Antibiotics

Antibiotics

History: In 1942, **Waksman** proposed the widely cited definition that "**an antibiotic is a substance produced by microorganisms, which has the capacity of inhibiting the growth and even of destroying other microorganisms**".

Later proposals have sought to both expand and restrict the definition to include **any substance produced by a living organism that is capable of inhibiting the growth or survival of one or more species of microorganisms in low concs.**

With the advances made by medicinal chemists to modify naturally occurring antibiotics and to prepare synthetic analogs, it has become necessary to permit the inclusion of ***semisynthetic*** and ***synthetic*** derivatives in the definition.

Classes of Antibiotics

1- β-Lactam antibiotics; two main subclasses are well known:

A- Classical β-Lactam antibiotics represented by penicillins and cephalosporins.

B- Non-Classical β-Lactam antibiotics such as:

monobactams, oxacephams and carbapenams.

2- Non β-Lactam antibiotics:-

a) Aminoglycosides: such as streptomycin and kanamycin.

b) Fused ring system: such as tetracyclines

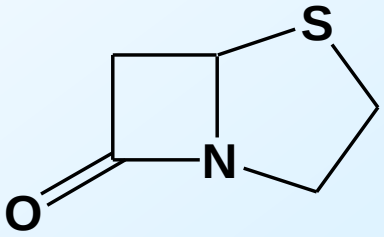
c) Macrolides: such as erythromycin and oleandomycin.

d) Polypeptides: such as polymyxin.

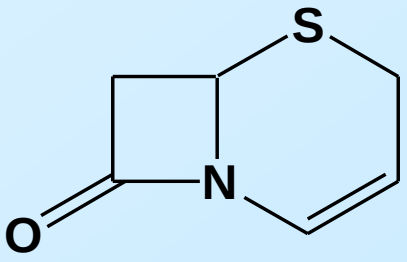
f) Polyene: such as amphotericin.

g) Miscellaneous: such as chloramphenicol

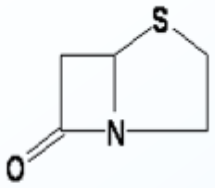
1- β-Lactam antibiotics



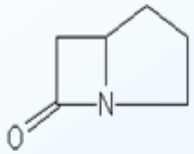
1- Penam (Penicillins)



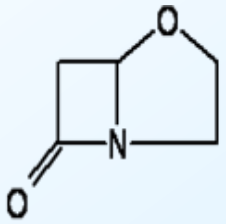
2- Cephem (Cephalosporins)



1. **Penam**



2. Carbapenam



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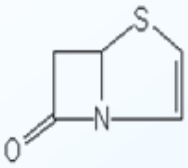
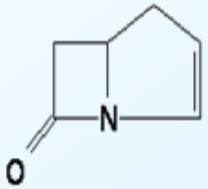
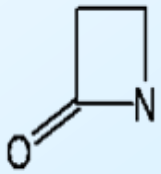


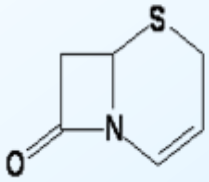
4. Penem



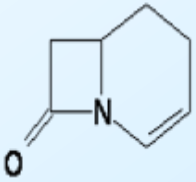
5. **Carbapenem**



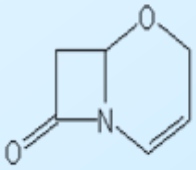
6. **Monobactam**



7. **Cephem**



8. Carbacephem

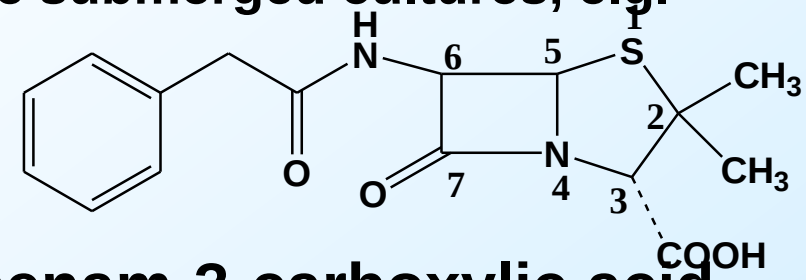


9. Oxacephem

Classification of Penicillins

1- Natural Penicillins

They are commercially produced from the submerged cultures, e.g. Benzylpenicillin



2,2-Dimethyl-6-phenylacetamido-penam-3-carboxylic acid.

Properties of benzylpenicillin

1- Active against Gram +ve bacilli (narrow spectrum).

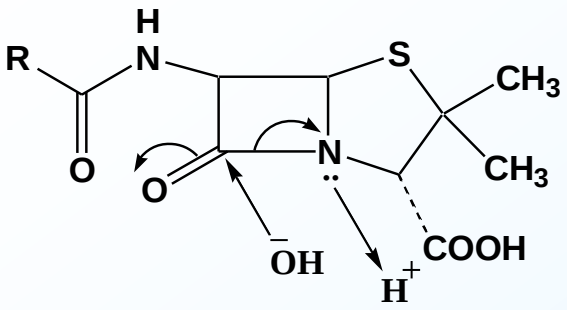
2- Ineffective when taken orally, since it breaks down in the acid of the stomach.

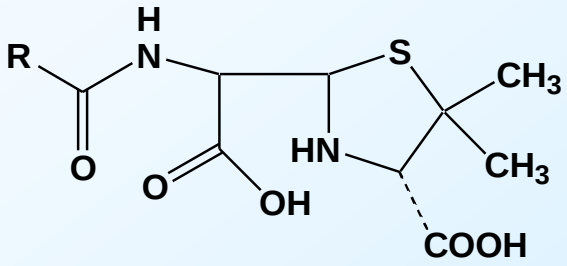
3- Sensitive to all known β-lactamases which are produced by penicillin resistant bacteria leading to the catalytic degradation of penicillin.

4- Allergic reactions are suffered by some individuals.

5- Non toxic.

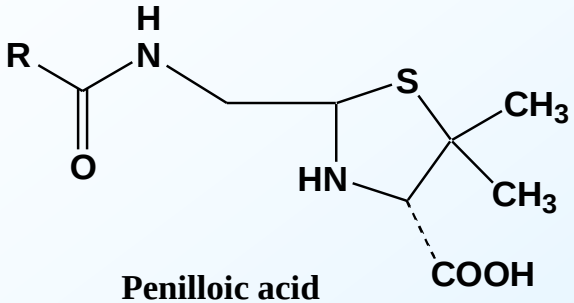
A. Nucleophilic attack (by OH^-)





