UNIT - 1

Antibiotics

- Historically, an antibiotic was defined as a substance produced by a microorganism which can prevent the growth of, or are fatal to other microorganisms even at low concentrations.
- Antibiotics can either kill or inhibit the growth of other bacteria.
- One thing to keep in mind that there is a difference in antibiotic and antibacterial. Both work against bacteria but antibiotics are used only for medicinal purpose but antibacterials also include soaps, detergents, disinfectants, etc.

- Classification

1) Based on their mechanism of action.
   i) Inhibit cell wall synthesis
      e.g. penicillins, cephalosporins
   ii) Inhibit protein synthesis
      e.g. Tetracyclins, chloremphenicol

2) Based on their range of action

Broad spectrum
- effective against gram +ve and gram -ve.
e.g. tetracycline
chloramphenicol

Narrow spectrum
- effective against gram +ve bacteria.
e.g. Penicillin
erythromycin.

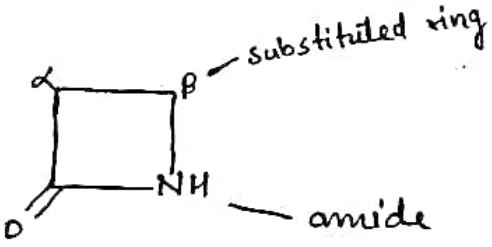
3) Based on their type of action

Bacteriostatic
- inhibit the growth of bacteria.
e.g. Tetracyclines
chloramphenicol

Bactericidal
- Kills bacteria
e.g. Penicillins
cephalosporins.

β-Lactam Antibiotics

- The β-Lactam antibiotics belong to a broad category in which all the antibiotics have a β-lactam nucleus in their molecular structure. Members of this antibiotic class possess a highly reactive 3-carbon and 1-Nitrogen ring.
- They are the most widely used among all the antibiotics and act by inhibiting the cell wall synthesis of bacteria.
- The β-lactam antibiotics are generally given with β-lactamase inhibitors because the bacteria obtain resistance to β-lactam antibiotics by producing β-lactamase enzyme which attacks the β-lactam ring.



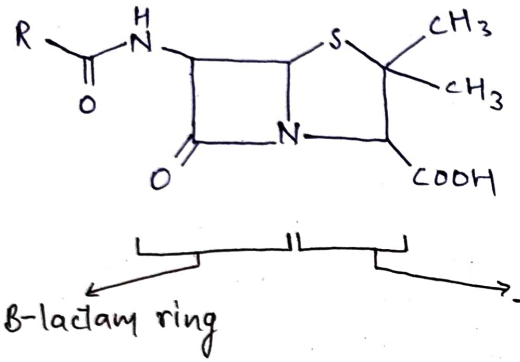
β-lactam ring

Classification

- **β-Lactam Antibiotics**
  - **Penicillins**
    - Penicillin-G
    - Penicillin V
    - Oxacillin
    - Amoxicillin
    - Methicillin
    - Cloxacillin
    - Dicloxacillin
    - Azocillin
    - Cefoxitin
    - Piperacillin
    - Carbenicillin
  - **Cephalosporins**
    - 1st generation
      - Cephalexin
      - Cefadroxil
    - 2nd gen.
      - Cefazolin
      - Cefamandol
    - 3rd gen.
      - Cefaclor
      - cefoperazone
    - 4th gen.
      - Cefapime
      - Cefozopran
  - **Monobactams**
    - Aztreonam
    - Nacardicin A
  - **Carbapenems**
    - Biapenam
    - Doripenam
    - Imipenem

Penicillin

Penicillin is the first antibiotic to be discovered.



- The two rings together form 6-amino-penicillanic acid. All penicillins are composed of this, with different side chains.
- The side chains determine the antibacterial and pharmacological properties.

History

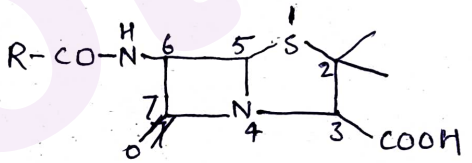
- Penicillin was discovered by Alexander Fleming in 1928, however, its invention was first reported in 1929 and was clinically used in 1941.
- He accidentally obtained this antibiotic from a fungus dwelling in soil, called Penicillium notatum.

Nomenclature

There are two types of numbering depending upon whether which atom is assigned 1st position.

