Definition

An antibiotic is an agent that either kills or Inhibits the growth of a microorganism

Antibiotics are classified by **mechanism of action**, **chemical structure**, **action type**, or **spectrum of activity**.

Based on chemical structure of antibiotic

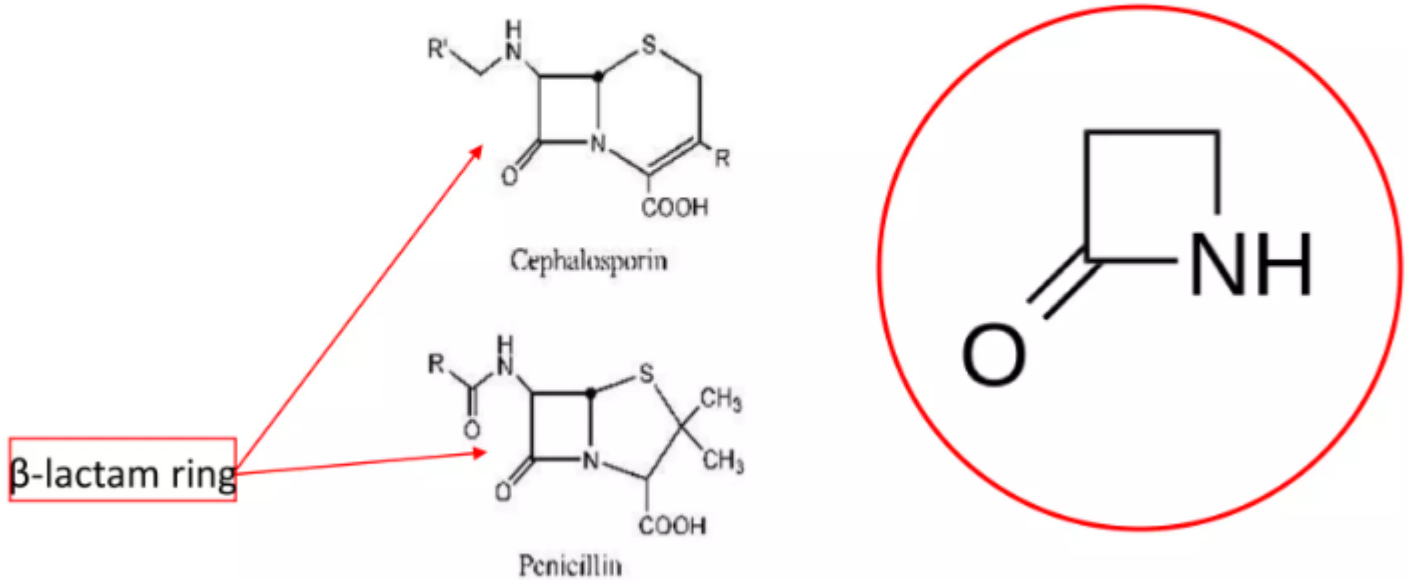
Beta lactam antibiotic

Penicillins: Penicillin G, Amoxicillin.
Cephalosporins: Cephalexin, Ceftriaxone.

Macrolides: Erythromycin, Azithromycin.
Tetracyclines: Doxycycline, Tetracycline.
Quinolones:
Aminoglycosides: Gentamicin, Tobramycin.
Glycopeptides: Vancomycin

Oxazolidinones

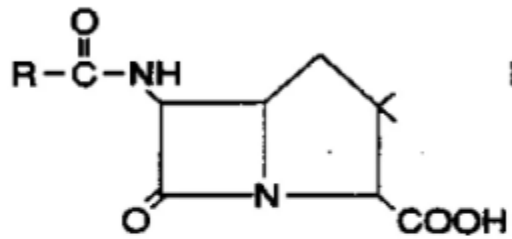
Beta-Lactam Antibiotics



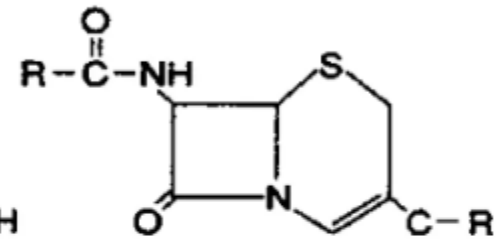
•Contains a beta-lactam ring in their molecular structures.