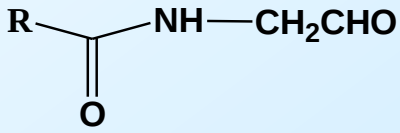
Penicilloic acid

- CO2



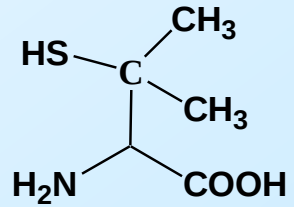
Penilloic acid

$HgCl_2$



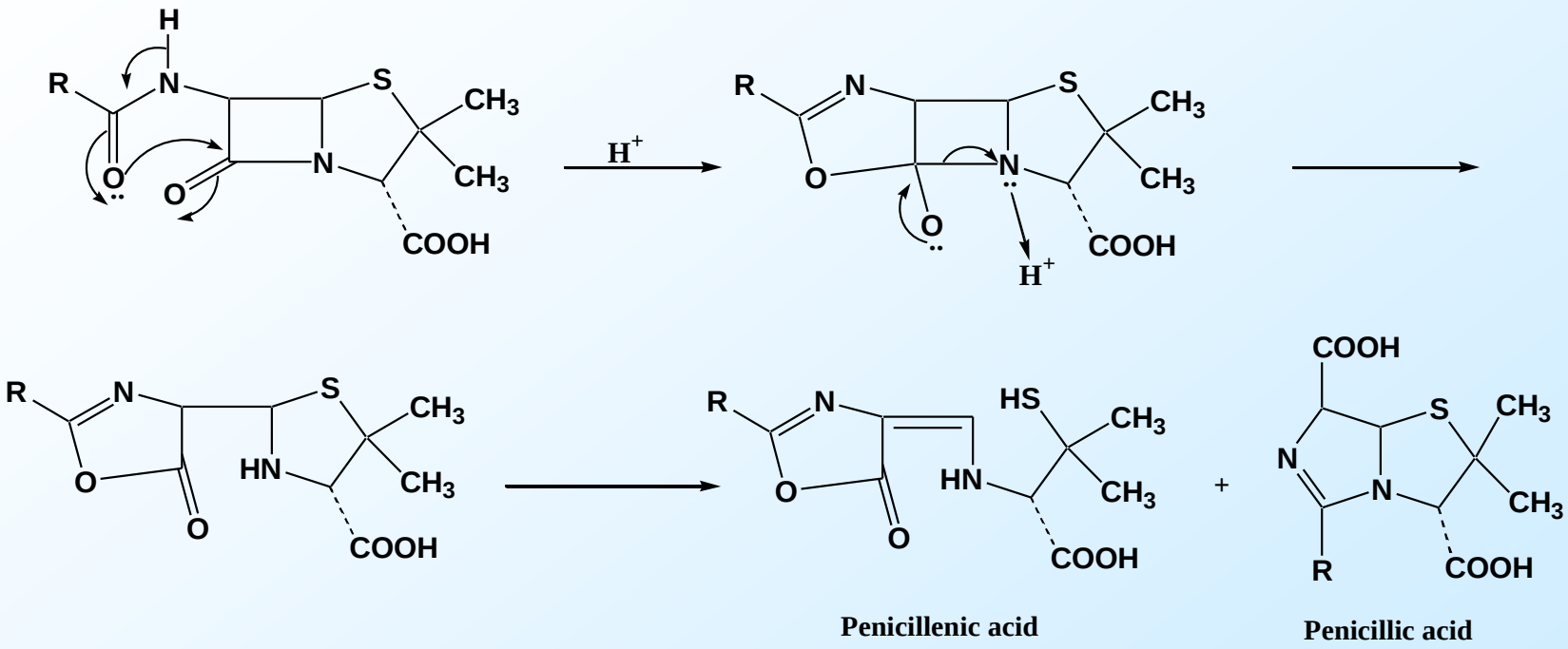
Penilloaldehyde

+



penicillamine

B. Electrophilic attack (by gastric acidity)

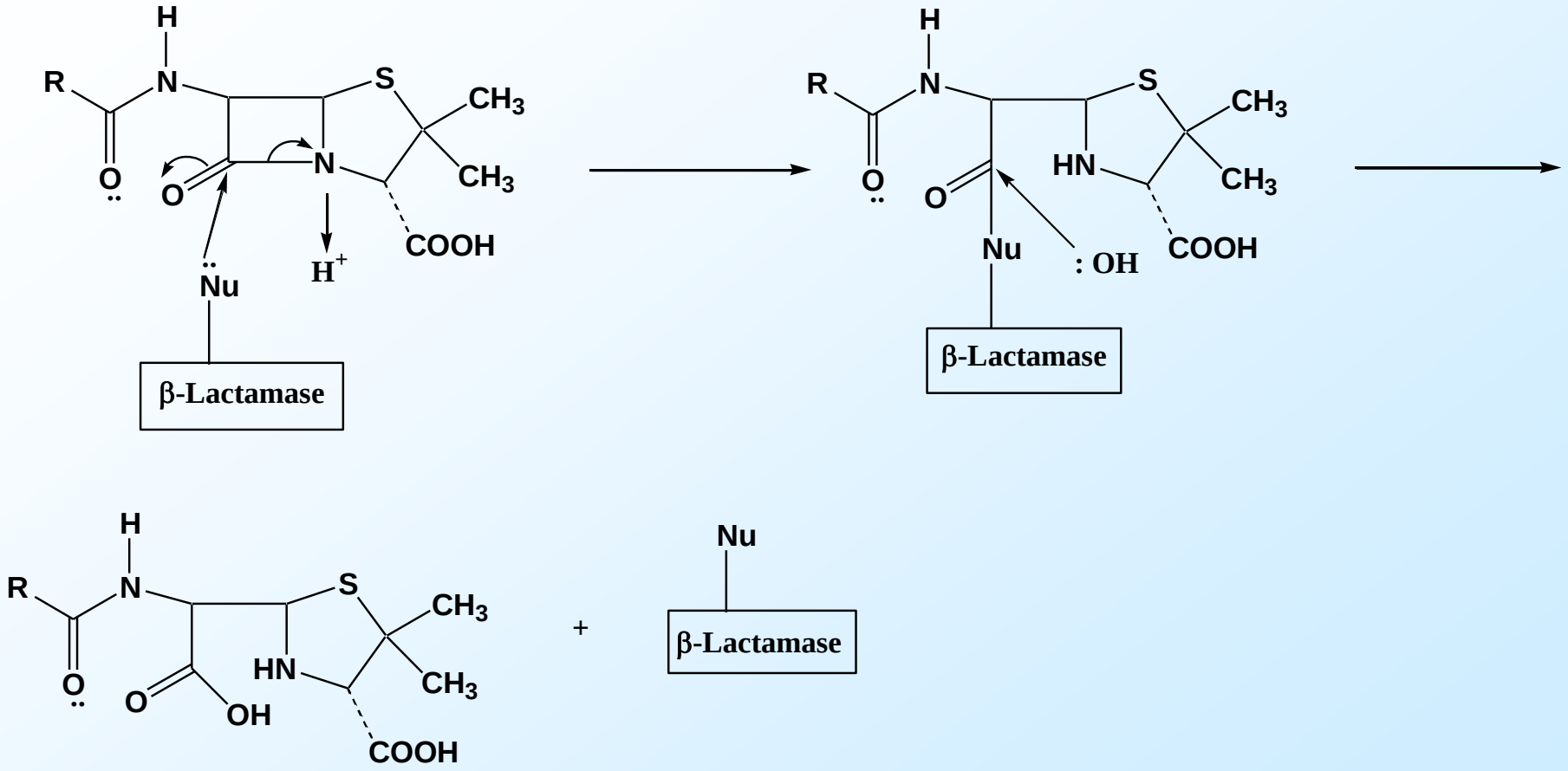


Penicillenic acid

Penicillic acid

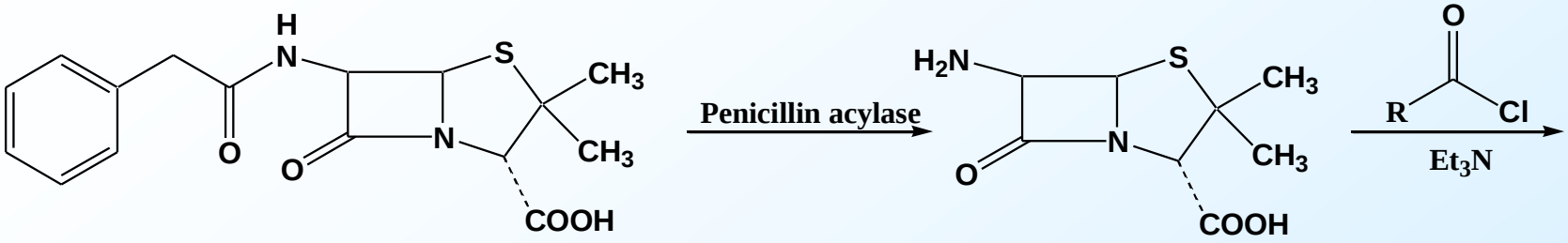
C. Penicillins sensitive to β-lactamases:-

β-Lactamases are enzymes which catalyze the hydrolysis of β-lactam ring.

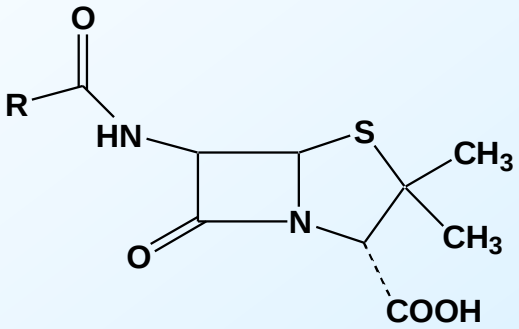


II. Semisynthetic Penicillins

Obtained from the natural penicillins through:-



Benzylpenicillin **6-APA**

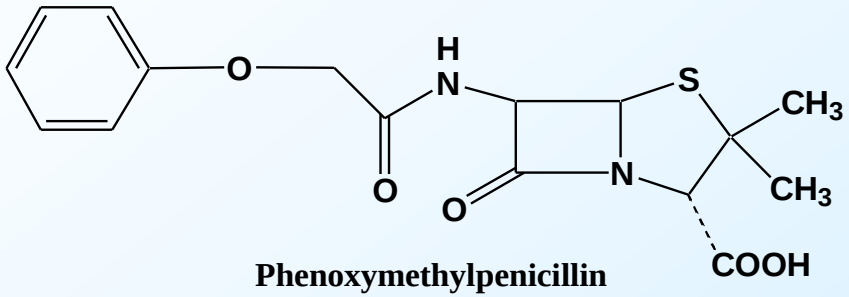


Different penicillins

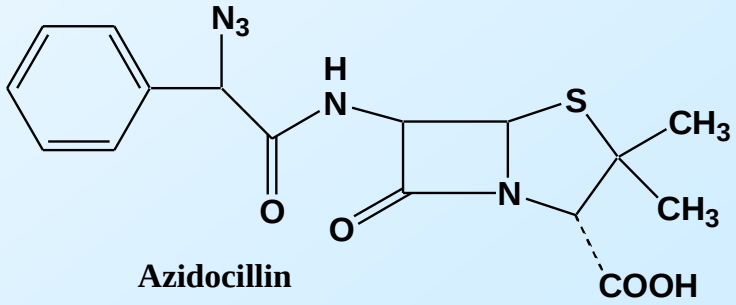
Types of semisynthetic penicillins

A. Acid stable semisynthetic penicillins

Introduction of an electron withdrawing group in the α-position of the amide side chain decreases the nucleophilicity of the side chain amide carbonyl oxygen towards participating in β-lactam ring opening to form penicillenic acid.



Phenoxymethylpenicillin
(Penicillin V)



Azidocillin

It is more active than penicillin V

This group of drugs is still affected by β-lactamases.

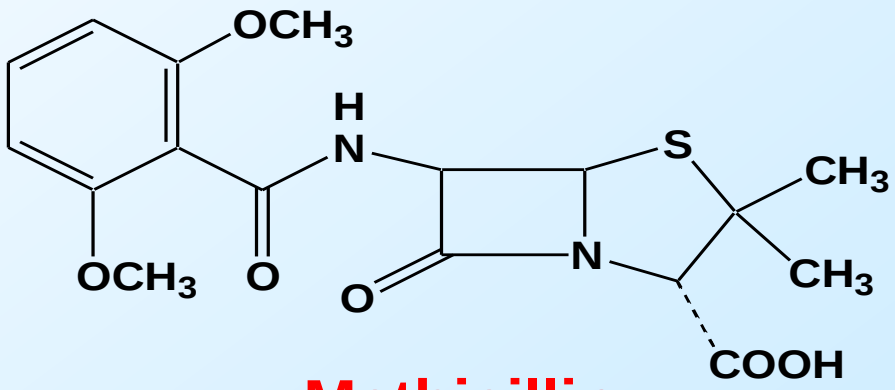
B. β-Lactamase stable penicillins

By introducing of a bulky group on the side chain which would sterically block the attack and prevent the fitting of the β-lactamase enzyme on the β-lactam ring.

This could be achieved by:-

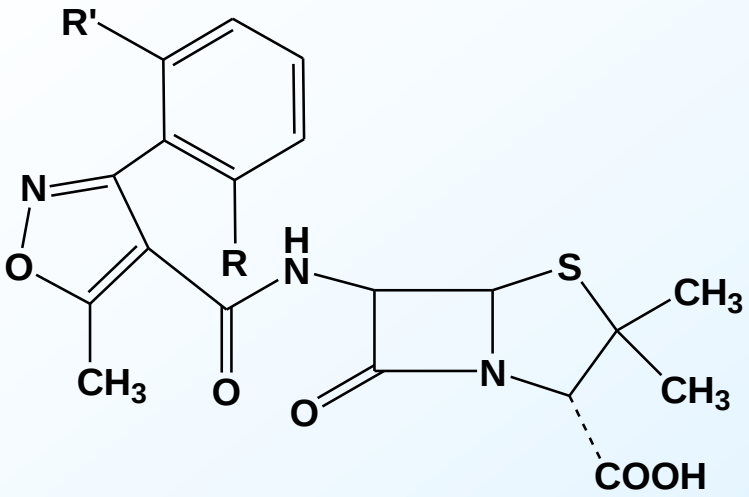
i- Introduction of an aromatic group having two ortho-positioned methoxy groups to shield the lactam ring, e.g., Methicillin (2,6-dimethoxyphenylpenicillin)

It has no electron withdrawing group on the side chain, so it is acid sensitive and has to be administered by injection.



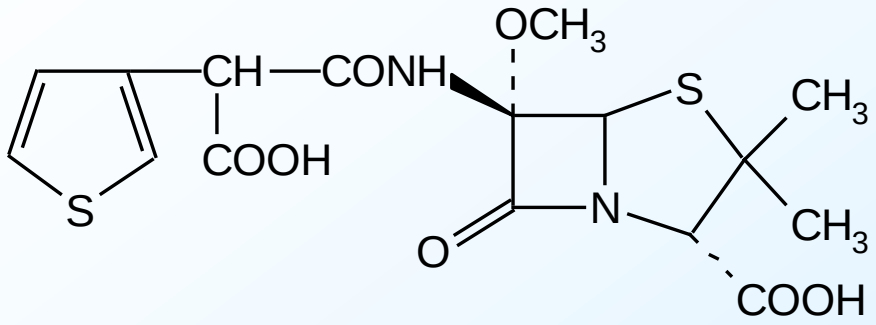
Methicillin

ii. By introducing a five-membered heterocyclic isoxazole ring into the side chain with bulky substitution in its near position. This ring acts as a steric shield and also to be electron withdrawing.



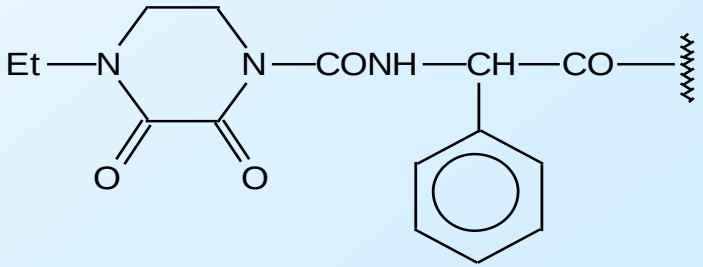
Oxacillin	**R = R' = H**
Cloxacillin	**R = Cl, R' =H**
Dicloxacillin	**R = R' = Cl**
Flucloxacillin	**R = Cl, R' = F**

Temocillin



- Introduction of 6-α-methoxy group to penicillins give highly resistant derivatives to bacterial β-lactamases
- Not absorbed orally & used as Na salt for parenteral administration.

e.g., Piperacillin. It is also parenteral broad-spectrum penicillin with antipseudomonal activity. It is usually co-administered with tazobactam

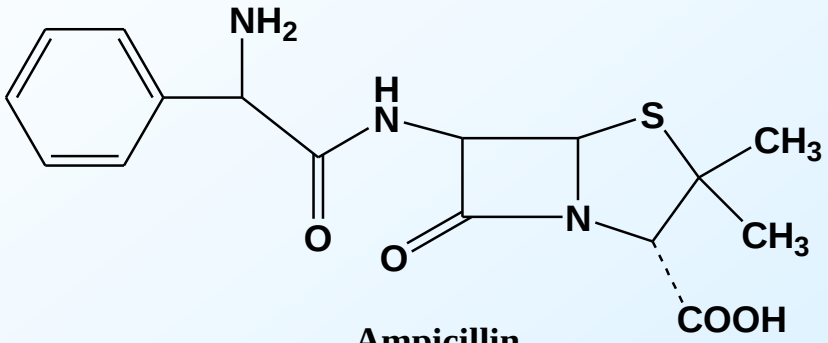


C. Broad spectrum penicillins:-

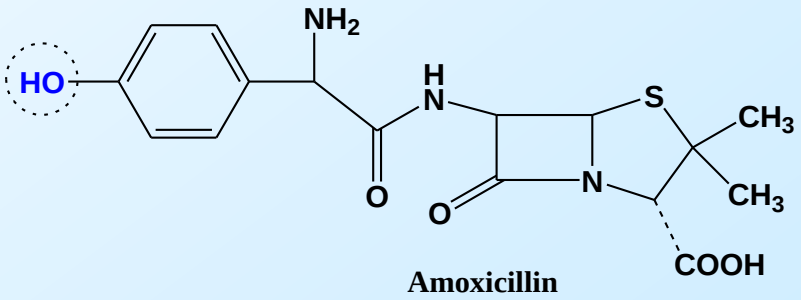
The introduction of an amino group in the α-position of the side chain of benzylpenicillin, confers a high degree of acid stability together with enhanced activity against Gram -ve bacteria.

