Unit-1
Medicinal Chemistry - III

B.Pharma 6th Sem Notes

Unit: 1

Antibiotics

Historical background, Nomenclature, Stereochemistry, Structure activity relationship, Chemical degradation classification and important products of the following classes.

- **β-Lactam antibiotics:** Penicillin, Cepholosporins, β- Lactamase inhibitors, Monobactams
- **Aminoglycosides:** Streptomycin, Neomycin, Kanamycin
- **Tetracyclines:** Tetracycline,Oxytetracycline, Chlortetracycline, Minocycline, Doxycycline

Antibiotics:

- Antibiotics are **chemical substances** (produced naturally by microorganisms or synthesized artificially) that inhibit the growth of or kill other microorganisms, especially bacteria.
- They are a major milestone in medical science, revolutionizing the treatment of infectious diseases.
- **Origin:** The first discovered antibiotic was **Penicillin**, by *Alexander Fleming* in 1928.

History of Antibiotics:

Antibiotics began with the growing acceptance of the germ theory of disease (Louis Pasteur was one of the first recognized physicians who observed that bacteria could be used to kill other bacteria).

1. **1871=** The surgeon Joseph Lister found urine contaminated with mould could not kill the bacteria.
2. **1890's =** German doctors Rudolf Emmerich, Oscar low made Pyocyanse from microbes. It was the first antibiotic used in hospitals but the drug did not work
3. **1909 =** First modern chemotherapeutic agent Salvarsan for the treatment of syphilis (Paul Ehrlich)
4. **1928 =** Scottish bacteriologist Sir Alexander Fleming discovered enzyme lysozyme and the antibiotic substance penicillin
5. **1932=** Gerhard Domagk discovered Prontosil a prodrug.
6. **1936=** Sulfanilamide the first synthetic sulfonamide in human medicine
7. **1940 =** Invention of Modern Drug Discovery: Ehrlich & The Magic Bullet means compound that selectively targets a disease causing organism while having no Negative effect on human tissue.
8. **1940 =** First therapeutic use of penicillin by Floury.
9. **1944** Selman Waksman made Streptomycin from soil bacteria.
10. **1948** = Chlortetracycline.
11. **1957=** Nystatin (fungal infections)
12. **1970s=** A New quinolone (pipemidic acid, oxolinic acid, cinoxacin)
13. **1980=** Norfloxacin the first fluoroquinolone.
14. **1980=** Enrofloxacin
15. **1998=** Smithkline Beecham patented Amoxicillin/ clavulanate potassium.

Classification of Antibiotics

Antibiotics can be classified in different ways:

A. Based on Origin

1. **Natural antibiotics** – obtained directly from microorganisms.
   Example: Penicillin G, Streptomycin.
2. **Semisynthetic antibiotics** – modified forms of natural antibiotics.
   Example: Amoxicillin, Cephalexin.
3. **Synthetic antibiotics** – completely synthesized in laboratory.
   Example: Ciprofloxacin, Sulfonamides.

B. Based on Spectrum of Activity

1. **Narrow-spectrum** – effective against specific bacteria (Gram-positive *or* Gram-negative).
   Example: Penicillin G (Gram-positive).
2. **Broad-spectrum** – effective against both Gram-positive and Gram-negative bacteria.
   Example: Tetracycline, Chloramphenicol.

C. Based on Mechanism of Action

1. **Inhibition of cell wall synthesis**
   Example: Penicillins, Cephalosporins.
2. **Inhibition of protein synthesis**
   Example: Tetracyclines, Aminoglycosides, Macrolides.
3. **Inhibition of nucleic acid synthesis**
   Example: Fluoroquinolones, Rifampicin.
4. **Alteration of cell membrane permeability**
   Example: Polymyxins.
5. **Antimetabolite action** – interfering with metabolic pathways.
   Example: Sulfonamides, Trimethoprim.

D. Based on Chemical Structure

- **β-lactam antibiotics** – Penicillins, Cephalosporins, Carbapenems.
- **Aminoglycosides** – Streptomycin, Gentamicin.
- **Tetracyclines** – Doxycycline, Minocycline.
- **Macrolides** – Erythromycin, Azithromycin.
- **Quinolones** – Ciprofloxacin, Levofloxacin.

β-Lactam antibiotics: Penicillin, Cepholosporins, β- Lactamase inhibitors, Monobactams.

Definition

β-Lactam antibiotics are a **large group of antibiotics** that contain a **β-lactam ring** in their chemical structure.
They work by **inhibiting bacterial cell wall synthesis**, leading to cell lysis and death.

Classification

1. **Penicillins** – Penicillin G, Ampicillin, Amoxicillin.
2. **Cephalosporins** – Cephalexin, Ceftriaxone.
3. **Carbapenems** – Imipenem, Meropenem.
4. **Monobactams** – Aztreonam.

Mechanism of Action

- Bind to **Penicillin-Binding Proteins (PBPs)** in bacterial cell membrane.
- Inhibit **transpeptidation** step in **peptidoglycan synthesis**.
- Weakens the bacterial cell wall → cell lysis (bactericidal).

Spectrum of Activity

- Varies with each subclass.
- Includes **Gram-positive** and **Gram-negative** bacteria.
- Many broad-spectrum derivatives available.

Resistance

- **β-lactamase enzymes** (produced by bacteria) break the β-lactam ring, making the drug inactive.
- Solution: Use **β-lactamase inhibitors** (e.g., Clavulanic acid, Sulbactam) in combination.

Uses

- Respiratory tract infections.
- Urinary tract infections.
- Skin & soft tissue infections.
- Septicemia, meningitis.
- Surgical prophylaxis.

Adverse Effects

- Allergic reactions: rash, urticaria, anaphylaxis.
- Gastrointestinal upset.
- Rare: neurotoxicity, nephrotoxicity.

Penicillins

1. Introduction

- Penicillins are **β-lactam antibiotics** derived from *Penicillium* species.
- They were the **first antibiotics** used clinically, discovered by **Alexander Fleming** in 1928.
- They act by **inhibiting bacterial cell wall synthesis**.
- Most active against **Gram-positive** bacteria; some derivatives have broad-spectrum activity.

