Peptide Antibiotics

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Peptide Antibiotics

- Natural sources: extracted from bacterial cultures:
- ✓ *Bacillus; Streptomyces spp.; Actinomycetes*
- Structural characteristics:
- ✓ cyclo-peptide
- ✓ glyco- peptides
- ✓ semi-synthetic modified peptides
- MOAs are not the same for all of the peptide antibiotics.
- Include:
- ✓ Cycloserine
- ✓ Bacitracin
- ✓ Vancomycin
- ✓ Teicoplanin
- ✓ Daptomycin
- ✓ Streptogramins
- ✓ Capreomycin
- ✓ Polymyxins
- ✓ Colistin

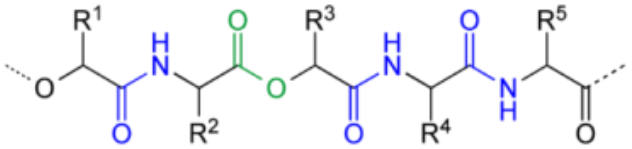
Structural Characteristics for Peptide Antibiotics

- Linear, cyclic & polycyclic structures

✓ cross linked amino acids

✓ aromatic amino-acids

✓ D-stereo-chemistry amino-acids



✓ un-natural amino acids as building blocks

✓ polyketides: structures which have both ketone & amide bond

✓ depsi-peptides: structures which have both ester & amide bond

✓ charge of protein: depends on the nature of amino acids: acid, base & zwitter

✓ water solubility & oral absorption: depends on the nature of amino acids

- Peptide antibiotics: mostly cyclo-peptides & glyco-peptides
- Derived building blocks: lipo-peptide, carbo-peptide, …: antigenic

➢ Hence: challenging synthetic targets: semi-synthetic approaches

Structure of PPG in Cell Wall

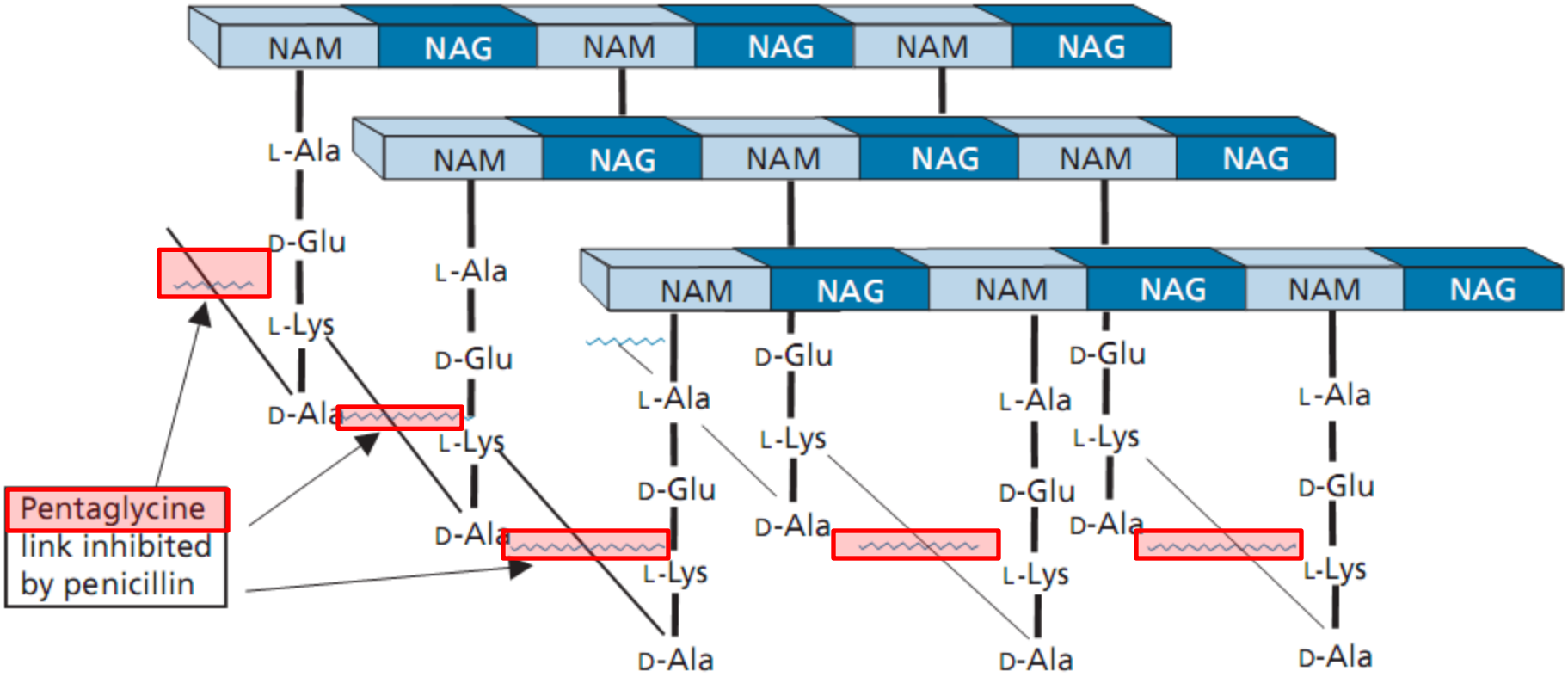
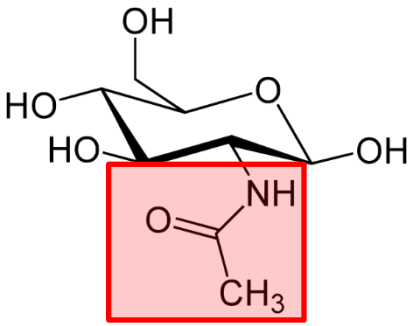


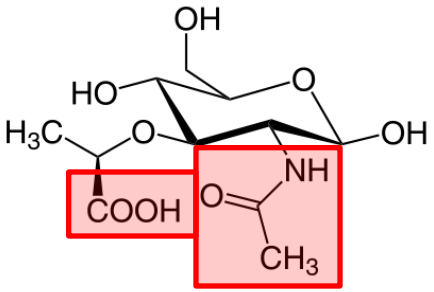
FIGURE 19.13 Peptidoglycan structure of bacterial cell walls.