The α-amino group is protonated in the gastric juice and acquires electron withdrawing property and the molecule becomes acid resistant.

These compounds are sensitive to penicillinase enzyme and could be combined with β-lactamase inhibitors



Ampicillin

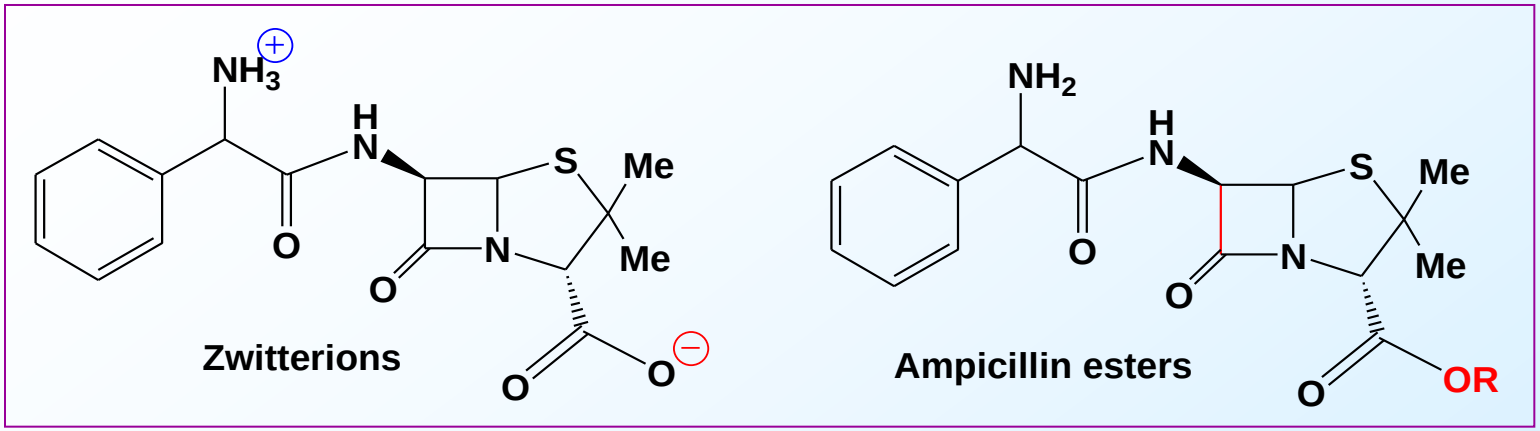


Amoxicillin

** α-NH_2 creates new asymmetric center;

D-isomer is 8 times more active > L-isomer.

** *The presence of OH gp. increase its oral absorption* over ampicillin



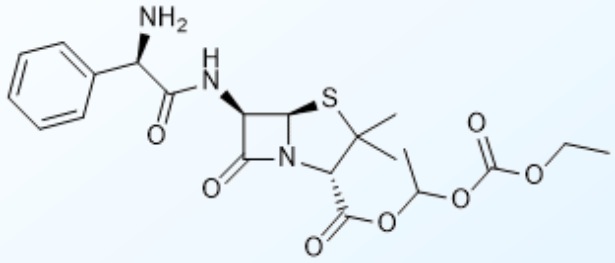
- The existence of NH_2 & COOH in the same molecule renders it amphoteric & forms Zwitter ions that its solubility becomes difficult in both acid & alkaline media.
- Only **40 %** of the dose of Ampicillin is absorbed orally from the GIT

To overcome this bad absorption:

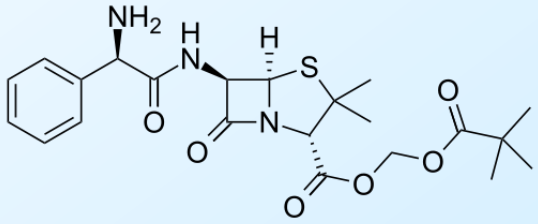
- **Esterification of the COOH gp gives prodrugs with ↑ lipid solubility & improves oral bioavailability.**
- **The esters are lipophilic compounds e.g. pivampicillin, bacampicillin.**
- **They are devoid of antibacterial activity (inactive) in vitro, but hydrolyzed by tissue esterases & liberate ampicillin in vivo.**

** Ampicillin is administered orally and parenterally as Na salt.

** Formulations with sulbactam are also available.

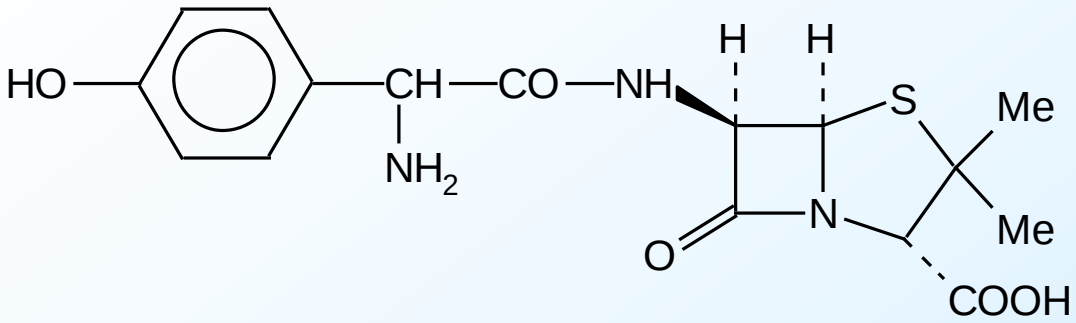


Bacampicillin



Pivampicillin

Amoxicillin

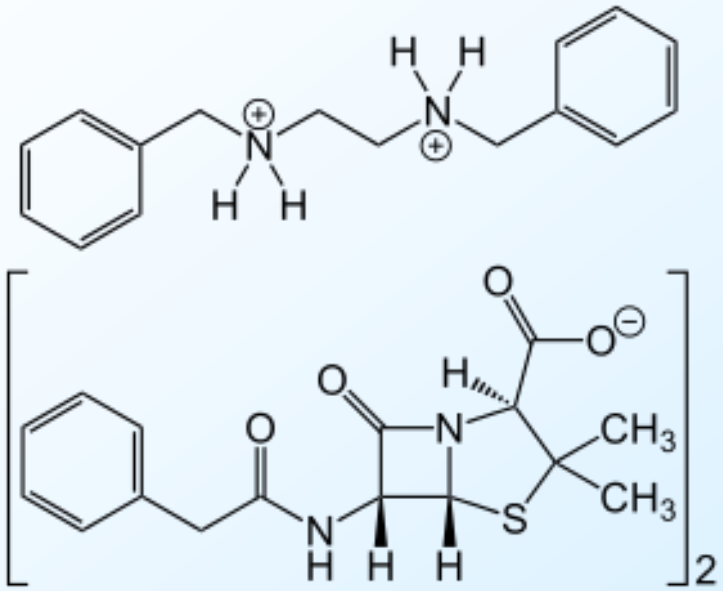


D-(-)-α-Amino-*p*-hydroxybenzylpenicillin.

- **Used as trihydrate for oral administration & as Na salt for parenteral use.**
- **Used also with clavulanic acid**
- **It has superior oral absorption producing around 2.5 times the plasma peak concentration achieved by comparable doses of ampicillin.**
- **It's absorption from G.I.T is unaffected by food.**

Long acting penicillins

Benzathine benzylpenicillin



It is in the penicillin Class of medications. It is slowly absorbed into the circulation, after intramuscular injection ،and hydrolyzed to benzylpenicillin *in vivo* It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate, allowing prolonged antibiotic action over 2–4 weeks after a single IM dose

β-Lactamase Inhibitors

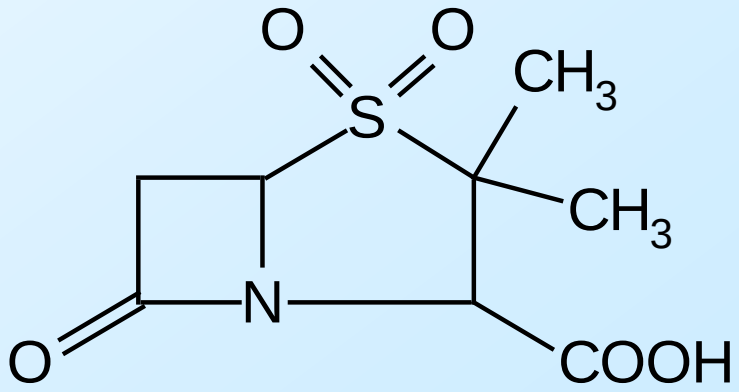
the production of β-lactamases increase the threat of bacterial resistance.

So how can we combat this dangerous enemy?

β-lactamase inhibitors

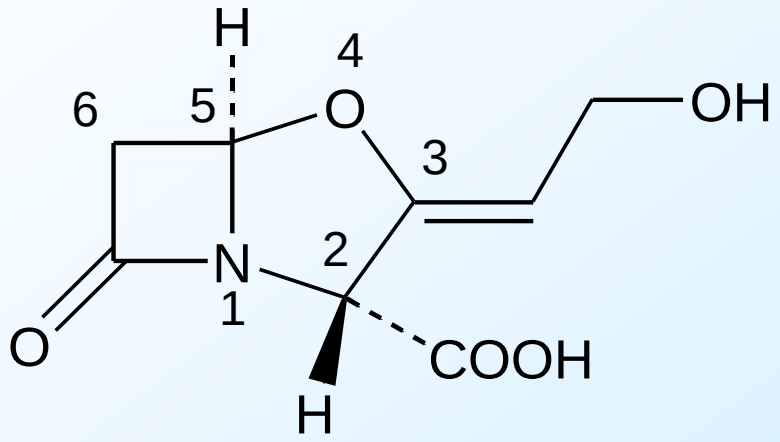
- Suicidal inhibitors with **weak** antibacterial activity,
- but have higher capacity to inactivate many β-lactamases.
- Used in combination with penicillins to overcome resistance problems
- e.g. clavulanic acid & sulbactam.

i. Sulbactam



- A penicillenic acid sulfone available as the sodium salt.
- It is coadministered with Ampicillin (**Unasyn IM or IV**)

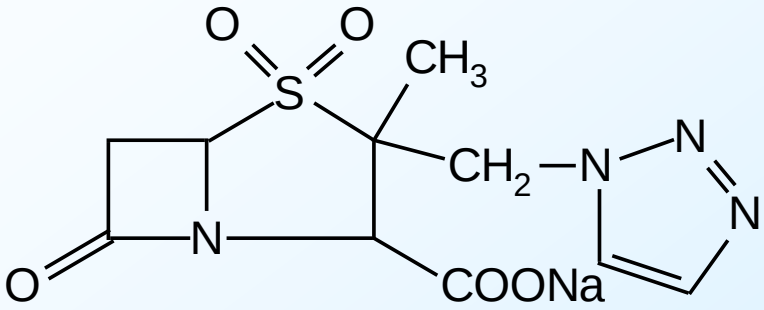
Clavulanic Acid

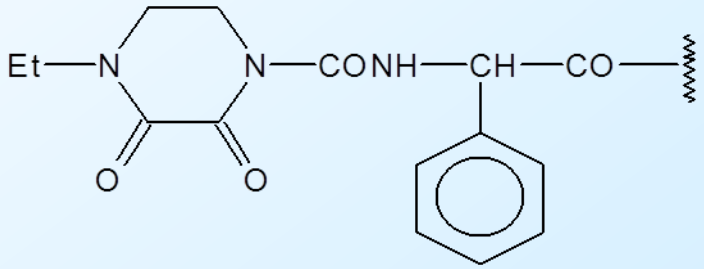


Clavulanic acid inhibits the β-lactamase enzyme by irreversible binding to the enzyme and allows the penicillin molecule to attack the peptidoglycan cell wall in order to destroy the bacterial cell.

iii. Tazobactam

It is formulated with piperacillin. The combination is mainly used intravenously in intensive care medicine (pneumonia, peritonitis) and





Piperacillin

Mechanism of action

Through inhibition of bacterial cell wall synthesis. Specifically; inhibition of the biosynthesis of dipeptidoglycan that is needed to provide strength and rigidity to the cell wall.

