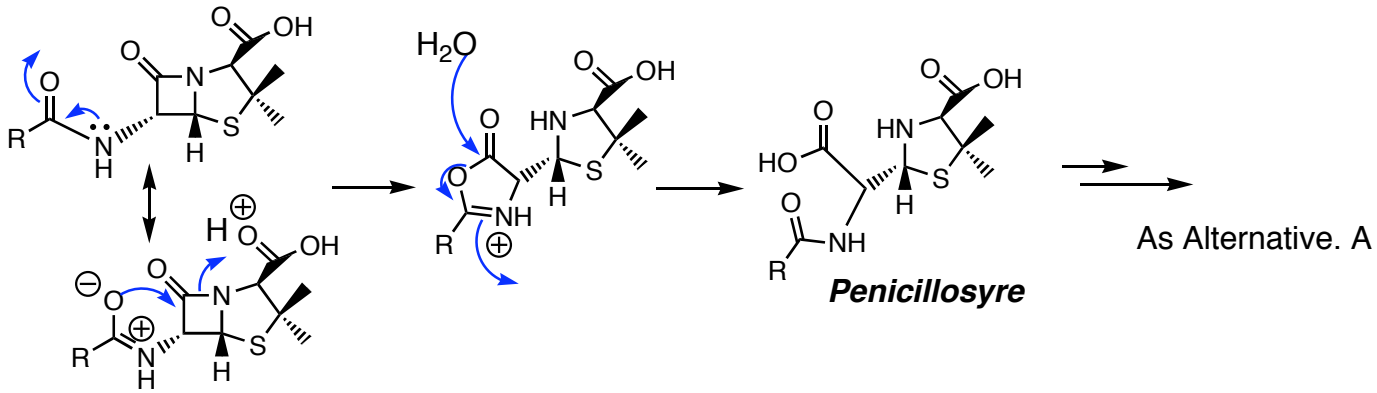
stabile pH≥7

Penicillo syre

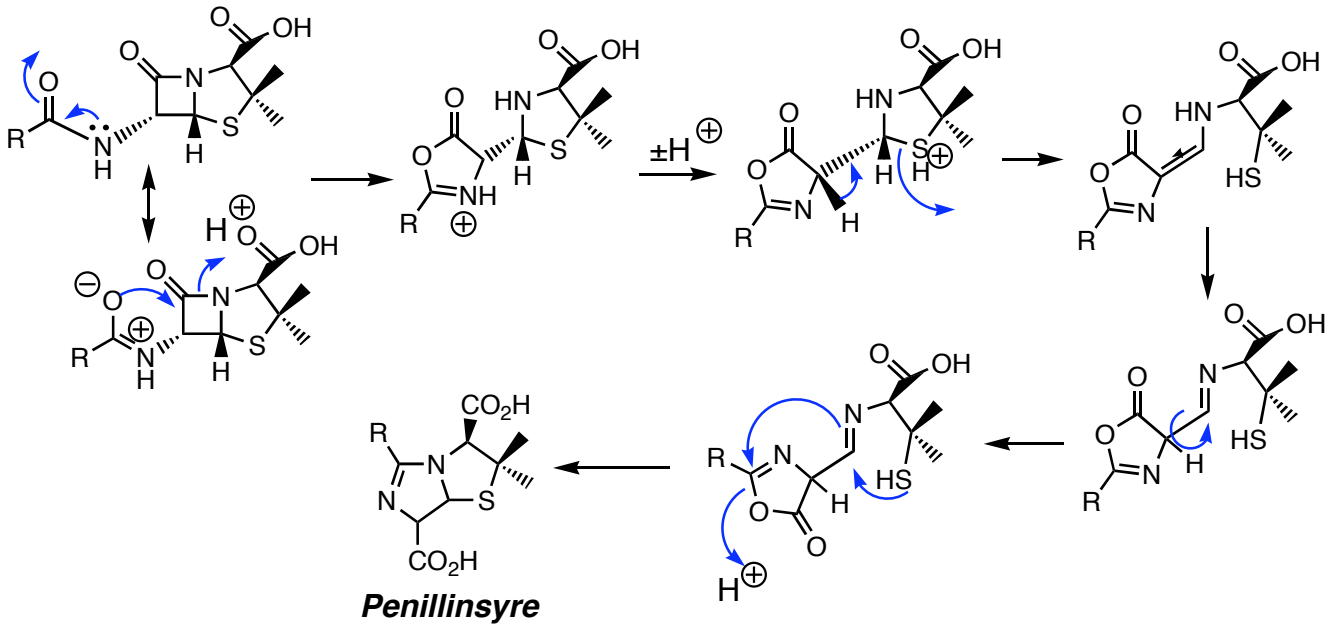
Acidic hydrolysis
Alternative A



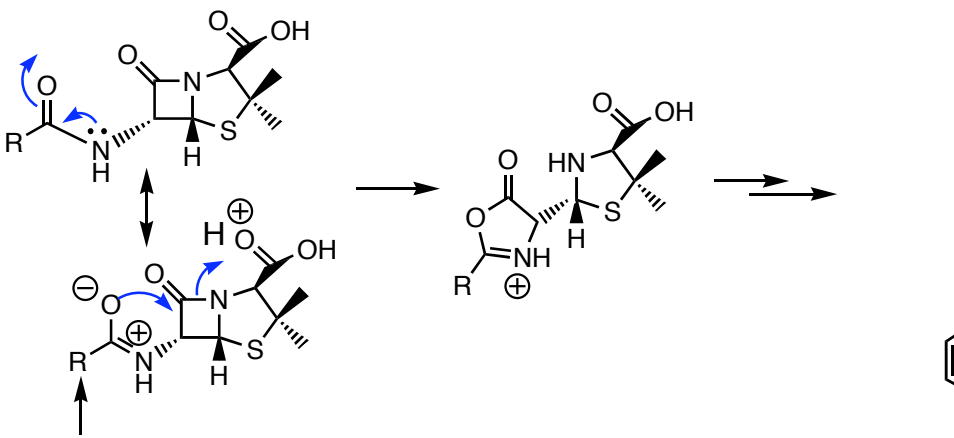
Acidic hydrolysis
Alternative B



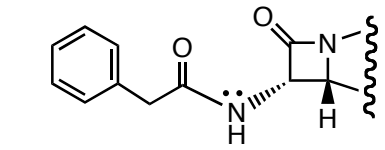
Acidic hydrolysis
Alternative C



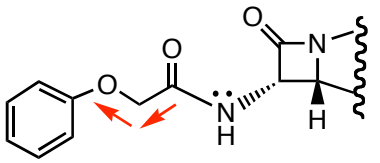
Structure acide stabile pennicillines



EWG R; Olessnukleofilic



BensylP. acid labile



PhenoxymethylP.acid stabile

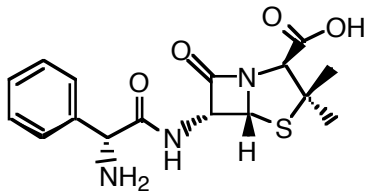
Indictive electron withdrawing effect

Nat. occuring P.

