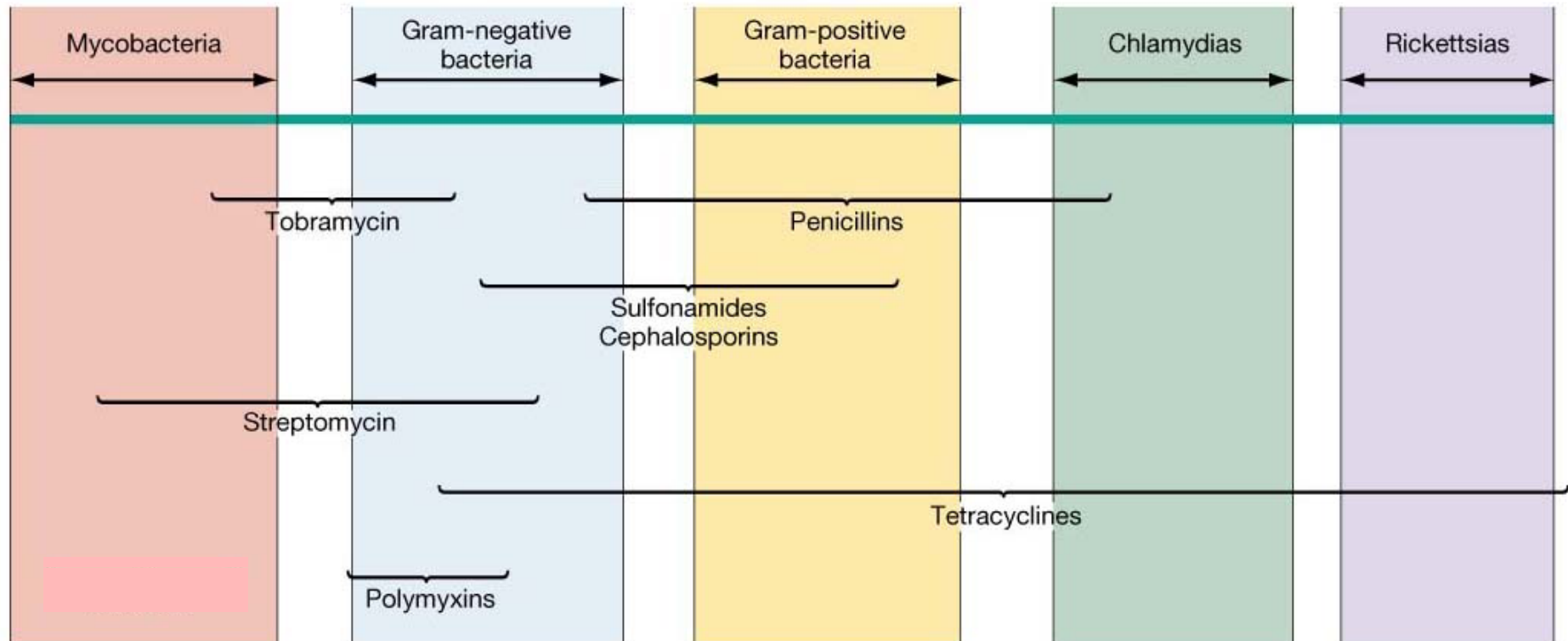


Tetraciklini, makrolidi, aminoglikozidi, ostali antibiotiki

Izr. prof. dr. Marko Anderluh

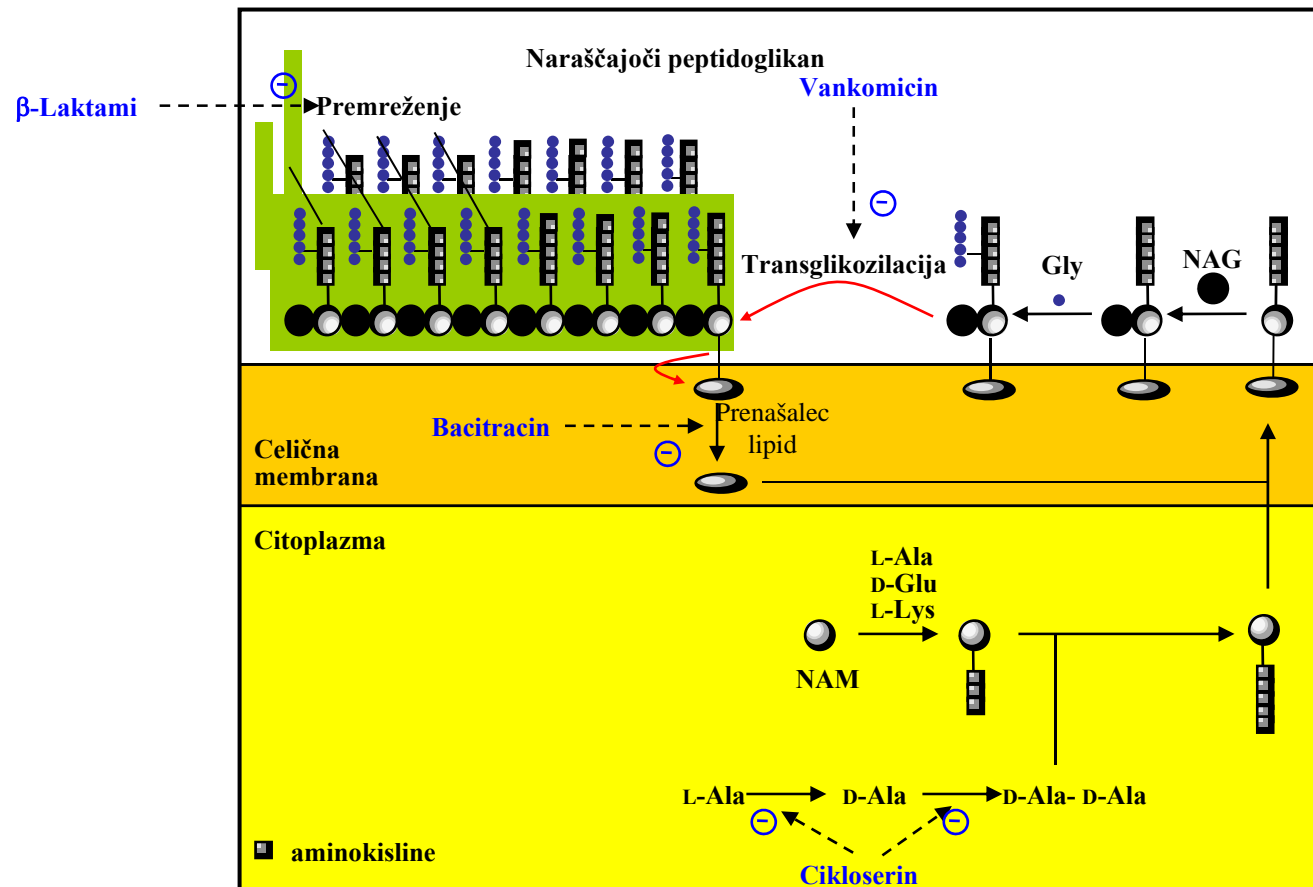
10. januar 2013

Spekter delovanja



Inhibicija biosinteze peptidoglikana

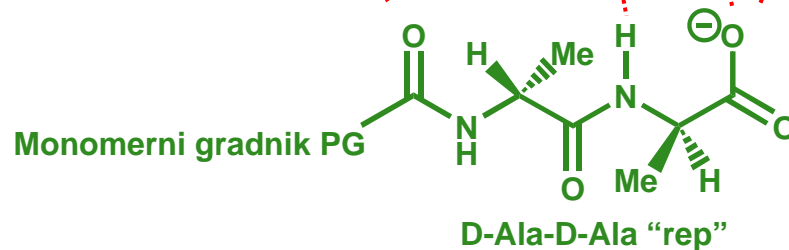
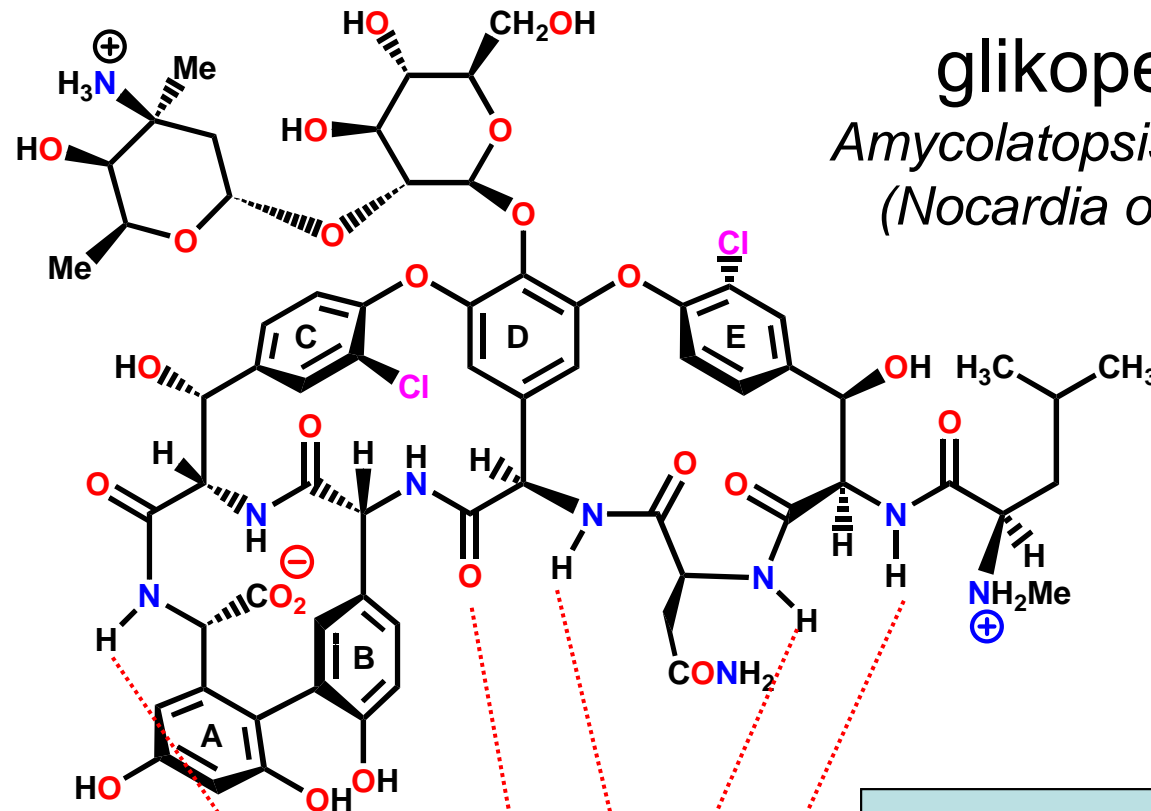
- Vankomicin, glikopeptidi



