MEDICINAL CHEMISTRY - III

UNIT 1 NOTES

ANTIBIOTICS

- BETA LACTAM ANTIBIOTICS
- AMINOGOYCOSIDES
- TETRACYCLINES

IMPERFECT PHARMACY

CONNECT WITH US ON :

IMPERFECT PHARMACY APP

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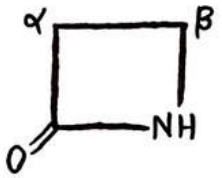
BETA-LACTAM ANTIBIOTICS

- β-Lactam antibiotics are the antibiotics agents that contains a common chemical structure called β-Lactam ring.
- This ring is essential for their antibiotic activity.



β-LACTAM RING

CLASSIFICATION OF β-LACTAM ANTIBIOTICS

According to our syllabus it is classified into 4 types:

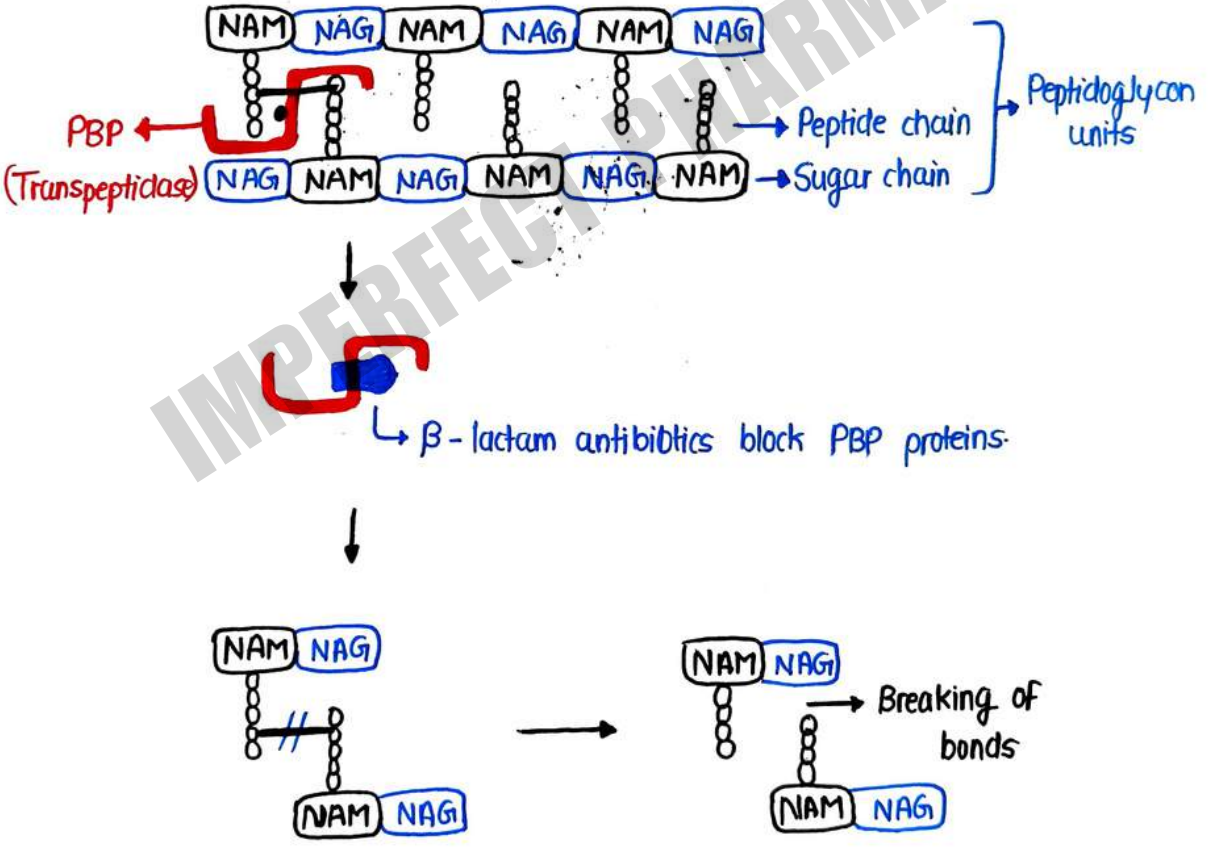
1. Penicillin
2. Cephalosporins
3. β-Lactamase Inhibitors
4. Monobactams

Mechanism Of Action

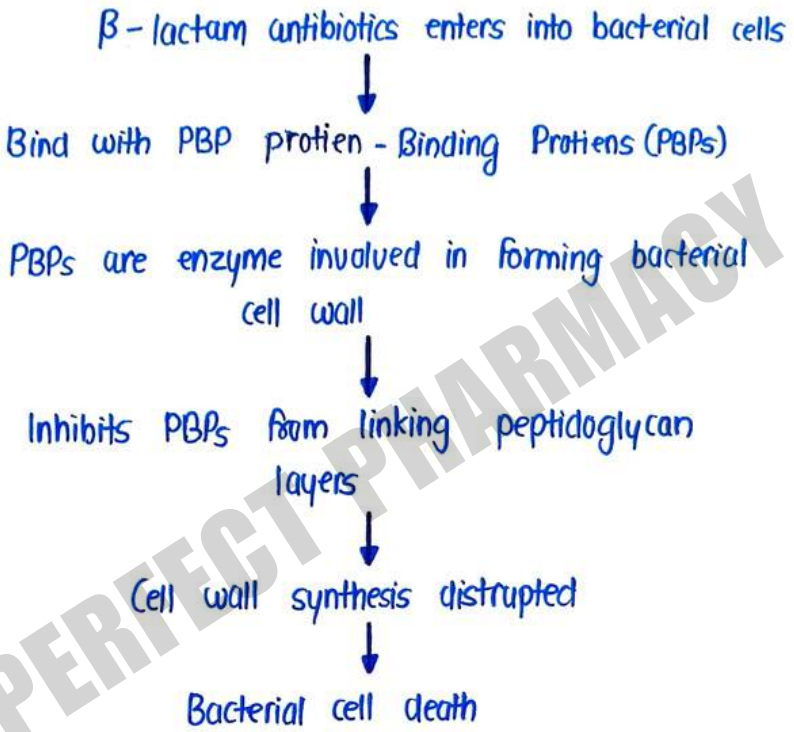
- β-lactam antibiotics kill bacteria by inhibiting the synthesis of bacterial cell wall, which is essential for bacterial survival.
- Bacterial cell made of peptidoglycon units.
- Peptidoglycon has two main parts:

① Sugar chains (NAG, NAM)

② Peptide chains

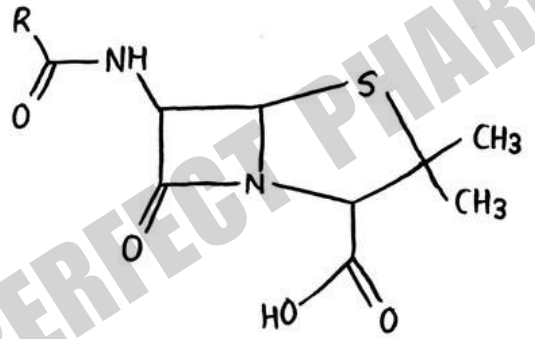


Mechanism Of Action (As Flowchart)



PENICILLIN

- Penicillin was the first antibiotic to be used clinically in 1941.
- It is derived from the mold Penicillium Notalum.
- It is used to treat bacterial infections by killing or inhibiting the growth of bacteria.
- It was discovered by Alexander Flaming in 1928 & marked by begining of modern antibiotics.



GENERAL STRUCTURE

MECHANISM OF ACTION

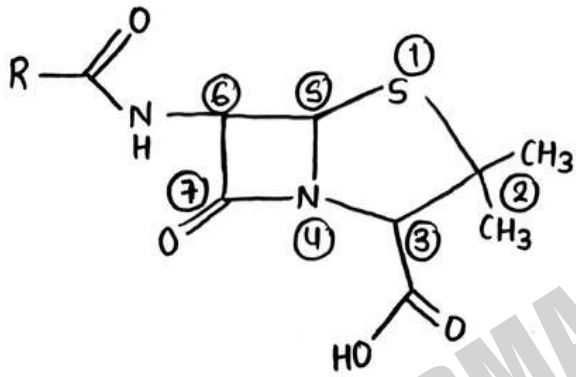
Same as mentioned in β-lactam Antibiotics

NOMENCLATURE

Nomenclature of penicillin is done by two types:

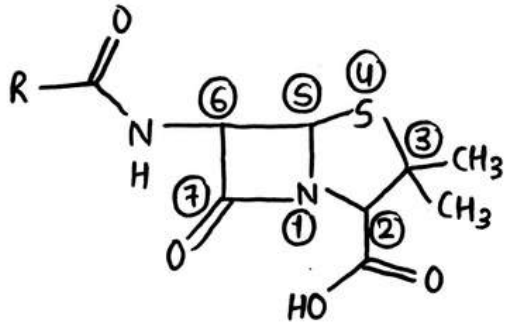
① Chemical Abstract System
② United State Pharmcopoeia (USP) System