Semisynthetic, increased acid stability

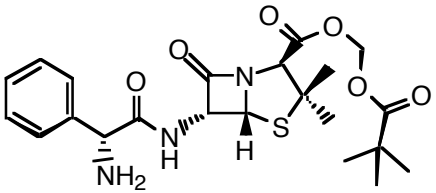
Ampicillin

Pentrexyl®,



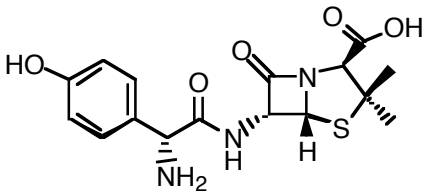
Pivampicillin

Pondocillin®,



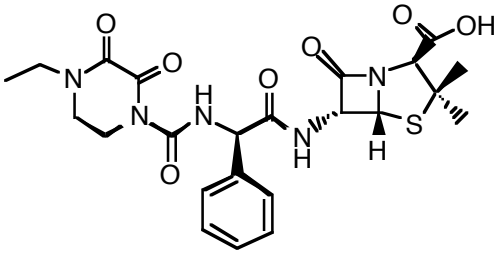
Amoxicillin

Amoxicillin®,

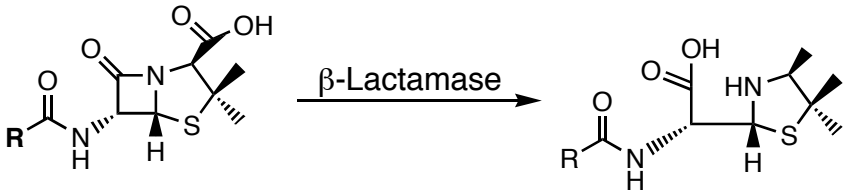


Piperacillin

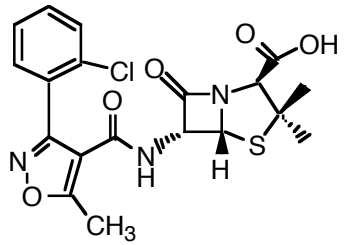
Tazocin®

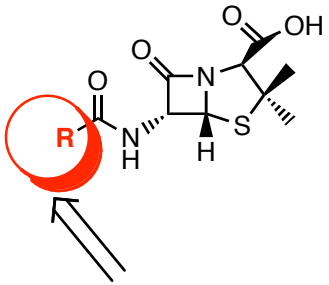


Resistant strains

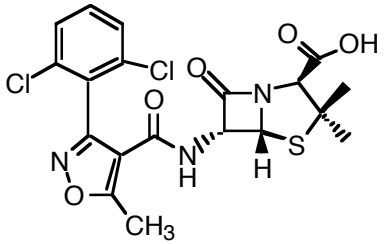


Kloksacillin
Ekvacillin®



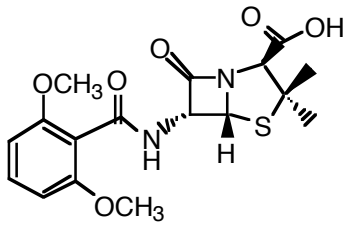


Dikloksacillin
Diclocil®



Larger R; effect on β-lactamase resistant bacteria (starical hindrance)

Meticillin

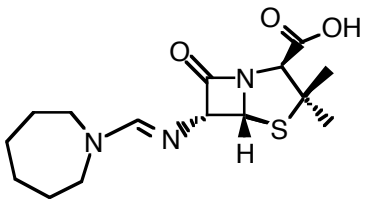


Acid labile, last resort drug resist. strains

Semisynthetic, Broad spectrum, Imines

Meticillinam

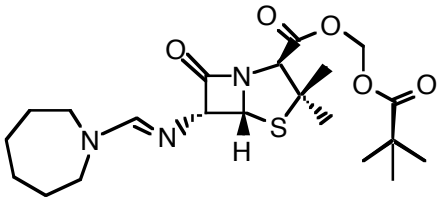
Selexid®



No nucleophilic cabronyl

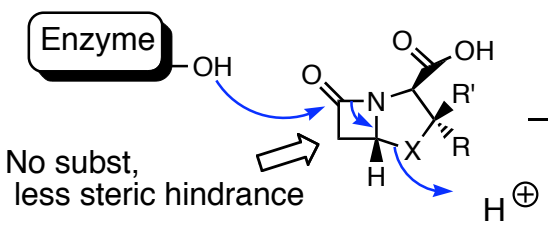
Pivmeticillinam

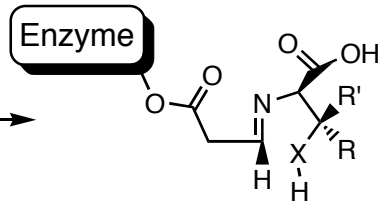
Selexid®



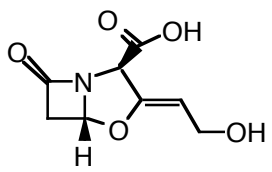
β-Lactamase Inhibitors

Combination with penicillines

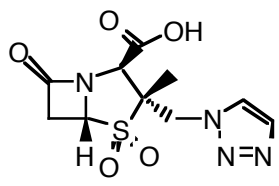




Clavulanic acid



Tazobaktam

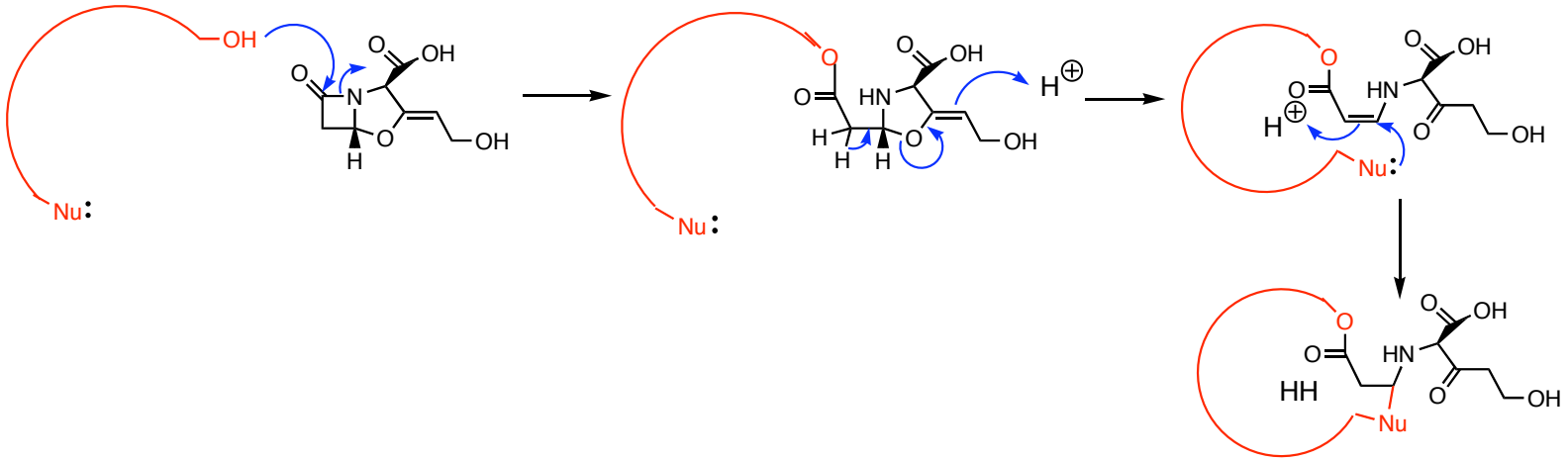


- **Mechanism based irreversible enzyme inactivators**

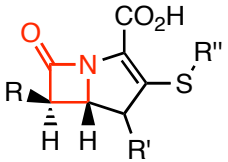
Suicide substrate - kcat inhibitors - Trojan horse inhib. - latent alkylating agent