The peptidoglycan layer is a highly cross-linked amino sugar polymer consisting the cell wall of the bacterial cell.

Assay of penicillins

Iodometric titration:-

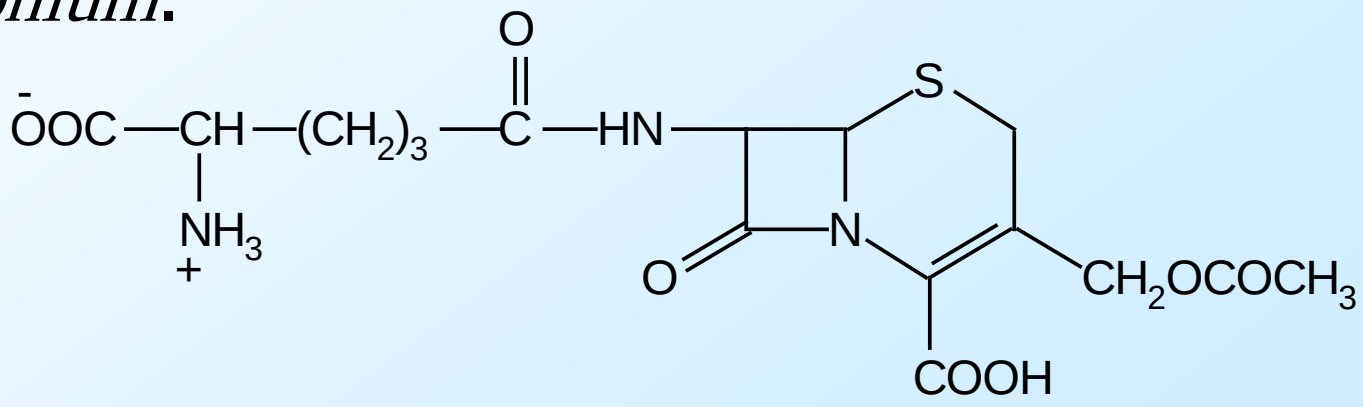
Hydrolysis with NaOH, then add xss of standard I_2 solution, xss I_2 is titrated with sodium thiosulfate in the presence of starch as indicator.

Cephalosporins

Cephalosporins are similar to penicillins in terms of mechanism of action, chemical structure, and toxicities.

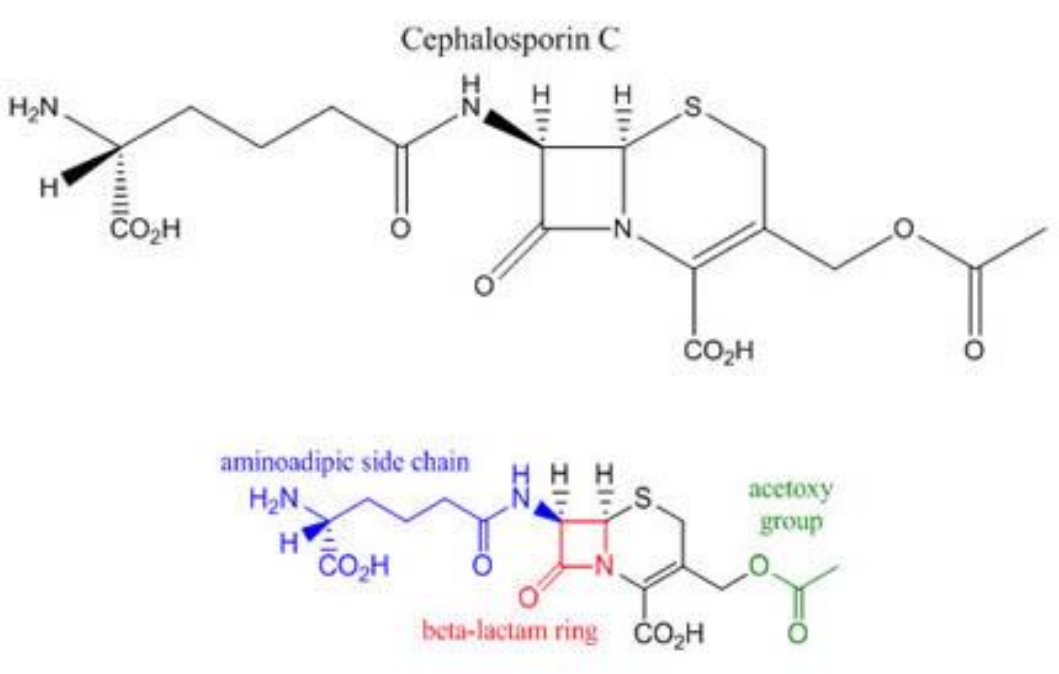
Cephalosporins are the second major group of β-lactam antibiotics to be discovered.

All cephalosporins molecules are based on cephalosporin C, which was discovered by Edward Abraham and his colleagues in Oxford as a minor component of the antibiotic complex produced by *Cephalosporium acremonium*.



- **The structure of cephalosporin C involves:**

1. A **six membered dihydrothiazine** ring with an **acetoxymethyl group** at its 3-position. This ring is fused to four membered β-lactam ring.
2. An **α-aminoadipoyl side chain**, that on hydrolysis yields 7-aminocephalosporanic acid (7ACA).



- **Properties of Cephalosporin C**

2. Low potency.

3. Not absorbed orally. 4. Non toxic.

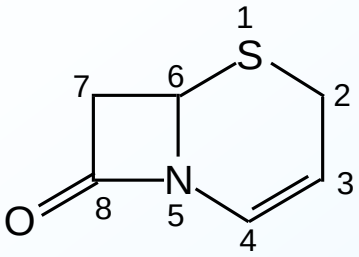
5. Relatively stable to acid hydrolysis compared to penicillins.

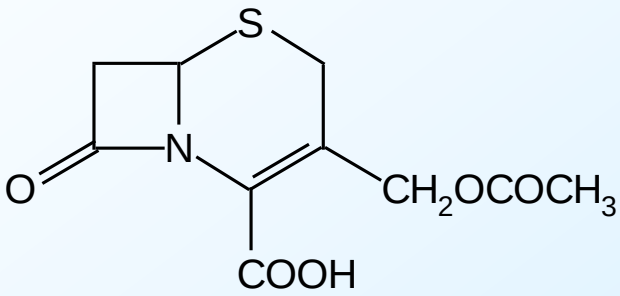
6. More stable to penicillinase than penicillin G.

7. The 7-aminocephalosporanic acid can be modified at a number of positions to obtain the semisynthetic cephalosporins.

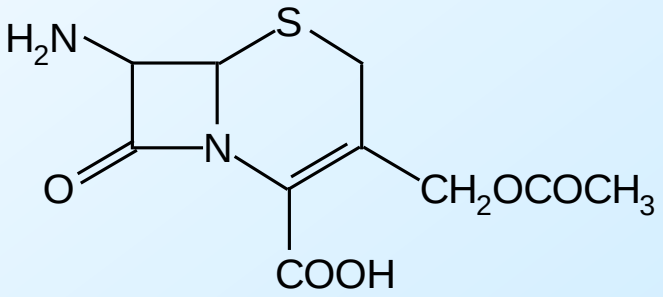
8-Moreover, the likelihood of causing allergic reactions is less. As a result, cephalosporin C became a useful lead compound for the development of better antibiotics

