Program	B. Pharmacy
Semester	VI
Subject /Course	Medicinal Chemistry III
Subject/Course ID	BP 601T
Module No.	01
Module Title	Antibiotics
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Learning Outcome of module-1

LO	Learning Outcome (LO)	Course Outcome Code
LO1	To Understand the Nomenclature& Stereochemistry of the drugs	BP601.1
LO2	To understand the Structure activity relationship of drugs.	BP601.4
LO3	To understand the Chemical degradation classification and important drugs	BP601.1

Content

Topics
β-Lactam antibiotics
Penicillin
Cephalosporins
β- Lactamase inhibitors
Monobactams.
Aminoglycosides
Streptomycin
Neomycin
Kanamycin.
Tetracyclines
Tetracycline
Oxytetracycline
Chlortetracycline
Minocycline
Doxycycline.

ANTIBIOTICS

INTRODUCTION

The term antibiotic has its origin in the word antibiosis (i.e. against life). Antibiotics are chemical substances obtained from various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms and eventually may destroy them. The probable points of difference amongst the antibiotics may be physical, chemical, pharmacological properties, antibacterial spectra, and mechanism of action. They have made it possible to cure diseases caused by bacteria, such as pneumonia, tuberculosis, and meningitis, and they save the lives of millions of people around the world.

CLASSIFICATION

Antibiotics are classified on the basis of their mechanism of action and by its chemical nature.

Classification Based on Mechanism of Action

1. ***Agents that inhibit the synthesis of bacterial cell wall*:** These include the penicillins and cephalosporins that are structurally similar and dissimilar agents, such as cycloserine, vancomycin, bacitracin and the imidazole antifungal agents.

2. ***Agents that act directly on the cell membrane of the microorganisms, affecting permeability, and leading to leakage of intracellular compounds*:** These include polymyxin, polyene antifungal agents, nystatin, and amphotericin B that bind to cell wall sterols.

3. ***Agents that affect the function of 30s and 50s ribosomal subunits to cause reversible inhibition of protein synthesis*:** These include tetracyclines, erythromycins, chloramphenicol, and clindamycin.

4. *Agents that bind to the 30s ribosomal subunit and alter protein synthesis*: These include aminoglycosides that leads to cell deaths eventually.

5. ***Agents that affect nucleic acid metabolism:*** Such as rifamycins, which inhibit DNA dependent RNA polymerase

Classification Based on Chemical Structure

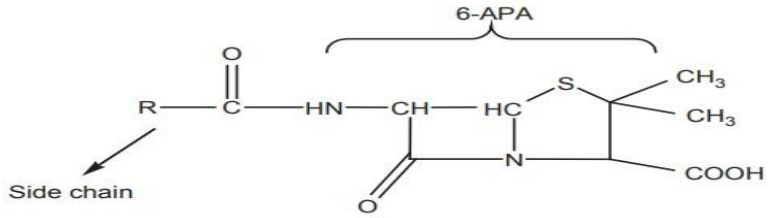
1. β-lactam antibiotics
2. Aminoglycoside antibiotics
3. Tetracycline antibiotics
4. Polypeptide antibiotics
5. Macrolide antibiotics
6. Lincomycins
7. Other antibiotics

1. β-lactam antibiotics

This consists of two major classes of agents, that is penicillins and cephalosporins.

a. Penicillins

Penicillin, the most important antibiotic, was first extracted from the mould *Penicillium notatum*. Subsequently, a mutant of a related mould, *P. chrysogenum*, was found to give the highest yield of penicillin and is employed for the commercial production of this antibiotic. Penicillin belongs to a group of antibiotics called β-lactam antibiotics. The basic structure of the penicillins consists of a thiazolidine ring fused with a β-lactam ring, which is essential for antibacterial activity. These two rings constitute the fundamental nucleus of all the penicillins, namely, 6-amino penicillanic-acid (6-APA) A variety of semisynthetic penicillins are produced by altering the composition of the side chain attached to 6-APA nucleus. Both the 6-APA nucleus and side chain are essential for the antibacterial activity.



Basic structure of penicillin

Nomenclature

Penicillins are named in the following ways:

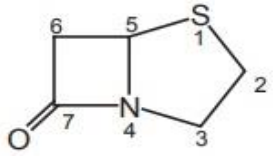
a. Chemical abstract

The penicillins are described as 4-thia-1-azabicyclo (3.2.0) heptanes.

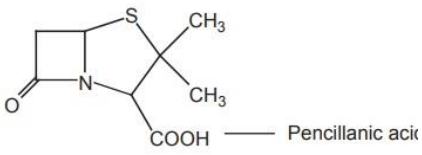
Benzyl penicillin is 6-(2-phenylacetamido)-3, 3-dimethyl-7-oxo-4-thia-1-azabiclo (3.2.0) heptane2-carboxylic acid.

b. Penam

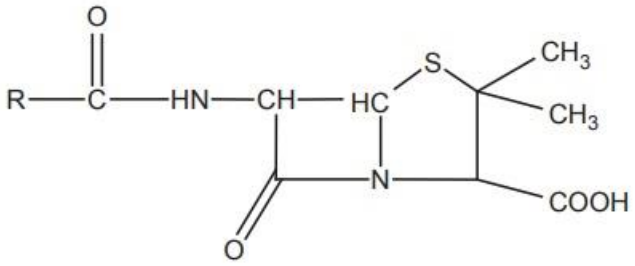
In order to simplify the unsubstituted bicyclic ring system of penicillin, it is given the name penam. Accordingly, the penicillins are 6-acylamino-2, 2-dimethyl penam-3-carboxylates.

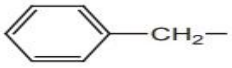
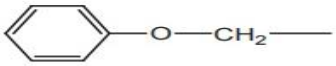
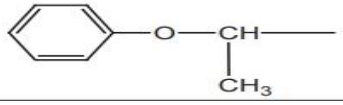


c. Pencillanic acid derivatives



Classification of penicillins

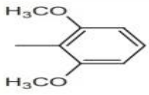
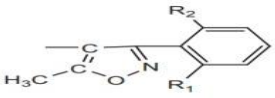
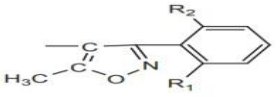
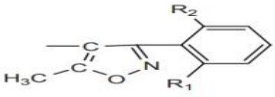
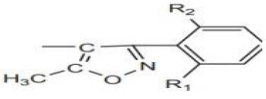
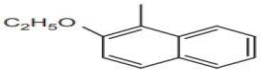


Name	Nature of Substituent (R)
Penicillin G (Benzyl penicillin)	
Penicillin V (Phenoxy methyl penicillin)	
Phenethicillin	

I. Penicillinase-susceptible penicillins

The general impact on antibacterial activity is as follows:

- Good gram-positive potency against susceptible *Staphylococci* and *Streptococci*
- Useful against some gram-positive *cocci*
- Not effective against gram-negative bacilli.

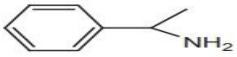
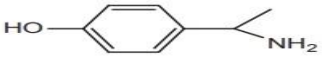
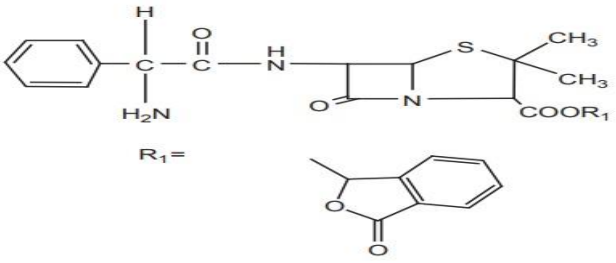
Name	R
(i) Methicillin	
(ii) Oxacillin (R_1=R_2=H)	
(iii) Cloxacillin (R_1=H, R_2=Cl)	
(iv) Dicloxacillin (R_1= R_2=Cl)	
(v) Floxacillin (R_1=F, R_2=Cl)	
(vi) Nafcillin	

II. Penicillinase-resistant penicillins

General impact on antibacterial activity is as follows:

- Decreased susceptibility to many penicillinases.
- Active against microrganisms, resistant to early penicillin.
- Oxacillins offer good oral activity.

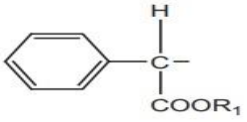
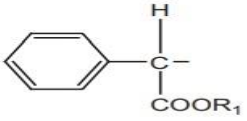
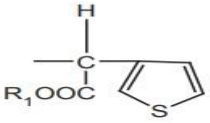
III. Aminopenicillins

Name	R
Ampicillin	
Amoxicillin	
Talampicilin	

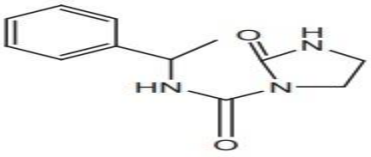
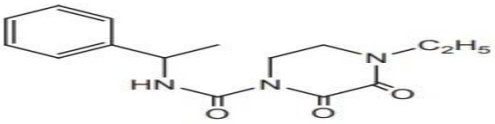
General impact on antibacterial activity is as follows:

- ✓ Extended spectrum of activity against some gram-negative bacteria and retention of gram-positive potency
- ✓ Ineffective against *Pseudomonas aeruginosa*

IV. Antipseudomonal penicillins (Carboxy Penicillins)

Name	R
Carbenicillin (R_1=H)	
Indanyl carbenicillin (R_1=5-indanol)	
Ticarcillin (R_1 = H)	

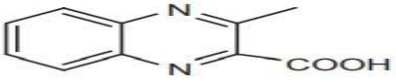
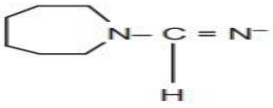
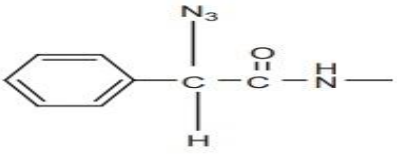
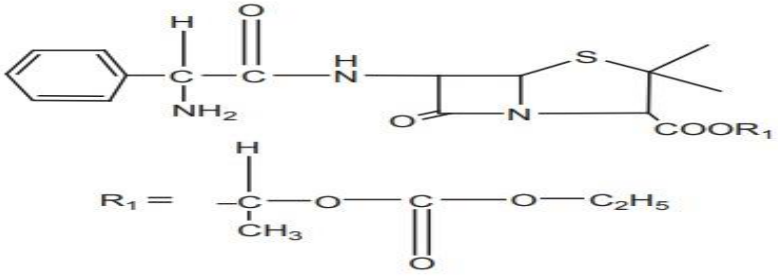
V. Ureidopenicillins

Name	R
Aziocillin	
Piperacillin	

General impact on antibacterial activity is as follows:

- Enhanced spectrum of activity against *P. aeruginosa* and expanded activity against *Klebsiella.*
- Good potency against gram-positive bacteria, but generally not effective against penicillinase producers.
- Good pharmacokinetic profile.
- Good activity against *Escherichia coli, Klebsiella, Shigella, Salmonella,* and many other resistant species.

