CHAPTER 1

ANTIBIOTICS - I

1.1 β-Lactam Antibiotics

Definition

Medicinal Chemistry: It deals with the discovery, design, development and both pharmacological and analytical characterization of drug substances.

Drug: A chemical substance used in the treatment, cure, prevention or diagnosis of disease.

Antibiotic: These are chemical substances produced by various species of microorganisms that, in small concentrations, destroy or inhibit the growth of other species of microorganisms.

- ✓ Antibiotics; the term is extended to synthetic antibacterial agents such as sulphonamides and quinolones.
- ✓ Bacteria, fungi, and actinomycetes are the various species from which antibiotics are produced.

Historical Background

- ✓ Chinese people (500-600 BC) used molded curd to treat boils and carbuncles (a red, swollen, and painful cluster of boils that appeared under the skin).
- ✓ In the meantime, the **science of bacteriology** (the study of bacteria and their relation to medicine) was developed. During studies, it has been observed that microorganisms are capable of producing some therapeutic (relating to the healing of disease) agents.
- ✓ In the year 1877 - **Louis Pasteur** & **Joubert** found that an injection of *anthrax bacillus* into lab animals did not produce any harmful effect and did not have the deadly effect if common bacteria were injected along with it.
- ✓ After 1929 - the modern history of antibiotics was started.
- ✓ **Sir Alexander flaming** (Fig. 1.1), a British bacteriologist, detected a chemical substance from *Penicillium notatum* (a species of fungus in the genus *Penicillium*) which have bacteriostatic in nature. Later, another researcher developed the preparation and structure of the active compound that produced from the mould.

- ✓ 1941 - The **Penicillin** was first used clinically as an antibacterial agent.
- ✓ 1944 - **Selman A Waksman** (Fig. 1. 8) isolated streptomycin from *Streptomyces griseus* (*Actinomycete* species). After that large number of antibiotics were discovered by other scientist. These includes natural origin and semisynthetic (structural analogues of natural origin) antibiotics. While a very small proportion of antibiotics have shown therapeutic value.
- ✓ The efficacy, toxicity, stability, economics of production, and rendering into suitable formulation are the parameters that should meet the acceptance of new antibiotics products. After successful evaluation, the new antibiotics are included in different pharmacoapeias as monograph.

Nature of antibiotics: Either, it has shown as **bactericidal** and **bacteriostatic** in nature.

Bacteriostatic: An antibiotic reversibly inhibits the growth of susceptible microorganisms.

Bactericidal: Antibiotics shall kill or destroy the microbes in *in vitro*.

Antibacterial property of antibiotic in concentration label: At low concentration antibiotic produces **bacteriostatic** action. While, at certain or higher concentration antibiotic produces **bactericidal** action.

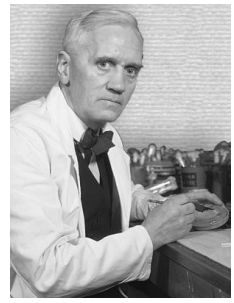


Fig. 1.1 Sir Alexander Fleming at St Mary's, Hospital, London (1943).

Drawbacks of frequent use of antibiotics: Microbial resistance may develop during prolonged use of antibiotics. Microbes could develop resistance to one antibiotic and another antibiotic, termed "cross-resistance". The resistance develops due to a stable genetic change that passes from generation to generation.

Classification

1. On the basis of antimicrobial properties:

(a) **Narrow spectrum antibiotics:** These types of antibiotics are effective against a few species of bacteria, gram-positive or gram-negative, fungi, or protozoa.

(b) **Broad-spectrum antibiotics:** These types of antibiotics are effective against a variety of microorganisms, including both gram-positive and gram-negative bacteria, rickettsia, and even protozoa.

2. On the basis of chemical classification:

(a) Amino acid derivatives: Ex. cycloserine and chloramphenicol

(b) β-lactam ring containing antibiotic (Natural): Ex. benzylpenicillin, procaine penicillin

(c) Semisynthetic penicillin: Ex. ampicillin, amoxycillin, cloxacillin

(d) Cephalosporin group antibiotic: Ex. cephalosporin group also called as "C family"

(i) First generation: Ex. cephaloridine, cefatrizine
(ii) Second generation: Ex. cefoxitin
(iii) Third generation: Ex. cefotaxime
(iv) Fourth generation: Ex. cefepime

(e) Non-β-lactam ring containing antibiotic: Ex. imipenem

(f) β-lactamase inhibitor: Ex. clavulanic acid

(g) Polypeptide antibiotic: Ex. bacitracin A, polymyxin B

(h) Aminoglycoside antibiotic- derived from sugars: Ex. gentamicin, amikacin, tobramycin, neomycin, and streptomycin

(i) Derived from acetate or propionate unit: Ex. tetracycline, oxytetracycline, chlortetracycline

(j) Fusidic acid containing antibiotic: Ex. clindamycin, vancomycin

(k) Macrolide ring containing antibiotic: Ex. Erythromycin, azithromycin, clarithromycin

(l) Miscellaneous: chloramphenicol

1.1.1 Penicillin

Historical Background

- ✓ **Penicillin** was the first & most important group of antibiotics.
- ✓ In 1928- **Sir Alexander Fleming** (worked at Saint Mary's Hospital. London (Fig. 1.1) of Scotland observed that a mould (*Penicillium notatum*) contaminated culture medium (*Penicillium notatum*) prevented the growth of *staphylococcal* bacterial in the culture media. Later, he identified that the mould has antibacterial properties. Thereafter, the chemical substance is named Penicillin, Penicillin II, or Penicillin G.
- ✓ In 1938 - **Howard Walter Flory** (an Australian pharmacologist and pathologist), **Ernest Boris Chain** (German refugee & a German-British biochemist), and **Edward Abraham** (an English biochemist) found that the crude material of the mould had antibacterial properties against *streptococcal* infected mice. They won a Nobel Prize in 1945 with Fleming.
- ✓ In 1941 - Penicillin has undergone a clinical trial. The first dose of penicillin was administered to a policeman at Oxford, who suffered from mixed *staphylococcal* and *streptococcal* infection.
- ✓ Same year, penicillin was produced by the deep fermentation process at the Northern Regional Research Laboratory, USA, and a clinical trial was held at Yale University and the Mayo Clinic in 1942. The penicillin was named as **Penicillin I** or **Penicillin F**.
- ✓ The yield of penicillin from *Penicillium notatum* was low, and it was replaced by *P. chrysogenum*

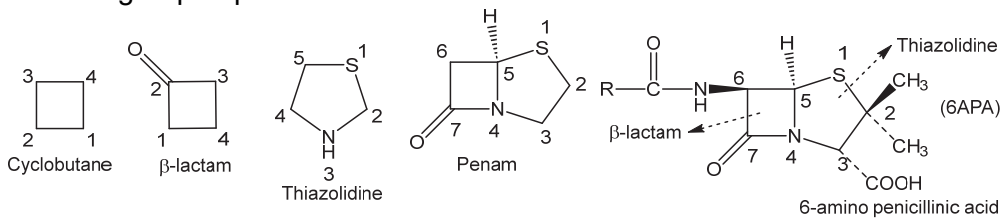
- ✓ 1943 - The chemical structure of penicillin was determined by **Sir Robert Robinson** of Oxford and **Karl Folkers** of Merck.
- ✓ 1957 - Penicillin was synthesized by **John Sheehan** and **K R Henery-Logan** of MIT, USA.

