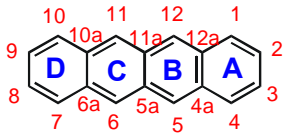
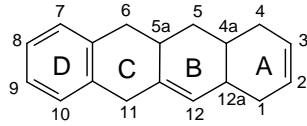


**ХИДРОНАФТАЦЕНОВИ АНТИБИОТИЦИ**



**Naftacene**



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

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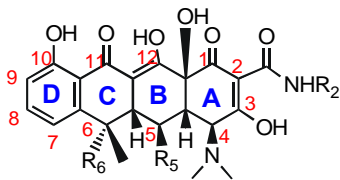
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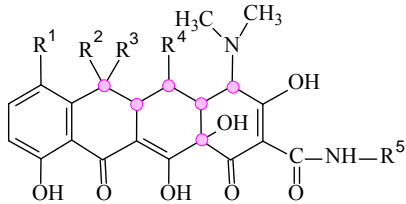
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**Tetracyclines: Gen. struct.**




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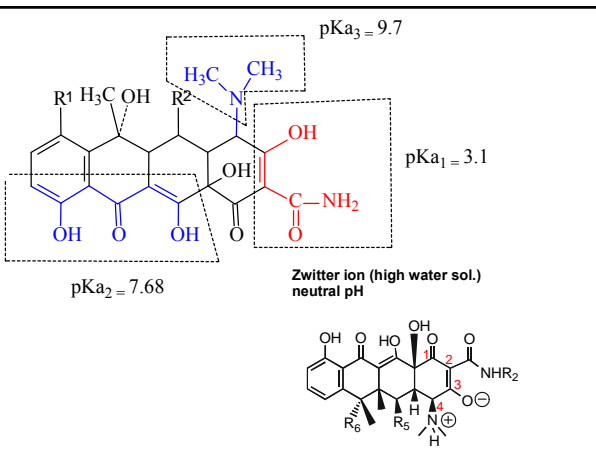
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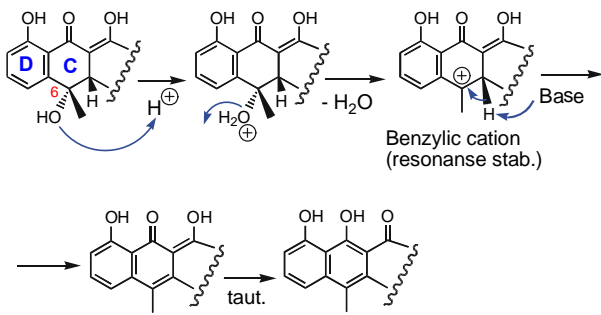
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**Стабилност в кисела среда**

pH=2: Дехидратация и ароматизация на пръстен C (R<sub>6</sub>=OH)




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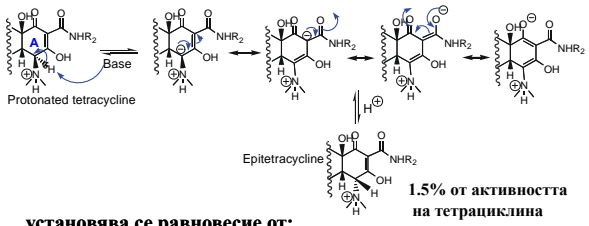
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**Стабилност в кисела среда**

pH 2-6: Епимеризация при C-4



установява се равновесие от:

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

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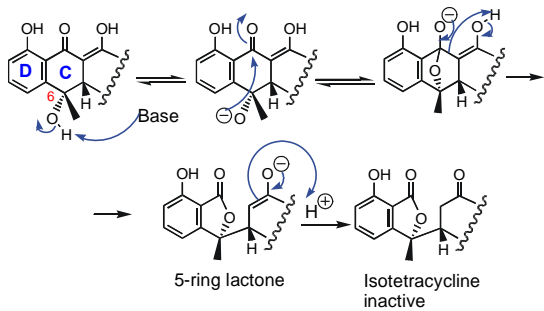
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**Стабилност в алкална среда**

pH 7.5 : Прегрупиране до изотетрациклин (R<sub>6</sub>=OH)