2. Classification of Penicillins

A. Based on Source / Production

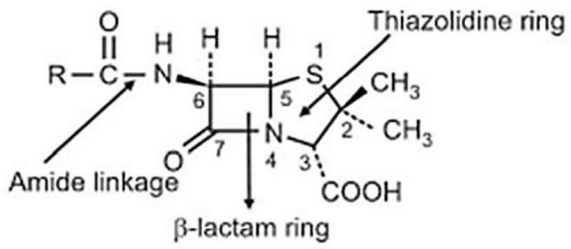
1. **Natural Penicillins**
    - Penicillin G (Benzylpenicillin)
    - Penicillin V (Phenoxymethylpenicillin)
2. **Semisynthetic Penicillins**
    - **Aminopenicillins**: Ampicillin, Amoxicillin
    - **Antistaphylococcal penicillins**: Cloxacillin, Dicloxacillin
    - **Extended-spectrum (antipseudomonal)**: Ticarcillin, Piperacillin

B. Based on Spectrum

- **Narrow spectrum**: Penicillin G, Penicillin V
- **Broad spectrum**: Ampicillin, Amoxicillin
- **Extended spectrum**: Piperacillin, Ticarcillin

Structure:

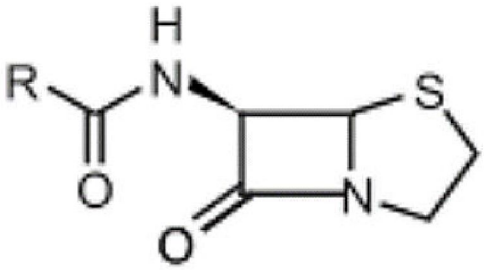
- It contains two rings fused with each other- Thiazolidine ring and β-Lactam ring.



Nomenclature:

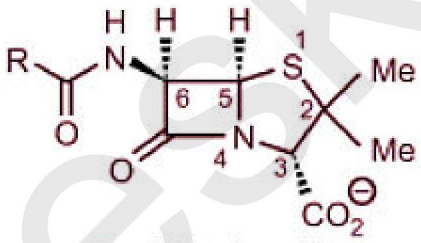
(a) There are two types of numbering for the fused bicycling system of penicillin: whether which atom is number one Sulfur or Nitrogen.

(b) Penam nucleus is used in naming which comprise bicyclic system with the amide carbonyl group. Penicillin is named as 6-acylamino-2,2-dimethylpenam-3-carboxylic acid.



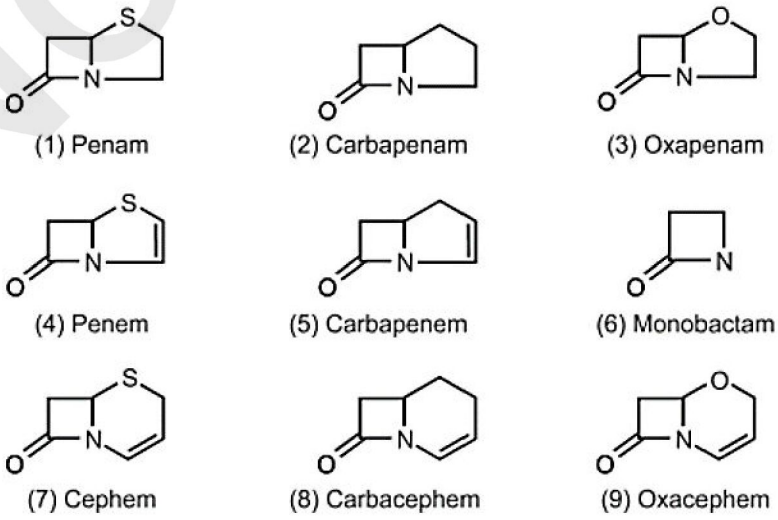
Penam

(c) Penicillanic acid nucleus: Which includes the 2,2-dimethyl and 3-carboxyl groups. Penicillin is named as 6- carbonylaminopenicillanic acid.



Penicillanic acid

(d) Penicillin nucleus: Which includes 6-carbonyl aminopenicillanic acid. So Penicillin G is named benzylpenicillin if R is benzene ring.



Stereochemistry:

a. The penicillin molecule contains three chiral carbon atoms at C-3, C-5 and C-6
b. All natural and synthetic penicillins have the same absolute configuration about these three centers
c. The 6 carbon atom bearing the acyl amino group has the L-configuration, whereas the carbon to which the carboxyl group was attached has the D-configuration.
d. The acyl amino group and carboxyl group are trans to each other, with the former and latter in the β orientation relative to penam ring.
e. The absolute stereochemistry of the penicillins is designated as 35: 5R: 6R.
f. The atoms composing the 6-aminopenicillanic acid are biosynthetically derived from two amino acids, Lcysteine and D-valine.

Mechanism of Action (MOA)

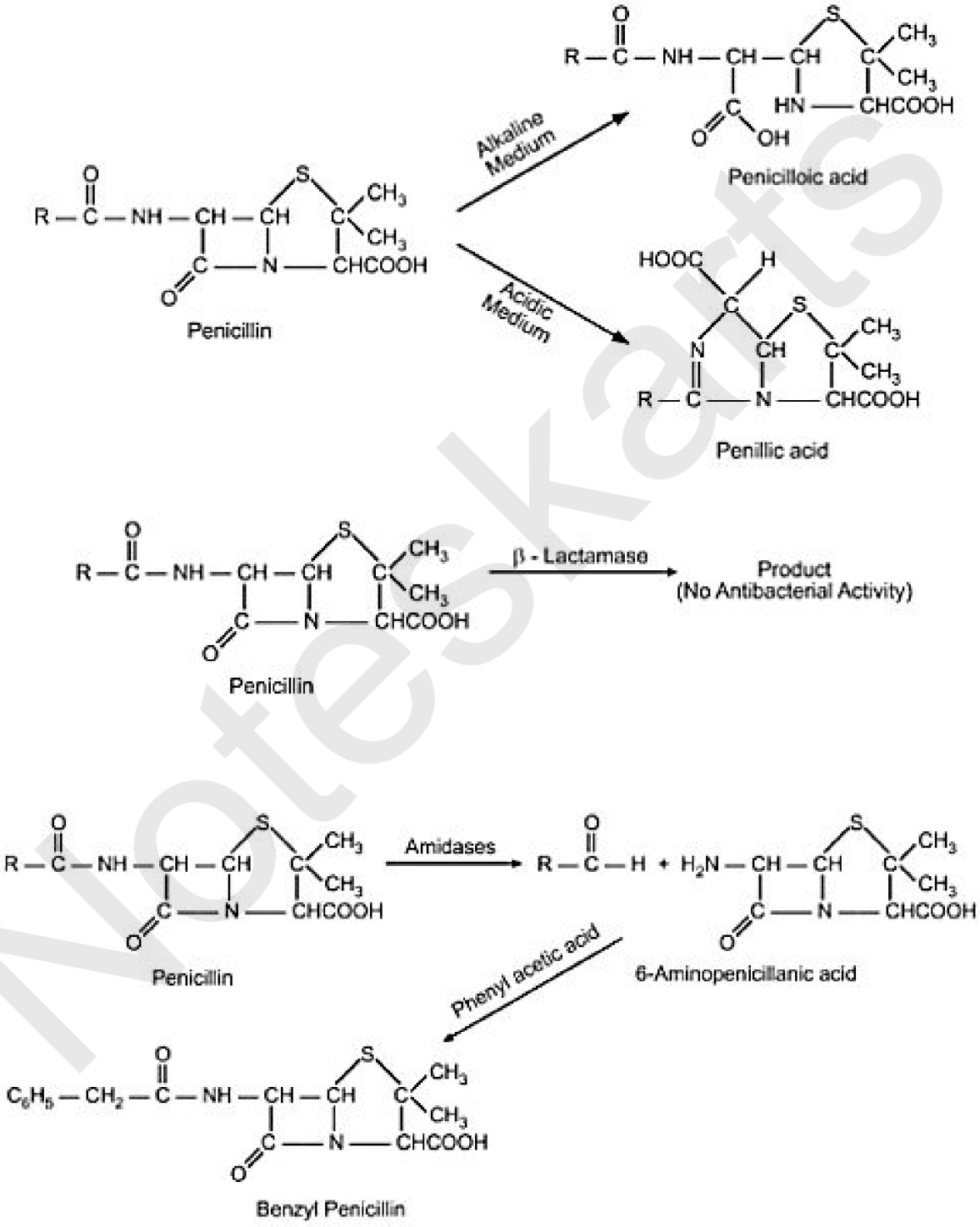
1. **Target** – Bacterial cell wall synthesis.
2. **Action Steps**:
    - Penicillins bind to **PBPs** (transpeptidase enzymes) in bacterial cell membrane.
    - Block **transpeptidation reaction** → prevents cross-linking of **peptidoglycan chains**.
    - Weak cell wall cannot withstand osmotic pressure → **cell lysis** (bactericidal).
3. **Selectivity** – Human cells lack peptidoglycan → no effect on host cells.