Nomenclature: Basic Chemical Structure of Penicillin ring

The basic structure of penicillin consists of a thiazolidine ring which is fused with a β-lactam ring, and there is a side chain at the C-6 position (Fig.1. 2).

Structure-Activity Relationship of Penicillin group (**Fig**.1.2)

1. Substitution at R = $C_6H_5CH_2$ group obtained as a **Benzyl Penicillin** or **Penicillin G** which occurs from *P. notatum*. It is a narrow spectrum of antibiotic and only natural occurring penicillin and used as clinically.
2. By substituting R = $C_6H_5OCH_2$ (2-Phenoxymethyl) group at C-6; forms a new antibiotic product known as Penicillin V, and the resultant compound shows antimicrobial activity.
3. A wide range of penicillin has been prepared by changing substitutions in the 6-amino group of penicillin.



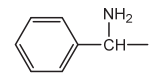
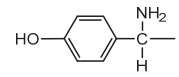
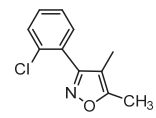
Example of Penicillin compound	Chemical Name	R = Substitution group
Benzyl Penicillin	6-(2-Phenylacetamido) penicillinic acid	$C_6H_5CH_2$--
Phenoxy methyl Penicillin or Penicillin - V	6-(2-Phenoxyacelamido) penicillinic acid	$C_6H_5OCH_2$--
Ampicillin	6-(α-D-Phenylglycylamino) Penicillic acid	
Amoxycillin	6-(α-D-P-hydroxy Phenyl glycylamino) Penicillic acid	
Cloxacillin	6-(3-(2-chlorophenyl)5-methylisoxazol-4-carboxamido)penicillinic acid	

Fig. 1.2 General Structure of Penicillin and their derivatives.

4. The acylated product of penicillin is termed semisynthetic penicillin. The nature of the acyl group (C=OR) has a significant effect on properties of the penicillin. The derived product has greater acid stability and resistance against penicillinase-producing bacteria. Hence, they are termed as a broader spectrum of antibiotics.

5. Methicillin was the first product of the penicillin group which shows resistance against penicillinase-producing *staphylococcal* bacteria. There are several aromatic (ampicillin) and heteroaromatic (oxacillin, carbenicillin, amoxycillin, etc.) substitutions in the C6-amino group that are more active than benzylpenicillin. However, they are not resistant to penicillinase enzyme-producing bacteria.

6. D--amino phenyl acetamido side chain of ampicillin has shown acid stability and is effective against gram-ve bacteria. While *P*-hydroxyl of benzene nucleus of amoxycillin shows better absorption in GIT.
7. S-atom at position 1 & N at 5 positions of the penicillin is essential for antibacterial activity.
8. Dimethyl group at C-2 of penicillin possesses antibacterial activity.

Chemical Degradation of Penicillin (**Fig.1.3)**

1. Penicillin is a strong monobasic acid. The free acid in penicillin is unstable.
2. The dry form of penicillin salt (either with an alkali metal or organic acid) is stable. The breakdown of the chemical structure of penicillin occurs under different conditions, such as biochemical and chemical processes.
3. The enzyme penicillinase or in the presence of an alkali, brake up the *β*-lactam system. Penicillin forms penicilloic acid, which on further heating, undergoes decarboxylate to form penilloic acid. This acid was then reacted with $HgCl_2$ to produce penilloaldehyde.
4. In a dilute acid solution (pH 5.0), intermolecular rearrangement occurs which forms penilic acids. This acid was then reacted with $HgCl_2$ to produce penillamine.
5. In the presence of strong mineral acids or mercuric chloride break up the thiazolidine ring. Thus, penicillin forms penicillamine and penaldic acid (unstable state). The unstable state of penaldic acid on further reaction with penilloaldehyde to form the desired product.

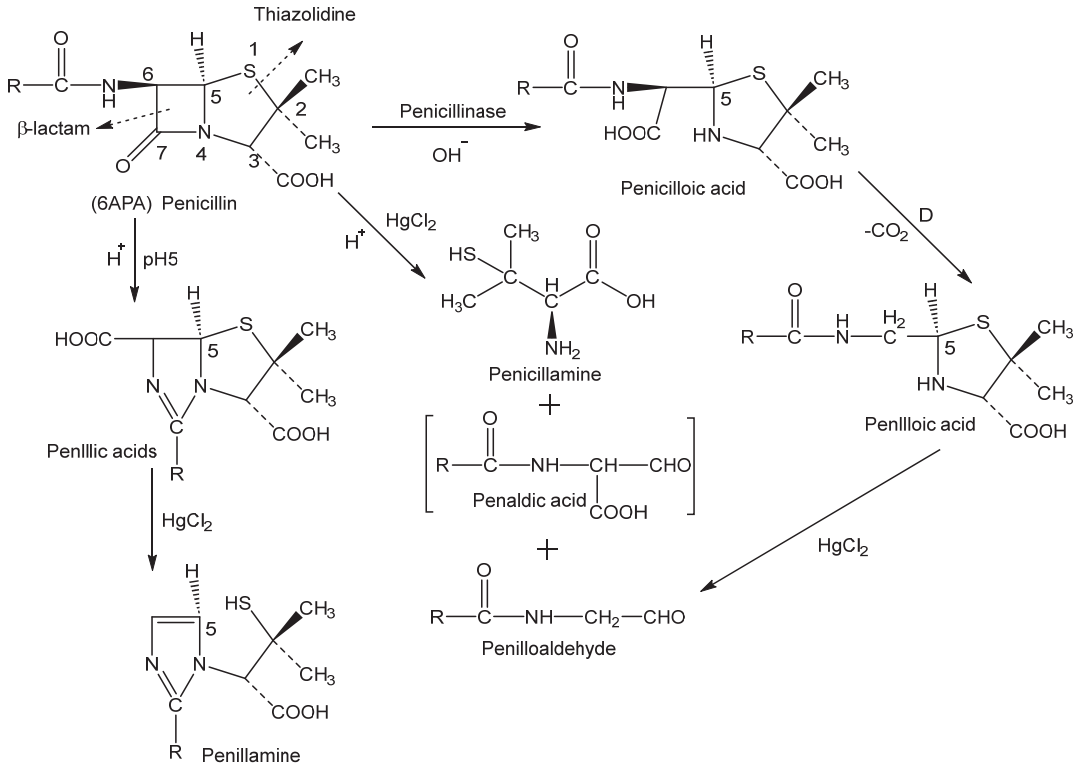


Fig. 1.3 Break down product of Penicillin.