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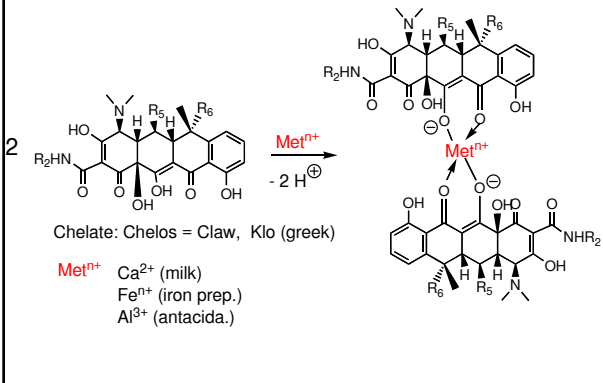
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### Хелатообразуване




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

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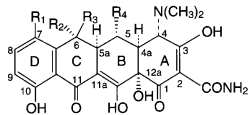
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### STRUCTURE OF TETRACYCLINES



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
Tetracycline	H	CH <sub>3</sub>	OH	H
Chlortetracycline	Cl	CH <sub>3</sub>	OH	H
Oxytetracycline	H	CH <sub>3</sub>	OH	OH
Demeclocycline	Cl	H	OH	H
Methacycline	H	CH <sub>2</sub>		OH
Doxycycline	H	H	CH <sub>3</sub>	OH
Minocycline	N(CH <sub>3</sub> ) <sub>2</sub>	H	H	H

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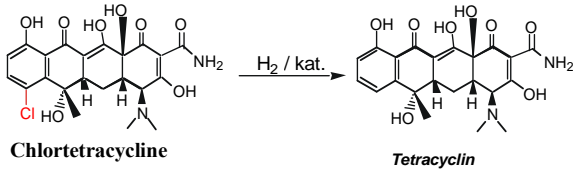
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**Tetracyclin**

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



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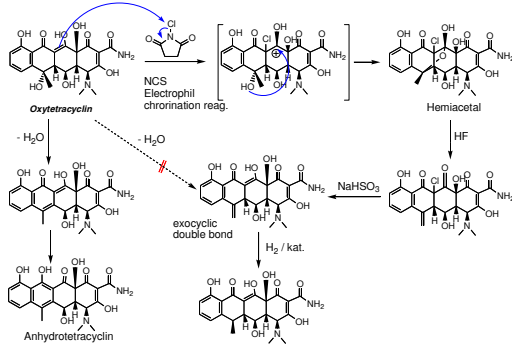
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**Doxycyclin**

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



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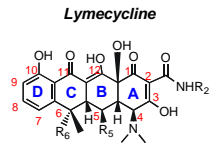
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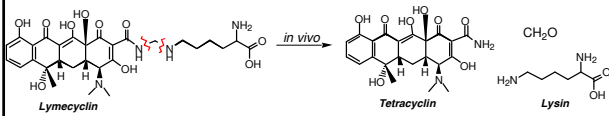
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**Lymecyclin**

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



$R_5$  -H  
 $R_6$  -OH  
 $R_2$  -CH<sub>2</sub>NHCH<sub>2</sub>NH(CH<sub>2</sub>)<sub>4</sub>CH(NH<sub>2</sub>)CO<sub>2</sub>H



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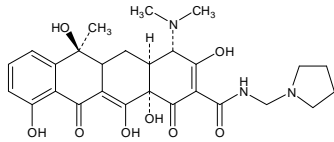
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Rolitetracycline




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**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.

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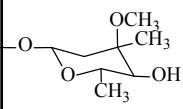
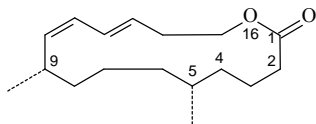
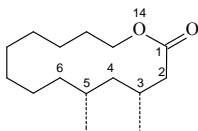
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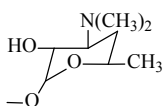
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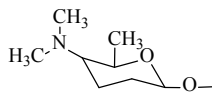
**МАКРОЛИДНИ АНТИБИОТИЦИ**



Z1  
кладиноза



Z2  
дезозамин



Z3  
фуразамин

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- Isolated from *Streptomyces* sp.
- Relatively narrow spectrum, mainly G+. Low tox.
- Binds 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

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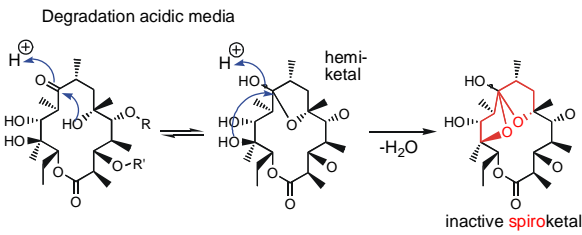
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при pH ≈ 2.4 – 4 образуват полуацетали и ацетали чрез вътрешномолекулна “гликозидна” връзка между функционалните групи на 7-мо и 10-то място и 10-то и 13-то място. Макролактонът обаче е стабилен в кисела среда.




