11/Tuesday

ANTIBIOTICS

Q Classify antibiotics

An antibiotic or antibiotic subs. is a subs produced by micro-organisms, which has the capacity of inhibiting the growth and even of destroying other micro-organisms.

Any subs. produced by a living org. that is capable of inhibiting the growth or survival of one or more species of micro-organisms in low conc^{n}s.

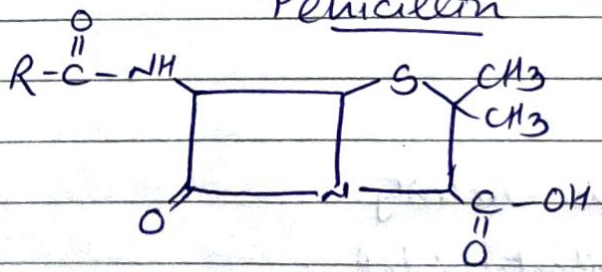
Antibiotics are molecules that kill or stop the growth of micro-organisms, including both bacteria and fungi.

Antibiotics that kill bacteria are called "bactericidal".
Antibiotics that stop growth of bacteria are called "bacteriostatic".

Classification

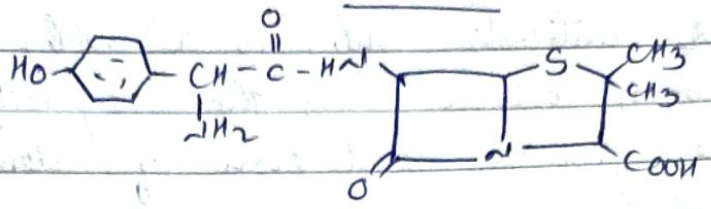
I Natural antibiotics.
Eg: Penicillin*, Streptomycin, Chlortetracycline, Chloramphenicol

☆ Penicillin



II Semisynthetic
Eg: Amoxicillin*
Ampicillin

Amoxicillin

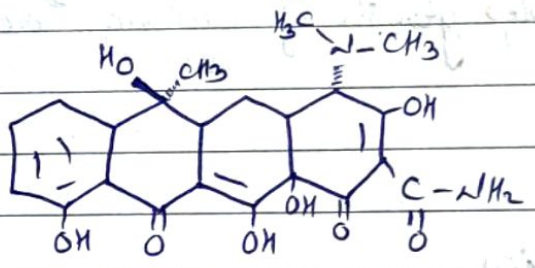


6 (α-amino-parahydroxyphenyl acetamido) penicillanic acid

III Based on spectrum of activity.

A) Broad spectrum antibiotics
Eg: Chloramphenicol
Tetracycline

Tetracycline



B) Narrow spectrum antibiotics
Eg: Nystatin
Bacitracin

IV Based on antibiotic activity.

A) Antibacterial — Bactericidal
— Bacteriostatic

B) Antifungal
Griseofulvin

C) Anthelmetic

D) Anticancer

E) Antiamodine

V Based on mechanism of action

A) Cell wall synthesis inhibitor - Cephalosporin, Penicillin

B) Cell membrane inhibitor Nystatin, Amphotericin B, Polymyxin

C) Protein synthesis inhibitor Erythromycin, Tetracycline

VI Based on chemical structure.

A) β-lactam antibiotics
Eg: Penicillin
Cephalosporin
Monobactams

B) Aminoglycoside antibiotics
Eg: Streptomycin
Gentamycin
Neomycin

C) Tetracycline antibiotics
Eg: Tetracycline
Chlortetracycline
Oxytetracycline

D) Macrolides antibiotics
Eg: Erythromycin

E) Polypeptide antibiotics
Eg: Actinomycin
Polymixin-B

F) Polyenes antibiotics
Eg: Amphotericin-B, Nystatin.

G) Lincomycin
Eg: Clindamycin
Lincomycin

H) Miscellaneous agents
Eg: Chloramphenicol
Novomycin

Q. Short note on β-lactam antibiotics

β-lactam antibiotics
- These are antibiotics having a β-lactam ring.
- The two major groups are penicillins and cephalosporins.
- Monobactams and carbapenems are relatively later addition - share a common MoA and inhibitor of the synthesis of bacterial peptidoglycan cell wall
- Broad spectrum of antibacterial action. The unequaled importance of β-lactam antibiotics in chemotherapy is due to
  ~ potent lethal bactericidal action on the growth phase
  ~ Low frequency of toxic and other adverse effects.