Uses of Penicillin

- Skin infection
- Dental infection
- Ear infection
- An infection of the nose, throat, or lungs
- Urinary tract infection
- Other bacterial infections

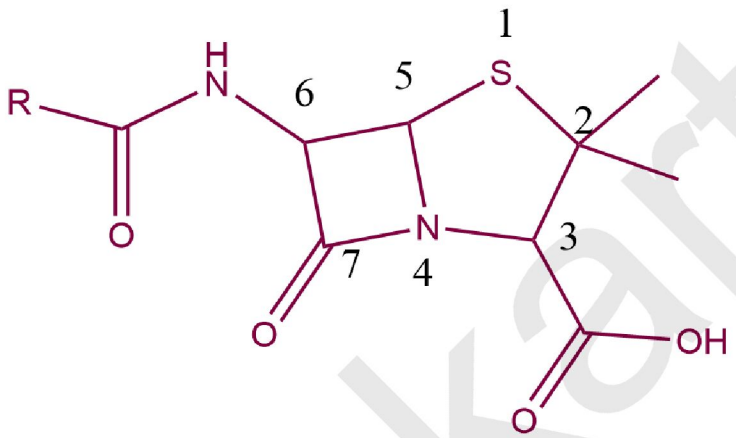
Chemical Degradation:

The Penicillins gets degraded under the acidic and basic conditions as well as in the presence of β-lactamases. The degradation is shown below.



Structure activity relationship:

- Position 1 — Oxidising the sulfur atom of the Thiazolidine ring to a sulfone or sulfoxide enhances acid stability but decreases the activity of the agent.
- Position 2 — No substitutes are permitted at this position; any change will result in a lower activity. The methyl groups are required.
- Position 3 — Thiazolidine's carboxylic acid is necessary for action. If it is converted to an alcohol or ester, its activity decreases.



- Position 4 — Nitrogen is required.
- Position 5 — No substitutes are permitted.
- Position 6 — Substitutions on the amide's side chain are permitted.
- Position-7 – Carbonyl on the Beta-lactam ring is required in position 7.
- Because this substitution makes the amide oxygen less nucleophilic, an electron-withdrawing group added at this position improves acid stability.
- The addition of a bulky group near the ring strengthens the compound's resistance to Beta-lactamases.
- The Beta-lactam ring is protected by steric hindrance.

Cephalosporins

Introduction

- Cephalosporins are **β-lactam antibiotics** derived from *Cephalosporium acremonium* (now *Acremonium* species).
- First discovered in **1945** by **Giuseppe Brotzu** from sewage near the coast of Sardinia, Italy.
- Structurally and functionally related to penicillins.
- More resistant to **β-lactamase enzymes** than natural penicillins.

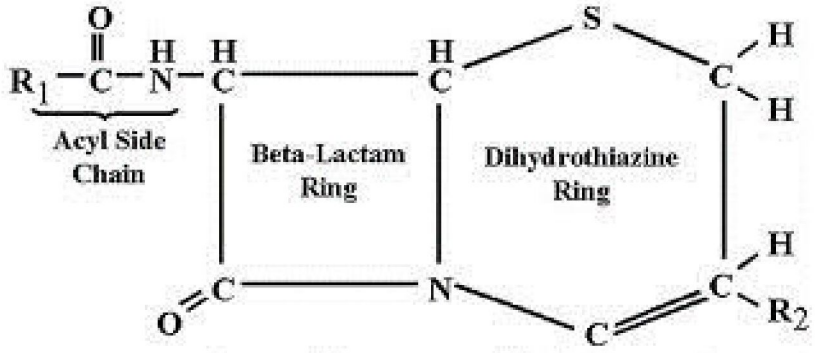
Classification of Cephalosporins

Based on Generation (according to antimicrobial spectrum):

1. **First Generation**
    - *Examples*: Cephalexin, Cefazolin
    - Mainly Gram-positive coverage.
2. **Second Generation**
    - *Examples*: Cefuroxime, Cefaclor
    - Improved Gram-negative coverage.
3. **Third Generation**
    - *Examples*: Ceftriaxone, Ceftazidime, Cefotaxime
    - Broad-spectrum, better Gram-negative activity, some cross blood–brain barrier.
4. **Fourth Generation**
    - *Example*: Cefepime
    - Strong Gram-positive and Gram-negative activity, highly resistant to β-lactamase.
5. **Fifth Generation**
    - *Example*: Ceftaroline
    - Active against MRSA (Methicillin-resistant *Staphylococcus aureus*).

Structure:

Cephalosporin nucleus consists of a β-Lactam ring fused with dihydrothiazine ring (7-Aminocephalosporanic acid).