Beta-Lactam Structure

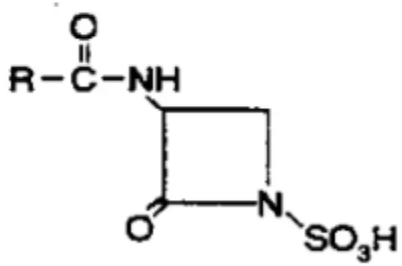
Penicillins



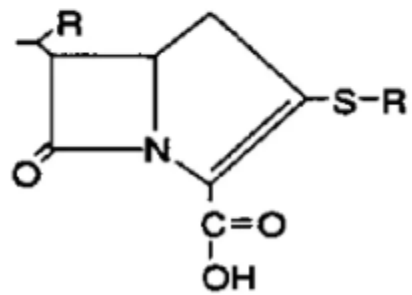
Cephalosporins



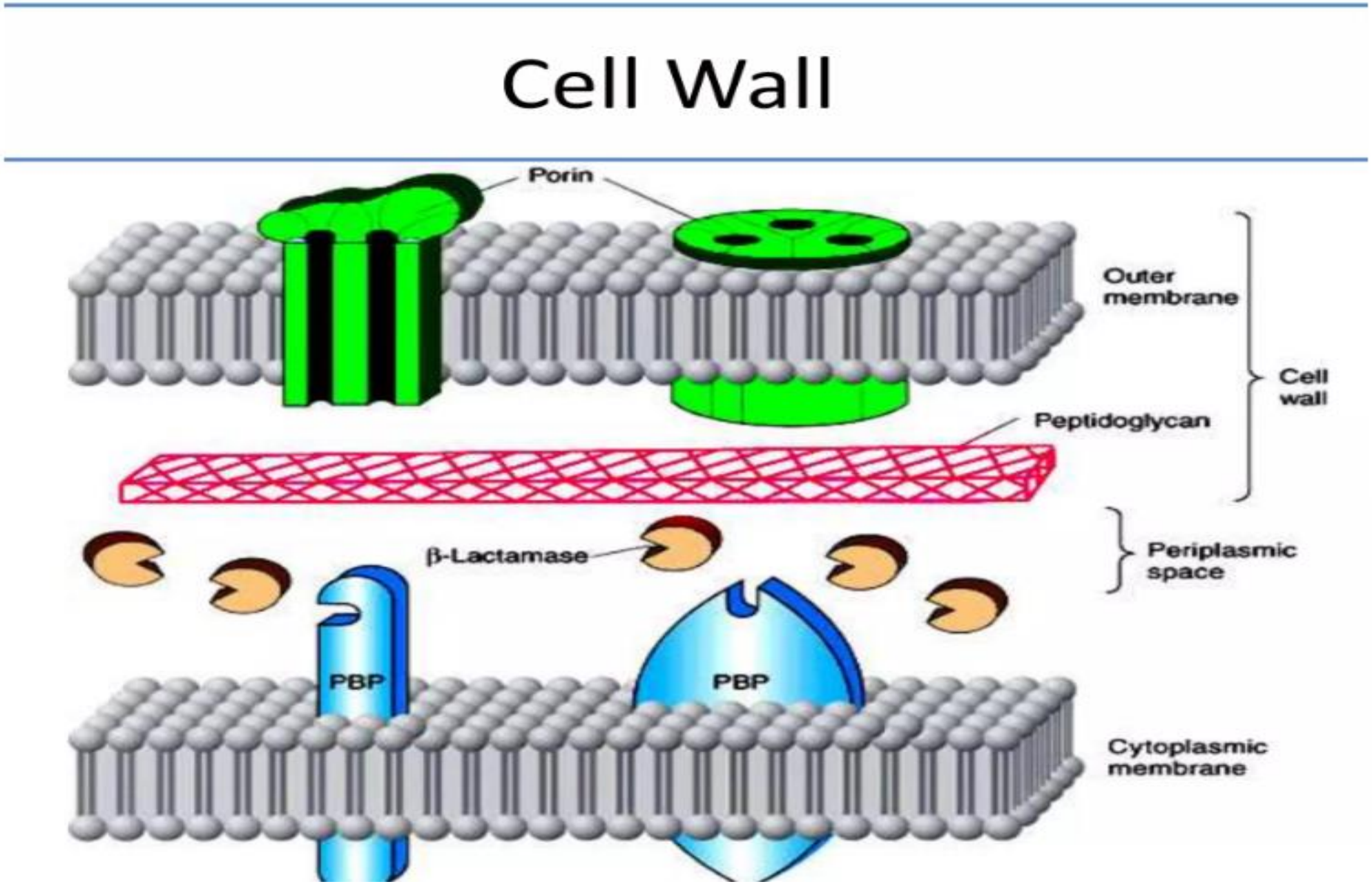
Monobactams



Carbapenems

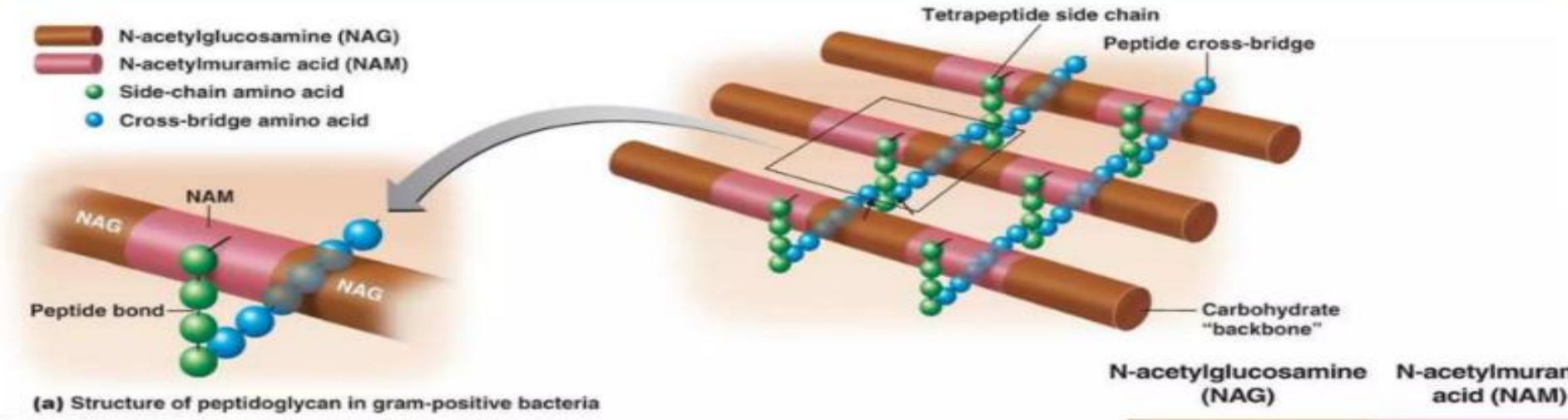


Beta lactam antibiotic

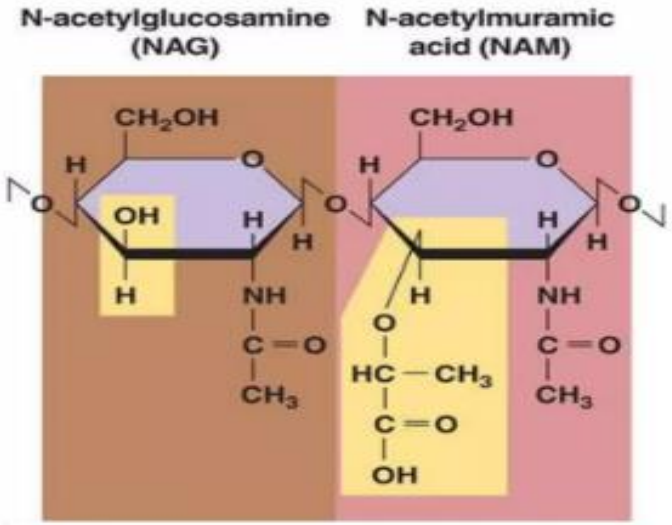


Beta lactam antibiotic

Structure of Peptidoglycan layer



(a) Structure of peptidoglycan in gram-positive bacteria



- Peptidoglycan is a carbohydrate composed of alternating units of NAMA and NAGA.
- The NAMA units have a peptide side chain which can be cross linked from the L-Lys residue to the terminal D-Ala-D-Ala link on a neighboring NAMA unit.

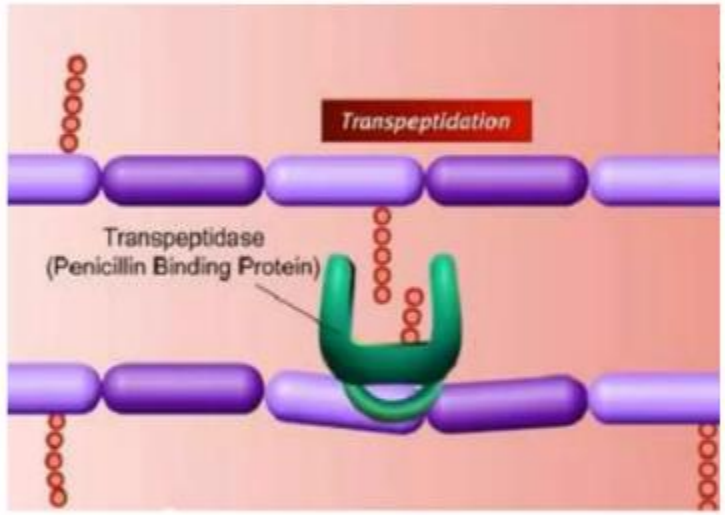
Beta lactam antibiotic

Transpeptidase Enzyme

•The cross linking reaction is catalyzed by a class of transpeptidases known as penicillin binding proteins

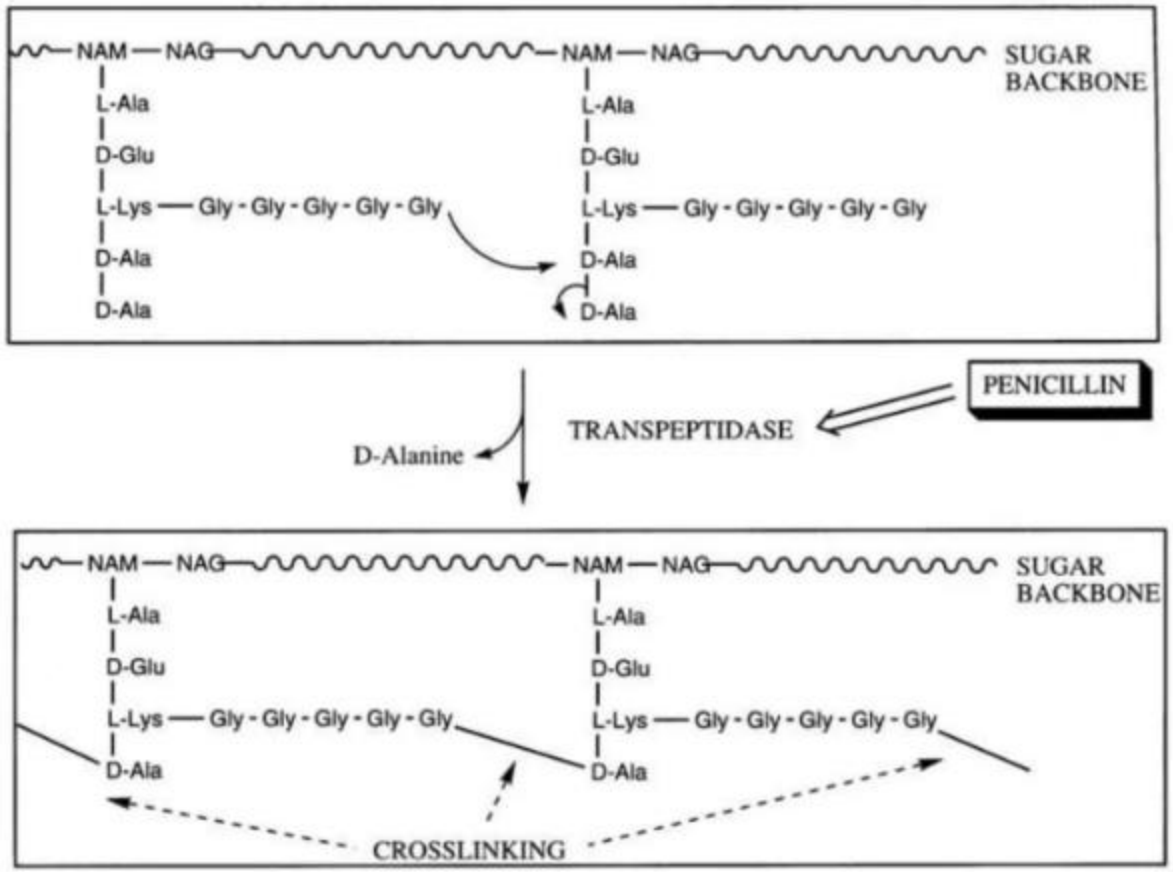
•A critical part of the process is the recognition of the D-Ala-D-Ala sequence of the NAMA peptide side chain by the PBP. Interfering with this recognition disrupts the cell wall synthesis.