VI. Miscellaneous penicillins

Name	R
Quinicillin	
Amidinopencillins (Mecillinam)	
Azidocillin	
Bacampicillin	

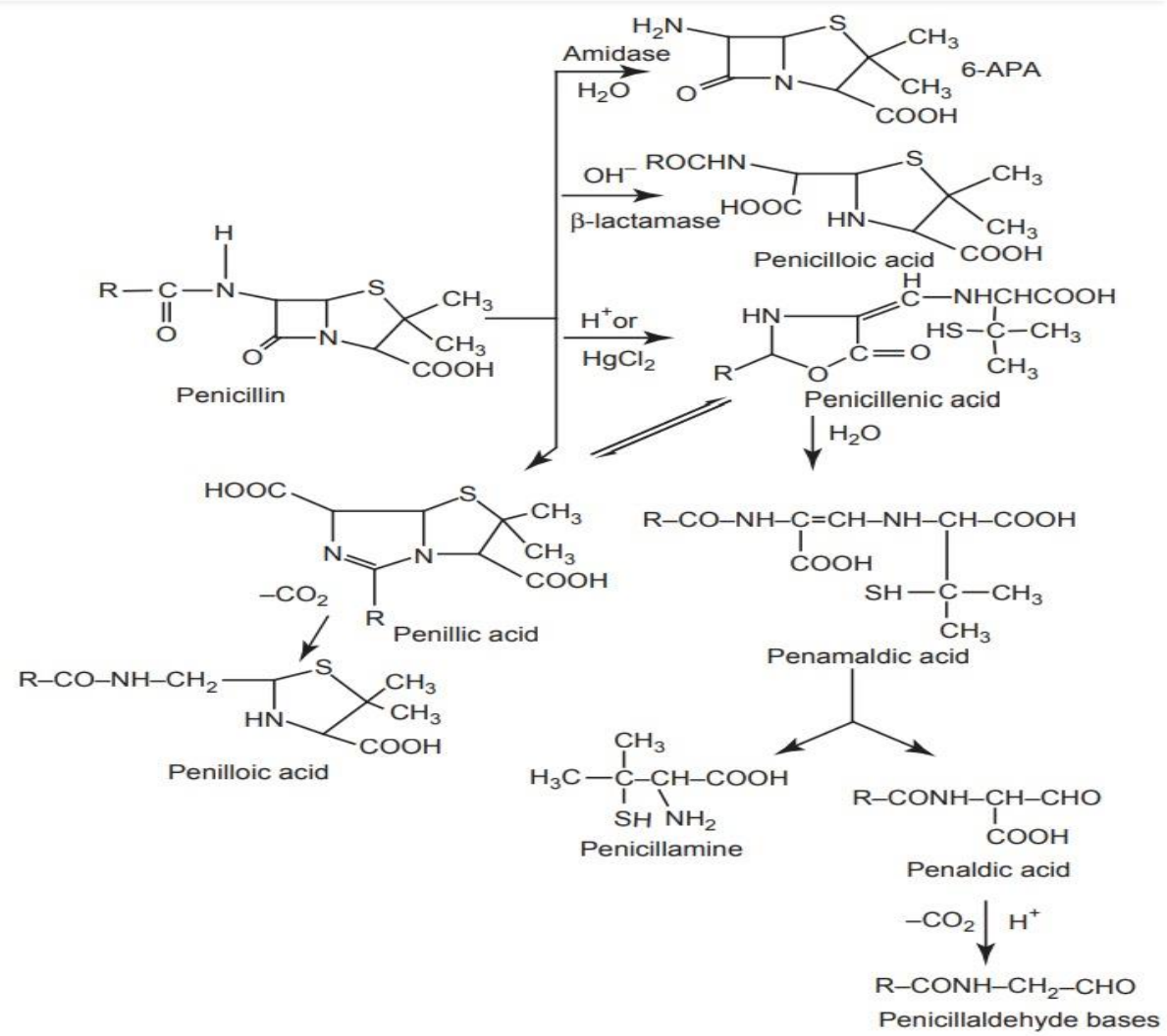


Figure 4.1 Chemical degradation of penicillins.

Inactivation of penicillins by acids, bases, and β-lactamases is as follows:

The penicillins are very reactive due to the strained amide bond in the fused β-lactum of the nucleus.

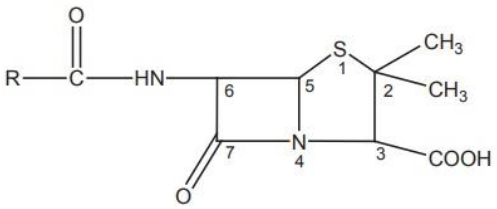
Penicillins undergo a complex series of reactions leading to a variety of inactive degradation products.

They are extremely susceptible to nucleophilic attack by water or hydroxide ion to form the penicilloic acid.

β-Lactamses also cleave the β-lactam ring to give penicilloic acid with a consequent loss of antibacterial activity.

In strongly acidic solutions (pH < 3), penicillin is protonated at the β-lactam nitrogen, and this is followed by nucleophillic attack of the acyl oxygen atom on the β-lactam carbonyl carbon. The subsequent opening of the β-lactam ring destabilizes the thiazoline ring, which opens to form penicillenic acid that degrades into two major products penicillamine and penilloic acid. A third product, penicilloaldehyde is also formed.

SAR of Penicillins



6-Acyl side chain: The substitution of R on the primary amine with an electron withdrawing group decreases the electron density on the side chain and protects from acid degradation. Substituents on the α-carbon of the side chain, such as amino (ampicillin), chloro, and guanidine exert good resistance to inactivation by acids. Benzyl penicillin undergoes acid and alkali degradation and is susceptible to all known β-lactamase. The increased latitude in varying the acyl amino side chain through acylation of 6APA results with superior biological activity. Substitution of α-aryl of the alkyl group in the side chain gives increased stability and oral absorption.

1. Substitution of bulky groups on α-carbon of the side chain confers β-lactamase resistance. Examples: methicillin, nafcillin, oxacillin, etc. In all these penicillins, an aromatic ring is attached directly to the side chain amide carbonyl, and there is substitution at both positions ortho to the point of attachment. The size of the ring systems plays an important role in determining the ability of the ortho substitutent to confer penicillinase resistance.

2. The isomeric forms of penicillins differs in their activity. Example: $_{D}$-isomer is 2–8 times more active than $_{L}$-isomer of amoxicillin. The introduction of polar group or ionized molecule into the α-position of the side chain in the benzyl carbon atom of penicillin-G confers against the gram-negative bacilli. Amino, hydroxyl, carboxyl, and sulphonyl increases gram-negative activity. Example: ampicillin and carbenicillin.

3. Replacement of acyl side chain with hydroxymethyl groups shows improved gram-negative activity and introduction of C-6 α-methoxy group produces greater stability against β-lactamase. N-acylated ampicillins (ureidopenicillins) have increased activity against Pseudomonas.

4. Many esters of the carboxyl group attached to C-3 have been prepared as prodrugs to increase lipophilicity and acid stability. Example: Acetoxymethyl ester derivatives are used for preparing prodrugs.

5. The sulphur of the thiazolidine ring with O, CH , and CH-β-CH_3 gives broad-spectrum antibacterial activity. The geminal dimethyl group at C-2 position is a characteristic of the penicillin. In general, derivatization of the C-3 carboxylic acid functionality is not tolerated unless the free penicillin carboxylic acid can be generated in vivo. Doubly activated penicillin esters, undergo rapid cleavage in vivo to generate active

penicillin. Example: pivampicillin and becampicillin. The antibacterial activity is evidented by N-4 atom at ring junction.

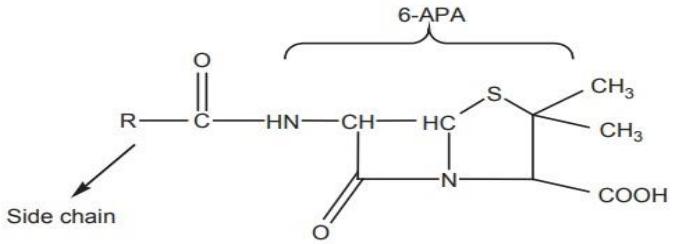
6. In vitro degradation is retarded by keeping the pH of the solution between 6.0 and 8.0. More lipophilic side chain increases the plasma protein binding. Example: Ampicillin: 25% plasma protein bound and phenoxy methyl penicillin: 75% plasma protein bound.

Acid-catalyzed degradation in the stomach contributes in a major way to the poor oral absorption of penicillin. Thus, efforts to obtain penicillins with improved pharmacokinetic and microbiologic properties have sought to find acyl functionalities that would minimize sensitivity of the β-lactam ring to acid hydrolysis and at the same time, maintain antibacterial activity.

Substitution of an electron-withdrawing group for the α-position of the benzyl penicillin has stabilized the penicillin to acid catalyzed hydrolysis. The increased stability imparted by such electron-withdrawing groups has been attributed to a decrease in the reactivity of the side chain amide carbonyl oxygen atom towards participation in β-lactam ring opening to form the penicillenic acid.

Mode of action: The cell wall of bacteria is essential for the normal growth and development. Peptidoglycan is a heteropolymeric component of the cell wall that provides rigid mechanism for stability by virtue of its highly cross-linked lattice-wise structure. The peptidoglycan is composed of glycan chains, which are linear strands of two alternating amino sugars (*N*-acetyl glucosamine and *N*-acetylmuramic acid) that are cross-linked by peptide chains of an enzyme, transpeptidase. Penicillins inhibit the transpeptidase activity to the synthesis of cell walls. They also block cleavage of terminal $_D$-Alanine during the cell wall synthesis. The biosynthesis of peptidoglycan involves three stages.

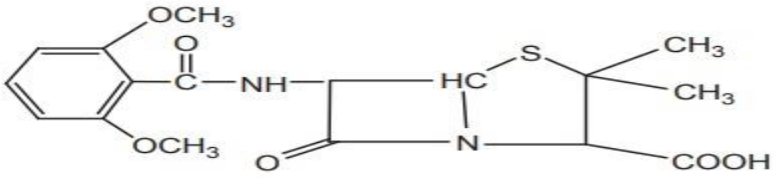
β-lactam antibiotics inhibit the last step in peptidoglycan synthesis. The transpeptidase enzyme that contains serine is probably acylated by β-lactam antibiotics with the cleavage of -CO-N-bond of the β lactam ring. This renders the enzyme inoperative and inhibits peptidoglycan synthesis.



Basic structure of penicillin

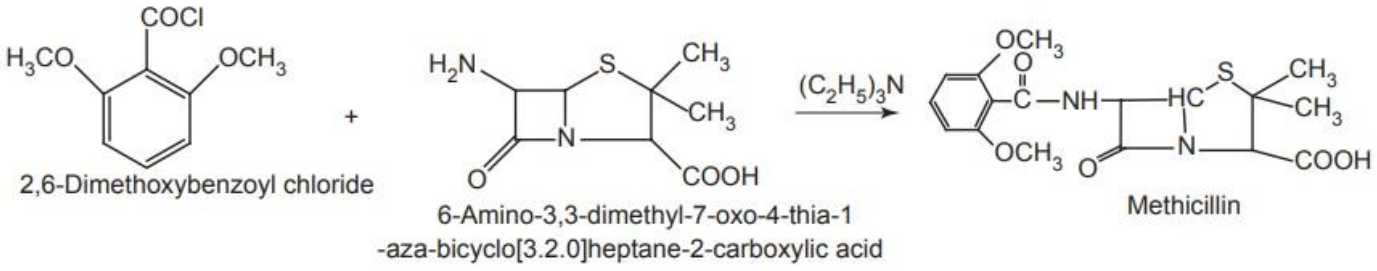
Penicillinase resistant penicillins

i. Methicillin



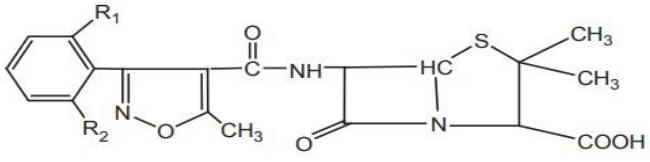
2,6-Dimethoxyphenyl penicillin

Synthesis



Properties and uses: Methicillin sodium is a white crystalline solid, odourless, soluble in water, slightly soluble in chloroform, but insoluble in ether. It is particularly resistant to inactivation by the penicillinase found in S*taphylococci* and somewhat more resistant than penicillin G to penicillinase from *Bacillus cereus*. Methicillin sodium has been introduced for use in the treatment of *Staphylococci* infections caused by the strains resistant to other penicillins. It is given by IM or by slow IV infusion every 4–6 h.