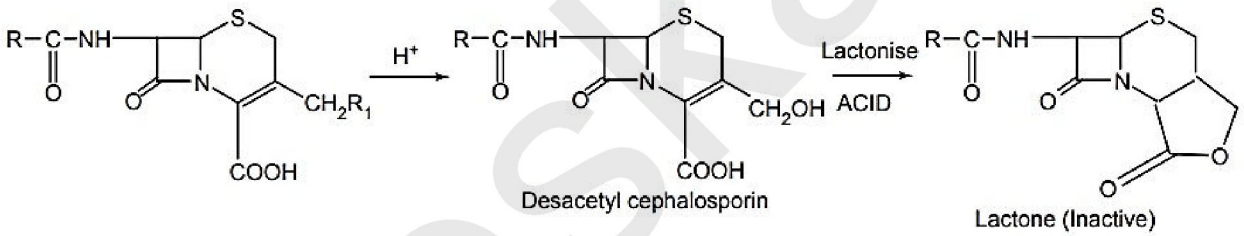


General Structure of Cephalosporins

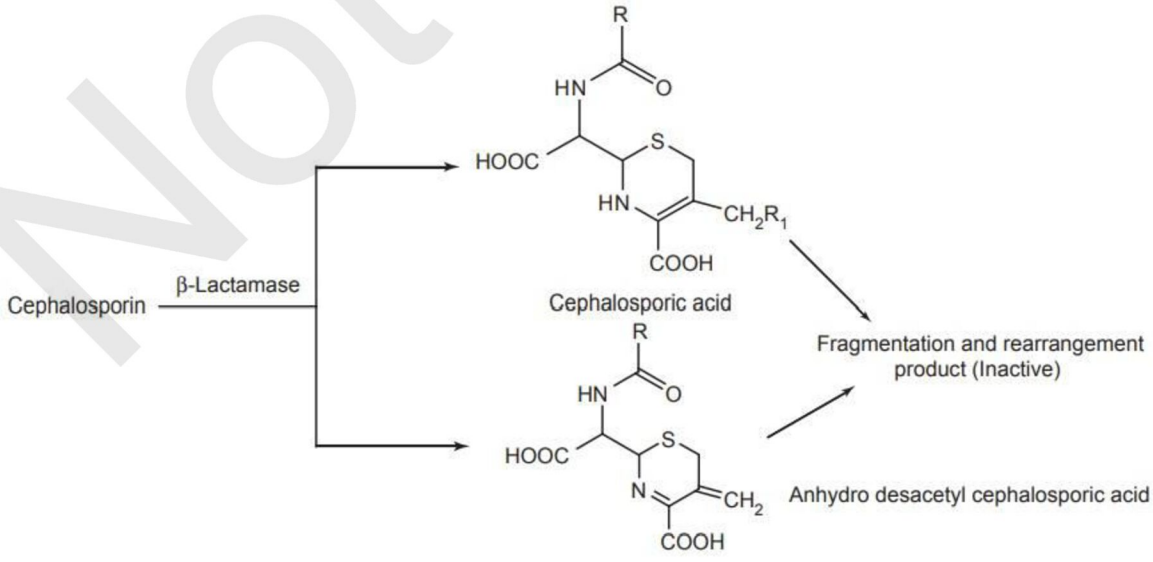
Chemical Degradation

Cephalosporins experience a variety of hydrolytic degradation reactions.