•β-lactams mimic the structure of the D-Ala-D-Ala link and bind to the active site of PBPs, disrupting the cross-linking process.



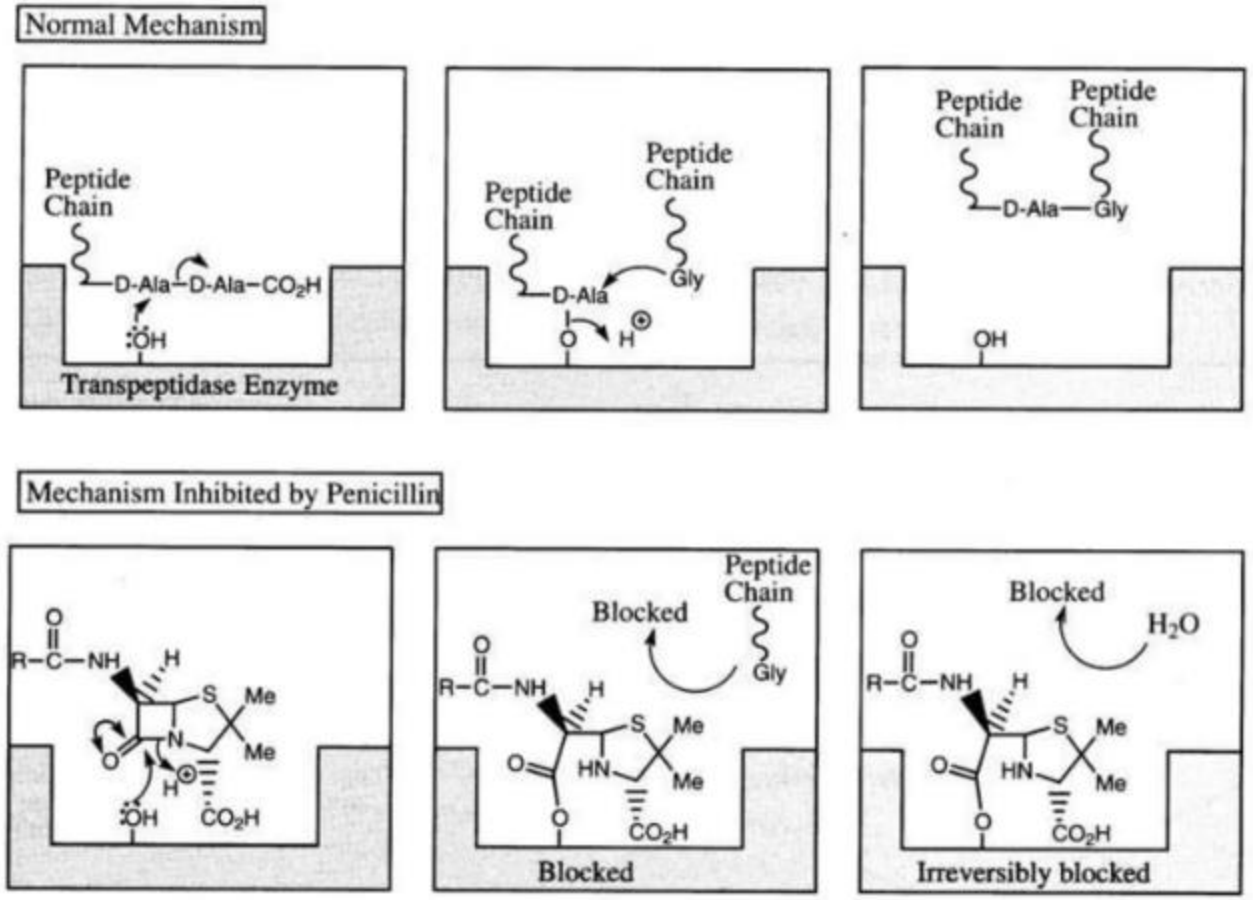
Beta lactam antibiotic

Transpeptidation mechanism



Beta lactam antibiotic

Transpeptidation mechanism



Beta lactam antibiotic

How do they work?

1. The β-lactam binds to Penicillin Binding Protein (PBP)
2. PBP is unable to crosslink peptidoglycan chains
3. The bacteria is unable to synthesize a stable cell wall
4. The bacteria is lysed

Beta lactam antibiotic

Amoxicillin

EFFECTIVE AGAINST:

- Gram positive + Gram negative bacteria

TREATMENT FOR:

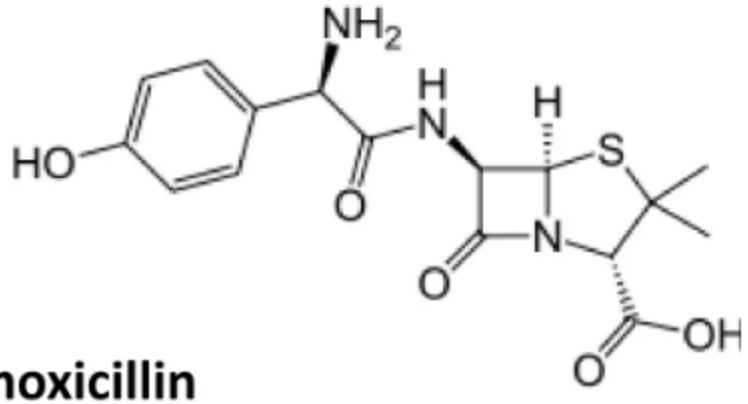
- Skin infection
- Sinusitis
- Urinary tract infections
- Streptococcal pharyngitis

CHARACTERISTICS:

- Broad spectrum
- Can be given orally and parenterally
- Prone to beta-lactamase

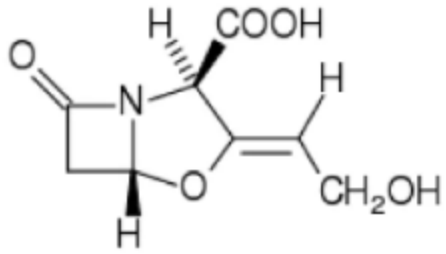
SIDE-EFFECTS:

- Rash, diarrhea, vomiting, nausea, edema, stomatitis, and easy fatigue.



