Lecture 1

Pharmaceutical Chemistry

Antibacterial - Antibiotics

B-lactam Antibiotics

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Introduction

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

Later proposal shave sought both to expand and to 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 concentrations.

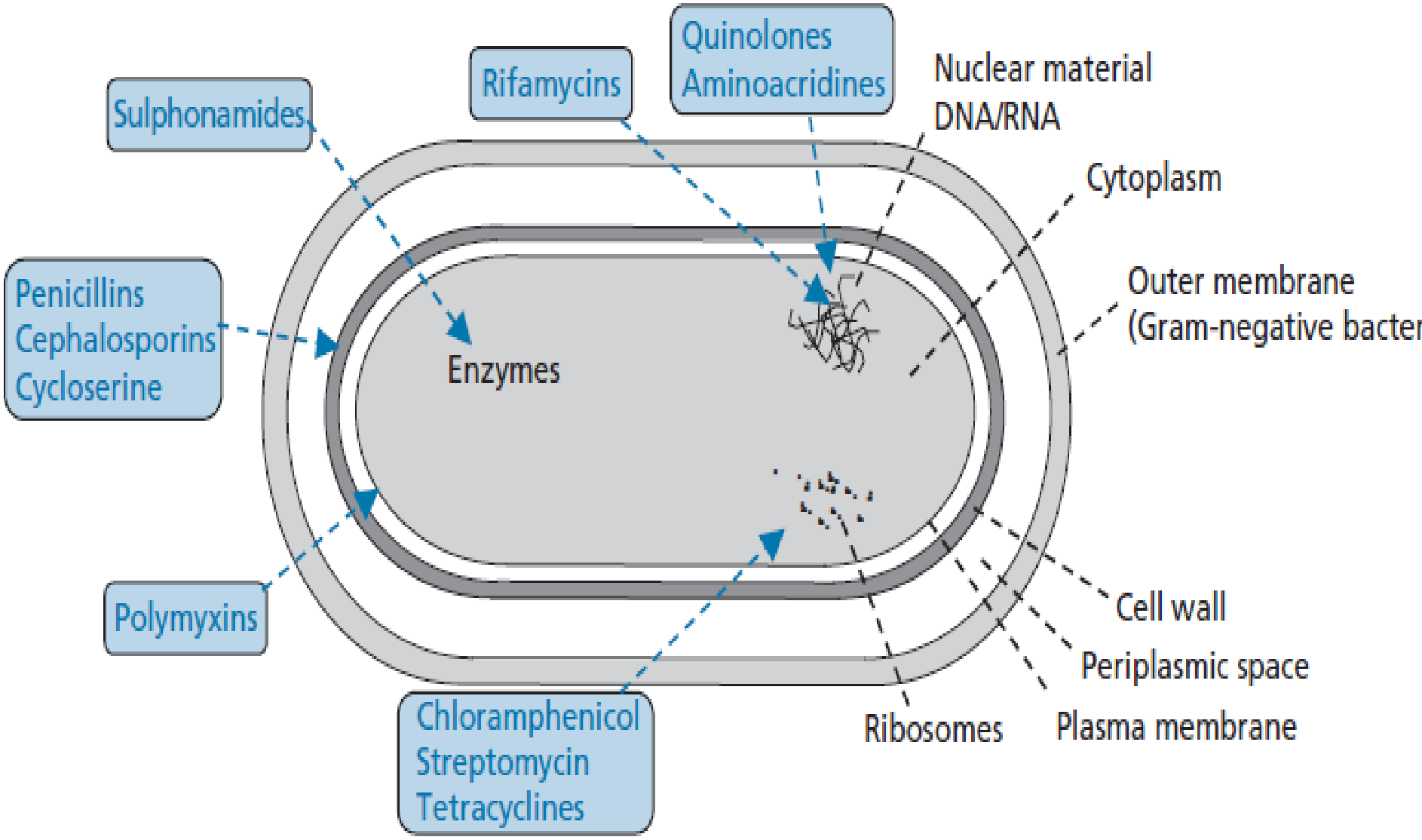
The advances made by medicinal chemists to modify naturally occurring antibiotics and to prepare synthetic analogs necessitated the inclusion of semisynthetic and synthetic derivatives in the definition. Therefore,

Antibiotic: Chemical produced by a microorganism that kills or inhibits the growth of another microorganism

Antimicrobial agent: Chemical that kills or inhibits the growth of microorganisms

A substance is classified as an antibiotic if the following conditions are met:

1. It is a product of metabolism (although it may be duplicated or even have been anticipated by chemical synthesis).
2. It is a synthetic product produced as a structural analog of a naturally occurring antibiotic.
3. It antagonizes the growth or survival of one or more species of microorganisms.
4. It is effective in low concentrations.