Vankomicin

glikopeptid

Amycolatopsis orientalis
(*Nocardia orientalis*)

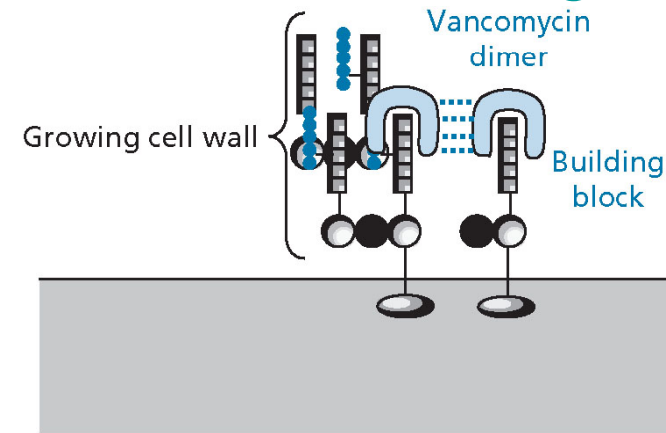


**H-vezi med vankomicinom in
peptidnim skeletom
monomernega gradnika
peptidoglikana**

Vankomicin

- Mehanizem:

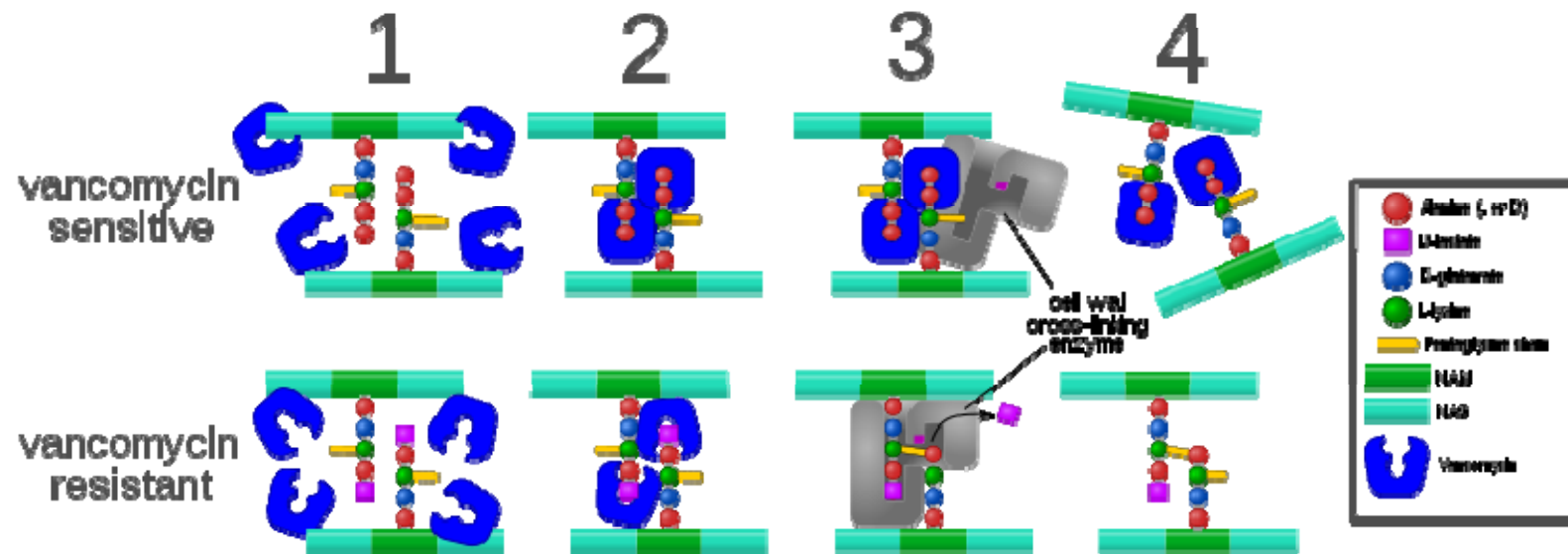
<http://student.ccbcmd.edu/courses/bio141/lecguide/unit2/control/vanres.html>



- Ozkospektralen: G+, ne G-!
- Parenteralna uporaba, per os zoper *Clostridium difficile*
- Pomen vankomicina – MRSA!

Vankomicin

- Rezistentni sevi



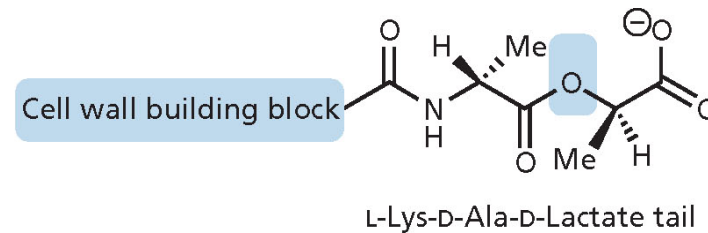
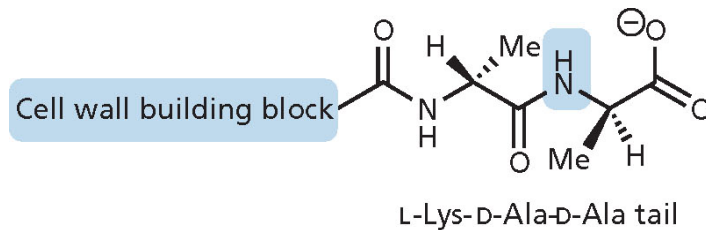
Vankomicin

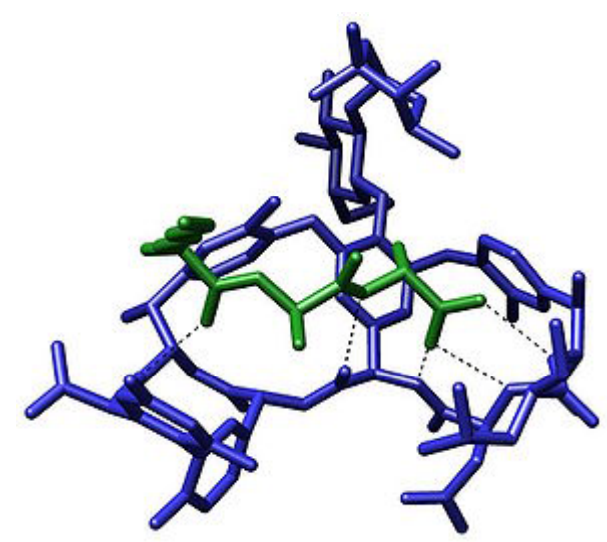
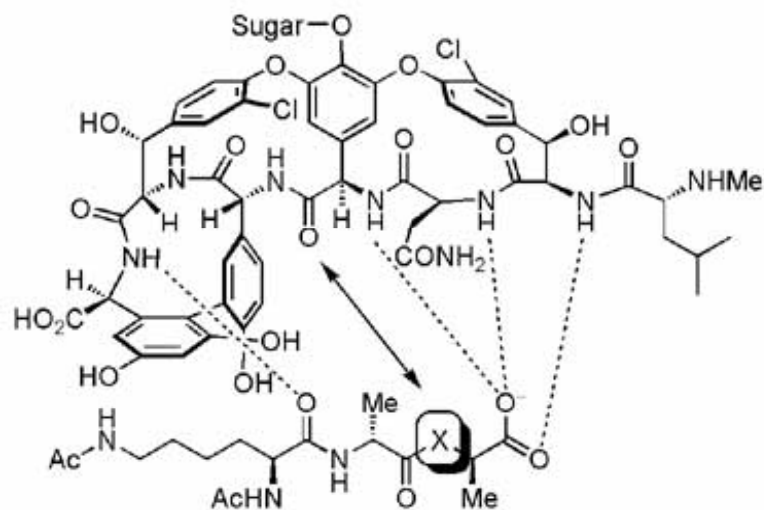
- Rezistentni sevi



Illustration: Don Smith

- VRSA (*S. aureus*), VRE (*enterococci*)





Clinical vancomycin resistance
X = O, affinity drops 1000-fold

H-bond
Increases K_a 10-fold (1.5 kcal/mol)

	K_a	ΔG° (25° C)
X = NH	4.4×10^5	7.7 kcal/mol
X = CH ₂	3.3×10^4	6.2 kcal/mol
X = O	4.3×10^2	3.6 kcal/mol