Components of Peptidoglycan in Cell Wall

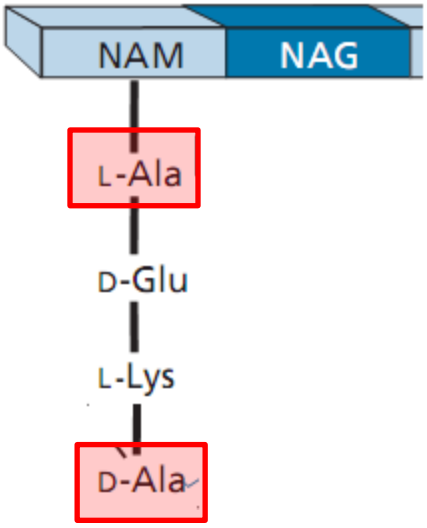
N-Ac-Glucose-amine



+ N-Ac-muramic acid



+ 3 to 5 amino acid residues



MOA for Major Peptide Antibiotics Involved in Bacterial Cell Wall Biosynthesis

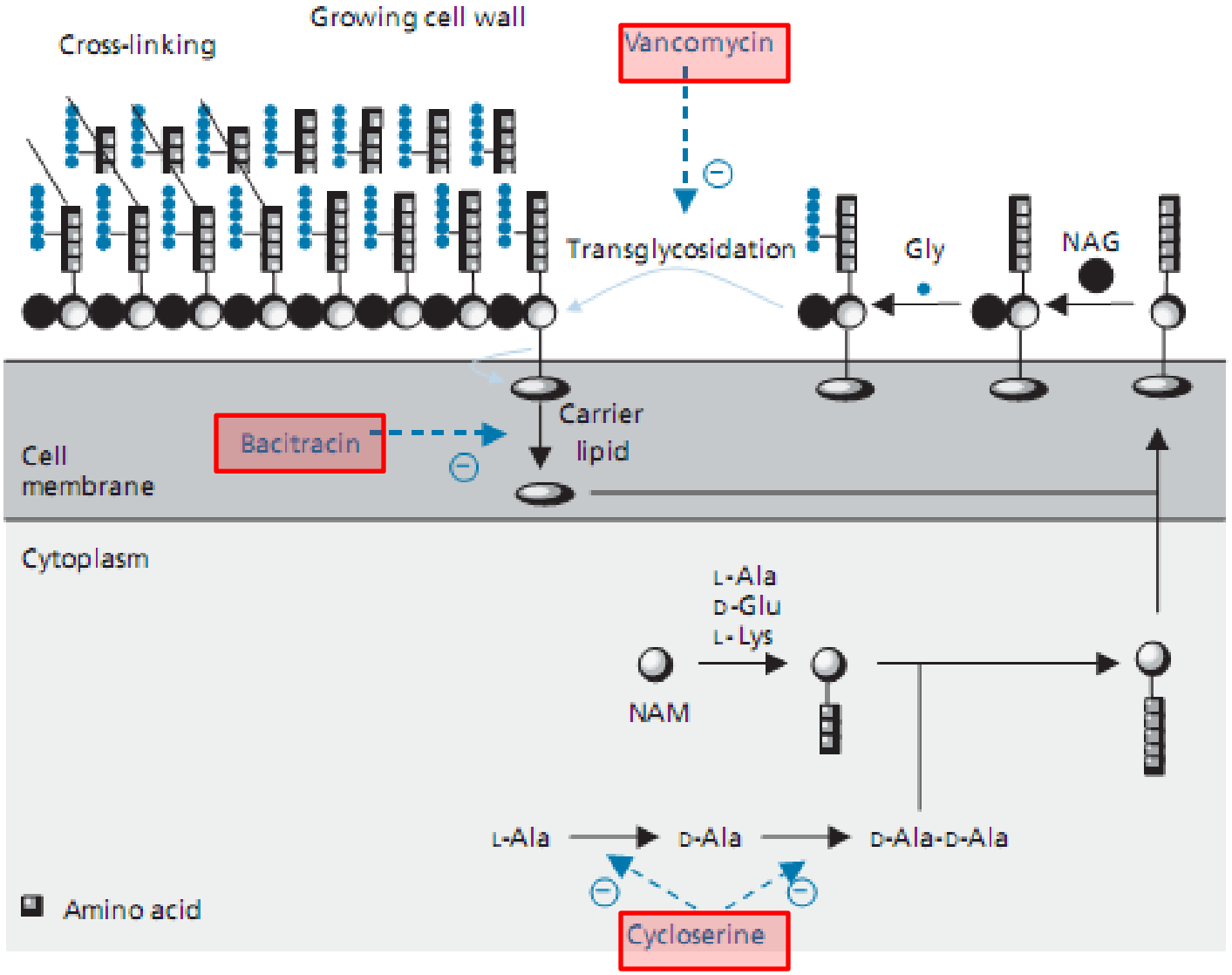
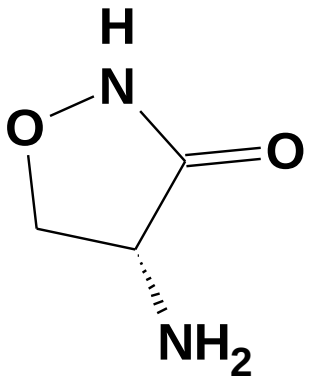


FIGURE 19.52 Cell wall biosynthesis.

Cyclo-Peptide Antibiotic: Cycloserine

- Chemistry: mimics cyclic analogue of serin
- MOA: inhibit two enzymes:

✓ L-Ala racemase & D-Ala - D-Ala ligase



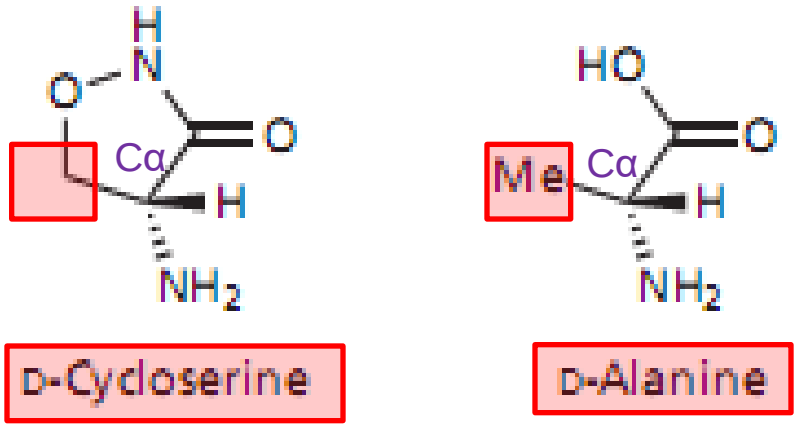


FIGURE 19.53 D-Cycloserine as a mimic for D-alanine.

Cycloserine: Sites of Action: Inhibition of L-Ala racemase & D-Ala – D- Ala ligase