≈ Pro-drug, must be activated by the enzyme

Clavulanic acid irreversibly inhibits β-lactamase



Carbapenems / Carbapenins

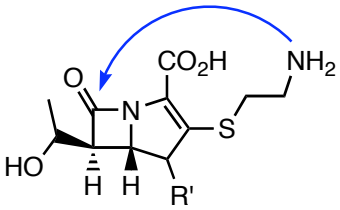


No S in
5-membered ring

Tienamycin from
Streptomyces cattleya
1976

Broad spectrum

Not substr. for β–lactamase

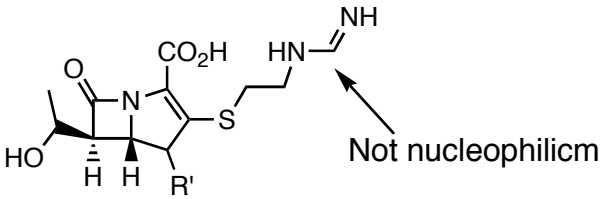


Labile, acidic and basic media

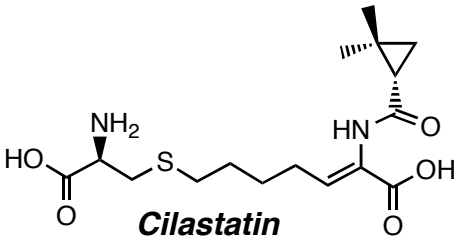
Cleaved *in vivo* av DHP-I
(dehydropeptidase I)

Imipenem + cilastan

Tienam®



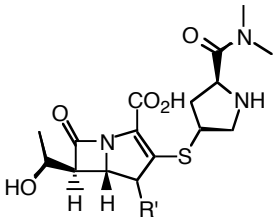
Imipenem



Cilastatin
DHP-I inhib.

Meropenem

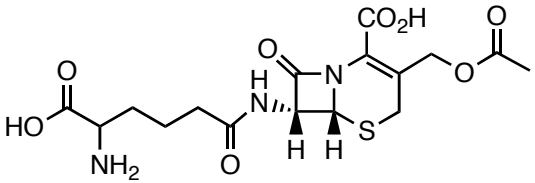
Meronem®

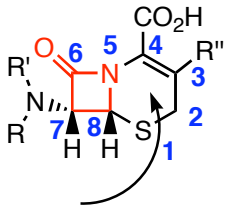


2. Gen.
Not cleaved by
DHP-1

Cephalosporins

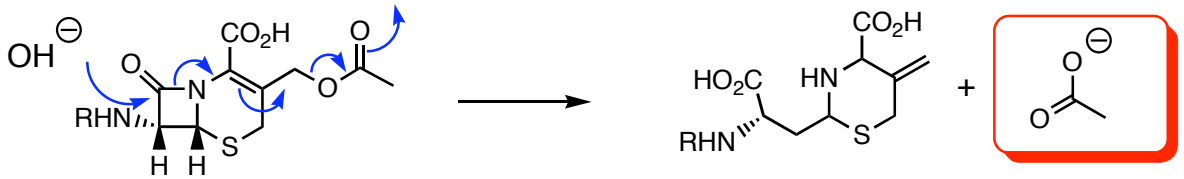
Cefalosporin C from *Cephalosporium acremonium* 1945





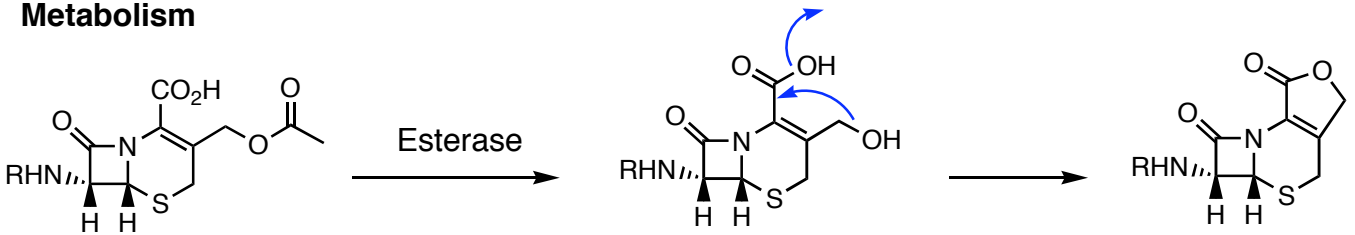
6- membered ring; Less ring strain than penicillins

Subst in 3-pos., important for hydrolyttic stability



Good leaving group

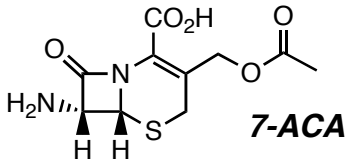
Metabolism



Inactive lactone

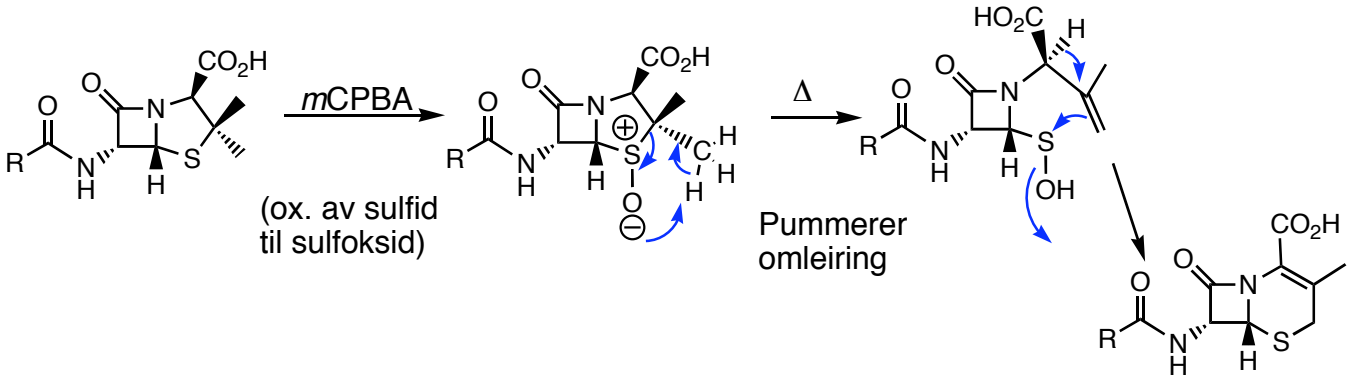
Isolation from *Cephalosporium sp*

or semisynth from ***7-aminocefalosporic acid (7-ACA)***



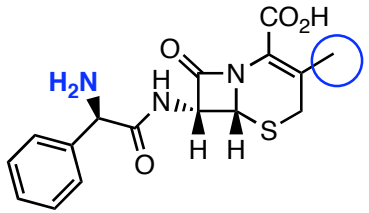
7-ACA

Semisynth from penicillins



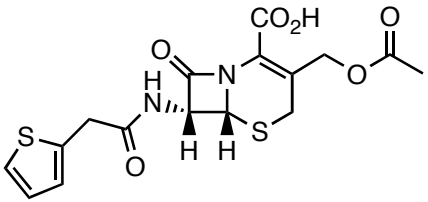
1. generation: Relatively broad spectrum (G+, some G-)
Cleaved by β-Lactamase

Cephalexin
Cefalex® Keflex®



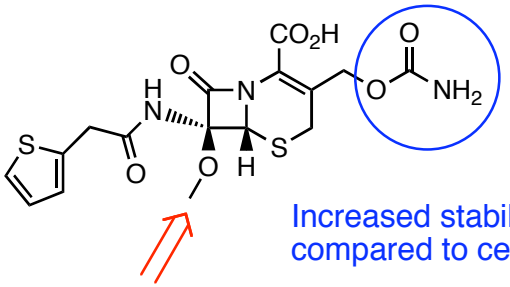
Realtively diff. to hydrolyze
Only oral Ceph.