① Chemical Abstract



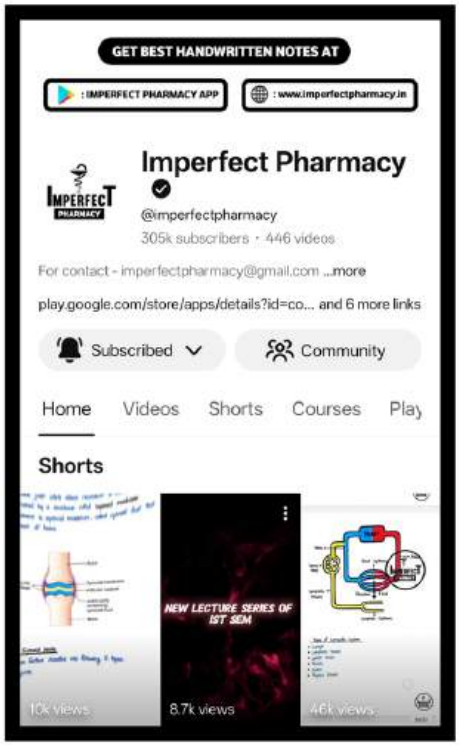
6- acylamino , 2,2- dimethyl -3 carboxylic acid

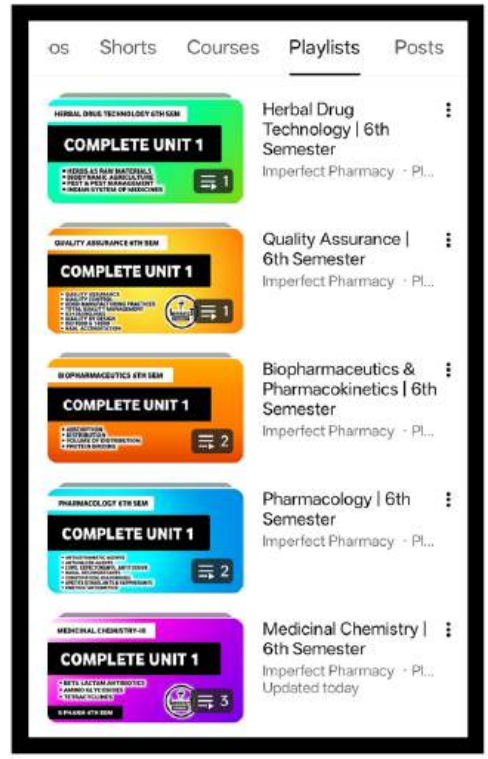
② United States Pharmacopoeia (USP) System



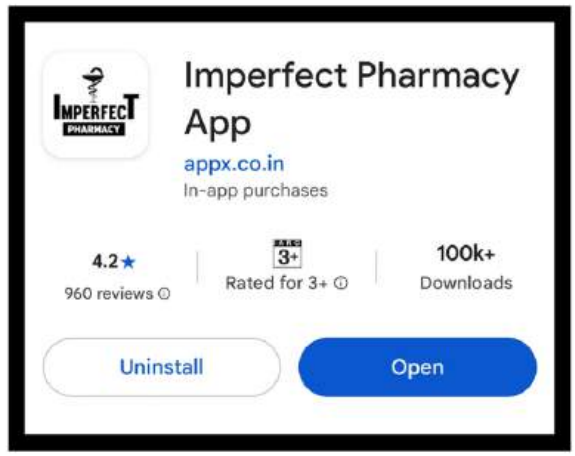
4 - thia - 1 - azabicyclo heptone

FOR LECTURE VIDEOS VISIT OUR CHANNEL

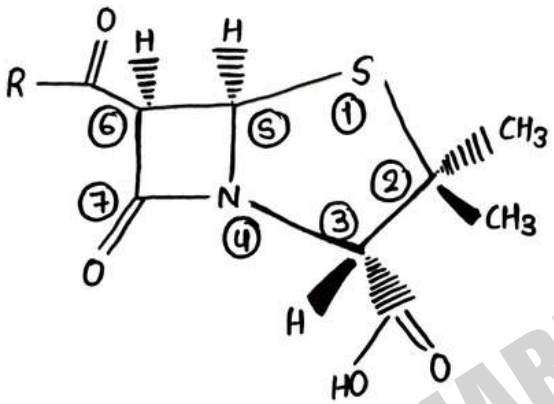




FOR MORE CONTENT : VISIT OUR APP



Stereochemistry Of Penicillin



① Core Structure

Penicillin contains :

- A β lactam ring
- A thiazolidine ring
- A side chain at 6th position.

② Chirality

Penicillin has 3 chiral centers at :

- C-3
- C-5
- C-6

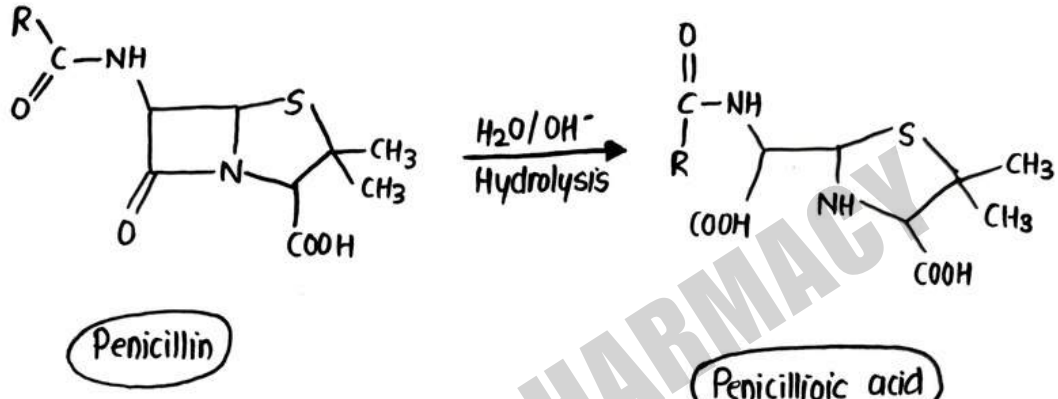
These centers have specific stereochemistry that must be preserved for antibiotic activity.

③ Configuration

- C_3 : R configuration
- C_5 : S configuration
- C_6 : R configuration

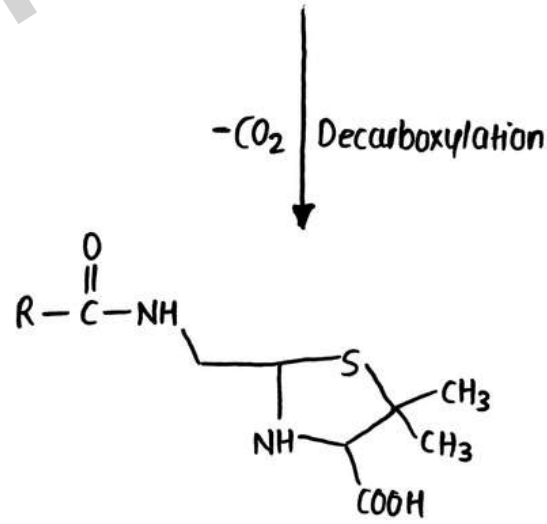
Chemical Degradation Of Penicillin

① Via Hydrolysis & Decarboxylation



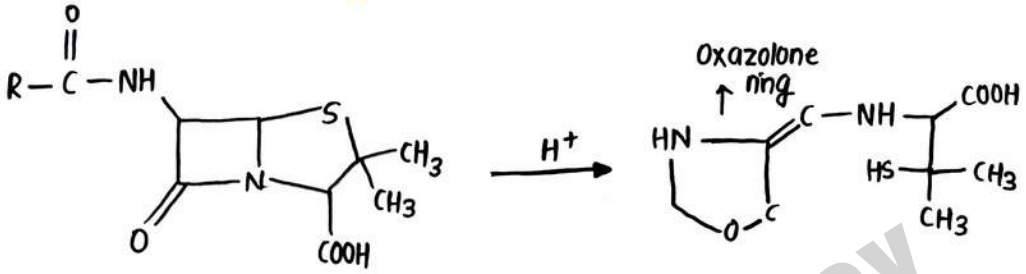
Penicillin

Penicillioic acid



Penilloic Acid

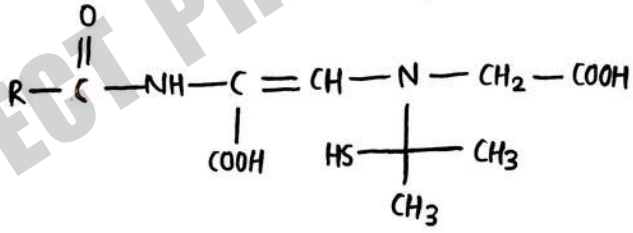
② In the presence of strong acidic solutions



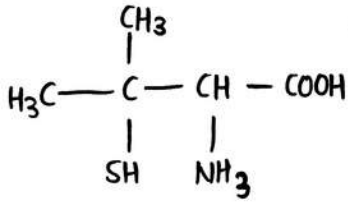
Penicillin

Penicillenic Acid

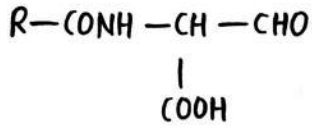
H_2O



Penamaldic Acid

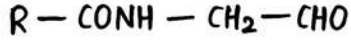


Penicillamine



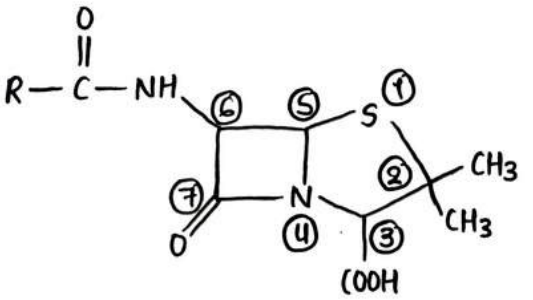
Penaldic Acid

$-CO_2$, H^+



Penicilloaldehyde

SAR OF PENICILLINS



① β-lactam ring

- The β-lactam ring is crucial for binding to bacterial penicillin-binding protiens.
- Opening or altering this ring destroys antibacterial activity.