Amoxicillin

+



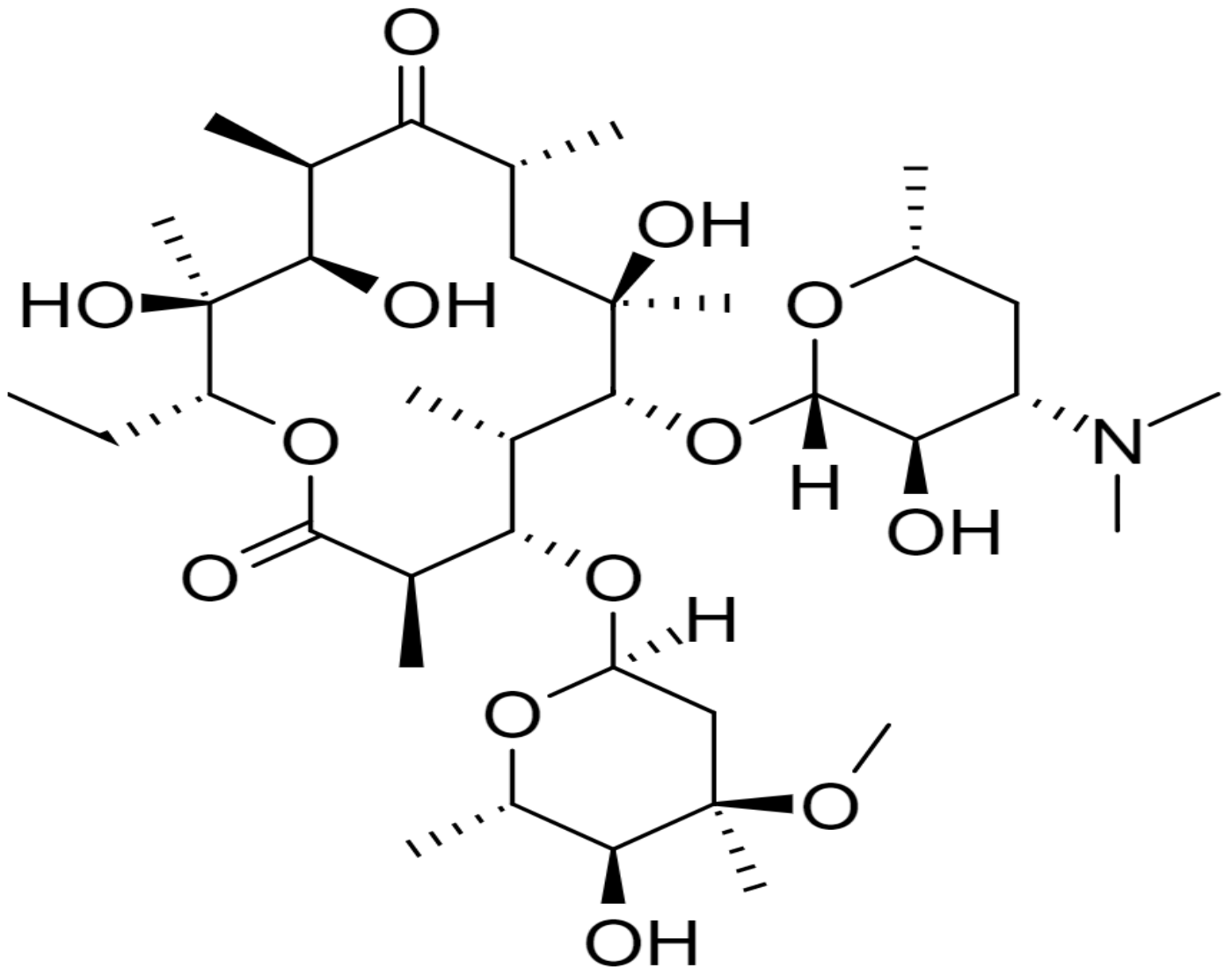
Clavulanic Acid

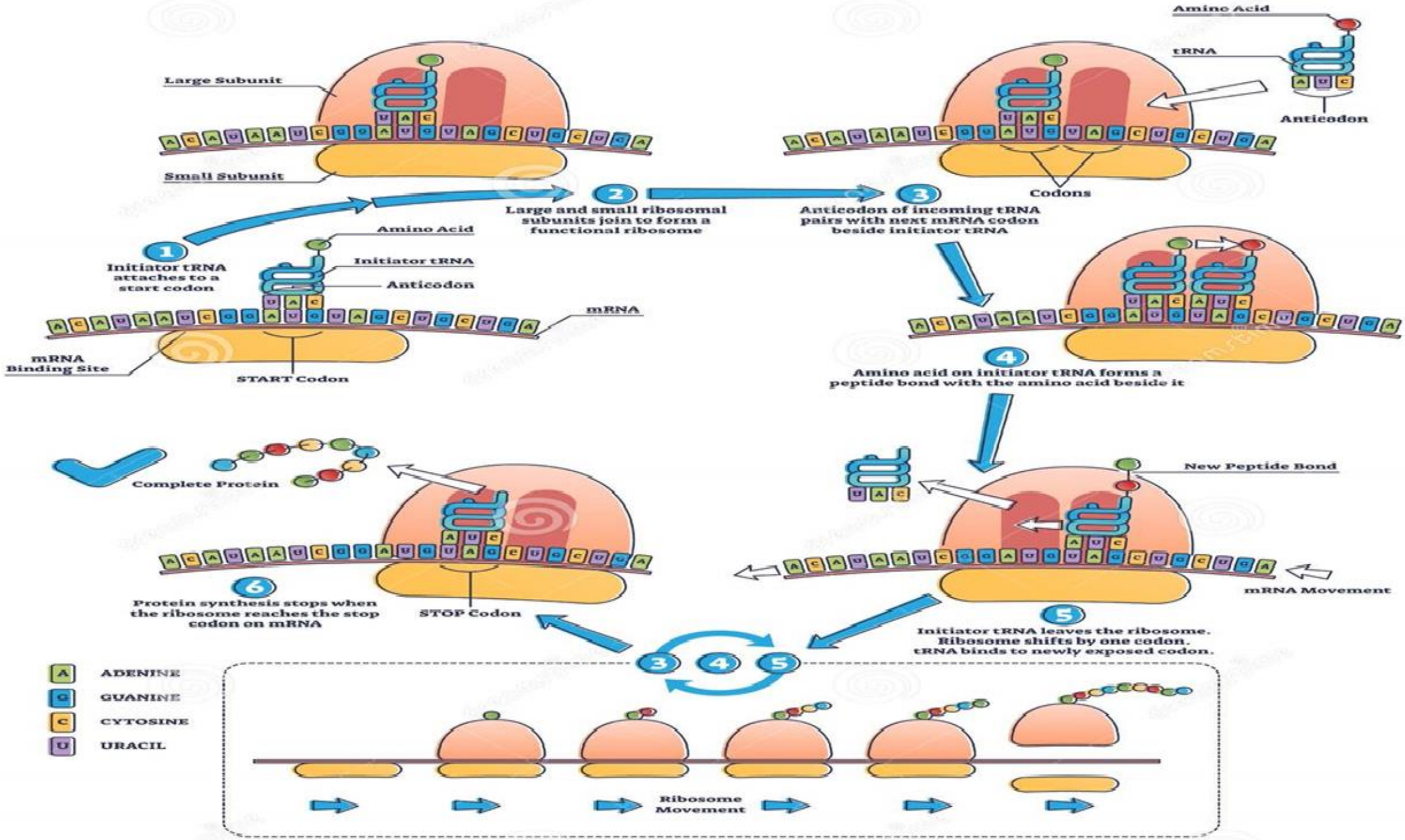
II

Augmentin

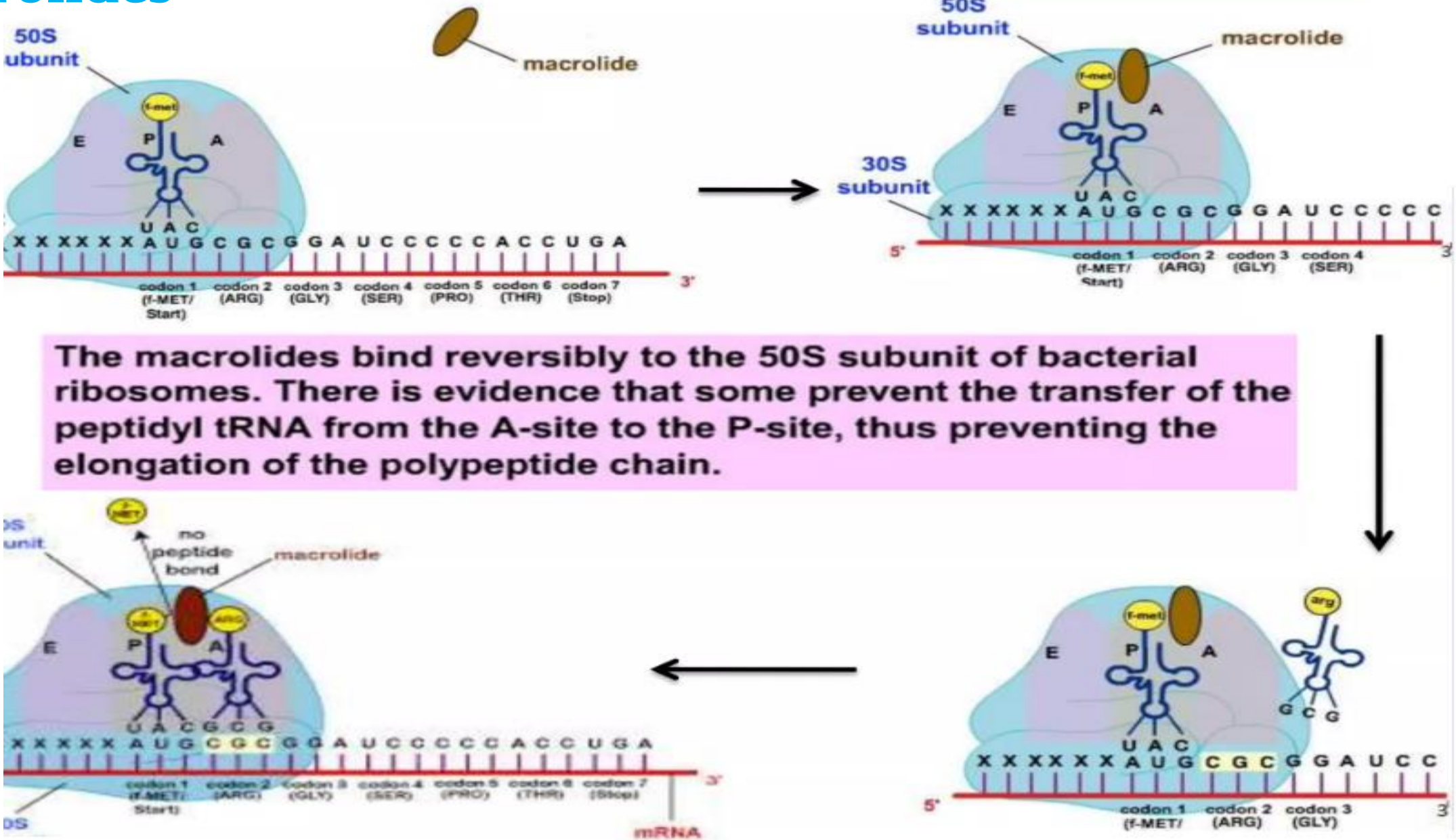
Macrolides

- Macrolides
  - Erythromycin
  - clarithromycin
  - Azithromycin
  - Telithromycin
  - Roxithromycin
  - Spiramycin
  - Rokitamycin




Large Subunit
Small Subunit
Amino Acid
tRNA
Anticodon
Codons
1
Initiator tRNA attaches to a start codon
Amino Acid
Initiator tRNA
Anticodon
mRNA
mRNA Binding Site
START Codon
2
Large and small ribosomal subunits join to form a functional ribosome
3
Anticodon of incoming tRNA pairs with next mRNA codon beside initiator tRNA
4
Amino acid on initiator tRNA forms a peptide bond with the amino acid beside it
New Peptide Bond
mRNA Movement