MOA

The lethal antibacterial action is due to the selective inhibition of bacterial cell wall synthesis. Specifically it inhibits the biosynthesis of peptidoglycan which provides strength and rigidity to the cell wall

Penicillins and cephalosporins acylate specific bacterial transpeptidases (Penicillin binding proteins) and make them inactive.

PBP 1a & 1b - transpeptidases involved in peptidoglycans synthesis associated with cell elongation. Inhibition causes lysis.

PBP 2 - transpeptidase involved in maintaining the rod shape in bacilli. Inhibition causes ovoid or round forms which undergo lysis

PBP 3 - transpeptidase required for septum formation in cell division. Inhibition results in formation of filamentous forms

PBP 4 - carboxypeptidase responsible for the hydrolysis of the terminal peptide bonds of crosslinking peptides. This cleavage of bond is required before peptide crosslinkage. But inhibition of these enzymes are not lethal

The various β-lactam antibiotics differ in their affinities for the PBPs.

Q Short note on Penicillin antibiotic

Date:

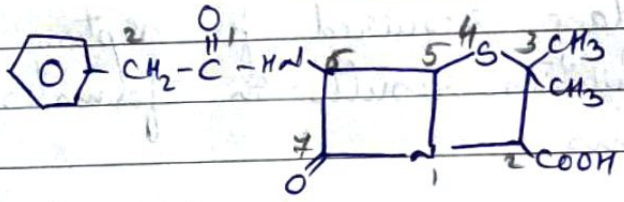
PENICILLIN

- In 1928, Alexander Fleming noticed killing effect of mold accidentally blown onto his agar plate. After attempt at isolation of compound responsible, judged to be too unstable for use as antibiotic.
- In 1938, problem of isolating penicillin solved by Florey and Chain using a process called "freeze drying" now called lyophilization
- In 1941, first clinical trial of penicillin were successful
- In 1945, structure of penicillin was solved

✱ Classification

I Natural penicillin
Eg: Penicillin G ✱
Penicillin V

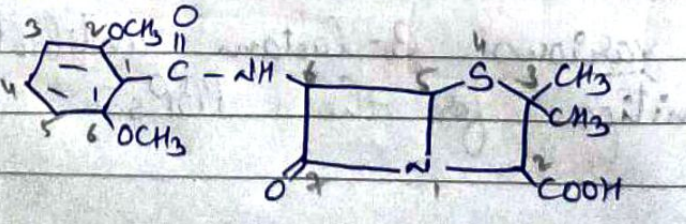
✱ Penicillin G / Benzylpenicillin



6 [(2-phenyl) acetamido] penicillanic acid

II Semisynthetic penicillinase resistant penicillin ✱
Eg: Methicillin
Nafcillin
Isoxazolyl penicillin

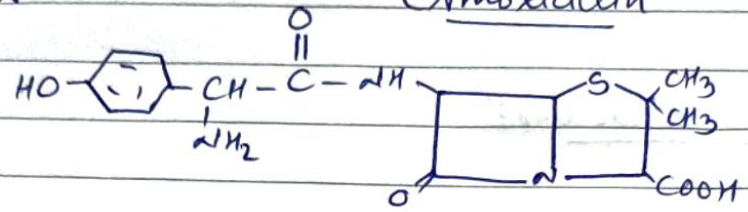
✱ Methicillin



2,6-dimethoxyphenyl penicillin

III Aminopenicillin (Semi-Synthetic penicillinase-sensitive to broad spectrum penicillins)
Eg: Amoxicillin ☆
Ampicillin