- **Nomenclature of the Semisynthetic Cephalosporins**





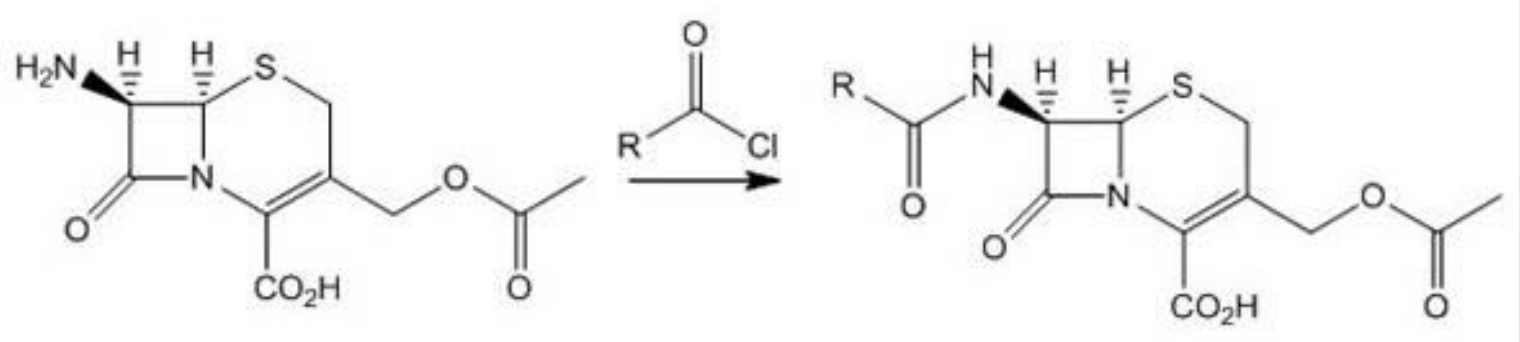
3-Cephem



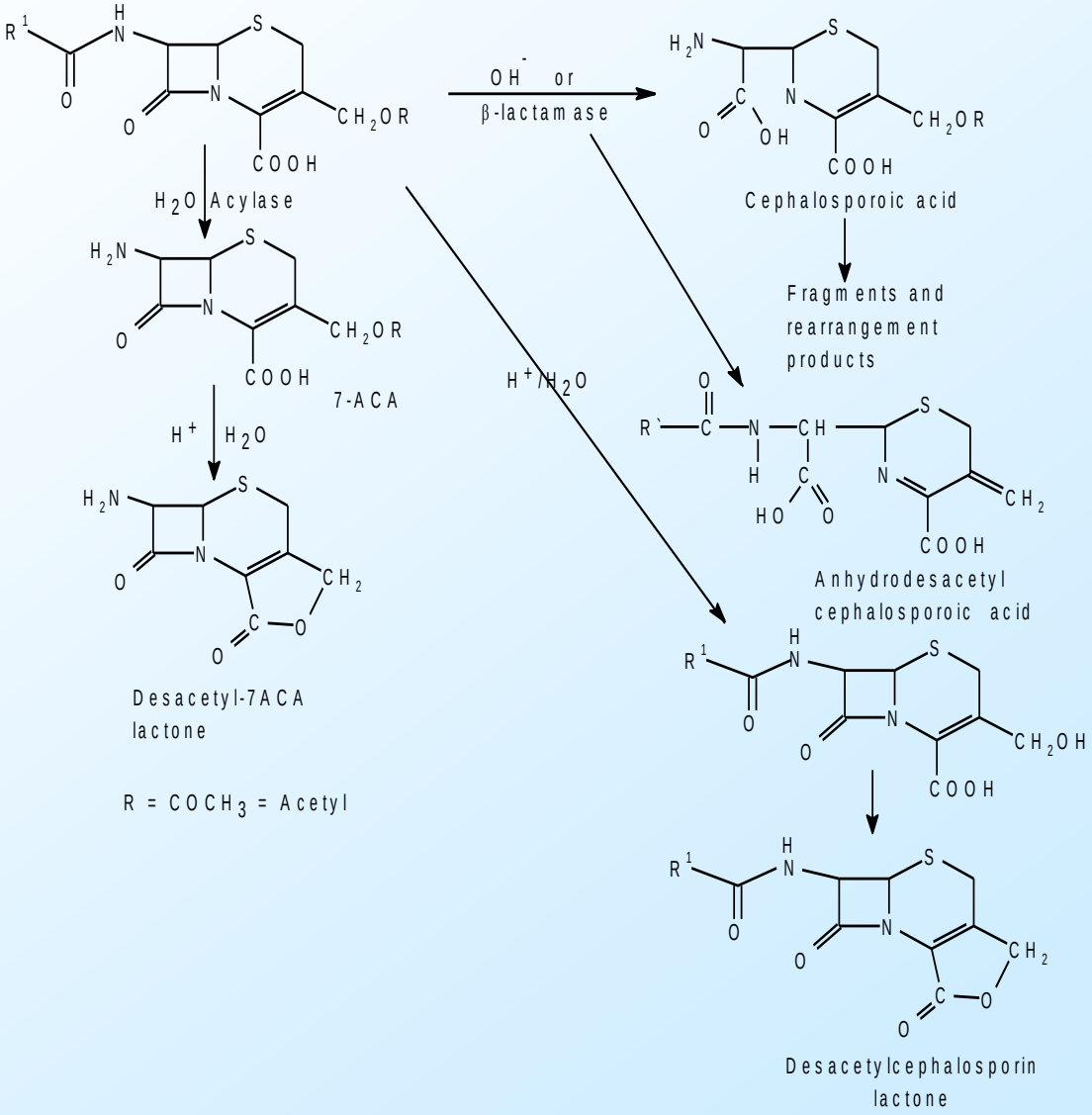
Cephalosporanic acid 7-Aminocephalosporanicacid (7-ACA)

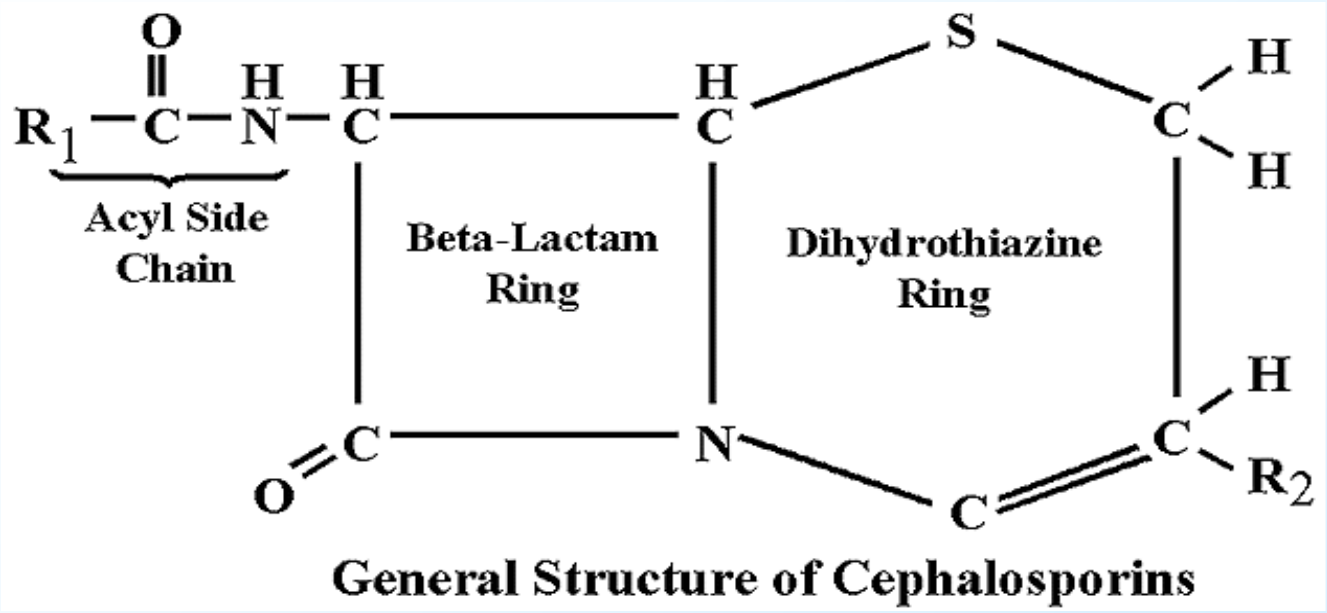
7-aminocephalosporinic acid (7-ACA) is used as the precursor of many cephalosporins.

Cephalosporin analogues may be formed by reacting 7-ACA with acid chlorides.



ability of Cephalosporins





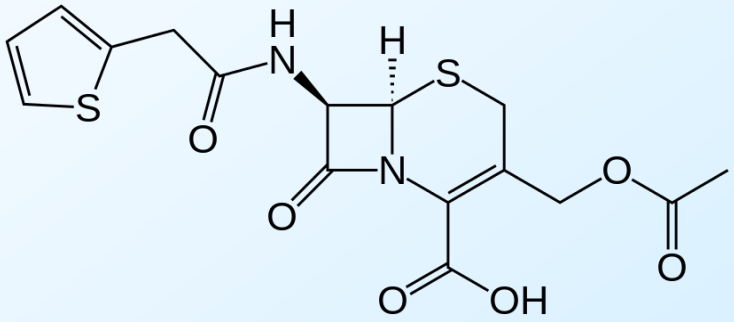
General Structure of Cephalosporins

rst Generation Cephalosporins

-Produced between 1960-1970.
-Broad-spectrum activity against many Gram-positive bacteria.
-They are not significantly active against Gram-negative organisms.
-Poor ability to penetrate cerebrospinal fluid.-
-Inactive against Pseudomonas.

A. Parenteral Agents

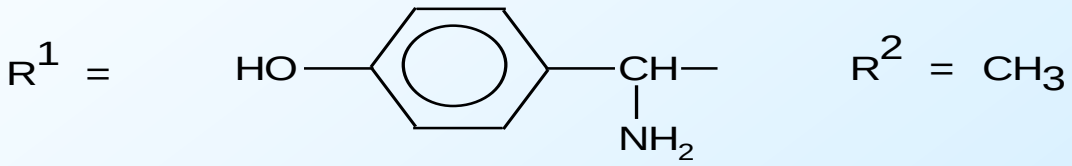
Cefalotin (Cephalothin)



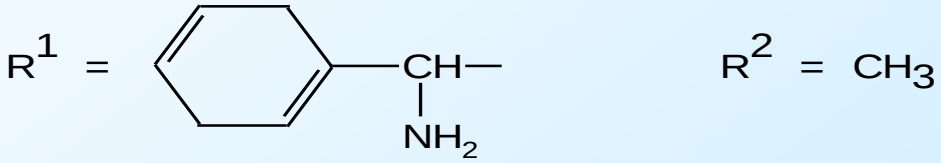
-Thienylacetamido)-3-acetoxymethyl-Δ^3-Cephem-4-carboxylic acid

- **B. Oral Agents**

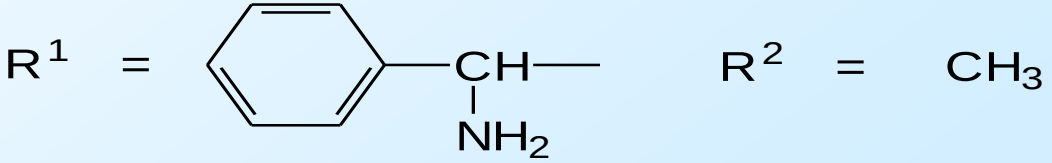
i. Cefadroxil



ii. Cephradine

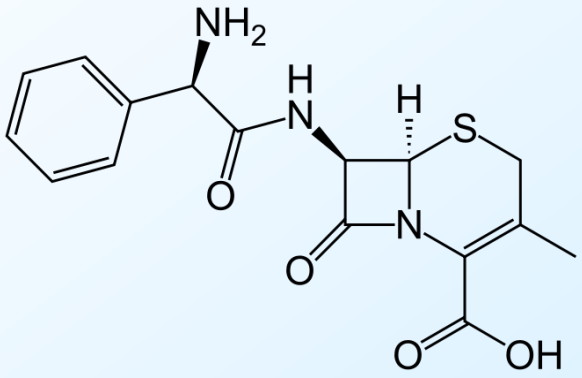


iii. Cephalexine



Cephalexine

7-[(D-α-amino-α-phenyl)acetamido]-3-methyl-Δ3- cephem-4-carboxylic acid.



- **Second Generation Cephalosporins**

  Produced between 1970-1980.

  Broad-spectrum activity especially against Gram-positive bacteria and including H. influenzae and some **increased activity against Gram-negative** organisms.

  Some drugs can pass the cerebrospinal fluid.

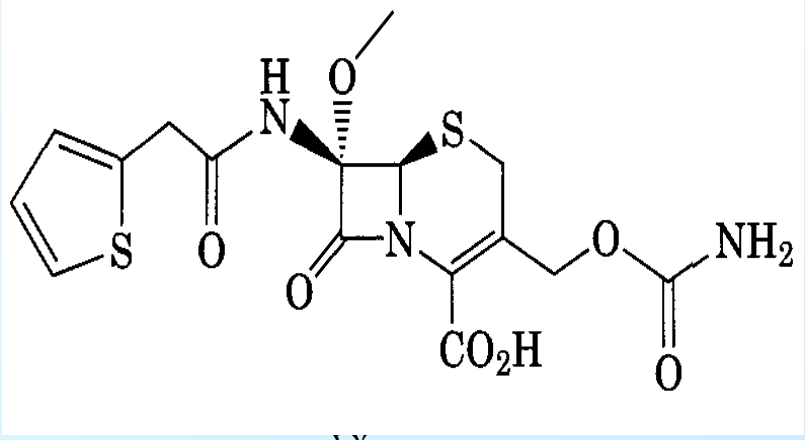
  Many drugs are for parenteral use.

- **A. Parenteral Agents**

i. Cefoxitin

7-[2-(2-Thienyl)acetamido]-7-α-methoxy-3-carbamoyloxymethyl-Δ3-cephem-4-carboxylic acid.