② Thiazolidine Ring

- The 5-membered thiazolidine ring is fused to the β-lactam ring & helps maintain the correct shape for activity.

③ 6-Acyl side chain

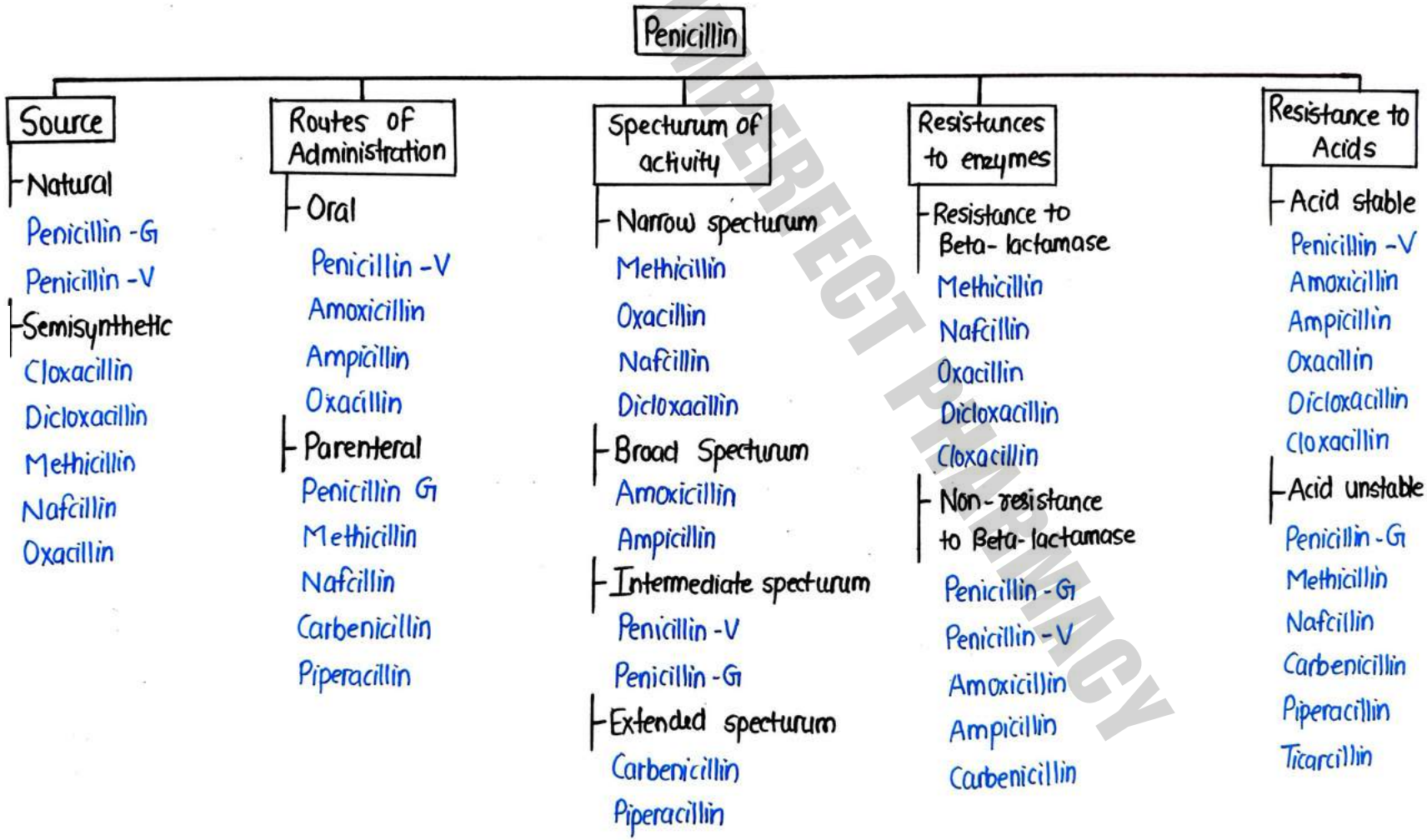
Modifying the side chain changes the specturum of activity, stability & resistance to β-lactamase.

- Electron withdrawing groups can increase acid stability.
- Bulky groups near the β-lactam ring can protect against β-lactamase enzymes.
- Polar groups can increase gram-negative activity.

④ Carboxylic Acid Group at C-3

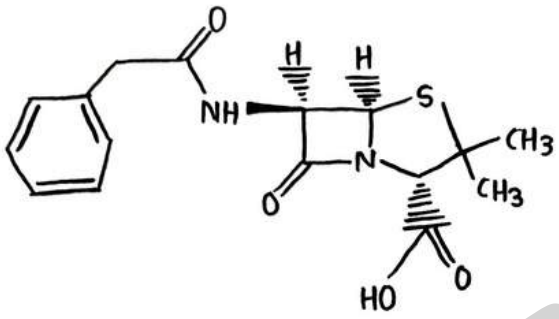
- This is important for binding to PBPs & cannot be removed.

Classification Of Penicillin



Some Important Penicillins

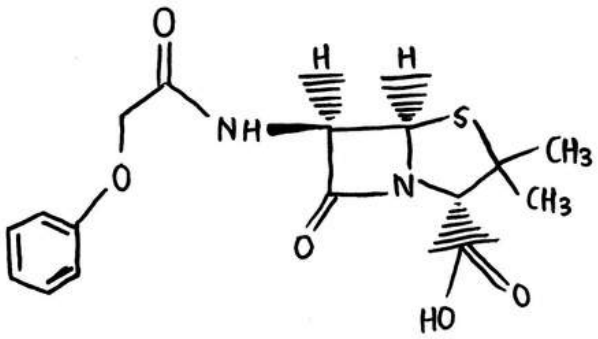
① Penicillin-G (Benzylpenicillin)



Uses

- Streptococcal infection
- Meningitis
- Syphillis

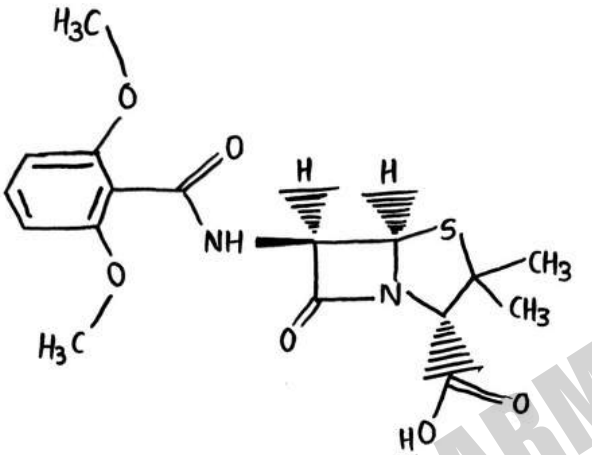
② Penicillin-V (Phenoxymethylpenicillin)