Mechanism of Action of Antibiotic

Each class of antibiotic has a different type of mechanism of action. Some may have disorganized cell walls that cause loss of viability, which leads to cell death. Others may act on the cell membrane of the microorganism. Certain types of antibiotics affect the function of ribosomes and cause reversible inhibition of protein synthesis. Some antibiotics affect the function of the 30S or 50S subunits of the ribosome and change protein synthesis. Another type of antibiotic may affect nucleic acid metabolism.

Mechanism of Action of Penicillin

The term penicillin is used generically for the entire group of penicillins (prepared from biosynthetic or semisynthetic sources). They are usually bactericidal. They have inhibitory effects on the synthesis of the bacterial cell wall. The biological half-life is 30-60 minutes (a short period). They are well absorbed and widely distributed throughout the body. They are rapidly eliminated through glomerular filtration and renal tubular secretion.

Benzylpenicillin could be considered the parent compound of the penicillin family. It is active against gram-+ve bacteria, gram-ve *cocci*, *actinomycetes*, and *spirochetes*. In the presence of gastric acid, it becomes unstable and inactivated by bacteria that produce penicillinase-producing bacteria. **Penicillin V** is acid stable.

β-lactam Antibiotics inhibit peptidoglycan synthesis. Peptidoglycan is a heteropolymeric component of the cell wall. It is essential for the normal growth and development of bacteria. This provides mechanical stability for a highly cross-linked structure. It inhibits the enzyme transpeptidase and makes it inactive. So the synthesis of peptidoglycan is inhibited.

Uses:

- ✓ Treatment of *streptococcal* infection & rheumatic fever.
- ✓ Used in less sever types of microbial infection & UTI.

1.1.2 Cephalosporins

Historical Background

- ✓ Cephalosporins were discovered from *Cephalosporium acremonium* by **G. Brotzn** in the year 1945. He collected the fungus from seawater near a sewage outlet on the coast of Sardinia (a large Italian island). He found that the fungus has shown therapeutic activity against *staphylococcal* infections and typhoid fever.
- ✓ Many workers have shown interest in *Cephaosporium* species. Seven different antibiotic products were isolated from the species. Among them, five are fat soluble (one is steroidal - **Cephalosporin P**) and two (**Cephalosporin N & C**) are water-soluble.
- ✓ During the study, it was proved that **Cephalosporin N** is a penicillin-type. Later, it was marketed as **Penicillin N**. **Cephalosporin C** type is studied here due to its therapeutic value and the number of antibiotics generated by this group, and many of them possess its therapeutic value.

General Structure of Cephalosporin

- ✓ Official cephalosporin group is resembling the cepham general structure. But the chemical name for the official drug refers to the two general structures.
- ✓ Structure of cephalosporins corresponds to cepham (Structure - I) or 5-thia-1-azabicyclo [4.2.0] octane (Structure-II) (Fig.1.4).

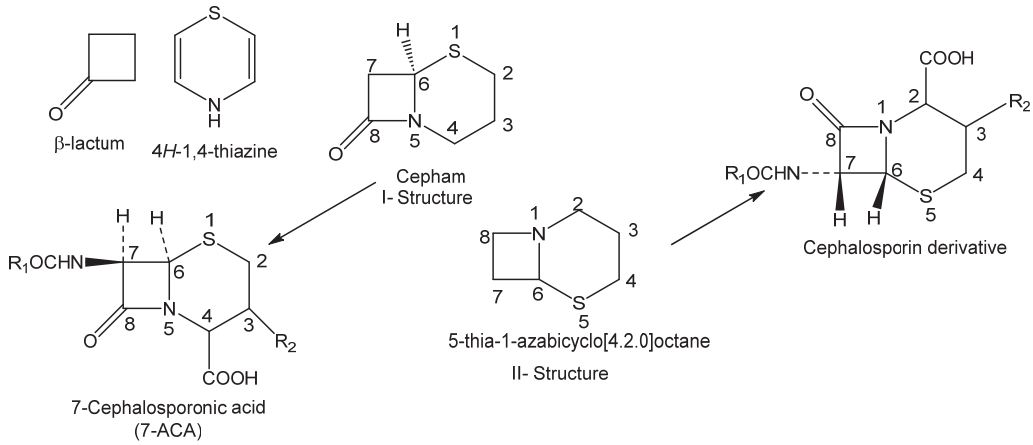


Fig.1.4 General structure of Cephalosporin.

- ✓ The β-lactam ring is fused with the 1,3 dihydro thiazine ring in place of the thiazolidine ring of penicillin. The fusion of the thiazine ring with β-lactam produces a stable antibiotic product. But, it is unable to resist acid and penicillinase-producing microbes.
- ✓ 7-amino acylation (acyl (R-C=O) group) at C-7 of the cephalosporin (Fig.1.4) structure produces a number of semisynthetic compounds.

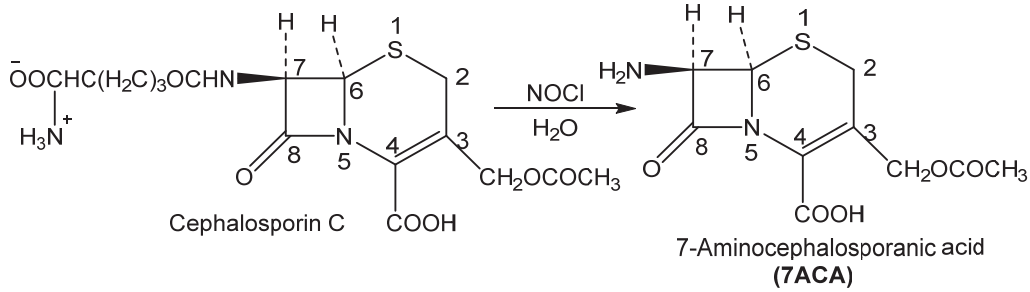


Fig.1.5 Chemical degradation of Cephalosporin C.

