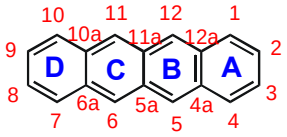
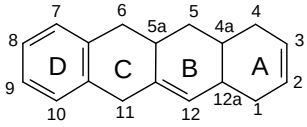
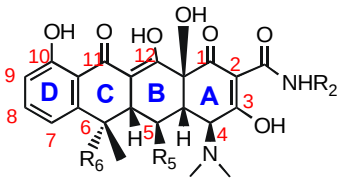
ХИДРОНАФТАЦЕНОВИ АНТИБИОТИЦИ



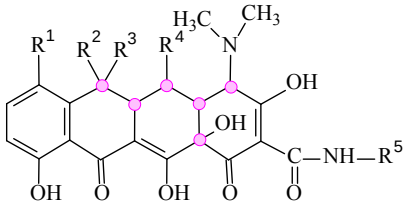
Naftacene

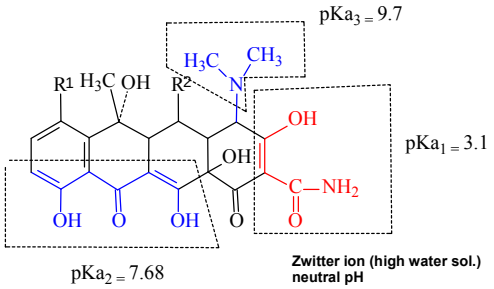


1,4,4a,5,5a,6,11,12a-octahydronaftacene

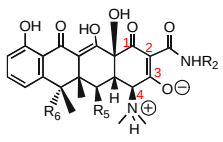


Tetracyclines: Gen. struct.



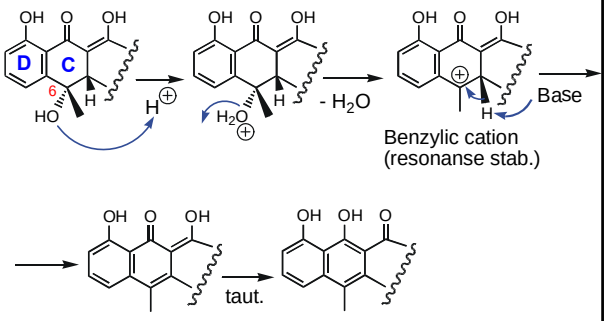


Zwitter ion (high water sol.) neutral pH



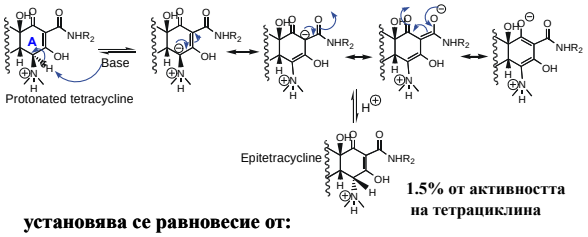
Стабилност в кисела среда

pH=2: Дехидратация и ароматизация на пръстен C(R_6=OH)



Стабилност в кисела среда

pH 2-6: Епимеризация при C-4



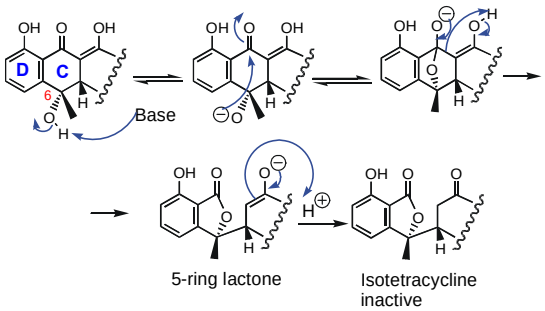
1.5% от активността на тетрациклина

установява се равновесие от:

- **2/3 тетрациклин и**
- **1/3 епитетрациклин**

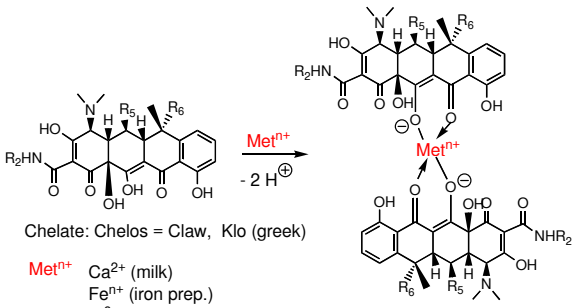
Стабилност в алкална среда

pH 7.5 : Прегрупиране до изотетрациклини(R_6=OH)