5
Initiator tRNA leaves the ribosome. Ribosome shifts by one codon. tRNA binds to newly exposed codon.
6
Protein synthesis stops when the ribosome reaches the stop codon on mRNA
STOP Codon
Complete Protein
3 4 5
A ADENINE
G GUANINE
C CYTOSINE
U URACIL
Ribosome Movement

Macrolides



The macrolides bind reversibly to the 50S subunit of bacterial ribosomes. There is evidence that some prevent the transfer of the peptidyl tRNA from the A-site to the P-site, thus preventing the elongation of the polypeptide chain.

Macrolides

- They bind to **50 S** ribosomal sub-unit of the sensitive bacteria (simple diffusion)

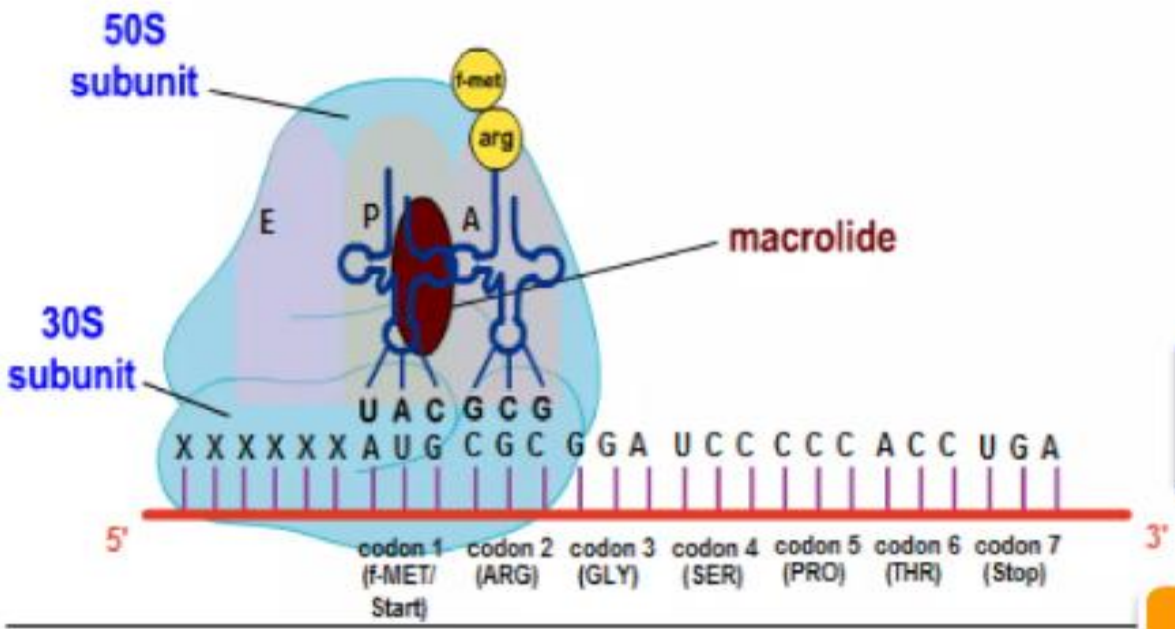
- They **block the aminoacyl translocation reaction** and **formation of initiation complex.**