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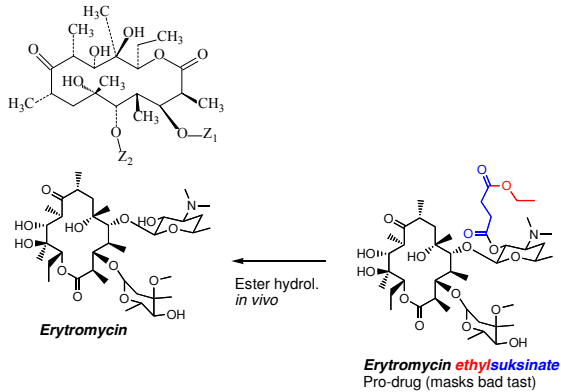
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**Erythromycin**




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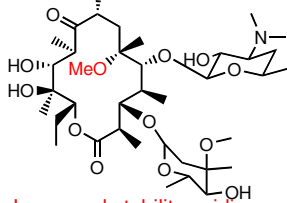
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**Clarithromycin**



Increased stability acidic media  
No intramolec. hemikatalisation

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

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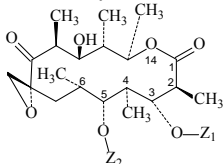
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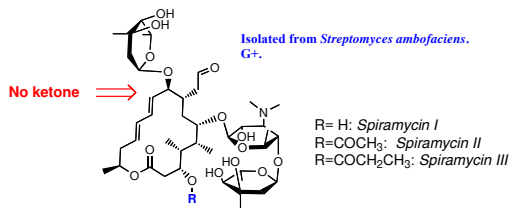
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**Oleandomycin**



**Spiramycin (Rovamycin)**



Isolated from *Streptomyces ambofaciens*.  
G+.

R= H: Spiramycin I  
R=COCH<sub>3</sub>: Spiramycin II  
R=COCH<sub>2</sub>CH<sub>3</sub>: Spiramycin III

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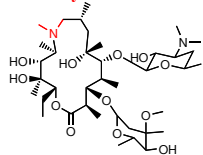
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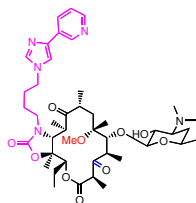
**Azitromycin**



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

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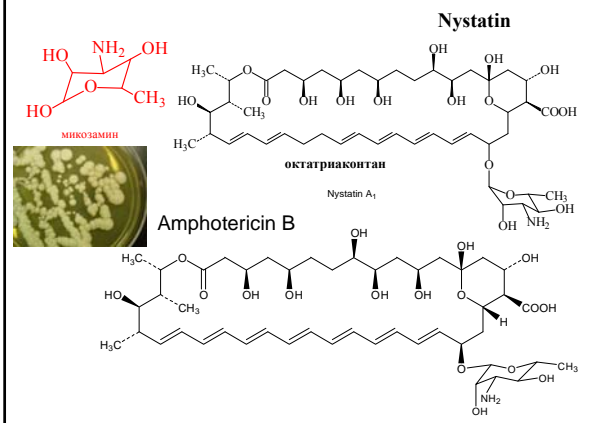
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## ПОЛИЕНОВИ АНТИБИОТИЦИ




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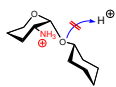
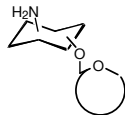
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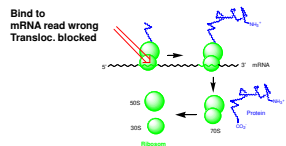
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## АМИНОГЛИКОЗИДНИ АНТИБИОТИЦИ

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



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




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## 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)