Uses

- Dental infection
- Streptococcal infection

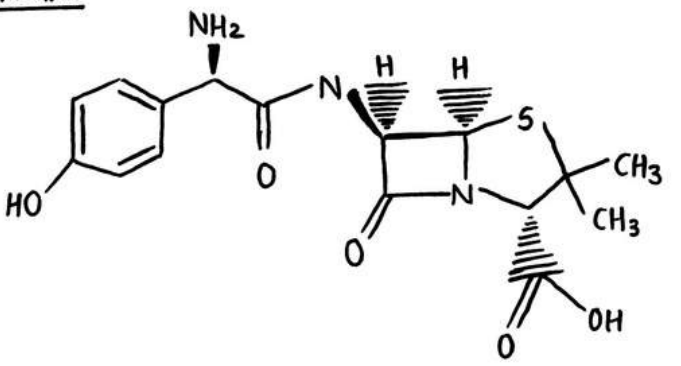
③ Methicillin



Uses

- Pneumonia
- Bone & Joint Infection
- Streptococcal Infection

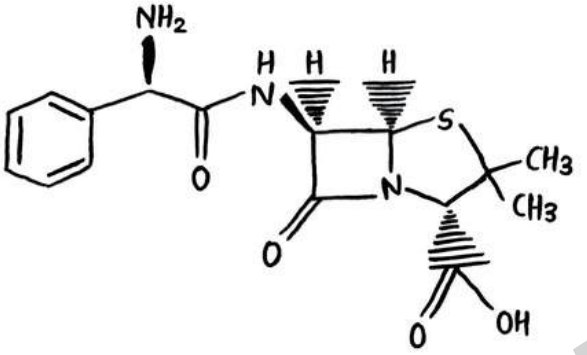
④ Amoxicillin



Uses

- Respiratory Tract Infection
- H. Pylori Infection
- Dental Infection

⑤ Ampicillin

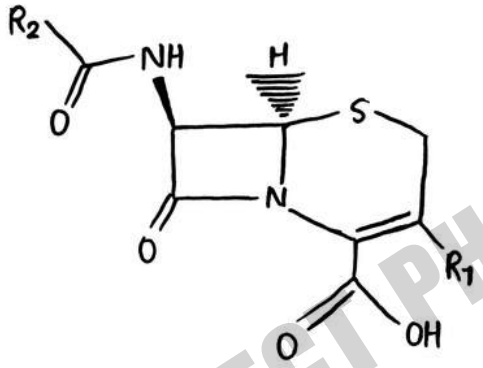


Uses

- Urinary Tract infection
- Gastrointestinal Infection
- Respiratory Tract Infection

CEPHALOSPORINS

- Cephalosporins belongs to group of β-lactam antibiotics that are structurally & functionally related to penicillins.
- They are derived from Cephalosporin-C, which was first isolated from the fungus Cephalosporium acremonium.
- Cephalosporin C is the prototype of Cephalosporins.



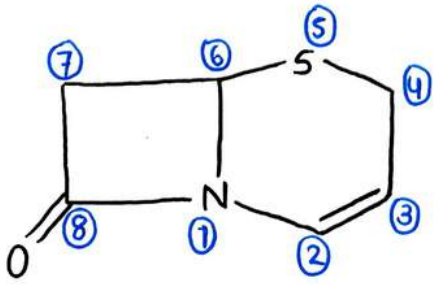
General structure of cephalosporins

MECHANISM OF ACTION

Same as mentioned in β-lactam antibiotics.

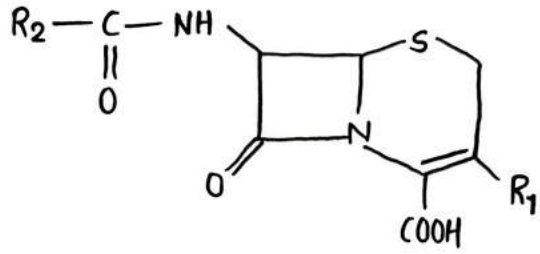
NOMENCLATURE

The general naming of Cephalosporins is 5-thia-1 azabicyclo octanes also refferred as Cephem



Cephem

Structure Activity Relationship (SAR)



① β-lactam ring

- It is essential for inhibitors penicillin-binding protiens (PBPs).
- Interference or opening the ring destroys antimicrobial activity.

② Dihydrothiazine ring

- It is fused with β-lactam ring to form the cephem nucleus.
- It provides more chemical stability than penicillin.

③ Acyl side chain on β-lactam ring

- It determines antibacterial specturum & β-lactamase resistance.
- Electron-withdrawing groups increase resistance to β-lactamase.
- Modifications can expand activity to include Gram-negative bacteria.

④ Substituent on the dihydrothiazine ring

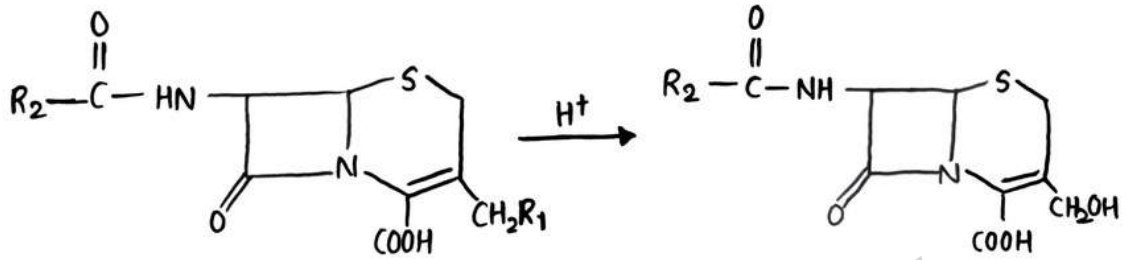
It affects pharmacokinetics, including:

- Oral absorption
- Metabolism
- Renal excretion

For example, an acetoxymethyl group at position 3 improves, Oral bioavailibility.

Chemical Degradation Of Cephalosporins

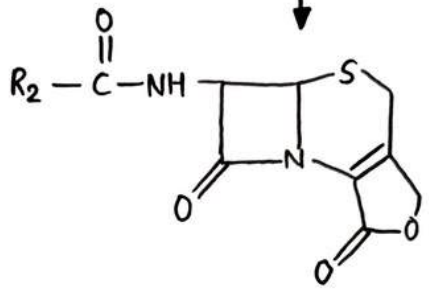
① In strong acid solutions



Cephalosporin

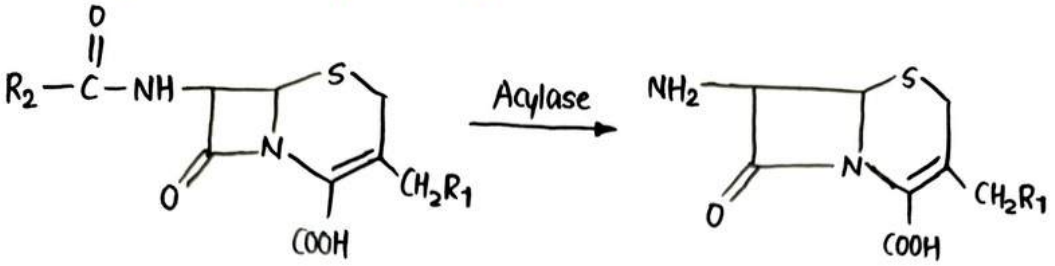
Desacetylcephalosporin

Lactonise Acid



Desacetylcephalosporin Lactone

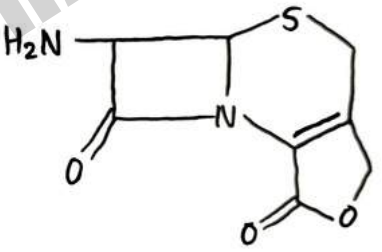
② In the presence of acylase enzyme.



Cephalosporin

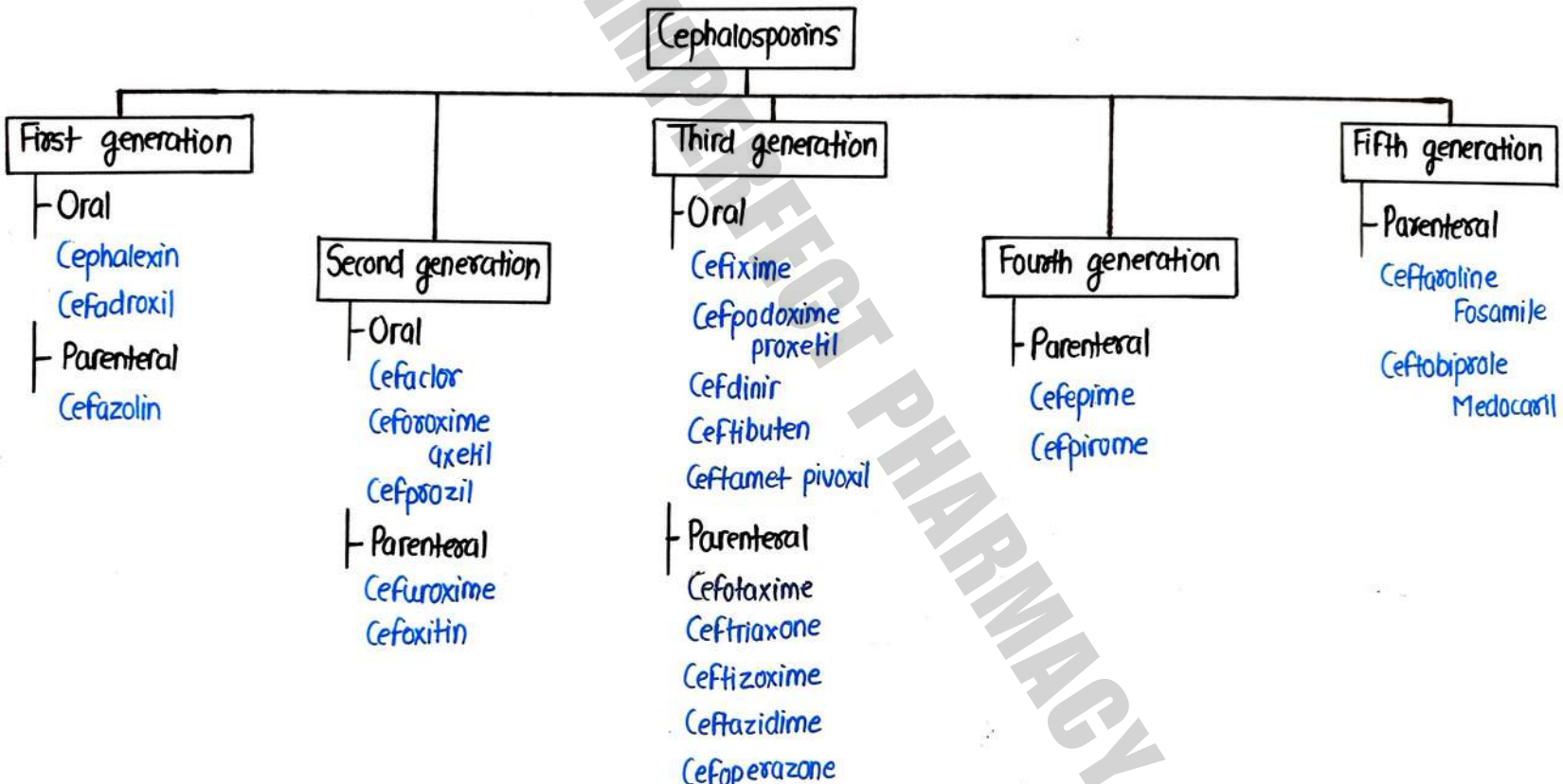
7-ACA
(Aminocephalosporin Acid)