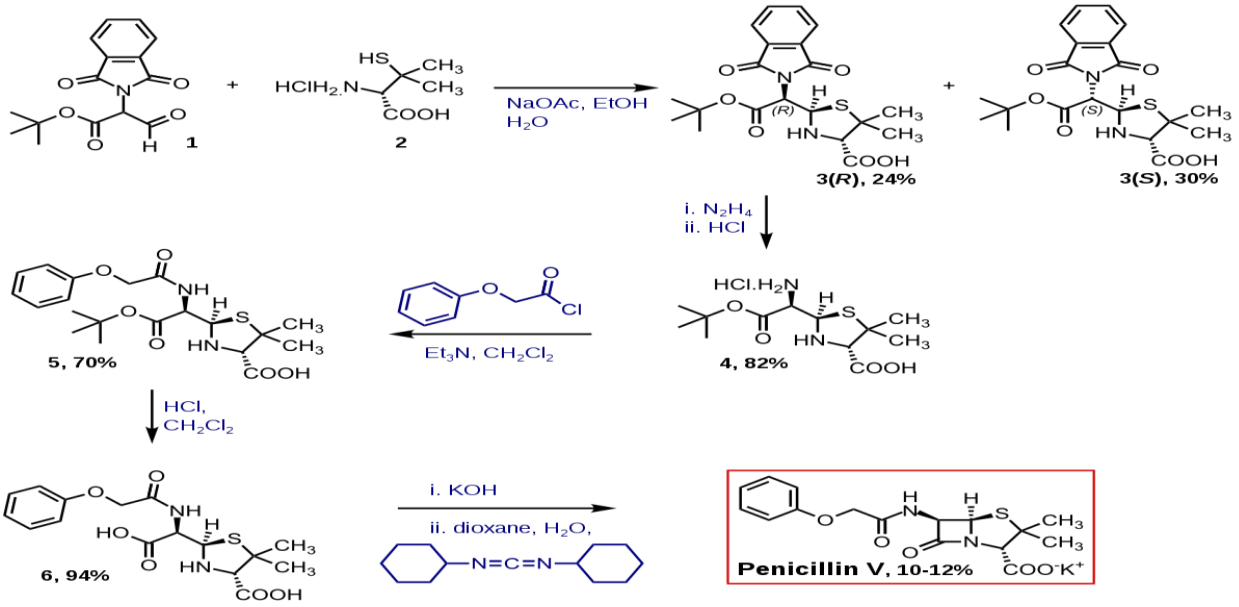
ii. Oxacillin (Isoxazolyl penicillins)



Properties and uses: Oxacillin sodium monohydrate is a white powder, soluble in water and methanol, insoluble in methylene chloride. The use of oxacillin and other isoxazolyl penicillins should be restricted to

the treatment of infections caused by *Staphylococci* that are resistant to penicillin G, although their spectrum of activity is similar to that of penicillin G.

Synthesis

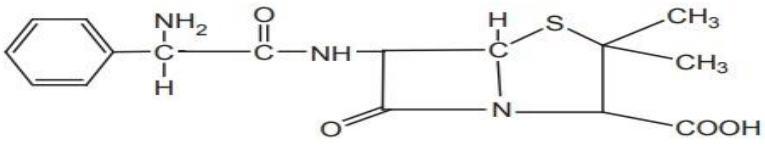


Properties and uses: Penicillin V is a white, odourless, crystalline powder with slightly bitter taste and soluble in water. It is more resistant to inactivation by gastric juice than penicillin G and better absorbed from the gastro intestinal (GI) tract. Equivalent oral doses provide two or five times greater plasma concentration than penicillin G. Penicillin V is given to treat 'trench mouth'. It is useful in the treatment of streptococcal pharyngitis, pneumonia, arthritis, meningitis, and endocarditis caused by *S. pyrogenes.*

Dose: Dose of penicillin V by oral route is 125–500 mg six times daily for 10 days. For prophylaxis of rheumatic fever, the dose is 125–250 mg twice daily.

Amino penicillins

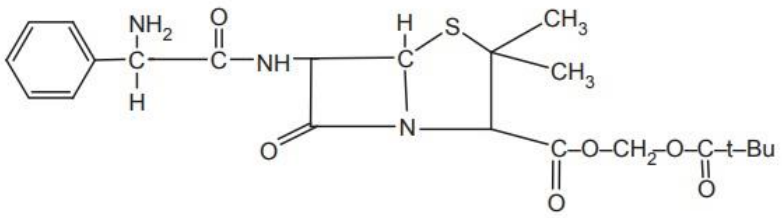
i. Ampicillin (Amcil, Omnipen)



6[D-α-Aminophenylacetamido] penicillanic acid

Properties and uses: Ampicillin is a white hygroscopic powder, freely soluble in water, sparingly soluble in acetone, practically insoluble in fatty oils and liquid paraffin. The corresponding product from acylation with 2-azido-4-hydroxyphenyl acetyl chloride is amoxicillin. The protonated α-amino group of ampicillin has a pKa of 7.3 and is thus extensively protonated in acidic media, which explains ampicillin's stability towards acid hydrolysis and instability towards alkaline hydrolysis. The α-amino group plays an important role in the broader activity. It is used to treat urinary tract infections and respiratory tract infections.

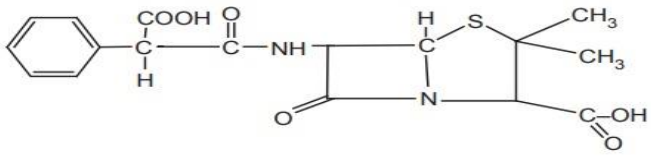
ii. Pivampicillin



Properties and uses: Pivampicillin is a white crystalline powder, practically insoluble in water, soluble in methanol, ethanol, and dilute acids. It is a produg for ampicillin and in the in vivo esters hydrolyzes back to the parent ampicillin. It is used to treat urinary tract infections and respiratory tract infections.

Antipseudomonal penicillins

i. Carbenicillin

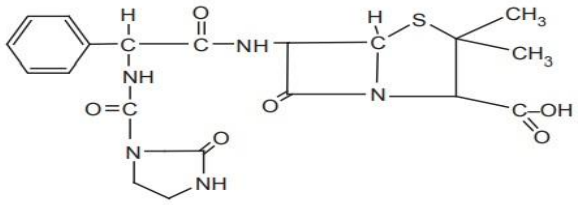


Properties and uses: It is a white to off white crystalline powder with bitter taste, hygroscopic in nature, soluble in water or alcohol, insoluble in chloroform or ether. It differs from ampicillin by having an ionizable carboxyl group substituted on the alpha carbon atom of the benzyl side chain rather than an amino group. The carboxyl group is thought to provide improved penetration of the molecule through the cell wall barriers of gram-negative bacilli as compared with other penicillins. A similar sequence starting with 3-thiophenylmalonic acid leads to the ticarcillin. It is acid labile being a malonic acid derivative, it

decarboxylates readily to penicillin G. It is effective in the treatment of systemic and urinary tract infections. It has low toxicity, except allergic sensitivity, and the drug interferes with platelet function resulting in bleeding.

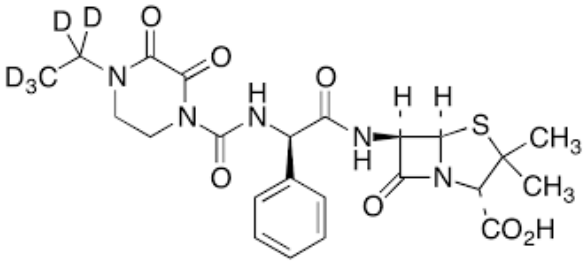
Ureido penicillins

i. Aziocillin (Azlin)



Properties and uses: It is the newest of ureidopenicillins, and is about 10 times more active than carbenicillin against *Pseudomonas* and *Streptococci.*

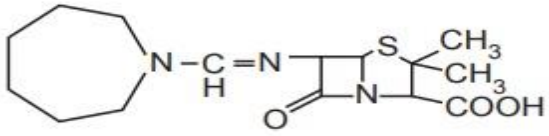
ii. Piperacillin (Pipracil, Pracil)



Properties and uses: Piperacillin sodium is a white hygroscopic powder, soluble in water and methanol, practically insoluble in ethyl acetate. It is available as a powder for solubilization and injection. It is best given in combination with an aminoglycoside antibiotic.

Miscellaneous penicillins

i. Mecillinam (Amdinocillin)



Properties and uses: Mecillinam is particularly active against enterobacteria including some ampicillin resistant strains and to treat urinary tract infections. It is structurally different from other penicillins, in that, it is not an acyl derivative, but rather alkylidene amino-(amidino) derivative of 6-APA, due to this difference, it has significant gram-negative antibacterial activity as compared to gram-positive antibacterial activity.

CEPHALOSPORINS

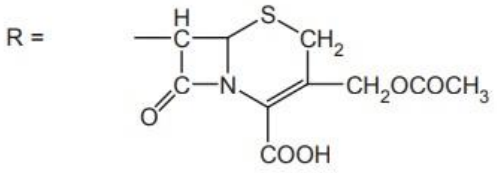
The cephalosporins were isolated from the fungus *Cephalosporium acremonium* in 1948 by Pro Tzu, Newton, and Abraham (1953). The main product being cephalosporin-C, the molecular modification of cephalosporin-C gave origin to semisynthetic substances. They are β-lactam antibiotics with same fundamental structural requirements as penicillins, the main difference between the two is that cephalosporins contain dihydrometathiazine ring, while penicillin contains a tetrahydrothiazole (thiazolidine) ring. The cephalosporins are much more acid stable than the corresponding penicillins and also have a mechanism of action similar to that of penicillins; they mainly inhibit the cross-linking of the peptidoglycan units in bacterial cell walls by inhibiting transpeptidase enzyme. However, they bind in the target proteins other than penicillins binding proteins.

Cephalosporins can be divided into three classes:

1. ***Cephalosporin N*:** It has a penicillin-like structure being a derivative of 6-aminopenicillanic acid.
2. ***Cephalosporin P*:** An acidic antibiotic, which is steroidal in nature.
3. ***Cephalosporin-C*:** It is a true cephalosporin and it is a derivative of 7 amino- cephalosphorinic acid.

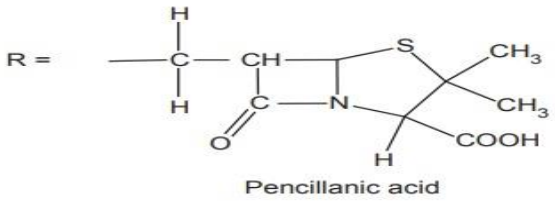
Generalized formula for cephalosporins

In cephalosporin C



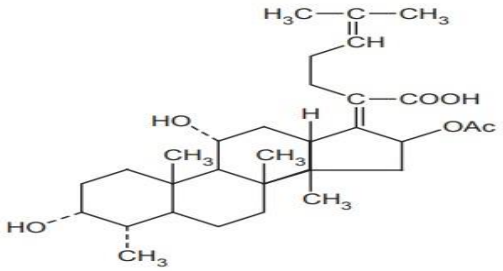
Cephalosporin C contains a side-chain derived from $_{D}$-α-aminoadipic acid, which is attached to 7-aminocephalosporanic acid.

In cephalosporin N



Pencillanic acid

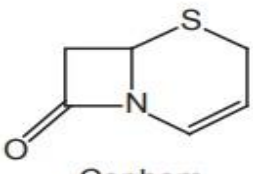
A compound structurally similar to cephalosporin P is called fusidic acid.