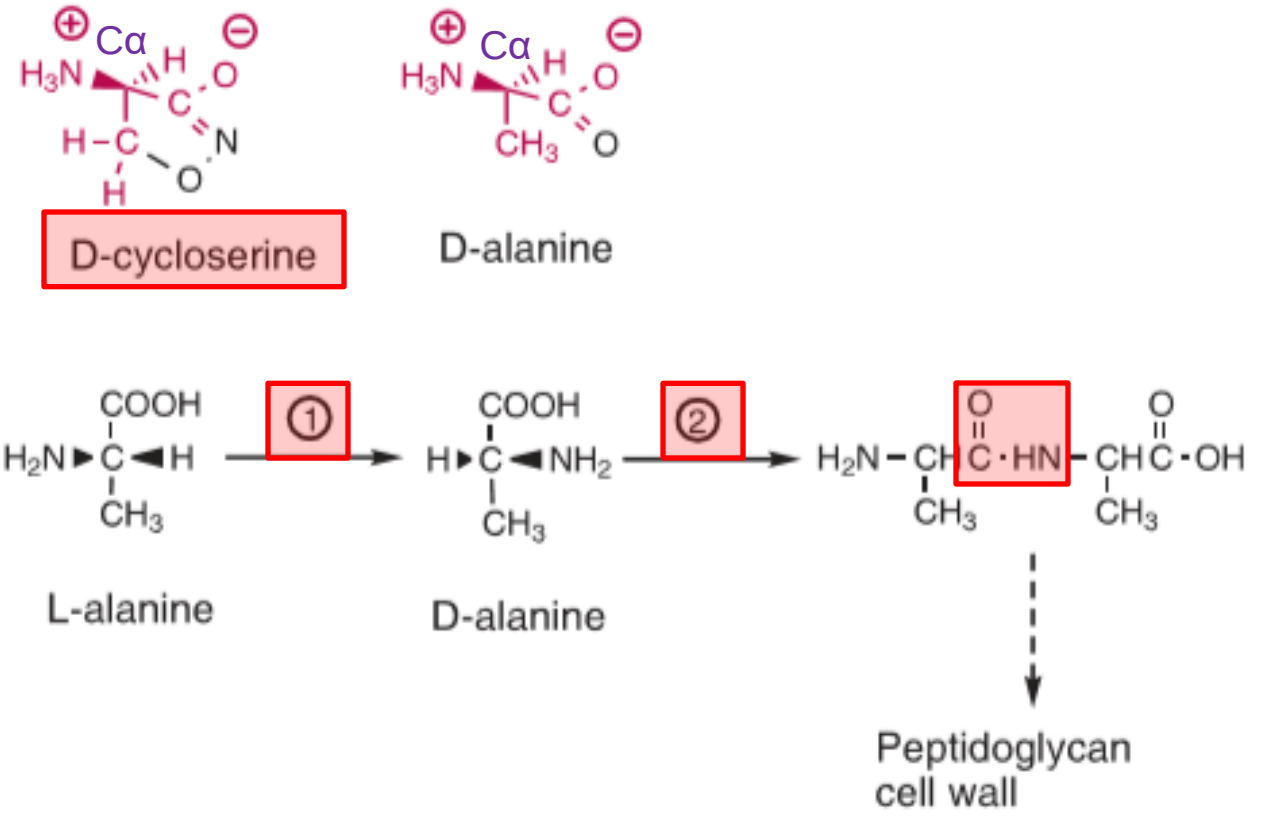


Figure 29.51 Sites of action of D-cycloserine: 1, D-alanine racemase and 2, D-alanine ligase.

Cyclo-Peptide Antibiotic: Bacitracin

- Source: fermentation of *Bacillus subtilis*
- Chemistry: cyclo-peptide

✓ no GI absorption

- MOA: inhibition of peptidoglycan biosynthesis

✓ & disruption of plasma membrane function:

✓ interferes with the dephosphorylation of C5-isoprenyl pyrophosphate, a molecule which carries the building blocks of the peptidoglycan

✓ against G^+

✓ as preventive antibiotic in minor cuts & burns

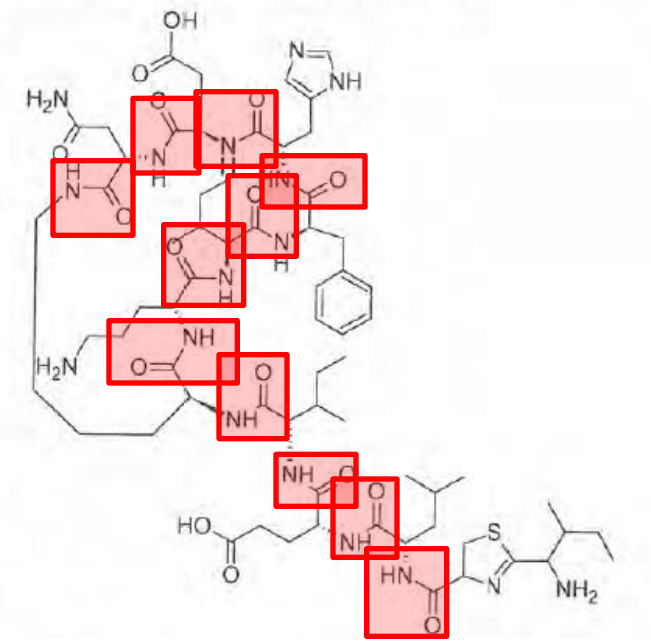
- Dosage forms: topical & injection
- SE_s:

✓ nephrotoxic

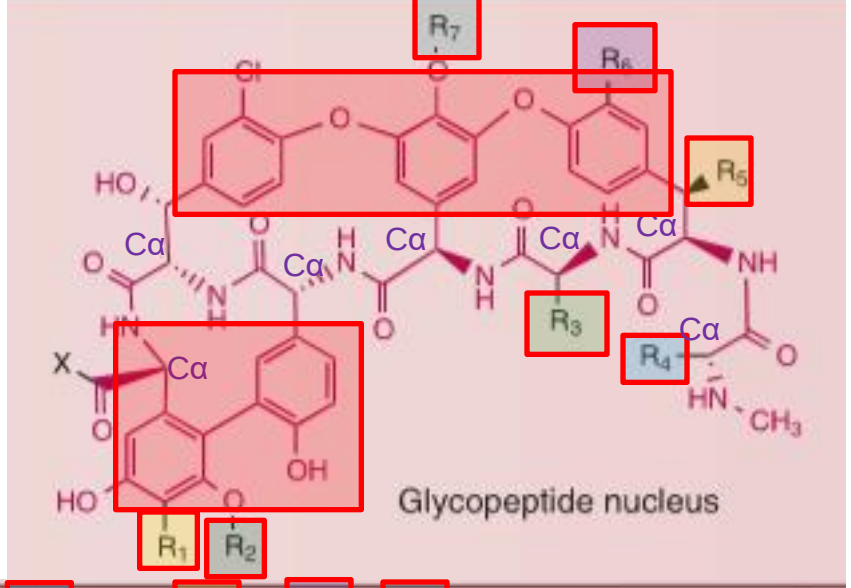
✓ neurotoxic

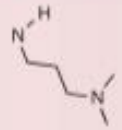
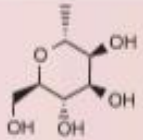
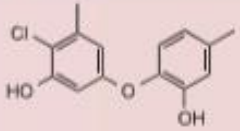
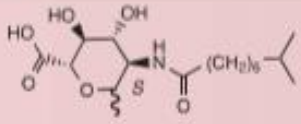
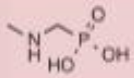
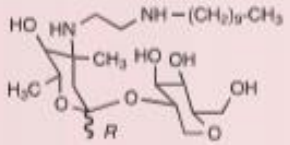
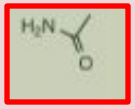
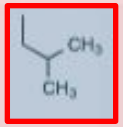
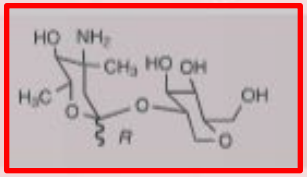
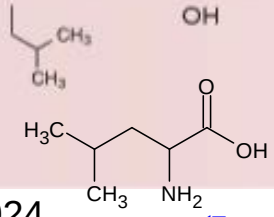
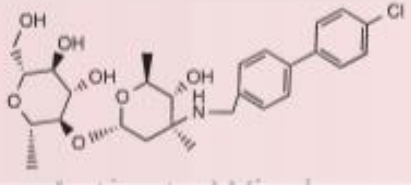
✓ blurred vision

- What is pharmacodynamic interaction with EDTA?