Хелатообразуване

2

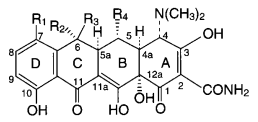


Chelate: Chelos = Claw, Klo (greek)

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

- **Механизъм: Свързват се с 30S рибозомалната субединица, чрез вкл. в комплекс на Mg^{2}+; блокират протеиновния синтез**
- **Широк спектър на действие (вкл. и срещу някои щамове гъбички, вируси и протозои).**
- **Бактериостатичен ефект.**
- **Атакува нормалната микрофлора в ГИ тракт (благоприятства *candida* инфекции.)**

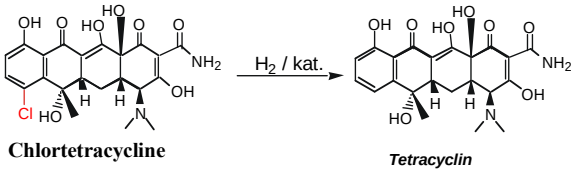
STRUCTURE OF TETRACYCLINES



	R_1	R_2	R_3	R_4
Tetracycline	H	CH_3	OH	H
Chlortetracycline	Cl	CH_3	OH	H
Oxytetracycline	H	CH_3	OH	OH
Demeclocycline	Cl	H	OH	H
Methacycline	H	CH_2		OH
Doxycycline	H	H	CH_3	OH
Minocycline	$N(CH_3)_2$	H	H	H

Tetracyclin

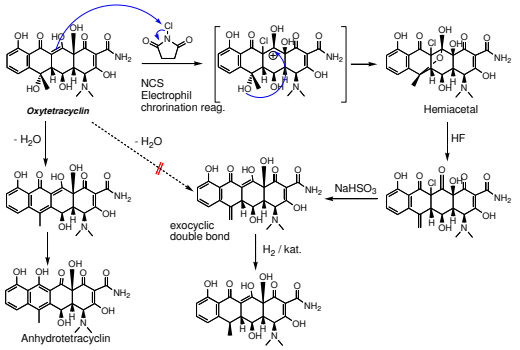
Isolation from *Streptomyces* sp,
Semisynth from chlorotetracycline more effective
(low bioavailability)



Chlortetracycline ***Tetracyclin***

Doxycyclin

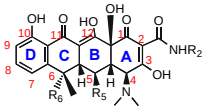
Not OH i 6-pos. More stabile in water solution (also mixture).
Longer $t_{1/2}$, good oral absorb.
Semisynth oxytetracyclin.



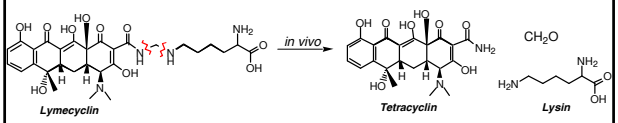
Lymecyclin

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

Lymecycline

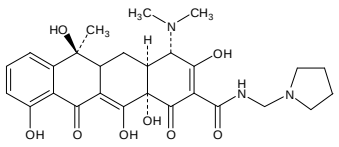


R_5	R_6	R_2
-H	-OH	$-CH_2NHCH_2NH(CH_2)_4CH(NH_2)CO_2H$



Lymecyclin ***Tetracyclin*** ***Lysin***

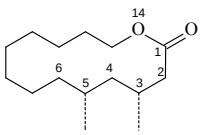
Rolitetracycline

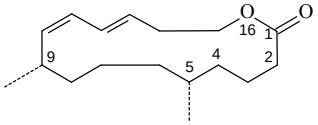


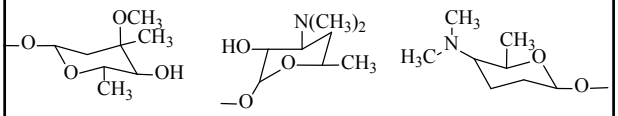
Противопоказания и взаимодействия с други лекарства

- Взаимодействат с антиацидни лекарствени вещества съдържащи йони на дву- и тривалентни метали, както и с някои храни – напр. мляко.
- Засилват действието на кумариновите производни защото потискат чревната микрофлора образуваща вит. К
- Могат, макар и рядко да предизвикат алергични реакции на кожата.
- Преминават през плацентарната бариера и се отлагат в костите на плода и забавят растежа му. Затова не бива да се прилагат през периода на бременността и при новородени до 3-годишна възраст.
- Противопоказни са при бъбречна и чернодробна недостатъчност.