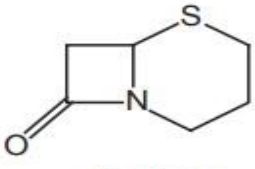
Nomenclatures

Cephalosporins are named in the following ways:

1. *Chemical abstracts*: 5-Thia-1-azobicyclo (4.2.0) octanes. Accordingly, Cephalothin is 3-(Acetoxy methyl)-8-oxo-7-(2-thienyl) acetamido-5thia-1-aza-bicyclo[4.2.0]-Oct-2ene-2-carboxylic acid.
2. *Cepham derivatives*: Cepham is the name given to the unsubstituted bicyclic lactam.



Cephem



Cepham

Classification

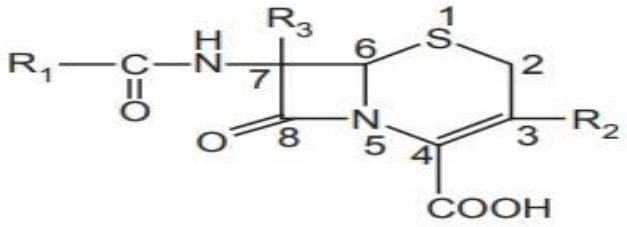
Cephalosporins are classified on the basis of their chemical structure, clinical pharmacology, antibacterial spectrum, or penicillinase resistance.

a. Orally administered: cephalexin, cephradine, and cefaclor
b. Parentrally administered: cephalothin, cephapirin, cephacetrile and cefazedone.
c. These agents are sensitivity to β-lactamase
d. Resistant to β-lactamase and parentrally administered: cefuroxime,

e. cefamandole, cefoxitin

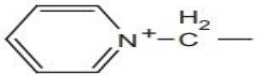
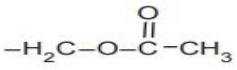
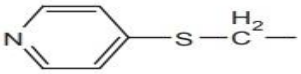
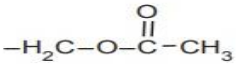
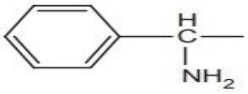
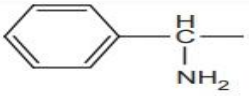
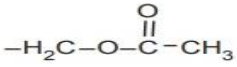
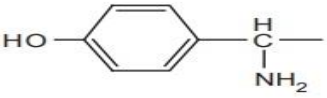
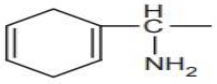
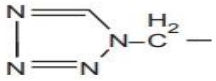
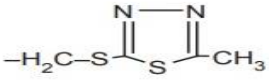
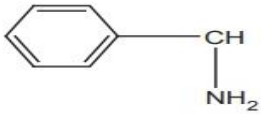
f. Metabolically unstable: cephalothin and cephapirin

Clinically used cephalosporins



I. First-generation cephalosporins

These drugs have the highest activity against gram-positive bacteria and the lowest activity against gramnegative bacteria.

Name	R_1	R_2	R_3
Cephaloridine			–H
Cephalothin			–H
Cephapirin			–H
Cephalexin		$-CH_3$	–H
Cephaloglycine			–H
Cefadroxil		$-CH_3$	–H
Cephradine		$-CH_3$	–H
Cefazolin			–H
Cephradine		$-CH_3$	–H

II. Second-generation cephalosporins

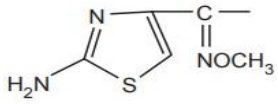
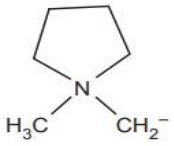
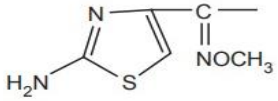
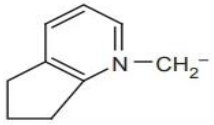
These drugs are more active against gram-negative bacteria and less active against gram-positive bacteria than first-generation members.

III. Third-generation cephalosporins

These drugs are less active than first-generation drugs against gram-positive organisms, but have a much expanded spectrum of activity against gram-negative organisms.

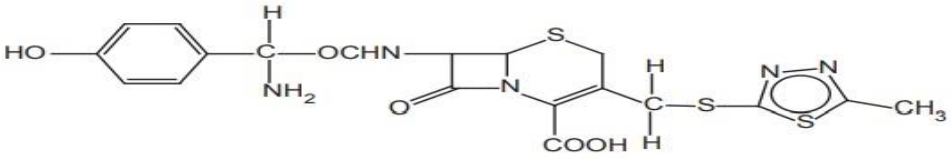
V. Fourth-generation cephalosporins

Cefepime and cefpirome are new fourth-generation parenteral cephalosporins with a spectrum of activity which makes them suitable for the treatment of infections caused by a wide variety of bacteria.

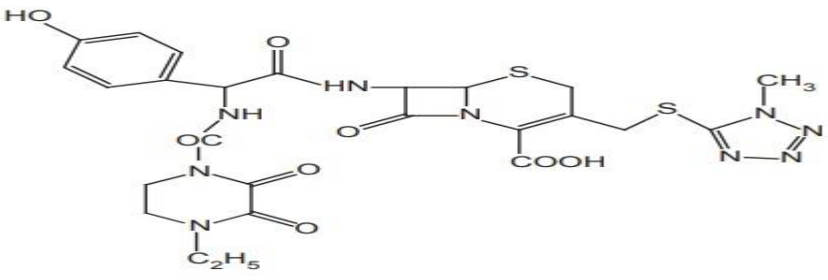
Name	R_1	R_2	R_3
Cefepime			–H
Cefpirome			–H

V. Micellaneous

i. Cefaparole



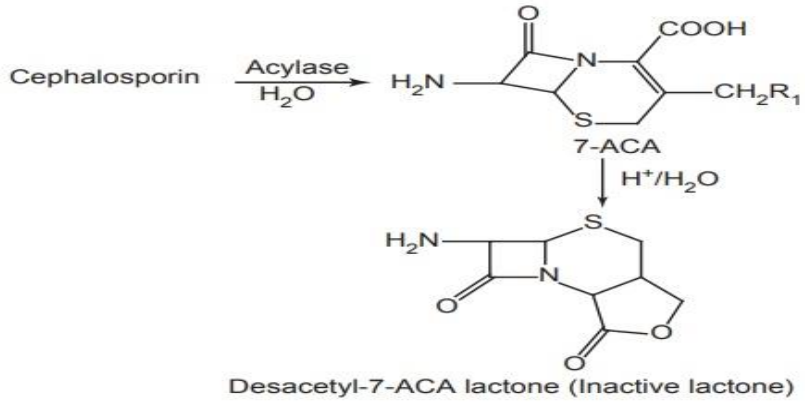
ii. Cefoperazone



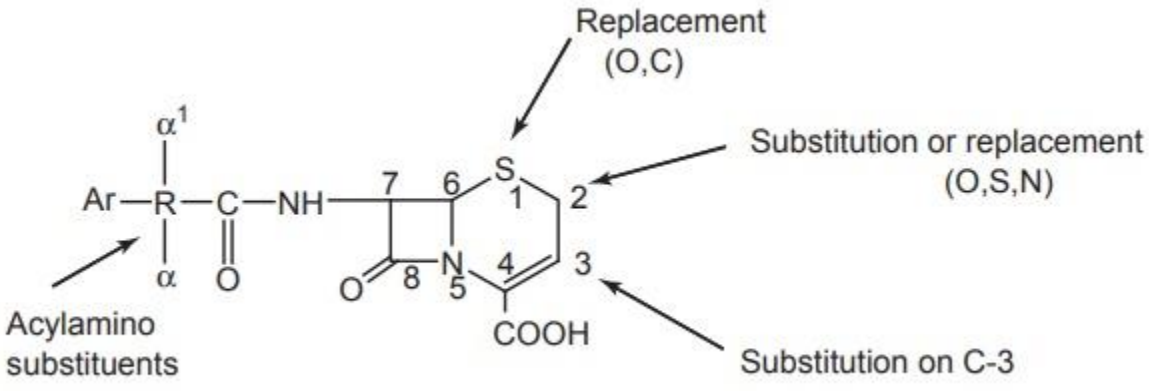
Degradation of Cephalosporins

Cephalosporins experience a variety of hydrolytic degradation reactions.

In strong acid solutions



SAR of Cephalosporins



1. 7-Acylamino substitution

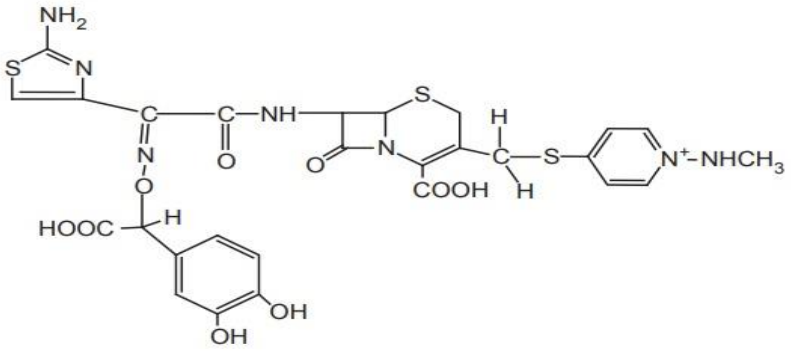
a. The addition of amino group and a hydrogen to α and α_1 position produces basic compound, which is protonated under acidic conditions of stomach. The ammonium ion improves the stability of β-lactum of cephalosporins and make active orally. Activity against positive bacteria is increased and gram negative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

b. When the new acyl groups are derived from carboxylic acids, it shows good spectrum of antibacterial action for gram-positive bacteria.

c. Substitutions on the aromatic ring phenyl that increase lipophilicity provide higher gram-positive activity and generally lower gram-negative activity.

d. 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.

e. 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 modification

a. Methoxy group at C-7, shows higher resistance to hydrolysis by β-lactamase.

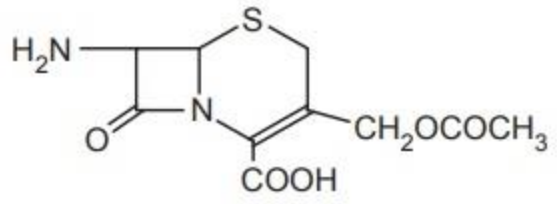
b. Oxidation of ring spectrum to sulphoxide or sulphone greatly diminishes or destroys the antibacterial activity.