Glyco- & Cyclo- Peptide



	X	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Dalbavancin (Dalvance)		H				H	H	
Telavancin (Vibativ)	OH0		H			OH	Cl	
Vancomycin (Vancocin)	OH	H	H			OH	Cl	
Oritavancin (Orbactiv)	OH	H	H			OH	Cl	

Leucine **(Leu)**

Cyclo-Peptide Antibiotic: Vancomycin: SAR

- Source: fermentation of *streptomyces orientalis Amycolatopsis* (Nocardia)
- Chemistry: cyclo- & glyco-peptide: glycon motif & aglycon motif

✓ glycon: glucose & vancosamine

✓ aglycon: heptapeptide:

5-amino acids in one cyclic portion

+ 1-amino acid as side chain

+ 1-amino acid as cross linked cyclized side chain

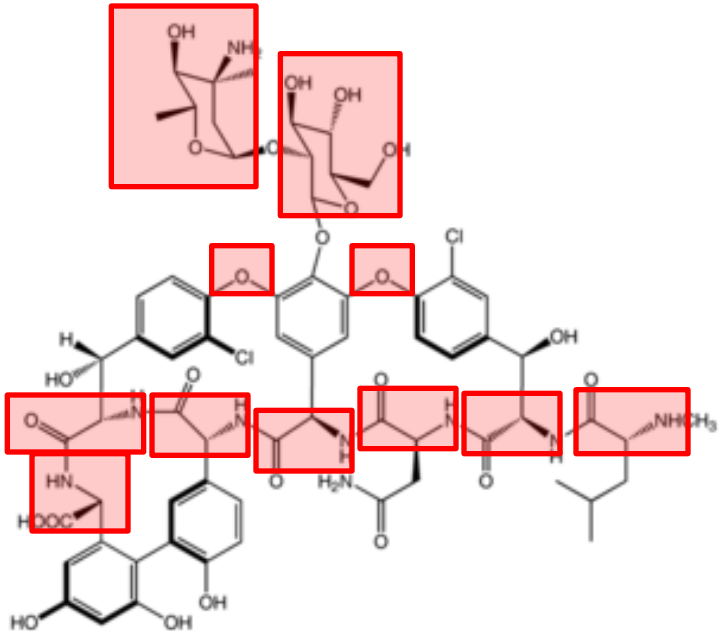
+ aryl ether & resorcinol ether

✓ consists of:

un-usual amino acid

cross linked amino acid

- As HCl salt



- MOA:

✓ in dimer form inhibits cross links in D-Ala blocks of peptidoglycan layers

Cyclo-Peptide Antibiotic: Vancomycin: MOA

- In dimer form inhibits cross links in D-Ala blocks of peptidoglycan layers

- Clinical indication: treatment & prophylaxis
- Against MRSA: particularly coagulase negative Staphylococcus

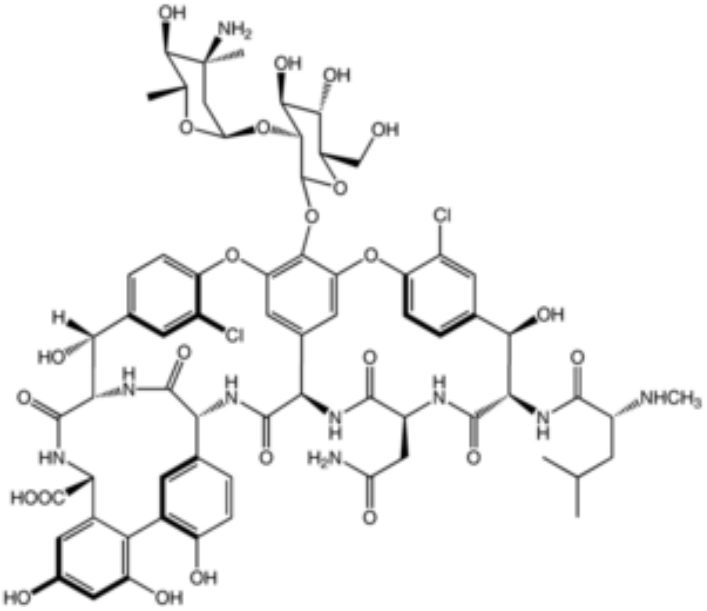
✓ restricted against G^+

✓ not against G^- except *Neisseria*

- SE_s:

✓ nephrotoxicity

✓ ototoxicity



Mechanism of Action for Vancomycin

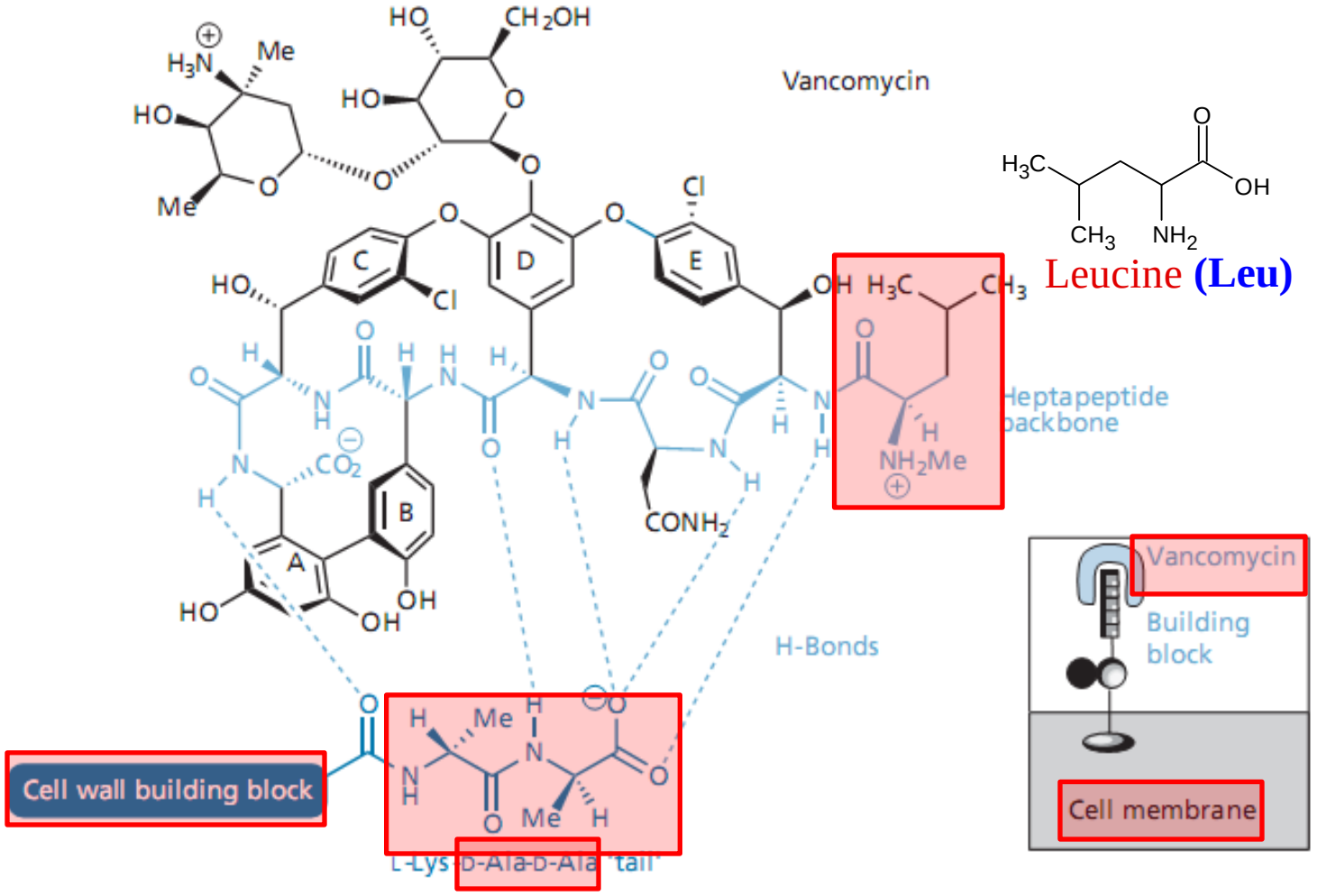


FIGURE 19.54 Vancomycin and its binding interactions to the L-Lys-D-Ala-D-Ala moiety.

Schematic View for Mechanism of Action for Vancomycin as Dimer Structure

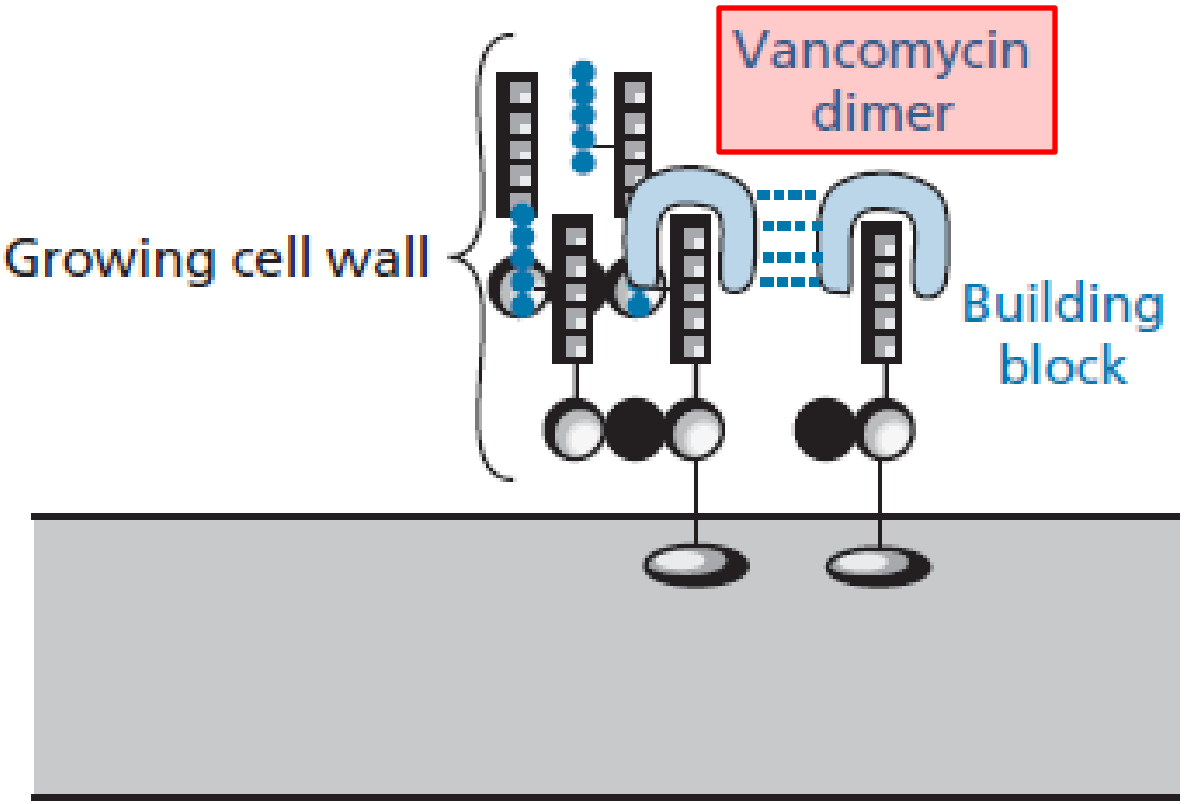


FIGURE 19.56 'Capping' of pentapeptide 'tails' by vancomycin.