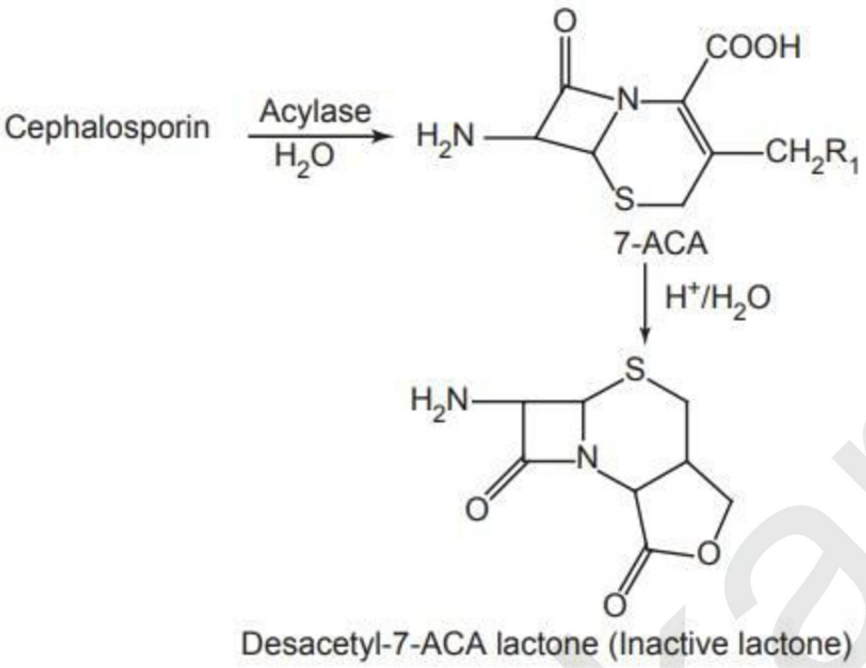
In strong acid solutions



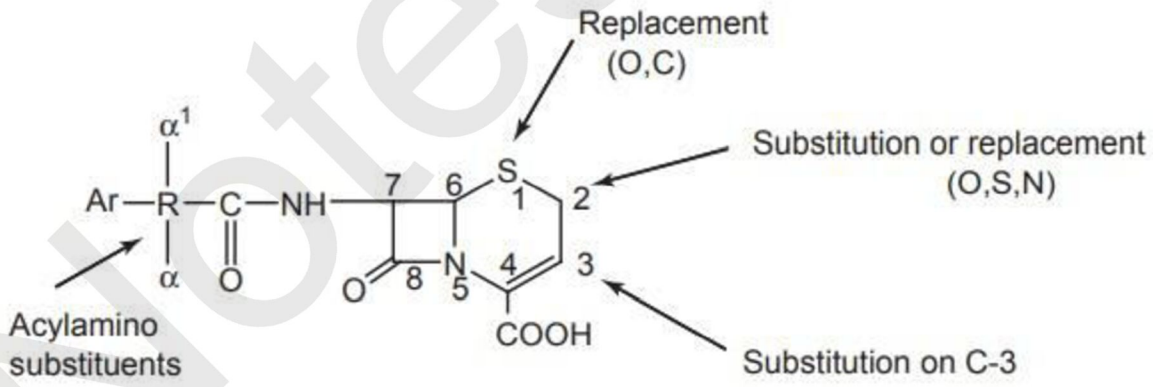
In the presence of β-lactamase



In the presence of acylase



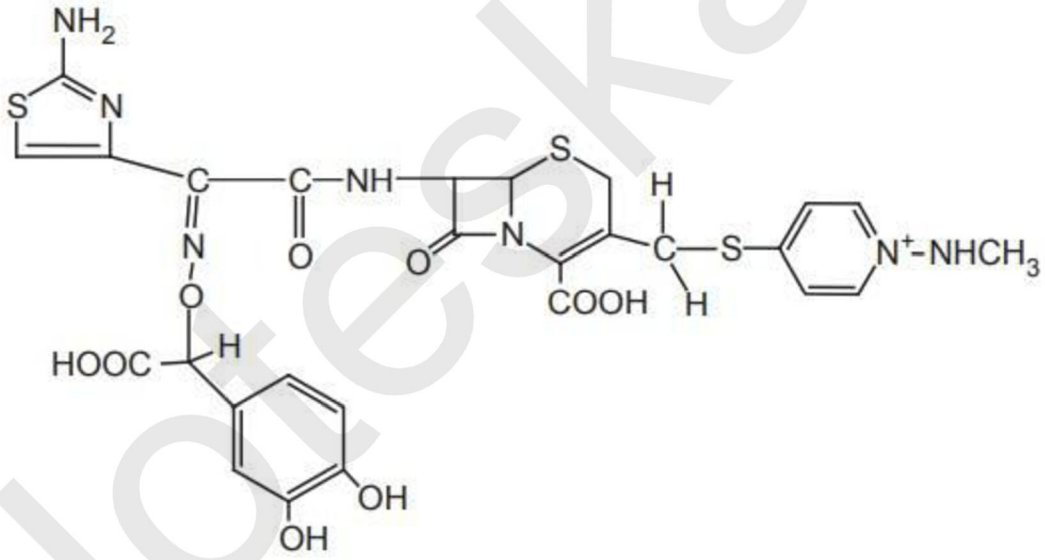
SAR of Cephalosporins



1. 7-Acylamino substitution

- The addition of amino group and a hydrogen to α and α_1 position produces basic compound, which is protonated under acidic conditions of stomach. The ammonium ion improves the stability of β-lactum of cephalosporins and make active orally. Activity against positive bacteria is increased and gram negative is decreased by acylation of amino group.

- When the new acyl groups are derived from carboxylic acids, it shows good spectrum of antibacterial action for gram-positive bacteria.
- Substitutions on the aromatic ring phenyl that increase lipophilicity provide higher gram-positive activity and generally lower gram-negative activity.
- The phenyl ring in the side chain can be replaced with other heterocycles with improved spectrum of activity and pharmacokinetic properties; these include thiophene, tetrazole, furan, pyridine, and aminothiazoles.
- The L-isomer of an α-amino α_1 -hydrogen derivative of cephalosphorins was 30–40 fold stable than D-isomer. Addition of methoxy oxime to α and $\alpha_1$increases the stability to nearly 100-fold. The presence of catechol grouping can also enhance activity, particularly, against Pseudomonas aeruginosa, and also retain some gram-positive activity, which is unused for a catechol cephalosporin.



These compounds penetrate into the cell by utilizing the bacterial ion β-dependent ion transport system. There is a reduction of Gram negative activity when the lipophilicity of this side chain is increased and effects of polar α-substituents are enhanced (OH, NH_2, SO_3H, COOH).

2. Modification in the C-3 substitution: The pharmacokinetic and pharmacodynamics depends on C-3 substituents. Modification at C-3 position has been made to reduce the degradation (lactone of desacetyl cephalosporin) of cephalosporins.

a. The benzoyl ester displayers improved gram-positive activity, but lowered gram-negative activity.

b. Pyridine, imidaozle replaced acetoxy group by azide ion yields derivative with relatively low gramnegative activity.
c. Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.
d. Orally active compounds are produced by replacement of acetoxy group at C-3 position with CH_3 and Cl.

3. Other modifications

a) Methoxy group at C-7, shows higher resistance to hydrolysis by β-lactamase.
b) Oxidation of ring spectrum to sulphoxide or sulphone greatly diminishes or destroys the antibacterial activity.
c) Replacement of sulphur with oxygen leads to oxacepam (latamoxet) with increased antibacterial activity, because of its enhanced acylating power. Similarly, replacement of sulphur with methylene group (loracavet) has greater chemical stability and a longer half-life.
d) The carboxyl group position-4 has been converted into ester prodrugs to increase bioavailability of cephalosporins, and these can be given orally as well.
e) The antibacterial activity depends on the olefinic linkage at C-3 and C-4 position and their activity is lost due to the ionization of double bond to 2nd and 3rd positions.

Mechanism of Action:

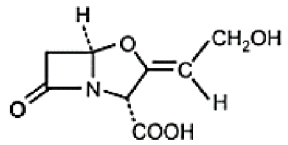
- Cephalosporins exert bactericidal effect in manner similar to that of Penicillins.
- Binding to specific PBPS
- Inhibition of cell wall synthesis by inhibiting transpeptidation of Peptidoglycan
- Activation of Autolytic enzymes: Autolysins or Murein Hydrolases

Uses:

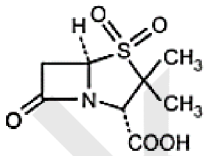
- Cephalosporins are widely used antibiotics. Unfortunately, overuse of these agents in situations where drugs with less broad spectrum activity would be more appropriate has led to the emergence of wide array of cephalosporin resistant bacteria.
- Cephalosporins are effective as both Prophylactically & Therapeutically.
- Alternative to Penicillins
- Respiratory tract infections caused by Klebsiella, Enterobacter, Proteus, Providencia, and Haemophilus species.
- Gonorrhoea
- Typhoid fever
- Meningitis

β-Lactamses inhibitors:

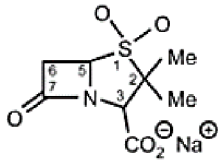
- β-lactamases are a family of enzymes involved in bacterial resistance to beta-lactam antibiotics.
- They act by breaking the beta-lactam ring that allows penicillin-like antibiotics to work.
- Strategies for combating this form of resistance have included the development of new beta-lactam antibiotics that are more resistant to cleavage and the development of the class of enzyme inhibitors called beta-lactamase inhibitors.
- Although β-lactamase inhibitors have little antibiotic activity of their own, they prevent bacterial degradation of beta-lactam antibiotics and thus extend the range of bacteria the drugs are effective against.



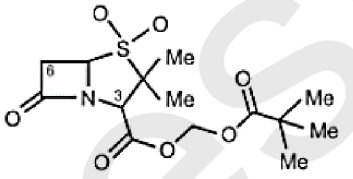
Clavulanic acid



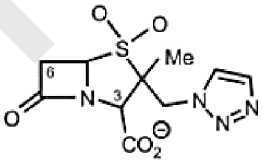
Sulbactam



Sulbactam



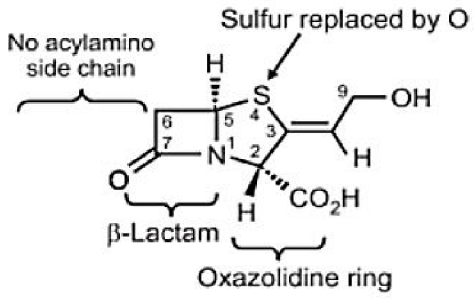
Sulbactam oral ester

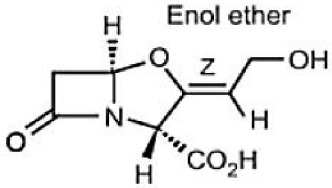


Tazobactam

Essential requirements for ß-lactamase inhibition are:

- Strained ß-lactam ring.
- Enol ether.
- The double bond of the enol ether has the Z-configuration (Activity is reduced, but not eliminated if the double bond is E).
- No substitution at C-6.
- R-Stereochemistry at positions 2 and 5.
- Carboxylic acid group.