↓

protein synthesis is inhibited

Macrolides

Mechanism of Action



Protein synthesis inhibitors

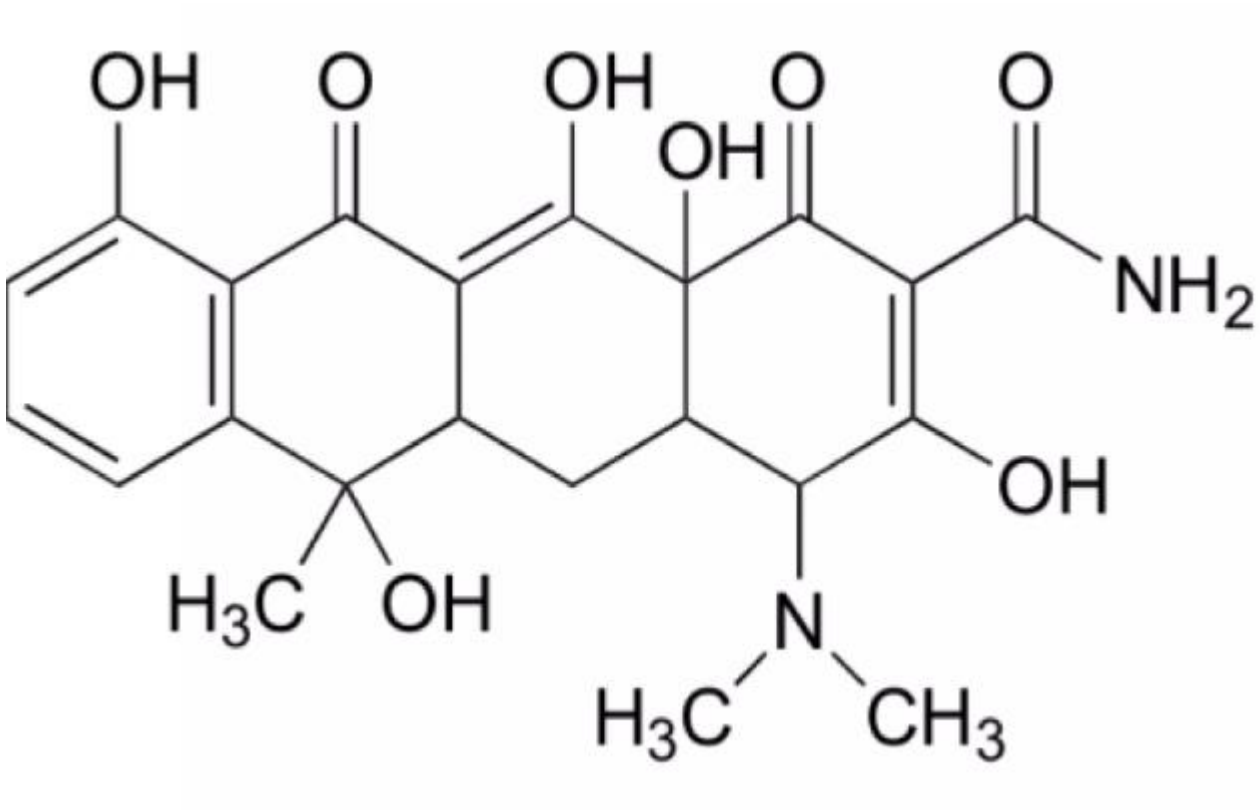
Bind to 50S ribosomal subunit

Inhibit polypeptide chain elongation and protein synthesis

Result in inhibition of growth and multiplication

- Preventing the Transfer of the Peptidyl tRNA from the A-site to the P-site.

Tetracycline



Tetracycline

Tetracyclines

⇩

actively taken up by susceptible bacteria

⇩

bind reversibly to 30s ribosomal subunit

⇩

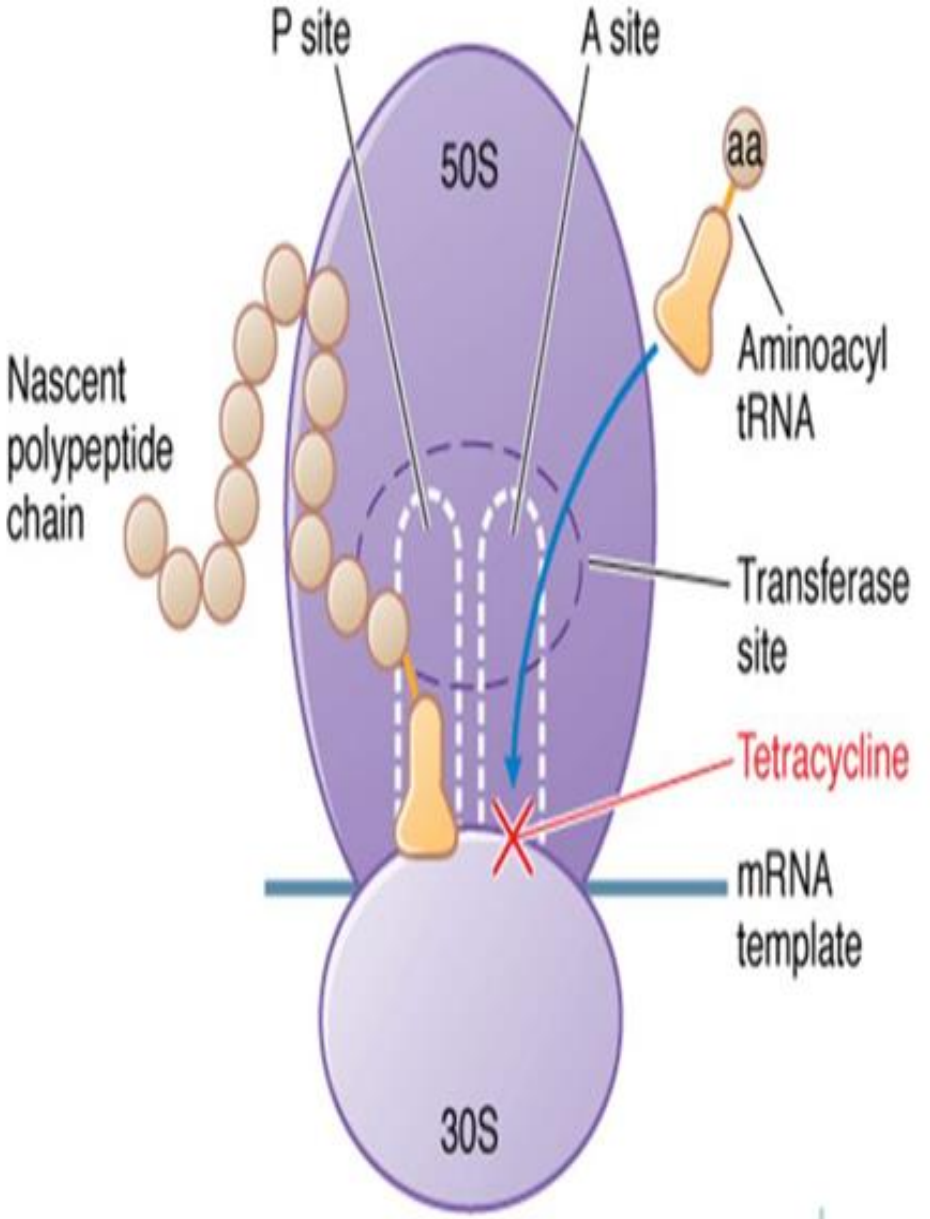
Prevent binding of aminoacyl tRNA to mRNA-ribosome complex

⇩

Prevent the addition of amino acid to the growing peptide chain

⇩

Inhibit bacteria protein synthesis (Bacteriostatic)