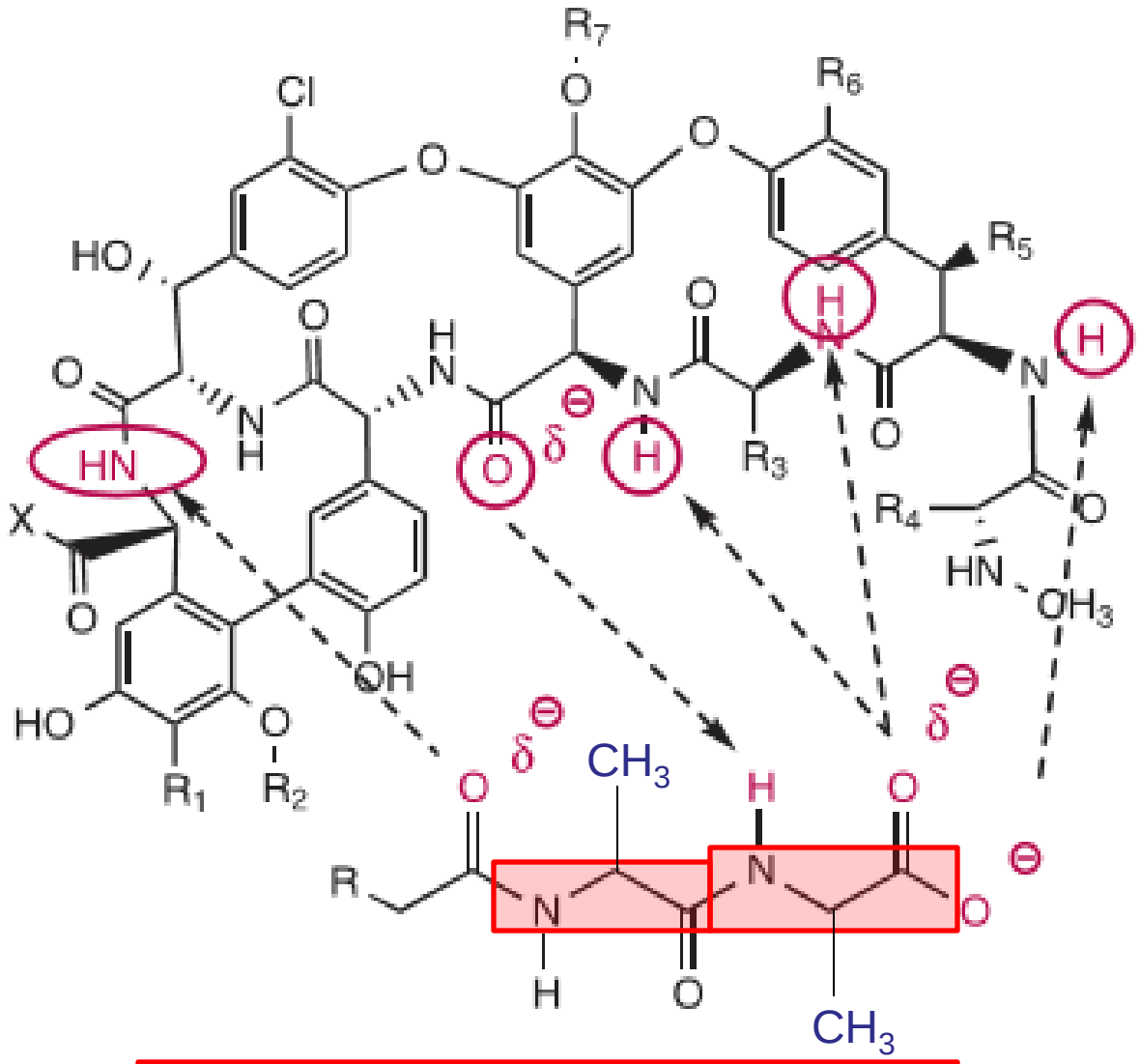


Figure 29.35 Binding of glycopeptide antibiotics to bacterial cell wall D-alanine-D-alanine moiety.

Cyclo-Peptide Antibiotic: Teicoplanin

- Find major difference to Vancomycin?
- Penta/hexa-peptide

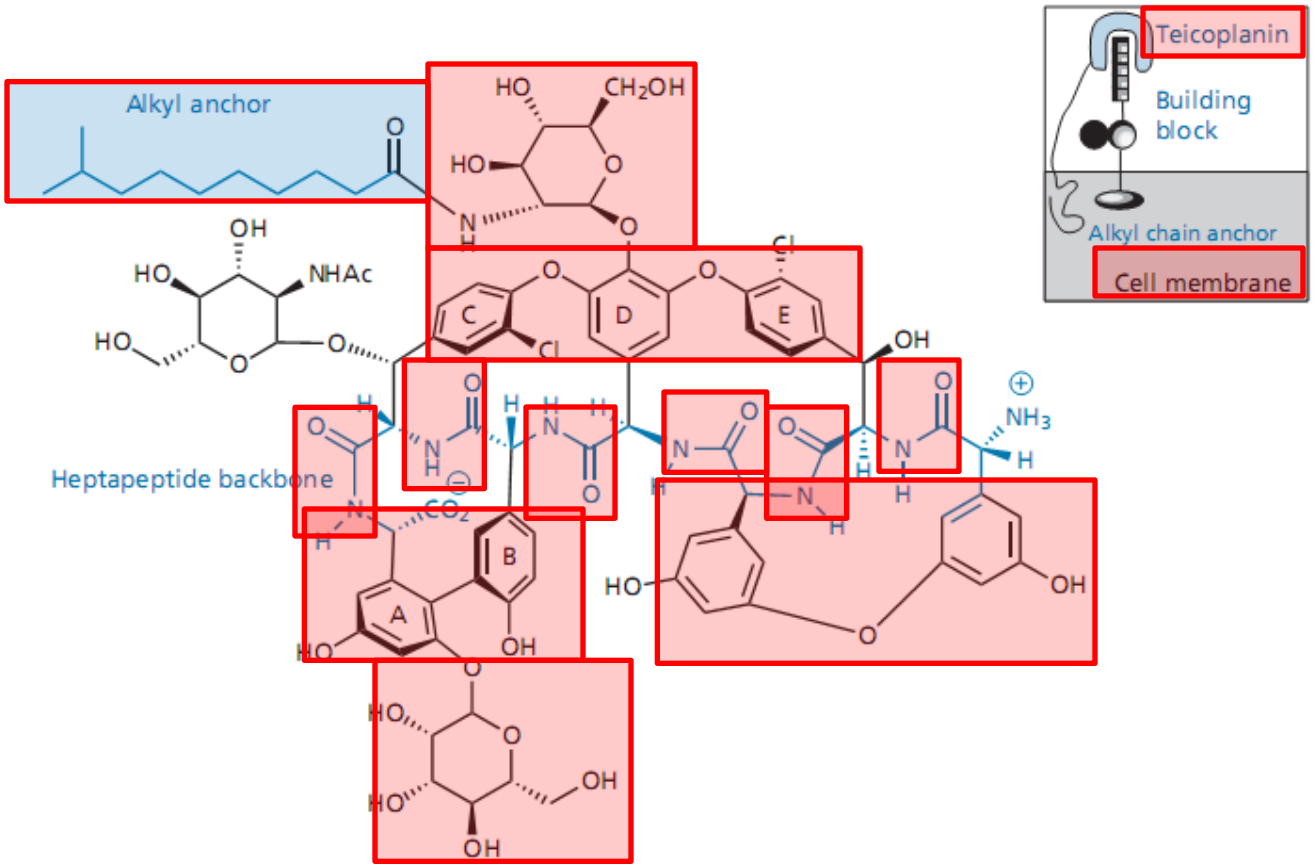
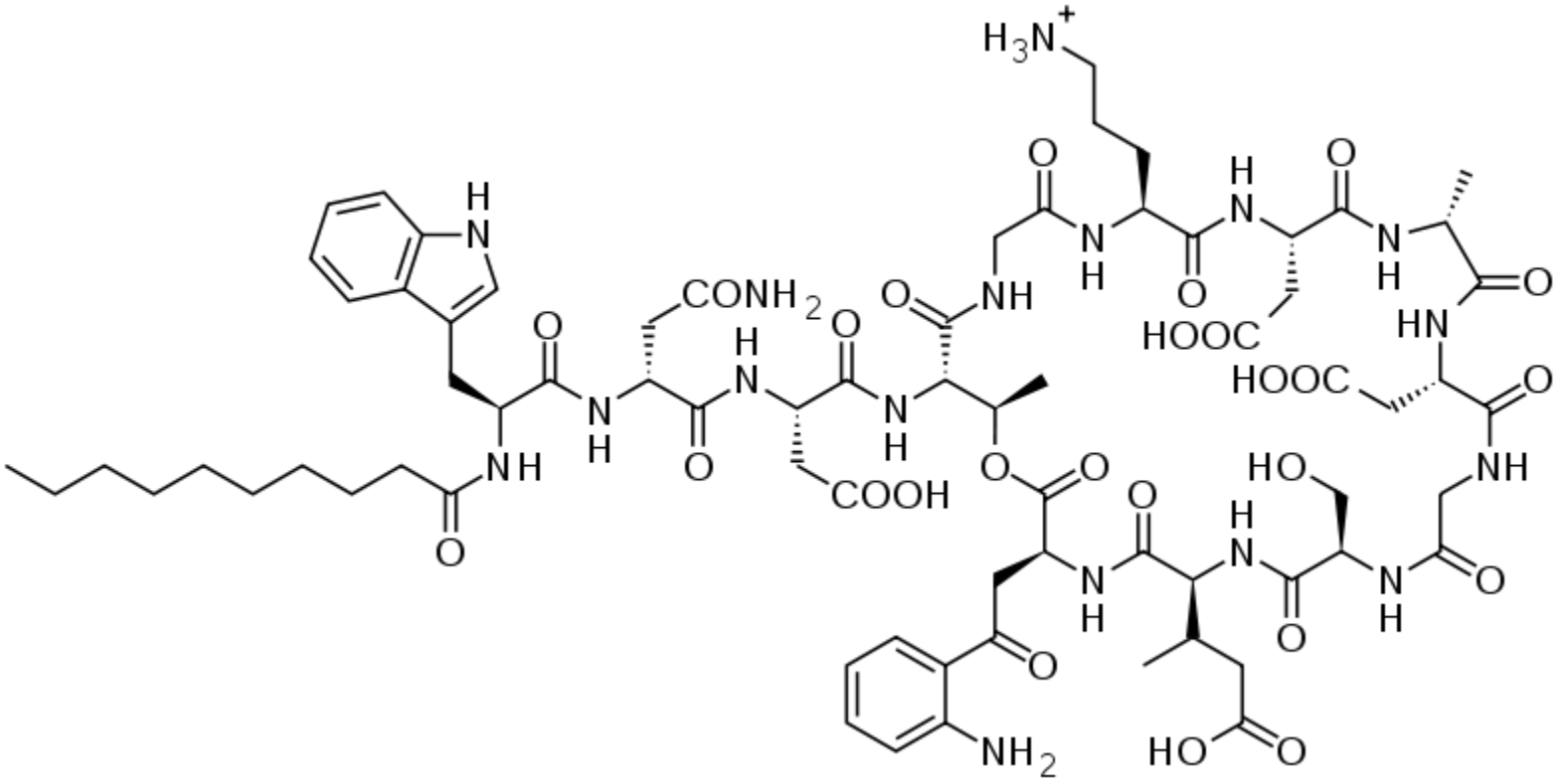