МАКРОЛИДНИ АНТИБИОТИЦИ







Z1
кладиноза

Z2
дезозамин

Z3
фурозамин

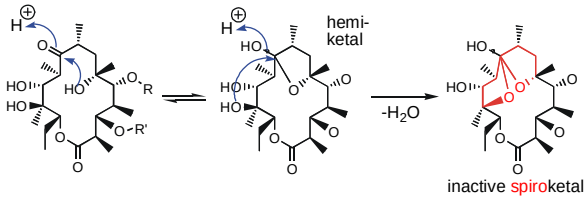
- **Isolated from *Streptomyces* sp.**
- **Reletively narrow spectrum, mainly G+. Low tox.**
- **Bindes to 50S part of ribosome, inhib. Protein synth.**

Structure / Activity:

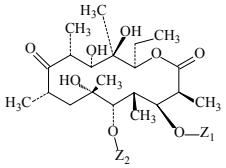
- **Macrolaktone (14-16-ring, smaller than antimycotic polyenes)**
- **Keto function**
- **No unsat. in lactone ring (spiramycin - dien) ? antimycotic polyenes**
- **Amino sugar**

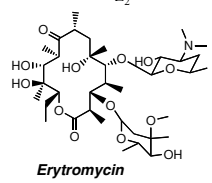
при pH ≈ 2.4 – 4 образуват полуацетали и ацетали чрез вътрешномолекулна "гликозидна" връзка между фенкционалните групи на 7-мо и 10-то място и 10-то и 13-то място. Макролактонът обаче е стабилен в кисела среда.

Degradation acidic media



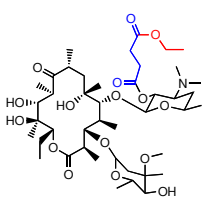
Erythromicin





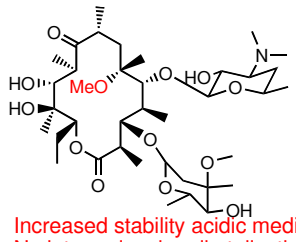
Erytromycin

Ester hydrol.
in vivo



Erytromycin ethylsuksinate
Pro-drug (masks bad tast)

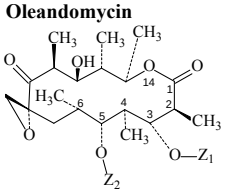
Claritromycin



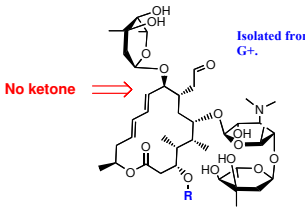
Increased stability acidic media
No intramolec. hemikatalisation

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

Oleandomycin



Spiramycin (Rovamycin)

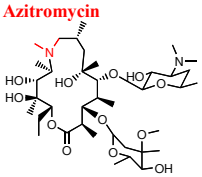


No ketone

Isolated from *Streptomyces ambofaciens*. G+.

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

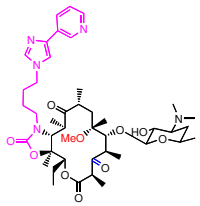
Azitromycin



Increased stability acidic media
No intramolec. hemikatalisation

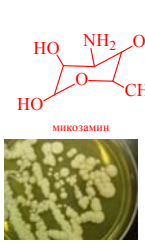
Increased stabil., bioavail.
More active G- less active G+

Telitromycin



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

ПОЛИЕНОВИ АНТИБИОТИЦИ

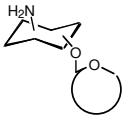


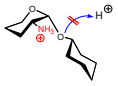
Amphotericin B

Nystatin

АМИНОГЛИКОЗИДНИ АНТИБИОТИЦИ

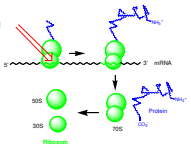
- Broad spectrum
- Toxic
- Inhib. protein synthesis
- -N o absorb. from GI, local treatment infect. GI tract.
- Systhemic infections – parenteral adm.