1) Chemical Abstract System

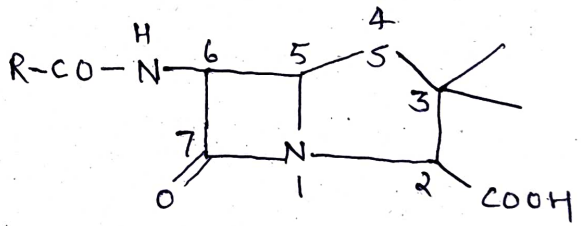
Numbering starts from Sulfur atom.



penicillin name → 6-acylamino-2,2-dimethyl-3-carboxylic acid.

2) United States Pharmacopoeia System

Numbering starts from Nitrogen atom.



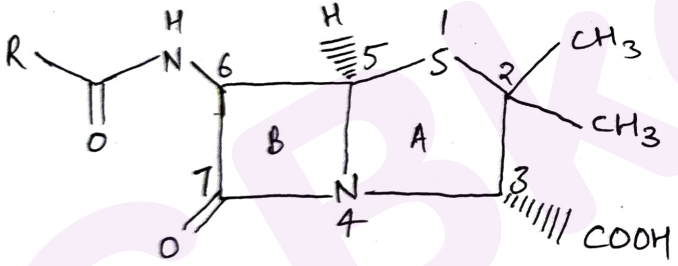
penicillin name

4-thia-1-azabicyclo heptone

Stereochemistry

- The penicillin molecule contains three chiral carbon atoms at C-3, C-5 and C-6.
- All natural and synthetic penicillins have the same absolute configuration about these three centres.
- The atoms composing of the 6-amino-penicillanic acid are biosynthetically derived from two amino acids, L-cysteine and D-valine.

SAR



At position-1 → When the sulfur atom of thiazolidine ring is oxidised to sulfone or sulfoxide, it improves acid stability but decreases the activity of the agent.

At position-2 → No substitutions allowed. The methyl groups are necessary.

At position-3 → The carboxylic acid of thiazolidine is required for activity.

At position-4 → The nitrogen is a must.

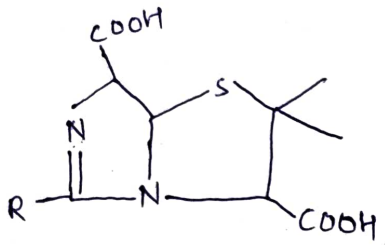
At position-5 → No substitution.

At position-6 → Substitutions are allowed on the side chain of the amide.

At position-7 → The carbonyl on the β-lactam ring is a must.

- substitution at position-6 by an electron-withdrawing group provides better acid stability to the compound.
- A bulky group added close to the ring will make the compound more resistant to β-lactamases.
- Steric hindrance provides protection to the β-lactam ring.

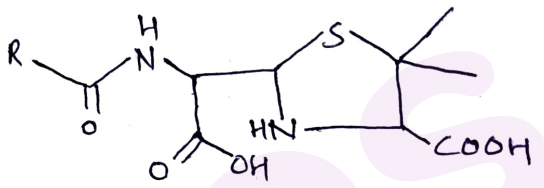
Chemical Degradation



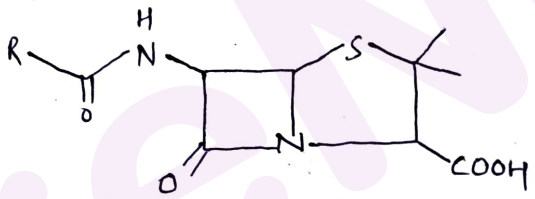
Penillic acid

acidic medium

Alkaline medium

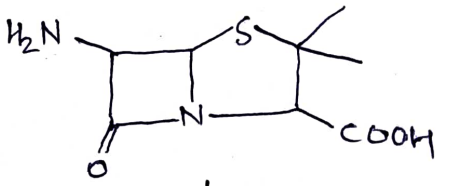


penicilloic acid



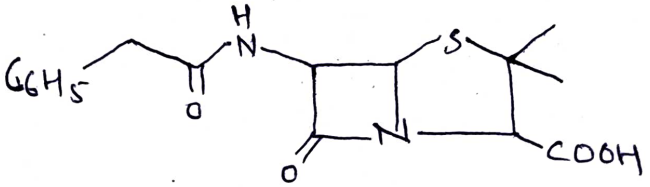
Penicillin

Amidases



6-APA

Phenyl acetic acid



Benzyl penicillin

The penicillins gets degraded under the acidic and basic conditions as well as in the presence of β-lactamases.