The bacterial cell and drug targets.

Antibiotic Classes

Medication Names

1. Aminoglycosides - Mycin
2. Cephalosporins - Cef/Ceph
3. Tetracyclines - Cycline
4. Penicillins - Cillin
5. Sulfonamides - Sulfa
6. Fluoroquinolones - Floxacin
7. Macrolides - Thromycin
8. Carbapenems - Penem
9. Lincosamides - Mycin
10. Glycopeptides - In (Mycin)

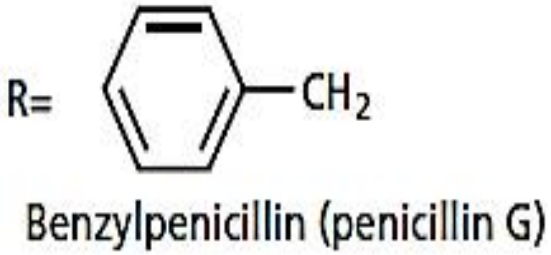
Antibacterial agents which inhibit cell wall synthesis.
(Penicillins) B-lactam antibiotics

Antibiotics that possess the β-lactam (a four-membered cyclic amide) ring structure are the dominant class of agents currently used for the chemotherapy of bacterial infections.

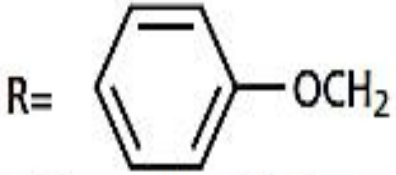
The first antibiotic to be used in therapy, penicillin (**penicillin G** or benzyl penicillin), and a close biosynthetic relative, phenoxy methyl penicillin (**penicillin V**), remain the agents of choice for the treatment of infections caused by most species of Gram-positive bacteria.

The key structural feature of the penicillins is the four-membered β-lactam ring; this structural moiety is essential for penicillin's antibacterial activity.

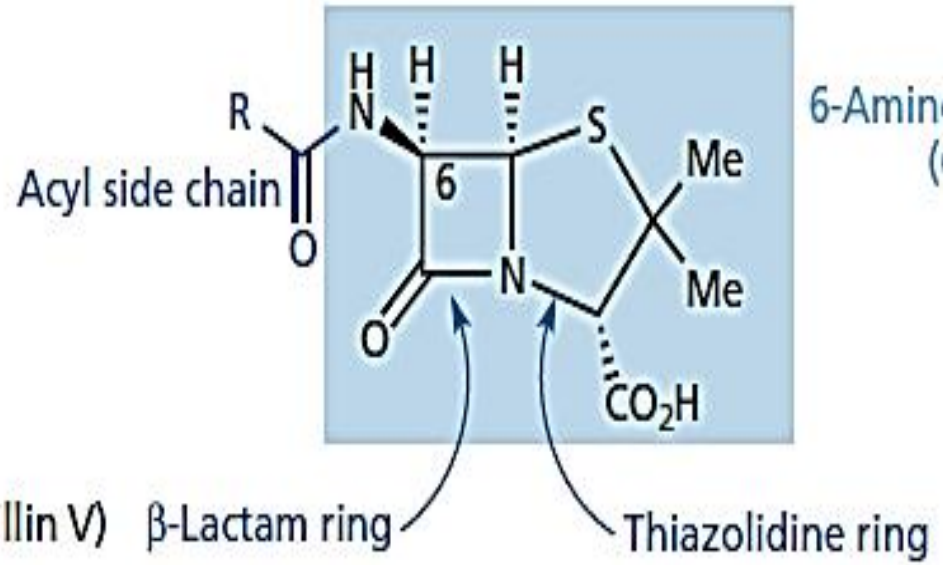
The β-lactam ring is itself fused to a five-membered **thiazolidine ring**. The fusion of these two rings causes **the β-lactam ring** to be more reactive than monocyclic β-lactams because the two fused rings distort the β-lactam amide bond and therefore remove the resonance stabilization normally found in these chemical bonds.