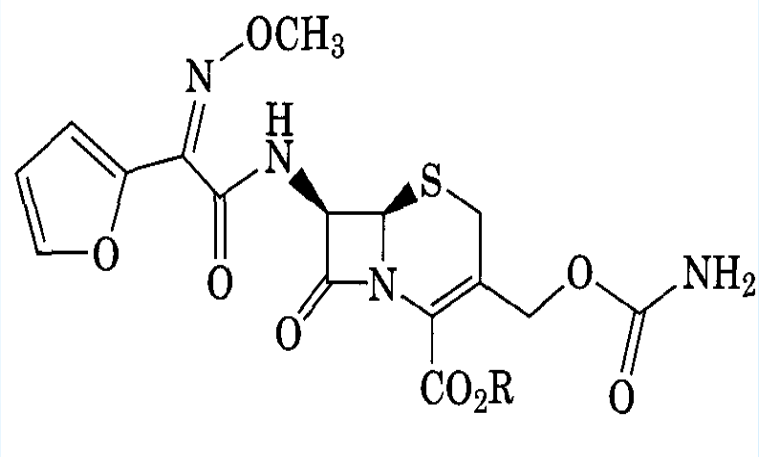
The α-Methoxy group at C-7 ⟶ steric hindrance ⟶ **high stability against β-lactamases.**



ii. Cefuroxime

Other parenteral drugs include Cefamandole and Cefonicid. Cefuroxime R = H

Cefuroxime axetil **R** = CH(CH3)0Ac

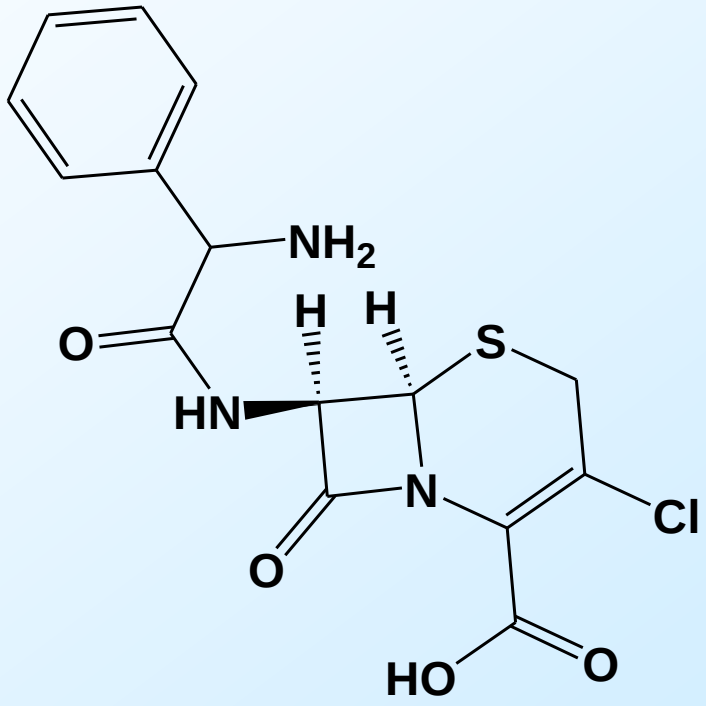


oxime group increases the stability against β-lactamases

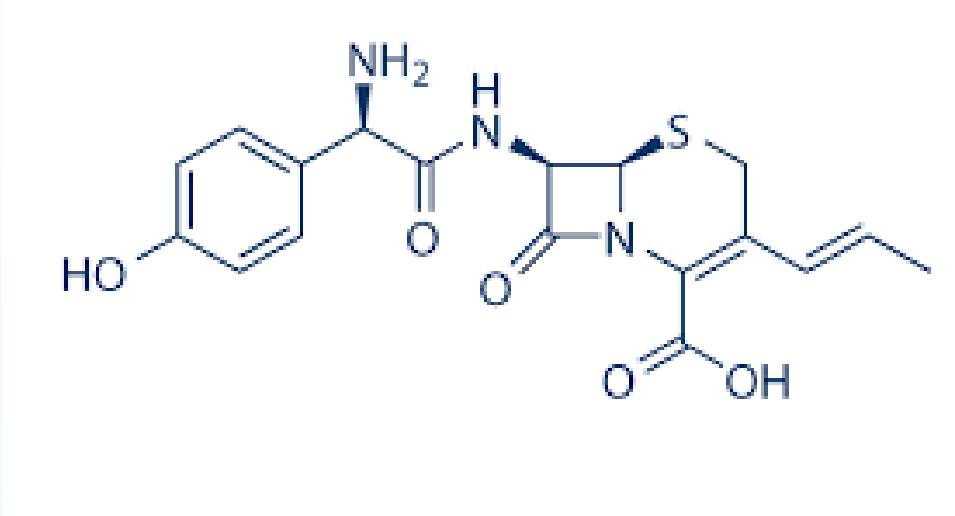
B. Oral Agents

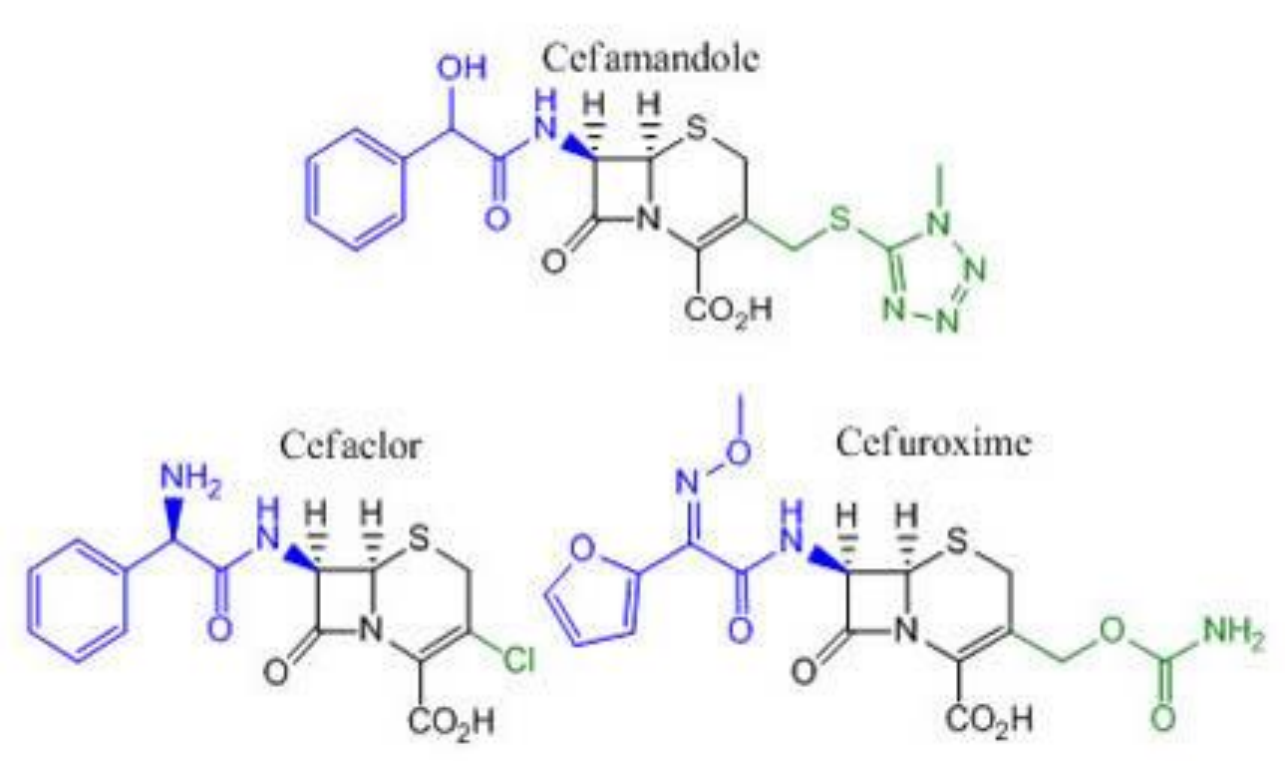
i. Cefaclor

7-[(D-α-amino-α-phenyl)acetamido]-3-chloro-Δ3-cephem-3-carboxylic acid.



Cefprozil





The presence of the iminomethoxy group appears to increase stability against certain β-lactamases

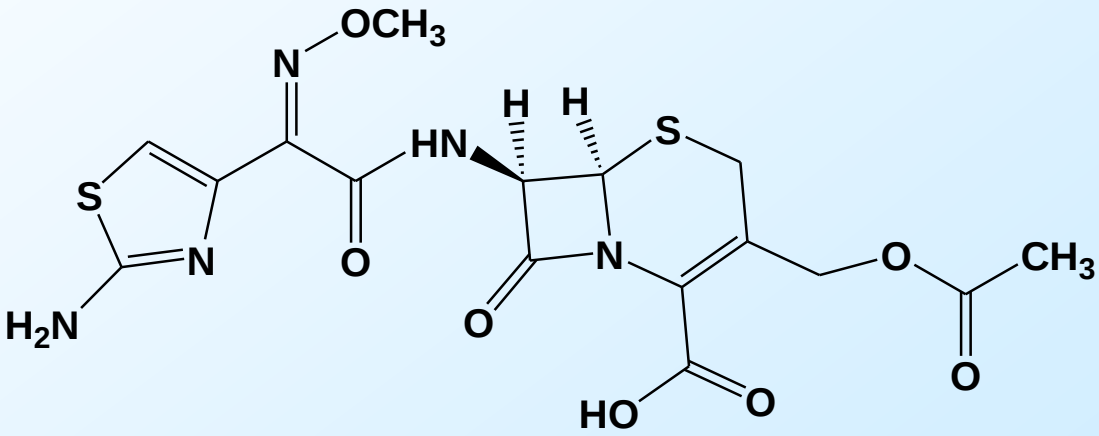
Third Generation Cephalosporins

- Produced after1980.
- **Broader spectrum** against Gram-negative organisms on the expense of their Gram-positive activity. They are effective in treating a large variety of infections resistant to many other drugs.
- Some drugs have **high activity** against Pseudomonas aeruginosa.
- Many drugs are for **parenteral use**.
- **More resistance** to β-lactamases.
- They are **very expensive**.

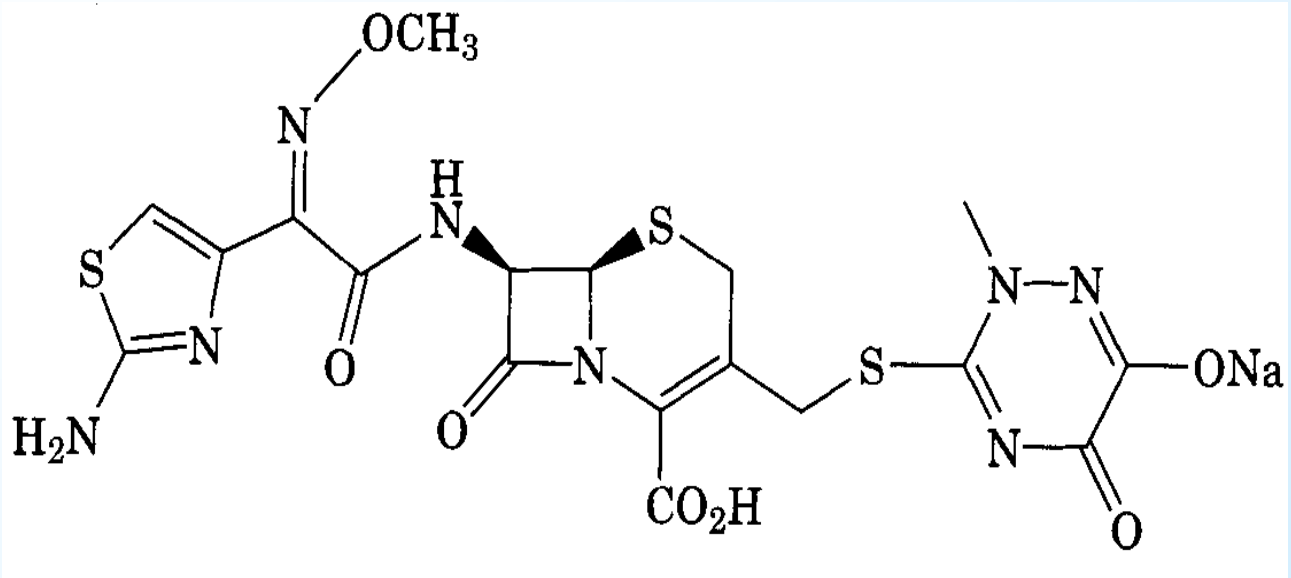
- **A. Parenteral Agents**
- **Cefotaxime**

7-[(2-Amino-4-thiazolyl)-2-methoxyimino)-acetamido]-3-acetylyloxy-methyl-Δ3-cephem-4-carboxylic acid.