Mechanism of Action (MoA)

1) Inhibition of cell wall synthesis

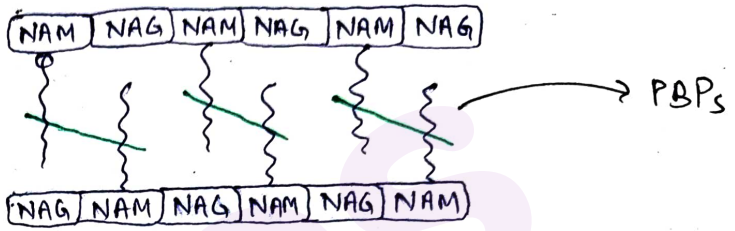
Penicillin acts as an alternative substrate and binds to Penicillin Binding Protein (PBP) receptor present on the surface of bacterial cell wall. After binding, penicillin inhibits transpeptidase that further inhibits cell wall synthesis.

2) Activation of autolytic enzymes

i) Autolytic enzymes after ~~enzymes~~ activation destroy bacteria by creating lesions on them.

ii) Autolysins, present on bacterial cell wall, maintain the appropriate shape and size of cell and also facilitate cell division. Activity of autolysin is regulated by cell wall and teichoic acid.

iii) Penicillin destroys the bacterial cell wall and disintegrates teichoic acid, thus activating autolysin and destroying the bacterial cell.

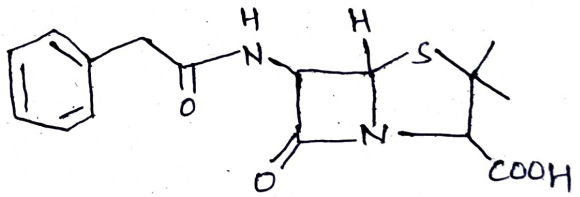


The enzymes transpeptidases and carboxypeptidases are responsible for transpeptidation.
↳ cross linking

Important Products

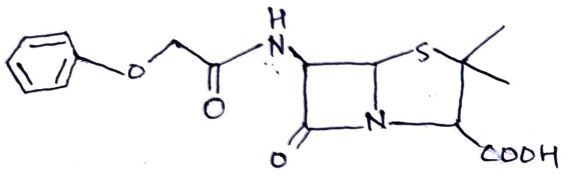
1) Penicillin G (Benzyl Penicillin)

- narrow spectrum natural penicillin.
- shows poor oral absorption, thus is administered intravenously or intramuscularly.



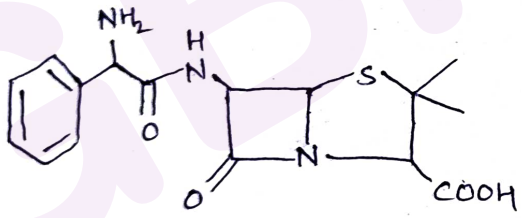
- exists as an amorphous white powder.
- used in septicaemia, meningitis and severe pneumonia caused by penicillin G- susceptible microorganisms.

2) Penicillin V (Phenoxy Methyl Penicillin)



- natural penicillin and better than others as it is not affected by the action of gastric juices.
- white crystalline powder, has a bitter taste and is odourless.
- Used in mild to moderately severe infections (e.g. dental infection, middle ~~yea~~ ear infections, rheumatic fever, etc.)

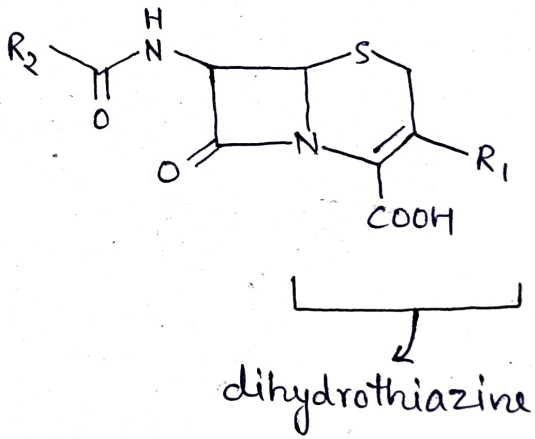
3) Ampicillin



- broad spectrum antibiotic of semi-synthetic origin.
- It is not hydrolysed by various β-lactamases
- It is bactericidal.
- Ampicillin is used in gastrointestinal infections, respiratory infections, UTIs, etc.