Chemical Degradation of Cephalosporin (Fig.1.5)

- ✓ **6-aminopenicillinic acid (6-APA)** is used for the preparation of semisynthetic penicillin. While **7-aminocephalosporanic acid (7-ACA)** is used for the preparation of semisynthetic cephalosporin compounds. There are a number of cephalosporin compounds generated by modification or substitution at the C-3 & C-7 positions.
- ✓ The breakdown of cephalosporin C with nitrosyl chloride (NOCl) in the presence of formic acid and followed by hydrolysis gives a new compound known as 7-aminocephalosporanic acid (Fig.1.5).
- ✓ Any suitable substitution at C-7 affects the antibacterial activity, and substitution at C-3 changes the pharmacokinetic properties of the compound.

Classification of Cephalosporin C (Fig. 1.6).

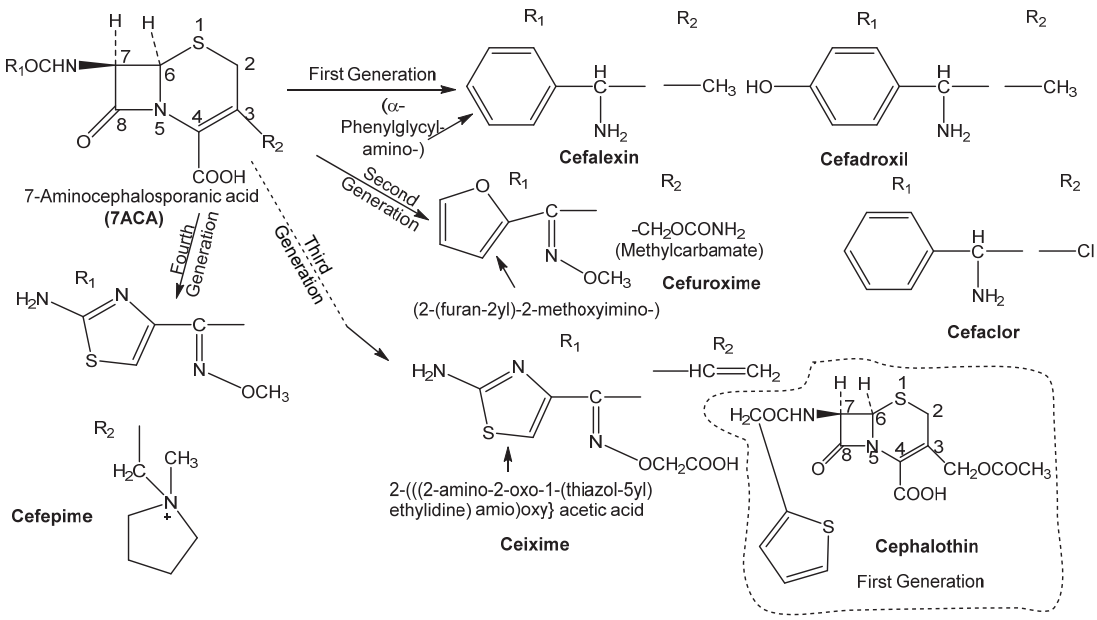


Fig. 1.6 Different classified generation of cephalosporin compounds.

1. **First generation Cephalosporins:** Ex. **Cephalothin** was first introduced and **Cephaloridine, Cephalexin, Cefadroxil, Cefradine, and Cefatriazine** were included in this group. These compounds are active against both gram-+ve and gram-ve bacteria and administered through the parental route due to their poor absorption character.
2. **Second generation:** Ex. **Cefamandole** was the first drug available in this group**.** Later, **Cefaclor, Cefoxitin, and Cefuroxime** are included in this group. These compounds are less active against gram+ve bacteria and more stable against β-lactamase-producing gram-ve bacteria.
3. **Third generation:** Ex. **Cefotaxime, Ceftriaxone, Cefixime,** and **Ceftazidine** are the compounds of this group. They are more active against gram-ve bacteria.
4. **Fourth generation:** Ex. **Cefepime.** It is active against a wide range of gram+ve and gram-ve bacteria.

Structure-Activity Relationship (Fig.1.6)

Any substitution at C-7 affects the antibacterial activity, and substitution at C-3 changes the pharmacokinetic properties of the compound.

1. Substitution at C-7 position of Cephalosporin ring.
   (a) Acylation (R-C=O) of the amino group, increases therapeutic potency against gram +ve bacteria.
   (b) Substitution of the aromatic ring increases its antibacterial property and lipophilic character.

(c) A heteroaromatic ring such as a thiophene, furan, or pyridine ring as a side chain improves its spectrum of activity.

(d) α-methoxy substitution improves the resistance to hydrolysis of β-lactamase-producing bacteria.

2. Substitution at C-3 position of Cephalosporin ring.
   (a) Substitution of a suitable group at C-3 affects its pharmacokinetic and antibacterial activity.
   (b) Substitution of the benzoyl ester group improves its gram +ve activity and lowers its gram -ve activity.
   (c) Substitution of a heterocyclic ring such as pyridine or pyrimidine improves its antibacterial property.
   (d) Substitution of aromatic thiol groups improves the antibacterial activity against gram -ve and pharmacokinetic properties.
   (e) Substitution of the $-CH_3$ & -Cl groups in place of the acetoxy ($-CH_3COO$) group improves its oral absorption property.
3. Oxidation of 'S' to sulfoxide (SO), decreases its antibacterial property.
4. The replacement of 'S' with 'O' retains its antibacterial properties. Similarly, replacing the -S group with the methylene group enhances chemical stability and has a longer biological half-life.
5. Carboxyl (C(=O)OH) group at C-4 has been converted to ester, shows increasing the bioavailability of the compound.
6. A double bond at the 2,3 position loses its antibacterial character.

Mechanism of Action

Cephalosporins have a similar mechanism of action as penicillin. Cephalosporins are bactericidal in nature. They inhibit bacterial cell wall synthesis. **First-generation** cephalosporin groups have effective antibacterial activity against gram +ve & moderate activity against some gram-ve bacteria. They are effective against *staphylococci* bacteria. **Second-generation** cephalosporins are less active against gram +ve but are stable to hydrolysis by gram-ve bacteria. They are active against Enterobacteriaceae and the influenza virus. **Third-generation** cephalosporins are more active against *β*-lactamase-producing gram-ve and less active against gram+ve bacteria. The **fourth generation** is effective against both gram+ve and *β*-lactamase-producing gram-ve bacteria.