☆ Amoxicillin

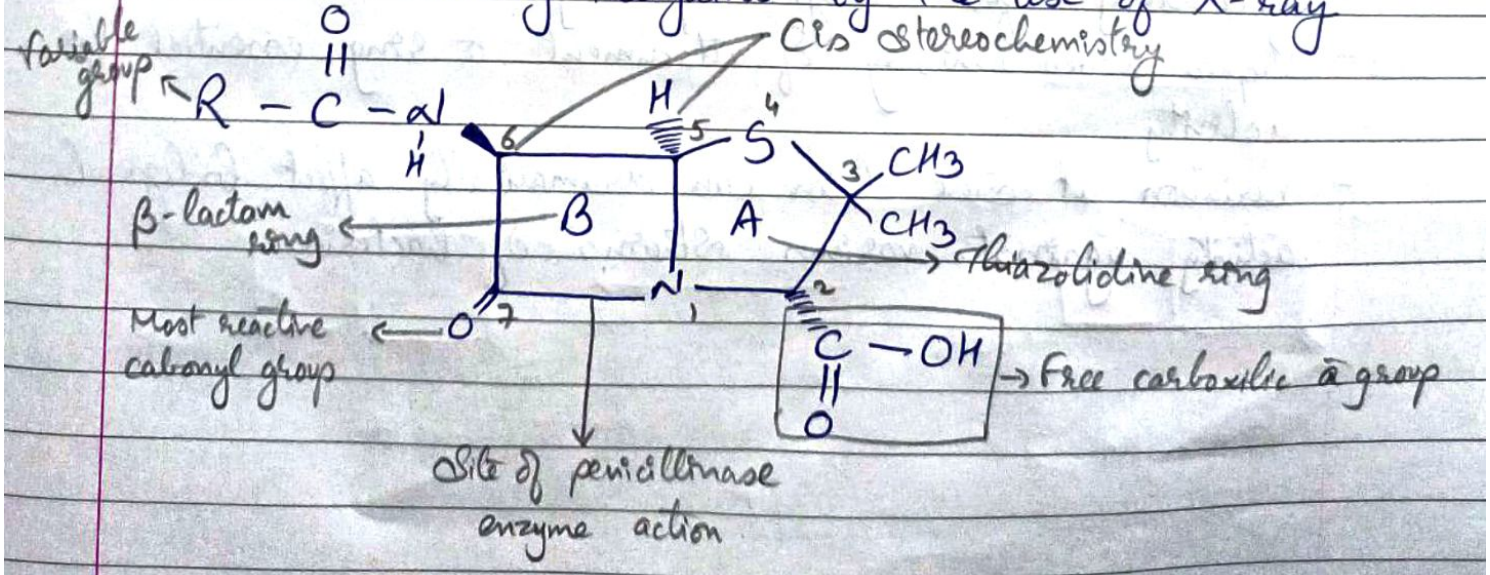


6(α-amino-parahydroxyphenyl acetamido) penicillanic acid

IV Carboxypenicillin (Synthetic penicillin sensitive to broad spectrum penicillin)
Eg: Carbenicillin
Carbenicillin phenyl

V Ureidopenicillin
Eg Piperacillin
Mezlocillin
Azlocillin

☆ Structure & chemistry
Structure of penicillin was established in 1945 by "Dorothy Hodgkins" by the use of X-ray



Penicillin contains a bicyclic system consisting of a four membered β-lactam ring fused to a five membered thiazolidine ring.

The over all shape of the molecule is like a HALF OPEN BOOK

Key features of structure:

1 β-lactam ring
- 'Lactam' is a word for any cyclic amide.
- a β-lactam means that the nitrogen is joined to the carbon which is beta to the carbonyl
- this creates strain in the ring, since it is a four membered ring
- β-lactam becomes good acylating agent for active site serine of penicillin binding protein

2 Carboxylate
- Negatively charged at neutral pH
- Anchors during in active site pocket (+vely charged)

3 Acylamido side chain
- Necessary for biological potency.
- Proper stereochemistry of attachment to ring essential for activity.
- Variation at side chain can dramatically affect biological activity against various strains of bacteria

✱ SAR

(i) Carboxylic acid - It is usually ionized and administered as sodium and potassium salt. Carboxylate ion bind to charged nitrogen of lysene in binding site.
Activity reduces when modified to alcohol and esters.

(ii) Thiazolidine ring - It is five membered nitrogen containing saturated ring
Sulphur is usually present but not essential.
At 5th position no substitutions are allowed

(iii) Stereochemistry features -
Cis stereochemistry is essential.

(iii)(iv) Acyl amino side chain - electron withdrawing group render amide oxygen, less nucleophilic.
Bulky group provide steric hindrance to β-lactamase enzyme.
Introduction of polar group makes it more hydrophilic

(iv) Carbonyl group - Lone pair of electron located on nitrogen atom not fed to carbonyl group to form a stabilize resonance structure and hence more electrophilic for nucleophilic attack

(v) Bicyclic system - It confers further strain on β-lactam ring. Greater the strain, greater the activity, greater instability to other factors.