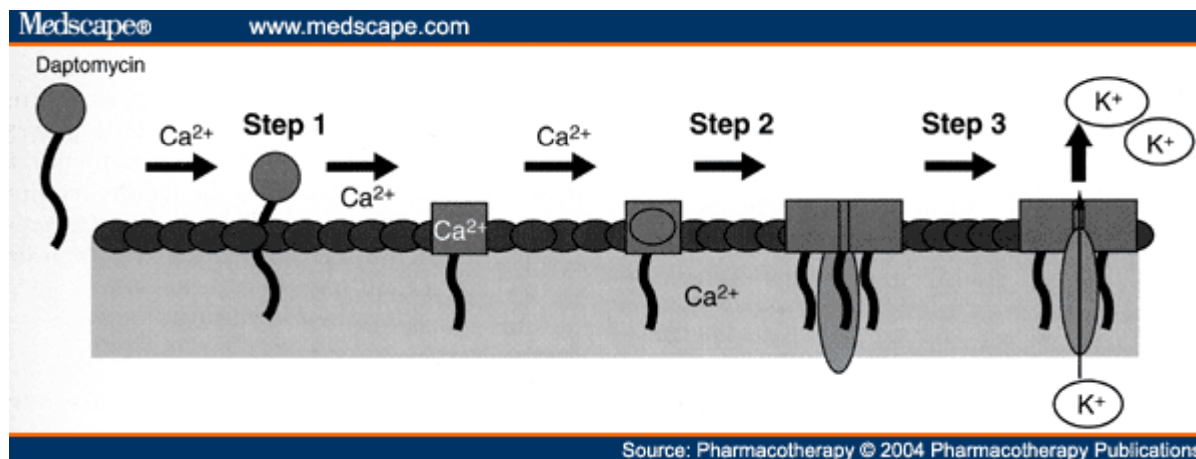
Electrostatic interaction
Decreases K_a 100-fold (2.6 kcal/mol)

Implications for reengineering vancomycin:
removing electrostatic destabilization should
improve binding to D-Ala-D-Lac 100-fold

Daptomicin (lipopeptidi)

Mehanizem delovanja – podobno valinomycin, gramicidin A (**PORINI**)

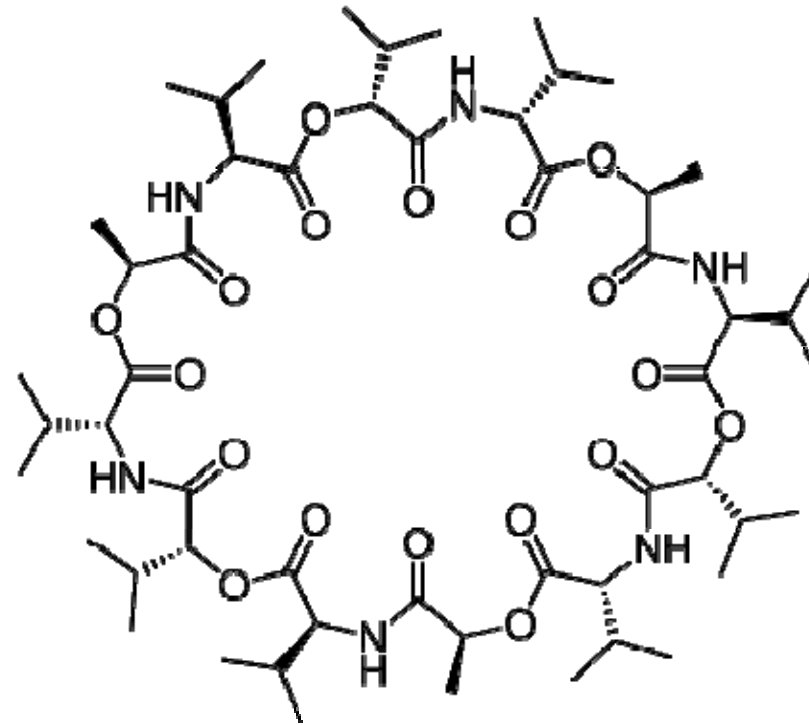
- 1: daptomicin se veže na cel. membrano, udeležen Ca^{2+}
- 2: daptomicin oligomerizira, tvori “ionofor”
- 3: hitra celična smrt zaradi izgube ionov