Uses

- ✓ Used in the treatment of *staphylococci*, *enterobacteriaceae*, and influenza virus infections.
- ✓ Cephalosporin is active against both gram+ve and gram-ve bacteria.

1.1.3 β-Lactamase Inhibitors

There have been certain agents developed that are structurally similar to *β*-lactams but they are not actually penicillin or cephalosporin compounds. Examples: Clavulanic acid and sulbactam are two such *β*-lactamase inhibitors.

Clavulanic Acid

It is isolated from *Streptomyces clavuligerus*. It consists of *β*-lactam ring with an oxazolidine heterocycle ring. Potassium clavulanate is an official product. It is well absorbed orally. It is given in combination with amoxicillin for oral and ticarcillin for parenteral use.

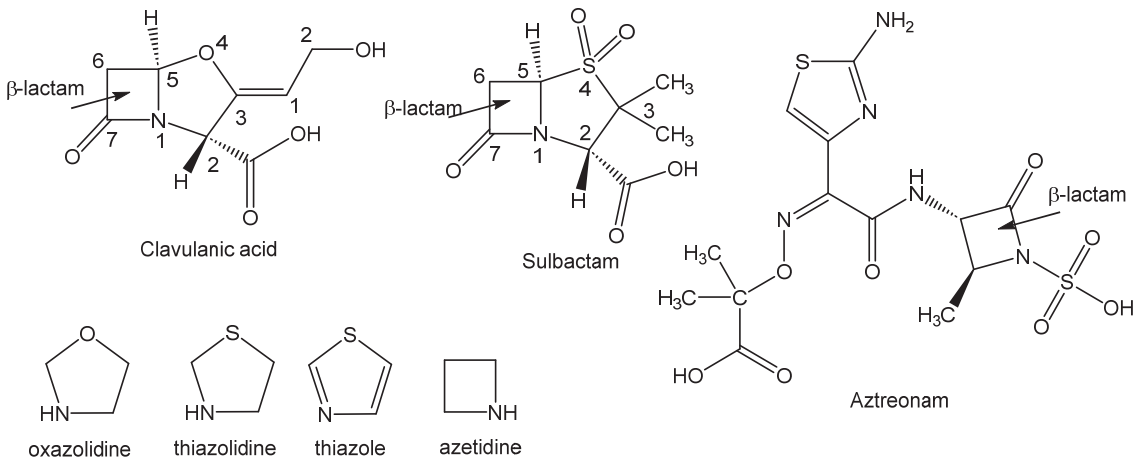


Fig. 1.7 Structure of Lactamase inhibitors and Monobactams.

Chemical Structure: see Fig.1.7

Chemical Naming:

(2R,5R,Z-)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo [3.2.0] heptane-2-carboxylic acid

Uses

- ✓ Given combination with amoxicillin as first-line treatment of different types of infections, including sinus and urinary tract infections.
- ✓ Given combination with penicillins and cephalosporins to treat infections caused by *β*-lactamase-producing microbes.

Mechanism of action: Clavulanic acid is a semisynthetic *β*-lactamase inhibitor antibiotic, isolated from *Streptomyces* spp. It binds strongly to *β*-lactamase at or near its active site. This protects other *β*-lactam antibiotics from *β*-lactamase catalysis, thereby increasing their antibacterial effects.

Sulbactam: It is a semi-synthetic *β*-lactamase inhibitor. Structurally, it is penicillanic acid 1, 1-dioxide.

Chemical Structure: see Fig. 1.7

Chemical Naming:

(2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide.

Uses

- ✓ Combining with β-lactamase susceptible antibiotic, such as penicillins or cephalosporins, to treat infections caused by β-lactamase-producing microbes.

Mechanism of Action

The *β*-lactam ring of sulbactam irreversibly binds to *β*-lactamase at or near its active site, thereby blocking enzyme activity. Many *β*-lactam-containing antibiotics act as substrates for *β*-lactamase enzyme-producing bacteria. *β*-lactamase inhibitors type of antibiotics are bound to the active site of *β*-lactamase enzyme-producing bacteria and prevent the destruction of *β*-lactam inhibitor antibiotics. It has poor antimicrobial properties but is active against *β*-lactamase enzyme-producing bacteria.

Structure-Activity Relationship

1. Any alteration of β-ring loses its potency.
2. Removal of the hetero 'N' atom by any other heteroatom results in an inactive compound.
3. Removal of the C=O group from the ring reduces or loses its activity.
4. Sulfone group of sulbactam is essential and increases its antibacterial activity.

Monobactams: Ex. Aztreonam

Aztreonam, a *β*-lactam ring, is not condensed with another ring. It is a monocyclic-lactam compound and is also called a monobactam compound. It was isolated from *Chromobacterium violaceum*. It can be synthesized from threonine (an amino acid).

Chemical Structure: see Fig. 1.7

Chemical Naming:

2-((((Z)-1-(2-aminothiazol-4-yl)-2-(((2S,3S)-2-methyl-4-oxo-1-sulfoazetidin-3-yl)amino)-2-oxoethylidene) amino)oxy)-2-methylpropanoic acid

Uses

- ✓ Infections caused by gram-ve bacteria such as *Pseudomonas aeruginosa.*
- ✓ Used in the treatment of bone infections, pneumonia, and urinary tract infections.
- ✓ It is administered parenterally in the treatment of gram-ve aerobic infections, including *Pseudomonas aeruginosa*.

Mechanism of Action

It inhibits the synthesis of the bacterial cell wall, by blocking peptidoglycan cross-linking. It is bactericidal, but less active than cephalosporin compounds. It is resistant to β -lactamase-producing bacteria. It has a narrow spectrum of antibacterial activity.

Structure Activity Relationship

1. The sulphate (SO_3-) group does not distort (alter) the β-lactam ring but is sufficiently electronegative to activate it.
2. Carboxyl group increases its antibacterial activity.
3. Aminothiazole oxime group of the structure imparts effective against gram-ve bacteria.
4. α-methyl group increases resistance to β-lactamase-producing bacteria.