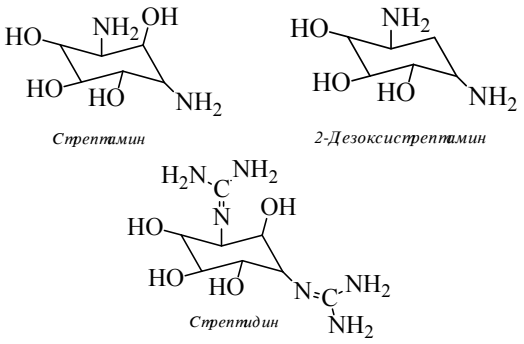
- Basic, water solubile salts phys. pH
- -Glykosides (= acetals) stabile acidic media because of protonated amino subst.

Bind to mRNA read wrong Transloc. blocked

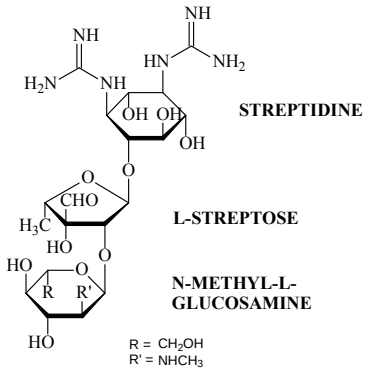


Aminoglycosides

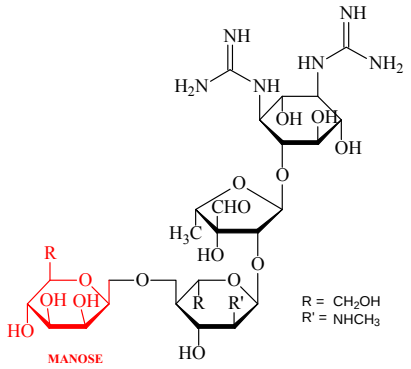
- Spectrum
  - Gram-negative bacilli, P. aeruginosa (use with anti-pseudomonas penicillins)
- Resistance
  - Antibiotic modifying agents cause antibiotics to be unable to bind to the ribosome
- Toxicity
  - Nephrotoxic (trough)
  - Ototoxic (concentrated in perilymph, corresponds with prolonged therapy and peak levels)
  - Neuromuscular blockade (think of this in Myasthenia Gravis)



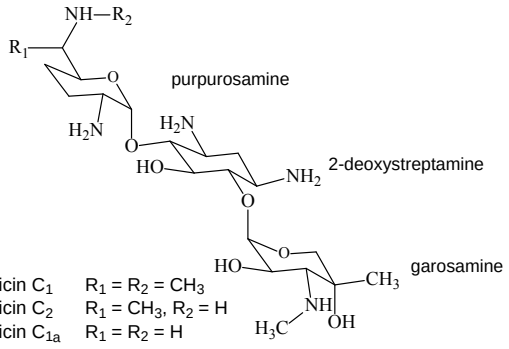
STREPTOMYCIN



STREPTOMYCIN B

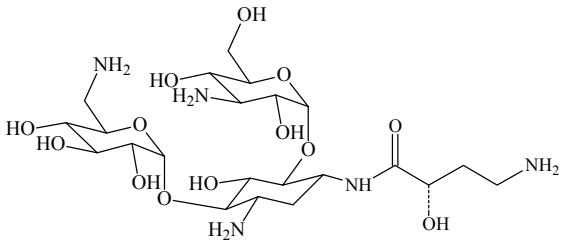


Gentamycin

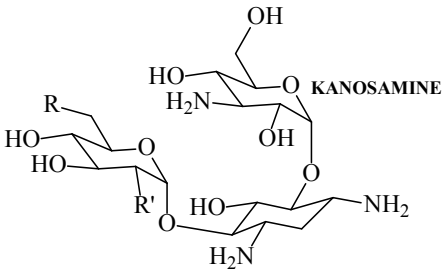


Gentamicin C_1	$R_1 = R_2 = CH_3$
Gentamicin C_2	$R_1 = CH_3$, $R_2 = H$
Gentamicin C_{1a}	$R_1 = R_2 = H$