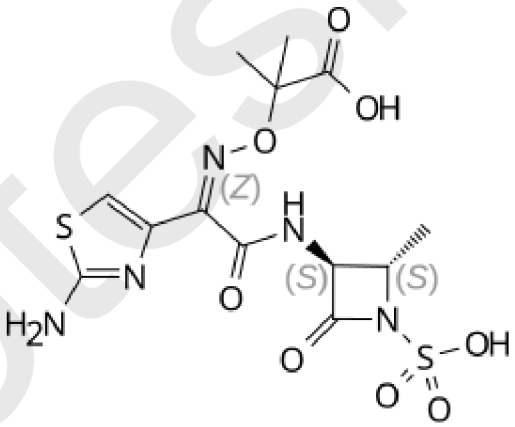
Uses:

- In the treatment of infections known or believed to be caused by gram-negative bacteria, as β-lactamase production is an important contributor to beta-lactam resistance in these pathogens.
- Addition of clavulanic acid re-establishes the activity of amoxicillin against β-lactamase producing resistant E. coli, H. influenzae, Klebsiella, N. gonorrhoeae, Proteus, Staph aureus, Salmonella and Shigella.

Monobactams:

- fermentation of unusual microorganism led to the discovery of a class of monocyclic B-lactam antibiotics.
- It is obtained from the bacterium chromobacterium violaceum.
- They are negative bacteria (eq. Neisseria, Pseudomonas) effective against only gram not effective against gram positive / anaerobes.

Aztreonam:



Aminoglycosides: Streptomycin, Neomycin, Kanamycin

Aminoglycosides

Introduction

- Aminoglycosides are **bactericidal antibiotics** containing **amino sugars** linked by **glycosidic bonds**.
- Discovered from *Streptomyces* and *Micromonospora* species.
- Effective mainly against **aerobic Gram-negative bacilli** and some Gram-positive bacteria.
- Usually given **parenterally** (except neomycin for local use) due to poor GI absorption.

2. Mechanism of Action

1. Bind **irreversibly** to the **30S ribosomal subunit** of bacteria.
2. Cause **misreading of mRNA** and block protein synthesis.
3. Leads to formation of abnormal proteins → disruption of bacterial cell membrane → **cell death**.
4. Oxygen-dependent uptake → ineffective against anaerobes.

Classification:

SYSTEMIC	TOPICAL
Streptomycin Amikacin Gentamicin Kanamycin Netilmicin Tobramycin Sisomicin	•Neomycin •Framycetin

SAR of Aminoglycoside Antibiotics

The aminoglycosides consist of two or more amino sugars joined in glycoside linkage to a highly substituted 1,3-diaminocyclo hexane (aminocyclitol), which is a centrally placed ring. The ring is a 2-deoxy streptamine in all aminoglycosides except streptomycin and dihydrostreptomycin, where it is streptidine.

Thus,

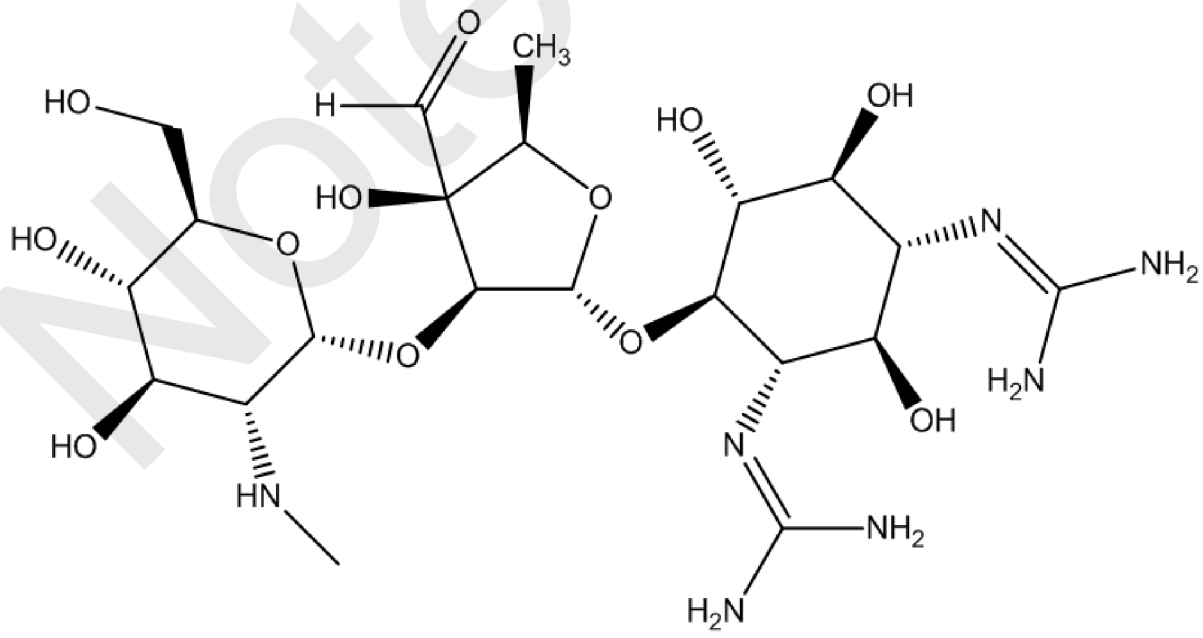
- In kanamycin and gentamycin families, two amino sugars are attached to 2-deoxy streptamine.
- In streptomycin, two amino sugars are attached to strepidine.
- In neomycin family, there are amino sugars attached to 2-deoxy streptamine.

The aminoglycoside antibiotics contain two important structural features. They are amino sugar portion and centrally placed hexose ring, which is either 2-deoxystreptamine or streptidine.

A. Streptomycin

- **Source**: *Streptomyces griseus*.

Structure:



- **Uses**:
  - First antibiotic effective against **tuberculosis** (in combination therapy).