- Samo G+, tudi anaerobi, MRSA, VRE

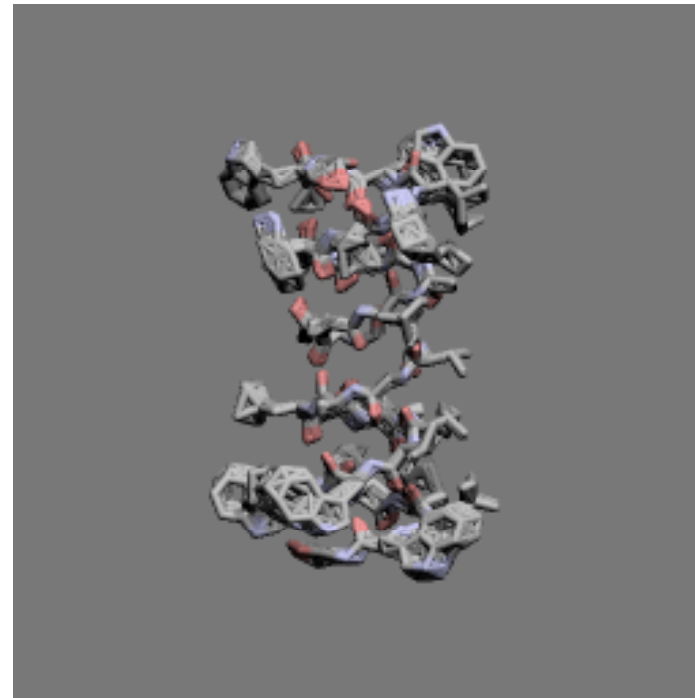
Ionofori

- Valinomycin
- Ionofor za K⁺



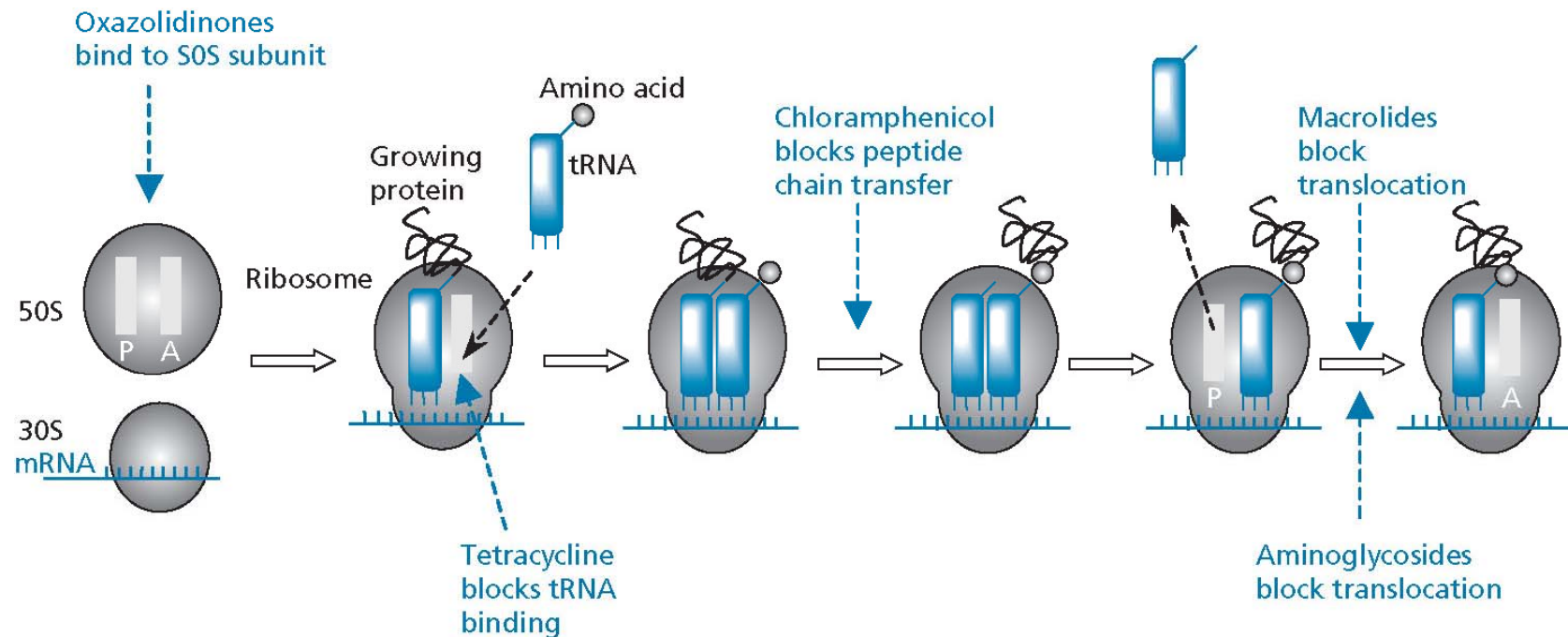
Ionofori

- Gramicidin A-D
- Ionofor za K^+
- G+ in G-
- Hemoliza! - topikalno



Inhibicija biosinteze peptidov

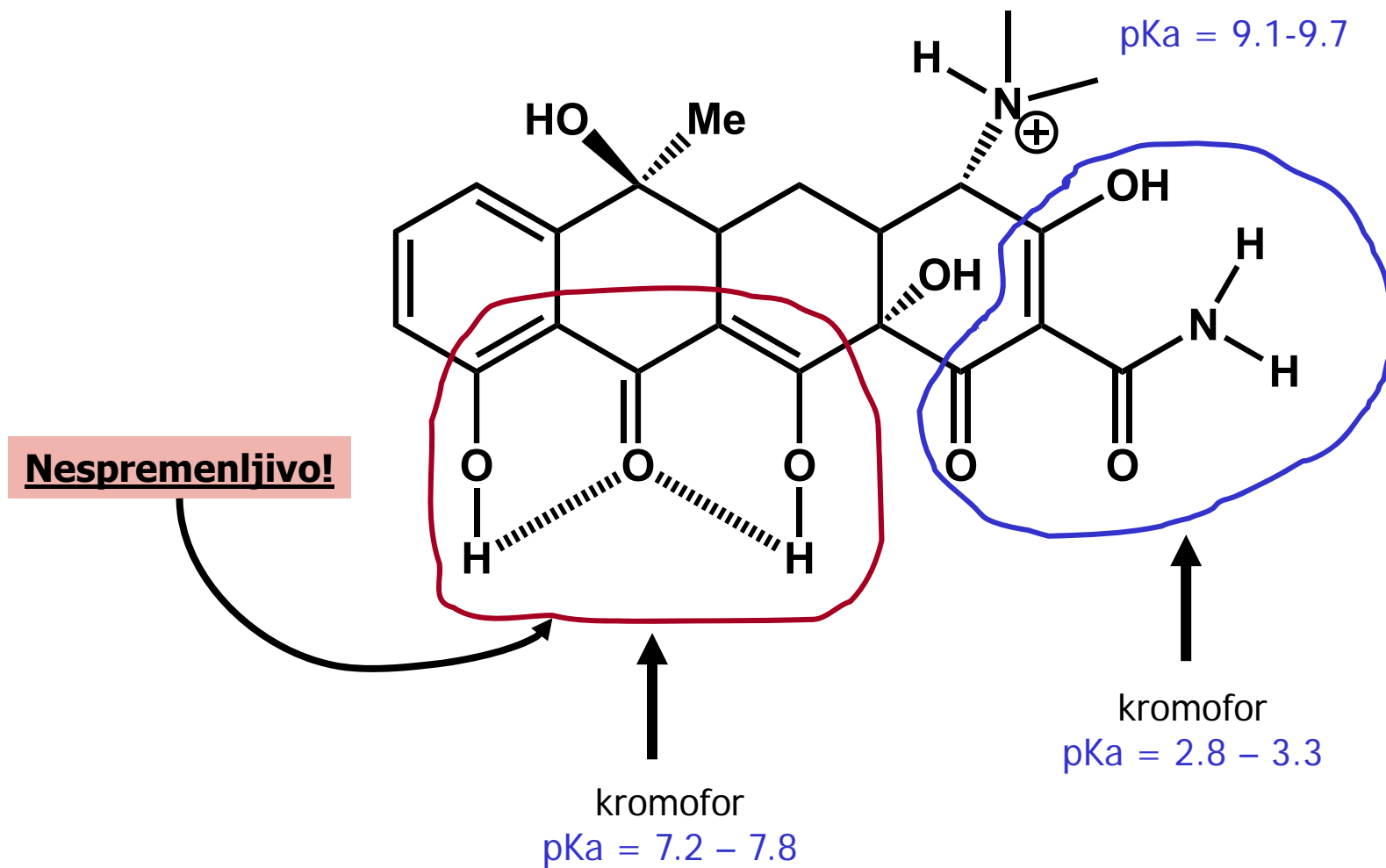
- Tarča za selektivno toksičnost



Tetraciklini

- Antibiotiki: tetraciklin iz *Streptomyces aureofaciens*
- Izjemno širokospektralni; G+ in G-
- Prva izbira pri rikecijah, koksielah, klamidijah
- Mehanizem: vezava na 30S podenoto bakterijskega ribosoma, preprečena vezava tRNA
- <http://student.ccbcmd.edu/courses/bio141/lecguide/unit2/control/tetres.html>

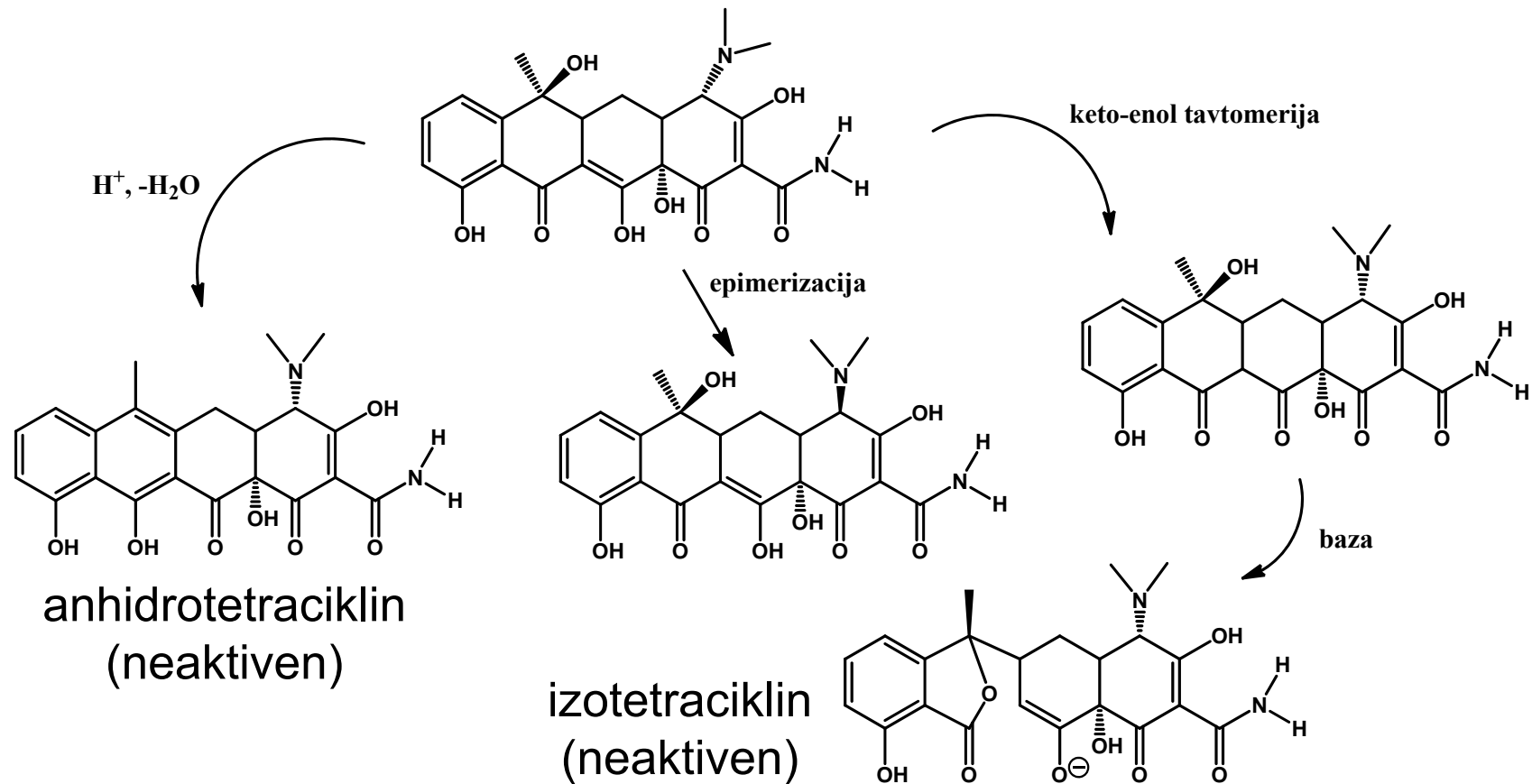




Ion dvojček pri pH = 4 – 7 (pH duodenuma)