Cefalotin
Cefalotin® Keflin®



2. generation: More broad spectrum
Not cleaved by β-Lactamase

Cefoxitin
Mefoxitin®

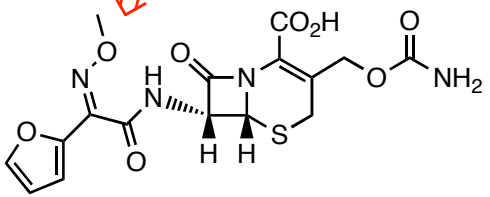


Increased stability
compared to cephalotin

Steric hindrance β-L

Cefuroxim
Cefuroxim® Zinacef®

Syn isomer, steric hindrance β-L
Anti cleaved by β-L

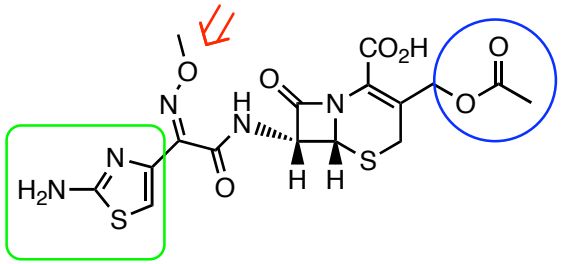


3. generation: Very broad spectrum, also *Pseudomonas sp*
Not cleaved by β-Lactamase
Acid labile

Cefotaxim

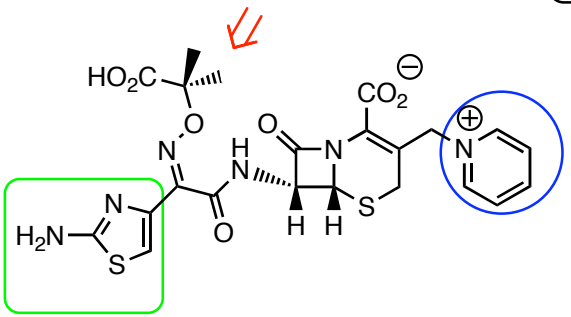
Cefotaxime®

Claforan®



Ceftazidim

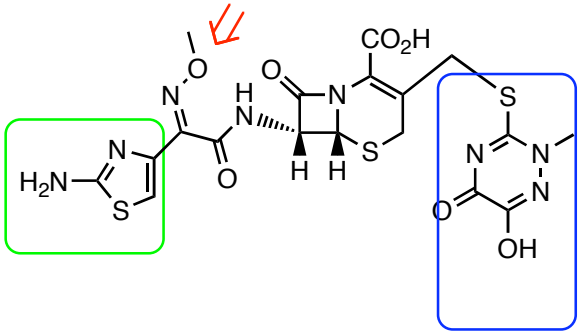
Fortum®



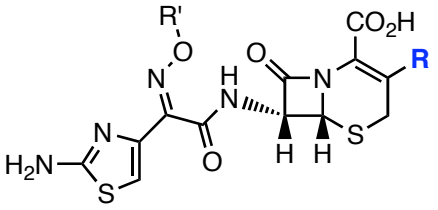
Good leaving group
Steric hindrance
G-

Ceftriaxon

Rohephalin®

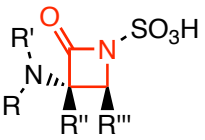


Oral 3. gen (not in N):



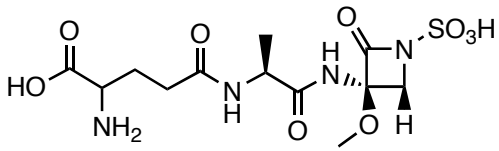
R: -H, -CH=CH$_2$, -CH$_2$OCH$_3$

Monobactams



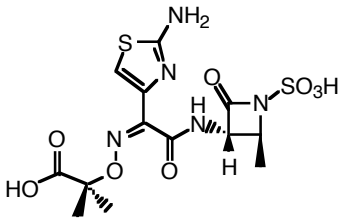
Only 4 membered ring

From ***Sulfacetin***;
weak antibacterial
Not substrate forr β-lactamase



Aztreonam

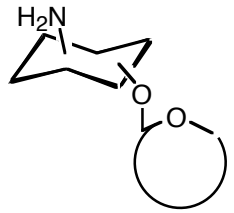
Azactam®

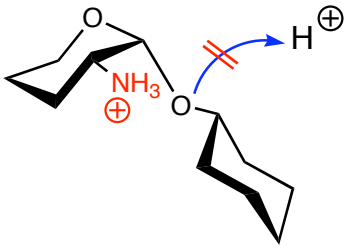


Mer stabil enn Sulfacetin
Bare effekt på G-

Aminoglycosides

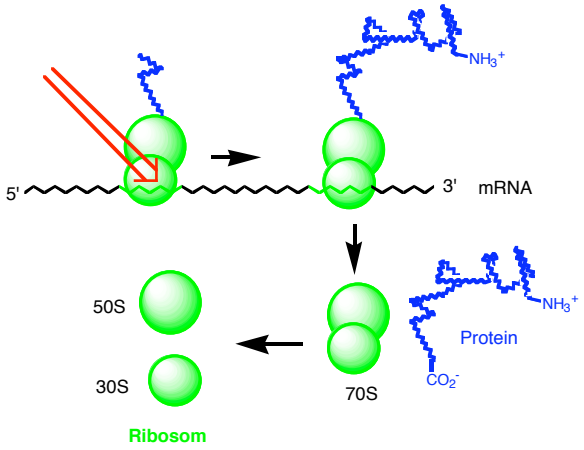
- **Broad spectrum**
- **Toxic**
- **Inhib. protein synthesis**
- **≈No absorb. from GI, local treatment infect. GI tract.**
- **Systhemic infections – parenteral adm.**

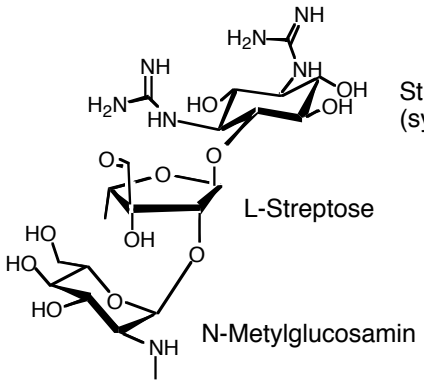




- **Basic, water solubile salts phys. pH**
- **-Glykosides (= acetals) stabile acidic media because of protonated amino subst.**

Bind to
mRNA read wrong
Transloc. blocked



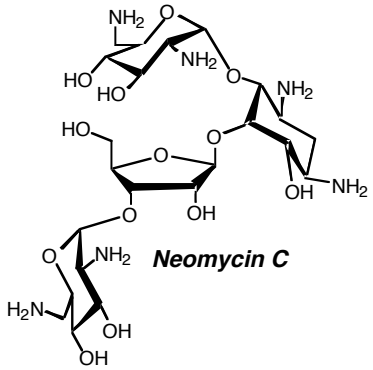


Streptomycin

- **First aminoglyc.: Streptomycin (ca 1944) from *Streptomyces griseus***
- **First antituberculosis drug.**
- **Toxic!**

Neomycin

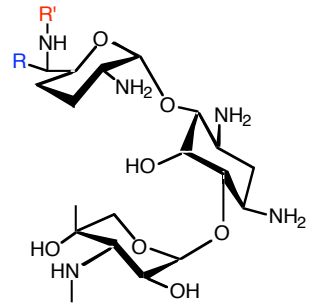
***Streptomyces fradia* (1949).**
Maxitrol®, eyedrops
Less tox. than streptomycin



Neomycin C

Gentamicin

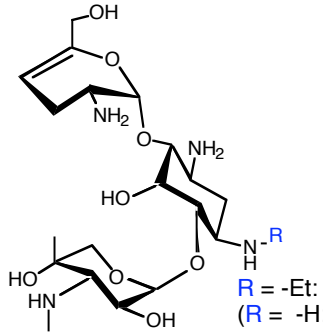
Garamycin®
From *Micromonospora purpurea*.