Cephalosporins

Cephalosporins are β-lactam antibiotic, prepared semi-synthetically and are derived from Cephalosporin-C*, which is obtained from cephalosporium (fungus). Their nucleus consists of a β-lactam ring fused to a dihydrothiazine ring



* Cephalosporin-C → precursor molecule for antibiotics used in humans

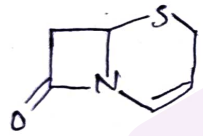
History → Giuseppe Brotzu first isolated cephalosporin compounds from Cephalosporium acremonium cultures from a sewer in Sardinia in 1948.

Nomenclature

1) Chemical Abstracts

Cephalothin is 3-(acetoxy methyl)-8-oxo-7-(2-theinyl) acetamido-5-thia-1-azabicyclooct-2-ene-2-carboxylic acid.

2) Cepham derivatives



Cephem

Cepham

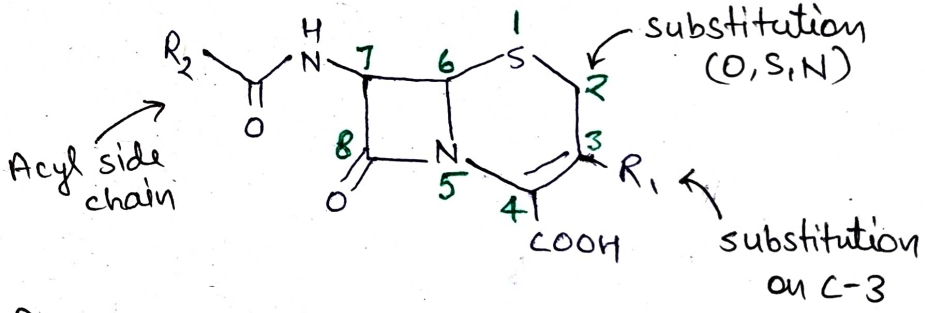
Stereochemistry

It has a bicyclic system containing 4-membered β-lactam ring fused to a six membered dihydrothiazine ring system.

Nucleus of most cephalosporin is 7-amino-cephalosporanic acid (7-ACA).

SAR

- SAR of cephalosporins is more or less similar to penicillins.
- The β-lactam ring is crucial to the mechanism
- The carboxylic acid at position 4 is important for binding.
- The bicyclic system is important in increasing ring strain.
- The acetoxy substituent is important to the mechanism.



Possible modifications

- 7- acylamino side chain
- Acetoxymethyl side chain
- Substitution at C-7

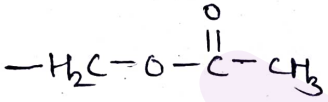
Classification & Important Products

1) First-Generation Cephalosporin

These drugs are highly active against gram +ve bacteria and least active against gram -ve bacteria.

e.g. Cephalothin

R_1

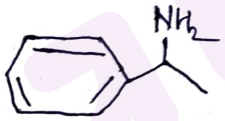


R_2

2) Second-Generation

These drugs are more effective against gram -ve bacteria than first-generation drugs.

e.g. Cefaclor



R_1

R_2

3) Third-Generation

These are less active against gram +ve bacteria than first generation drugs but have an expanded activity spectrum against gram-negative bacteria.

e.g. Ceftizoxime

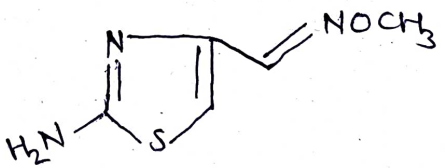
R_1

R_2

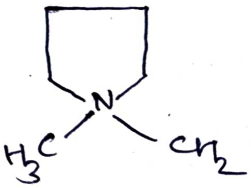
4) Fourth-Generation

These drugs are extended spectrum antibiotics and are resistant to β-lactamases.