✱ Stereochemistry

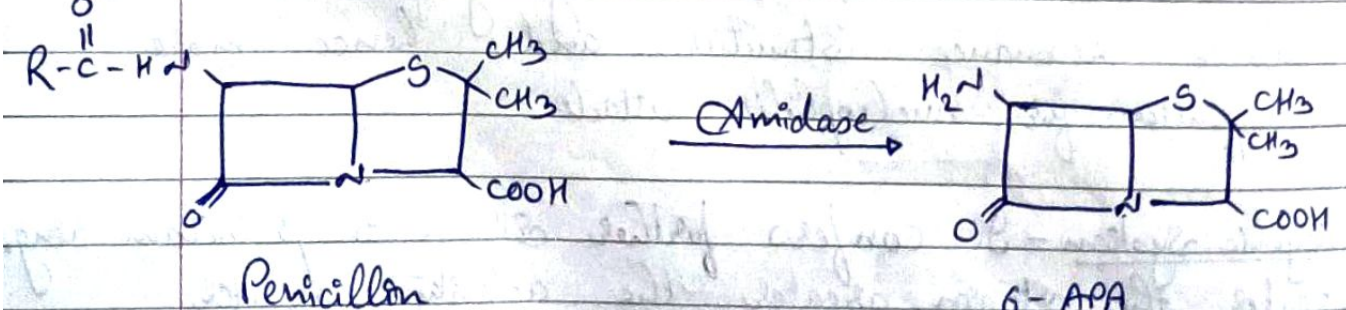
- Penicillin nucleus consist of three chiral carbon atom at C_3, C_5 and C_6 position
- The carbon atom bearing the acylamino group (C_6) has the L-configuration, whereas the carbon to which the carboxyl group is attached has the D-configuration
-
- The acylamino and carboxyl group are trans to each other with the former in the α and the latter in the β orientation relative to the penam ring system
- The atoms composing the 6-aminopenicillanic acid portion of structure are derived biosynthetically from two amino acids, L-cysteine and L-valine
- All Synthetic and semi-synthetic penicillin have same absolute configuration, that of natural penicillin i.e 3S:5S:6R ~~3S:5R:6R~~ 3S:5S:6R

✱ Uses

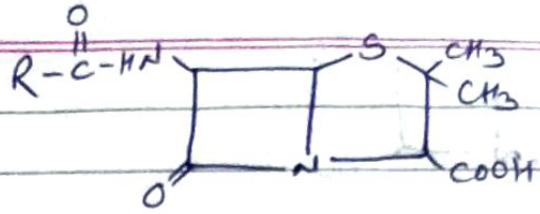
- It is used as bactericidal
- Used for infection caused by Bacillus
- Used against E. coli, Influenza etc