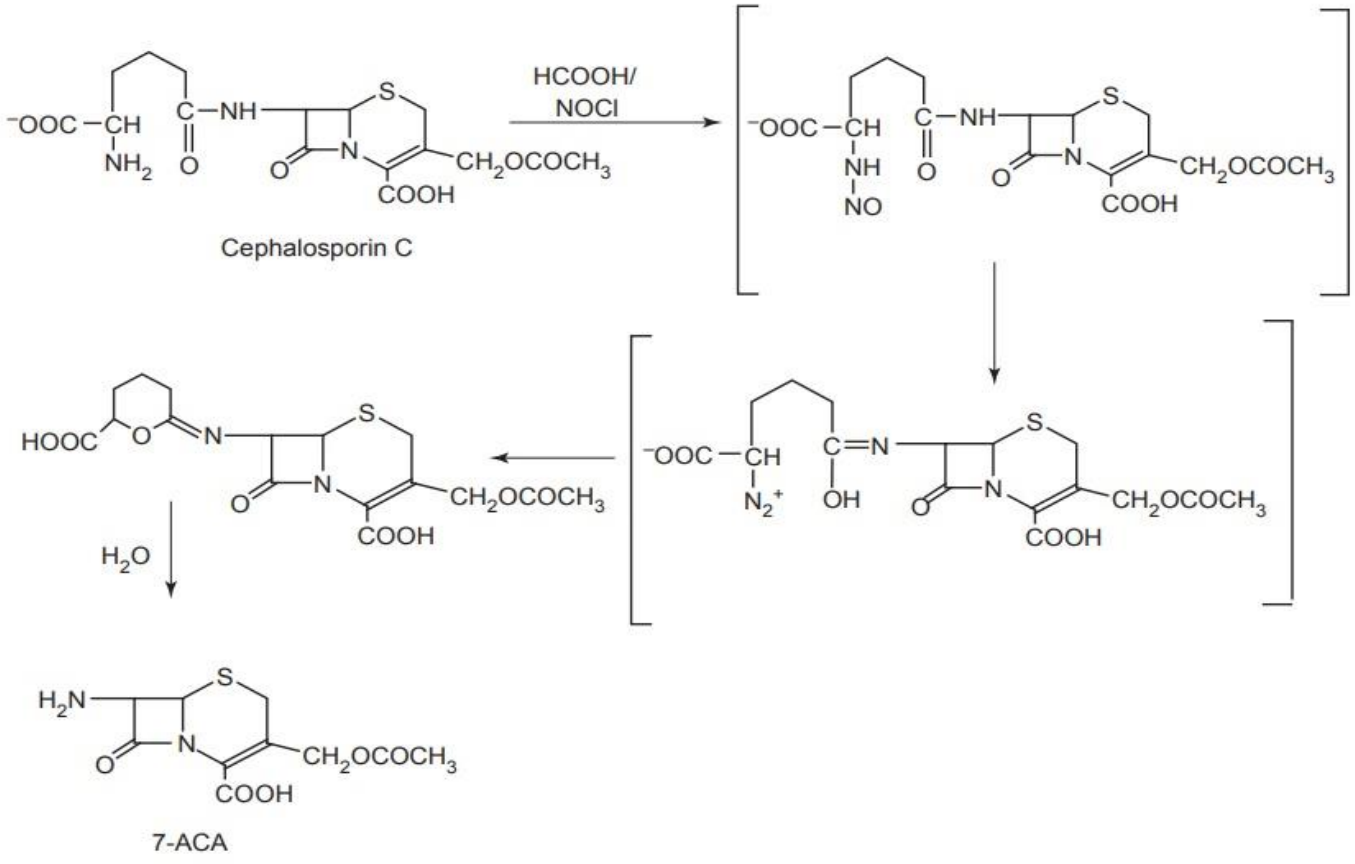
c. Replacement of sulphur with oxygen leads to oxacepam (latamoxet) with increased antibacterial activity, because of its enhanced acylating power. Similarly, replacement of sulphur with methylene group (loracavet) has greater chemical stability and a longer half-life.

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 oceanic 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.

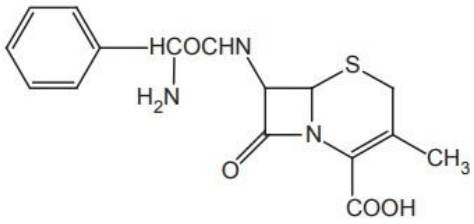
Cephalosporins - Synthesis and Drug Profile





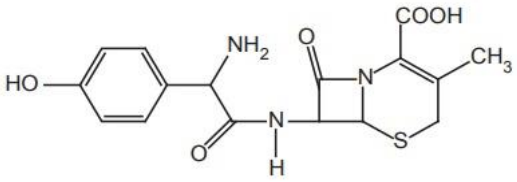
First-generation cephalosporins

i. Cephalexin (Keflex, Keforal)



Properties and uses: Cephalexin monohydrate is a white crystalline powder, sparingly soluble in water, and practically insoluble in alcohol. The α-amino group of cephalexin renders it acid stable. The 3-methyl group is responsible for the metabolic stability. It is particularly recommended for urinary tract infection.

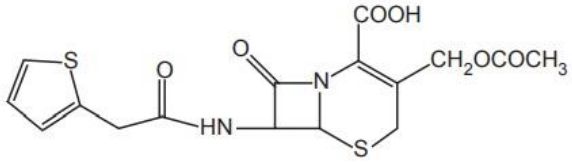
ii. Cefadroxil (Cefadrox, Droxyl, Codroxil)



7-(2-Amino-2-(4-hydroxyphenyl)acetamido)-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

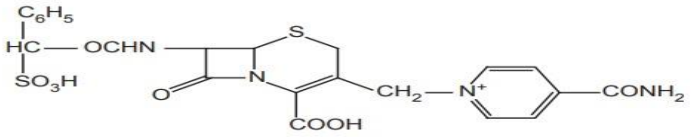
Properties and uses: It is indicated for use in staphylococcal and pseudomonal infections.

iii. Cephalothin (Keflin)



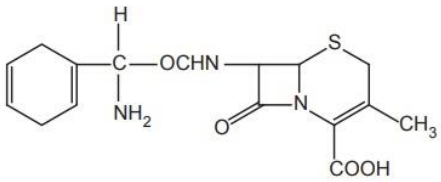
Properties: Cephalothin is a white, odourless, crystalline powder, insoluble in most organic solvents, soluble in organic solvents and it is acid stable. It is hygroscopic and decomposes on heating, and it has been described as broad-spectrum antibacterial compound, it is not in the same class as the tetracyclines.

iv. Cefsulodin



Properties and uses: It is indicated for use in staphylococcal and pseudomonal infections.

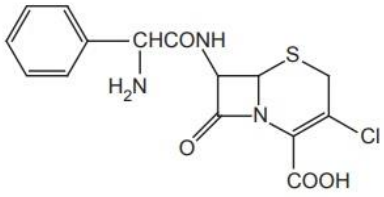
v. Cephradine



Properties and uses: Cephradine exists as colourless crystals, soluble in propylene glycol, but slightly soluble in acetone or alcohol. Used as an antibacterial agent.

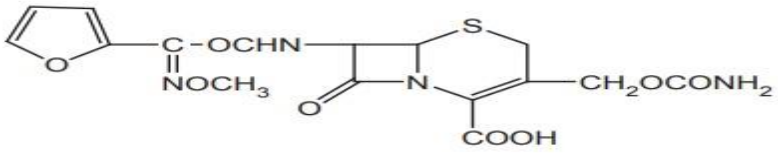
Second-generation cephalosporin

i. Cefaclor



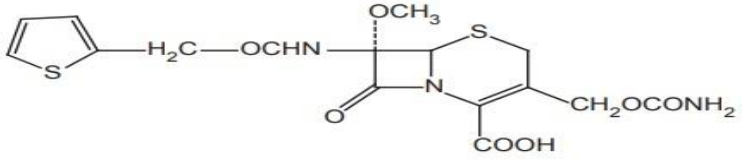
Properties and uses: Cefaclor is a white or slightly yellow powder, slightly soluble in water, practically insoluble in methanol and methylene chloride. It has chloro group at C-3 position, and hence, stable in acid and achieves sufficient oral absorption. Used in the treatment of upper respiratory tract infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.*

ii. Cefuroxime (Zinacef, Kefurox)



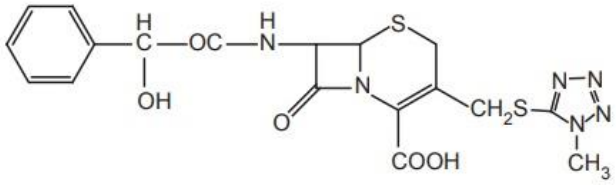
Properties and uses: Cefiroxime sodium is a white hygroscopic powder, freely soluble in water, and very slightly soluble in ethanol. It has excellent activity against all *gonococci*, hence, is used to treat gonorrhoea. It may be used to treat lower respiratory tract infections caused by *H. influenza* and *Para influenzae*, *Klebsiella* spp. *E.coli*, *Staphylococcus pneumoniae*, and pyrogens.

iii. Cefoxitin



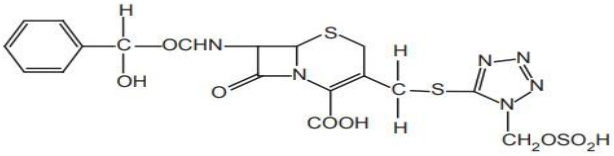
Properties and uses: Cefoxitin sodium is a white hygroscopic powder, soluble in water and sparingly soluble in alcohol. It is not the drug of choice for any infection, but it is an alternative drug for intra-abdominal infections, colorectal surgery, appendectomy, and ruptured viscus because it is active against most enteric anaerobes, including *Bacteroides fragilis*. It is approved for use in the treatment of bone and joint infections caused by *Staphylococcus aureus*, gynecological and intra-abdominal infections by *Bacteroides* spp.

iv. Cefamandole (Mandol, Kefadol)



Properties and uses: Cefamandole nafate is a white powder, soluble in water, and sparingly soluble in methanol. Cefamandole nafate is very unstable in solution and hydrolyzes rapidly to release cefamandole and formate. There is no loss of potency; however, these solutions are stored for 24 h at room temperature or up to 96 h by refrigeration.

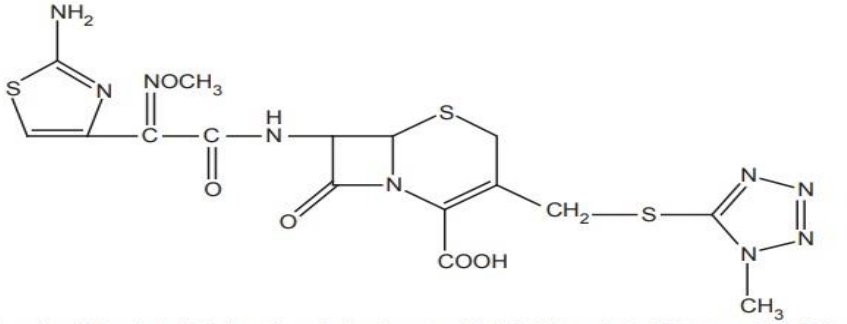
v. Cefonicid



Properties and uses: Cefonicid is a second-generation cephalosporin that is structurally similar to cefamandole, except that it contains a methane sulphonic acid group attached to the N-1 position of the tetrazole ring. Used in the treatment of bacterial infections.

Third-generation cephalosporins

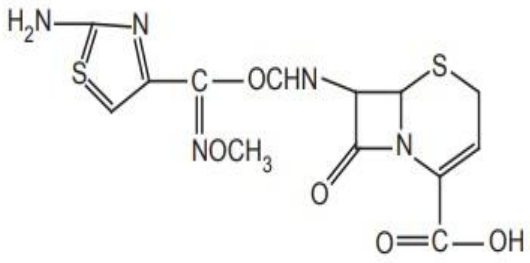
i. Cefotaxime Sodium



7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-3-((1-methyl-1*H*-tetrazol-5-ylthio methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

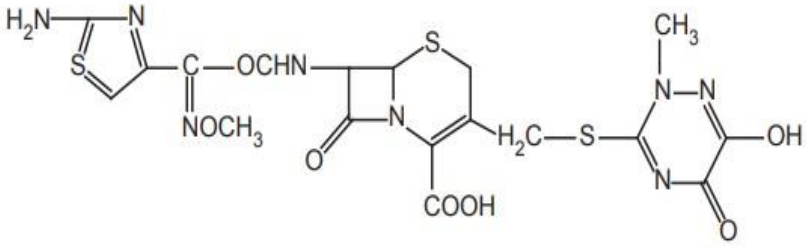
Properties and uses: Cefotaxime sodium exists as white solid and soluble in water, exhibits broad-spectrum activity against both gram-positive and gram-negative bacteria. Used in genitourinary infection and lower respiratory infection.

ii. Ceftizoxime sodium



Properties and uses: It is a beta lactamase resistant cephalosporin, used in lower respiratory infection and meningitis.