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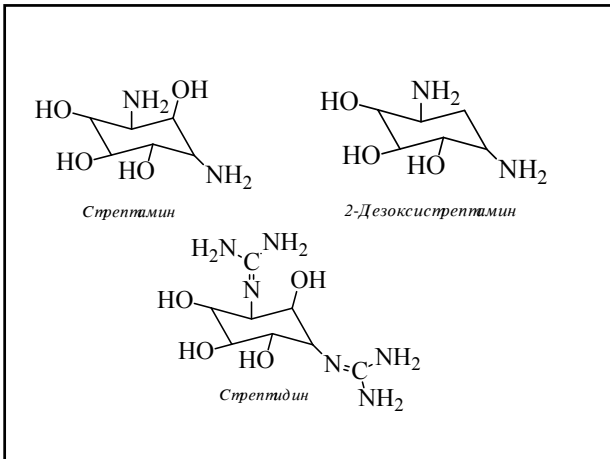
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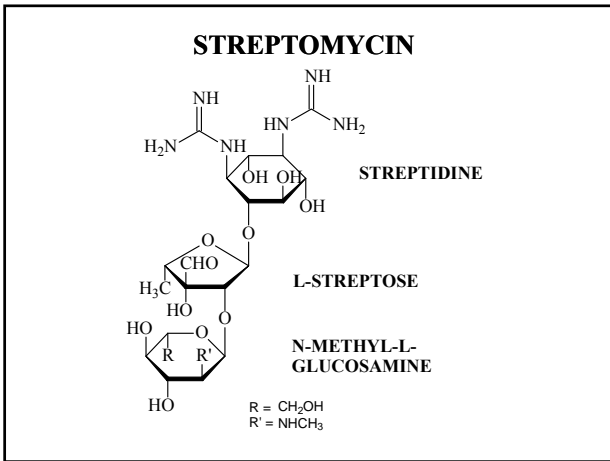
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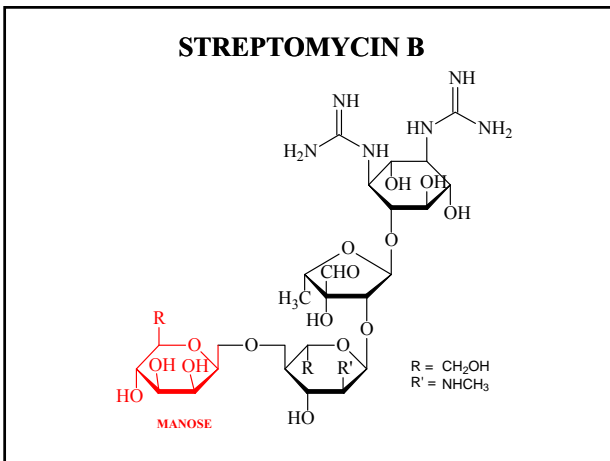
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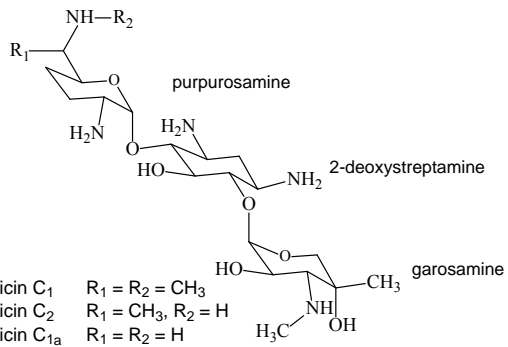
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**Gentamicin**



Gentamicin C<sub>1</sub>  
Gentamicin C<sub>2</sub>  
Gentamicin C<sub>1a</sub>

$R_1 = R_2 = CH_3$   
 $R_1 = CH_3, R_2 = H$   
 $R_1 = R_2 = H$

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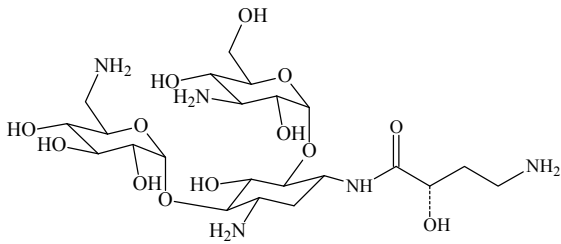
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**Amikacin**




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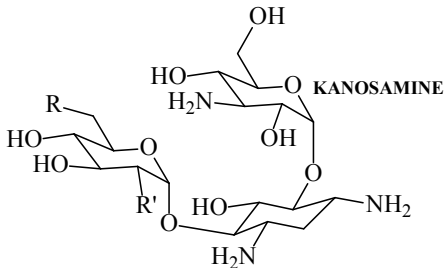
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**Kanamycin**



	<b>R</b>	<b>R'</b>
<b>Kanamycin A</b>	$NH_2$	$OH$
<b>Kanamycin B</b>	$NH_2$	$NH_2$
<b>Kanamycin C</b>	$OH$	$NH_2$