Q Note on degradation of penicillin

✱ Degradation

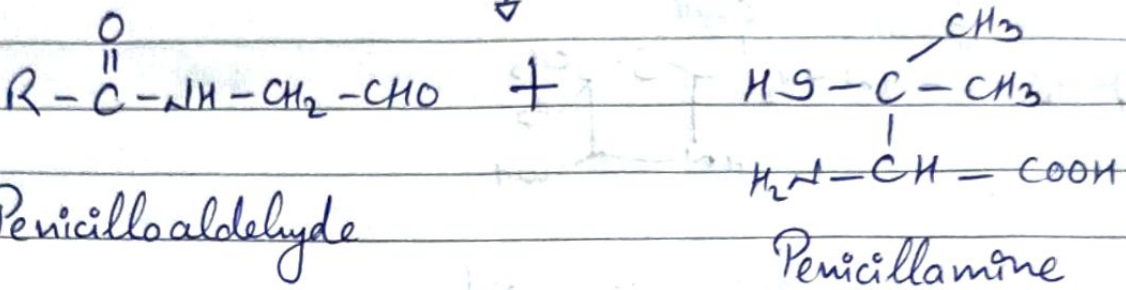


Penicillin 6-APA



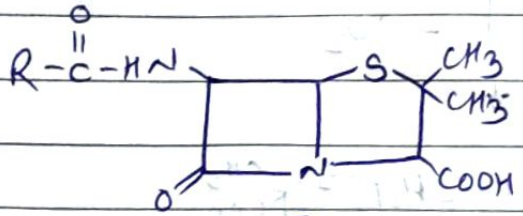
Penicillin

Strong acid
H^+



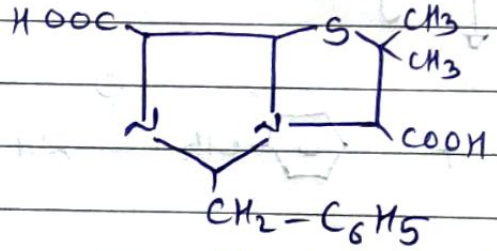
Penicilloaldehyde

Penicillamine



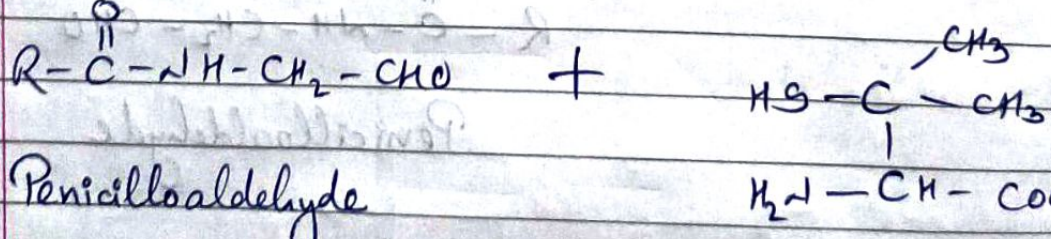
Penicillin

Dil. acid pH-5



Penillic acid

Strong acid / Mercurous pentachloride ($HgCl_5$)