It has an excellent broad spectrum activity against Gram -ve and Gram +ve aerobic and anaerobic bacteria.

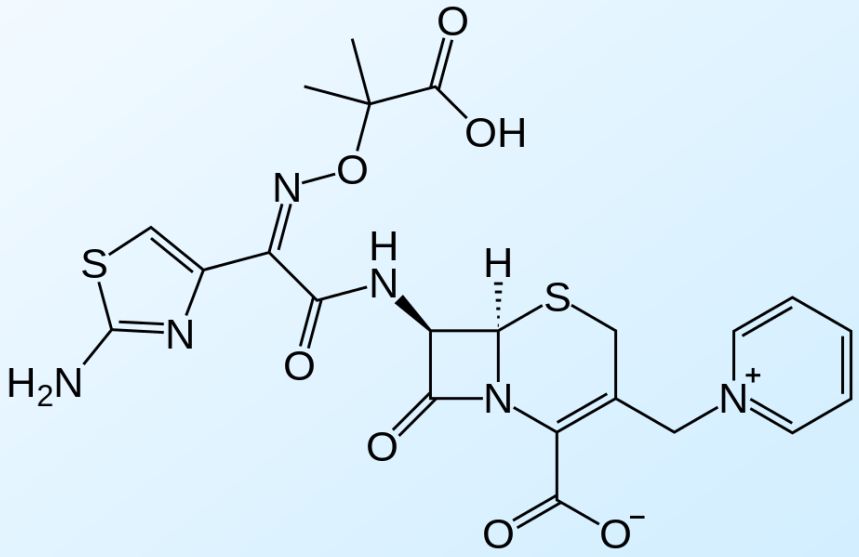


Ceftriaxone



Ceftazidime

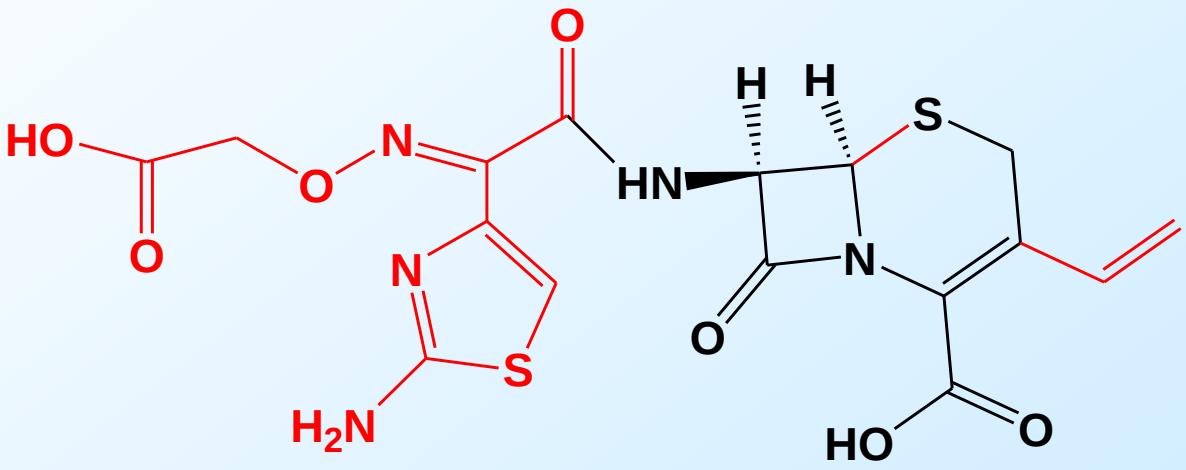
More pronounced β-lactamase stability, greater anti–pseudomonal activity, and increased activity against some Gram-positive organisms like *S. pneumonia* and *S. yogenes*.

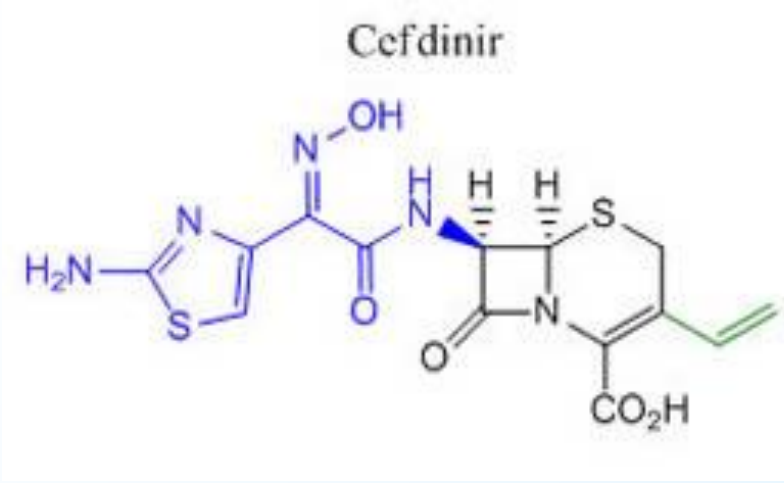


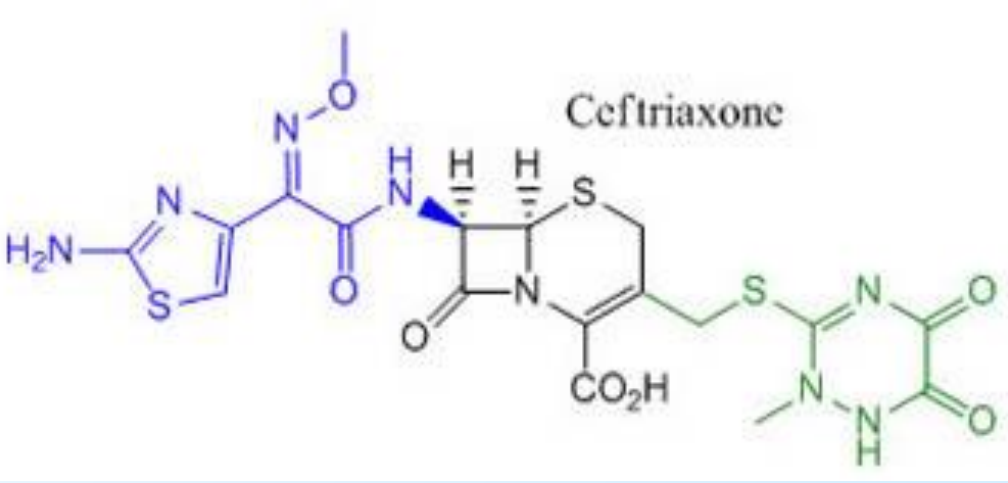
- **B. Oral Agents**

Cefixime

7-[(2-Amino-4-thiazolyl)-2-acetoxyimino)acetamido]-3-ethinyl-Δ3-cephem-4-carboxylic acid.







During 2008, cefdinir was one of the highest-selling cephalosporins. Ceftriaxone is marketed by Hoffmann-La Roche under the trade name Rocephin®.

- **Fourth Generation Cephalosporins**

They are recent drugs.

Broader spectrum against Gram -ve organisms and low activity against Gram +ve

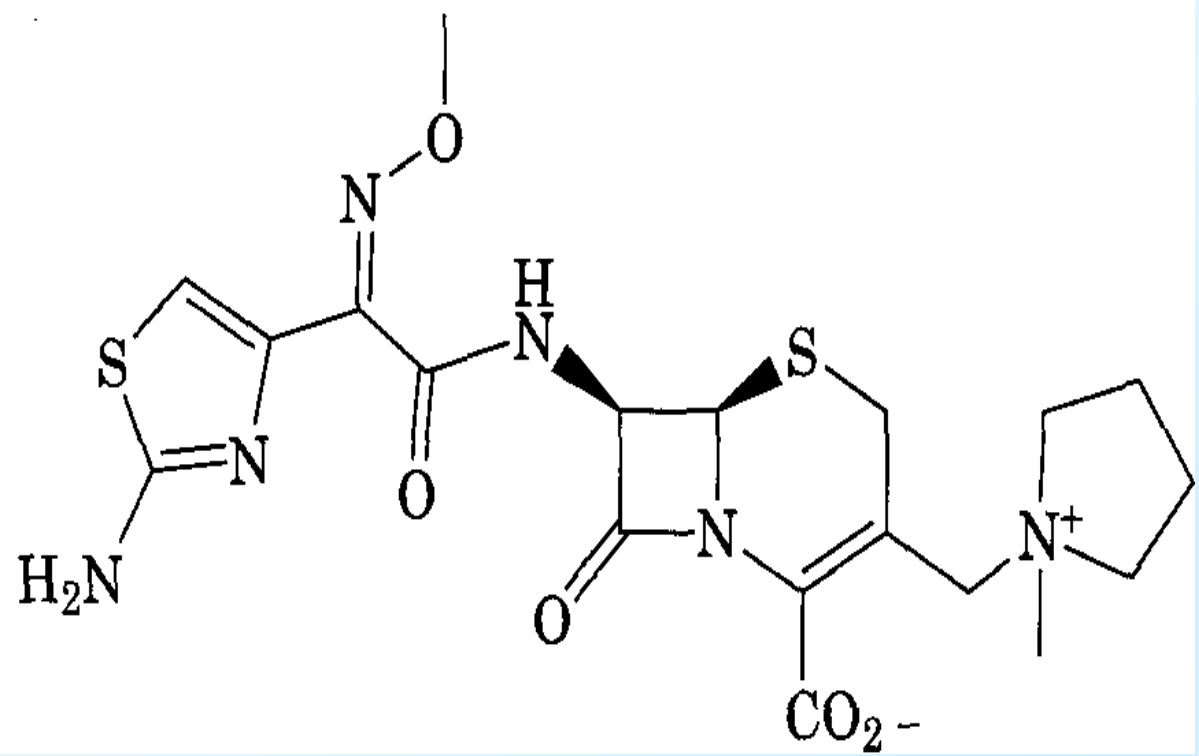
Some drugs have **high activity** against Haemophilus and Neiseria.

Mostly for **parenteral** use.

More resistance to β-lactamases.

High penetration into cerebrospinal fluid and very active against meningitis.

- **Cefepime**



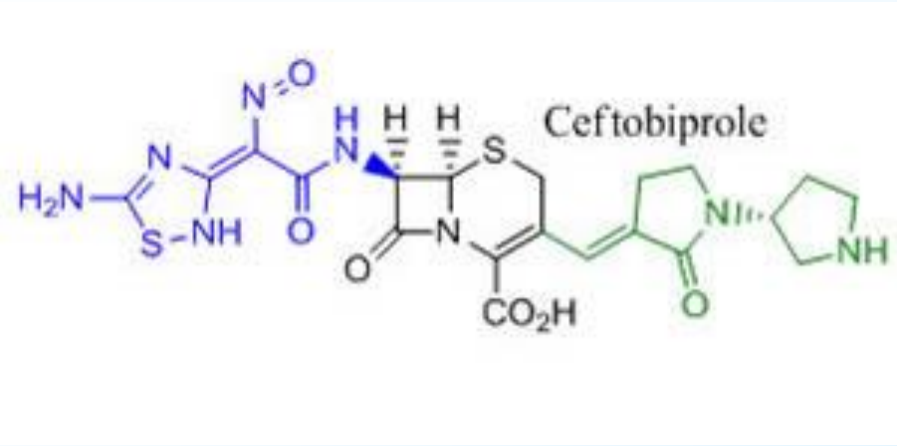
Fifth Generation Cephalosporins

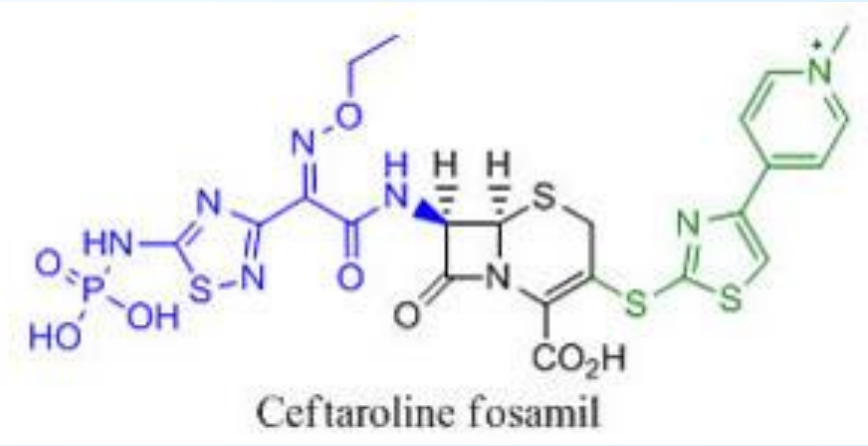
Currently, members of the scientific community have not reached agreement with regards to the use of the term 'fifth generation cephalosporins' Nevertheless, compounds that are regarded by some as fifth generation will be briefly mentioned.