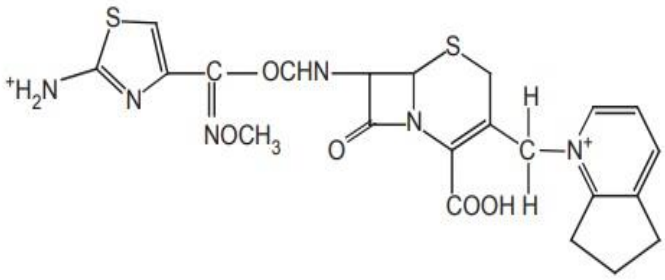
iii. Ceftriazone disodium



Properties and uses: It exists as white crystals, soluble in water, exhibits broad-spectrum activity against both gram-positive and gram-negative bacteria.

Fourth-generation cephalosporin

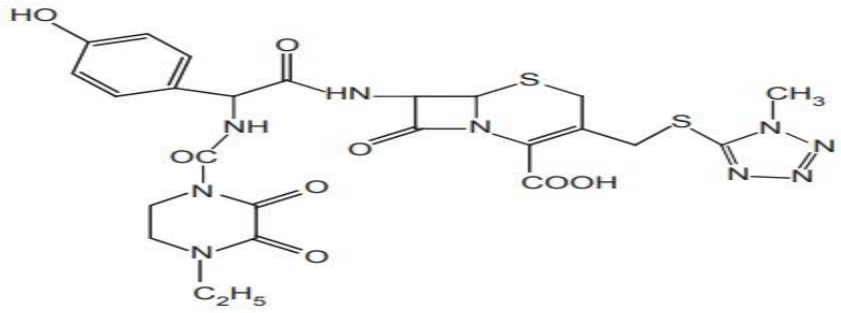
i. Cefpirome (Ceform, Ominorm, Taform)



Properties and uses: Cefpirome is used to treat susceptible infections, including urinary and respiratory tract infections, skin infections, septicaemia, and infections in immuno-compromised patients.

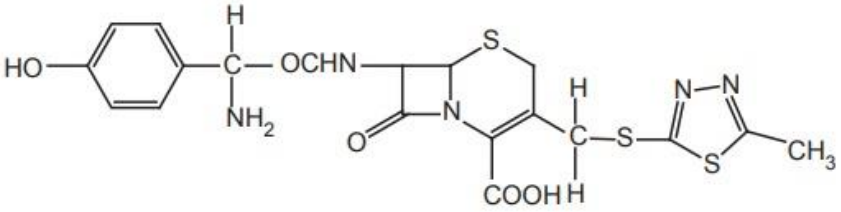
Miscellaneous

i. Cefoperazone



Properties and uses: Cefoperazone exists as white powder. It is a third-generation, antipseudomonal cephalosporin that resembles piperacillin, chemically and microbiologically. It is less active than cephalothin against gram-positive bacteria and less active than cefamandole against most of the enterobacteria.

ii. Cefaparole



AMINOGLYCOSIDE ANTIBIOTICS

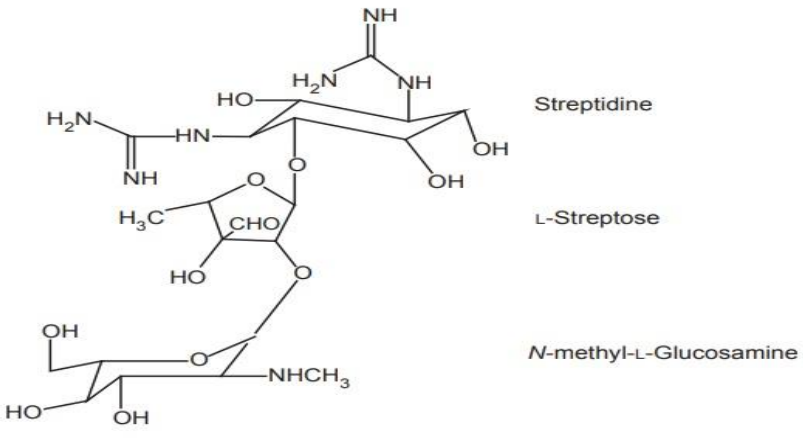
The aminoglycoside antibiotics contain one or more amino sugars linked to an aminocytitol ring by glycosidic bonds. These are broad-spectrum antibiotics; in general, they have greater activity against gram-negative than gram-positive bacteria. The development of streptomycin, the first antibiotic of this group, was a well-planned work of Waksman (1944) and his associates, who isolated it from a strain of S*treptomyces griseus.*

The aminoglycoside can produces severe adverse effects, which include nephrotoxity, ototoxicity, and neuro effects. These properties have limited the use of aminoglycoside chemotherapy to serious systemic indications. Some aminoglycosides can be administered for ophthalmic and topical purposes.

Mode of action: The aminoglycosides exhibit bactericidal effects as a result of several phenomena. Ribosomal binding on 30s and 50s subunits as well as the interface produces misreading; this disturbs the normal protein synthesis. Cell membrane damage also plays an integral part in ensuring bacterial cell death.

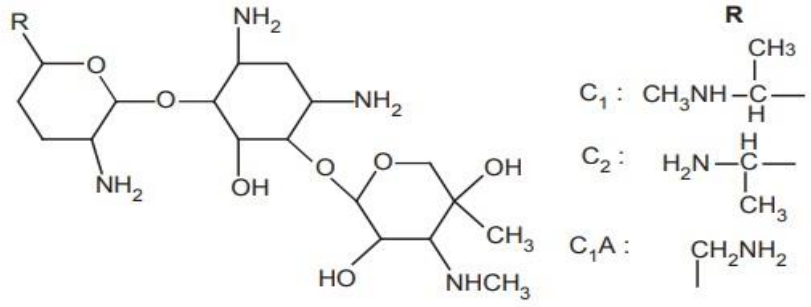
Name	Source
Streptomycin	*Streptomyces griseus*
Neomycin	*S. fradiae*
Kanamycin	*S. kanamyeleticus*
Gentamysin	*Micromonospora purpura*
Netilmicin	*Micromonospora species*
Tobramycin (Nebramycin)	*S. tenebrarius*
Framycetin (Soframycin)	*S. decaris*
Paromomycin	*S. rimosus and S. paramomycinus*
Amikacin	It is 1-L-(-) 4-amino-2-hydroxy butyryl kanamycin

a. Streptomycin and dihydrostreptomycin



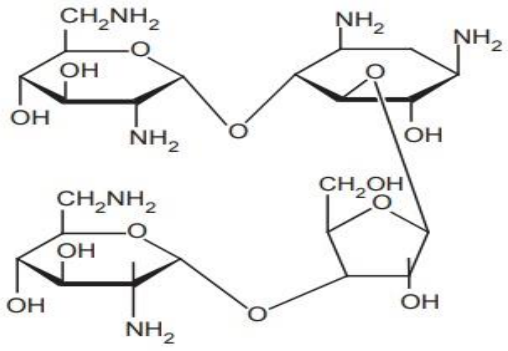
Properties and uses: Streptomycin sulphate is a white hygroscopic powder, very soluble in water, and practically insoluble in ethanol. The development of resistant strains of bacteria and chronic toxicity constitutes major drawbacks of this category. It is an aminoglycoside antibacterial also used as an antitubercular drug.

b. Gentamycins



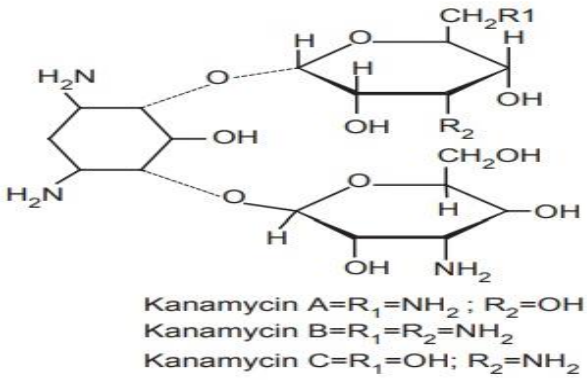
Properties and uses: Gentamycin is a mixture of C_1, C_2, and C_1A compounds, obtained commercially from *Micromonospora purpurea.* It is used in the treatment of infections caused by gram-negative bacteria of particular interest and has a high degree of activity against *P. aeruginosa*, where the important causative factor is burned skin. It is used topically in the treatment of infected bed-sores, pyodermata, burns, and in the eye infection.

c. Neomycin



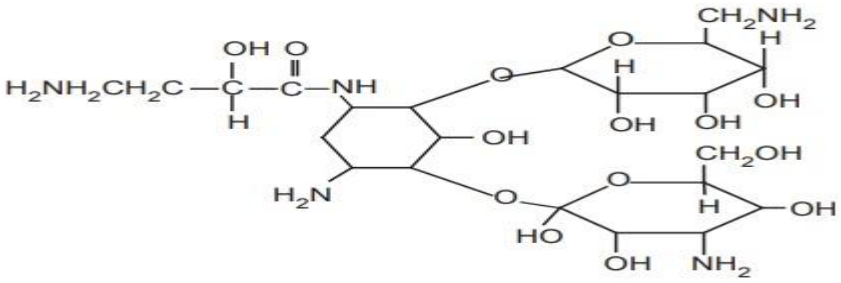
Properties and uses: Neomycin is a mixture of closely related epimers, neomycin B, and C. Neomycin B differ from neomycin C by the nature of the sugar attached terminally to $_D$-ribose, this sugar called neosamine. B1 differs from neosamine C in its stereochemistry. In neomycin B_1 , the neobiosamine moiety contains. β-$_L$-iodopyranosyl, whereas in neomycin C the configuration is inverted and it is 2-$_D$-glucopyranosyl. It is photosensitive and its main use is in the treatment of the ear, eye, and skin infections; these include burns, wounds, ulcer, and infected dermatoses.

d. Kanamycin



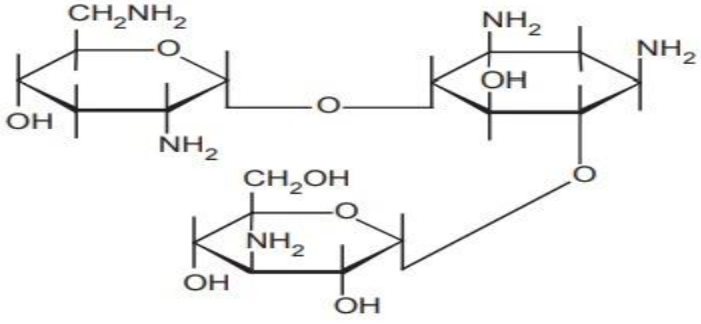
Properties and uses: Kanamycin sulphate is a white crystalline powder, soluble in water, practically insoluble in acetone and in alcohol. The mixture consists of three related structures, that is, Kanamycin A, B, and C. The kanamycins do not possess D-ribose molecule that is present in neomycins and paramomycins. The use of kanamycins is restricted to infections of the intestinal tract and to systemic infections.

e. Amikacin



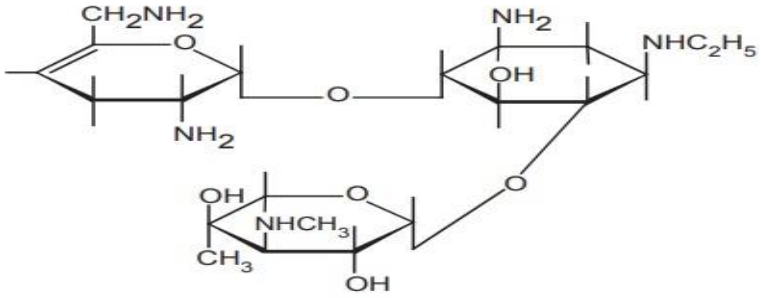
Properties and uses: Amikacin is a semisynthetic drug derived form kanamycin A. It retains 50% of the original activity of Kanamycin A. L-Isomer is more active than D-isomer. It resists attack by most bacterial inactivating enzyme. Therefore, it is very effective and less ototoxic than other aminoglycosides.

f. Tobramycin



Properties and uses: Its activity is similar to gentamycin. The superior activity of tobramycin against *P. aeruginosa* may make it useful in the treatment of bacterial oesteromyelitis, and pneumonia caused by *P. species.*

g. Netilmicin



Properties and uses: Netilmycin sulphate is a white or yellowish-white hygroscopic powder, very soluble in water, practically insoluble in acetone and alcohol. It is similar to gentamycin and tobramycin. The majority of the aminoglycoside inactivating enzymes do not metabolize it. It is useful for the treatment of serious infections due to susceptible enterobacteria and other aerobic gram-negative bacilli.