R = R' = -CH_3: ***Gentamicin C_1***
R = CH_3, R' = -H: ***Gentamicin C_2***
R = R' = -H: ***Gentamicin C_{1a}***

Netilmicin

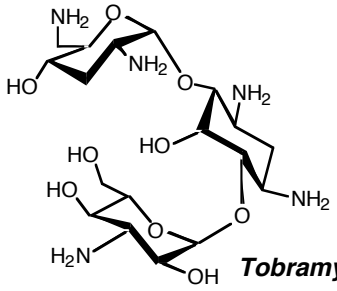
Netilyn® injek.
Semisynth from Sisomicin
(*Micromonospora inyoensis*)



R = -Et: ***Netilmicin***
(R = -H: ***Sisomicin***)

Tobramycin

Nebcina® Tobi®, Tobrex
***Streptomyces tenebrarius*.**



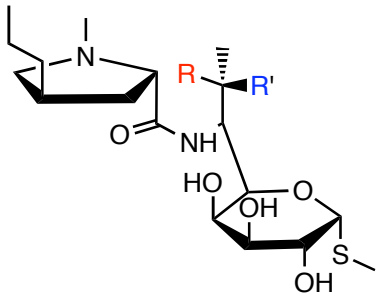
Tobramycin

Lincomycines

- **Sulfur cont. antibiotics from *Streptomyces lincolnensis;***
- **Naturally occuring: Linkomycin (not in N), more active semisynth der.**
- **Inhib protein synth, binds to 50S part of ribosome**

Klindamycin
Dalactin® Dalactin® Clindamycin®.

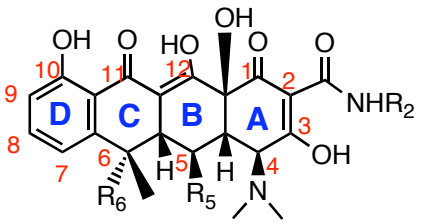
Semisynth from linkomycin



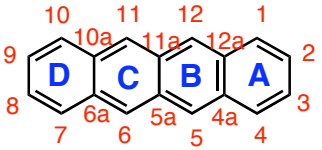
R= H, R'=Cl: ***Klindamycin***

R=OH, R'=H: ***Linkomycin***,

Tetrasyclines



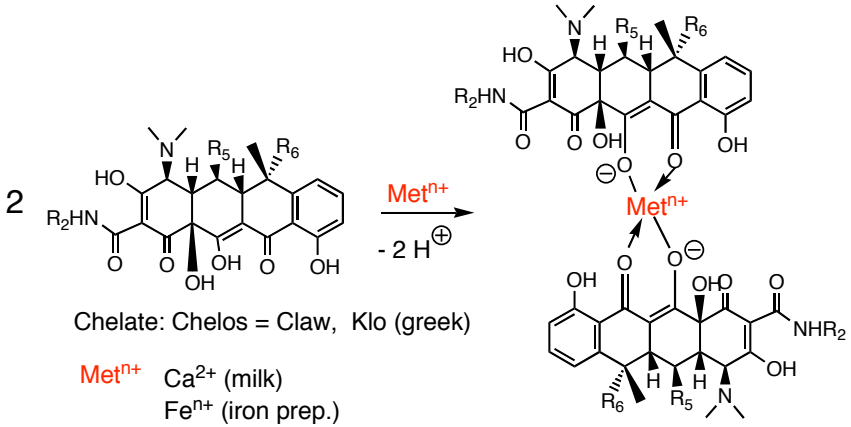
Tetracyclines: Gen. struct. (reg. in N.)



Naftacene

- **Mechanism: Bindes to 30S part of ribosome, inhibits protein synth.; komplexing Mg_{2+} involved.**
- **Binds also to 30S-rib. mammals, but bacteria cells also have active transport mech. for T uptake.**
- **The most broad spctrum antibiotic known to date.**
- **Bakteriostatic, not baktericid.**
- **Attacks natural bacteria flora in GI tract (oportunistic *candida* infect.)**

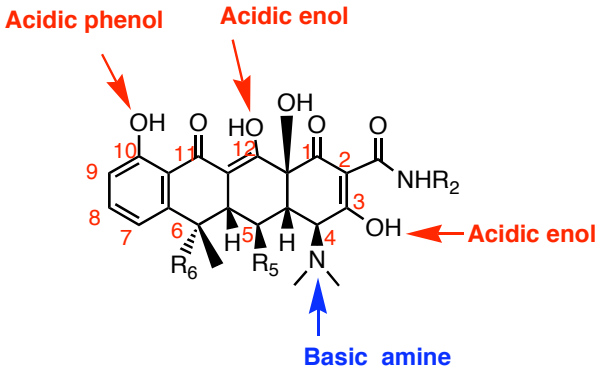
Chelate



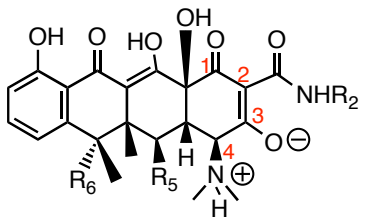
Chelate: Chelos = Claw, Klo (greek)

Met^{n+} Ca^{2+} (milk)
Fe^{n+} (iron prep.)
Al^{3+} (antacida.)

Acid - Base prop.