Ceftobiprole has been described as a fifth-generation cephalosporin. this compound possesses good anti-*Pseudomonal* activity.

Ceftaroline fosamil is also another example of a cephalosporin that has been described as fifth-generation.

Fifth Generation Cephalosporins

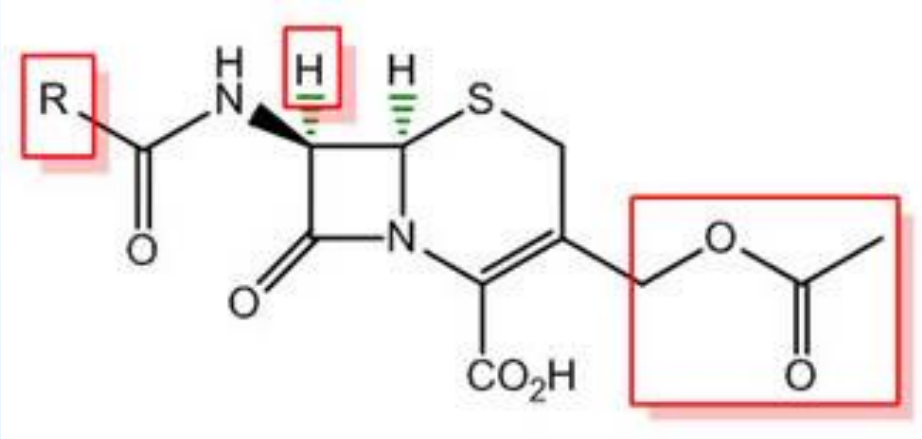




tructure-Activity Relationship of Cephalosporins

The β-lactam ring is crucial for activity Bicyclic ring system important in increasing ring strain The *cis*-stereochemistry at the positions highlighted in green is important

Site of modification



Site of modification

- 1. **Acylation of amino** group of 7-ACA ⟶ Different Cephalosporins.

  2. **Acetoxy group** at position 3 is easily leaving group in acid medium ⟶ **inactive lactone ring.**

  3. **Δ3-Cephem** ⟶ inactive.

  4. Removal of **-COOH at C4** ⟶ inactive.

  5. **Saturation of the double bond** of cephem ⟶ inactive.

  6. **A methoxy** group at **7 α-position** ⟶ increase in **resistance** against β-lactamases.

7. Replacement of S with O or CH2 of cephem at position 1⟶ No change in activity.

8. Substitution of acetoxy group at position 3

leads to:

a. Increase acid stability.

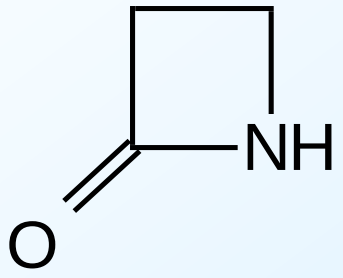
b. Broadening of the antibacterial activity.

c. Increase penetration ⟶ increase in activity against resistant bacteria.

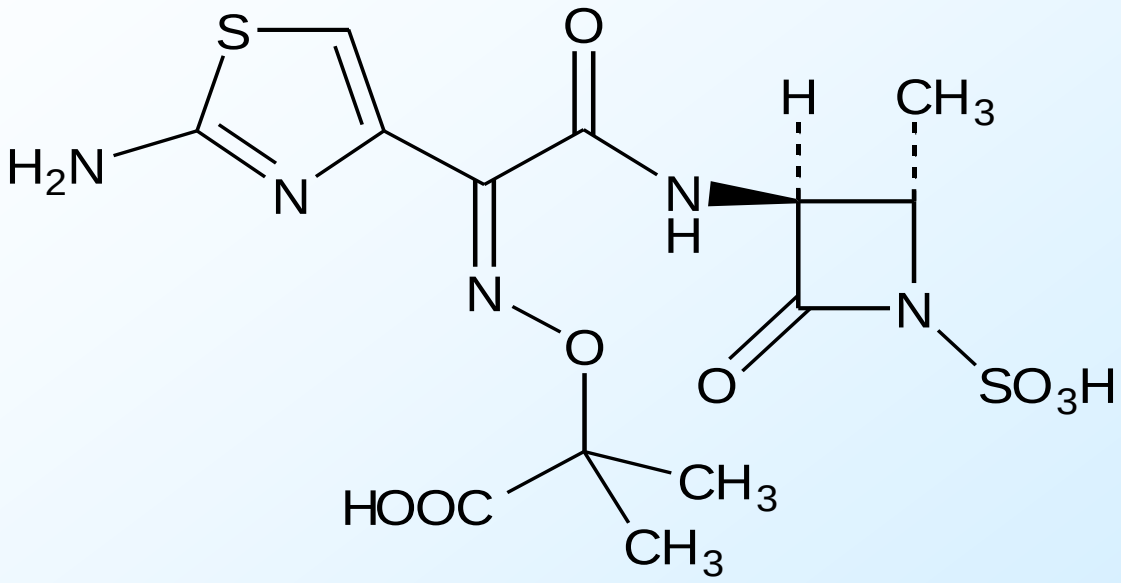
d. Decrease in allergenicity.

OTHER β-LACTAM ANTIBIOTICS

1. Monobactams



Aztreonam



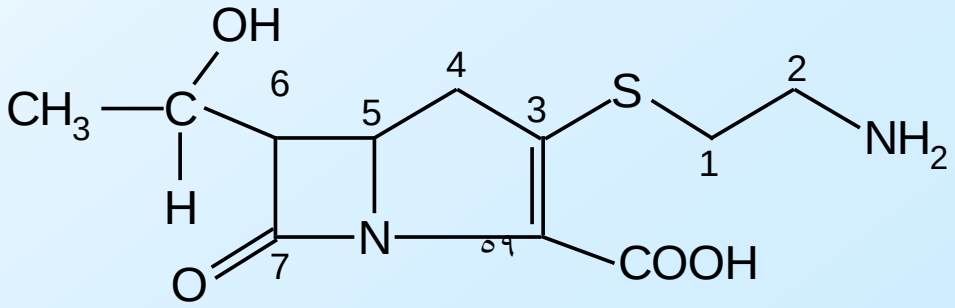
Aztreonam (Azactam) is a synthetic **monobactam** antibiotic, having a **monocyclic**, rather than a bicyclic nucleus.

- This agent inhibits synthesis of bacterial cell wall by high-affinity binding to penicillin-binding protein (PBP_3) which is found primarily in aerobic, Gram-negative microbes.
- **Aztreonam (Azactam)** is highly resistant to ß-lactamases.

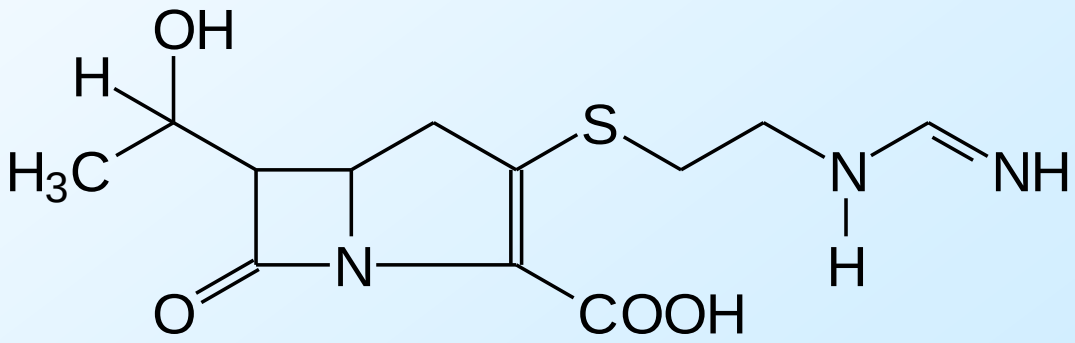
- Spectrum of activity includes aerobic, Gram-negative bacteria and is similar in activity to aminoglycosides **without causing ototoxicity or nephrotoxicity**
- **Aztreonam (Azactam)** is effective in treating Gram-negative urinary tract infections, lower respiratory tract, skin, intraabdominal, gynecologic infections and septicemia.

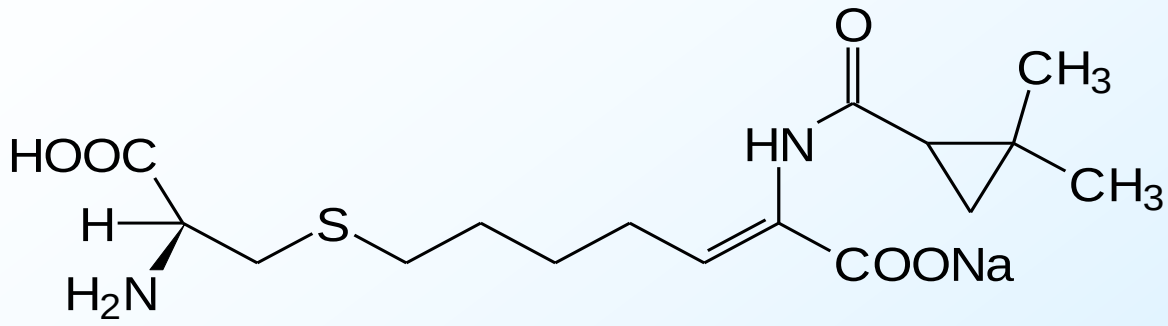
2. Carbapenem

- **i. Thienamycin**
- 3-β-[(2-Aminoethyl)thio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3,2.0]hept-2-ene-2-carboxylic acid
- The terminal NH2 in the side chain is a nucleophile which attacks β-lactam ring and decreases stability.
- The double bond at C2 increases the reactivity of β-lactam ring opening (More susceptible to hydrolysis in acid and alkaline solutions). **Thienamycin** is resistant to inactivation by most β-lactamases elaborated by Gram -ve and Gram +ve bacteria and therefore, is effective against many strains that are resistant to penicillins and cephalosporins.



- **Imipenem**
- It is N-Formimidoylthienamycin, the most successful of a series of chemically stable derivatives of **thienamycin** in which the primary amino group is converted to a non nucleophilic basic function. **Imipenem** is hydrolyzed by the renal enzyme **dehydropeptidase (DHP-1),** so it is protected by being coadministered with **Cilastatin which is an inhibitor for DHP-1.**





Cilastatin Na

■**Imipenem** inhibits bacterial cell wall mucopeptide synthesis and is bactericidal, very wide spectrum among the ß-lactams, providing good coverage of Gram-negative rods, Gram-positive bacteria, and anaerobes.

Meropenem

A semisynthetic carbapenem that has been formulated as the trihydrate for IM infusion. The β-methyl group at C4 confers increased stability to hydrolysis by dehydropeptidase 1 enzyme, thereby eliminating the need for a dehydropeptidase inhibitor in the dosing regimen.