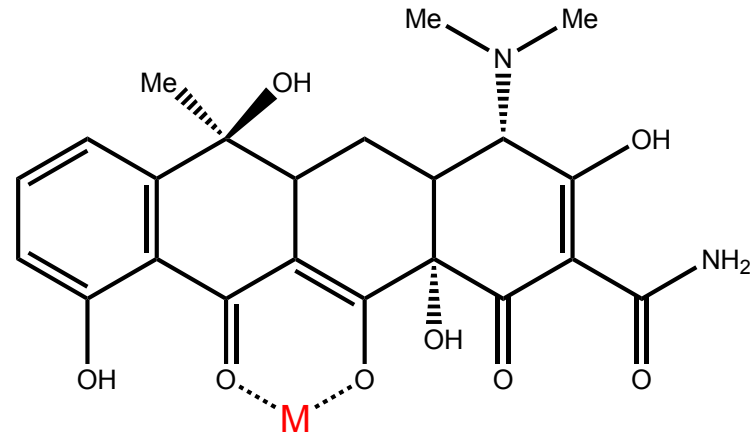
Tetraciklini

- Nestabilnost, tvorba epimera



Tetraciklini

- Vezava kationov

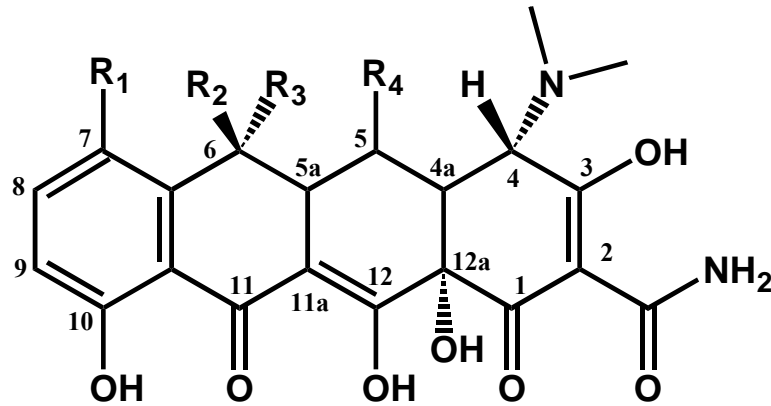


- Interakcije s kationi: hrana, ki vsebuje katione (npr. mleko), vsebniki



Tetraciklini

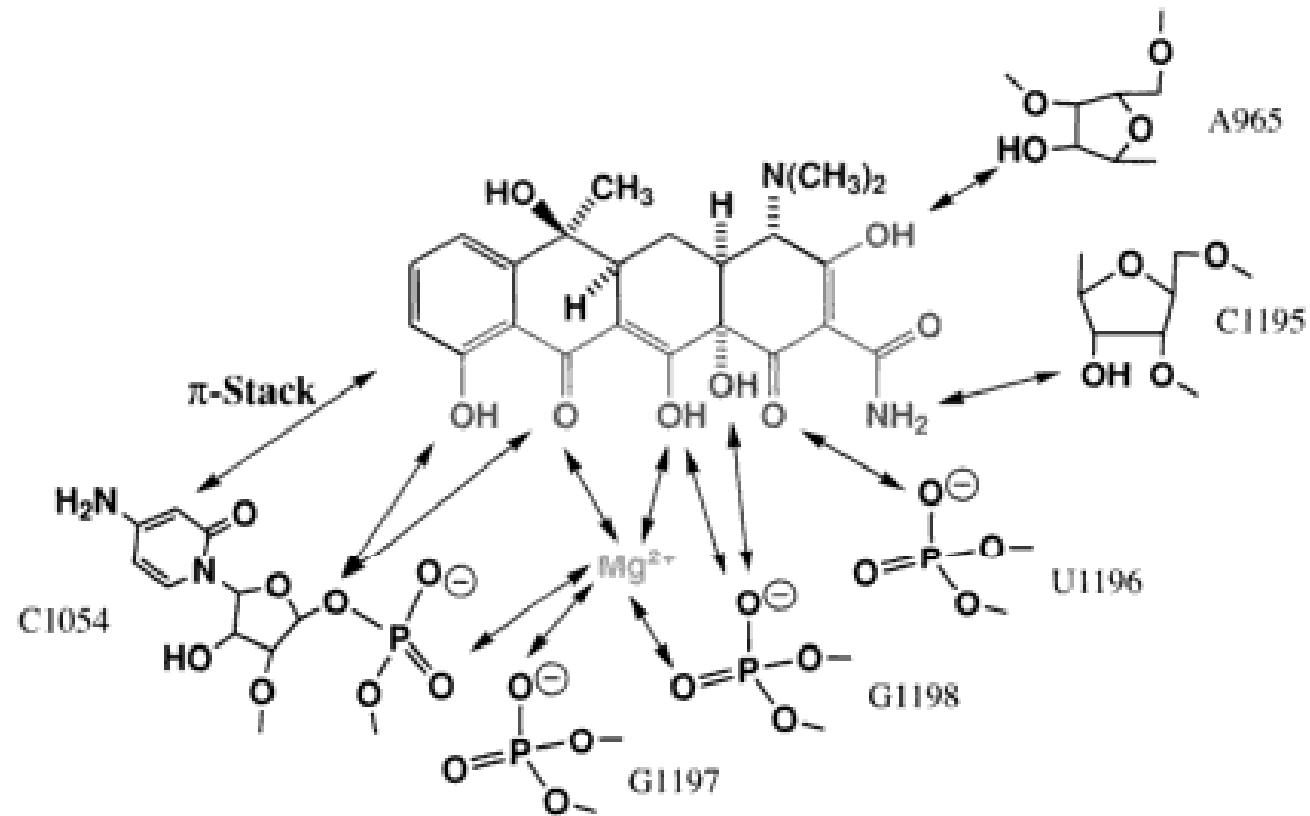
- SAR



- Dovoljene modifikacije na mestih 2, 5, 6, 7, 9

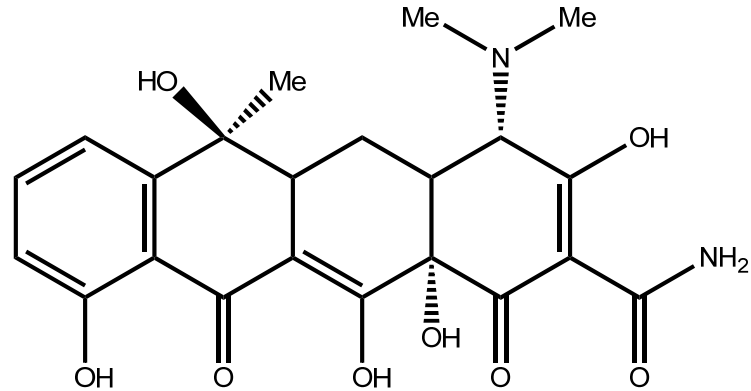
Tetraciklini

- Vezavne interakcije

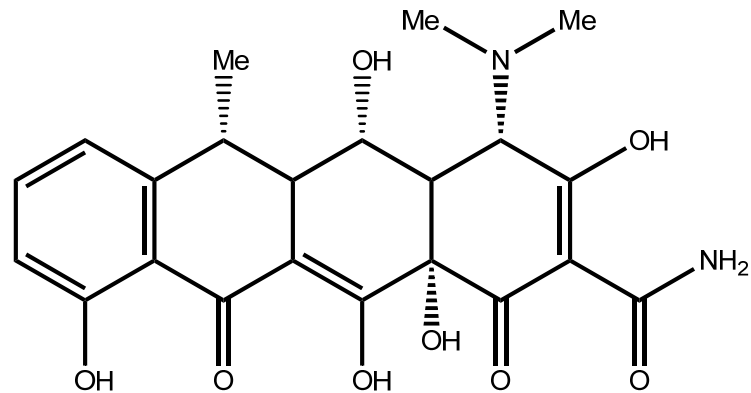


Tetraciklini

- tetraciklin

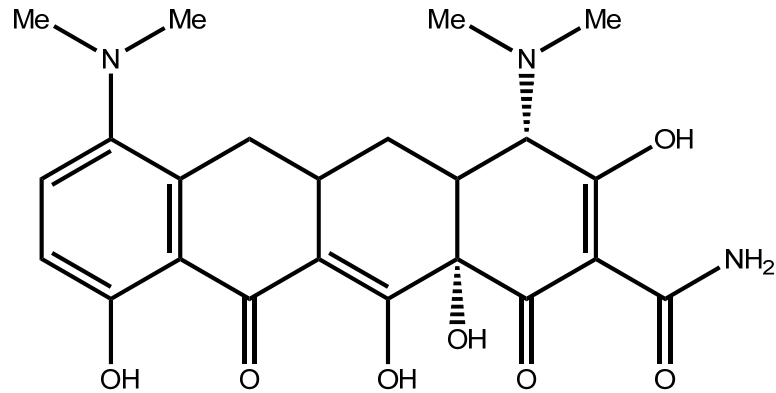


- doksiciklin

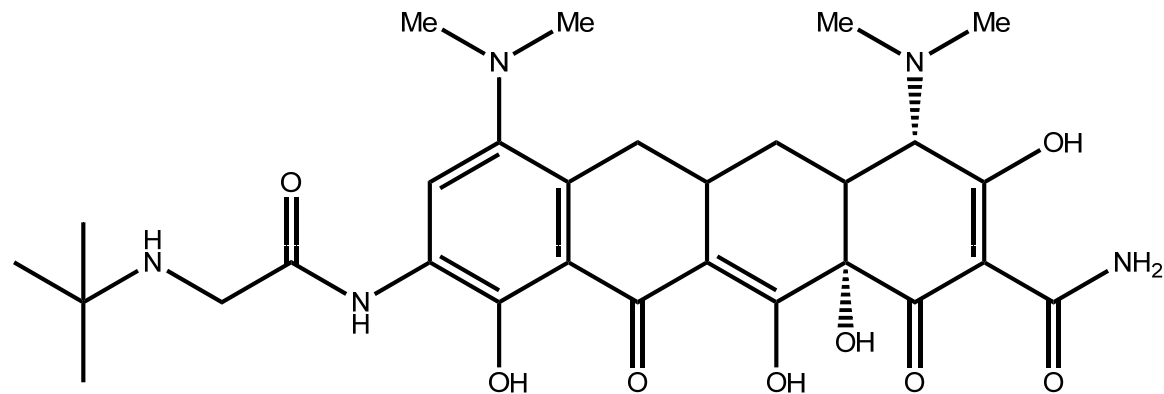


Tetraciklini

- Minociklin



- Tigeciklin - glicilciklin (2005)

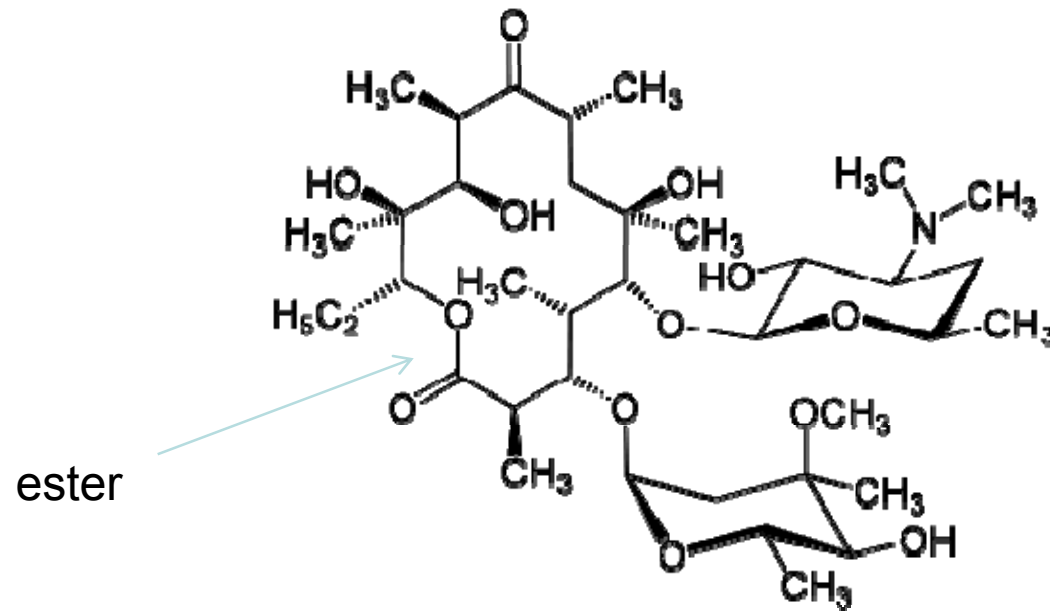


Makrolidi

- Mehanizem: interakcija s 50s podenoto bakterijskega ribosoma – inhibicija tvorbe nove peptidne vezi
- http://student.ccbcmd.edu/courses/bio141/lecguide/unit2/control/macresp_anim.html
- <http://pharmacologycorner.com/protein-synthesis-inhibitors-macrolides-mechanism-of-action-animation-classification-of-agents/>
- Bakteriostatično delovanje
- Podoben spekter delovanja kot penicilini: predvsem proti G+, tudi določene G- ter eksotične bakterije (rikecije, mikoplazme)