1.2 Aminoglycosides

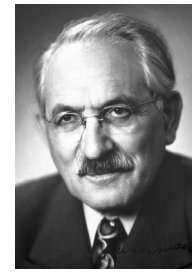


Fig. 1.8 Selman A. Waksman. N. Kresge, et al., 2004

- ✓ Aminoglycoside antibiotics are produced by (*Streptomyces* spp. Ex. **streptomycin, neomycin, framycetin, kanamycin** and **tobramycin** and *Micromonospora* spp. (Ex. **gentamicin** and **sisomicin**).
- ✓ Structurally, they are closely related to each other.
- ✓ They contain aminocyclitol (2-deoxystreptamine) with aminosugars linked glycosidically. Hence, they are called aminoglycosidic aminocyclitiols.

Mechanism of Action

Aminoglycoside antibiotics are bactericidal in nature. They are interfering with bacterial protein synthesis. They are most active against gram-ve rods (the shape of the bacteria). Gram+ve and anaerobic bacteria are resistant to aminoglycoside antibiotics. *Staphylococcus aureus* is resistant to aminoglycoside antibiotics. They have delayed absorption in GIT. Hence, it is preferred over the parental route. They are excreted through urine in unchanged form. Some of the members are useful as anti-tubercular drugs.

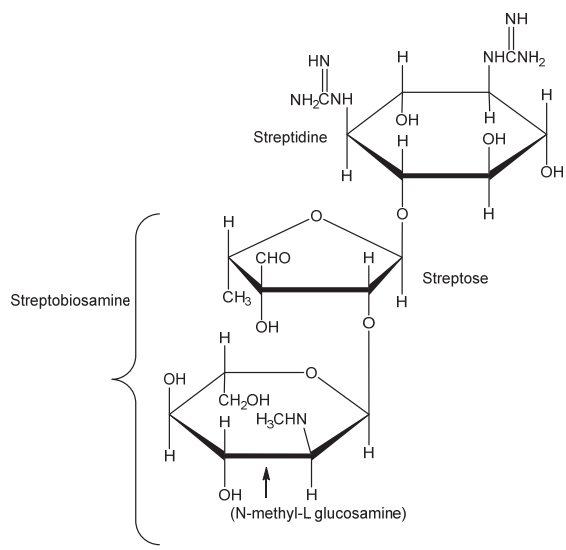


Fig. 1.9 Chemical structure of Streptomycin.

Toxicity: ototoxicity, nephrotoxicity, allergy, and neuromuscular blocking activity limit the use of aminoglycosides.

1.2.1 Streptomycin

Historical Background

1944 - **Selman A. Waksman** & his associates discovered streptomycin from *Streptomyces griseus*. It was the first aminoglycoside antibiotic and the first effective drug in the treatment of tuberculosis. He was considered the "Father of Antibiotics" (Fig. 1.8). Streptomycin sulphate is an official drug.

Chemical Structure

Streptomycin (Fig.1.9) is a triacidic base (capable of combining with three molecules of a monobasic acid) compound. The structure belongs to an aldehydic carbonyl group. It consists of three structural units of aminoglycoside **streptidine** (diguanidinyl compound corresponding to streptamine), **streptose,** and **N-methyl-L-glucosamine**. Each structure is connected through glycosidic linkages.

Chemical Breakdown of Streptomycin

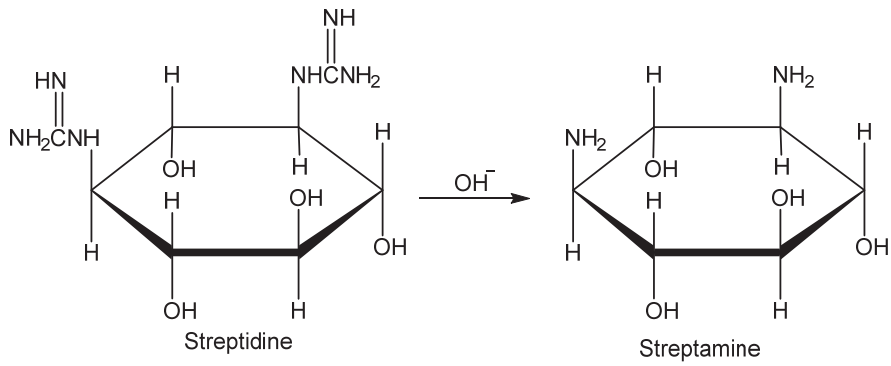


Fig.1.10 Chemical degradation of streptomycin.

1. Streptomycin on hydrolysis under acidic conditions gives diacidic base streptidine.
2. Streptidine on alkaline hydrolysis is converted to urea derivative and then diamine streptamine. It is a meso compound. (A meso compound or meso isomer is a non-optically active member of a set of stereoisomers, at least two of which are optically active. This means that despite containing two or more stereogenic centers, the molecule is not chiral.)
3. Mild hydrolysis with CH_3OH/HCl gives streptidine (Fig.1.10) and methyl streptobiosaminide dimethyl acetal.
4. Streptomycin on reduction gives dihydrostreptomycin, which is a semisynthetic antibiotic. During the conversion process, the aldehyde group of streptomycin is changed to a primary alcohol ($-CH_2OH$).
5. *Streptomyces humidus* fermentation has successfully isolated dihydrostreptomycin, which is also naturally occurring. However, dihydrostreptomycin is more ototoxicity than streptomycin. Therefore, it is used only for veterinary purposes and not for human use.

Uses

- ✓ It has particular activity against *Mycobacterium tuberculosis*. Therefore, its main use is in the treatment of tuberculosis, along with other antimycobacterial agents.
- ✓ It acts as an alternative to gentamycin. Hence, it has been given in combination with penicillin for the treatment of endocarditis (this is an infection of the endocardium, which is the inner lining of your heart chambers and heart valves)
- ✓ Used in the treatment of **plague** and **tularemia** (a severe infectious bacterial disease of animals transmissible to humans, characterized by ulcers at the site of infection, fever, and loss of weight)

1.2.2 Neomycin

Historical Background

1949 - **S. A. Waksman** & **H. A. Lechevalier** discovered neomycin, which is produced from *Streptomyces fradiae*. Neomycin sulphate is an official drug.

Chemical structure: Neomycins (Fig.1.11) is a mixture of three compounds such as neomycins A, B & C. The separation of the compound could be possible.