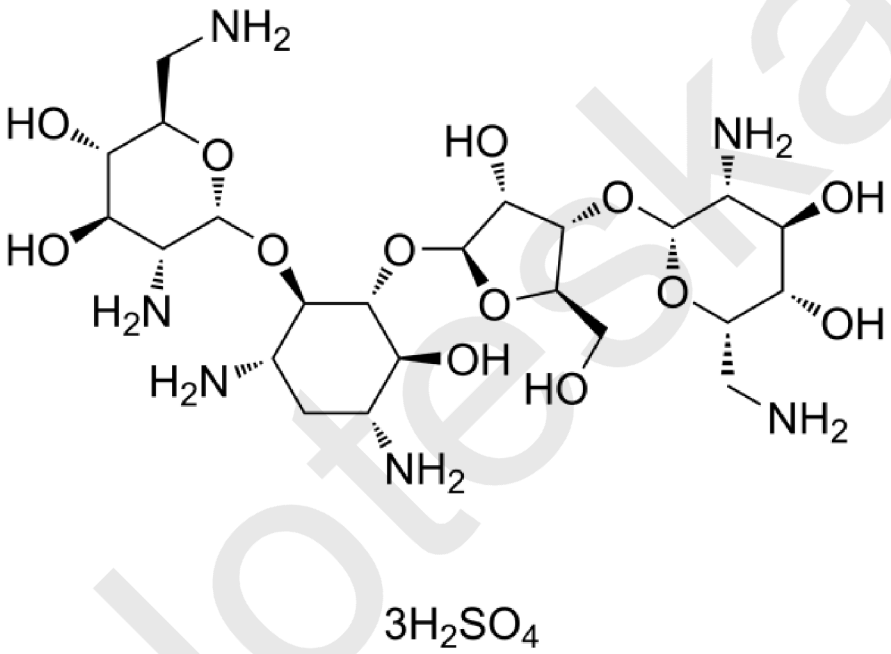
- Plague, tularemia, bacterial endocarditis (with penicillin).

- **Adverse effects**:
  - Ototoxicity (vestibular damage).
  - Nephrotoxicity.
  - Allergic reactions.

B. Neomycin

- **Source**: *Streptomyces fradiae*.

Structure:

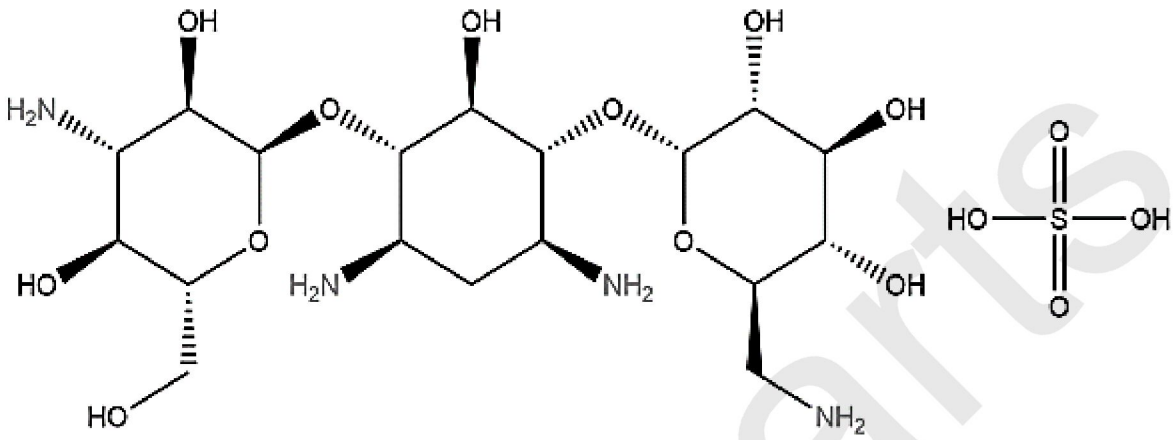


- **Uses**:
  - **Topical** for skin, ear, and eye infections.
  - Oral use for bowel sterilization before surgery.

- **Adverse effects**:
  - Highly nephrotoxic and ototoxic → **not used systemically**.
  - Contact dermatitis with prolonged topical use.

C. Kanamycin

- **Source**: *Streptomyces kanamyceticus*.



- **Uses**:
    - Reserved for infections resistant to other aminoglycosides.
    - TB (second-line drug), plague, severe Gram-negative infections.
- **Adverse effects**:
    - Ototoxicity (cochlear damage).
    - Nephrotoxicity.

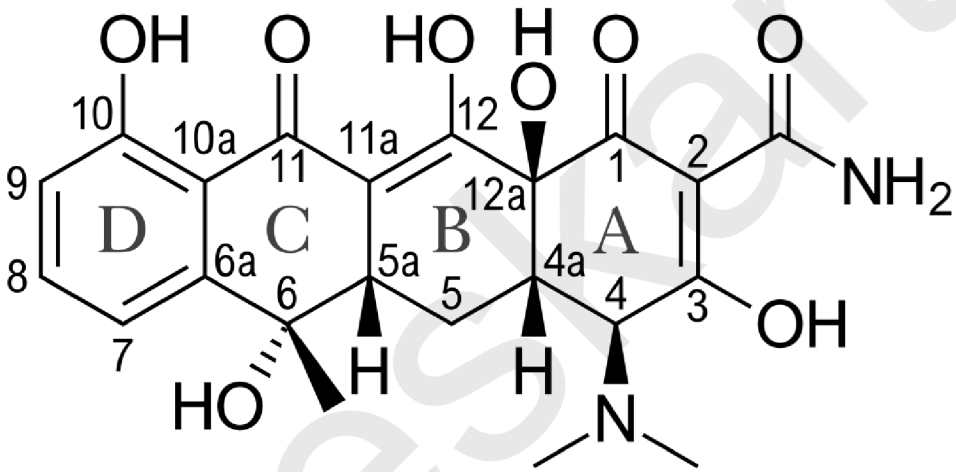
Tetracyclines: Tetracycline,Oxytetracycline, Chlortetracycline, Minocycline, Doxycycline

Tetracyclines

Introduction

- Tetracyclines are a group of **broad-spectrum, bacteriostatic antibiotics**.
- Discovered from *Streptomyces* species in the 1940s.
- Named "tetracyclines" because their structure contains **four fused rings**.
- Active against **Gram-positive, Gram-negative, rickettsiae, chlamydia, mycoplasma, spirochetes, protozoa**.

Structure:



Mechanism of Action

1. Enter bacterial cells by passive diffusion and active transport.
2. Bind **reversibly** to the **30S ribosomal subunit**.
3. Block attachment of aminoacyl-tRNA to the mRNA-ribosome complex.
4. Inhibit protein synthesis → **bacteriostatic effect**.