e.g. Cefepime

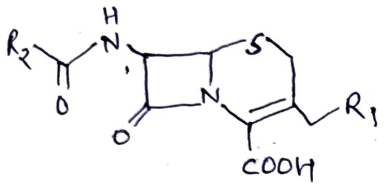


R_1



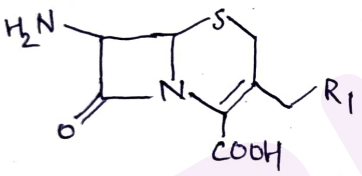
R_2

Chemical Degradation



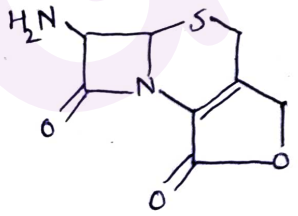
Cephalosporin

H_2O | Acylase



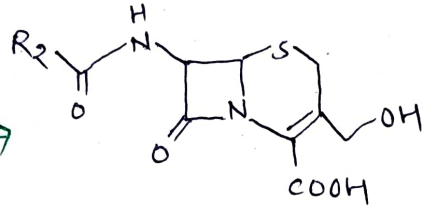
7-ACA

$H^+; -H_2O$



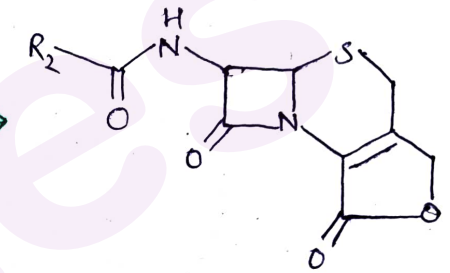
Desacetyl-7-ACA-lactone

β-lactamase; H_3O

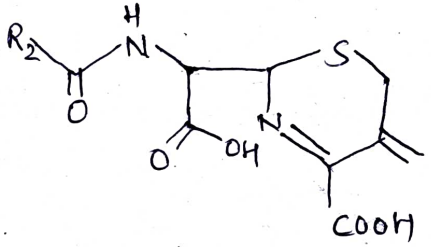


Desacetylcephalosporin

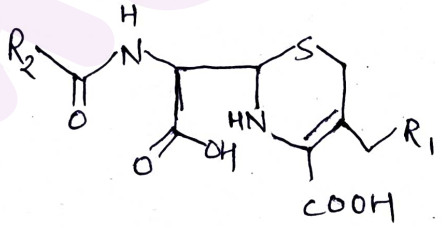
H^+ / $-H_2O$



Desacetylcephalosporin lactone



Anhydrodesacetylcephalosporanic acid



Cephalosporoic acid

Fragmentation

Here $R_1 = \text{OCOCH}_3$

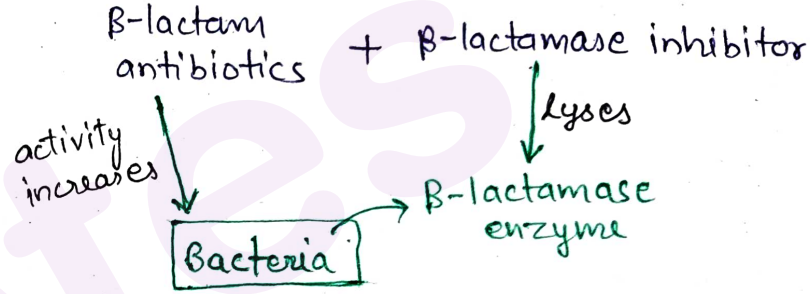
β-Lactamase Inhibitors

- These (→ β-lactamases) are enzymes produced by gram +ve and gram -ve bacteria that inactivate β-lactam antibiotics by lysing the β-lactam ring.
- The family of β-lactamases enables bacteria to resist against β-lactam antibiotics.
- β-lactamases inhibitors inhibit the activity of penicillinases or β-lactamases which are given in combination to other antibiotics.
- The clavulanic acid was developed as the first β-lactamase inhibitors. Others are:
  - Sulbactam
  - Tazobactam
  - Avibactam
  - Relebactam

Mechanism of Action

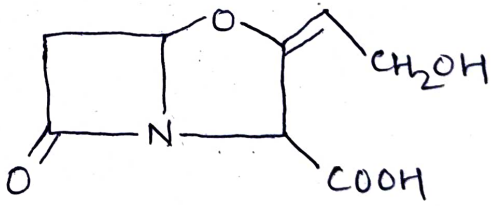
β-lactamase inhibitors bind with β-lactamase enzymes in bacteria at its active sites, then inactivates β-lactamases.

It enhances the activity of β-lactam antibiotics.



- β-lactam antibiotics are mainly used in intra-abdominal infections, skin and soft tissues infections, RT infections, etc.
- The major side effects associated with oral administration of β-lactamase inhibitors combinations are hypersensitivity reactions and GI side effects (nausea and diarrhoea).