Makrolidi

- Makrolid = makrociklični lakton
- Makrolidni antibiotiki vsebujejo 14, 15 ali 16 atomov



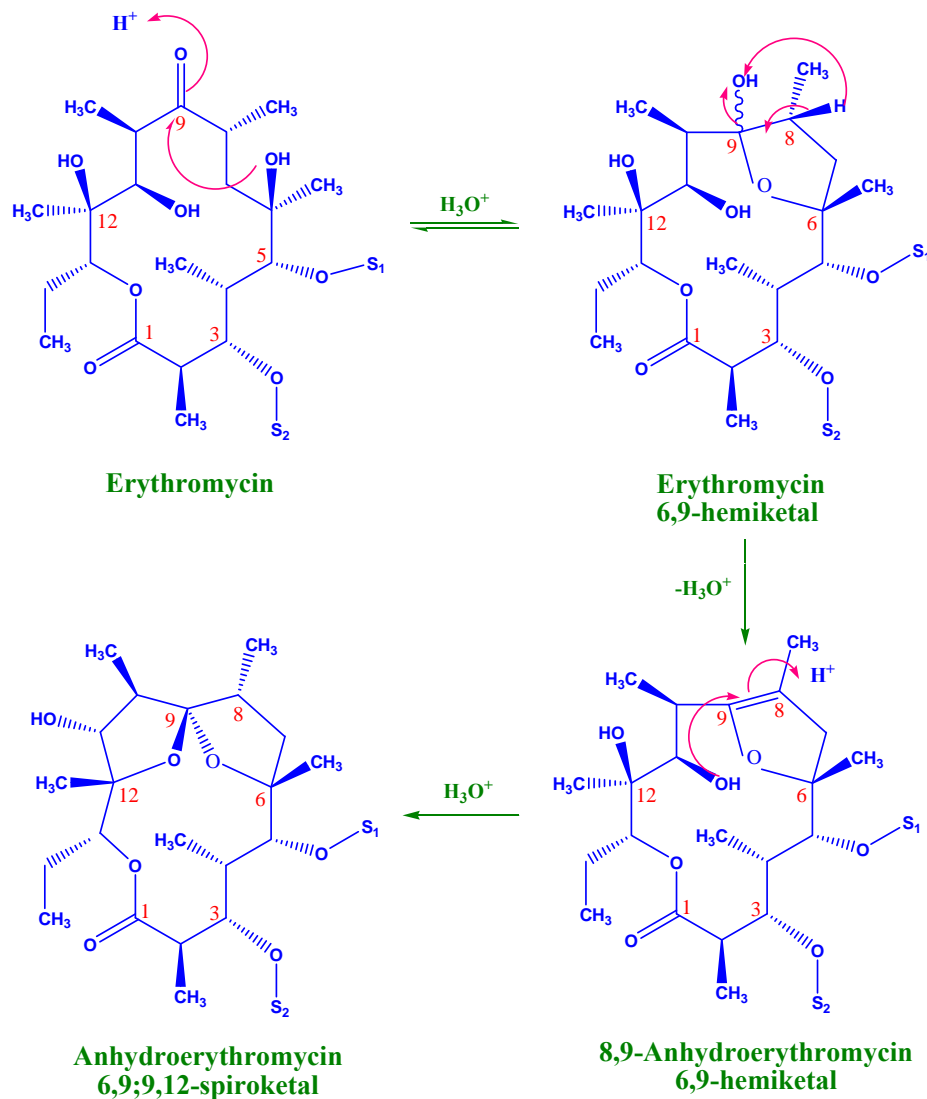
Makrolidi

- Eritromicin - iz *Streptomyces erythreus*
- makrolid + L-kladinoza + D-desozamin
- Šibko bazičen (pKa ~ 8)
- Kemijsko reaktiven
- inhibira CYP3A4; številne interakcije z ostalimi zdravili

Makrolidi

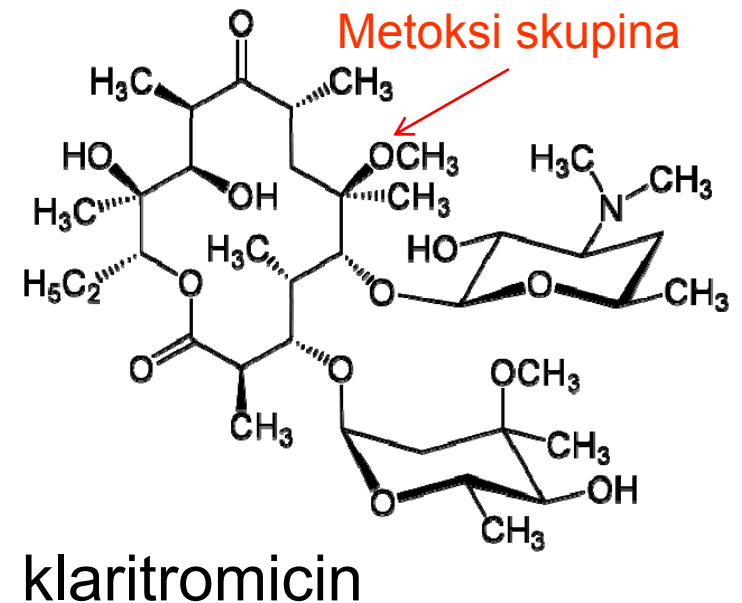
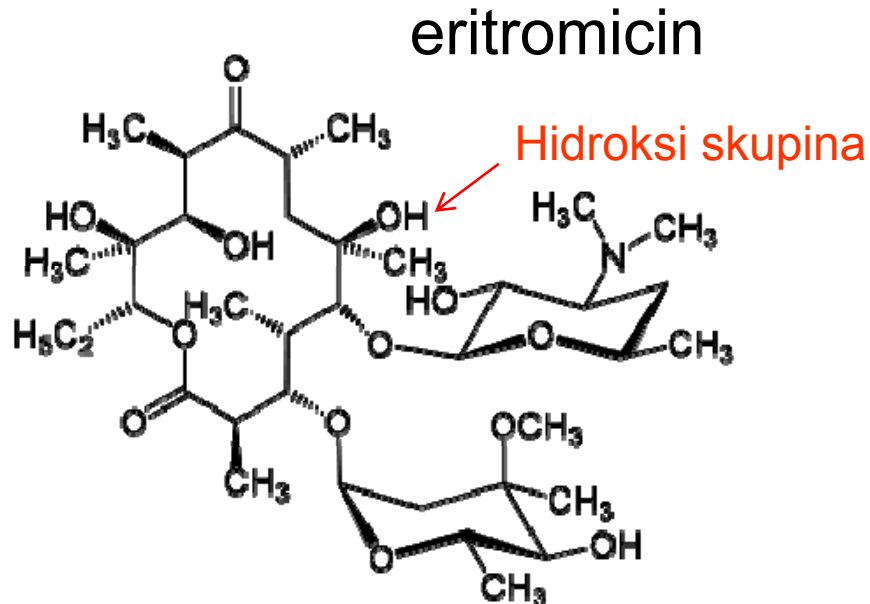
Eritromicin; reaktivnost

- Intramolekularna tvorba ketala v kislem
- Produkt neaktiven, povzroča stranske učinke – GIT motnje



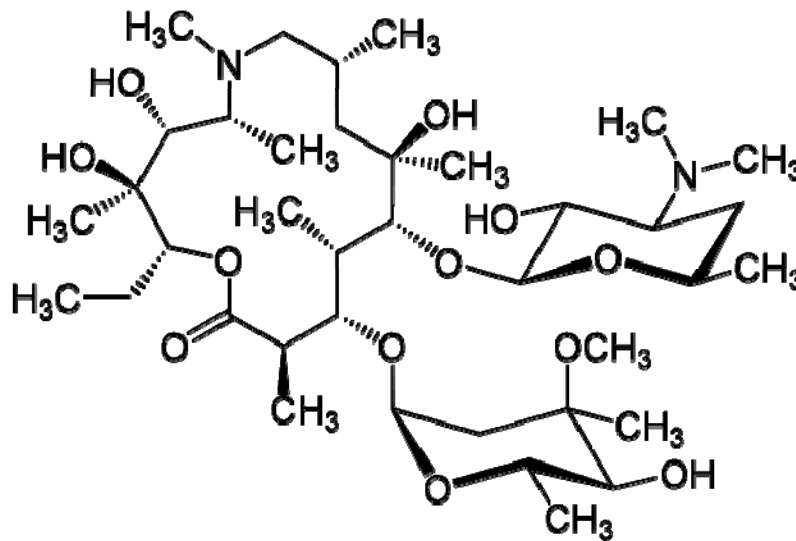
Makrolidi

- Klaritromicin
- Derivat eritromicina, metabolično stabilnejši
- Metoksi skupina namesto $-OH$ na mestu 6 – boljša acidorezistentnost