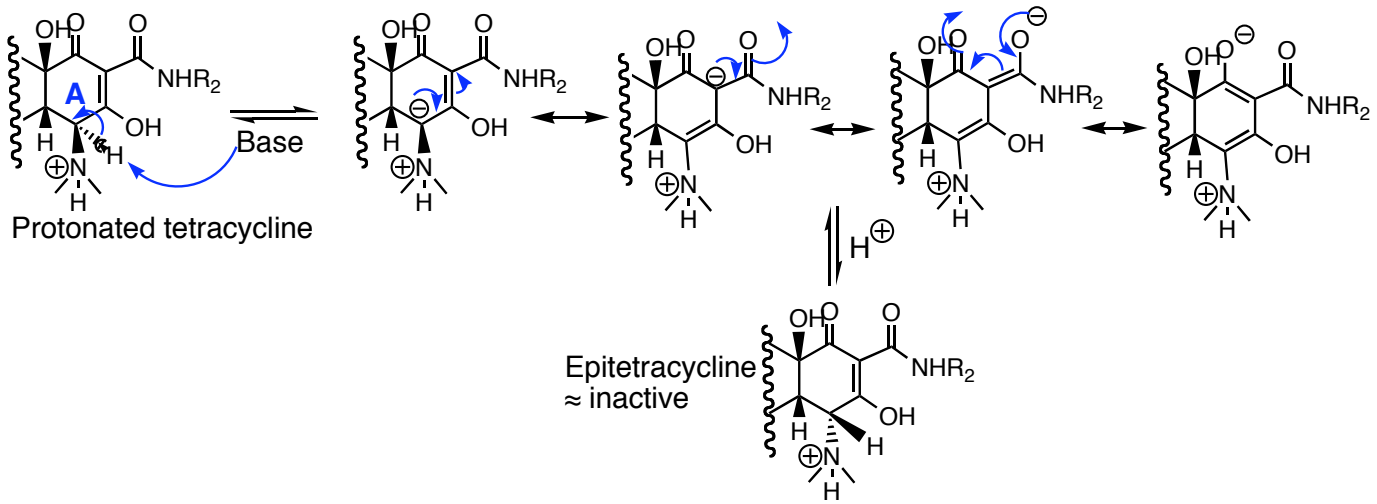


Zwitter ion (high water sol.) neutral pH

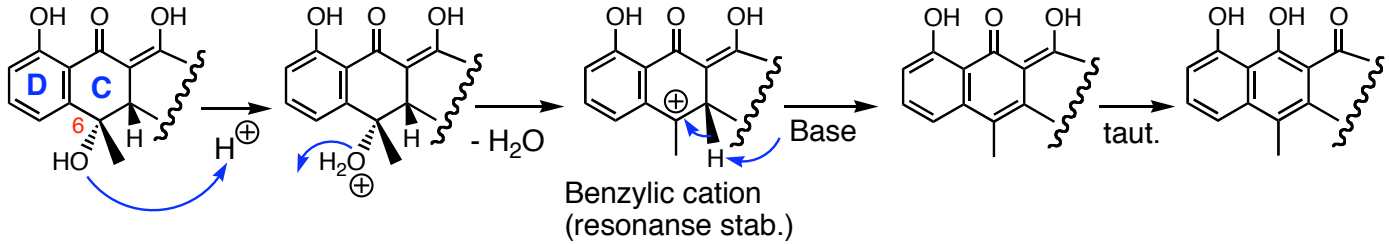


Stability; acid / base

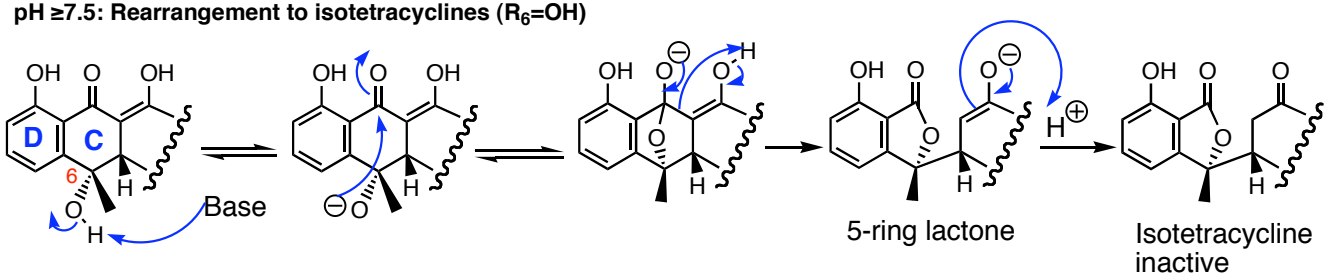
pH 2 - 6: Epimerisation C-4



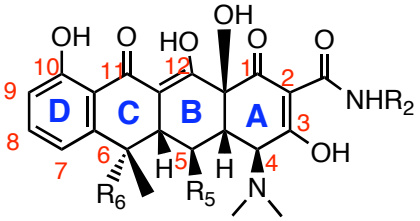
pH ≤2: Dehydratisation; Aromatisation C-ring (R_6=OH)



pH ≥7.5: Rearrangement to isotetracyclines (R_6=OH)

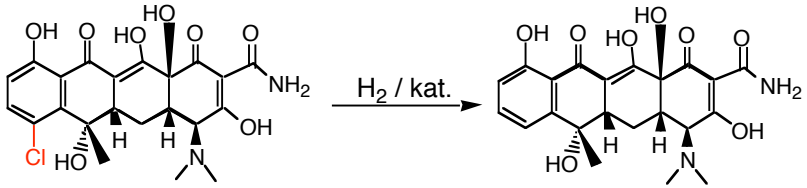


	R_5	R_6	R_2
Tetracycline	-H	**-OH**	-H
Oxytetracycline	-OH	**-OH**	-H
Doxycycline	-OH	-H	-H
Lymecycline	-H	-OH	$-CH_2NHCH_2NH(CH_2)_4CH(NH_2)CO_2H$



Tetracyclin

Isolation from *Streptomyces* sp,
Semisynth from chlorotetracycline more effective
(low bioavailability)