Quinolone

Fluoroquinolones

↓

Bind to the A-subunit of DNA gyrase (topoisomerase II type) enzyme

↓

Prevents the binding of substrate to the active site of DNA gyrase

↓

Absence of formation of enzyme – substrate complex

↓

Blockade of unwinding of double-stranded DNA into a single stranded structure

↓

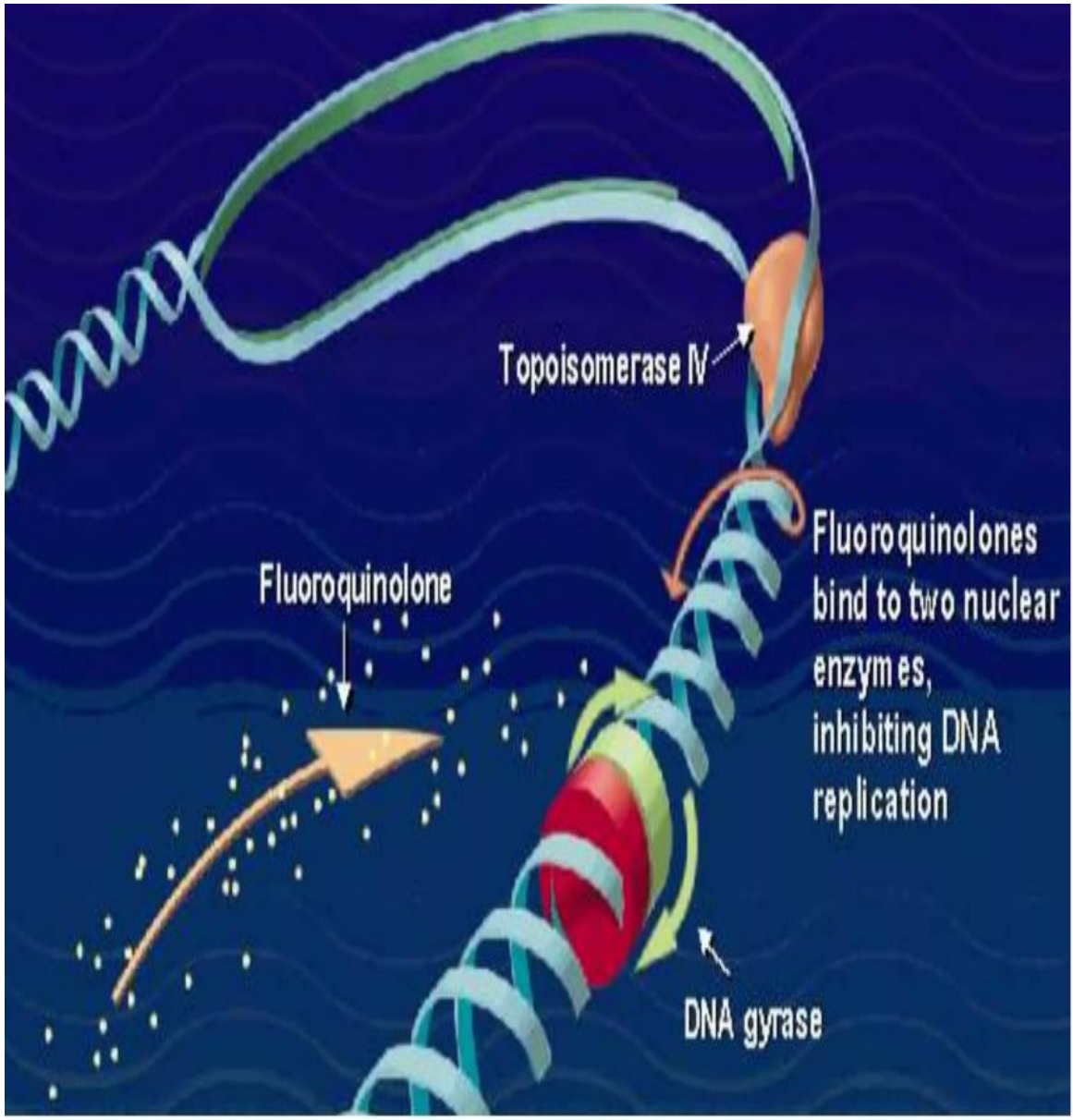
Prevention of synthesis of mRNA

↓

Inhibition of bacterial protein synthesis

↓

Antibacterial activity

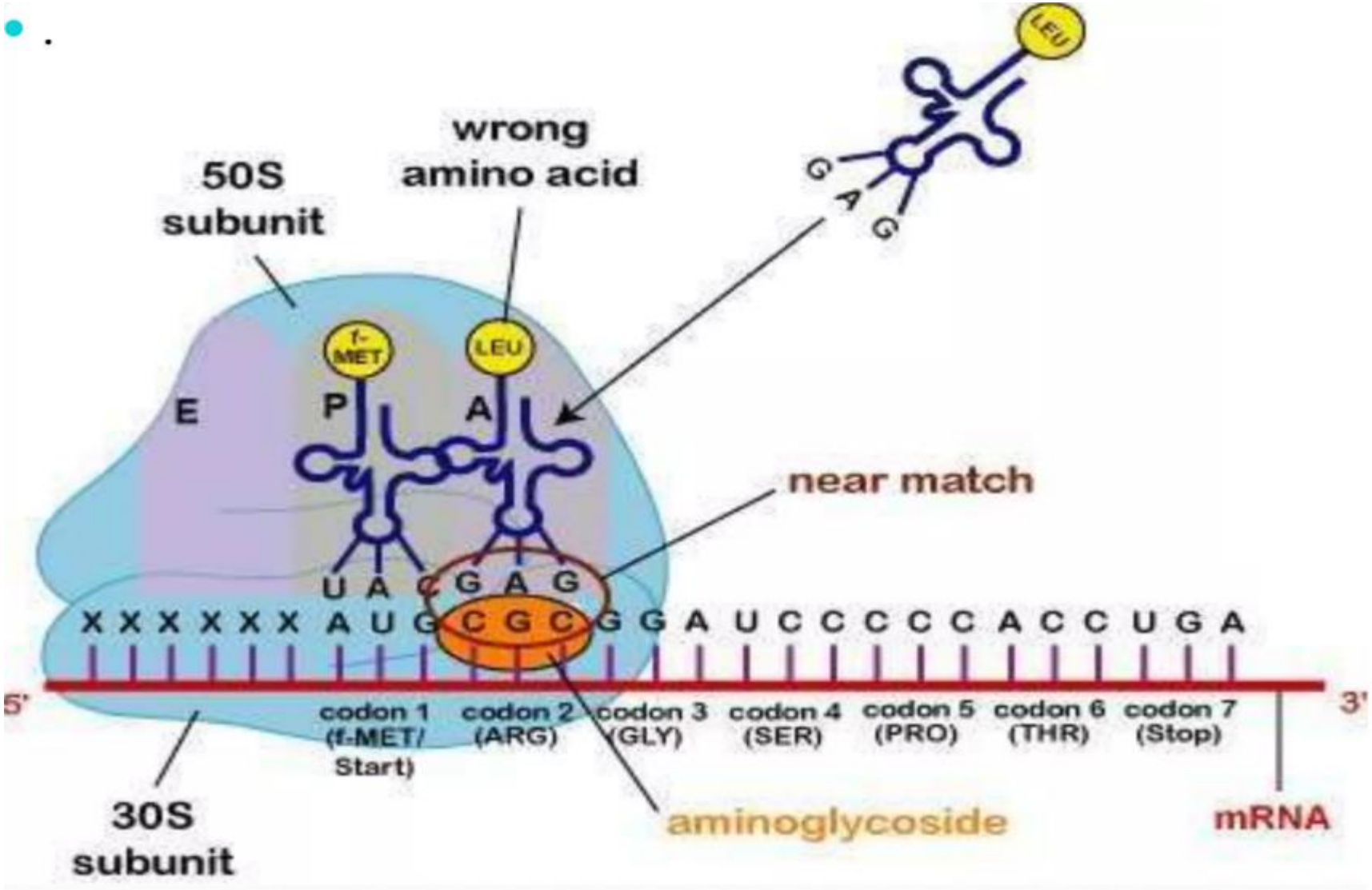


Aminoglycosides

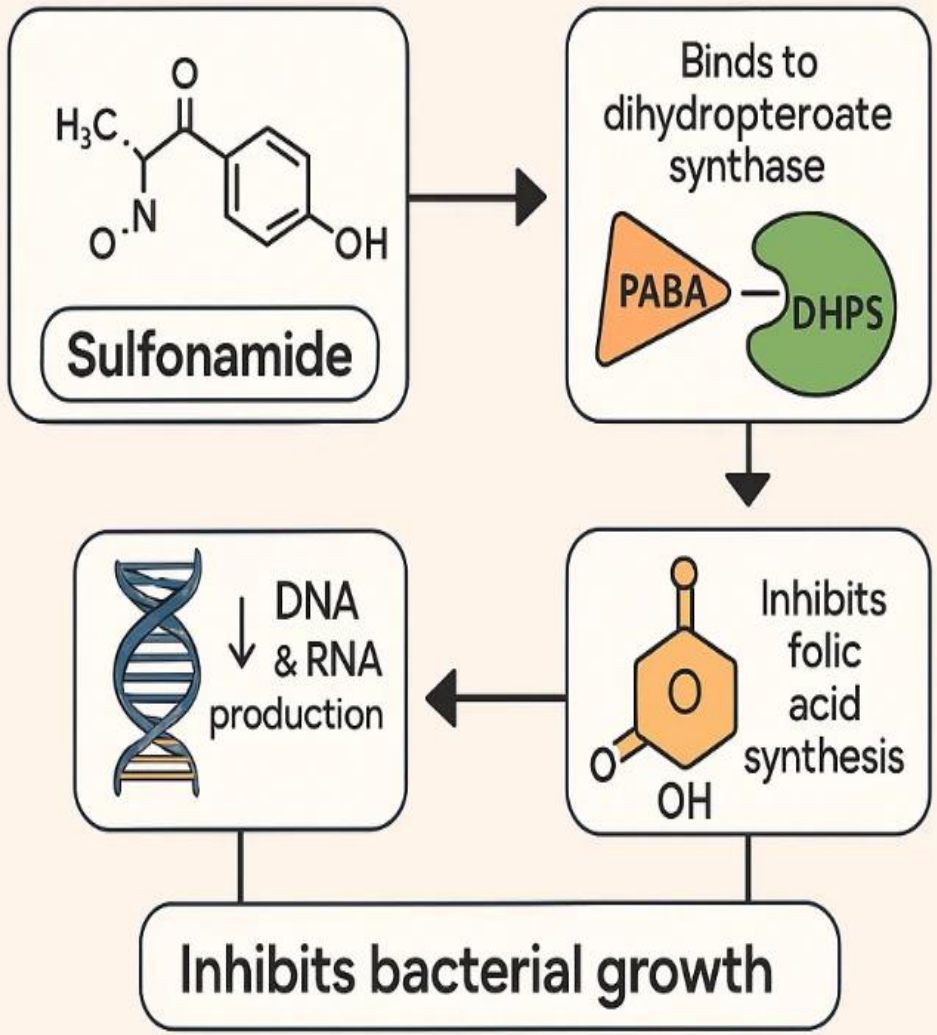
❑ Mode of action of Aminoglycosides :