H^+/H_2O



Desacetyl -7 - ACA lactone

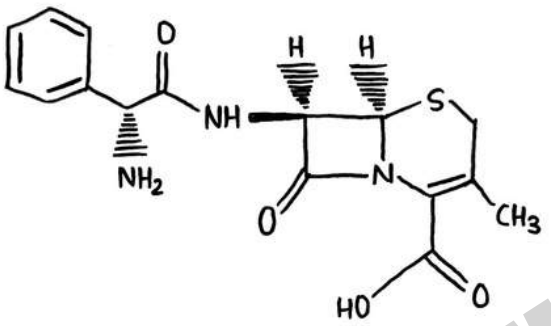
Classification Of Cephalosporins



Some Important Cephalosporins

① First Gen Cephalosporins

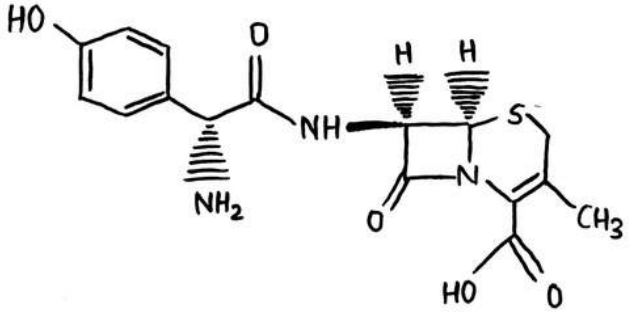
(a) Cephalexin



Uses

- Respiratory tract infections
- Urinary tract infections
- Dental infections

(b) Cefadroxil

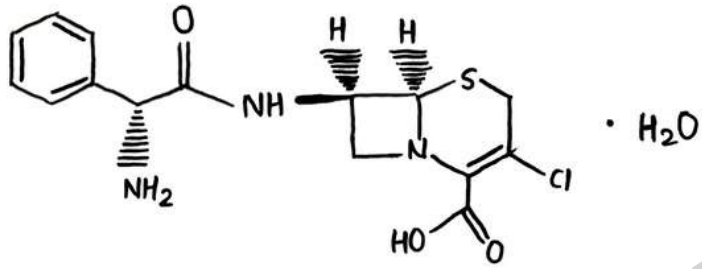


Uses

- Urinary tract infections
- Bone infections.

② Second Gen Cephalosporins

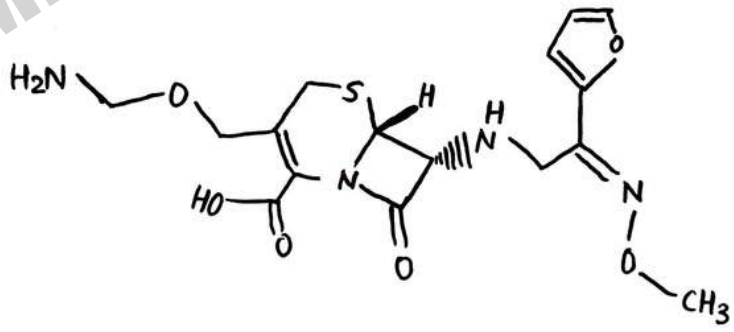
(a) Cefaclor



Uses

- Respiratory Tract Infections.
- Skin & soft tissue infections.
- Urinary tract infections.

(b) Cefuroxime

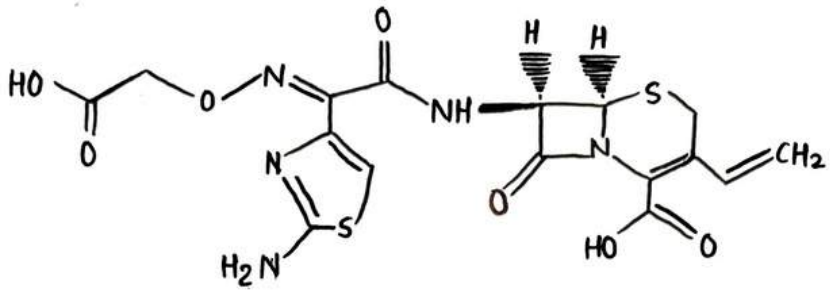


Uses

- Respiratory tract infections
- Ear infections
- Urinary Tract infections

③ Third Gen Cephalosporins

(a) Cefixime

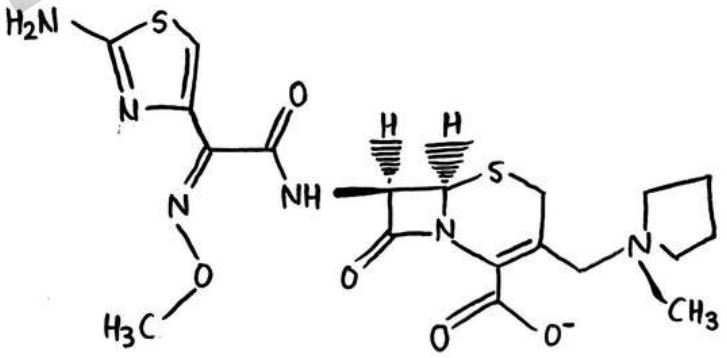


Uses

- Urinary tract infections
- Respiratory tract infections
- Sinusitis

④ Fourth Gen Cephalosporins

(a) Cefepime



Uses

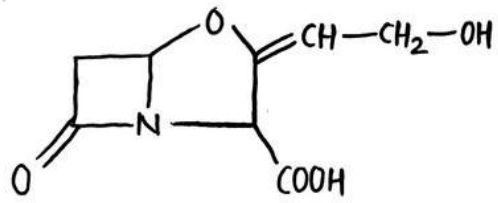
- Urinary tract infections
- Meningitis

β-Lactamase Inhibitors

- Beta- lactamase inhibitors are medications that block the activity of Beta-lactamase enzymes (an enzymes produced by certain bacteria to break-down beta- lactam antibiotics like penicillins & cephalosporins)
- They aren't antibiotics by themselves, but when combined with beta-lactam antibiotics, they protect the antibiotic from degradation, thus restoring or enhancing its antibacterial activity.
- It includes:

① Clavulanic Acid
② Sulbactam
③ Tazobactam

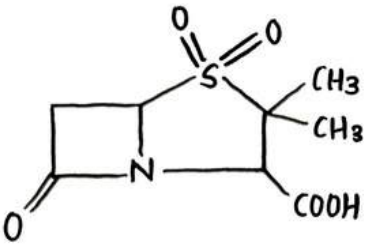
① Clavulanic Acid



Uses

- Pneumonia
- Sinusitis
- Urethritis

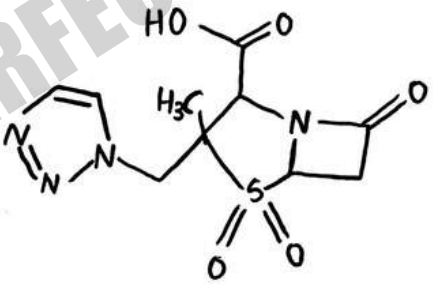
② SULBACTAM



Uses

- Urinary Tract infections
- Meningitis
- Sinusitis

③ TAZOBACTAM



Uses

- Pneumonia
- Sepsis
- Osteomyelitis

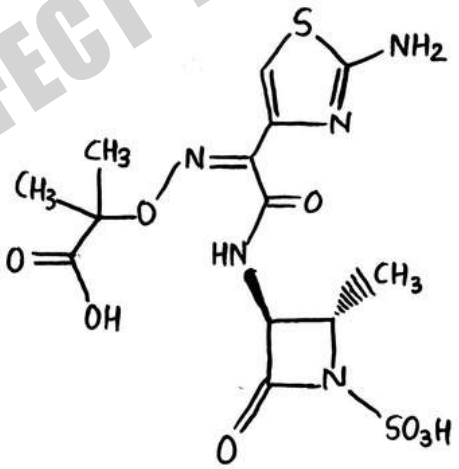
MONOBACTAMS

- Monobactams are class of beta-lactams antibiotics that contain a single beta-lactam ring, unlike penicillins & cephalosporins, which have fused ring structures.
- They work by against aerobic gram-negative bacteria.