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.

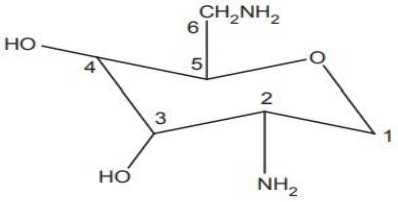
Thus,

- In kanamycin and gentamycin families, two amino sugars are attached to 2-deoxy streptamine.
- In streptomycin, two amino sugars are attached to streptidine.
- 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.

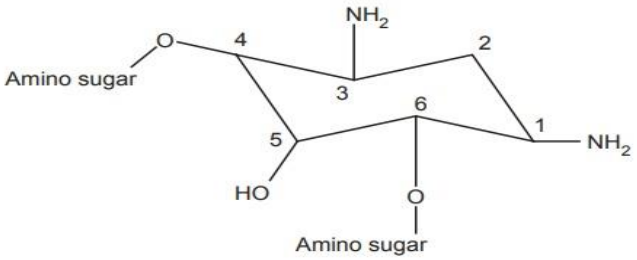
The aminoglycoside antibiotics contain two important structural features. They are amino sugar portion and centrally placed hexose ring, which is either 2-deoxystreptamine or streptidine.

1. Amino sugar portion



1. The bacterial inactivating enzymes targets C-6 and C-2 position, and the substitution with methyl group at C-6 increases the enzyme resistance.
2. Cleavage of 3-hydroxyl or the 4-hydroxyl or both groups does not affect the activity.

2. Centrally placed hexose ring (aminocyclitol ring)



1. Various modifications at C-1 amino group have been tested. The acylation (e.g. amikacin) and ethylation (e.g. 1-*N*-ethylsisomycin) though does not increase the activity helps to retain the antibacterial potency.
2. In Sisomicin series, 2-hydroxylation and 5-deoxygenation result in the increased inhibition of bacterial inactivating enzyme systems. Thus, very few modifications of the central ring are possible, which do not violate the activity spectrum of aminoglycosides.

Tetracycline antibiotics

Tetracyclines have a ring system of four linear annelated six-membered rings and are characterized by a common octahydronaphthacenes skeleton. They are potent, broad-spectrum antibacterial agents effective against gram-positive and gram-negative aerobic and anaerobic bacteria. As a result, the tetracyclines are drugs of choice or well-accepted alternatives for a variety of infectious diseases. Among these, they also play a role in the treatment of sexually transmitted and gonococcal diseases; urinary tract infections, bronchitis, and sinusitis remain prominent.

The majority of the marketed tetracyclines (tetracycline, chlorotetracycline, oxytetracycline, and demeclocycline) are naturally occurring compounds obtained by the fermentation of S*treptomyces spp.* broths. The semisynthetic tetracyclines (methacycline, doxycycline, minocycline) have the advantage of longer duration of antibacterial action. However, all these tetracyclines exhibit a similar profile in terms of antibacterial potency. In general, their activity encompasses many strains of gram-negative *E. coli, Proteus, Klebsiella, Enterobacter, Niesseria,* and *Serratia* spp., as well as gram-negative *Streptococci* and *Staphylococci* of particular interest is the potency of tetracyclines against *Haemophilus, Legionella, Chlamydia,* and *Mycoplasma.*

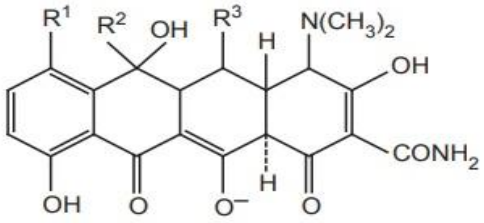
Classes of tetracyclines

I.Natrual tetracyclines (biosynthetic)

II. Semisynthetic tetracyclines

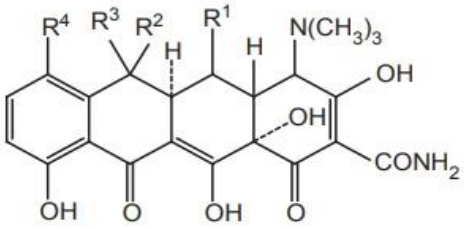
III. Protetracyclines

I. Natural tetracyclines



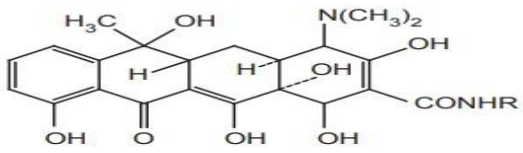
S. No.	Drug	R¹	R²	R³
1.	Tetracycline	–H	$–CH_3$	–H
2.	Chlortetracycline	–Cl	$–CH_3$	–H
3.	Oxytetracycline	–H	$–CH_3$	–OH
4.	Bromotetracycline	–Br	$–CH_3$	–H
5.	Dexamethyltetracycline	–H	–H	–H
6.	Dexamethylchlortetracycline	–Cl	–H	–H

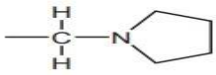
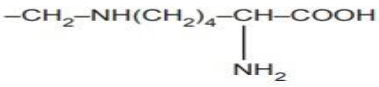
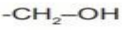
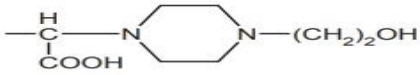
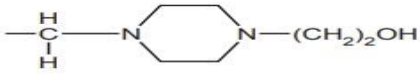
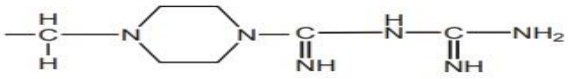
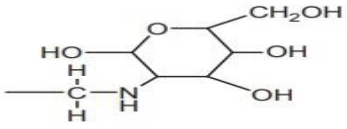
II. Semisynthetic tetracyclines



S. No.	Drug	R¹	R²	R³	R⁴
1.	Doxycycline	–OH	–H	$–CH_3$	–H
2.	Minocycline	–H	–H	–H	$–N–(CH_3)_2$
3.	Methacycline	–OH	$=CH_2$	–	–H
4.	Meclocycline	–OH	$=CH_2$	–	–Cl
5.	Sancycline	–H	–H	–H	–H

III. Pro-tetracyclines

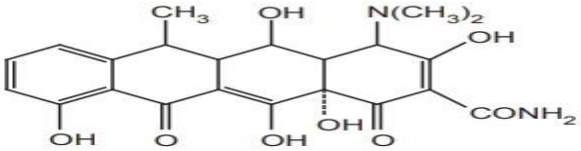


S. No.	Drug	R
1.	Rolitetracycline	
2.	Lymecycline	
3.	Clomocycline	
4.	Apicycline	
5.	Pipacycline	
6.	Guamecycline	
7.	Meglucycline	

General mode of action of tetracyclines

In bacterial protein synthesis, the messenger RNA attaches itself to 30S ribosomes. The initiation complex of mRNA starts the protein synthesis and polysome formation of the nascent peptide that is attached to 50S ribosomes. Its specific tRNA transports the next amino acid to the acceptor site of the ribosome, which is complementary to the base sequence of the next mRNA codon. The nascent peptide is transferred to the newly attached amino acid by peptide bond formation. Tetracyclines bind to 30S ribosomes and the attachment of aminoacyl tRNA to mRNA ribosome complex is interfered.

i. Doxycycline

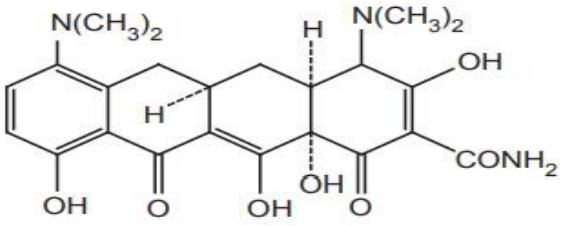


4-(Dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide

Synthesis

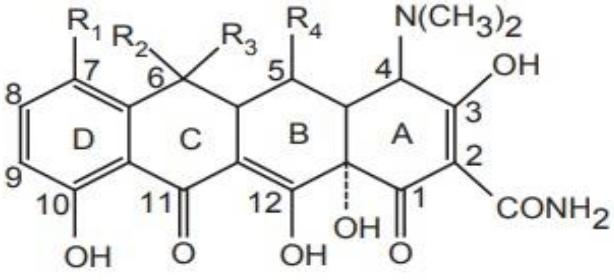
Properties and uses: It was first obtained in small yields by a chemical transformation of oxytetracycline. The 6α-methyl epimer is more than three times as active as its β epimer.

i Minocycline



Properties and uses: It is a yellow crystalline powder with slightly bitter taste, soluble in water. It is very active against gram-positive bacteria. It is especially effective against *Mycobacterium marinum*. As a prophylactic against streptococcal infections, it is the drug of choice. It lacks the 6-hydroxyl group, therefore, it is stable to acids and does not dehydrate or rearrange to anhydro or lactone forms.

SAR of Tetracyclines

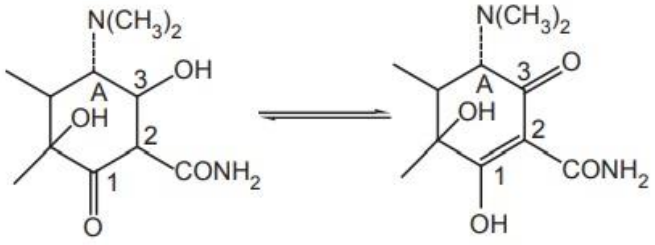


The key structural feature is a linearly fused tetracyclic nucleus and each ring needs to be six membered and purely carbocyclic. A tetracyclic backbone skeleton is essential for activity.

- The D-ring needs to be aromatic and the A-ring must be appropriately substituted at each of its carbon atoms for notable activity.
- The B-ring and the C-ring tolerate certain substitutent changes as long as the keto-enol systems (at C-11, 12, 12a) remain intact and conjugated to the phenolic D-ring.

- The D, C, B-ring phenol, keto-enol system is imperative and the A-ring must also contain a conjugated keto enol system.
- Specifically, the A-ring contains a tricarbonyl derived keto-enol array at positions C-1, 2, and -3. Other structural requirements for good antibacterial activity include a basic amine function at C-4 position of the A-ring.

Modification of C-1 and C-3 position: The keto-enol tautomerism of ring A in carbon atom 1 and 3 is a common feature to all biologically active tetracyclines, blocking this system by forming derivatives at C-1 and C-3 results in loss of antibacterial activity A–C = O, a function of C-1 and C-3 is essential for activity. In addition, equilibrium between non-ionized and Zwitterionic structure of tetracycline is essential for activity.