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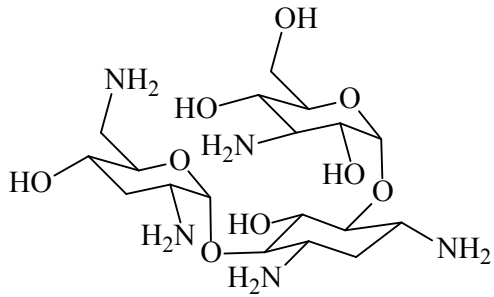
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**TOBRAMYCIN**



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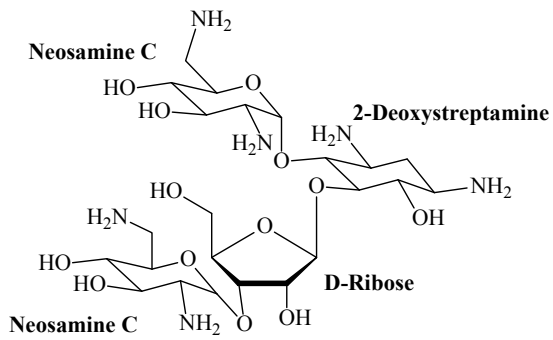
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**NEOMYCIN C**



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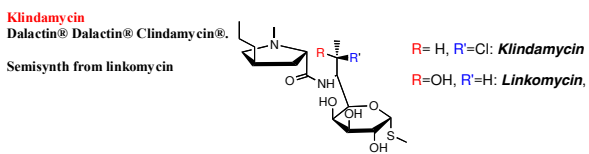
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**Lincomycines**

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



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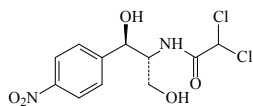
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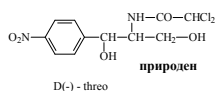
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## АРОМАТНИ НИТРОСЪЕДИНЕНИЯ

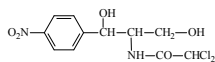
### Chloramfenicol



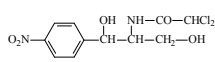
- > Isol. 1. time *Streptomyces venezuelae* (1947), later found in several microorg.
- > Broad spectrum. Inhib. Protein synth., mech. Not fully understood.
- > Rel. tox. (damage bone marrow – anemia, leukemia), seldom used systemically.
- > Simple structure – total synthesis.



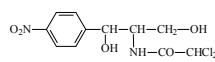
D(-) - threo



L(+)- threo



D(+)- erythro



L(-)- erythro

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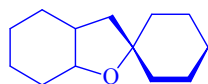
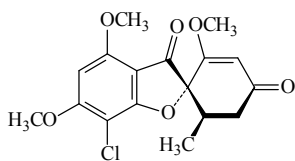
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## БЕНЗОФУРАНИ

### Griseofulvine



GRISANE

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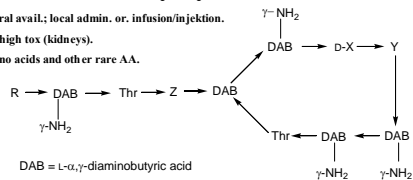
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## ПЕПТИДНИ АНТИБИОТИЦИ

### Polymyxins

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



Polymyxin B <sub>1</sub>	R = (+)-6-methyloctanoyl	X = Phe	Y = Leu	Z = DAB
B <sub>2</sub>	R = 6-methylheptanoyl	X = Phe	Y = Leu	Z = DAB
D <sub>1</sub>	R = (+)-6-methyloctanoyl	X = Leu	Y = Thr	Z = D-Ser
D <sub>2</sub>	R = 6-methylheptanoyl	X = Leu	Y = Thr	Z = D-Ser