Amikacin

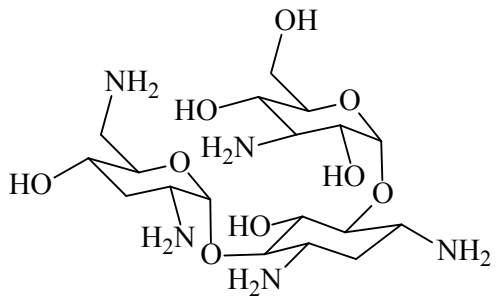


Kanamycin

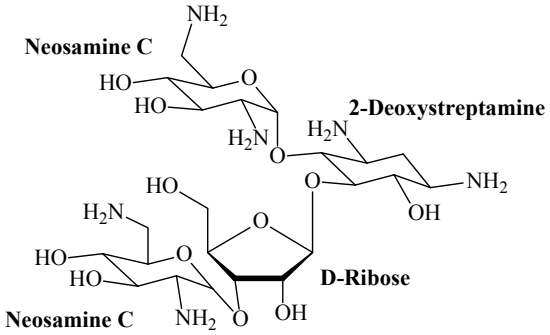


	R	R'
Kanamycin A	**NH_2**	**OH**
Kanamycin B	**NH_2**	**NH_2**
Kanamycin C	**OH**	**NH_2**

TOBRAMYCIN



NEOMYCIN C

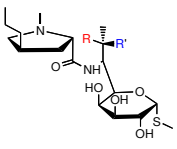


Lincomycines

- 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

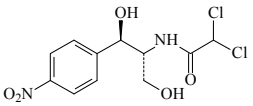


R= H, R'=Cl: ***Klindamycin***

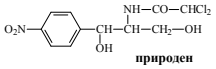
R=OH, R'=H: ***Linkomycin***,

АРОМАТНИ НИТРОСЪЕДИНЕНИЯ

Chloramfenicol

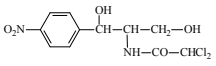


- **Isol. 1.time *Streptomyces venezuelae* (1947), later found in several microorg.**
- **Broad spectrum. Inhib. Protein synth., mech. Not fully understood.**
- **Rel. tox. (damage bone marrow – anemia, leukemia), seldom used systemically.**
- **Simple structure – total synthesis.**

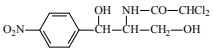


природен

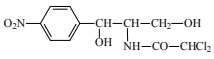
D(-) - threo



L(+) - threo



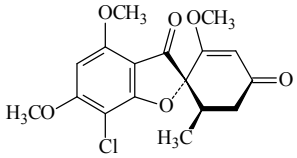
D(+) - erytro

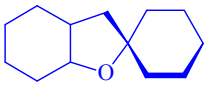


L(-) - erytro

БЕНЗОФУРАНИ

Griseofulvine



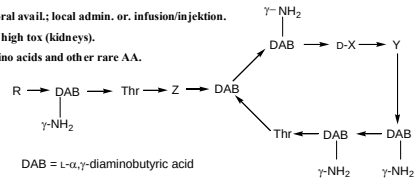


GRISANE

ПЕПТИДНИ АНТИБИОТИЦИ

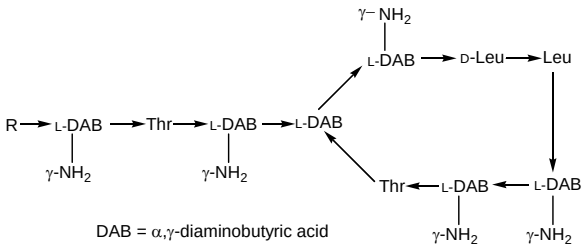
Polymyxins

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



DAB = L-α,γ-diaminobutyric acid

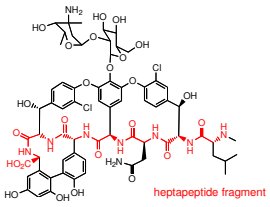
Polymyxin B_1	R = (+)-6-methyloctanoyl	X = Phe	Y = Leu	Z = DAB
B_2	R = 6-methylheptanoyl	X = Phe	Y = Leu	Z = DAB
D_1	R = (+)-6-methyloctanoyl	X = Leu	Y = Thr	Z = D-Ser
D_2	R = 6-methylheptanoyl	X = Leu	Y = Thr	Z = D-Ser