Makrolidi

- Azitromicin
- Naključen uspeh – vrinjen dušik med C9 in C10



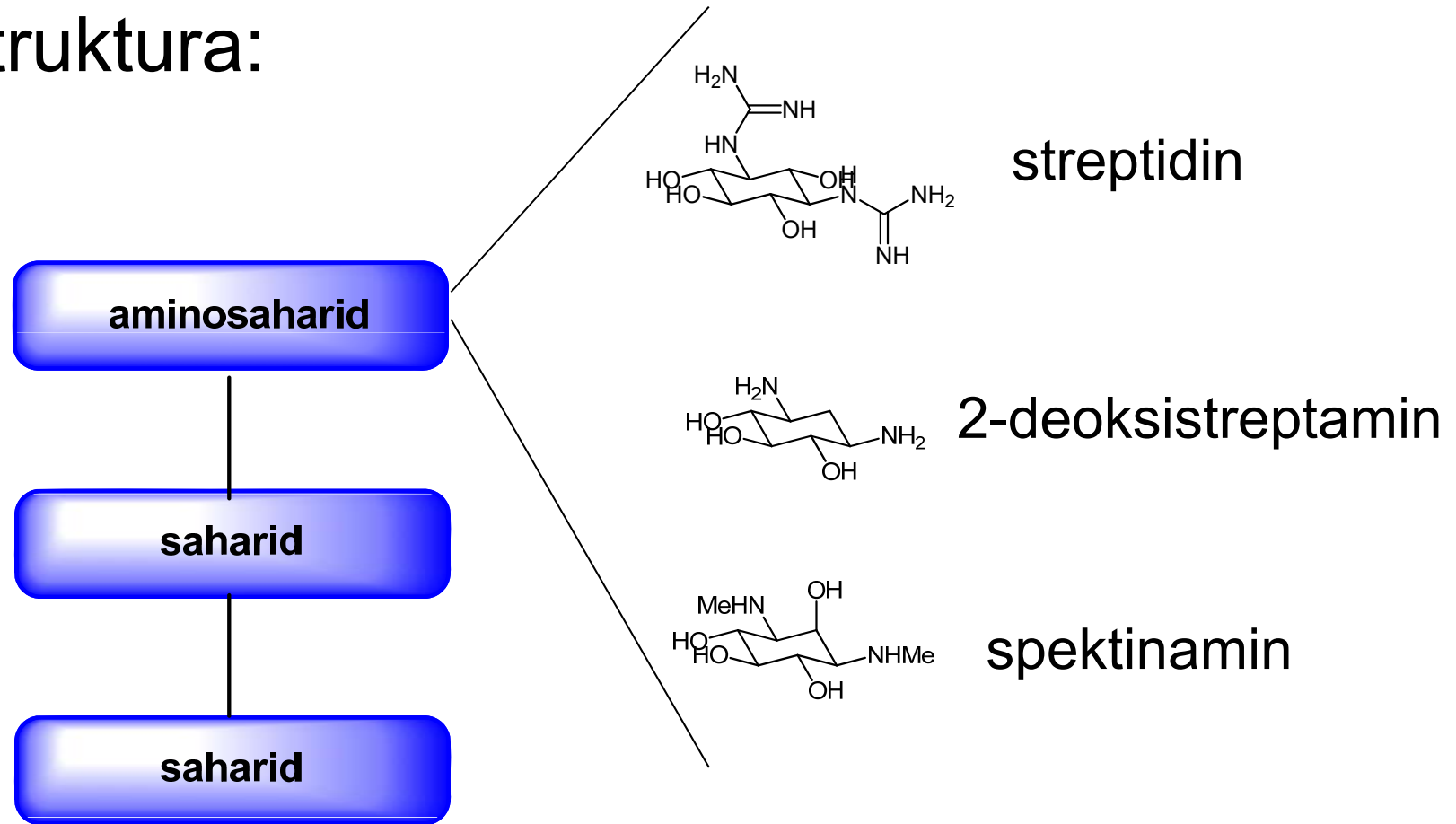
- Stabilen, izjemno dolg razpolovni čas (do 68h), širši spekter (G-)

Aminoglikozidi

- Mehanizem: ireverzibilna interakcija s 30s
http://student.ccbcmd.edu/courses/bio141/lecguide/unit2/control/aglyconoAP_anim.html
- V nizkih konc. – sinteza t.i. “nonsense” proteinov, v višjih konc. popolna ustavitev biosinteze proteinov
- Zoper G-, manj G+, mikobakterije
- Delovanje na po G- bakterijam: penetracija skozi zunanjo membrano zaradi + naboja
- Prenos v citoplazmo z aktivnim transportom; selektivna toksičnost rezultat kopičenja v bakterijah

Aminoglikozidi

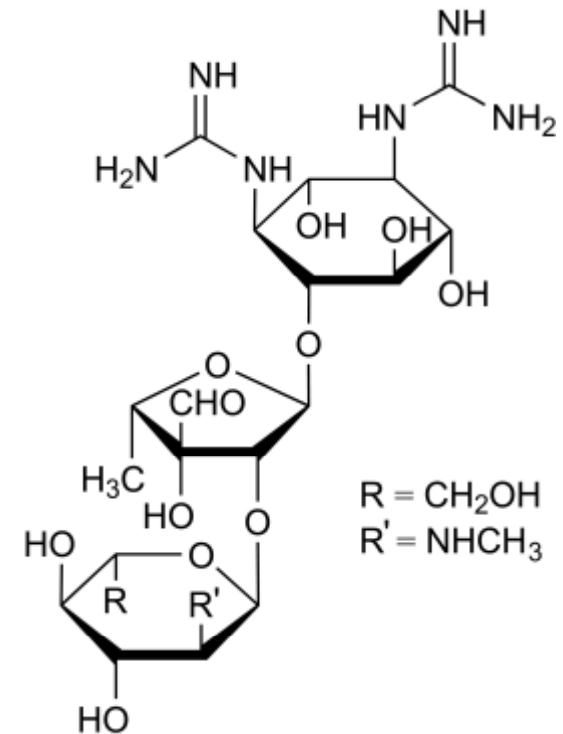
- Struktura:



Slaba absorpcija per os, IV ali delovanje v GIT

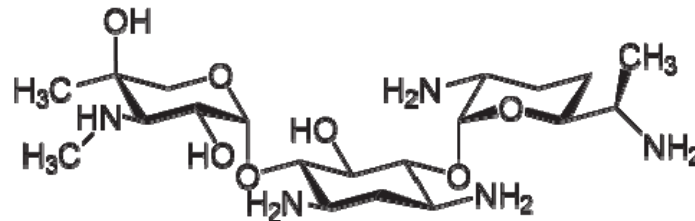
Aminoglikozidi

- Streptomycin
- Prvi aminoglikozid, iz *Streptomyces griseus*
- Terapija tuberkuloze
- Zelo nestabilen – neodporen na avtoklaviranje



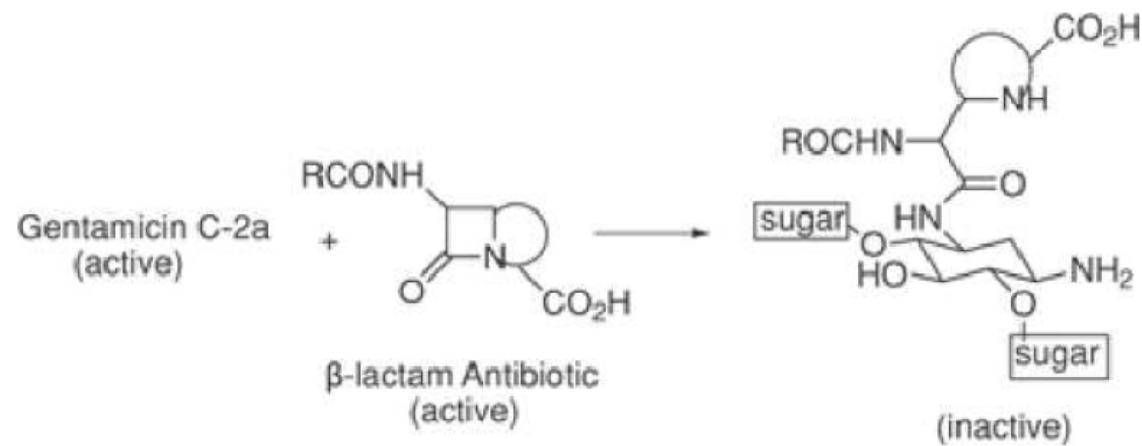
Aminoglikozidi

- **Gentamicin**
- Najpogosteje uporabljan aminoglikozid, mešanica iz *Micromonospora purpurea*
- Stabilna molekula
- Zoper G-, manj G+
- Sinergizem s penicilini, vendar inkompatibilni!
- Parenteralno, topikalno, v oftalmoloških pripravkih



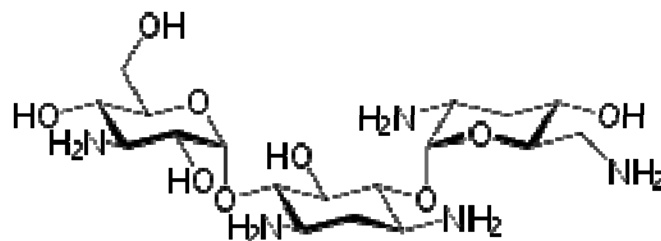
Aminoglikozidi

- **Gentamicin** – inkompatibilnost z beta-laktami



Aminoglikozidi

- Tobramicin
- Iz *Streptomyces tenebrarius*
- Topikalna, IM ali IV uporaba, tudi z inhalatorji zoper *P. aeruginosa*