Clavulanic Acid



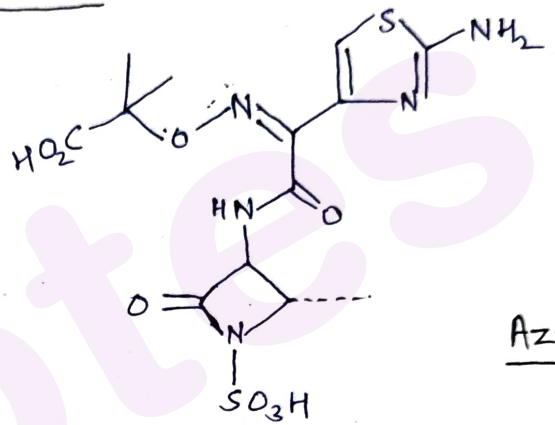
- given in combination with amoxicillin or ticarcillin.
- Clavulanic acid is derived from Streptomyces clavuligerus.
- Used in sinusitis, skin infections, UTIs, bone and joint infections, etc.

- Sulbactam is given in combination with ampicillin.
- Tazobactam with piperacillin.
- Avibactam with Ceftazidime.
- Relebactam with Imipenem.

Monobactams

- Monobactams are active against β-lactamase producing gram negative bacteria because they are resistant to the enzyme.
- They show extended activity spectrum against gram-negative than penicillins. However, they are inactive against gram-positive bacteria.

Aztreonam



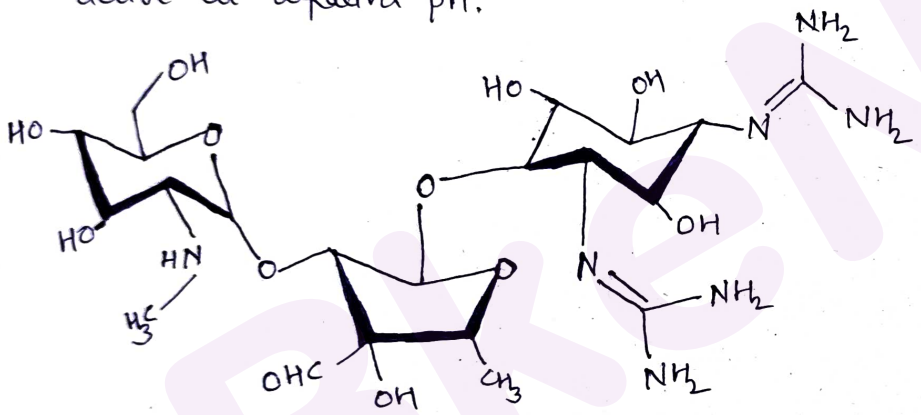
Aztreonam

- obtained from chromobacterium violaceum.
- monocyclic β-lactam antibiotic
- Used in the the infections related to meninges, bladder and kidneys caused by gram-negative bacteria.

Aminoglycosides

Aminoglycosides are a class of antibiotics which consists of 2 or more amino sugars attached by glycoside linkage to hexose nucleus.

These are bactericidal in nature and more active at alkaline pH.



History

- Waksman discovered streptomycin from the culture of *Streptomyces griseus*.
- streptomycin was the first aminoglycoside antibiotic and was effective in the treatment of TB.
- Neomycin was discovered by Waksman in 1949.
- Kanamycin by Umezawa in 1957.

Nomenclature

Aminoglycosides derived from bacteria of Streptomyces genus are named with the suffix - mycin while those derived from Micromonospora genus are named with the suffix - micin.

However, this nomenclature is not only for aminoglycosides. For example, vancomycin is a glycopeptide antibiotic.

Mechanism of action

Aminoglycosides bind to specific 30S sub-unit ribosomal proteins (S12 in case of streptomycin) and inhibit the protein synthesis in any of the following three ways:

1) They interfere with the initiation complex of peptide formation.

2) They misread the mRNA which causes incorporation of incorrect amino acids into the peptide, thus forming the non-functional or toxic protein.

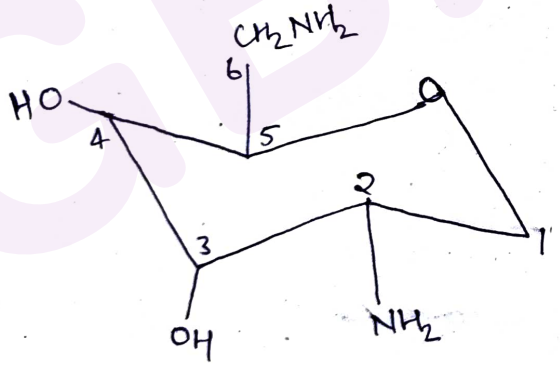
3) They irreversibly break the polysomes into non-functional monosomes and the overall effect is lethal for the cell.