- The aminoglycosides exhibit bactericidal effects as a result of several phenomena.
- Ribosomal binding on 30s and 50s subunits as well as the interface produces misreading; this disturbs the normal protein synthesis. Cell membrane damage also plays an integral part in ensuring bacterial cell death.
- The binding of streptomycin and other aminoglycosides to ribosomes also causes misreading mutations of the genetic code, apparently resulting from failure of specific aminoacyl RNAs to recognize the proper codons on messenger RNA (mRNA) and hence incorporation of improper amino acids into the peptide chain.

Aminoglycosides



Sulfonamides



1. **Analog of para-aminobenzoic acid (PABA)**

   Sulfonamides are structural analogs of **PABA**, a substrate for folic acid synthesis in bacteria.

2. **Inhibition of dihydropteroate synthase**

   Sulfonamides competitively inhibit the **dihydropteroate synthase** enzyme, blocking the conversion of PABA to dihydropteroic acid.

3. **Inhibition of folate synthesis**

   Without folic acid production, **tetrahydrofolate (THF)** is not formed, which is essential for **DNA synthesis and repair** in bacteria.

4. **Bacteriostatic effect**

   Inhibition of DNA synthesis halts bacterial cell division, making sulfonamides

Glycopeptides

➢ The **glycopeptide** antibiotics inhibit cell wall synthesis by binding strongly with cell wall precursors.

Mechanism of action

➢ Inhibition of cell wall synthesis in 'dividing' bacteria.

- Target : nascent peptidoglycan precursor units (lipid II)

↓

- Complexes formed via 5 hydrogen bonds with two carboxyl-terminal D-alanine residues of peptidoglycan precursors - acyl-D-ala-D-ala moiety

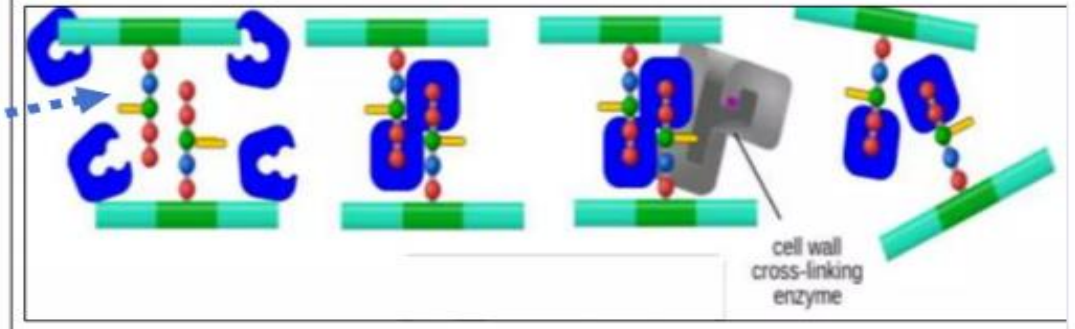
↓

Transglycosylation blocked

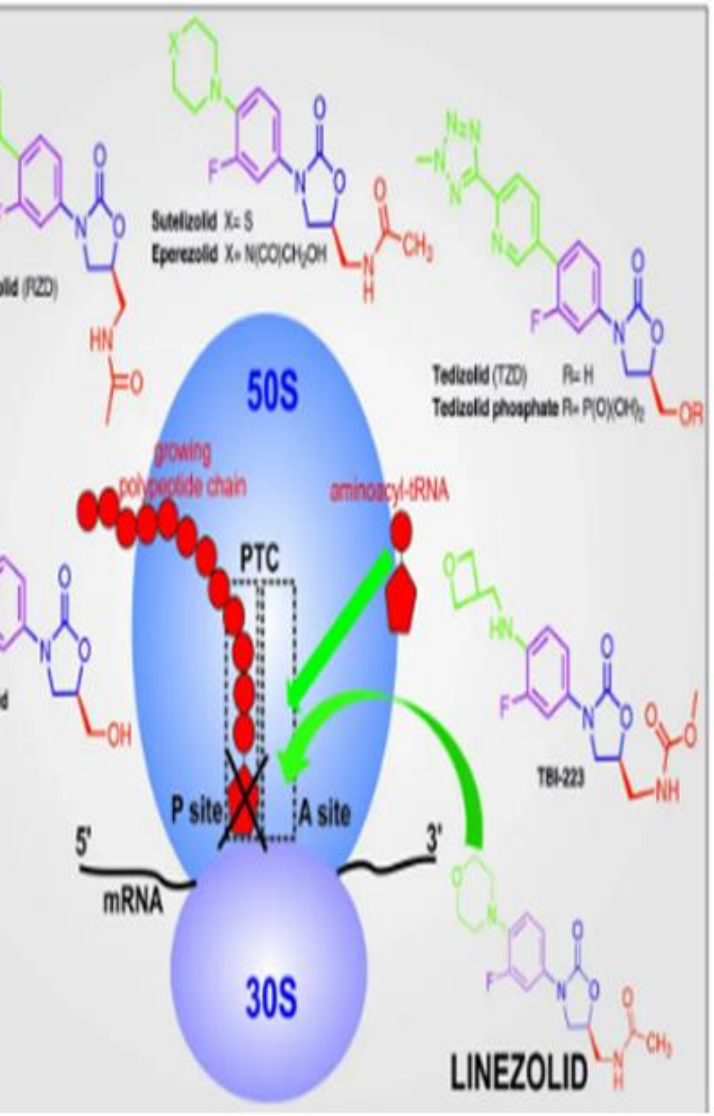
(blocks incorporation of disaccharide pentapeptide subunits into nascent peptidoglycan)

↓

- Prevents **cross linking** of peptidoglycans



Oxazolidinones



In the initiation step of bacterial translation, 50S subunit is associated with Met-t RNA and a complex composed of 30S ribosomal subunit and mRNA to form the functional initiation complex.

Linezolid interacts with the peptidyl-t RNA binding P site at the 50S subunit and it has no affinity to the 30S subunit. This interaction prevents binding of Met-t RNA to this site during the formation of the initiation complex.

By mechanism of Action

1. Cell wall synthesis inhibitors

-lactams (Penicillins, Cephalosporins, Carbapenems, Monobactams) and Glycopeptides (Vancomycin)

2. Protein synthesis inhibitors

Macrolides (Azithromycin), Aminoglycosides (Gentamicin), Tetracyclines (Doxycycline), and Oxazolidinones (Linezolid).

3. DNA/RNA synthesis inhibitors

Fluoroquinolones (Ciprofloxacin) and Rifamycins (Rifampin).

4. Metabolic Pathway Inhibitors

Sulfonamides.

By spectrum of activity:

Broad-spectrum

Effective against a wide range (Tetracyclines).

Narrow-spectrum

Effective against specific families (Penicillin G).

By Action type:

Bactericidal: Kill bacteria (Penicillins, Aminoglycosides).

Bacteriostatic: Stop bacteria from reproducing (Macrolides, Tetracyclines).