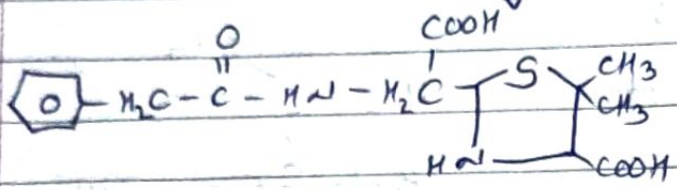


Penicilloaldehyde

Penicillamine

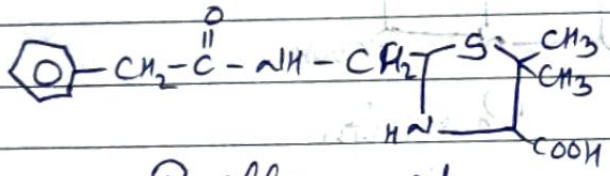
Penicillin

Penicillase



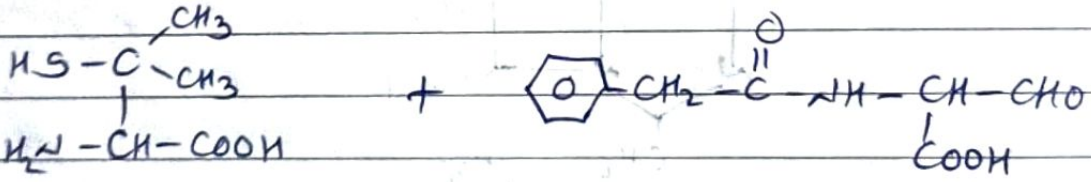
Penicilloic acid

$-CO_2$



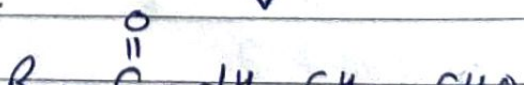
Penilloic acid

$HgCl_2$



Penicillamine

Penaldic acid



Penicilloaldehyde

Q. Give a note on generation of cephalosporin

Date

CEPHALOSPORIN

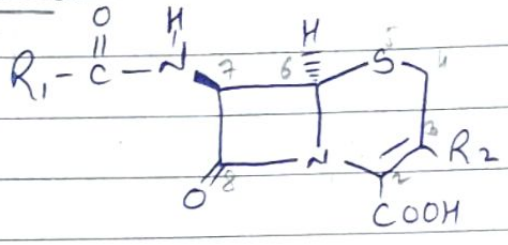
- The cephalosporins are β-lactam antibiotics isolated from Cephalosporium spp. or prepared semisynthetically
- Most of the antibiotics introduced since 1965 have been semisynthetic cephalosporins.
- Interest in Cephalosporium fungi began in 1945 with Giuseppe Brotzu's discovery that cultures of C. acremonium, inhibited the growth of wide variety of gram +ve & gram -ve bacteria
- The cephalosporin nucleus, 7-amino cephalosporanic acid (7-ACA) is derived from cephalosporin C
- The main product being cephalosporin C which is not sufficiently potent for clinical use and hence the molecular modification give origin to semisynthetic substances.
- It is same fundamental structural requirement as penicillin, the main difference b/w them is cephalosporin contain dihydrothiazine ring and penicillin contain thiazolidine ring
- Ch. Cephalosporin is divided into three classes:

(i) Cephalosporin N: it is like penicillin structure derived from 6-amino penicillanic a (6-APA), it is also called as penicillin N.

(ii) Cephalosporin P : it is an acidic antibiotic which is steroidal in nature. The compound which is structurally similar to cephalosporin P is fusidic ac

(iii) Cephalosporin C : it is true cephalosporin and it is derivative of 7-amino cephalosporanic acid

★ Structure



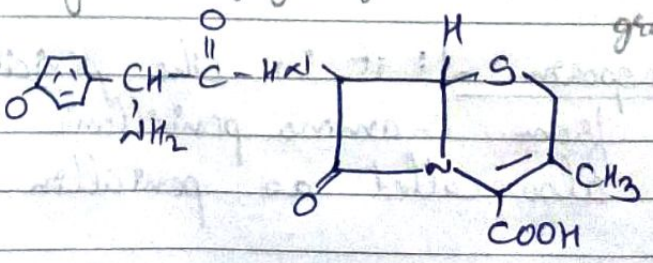
★ Classification / Generation of cephalosporins :
This is based roughly on their time of discovery and their anti-microbial properties.

Progression from 1st to 5th generation is associated with broadening of gram -ve antibacterial spectrum, some reduction in activity against gram +ve organism and enhanced resistance to β-lactamases

1st
I Generation : They are acid resistant. Have poor β-lactamase resistance. Have broad spectrum of activity & no antipseudomonal activity

Eg: Cefadroxil ★
Cefazolone - very effective against gram +ve bacteria. But somewhat effective against Gram -ve bacteria
Cefalothin - Highest activity against gram +ve bacteria & lowest activity against gram -ve bacteria

★ Cefadroxil



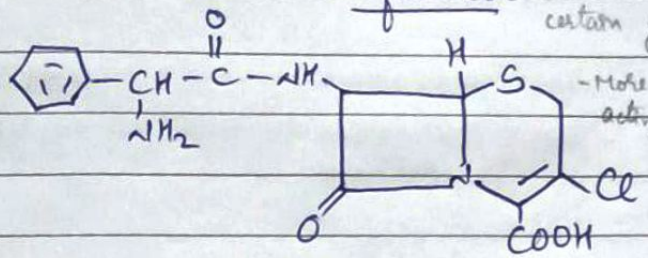
II 2nd Generation

Eg: Cefachlor *
Cefoxitin
Cefoxitin Cefuroxime

Cefaclor, Cefprozil have poor while Cefoxitin, Cefuroxime have good β-lactamase resistance
Cefaclor have broad while Cefoxitin, Cefuroxime have extended spectrum of activity
Have no antipseudomonal activity.

★ **Cefachlor**

- Target some types of gram +ve & gram -ve bacteria. But they're less effective against certain gram +ve bacteria than first generation
- More active against gram -ve bacteria & less active against gram +ve bacteria than first gen.