Modification of C-2 position: The antibacterial activity resides on the carboxamide moiety. The amide is best left unsubstituted or monosubstitution is acceptable in the form of activated alkylaminomethyl amide (Mannich bases). An example includes rolitetracycline large alkyl group on the carboxamide that may alter the normal keto-enol equilibrium of the C-1, 2, and 3 conjugated systems and diminishes inherent antibacterial activity. The replacement of carboxamide group or dehydration of carboxamide to the corresponding nitrile results in a loss of activity.

Modification of C-4 position: The keto-enolic character of the A-ring is due to the α-C-4 dimethyl amino substituent. Loss of activity is exerted when dimethyl amino group is replaced with hydrazone oxime or hydroxyl group.

Modification of C-4a position: The α-hydrogen at C-4a position of tetracyclines is necessary for useful antibacterial activity.

Modification of the C-5 and C-5a positions: Alkylation of the C-5 hydroxyl group results in loss of activity. Naturally occurring antibacterial tetracyclines have an unsubstituted methylene moiety at the C-5 position. However, oxytetracycline contains C-5 α-hydroxyl group, was found to be a potent compound, and has been modified chemically to some semisynthetic tetracyclines. Esterification is only acceptable if the free

oxytetracycline can be liberated in vivo; only small alkyl esters are useful. Epimerization is detrimental to antibacterial activity.

Modification at the C-6 position: The C-6 methyl group contributes little to the activity of tetracycline. The C-6 position is tolerant to a variety of substituents. The majority of tetracyclines have α-methyl group and α β-hydroxyl group at this position. Demeclocycline is a naturally occurring C-6 demethylated chlortetracycline with an excellent activity. Removal of C-6 hydroxyl group affords doxycycline, which exerts good antibacterial activity.

C-7 and C-9 substituents: The nature of the aromatic D-ring predisposes the C-7 position to electrophilic substitution. Substitution with electron withdrawing group such as nitro and halogen groups are introduced in some C-7 tetracyclines, which produces the most potent of all the tetracyclines in vitro, but there are compounds are potentially toxic and carcinogenic. The C-7 acetoxy, azide, and hydroxyl tetracyclines are inferior in terms of antibacterial activity.

C-10 substituents: The C-10 phenolic moiety is necessary for antibacterial activity. C-10 substitution with para or ortho hydrogen group activates the C-9 and C-7.

C-11 substituents: The C-11 carbonyl moiety is a part of one of the conjugated keto-enol system required for antibacterial activity.

C-11a substituents: No stable tetracyclines are formed by modifications at the C-11a position.

C-12/12a substituents: Esterification of the hydroxyl group leads to the incorporation of drug with the tissues due to the enhanced lipophilicity and it should undergo hydrolysis to leave the active tetracycline with hydroxyl group at 12a position, which is necessary to produce good antibacterial action. The transport and binding of these drugs depends on keto-enol system.

β-Lactamase inhibitor

Beta-lactum 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.[1] Although β-lactamase inhibitors have little antibiotic activity of their own,[2] they prevent bacterial degradation of beta-lactam antibiotics and thus extend the range of bacteria the drugs are effective against.

Medical uses

The most important use of beta-lactamase inhibitors is in the treatment of infections known or believed to be caused by gram-negative bacteria, as beta-lactamase production is an important contributor to beta-lactam resistance in these pathogens. In contrast, most beta-lactam resistance in gram-positive bacteria is due to variations in penicillin-binding proteins that lead to reduced binding to the beta-lactam.[3][4] The gram-positive pathogen *Staphylococcus aureus* produces beta-lactamases, but beta-lactamase inhibitors play a lesser role in treatment of these infections because the most resistant strains (methicillin-resistant *Staphylococcus aureus*) also use variant penicillin-binding proteins.

Mechanism of action

The Ambler classification system groups known beta-lactamase enzymes into four groups according to sequence homology and presumed phylogenetic relationships. Classes A, C and D cleave beta-lactams by a multi-step mechanism analogous to the mechanism of serine proteases. Upon binding, a serine hydroxyl group in the beta-lactamase active site forms a transient covalent bond to the beta-lactam ring carbonyl group, cleaving the beta-lactam ring in the process. In a second step, nucleophilic attack by a water molecule cleaves the covalent bond between the enzyme and the carbonyl group of the erstwhile beta-lactam. This allows the degraded beta-lactam to diffuse away and frees up the enzyme to process additional beta-lactam molecules.

Currently available beta-lactamase inhibitors are effective against Ambler Class A beta-lactamases (tazobactam, clavulanate, and sulbactam) or against Ambler Class A, C and some Class D beta-lactamases (avibactam). Like beta-lactam antibiotics, they are processed by beta-lactamases to form an initial covalent intermediate. Unlike the case of beta-lactam antibiotics, the inhibitors act as suicide substrates (tazobactam and sulbactam) which ultimately leads to the degradation of the beta-lactamase. Avibactam on the other hand does not contain a beta-lactam ring (non beta-lactam beta-lactamase inhibitor), and instead binds reversibly.

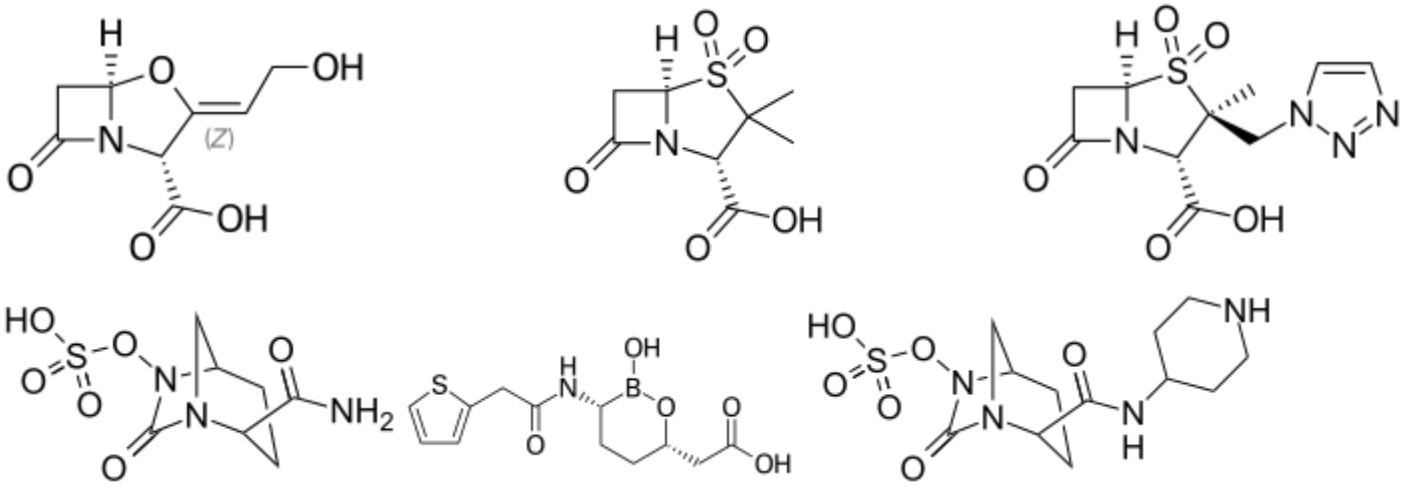
Ambler Class B beta-lactamases cleave beta-lactams by a mechanism similar to that of metalloproteases. As no covalent intermediate is formed, the mechanism of action of marketed beta-lactamase inhibitors is not applicable. Thus the spread of bacterial strains expressing metallo beta-lactamases such as the New Delhi metallo-beta-lactamase 1 has engendered considerable concern.

Commonly used agents

Currently marketed β-lactamase inhibitors are not sold as individual drugs. Instead they are co-formulated with a β-lactam antibiotic with a similar serum half-life. This is done not only for dosing convenience, but

also to minimize resistance development that might occur as a result of varying exposure to one or the other drug. The main classes of β-lactam antibiotics used to treat gram-negative bacterial infections include (in approximate order of intrinsic resistance to cleavage by β-lactamases) penicillins (especially aminopenicillins and ureidopenicillins), 3rd generation cephalosporins, and carbapenems. Individual β-lactamase variants may target one or many of these drug classes, and only a subset will be inhibited by a given β-lactamase inhibitor.[9] β-lactamase inhibitors expand the useful spectrum of these β-lactam antibiotics by inhibiting the β-lactamase enzymes produced by bacteria to deactivate them.

- β-lactamase inhibitors with a β-lactam core:
  - Tebipenem is the first carbapenem to be administered orally in the form of tebipenem-pivoxil. Structural and kinetic studies of tebipenem are available with *M. tuberculosis* beta-lactamase (BlaC).
  - Clavulanic acid or clavulanate, usually combined with amoxicillin (Augmentin) or ticarcillin (Timentin).
  - Sulbactam, usually combined with ampicillin (Unasyn) or cefoperazone (Sulperazon)
  - Tazobactam, usually combined with piperacillin (Zosyn and Tazocin)
- β-lactamase inhibitors with a diazabicyclooctane core:
  - Avibactam, approved in combination with ceftazidime (Avycaz), currently undergoing clinical trials for combination with ceftaroline.
  - Relebactam, used in combination with imipenem/cilastatin (Recarbrio).
- β-lactamase inhibitors with other types of non β-lactam cores:
- Vaborbactam, used in combination with meropenem (Vabomere). Has a boronic acid core.



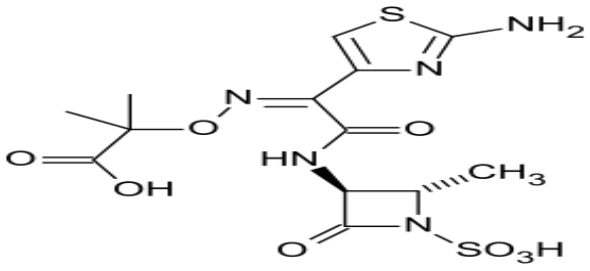
Monobactams

Monobactams are monocyclic and bacterially-produced β-lactam antibiotics. The β-lactam ring is not fused to another ring, in contrast to most other β-lactams. Monobactams are effective only against aerobic Gram-negative bacteria (e.g., *Neisseria*, *Pseudomonas*). Siderophore-conjugated monobactams show promise for the treatment of multi drug-resistant pathogens.

Aztreonam is a commercially available monobactam antibiotic. Other examples of monobactams are tigemonam, nocardicin A, and tabtoxin.

Adverse effects to monobactams can include skin rash and occasional abnormal liver functions.

Monobactam antibiotics exhibit no IgE cross-reactivity reactions with penicillin but have shown some cross reactivity with cephalosporins, most notably ceftazidime, which contains an identical side chain as aztreonam. Monobactams can trigger seizures in patients with history of seizures, although the risk is lower than with penicillins.



IMPORTANT QUESTIONS

Very short Answer Type Questions (2 marks)

Q1.What is the example of penicillin V drug?

Q2. Piperacillin drug is example of?

Q3. Which drug is not comes under cephalosporins class?

Q4. Which drug is not comes under penicillin class?

SHORTS ANSWER TYPE QUESTIONS (5 marks)

Q5. what are beta lactam rings write their chemistry.

Q6. Classify beta-lactam compounds.

Q7. Write in short about Beta lactamase inhibitors.

Q8. Draw the following structure

Minocycline

Doxycycline

Tetracycline

Streptomycin

Gentamycin

Kanamycin

Tobramycin

LONG ANSWER TYPE QUESTIONS (10 marks)

Q9. what are 'Aminoglycosides Antibiotics?

Q10. Give a brief account of the SAR of Tetracycline's'.

Q11. Discuss the SAR and stereochemistry of Penicillin.

Q12. Explain the SAR of cephalosporins.