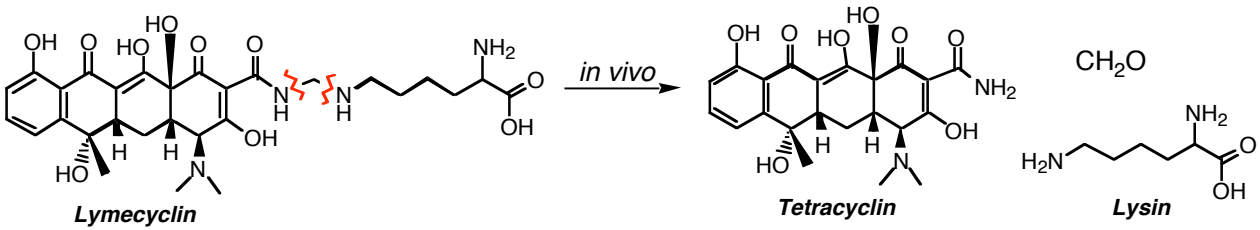


Klortetracyclin
fra fermenter. av *Streptomyces* arter

Tetracyclin

Lymecyclin

More water sol., pro-drug.
Semisynth from tetracycline



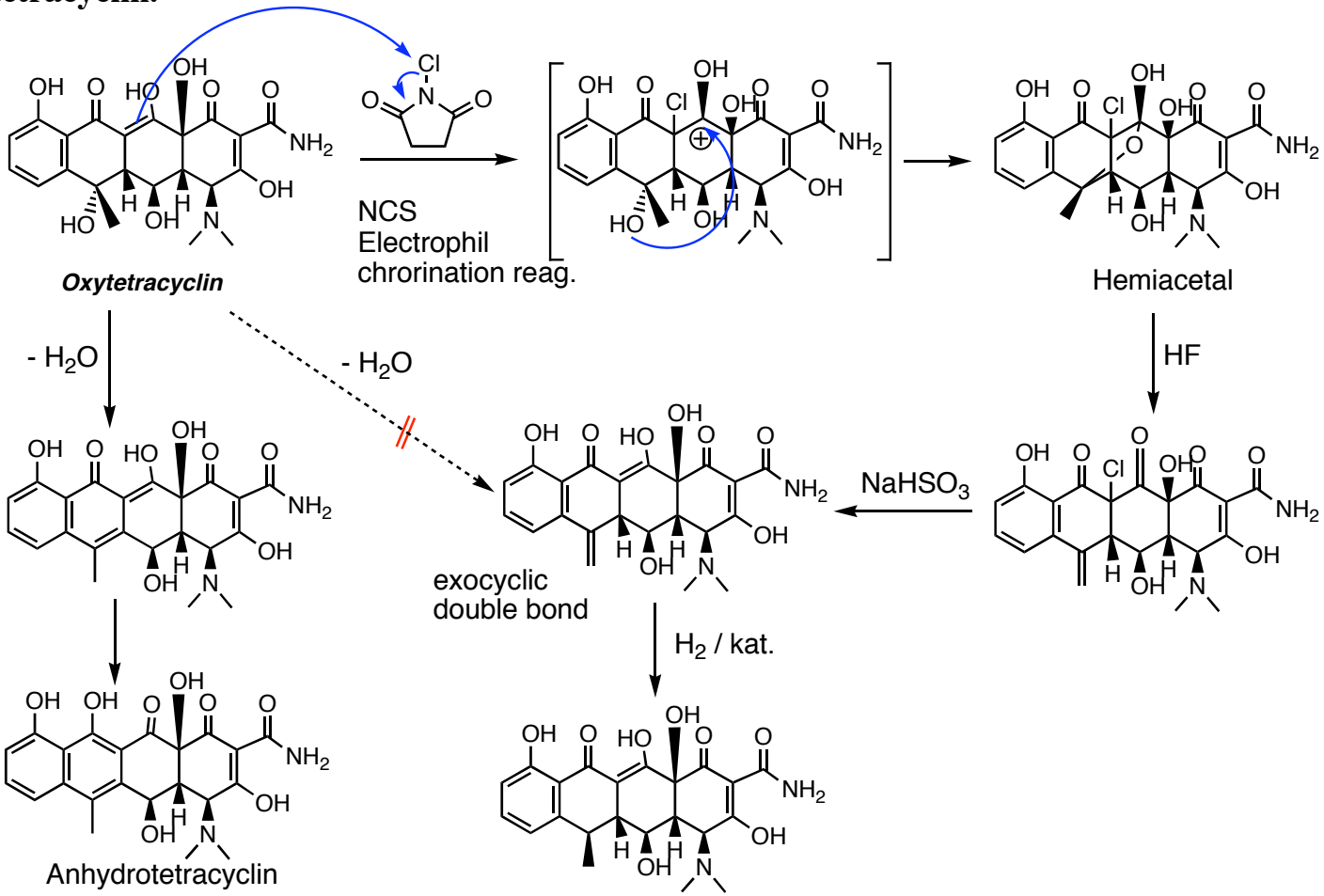
Lymecyclin

Tetracyclin

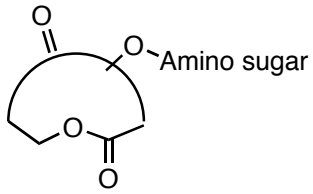
Lysin

Doxycyclin

Not OH i 6-pos. More stabile in water solution (also mixture).
Longer t $_{1/2}$, good oral absorb.
Semisynth oxytetracyclin.



Makrolides

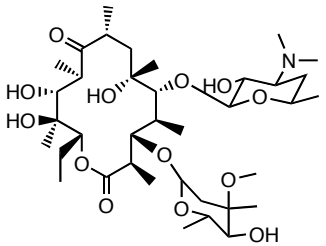


- **Isolated from soil-bakteria, *Streptomyces* sp.**
- **Reletively narrow spectrum, mainly G+. Low tox.**
- **Bindes to 50S part of ribosome, inhib. Protein synth.**

Structure / Activity:

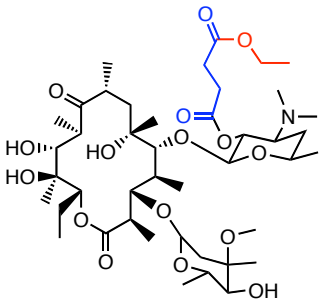
- **Macrolaktone (14-16-ring, smaller than antimycotic polyenes)**
- **Keto function**
- **No unsat. in lactone ring (spiramycin - dien) ≠ an timycotic polyenes**
- **Amino sugar**

Erytromycin



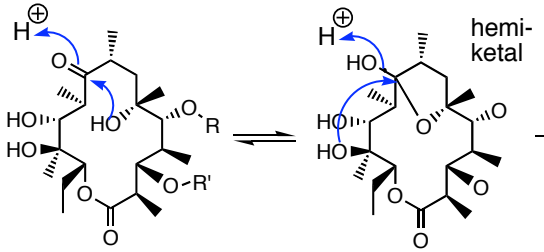
Erytromycin

Ester hydrol.
in vivo



Erytromycin ethylsuksinate
Pro-drug (masks bad tast)

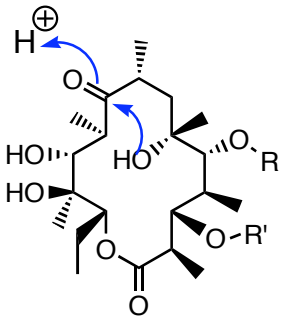
Degradation acidic media



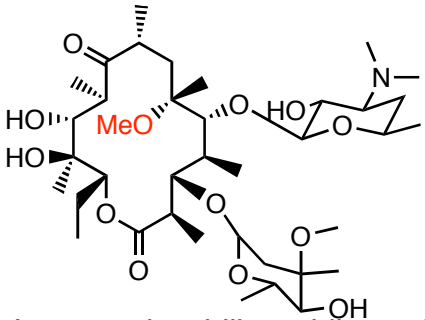
inactive spiroketal

Spiro-
forbindelse

Erythromycin



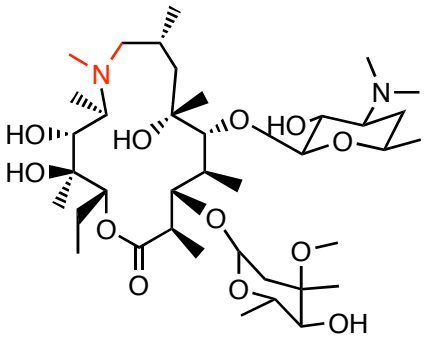
Klaritromycin



Increased stability acidic media
No intramolec. hemikatalisation

Increased stabil., bioavailability, less side effects
Somewhat more broad spectrum

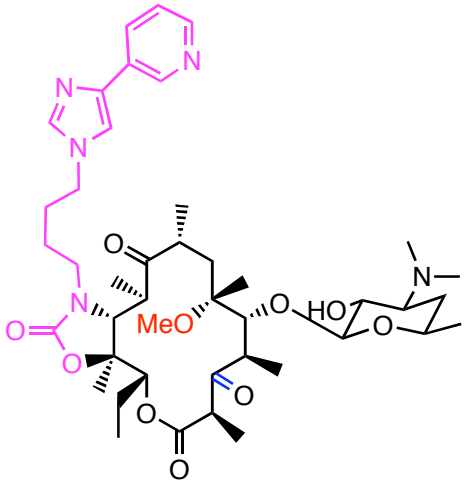
Azitromycin



Increased stability acidic media
No intramolec. hemikatalisation

Increased stabil., bioavail.
More active G- less active G+

Telitromycin

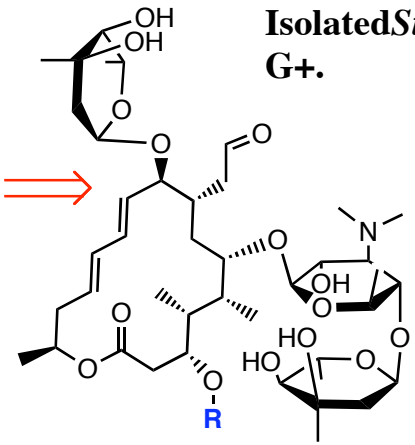


Increased stability acidic media
No intramolec. hemikatalisation
Improved ribosome binding, less resistans
Increased ribosome affinity

Spiramycin

Isolated *Streptomyces ambofaciens*. G+.

No ketone

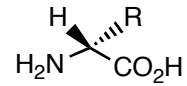


R= H: *Spiramycin I*
R=$COCH_3$: *Spiramycin II*
R=$COCH_2CH_3$: *Spiramycin III*

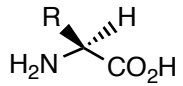
In N. 2002. Ketolide.