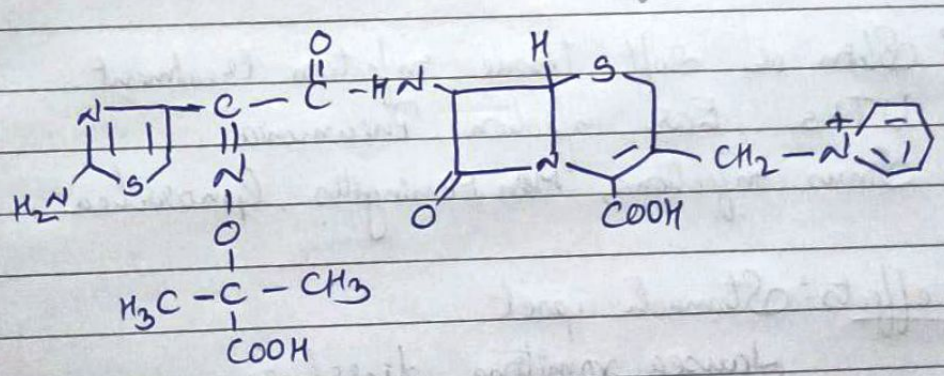
III 3rd Generation

Eg: Ceftazidime *
Cefixime
Cefotaxime

These have good β-lactamase resistance
Have extended spectrum of acting.
Do have antipseudomonal activity.
More effective against gram -ve bacteria compared to both 1st & 2nd gen.
Less active than previous gen. against gram +ve bacteria

★ **Ceftazidime**

- Less active against gram +ve than first gen,
Much expanded spectrum of activity against gram -ve



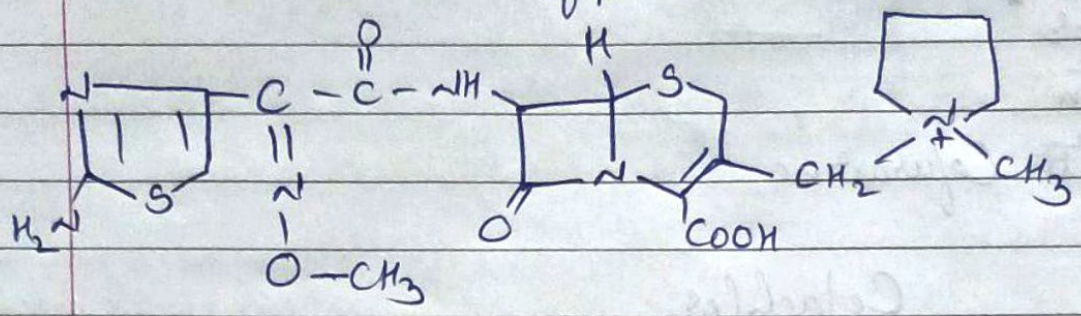
IV 4th Generation

Eg: Cefepime *
Cefpirome

Are not acid resistant
Have good β-lactamase resistance
Have extended spectrum of activity
Do have antipseudomonal activity.

- Effective against variety of gram +ve and gram -ve bacteria
- Treatment of infections caused by wide variety of bacteria

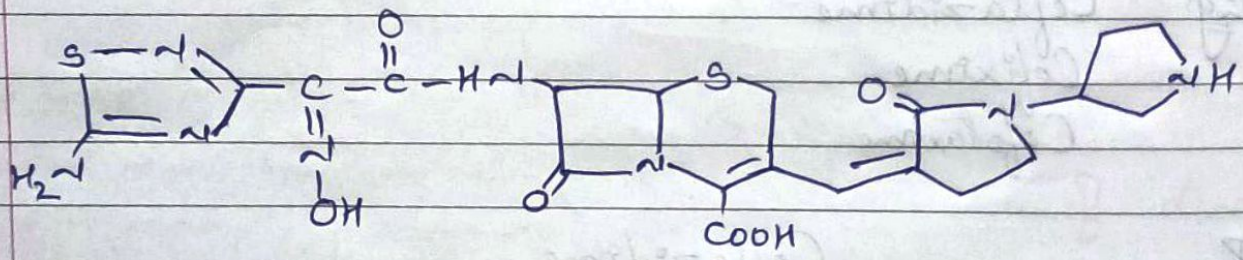
☆ Cefepime



V 5th Generation.
Eg: Ceftobiprole
Ceftaroline

Refered to as advanced generation cephalosporin used to treat bacteria like MRSA that are resistant to penicillin antibiotics

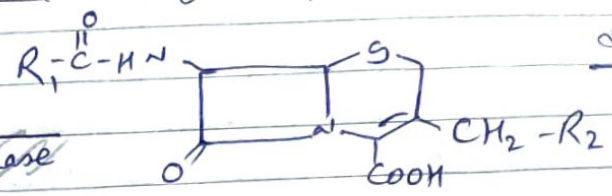
☆ Ceftobiprole



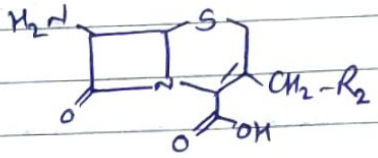
☆ Uses: Skin or soft tissue infection treatment.
UTIs, Ear infection, Pneumonia,
Sinus infections, Meningitis, Gonorrhea

☆ Side effects: Stomach upset
nausea, vomiting, diarrhoea
Dizziness.