FIGURE 19.59 Teicoplanin A_2–5.

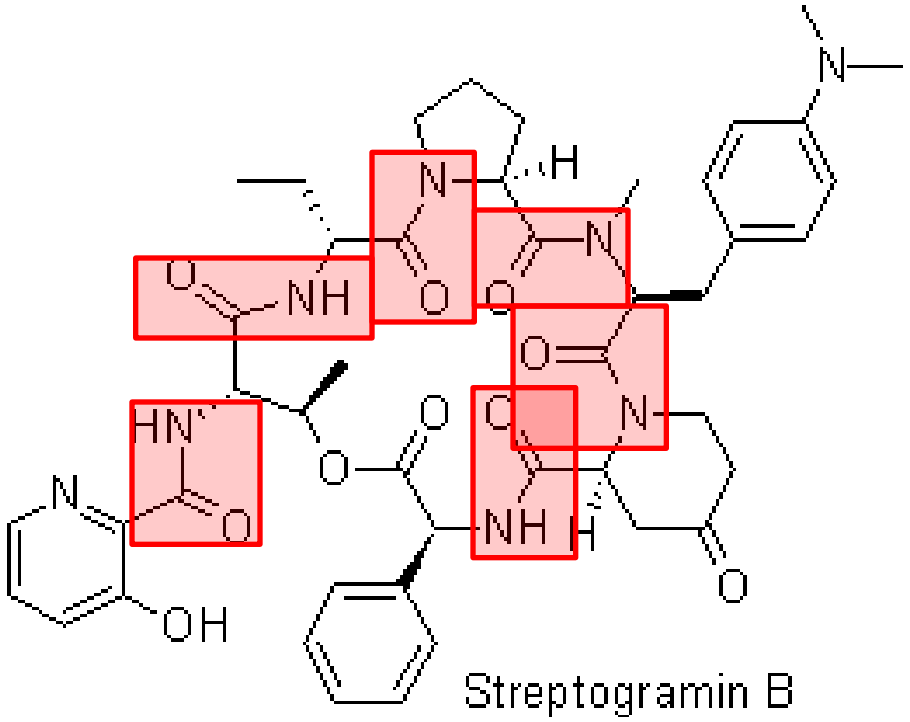
Lipo-Peptide Antibiotic: Daptomycin

- MOA: disrupts cell membrane by creating holes



Cyclo-Peptide Antibiotic: Streptogramins

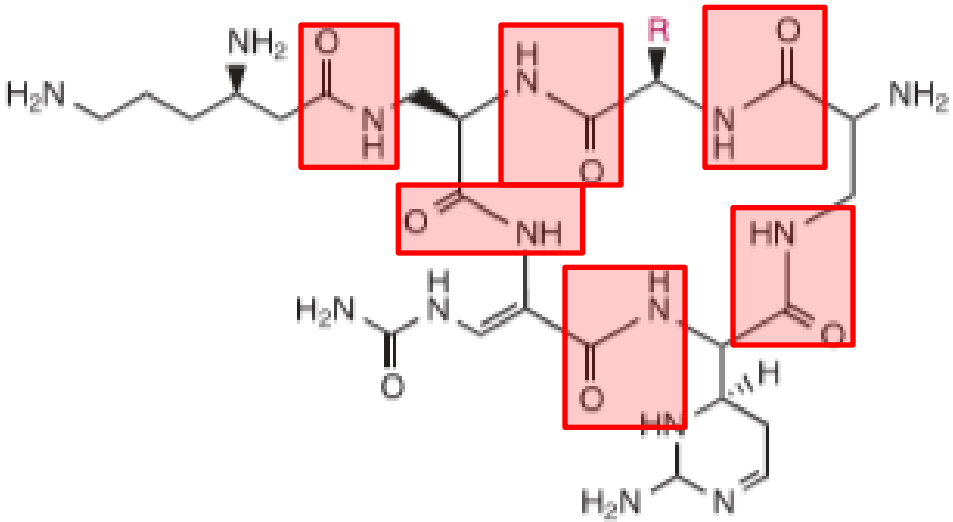
- Clinical indication: VRSA



Streptogramin B

Cyclic Peptide Antibiotic: Capreomycin

- MOA: binds to 30S & 50S



Capreomycin

Polypeptide Cyclic Peptide Antibiotic: Polymyxin B

- Fermentation of *Bacillus Polymyxa*
- Chemistry: cyclo-peptide: natural & un-natural amino acids
- MAO: binds to phosphate group in bacterial cytoplasmic membrane
- Against G $^{-}$: *Pseudomonas aeruginosa* (ophthalmic)
- Dosage forms:

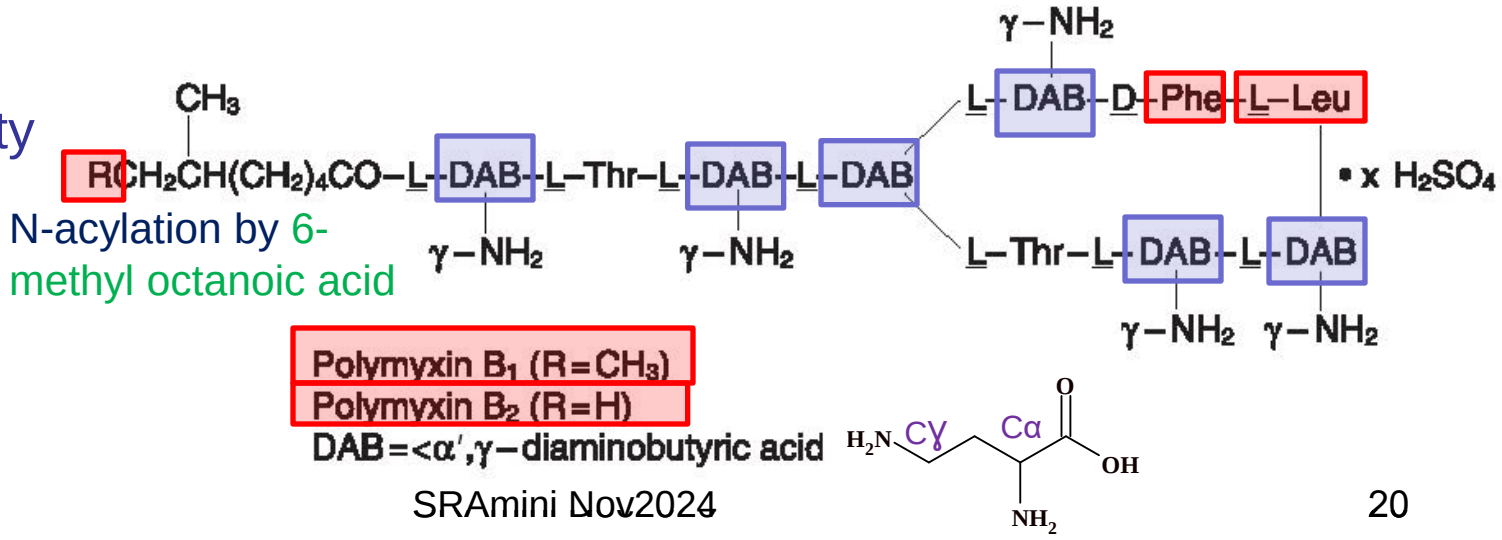
✓ topical

✓ oral for GI infection

- SE_s:

✓ Nephrotoxicity

✓ neurotoxicity

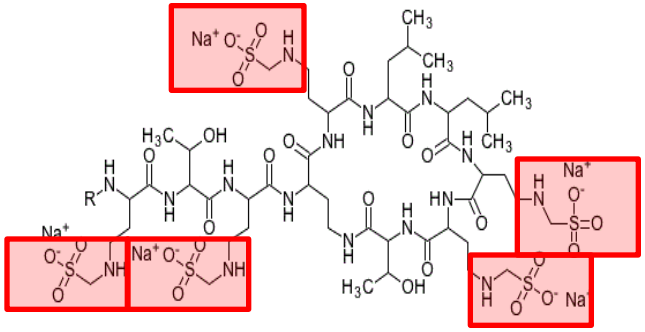


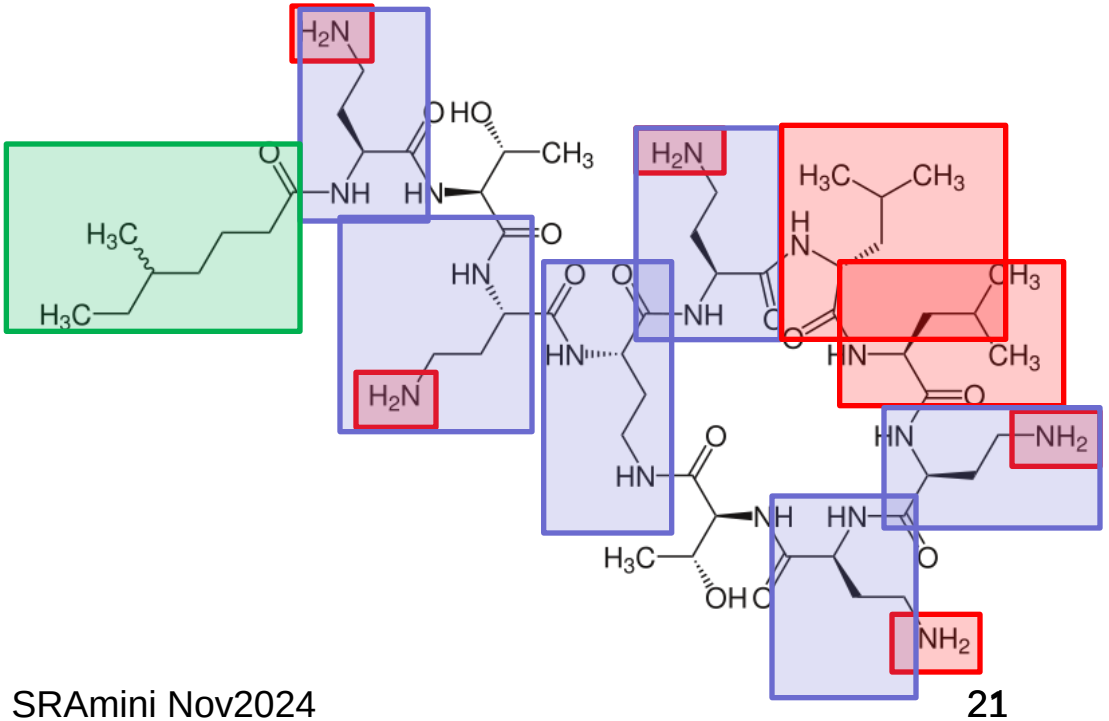
Cyclo-Peptide Antibiotic: Polymyxin E: Colistin

- Close structure to Polymyxin: can be called Polymyxin E
- Mixture of Colistin A & B
- The difference in Leu residue instead of Phe
- Consider N-acylation by 5-methyl heptanoic acid: lipopeptide
- Two derivatives applied in pharmaceutical formulations:

✓ Colistin sulfate

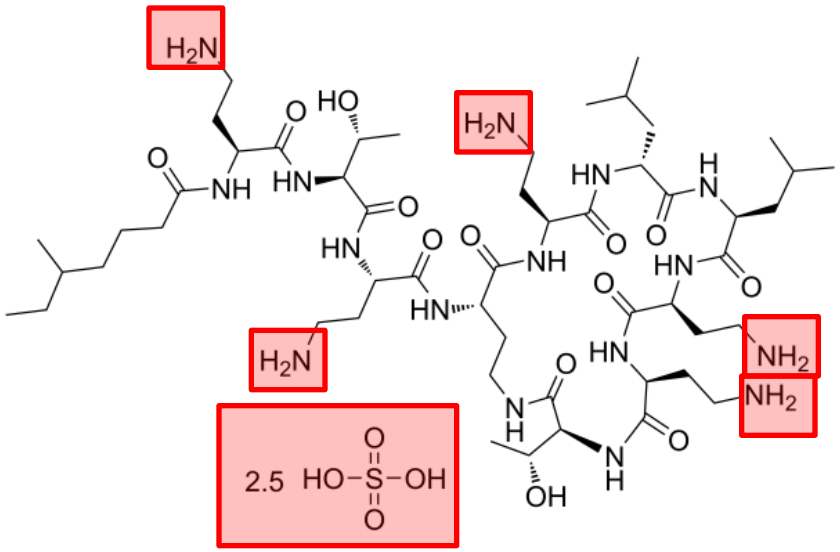
✓ Colistimethate sodium





Colistin Derivatives Applied in Pharmaceutical Formulations

Colistin sulfate



Colistimethate sodium