Classification

A. Natural Tetracyclines

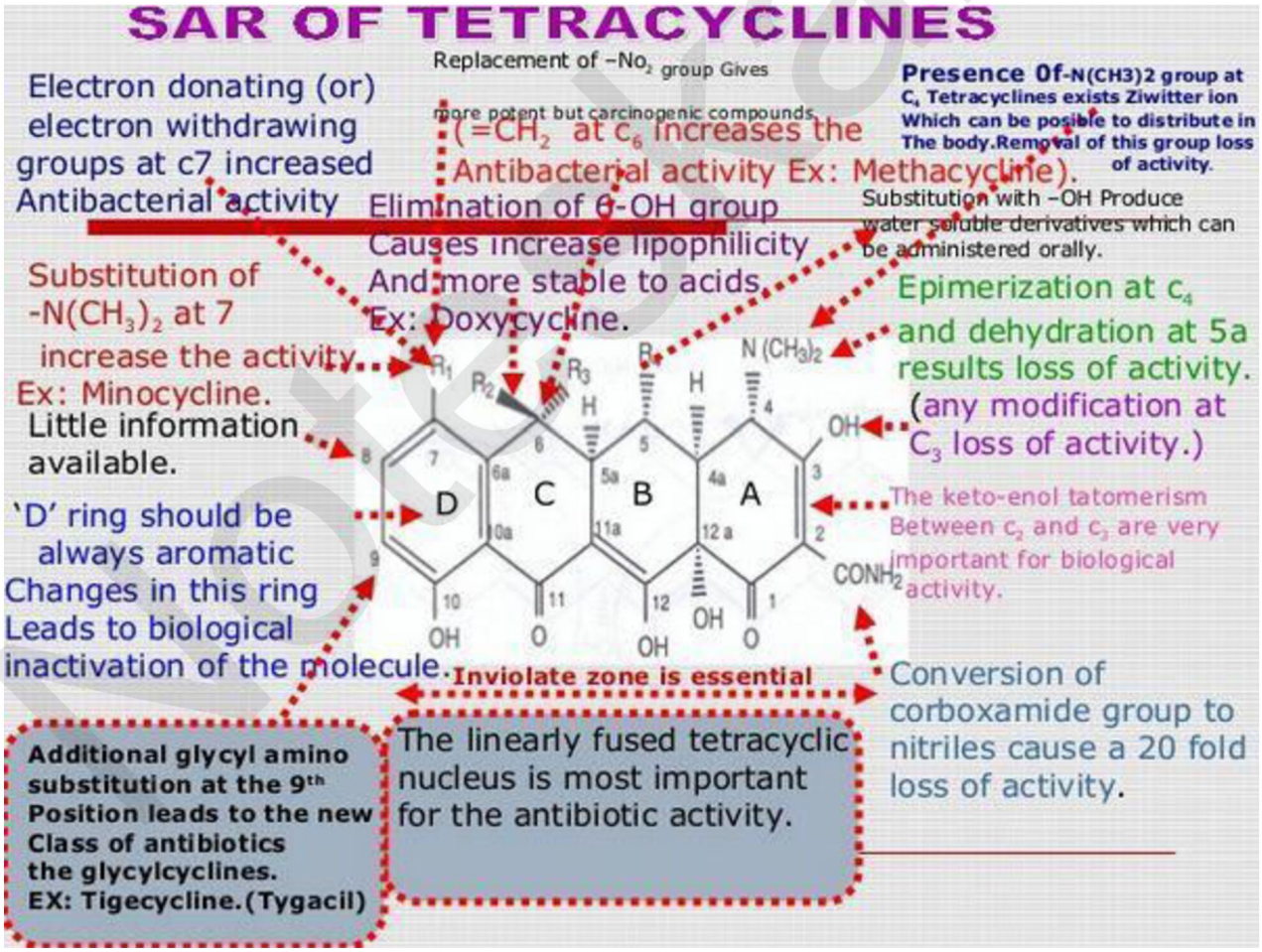
- Tetracycline
- Oxytetracycline
- Chlortetracycline

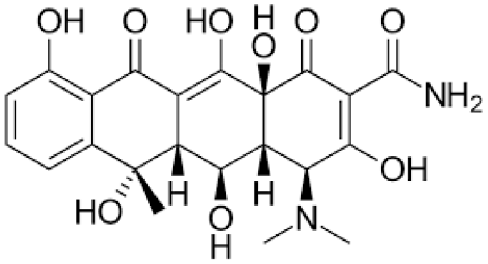
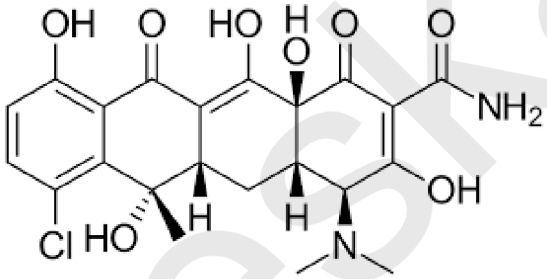
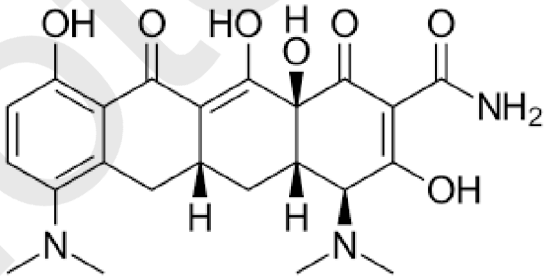
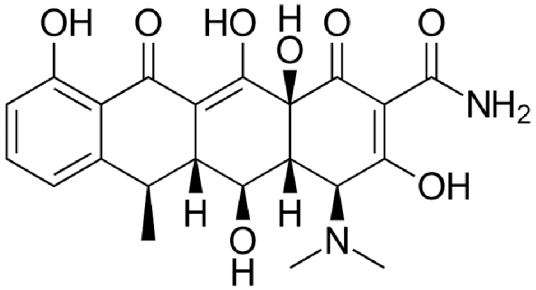
B. Semisynthetic Tetracyclines

- Doxycycline
- Minocycline

Structure-activity relationship:

- Tetracyclines are composed of a rigid skeleton of 4 fused rings.
- The rings structure of tetracyclines is divided into an upper modifiable region and a lower non modifiable region
- An active tetracycline requires a C10 phenol as well as a C11-C12 keto-enol substructure in conjugation with a 12a-OH group and a C1-C3 diketo substructure.
- Removal of the dimethylamine group at C4 reduces antibacterial activity.
- Replacement of the carboxylamine group at C2 results in reduced antibacterial activity but it is possible to add substituents to the amide nitrogen to get more soluble analogs like the prodrug lymecycline.
- The simplest tetracycline with measurable antibacterial activity is 6-deoxy-6-demethyltetracycline and its structure is often considered to be the minimum pharmacophore for the tetracycle class of antibiotics.
- C5-C9 can be modified to make derivatives with varying antibacterial activity



Drug	Structure	Uses	Special Points / Adverse Effects
Tetracycline	-	Respiratory infections, acne, rickettsial infections, cholera	GI irritation, absorption ↓ with milk/antacids
Oxytetracycline		Brucellosis, acne, atypical pneumonia, chlamydial infections	More GI upset than tetracycline
Chlortetracycline		Rarely used in humans; veterinary antibiotic	First discovered tetracycline (1948); high toxicity
Minocycline		Acne vulgaris, meningococcal carrier state	Vestibular toxicity (dizziness, vertigo)
Doxycycline		Malaria prophylaxis, leptospirosis, rickettsial & chlamydial infections, syphilis (alt.)	Long-acting, safe in renal impairment, well absorbed