MOA

Same as mentioned in Beta-lactam antibiotics.

① AZTREONAM



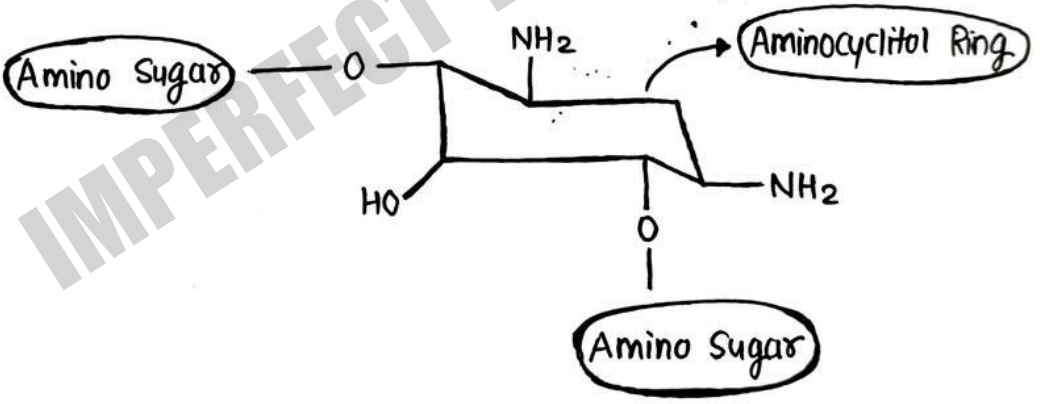
Uses

- UTIs
- Skin infections
- Lower Respiratory Tract Infections

AMINOGLYCOSIDES

- Aminoglycosides are a group of natural & semisynthetic antibiotics having aminocyclitol ring linked glycosidically to two or more aminosugar residues.
- They are primarily used to treat serious infections caused by Gram - negative bacteria.
- They are bactericidal in nature.
- These agents have broad antimicrobial activity but their use becomes limited because of its toxicity.

STRUCTURE & COMPOSITION



Mechanism Of Action

They binds with 30s ribosomes subunit of the bacterial ribosomes

↓

Causing misreading of mRNA & leading to the production of abnormal proteins

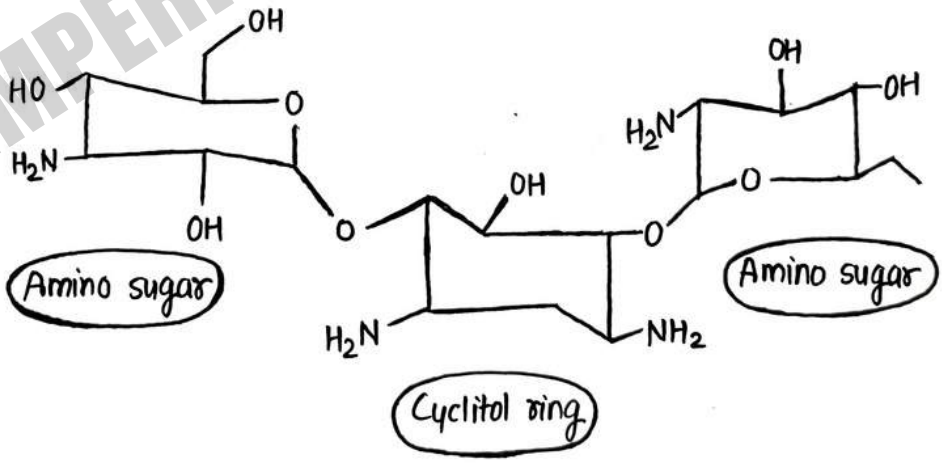
↓

Inhibition of protien synthesis

↓

Bactericidal effect/
Bacterial cell death

SAR Of Aminoglycosides



The SAR of Aminoglycosides can be understanding into two major parts :

① Cyclitol Ring

- This is the central ring present in most aminoglycosides (except streptomycin).
- This ring bind to the 30s units of ribosomes, which is essential for antimicrobial activity.
- Adding bulky or unnecessary groups can block ribosomes interaction and reduce activity.
- Amino sugars attach at position 1 & 3 of the ring - thier position matters for proper binding.

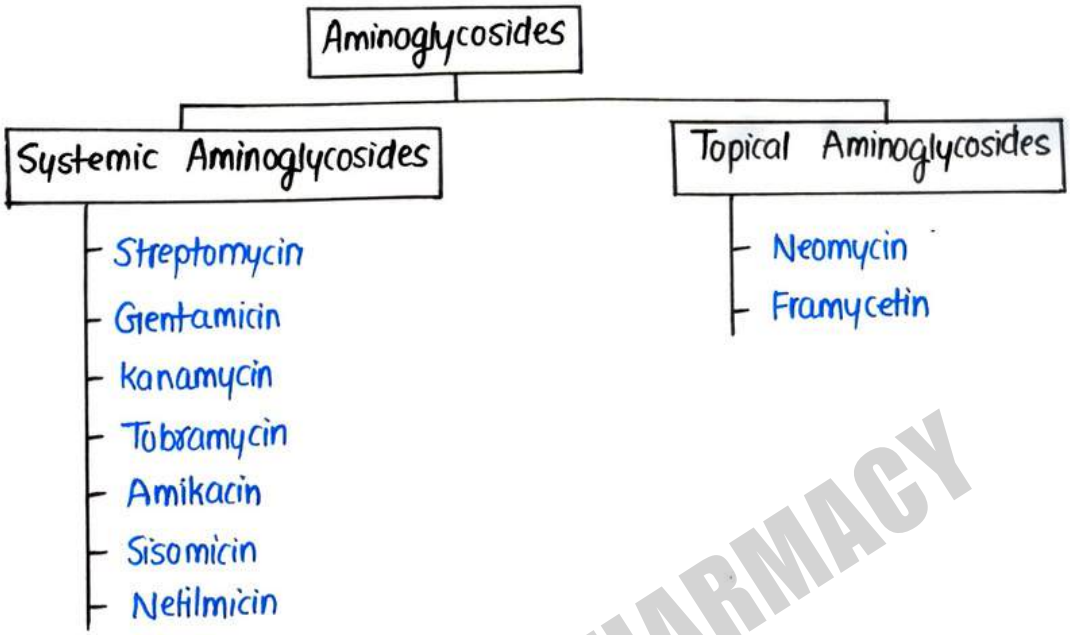
② Amino Sugar Groups

- These are attached to the cyclitol ring via glycosidic bonds.
- They contain amino ($-NH_2$) & hydroxyl ($-OH$) groups.
- These groups:
  - Enhancing binding to the ribosomes.
  - Provide positive charge, helping drug entry into the bacterial cell.