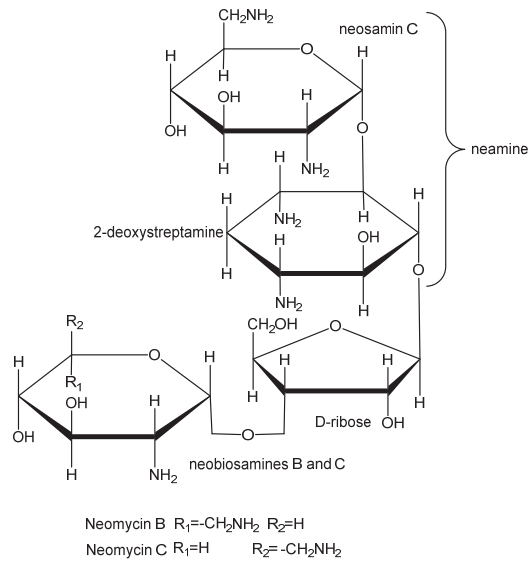


Fig.1.11 Chemical structure of Neomycin.

Chemical Breakdown of Neomycins

1. On methanolysis (alcoholysis using methanol) neomycins B & C gave methyl neobiosaminides B & C.
2. The difference between neobiosamines B & C can be distinguishing with stereochemistry at position 5 in the components neosamines B and C.
3. This is sole difference in between neobiosamines B & C and neomycins B and C.

Uses

- ✓ It is active against gram-ve bacteria and *Staphylococcus aureus*.
- ✓ It is applied topically in the treatment of ear, eye, and skin infections.
- ✓ It is given in combination with corticosteroids for topical application.
- ✓ It has been used as bowel preparation (cleansing the colon) before surgery and treatment of GIT.
- ✓ It possesses toxicity; which limits its use in systemic infections.

1.2.3 Kanamycin

Historical Background

1957 - **H. Umezawa** isolated the compound from cultures of *Streptomyces kanamyceticus*, the organism obtained from the soil of the Nagarov district of Japan.

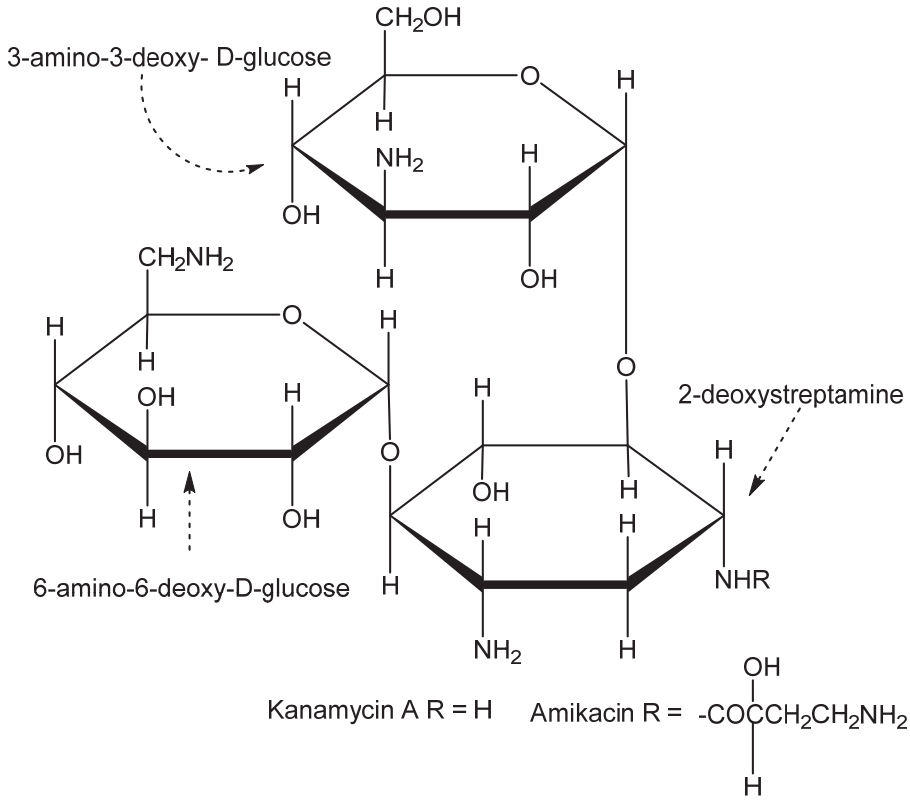


Fig.1.12 Chemical structure of Kanamycin.

Chemical Structure of Kanamycin

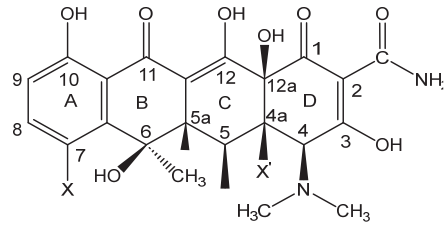
1. **Kanamycin A** (Fig.1.12) is the major and **kanamycins B** & **C** are the minor components.
2. The aminocyclitol 2-deoxystreptamine and 3-deoxy- 3-amino-D-glucose are present in all three components.
3. The difference is with regard to the second amino sugar, which is linked glyosidically to the 4-position of the central 2-deoxystreptamine. It is 6-amino- 6-deoxy-D-glucose in kanamycin A.
4. **Amikacin** is a semisynthetic derivative, The compound is prepared by acylation of the 1-amino group of 2-deoxystreptamine moiety with L-4-amino-2-hydroxybutyric acid of kanamycin A.

Uses

- ✓ Treatment of severe infections caused by microorganism resistance to gentamicin and tobramycin.
- ✓ Given in treatment of tuberculosis with other drugs. However, the toxicity of the drug limits its use.
- ✓ Treatment of intestinal infections and other infections caused by microorganisms.

1.3 Tetracyclines

Tetracycline (Fig.1.13) antibiotics are organic compounds. These group antibiotics are derived from acetic acid (CH_3COOH) & propionic acid (CH_3CH_2COOH) derivative compounds. Such derived antibioics as **tetracyclines, fusidic acid,** and **erythromycin** possess antibacterial properties. While, **griseofulvin**, **amphotericin**. and **nystatin** act as antifungal agents, **daunorubicin** and **doxorubicin** are antineoplastic agents.



Tetracycline X = X' = H
Oxytetracycline X = H, X = OH
Chlorotetracycline X = Cl, X' = H

Fig.1.13 Chemical structure of tetracycline group.

Historical Background

- ✓ Tetracyclines are a group of antibiotics originally derived from *Streptomyces* spp.
- ✓ **Chlorotetracycline** was discovered as the first antibiotic of the series.
- ✓ 1948 - **B. M. Duggar** isolated chlorotetracycline from *Streptomyces aureofaciens.*
- ✓ **Oxytetracycline** was the next member of this group. It is isolated from *Streptomyces rimosus* species.
- ✓ **Tetracycline** was the third member of this group and was first obtained by catalytic hydrogenolysis of Chlorotetracycline and thereafter by fermentation in low-chloride media.