Benzylpenicillin (penicillin G)



Phenoxymethylpenicillin (penicillin V)



6-Aminopenicillanic acid (6-APA)

The structure of penicillin.

Mechanism of β-Lactam Drugs

The amide of the β-lactam ring is unusually reactive due to ring strain and a conformational arrangement which does not allow the lone pair of the nitrogen to interact with the double bond of the carbonyl.

Because of this fused four five ring system this carbonyl carbone more partially positive , more ectrophilic and more reactive. So that why β-lactam ring easily hydrolyzed.

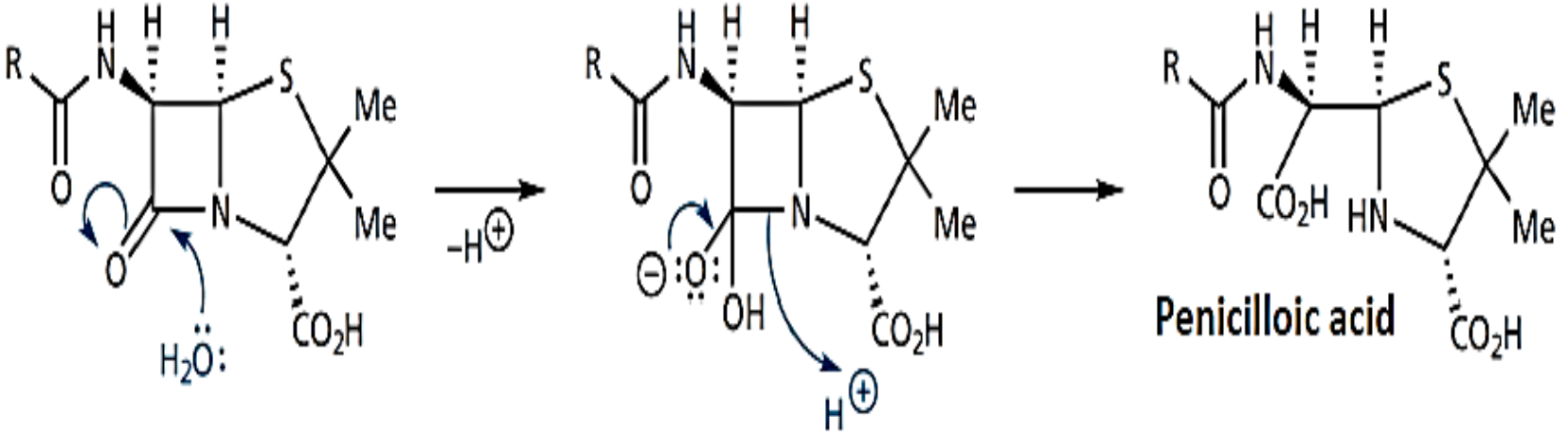
Two factors make β-lactam reactive

1. There is not as much resonance stabilization
2. Ring strain

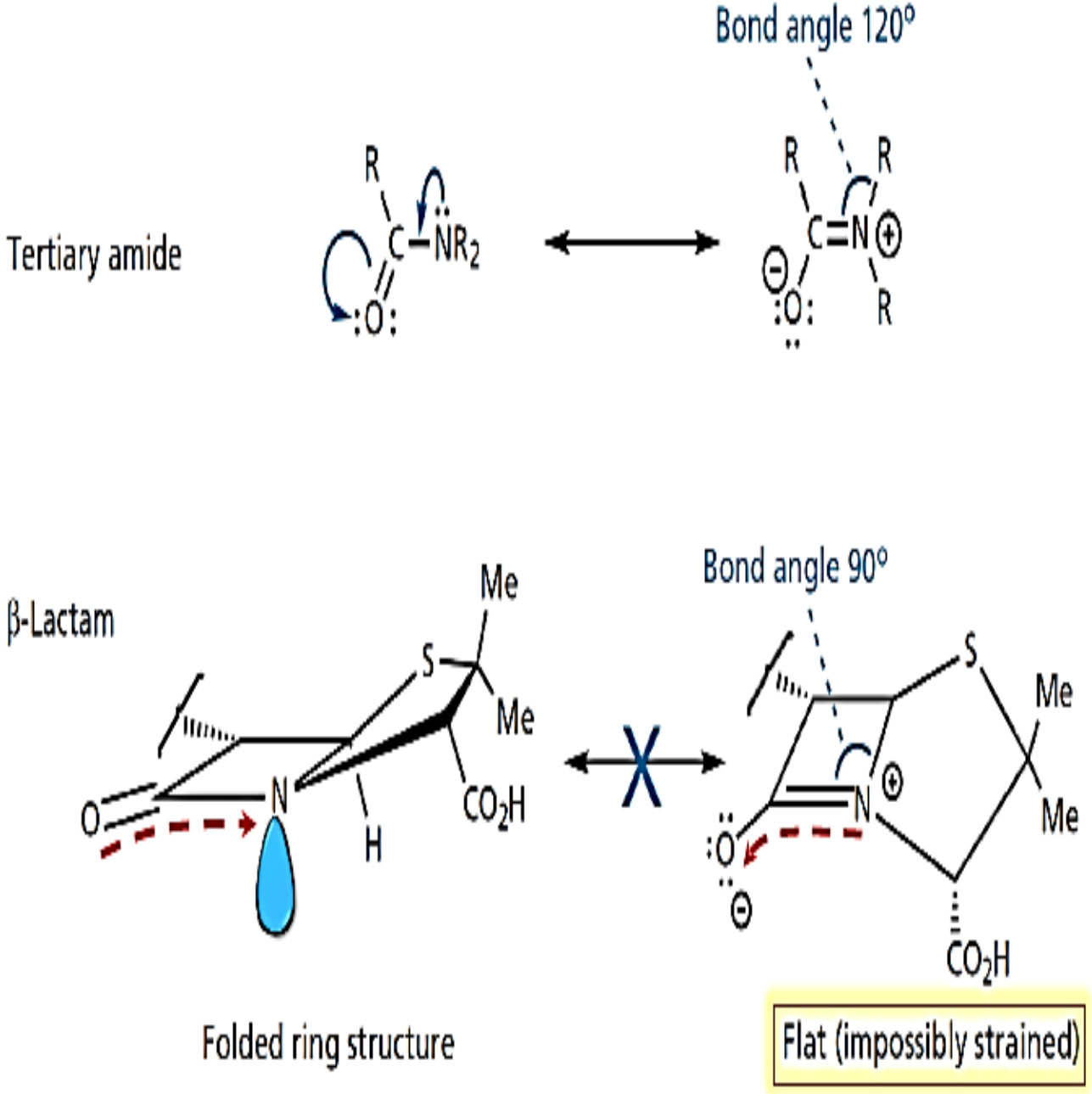
Problem of acid-sensitivity for penicillin

The main deterioration of penicillin is the reactivity of the strained β-lactam ring to hydrolysis. The hydrolysis is effected by pH. There are three main reasons for acid sensitivity of penicillin G:

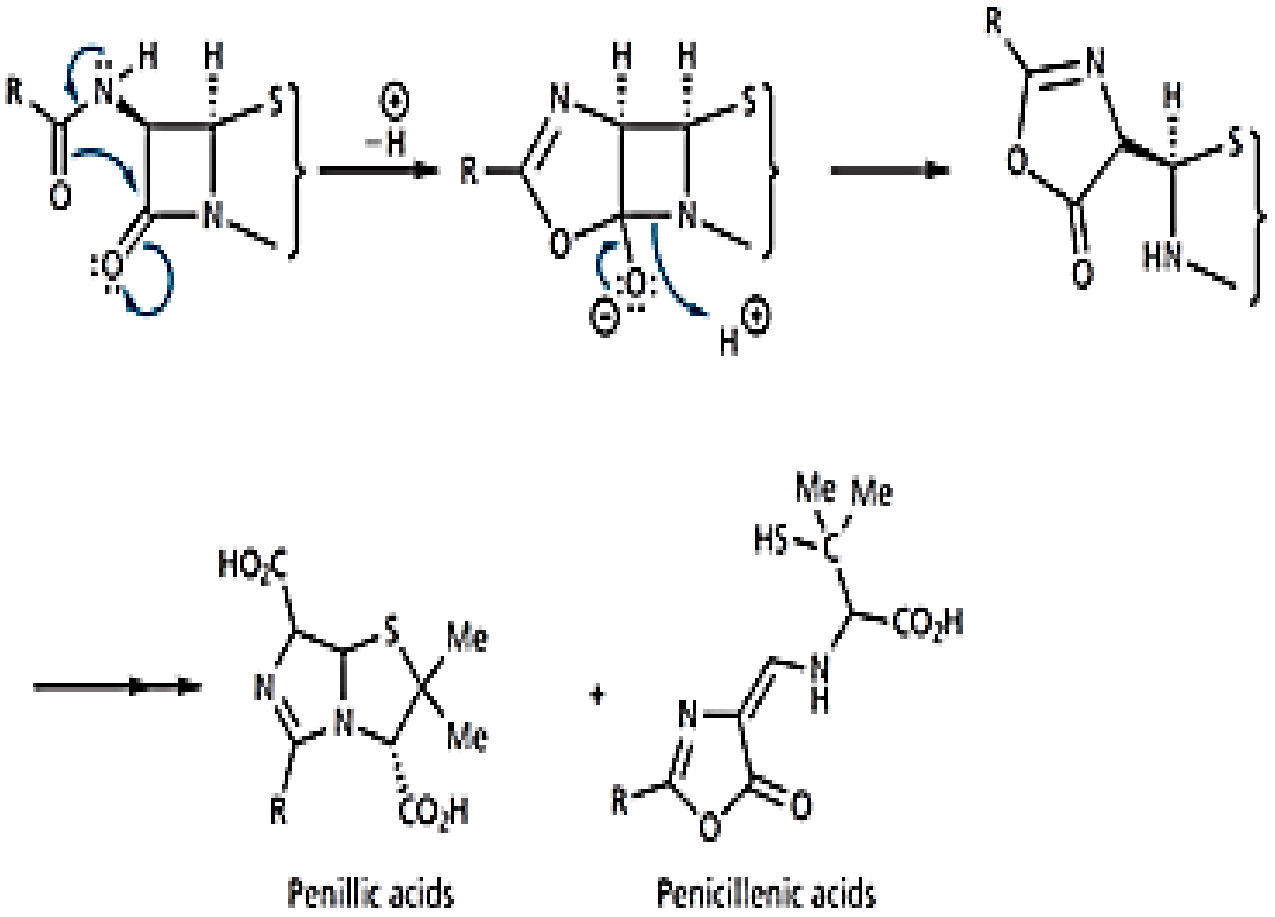
1) **Ring strain** : due to the fusion of β-lactam ring to thiazolidine ring. The strain is relieved by breaking the β-lactam ring which either started by nucleophilic attack at carbonyl using water (or OH- ions) or started with protonation of N which eventually lead to formation of penicilloic acid



2) **Highly reactive β-lactam carbonyl group:** the group (=O) is deprived from electrons (electrophile) due to inability to form resonance with neighboring N because of unusual geometry (90° instead of 120°)



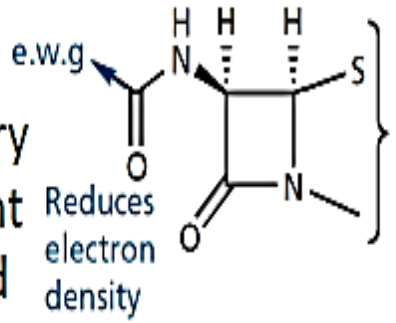
3) **Effect of R group at acylamido side chain:** the acyl group carbonyl (=O) is rich in electron (nucleophilic O) and able to attack the neighboring carbon of β-lactam (electrophilic C). Therefore, penicillin has self-destruction property which can be reduced by using electron withdrawing R group.

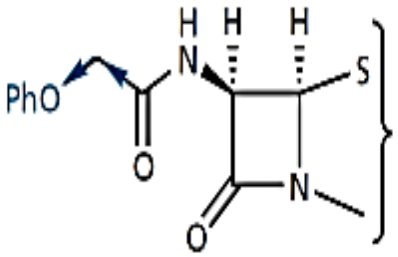


Solving problem of acid-sensitivity for penicillins

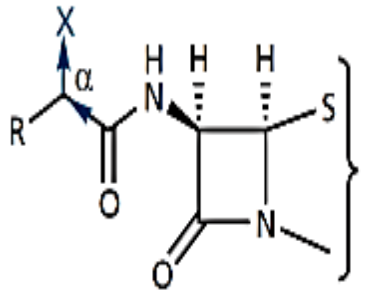
Treatment of acid sensitivity of penicillin G:

1) No change to β-lactam is allowed
2) No change to geometry of N at the fusion point between β-lactam and thiazolidine rings is allowed





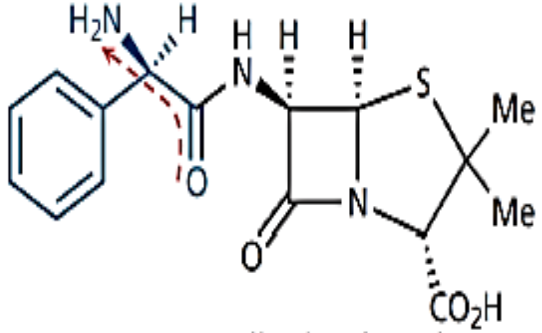
Penicillin V



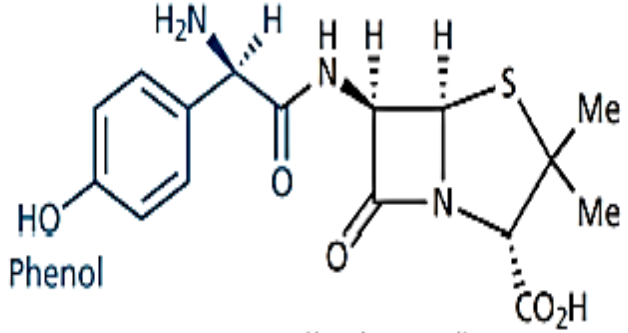
X = NH_2, Cl, PhOCONH, Heterocycles

FIGURE 19.26 Reduction of neighbouring group participation with an electron-withdrawing group (e.w.g

3) Can use electron withdrawing R group at acylamido side chain to reduce nucleophilicity of (=O). Examples of acid-stable penicillins are ampicillin and amoxicillin



Ampicillin (Penbritin)



Amoxicillin (Amoxil)

NH2 is ionized in acidic medium to $NH3^+$ which is a strong electron withdrawing group

Mechanism of action

- Penicillins inhibit a bacterial enzyme called the transpeptidase enzyme which is involved in the synthesis of the bacterial cell wall
- The β-lactam ring is involved in the mechanism of inhibition
- Penicillin becomes covalently linked to the enzyme's active site leading to irreversible inhibition