DAB = α,γ-diaminobutyric acid

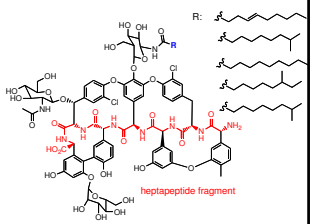
Colistin A R = (+)-6-methyloctanoyl
Polymyxin E_2 R = 6-methylheptanoyl

Vancomycin



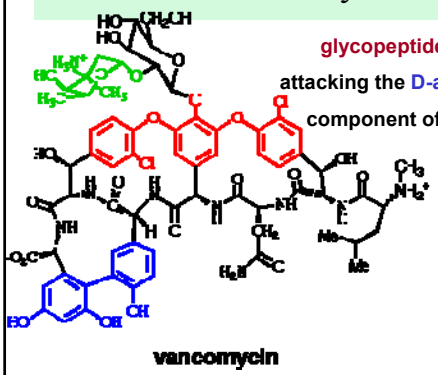
Isol. *Streptomyces orientalis* (= *Amycolatopsis orientalis*).
G+bakteria, *Neisseria sp* (G-).
Inhib. Synth of mucopeptide polymer in cell wall.
No oral uptake,
Minimal degrad. In Gi, local treatment GI infect.
Rel. tox., little resisence
Severe infections few other alternatives

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

Vancomycin

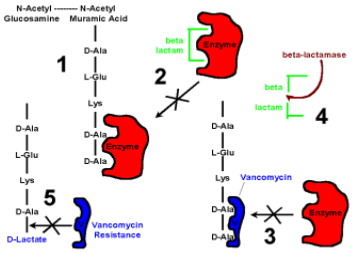


glycopeptide antibiotic,

attacking the D-alanyl-D-alanine component of the cell wall.

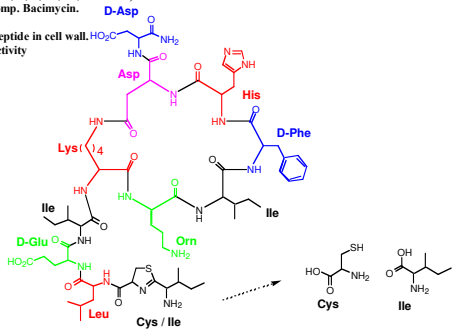
vancomycin

Inhibition of peptidoglycan cross-linking by Beta-Lactams and Vancomycin and mechanisms of resistance.



1. Transpeptidase enzyme binds to D-Ala-D-Ala for cross-linking.
2. Beta-lactam antibiotic binds to transpeptidase inhibiting cross-linking.
3. Vancomycin binds to D-Ala-D-Ala preventing binding of enzyme.
4. Beta-lactamase cleaves beta-lactam antibiotic.
5. Changing terminal D-Ala to D-Lactate prevents vancomycin binding.

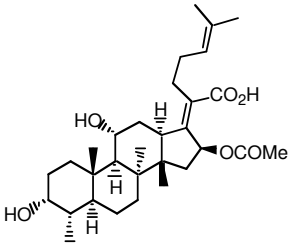
Bacitracin
Isol. *Baccilus subtilis*.
Mixt of struct
(Bacitracin A, A1, B, C, D, E, F1, F2, F3 and G)
Bacitracin A main comp. Bacimycin.
Mainly G+.
Inhib. Synth. mukopeptide in cell wall.
Requires Zn2+ for activity



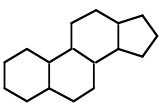
Други

Fusidinic acid

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



Stereoid



Mupirocin

- **Major component of the pseudomonic acids, an antibiotic complex produced by *Pseudomonas fluorescens*.**