Polypeptides

- **Low oral avail.; local admin. or. infusion/injektion.**
- **Often high tox (kidneys).**
- **D-amino acids and other rare AA.**

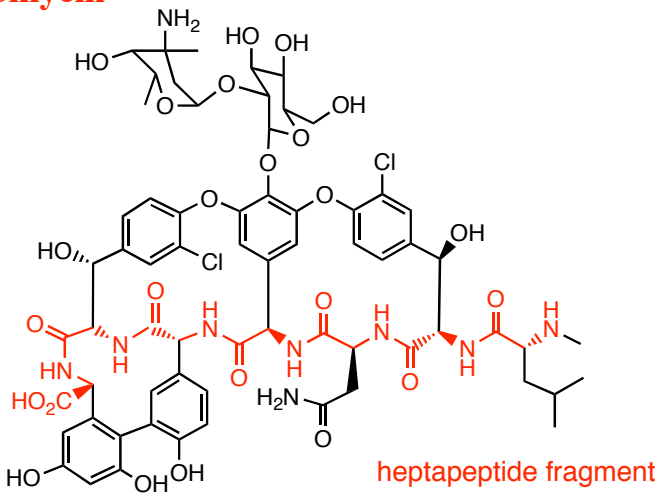


D-Amino acid



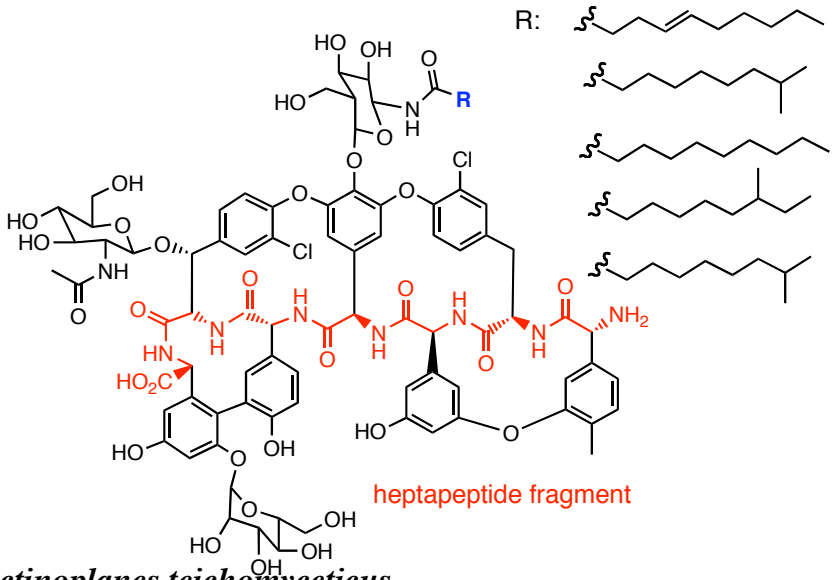
L-AA

Vancomycin



Isol. *Streptomyces orientalis* (= *Amycolatopsis orientalis*).
G+bakteria, *Neisseria sp* (G-).
Inhib. Synth of mucopeptide polymer in cell wall.
No oral uptake,
Minimal degrad. In Gi, local treatment GI infect.
Rel. tox., little resisence
Severe infections few other alternatives

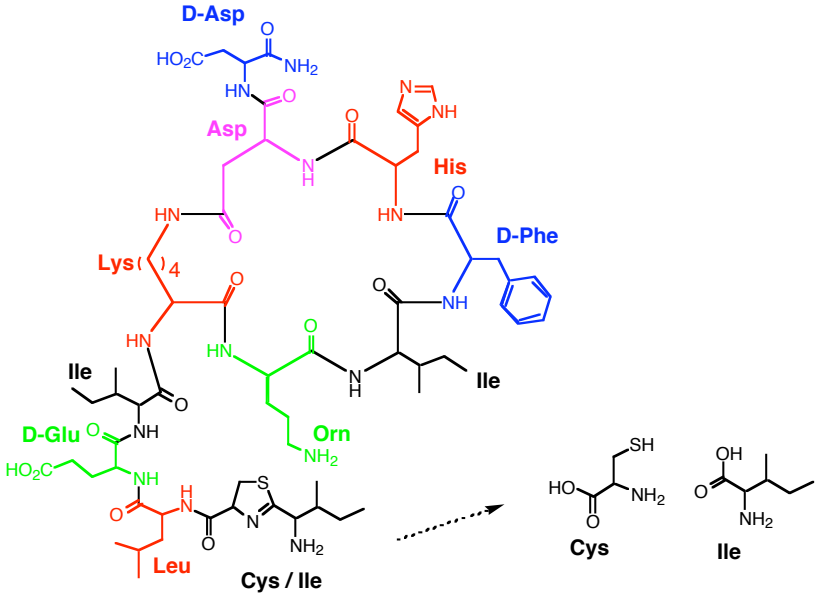
Teicoplanin



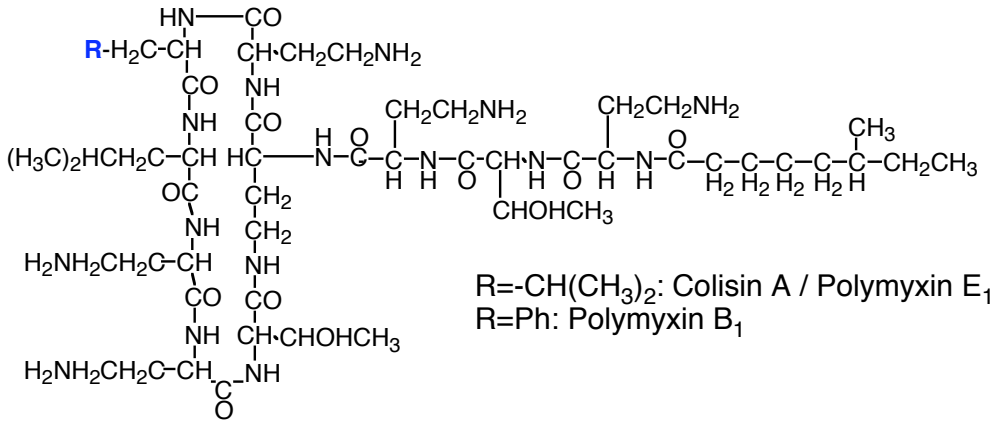
Isol. *Actinoplanes teichomyceticus*.
Only G+.
Mech as vanoc.m..
More lipid sol. than vancomycin, better distrib. In fat tissue
Little resistance tox. Less than vancomycin;
Severe infect., few alternatives

Bacitracin

Isol. *Baccilus subtilis*.
Mixt of struct
(Bacitracin A, A1, B, C, D, E, F1, F2, F3 and G)
Bacitracin A main comp. Bacimycin.
Mainly G+.
Inhib. Synth. mukopeptide in cell wall.
Requires Zn2+ for activity



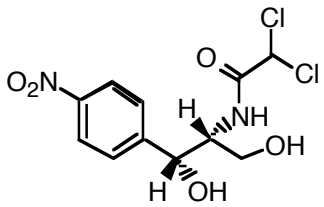
Colistin (Polymyxin E_1)
Polymixin B



R=-CH(CH$_3$)$_2$: Colisin A / Polymyxin E_1
R=Ph: Polymyxin B_1

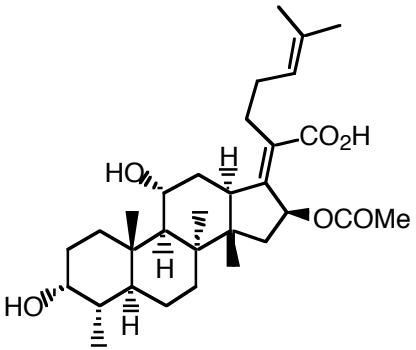
Others

Chloroamfenikol

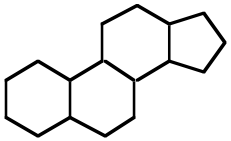


- **Isol. 1.time *Streptomyces venezuelae* (1947), later found in several microorg.**
- **Broad spectrum. Inhib. Protein synth., mech. Not fully understood.**
- **Rel. tox. (daqmage bone marrow – an emiea, leukemi), seldom used systhemically.**
- **Simple structure – total synthesis.**

Fusidinic acid



Stereoid



- **Narrow spectrum: G+; *Stafylloccocus aureus*, *corynebakteria* *Streptococcus* sp.(weak effect).**
- **Inhib. Protein synth.**
- **No cross resist.**