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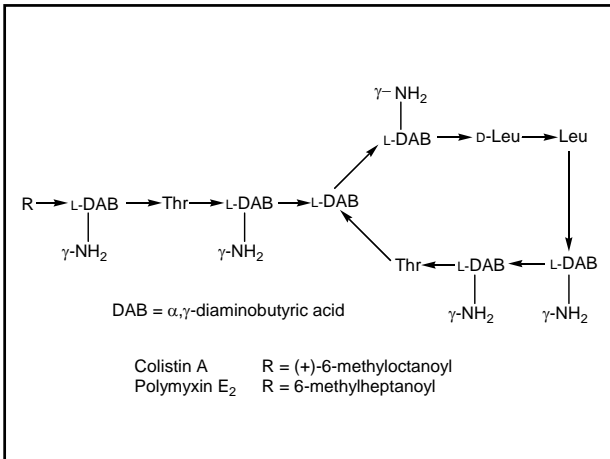
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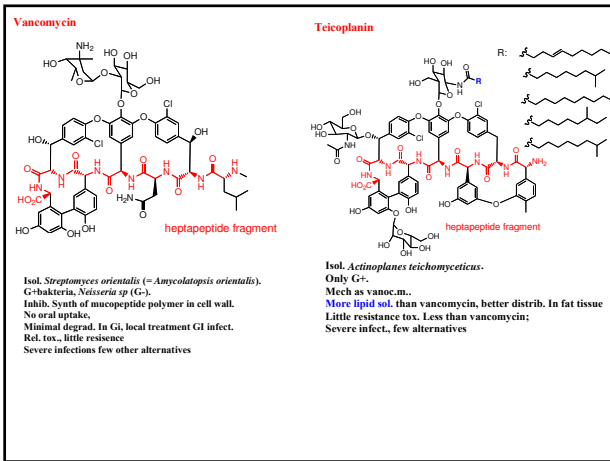
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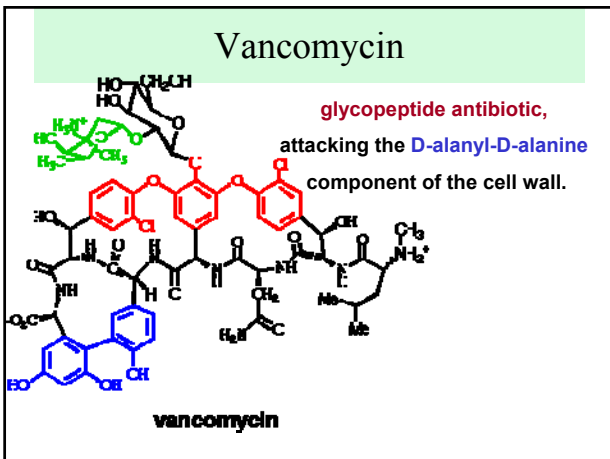
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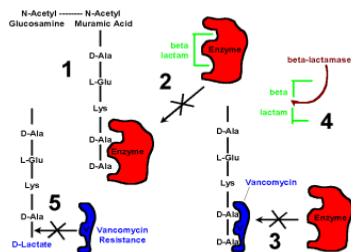
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**Inhibition of peptidoglycan cross-linking by Beta-Lactams and Vancomycin and mechanisms of resistance.**



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.

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**Bacitracin**

Isol. *Bacillus subtilis*.

Mixt of struct

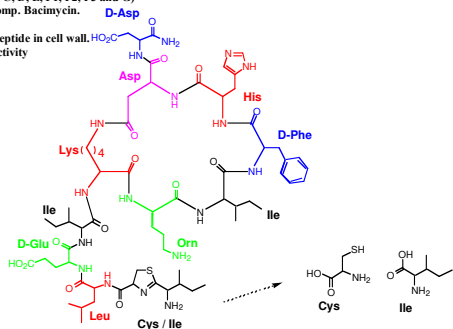
(Bacitracin A, A1, B, C, D, E, F1, F2, F3 and G)

Bacitracin A main comp. Bacimycin.

Mainly G<sup>+</sup>.

Inhib. Synth. mukopeptide in cell wall.

Requires Zn<sup>2+</sup> for activity




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**Други**

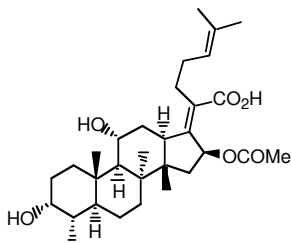
**Fusidinic acid**

> Narrow spectrum: G<sup>+</sup>; *Staphylococcus aureus*, *corynebacteria*

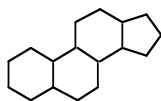
*Streptococcus* sp.(weak effect).

> Inhib. Protein synth.

> No cross resist.



**Steroid**




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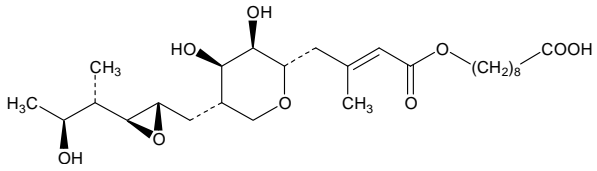
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**Mupirocin**

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



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