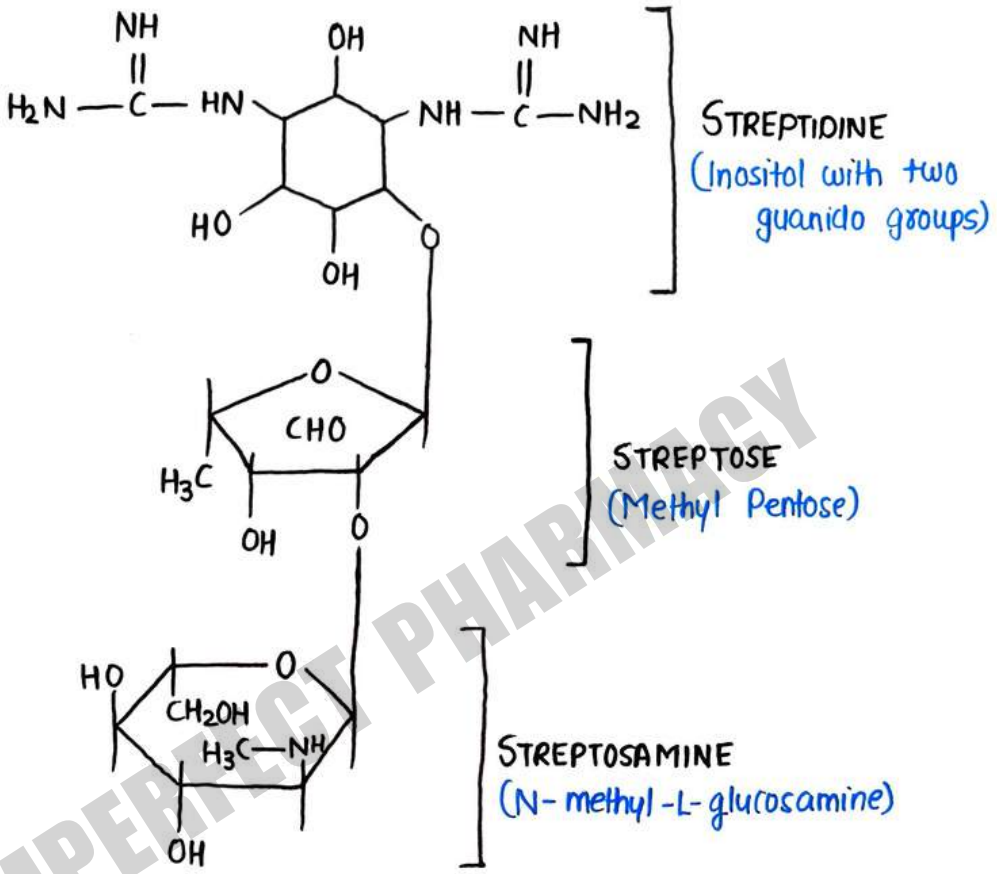
- However these amino sugar groups on the main targets of resistance enzymes (like acetyltransferase, phosphotransferases).
- Modifying these groups can increase resistance to enzyme degradation.

Example: Amikacin has a side chain that protects it from enzymes.

CLASSIFICATION



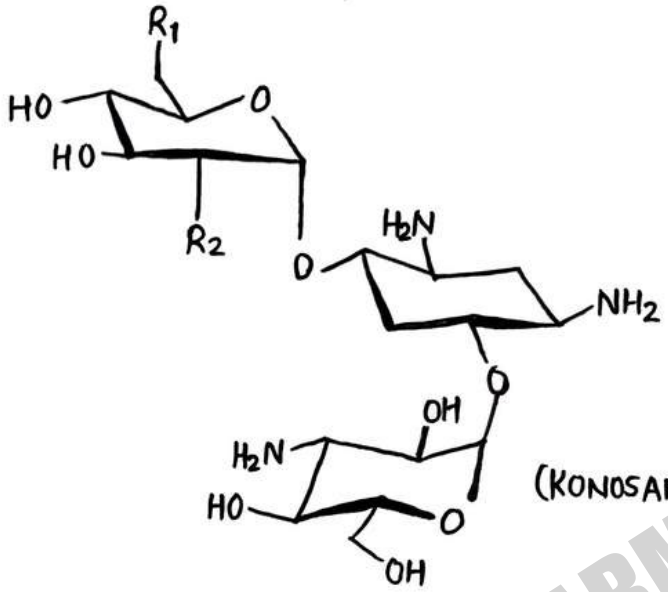
① STREPTOMYCIN



Uses

- Tuberculosis
- Cholera
- Meningitis

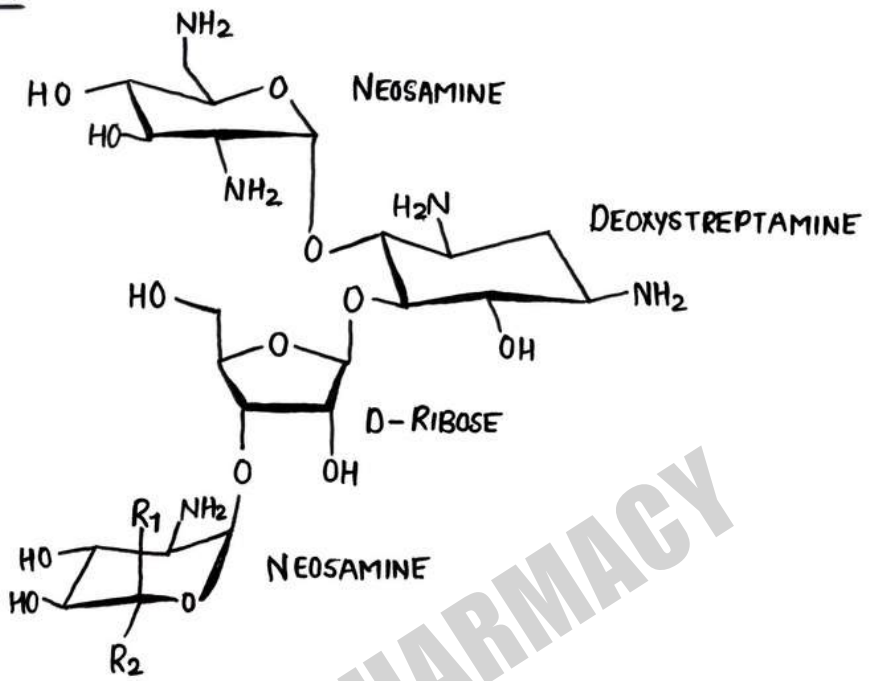
② KANAMYCIN



Uses

- Pneumonia
- UTIs
- Tuberculosis

③ NEOMYCIN



Uses

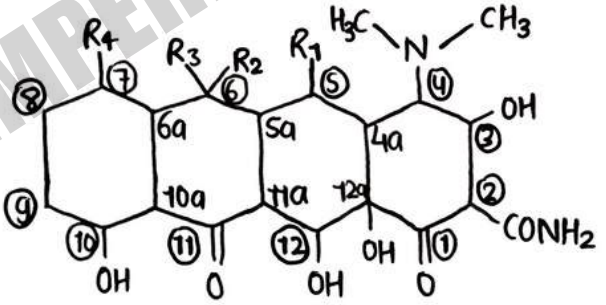
- Dermatitis
- Ulcers
- Burns & Wounds

TETRACYCLINES

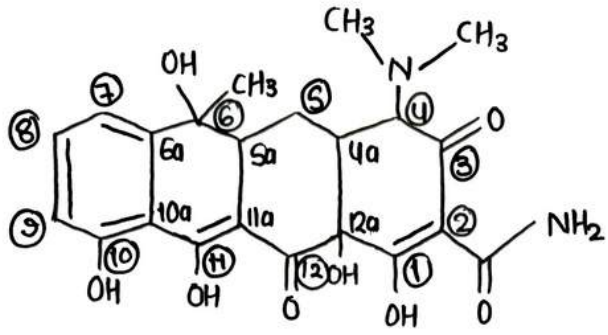
- They are potent broad spectrum antibacterial agents effective against gram-positive & gram-negative aerobic & anaerobic bacteria.
- They are widely used in both human & veterinary medicine due to their effectiveness against a diverse range of micro-organisms.
- In 1940s, a 71 years old Benjamin Minge Duggar head of the soil engineering department identified tetracycline as a therapeutic substance produced by soil micro-organisms.

CHEMICAL STRUCTURE

- Tetracyclines have four rings (tetracyclic) core structure & are characterized by a common octahydronapthacenes skeleton.
- Variations in functional groups at different positions on the core lead to different tetracycline derivatives.



STEREOCHEMISTRY OF TETRACYCLINES



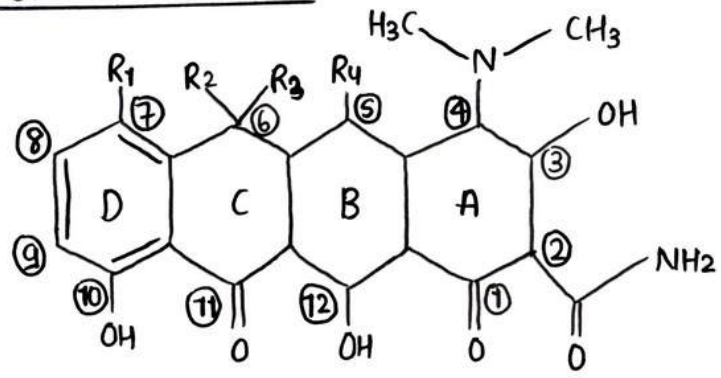
- Tetracyclines typically have 5 chiral centers located at C-4, C-4a, C-5a, C-6 & C-12a
- The C-4 position is especially important because:
- The 4s configuration is required for antibacterial activity
- Alteration in stereochemistry, especially at C-4 or C-6 can:
  - Reduce binding affinity
  - Impair antibacterial activity
  - Alter resistance profile

MOA

Here's is a step by step moa of tetracyclines:

- Entry into the bacterial cell via passive diffusion & active transport.
- Bind reversibly to the 30s ribosomes subunit.
- Prevent the attachment of aminoacyl-tRNA to the site of ribosome.
- This blocks the addition of new amino acids to the growing peptide chain.
- As a result, protein synthesis is halted.
- Since protein are essential for bacterial function & replication, this leads to bacteriostatic effect.