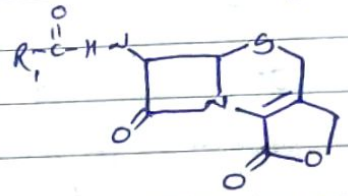
☆ Degradation of Cephalosporin



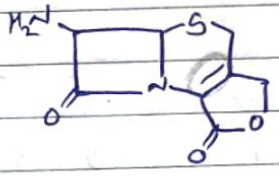
7- amino cephalosporanic ā



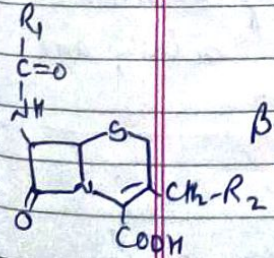
H^+/H_2O
(Acid hydrolysis)



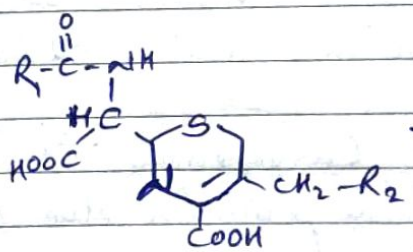
Lactone (Inactive)



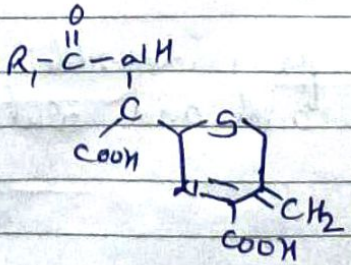
Inactive Lactone



β-lactamase



Cephalosporic acid

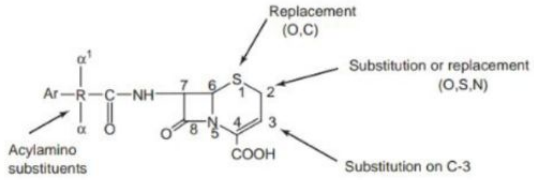


Anhydro desacetyl cephalosporic ā

Fermentation and Rearrangement Product (Inactive)

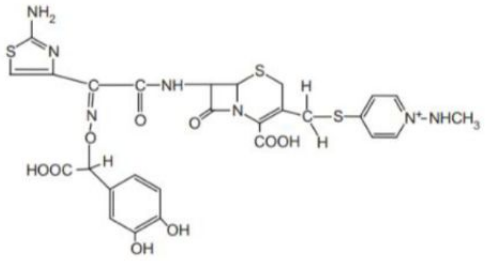
Desacetyl-7-ACA lactone (Inactive lactone)

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 α_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 gram-negative activity.
c. Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.
d. Orally active compounds are produced by replacement of acetoxy group at C-3 position with CH_3 and Cl.

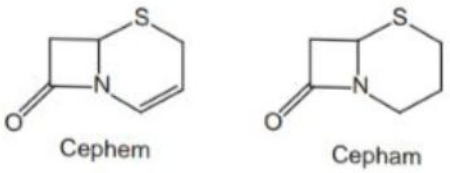
3. Other modifications

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

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.

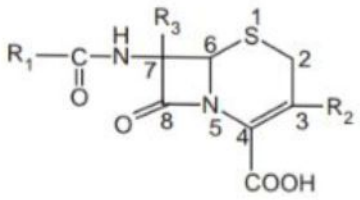


Classification

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. These agents are sensitivity to β-lactamase
c. Resistant to β-lactamase and parentrally administered: cefuroxime, cefamandole, cefoxitin
d. 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 gram-negative bacteria (Table 4.1)

II. Second-generation cephalosporins

These drugs are more active against gram-negative bacteria and less active against gram-positive bacteria than first-generation members (Table 4.2).

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 (Table 4.3).