Kloramfenikol

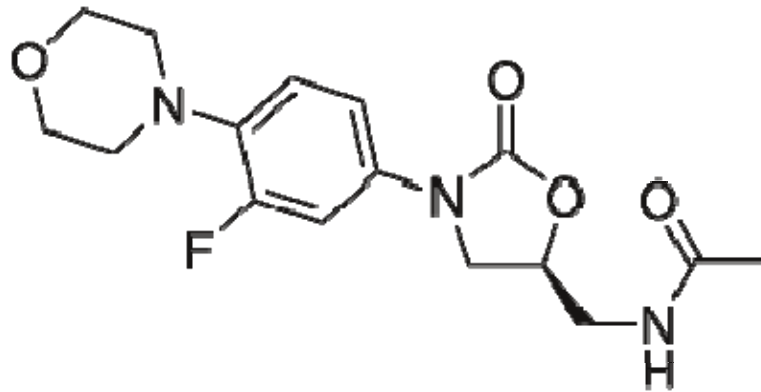
- Vežava na 50S podenoto bakterijskega ribosoma, preprečuje vezavo tRNA
- širokospektralen
- Izjemno razširjen
- Razmeroma toksičen: aplastična anemija, lahko fatalna!, pojavi se tedne po uporabi kloramfenikola
- Sindrom sivega dojenčka, pancitopenija

Oksazolidinoni

- Vezava na 50S, preprečujejo povezavo s 30S
- http://student.ccbcmd.edu/courses/bio141/lecguide/unit6/genetics/protsyn/translation/oxazolres_anim.html

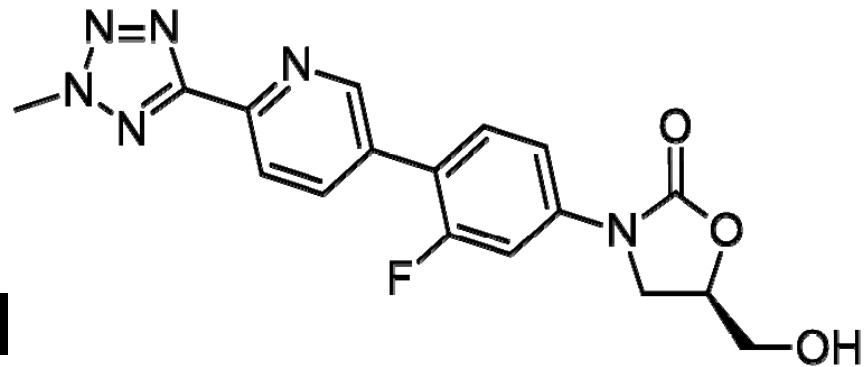
Oksazolidinoni

- Nove protibakterijske učinkovine
- Linezolid (2000)

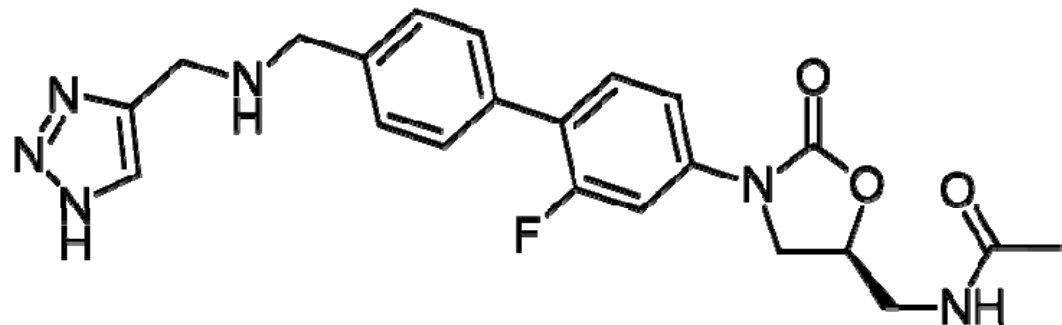


Oksazolidinoni

- Torezolid – faza III

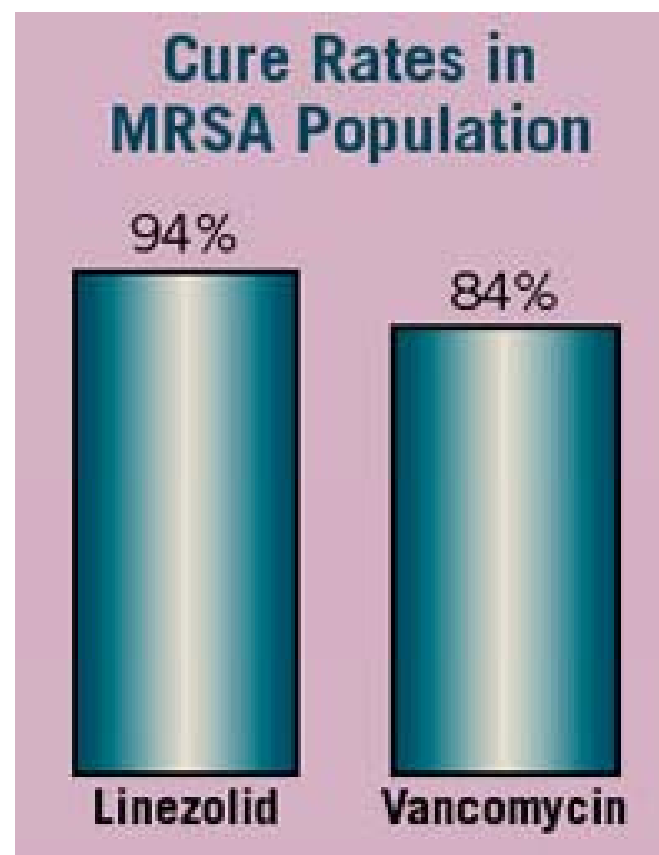


- Radezolid – faza II

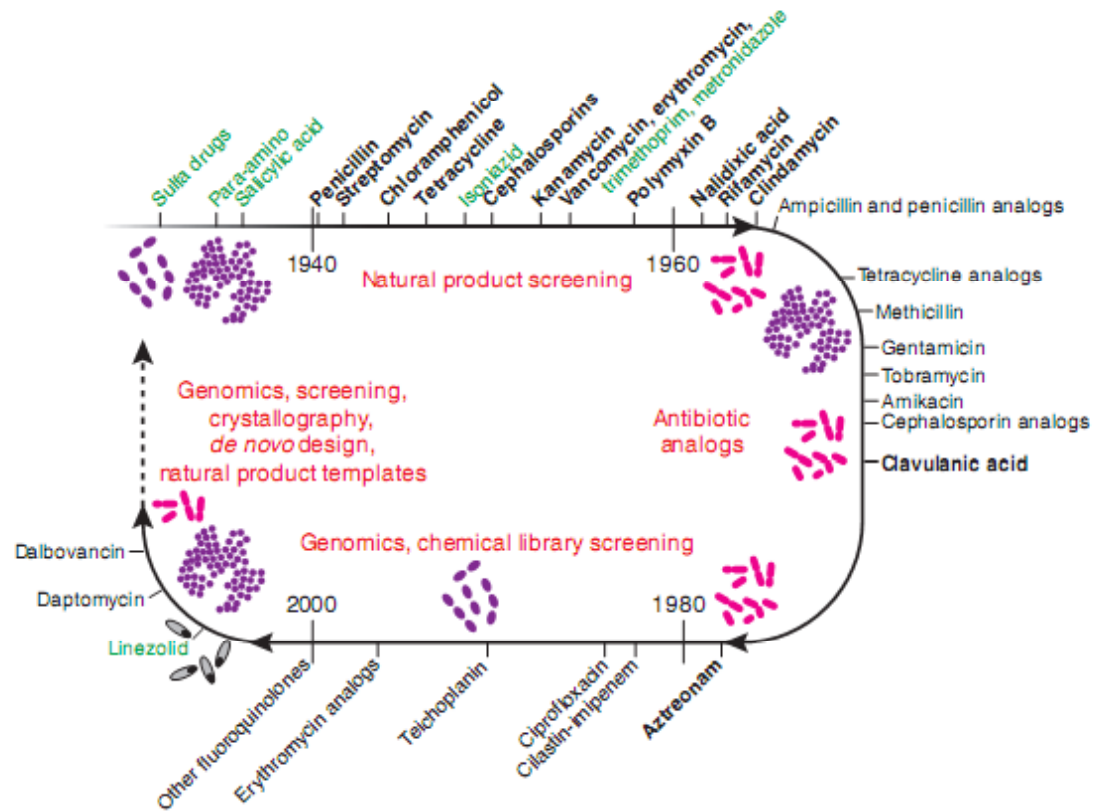


Oksazolidinoni

- Zoper G+, MRSA in VRE.
- Linezolid – novo upanje zoper MRSA, VRE



Protibakterijske učinkovine



Scenarij za prihodnost

- ?????

company	market share		comment
	2002	2011	
GSK	21.1	9.4	loss of augmentin
Pfizer	18.1	17.8	loss of azithromycin retain linezolid
Bayer	12.8	11.8	loss of ciprofloxacin retain moxifloxacin
Abbott	11.6	11.3	loss of clarithromycin ?gain ABT-773; ABT-492
J+J	7.9	2.9	loss of levofloxacin ?gain ceftobiprole



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Preface

Antibacterial Agents: Solutions for the Evolving Problems of Resistance

Antimicrobials

Antimicrobials: time to act!

Editorial overview

Patrice Courvalin and Julian Davies

Current Opinion in Microbiology 2003, 6:425–426



Why is big Pharma getting out of antibacterial drug discovery?

Steven J Projan

Literatura predavanj

G. L. Patrick: An introduction to medicinal chemistry, Oxford University press, 4. izdaja:

- 19. poglavje

Foye's Principles of Medicinal Chemistry, 5 izdaja:

- 34. poglavje