SAR Of Tetracyclines



① A - Ring

- The ketone group at C_1 is essential for activity : involved in ribosomal activity.
- The hydroxyl group at C_3 is important for potency & solubility.
- Amide group at C_2 is also essential for activity.

② B & C Ring

- Generally conserved for core structure integrity
- Maintain planarity, crucial for fitting into the ribosomal binding site.

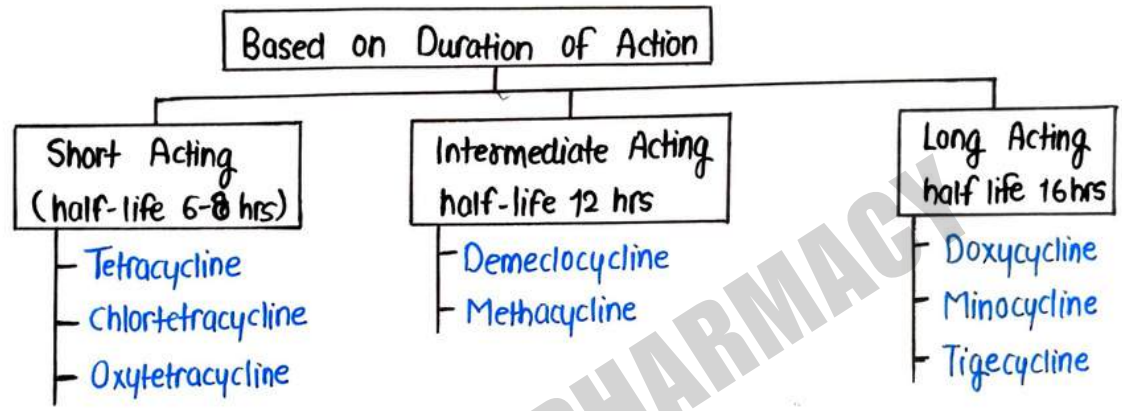
④ D - Ring

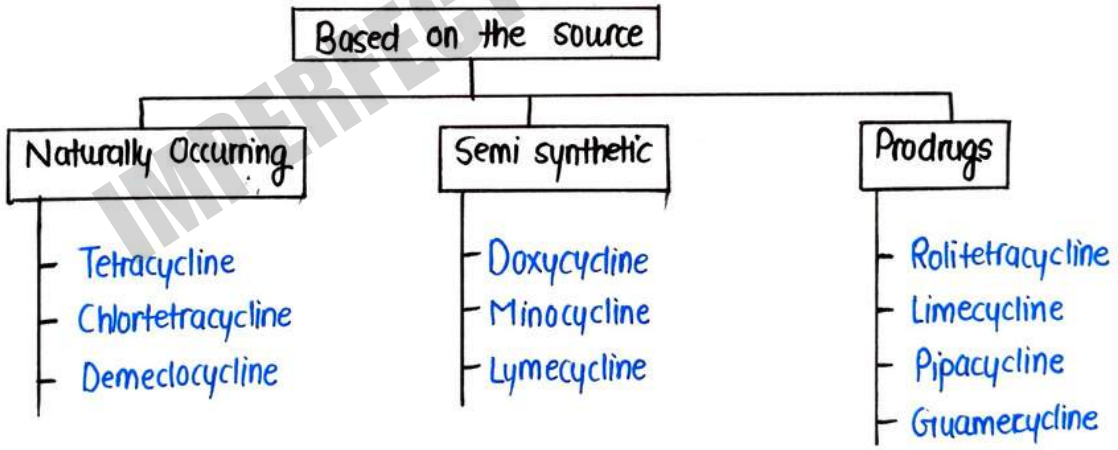
- $C_5 - C_9$ substitutions allowed for modifications without completely losing activity.
- These are the sites for structural changes to develop newer derivatives (e.g. Minocycline doxycycline).
- Modification here leads to improved lipophilicity & oral absorption.

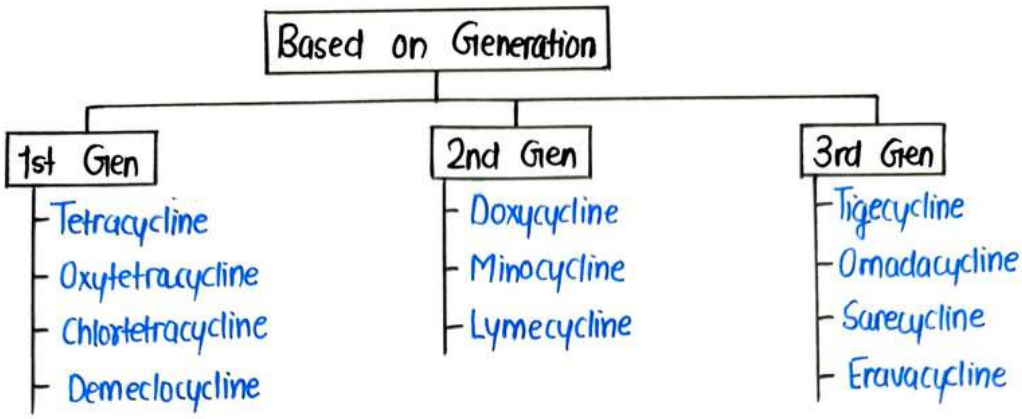
CLASSIFICATION

It can be classified on the basis of 3 types :

- Based on Duration of Action
- Based on Source
- Based on Generation



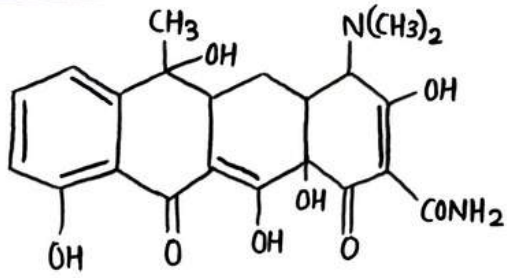




Drugs In Our Syllabus

- Tetracycline
- Oxytetracycline
- Chlortetracycline
- Minocycline
- Doxycycline

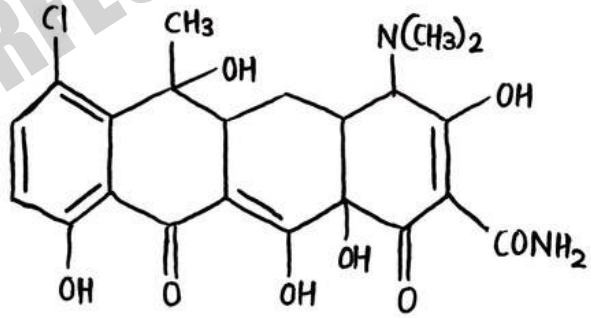
① TETRACYCLINE



Uses

- Syphillis
- Cholera
- Malaria

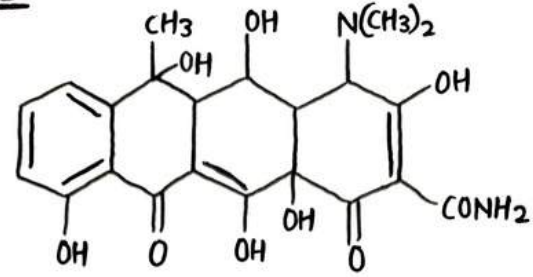
② CHLORTETRACYCLINE



Uses

- Pneumonia
- Chlamydia
- Urethritis

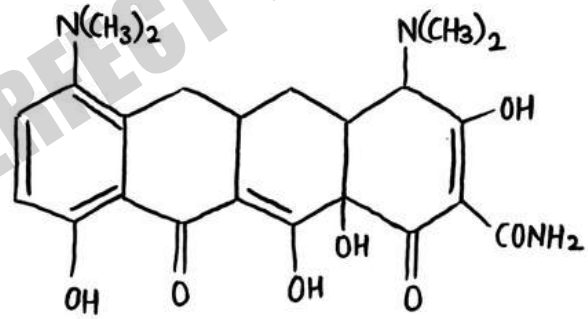
③ Oxytetracycline



Uses

- Malaria
- Chlamydia
- Pneumonia

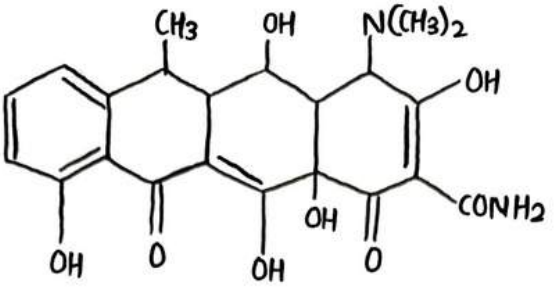
④ Minocycline



Uses

- Urinary tract infections
- Respiratory infections
- Skin diseases

⑤ Doxycycline



Uses

- Gonnorrhea
- Syphillis
- Malaria

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

IMPERFECT PHARMACY

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