SAR

The aminoglycoside antibiotics contain two important structural features:

1) Amino Sugar Portion
2) Centrall placed hexose ring (Aminocyclitol)

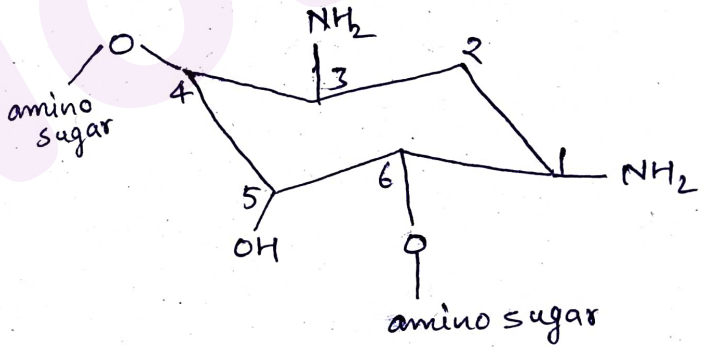
SAR of amino sugar portion



i) The amino targets C-6 and C-2 and substitution with methyl group at C-6 increases the enzyme resistance.

ii) Cleavage of 3-hydroxyl or the 4-hydroxyl or both groups does not affect the activity.

SAR of aminocyclitol ring



i) Modifications at C-1 amino group have been tested. Acylation and ethylation does not increase the activity but helps to retain antibacterial activity.

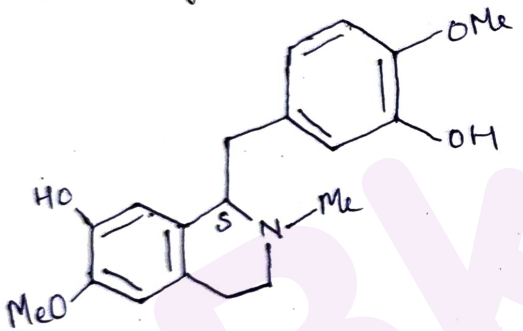
ii) In sisomicin series, 2-hydroxylation and 5-deoxygenation result in increased inhibition of bacterial inactivating enzyme systems.

Adverse Effects

i) Ototoxicity (Vestibular and Cochlear)
ii) Nephrotoxicity
iii) Neuromuscular Paralysis
iv) Allergic Reactions

Important Products

1) Streptomycin



- produced by a soil actinomycete Streptomyces griseus.
- anti-bacterial and anti-micobacterial.
- In MoA, Streptomycin irreversibly binds to specific 30S sub-unit proteins, and 16S rRNA. This interferes with the protein synthesis code.

Uses

i) Streptomycin is used in treatment of TB.
ii) In combination of other drugs, it is used for treating plague, tularemia.

2) Neomycin

- Neomycin is derived from streptomyces fradiae.
- It is bactericidal.
- MoA similar to streptomycin.

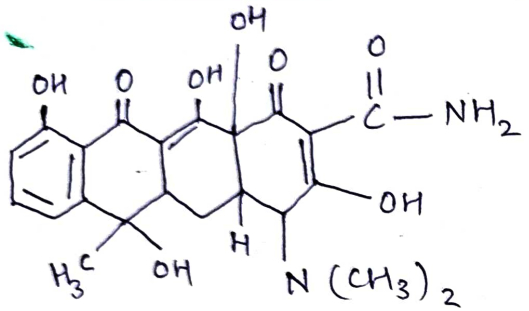
Uses

i) Neomycin is used in eye infections, skin lesions, otitis externa, etc.
ii) It is administered orally in hepatic encephalopathy.

3) Kanamycin

- It is an bactericidal antibiotic that is isolated from Streptomyces kanamyceticus.
- used in the form of kanamycin sulphate.
- It is administered orally, intravenously and intramuscularly.
- similar MoA as both of above.

Tetracyclines



Tetracycline is a potent, broad-spectrum anti-bacterial agent with activity against gram +ve and gram -ve aerobic and anaerobic bacteria.

They occur naturally and are obtained by the fermentation of streptomyces species.