Classification of Tetracyclines: On the basis of duration of action (biological half-life):

- ✓ **Short acting tetracyclines** - Ex. Chlorotetracycline (6hr), Oxytetracycline (8hr), Tetracycline (9hr)
- ✓ **Intermediate acting (12-14hr):** Ex. Demeclocycline and Methycycline
- ✓ **Long acting (16-18hr):** Ex. Minocycline and Doxycycline

Chemical name of tetracycline: 4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4, 4a,5,5a,6,11,12aoctahydrotetracene- 2-carboxamide OR 4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-meth-1, 11-dioxo-naphthacene-2-carboxamide.

Structural Elucidation

1. Structurally, tetracyclines have a common tetracyclic ring known as the **octahydronaphthacene** nucleus.
2. Each structure of this group has close chemical similarities. The difference in between the two antibiotics is that Chlorotetracycline has a chloro group(-Cl)group at the C-7 position and in **Oxytetracycline** has a hydroxyl (-OH) at position C-5.
3. **Chlortetracycline, oxytetracycline** and **tetracycline** are natural occurring product. Structurally, tetracycline has differ from chlortetracycline only by the absence of the methyl group at C-6. While doxycycline and minocycline are semisynthetic compounds.
4. In **Tetracycline** there are five chiral centers, and each of these centers has an S configuration. Tetracycline HCl is an official product. Eye ointment and drops of the product are used to treat ocular infections.

Structure-Activity Relationship

1. Keto-enol system of the ring A for antibacterial activity. If changes the functional group in this ring changes its character or loses its activity.
2. Carbamoyl group at C-2 is essential for antimicrobial activity. Unsubstitution or monosubstitution is acceptable. The large alkyl group in replacement of this position loses its antibacterial activity.
3. Keto-enol system at C-3 is suitable for antibacterial activity.
4. Dimethyl amino at C-4, which favorably contributes to the keto-enol system of the ring A. replacement of this group causes the loss of its activity.
5. α-hydrogen atom at C-4a & 5a is necessary for their antibacterial activity.
6. Substitution of hydroxyl group at C-5 (in the case of oxytetracycline) shows the more potent antimicrobial or broad spectrum of activity.
7. The antimicrobial activity is related to the substitution of the CH_3 group at C-6 and the -OH group. Replacement of the -OH group in this position forms a novel product known as doxycycline which also possesses a broad spectrum of activity.
8. Cl group at C-7 (Chlortetracycline) has produced potent antibiotics. Replace the group with NO_2 to produce a toxic effect against the host.
9. Hydroxyl group at C-10 is necessary for a broad spectrum of activity.
10. Keto-enol system at C-11 is required for antibacterial activity and at C-11a for binding of bacterial cell walls.
11. Hydroxyl group at 12a improves its lipophilicity character and is essential for antibacterial activity.

Mechanism of Action

At therapeutic concentrations, tetracyclines act as bacteriostatic agents. They interfere with protein synthesis, such as aminoglycoside antibiotics. The main site of action of

tetracyclines is the bacterial ribosomes. They bind to the 30S bacterial ribosomes and prevent the access of aminoacyl tRNA to the acceptor (A) site on the mRNA -ribosome complex.

It possesses a wide spectrum of microbial activity, which includes gram+ve, gram-ve bacteria, chlamydiae, rickettsia, mycoplasma, spirochaetes, mycobacteria, and protozoa.

1.3.1 Oxytetracycline

Oxytetracycline dihydrate, oxytetracycline calcium, and HCl are the official products. Tablets, capsules, and injections are used in topical applications.

Chemical Name:

4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6, 11, 12a-octahydronaphthacene-2-carboxamide

Structural Elucidation

1. Oxytetracycline (Fig.1.13) carries one additional chiral center at the C-5 position of S-configuration.
2. The configuration at positions 4a & 5a is the same as tetracycline.

1.3.2 Chlorotetracycline

Chlorotetracycline (Fig.1.13) HCl is the official product. The product is applied topically as an ointment to the eye or as a cream or ointment to the skin.

Chemical Name

(4S,4aS,5aS,6S,12aS)-7-chloro-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6- methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene (or naphthacene)-2-carboxamide.

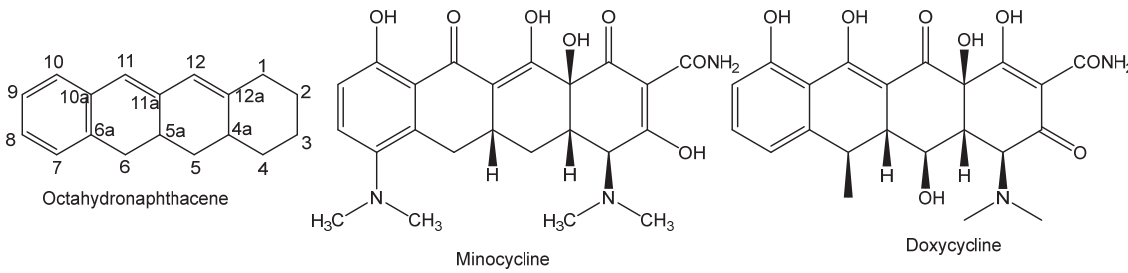


Fig. 1.14 Chemical structure of Doxycycline and Minocycline.

1.3.3 Doxycycline

Doxycycline (Fig.1.14) HCl, IP, and Doxycycline hyclate, BP are the official product. it is given in the oral route and occasionally given in the parental route.

Chemical Name

(4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3, 12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide

Structural Elucidation

1. Chemical naming of Doxycycline is similar to chemical naming of oxytetracycline.
2. Methyl group at C-6 are similar in both but Hydroxyl group at C-6 is absent.
3. The absolute configuration at the position has R-configuration in Doxycycline. While, it is S-configuration in oxytetracycline.

1.3.4 Minocycline

Minocycline (Fig.1.14) HCl, BP is the official product. Preferable, it is given in oral route.

Chemical Name

(4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

Uses

- ✓ Used in the treatment of *Rickettsia,* Mycoplasma, and Chlamydia infections and pelvic inflammatory disease. Tetracyclines are not suitable for the treatment of gram+ve and gram-ve infections.
- ✓ Treatment of cholera, severe acne, and amoebic dysentery.
- ✓ Given in combination with streptomycin or rifampicin in treatment of plague. In cases of malaria (*P. falciparu*m), given in combination with quinine.
- ✓ Preferred route of administration is the oral route, but most cases are given via the IV route and are rarely chosen as IM. Except for use in the eye, topical application shall be avoided, because it poses a high risk of toxic effects.