History

Benjamin Minge Duggar discovered the first tetracycline antibiotic, i.e., chlortetracycline in 1945.

In 1950, Robert Burns Woodward decided the compound structure of oxytetracycline.

Nomenclature

Methacycline: 6-methylene-5-oxytetracycline

Doxycycline: α-6-deoxy-5-oxytetracycline

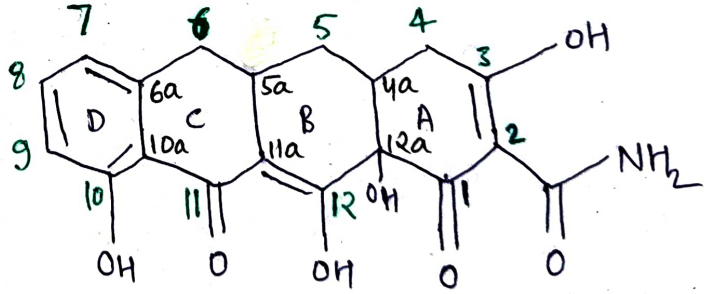
Rolitetracycline: N-(Pyrolidinomethyl)-tetracycline

Stereochemistry

Stereochemistry of tetracyclines is very complex. Chiral carbon atoms are 4, 4a, 5, 5a, 6 and 12a, depending on substitution.

oxytetracycline and doxycycline, each with a 5α-hydroxyl substituent, have six asymmetric centres; the others lacking chirality at C-5, have only five.

SAR



- Ring A and B should have cis-fusion with OH at C-12a.
- OH group at C-12a must be free, esterification abolished the activity.
- Hydrophobic substitution at C-5, 5a, 6, 7, 8, 9 resulted in retention and sometimes improvement in activity.
- The presence of 5-OH does not have important role in activity.

Classification

Short acting
Half life (6hrs.)
- Chlortetracycline
- Oxytetracycline

Intermediate
Half life (16hrs.)
- Demeclocycline
- Methacycline

Long acting
Half life (18-24 hrs.)
- Doxycycline
- Minocycline

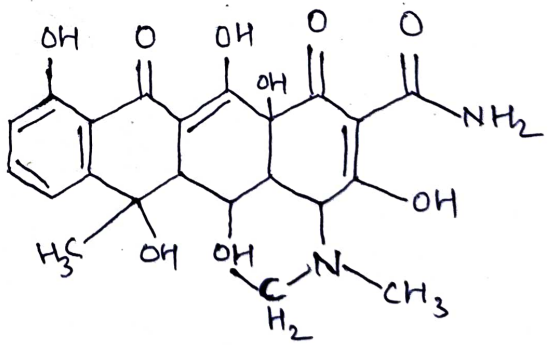
Chemical Degradation

Tetracyclines undergo epimerisation at C-4 solutions of intermediate pH range, and results in the formation of isomers called epitetracyclines.

Important Products

1) Oxytetracycline

- It is a tetracycline analogue isolated from the streptomyces rimosus,
- Oxytetracycline inhibits cell growth by inhibiting translation.
- oxytetracycline is used in infections caused by gram-negative and gram positive microbes.
- Side effects include irritation at injection site, nausea, stomach upset, vomitting, diarrhoea, etc.



2) Chlortetracycline

It is the first member of tetracycline family. It was discovered in 1945 by Benjamin Duggar.

MoA → Chlortetracycline competes for A site of the bacterial ribosome with t-RNA carrying amino acids, thus prevents the addition of more amino acids to the peptide chain. This inhibits bacterial cell growth.

Uses → It is used in the manufacturing of medicated animal feeds.

It inhibits bone and tooth mineralisation in growing and unborn animals as side effects.

3) Minocycline

Minocycline is a tetracycline analogue, 7-dimethylamino but lacking 5-methyl and hydroxyl groups. It is effective against tetracycline-resistant staphylococcus infections.

MoA → Minocycline crosses the lipid bilayer through porin channels in the bacterial membrane. It interferes with protein synthesis.

Minocycline is used in upper RT infections, typhus fever, UTIs.

4) Doxycycline

Doxycycline is a broad-spectrum antibiotic and a synthetic derivative of oxytetracycline.

MoA → interferes in protein synthesis.

Uses

- in typhus fever
- RT infections caused by Mycoplasma pneumonia.

Common side effects of doxycycline include loss of appetite, nausea, vomitting, diarrhoea, rash, etc.