- Covalent bond formed to transpeptidase enzyme
- Irreversible inhibition

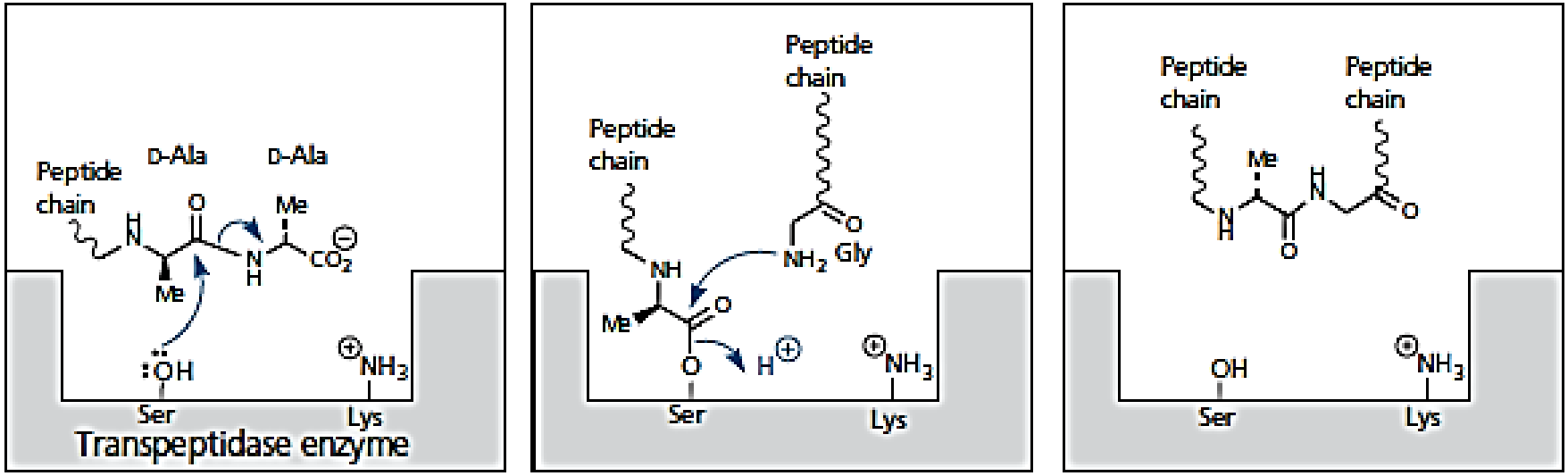
Mechanism of Action

The basic mechanism involved is inhibition of the biosynthesis of the dipeptidoglycan that provides strength and rigidity to the cell wall.

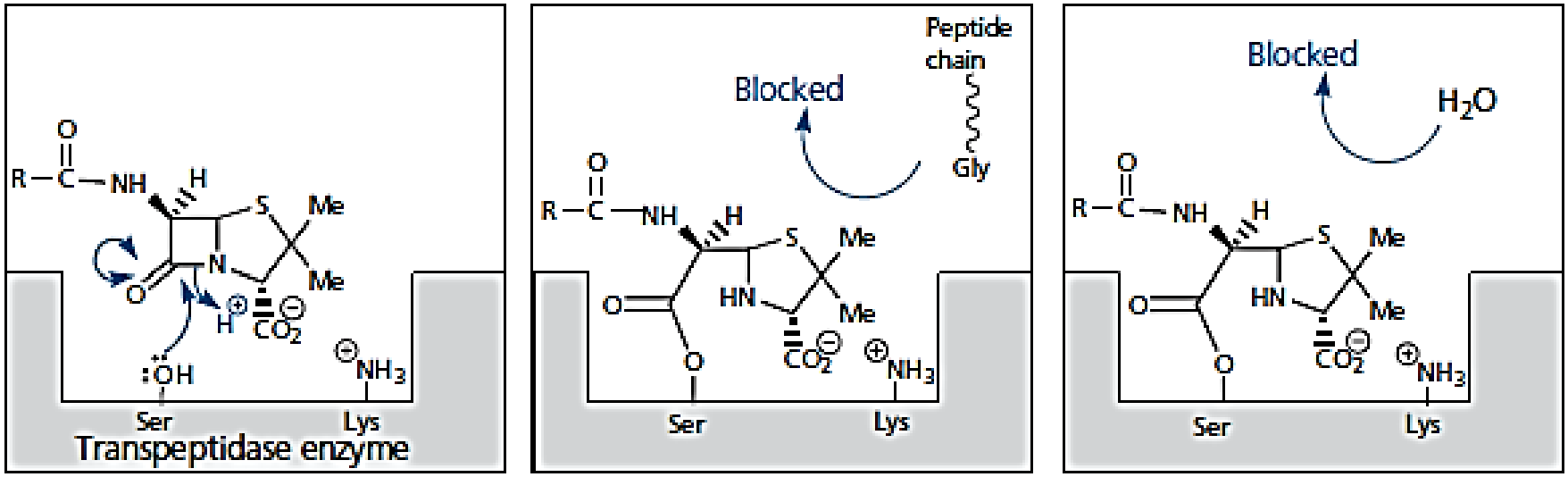
Penicillins and cephalosporins acylate a specific bacterial D-trans peptidase, β-Lactams acylate the hydroxyl group on the serine residue of PBP active site in an irreversible manner.

-OH act as nucleophile and going to attack carbonyl Carbone which is more electrophilic than the most amide.

(a) Transpeptidase cross-linking



(b) Penicillin inhibition



Mechanisms of transpeptidase cross-linking and penicillin inhibition.

Structure-activity relationship (SAR)

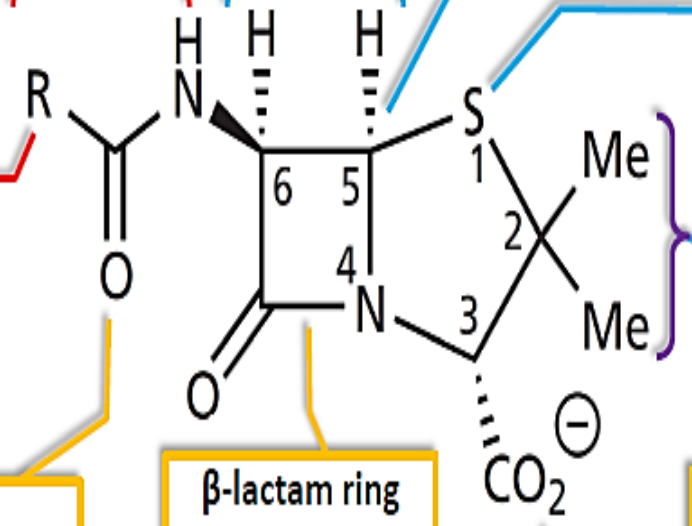
Acylamido side chain is essential

Cis-stereochemistry is essential

No substitution allowed

R group:

1. Electron withdrawing groups →↓nucleophilicity of carbonyl oxygen → ↑stability
2. Bulky groups provides resistance to β-lactamase
3. Polar groups make structure more hydrophilic



Sulfur is usual but not essential.

Thiazolidine

5-membered saturated ring contains nitrogen. The geminal dimethyl group at C-2 position is a characteristic of the penicillin

Carbonyl oxygen:
Is electrophilic because the lone pair electrons on N is not provided for resonance.
Thus =O is ready for nucleophilic attack

β-lactam ring strain is essential

Carboxylic group

1. Is usually ionized to form sodium of potassium salts.
2. Bind amino group of Lys at binding site
3. Is important for activity which is reduced if modified to alcohol or ester

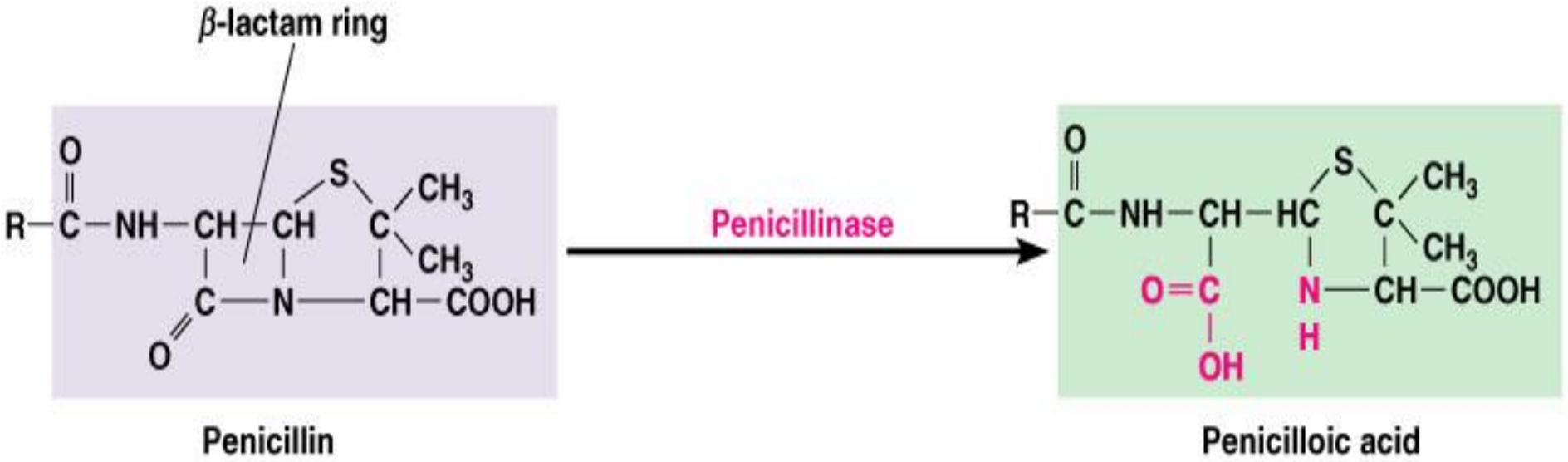
Bicyclic system confers further strain to β-lactam ring
↑strain →↑activity→↑instability

Bacterial Resistance

Most species of Gram-negative bacilli, are naturally resistant to the action of penicillins. Other normally sensitive species can develop penicillin resistance (either through natural selection of resistant individuals or through mutation).

The most important biochemical mechanism of penicillin resistance is the bacterial elaboration of enzymes that inactivate penicillins. Such enzymes, which have been given the nonspecific name **penicillinases**, are of two general types:

β- lactamases and acylases. By far, the more important of these are the β-lactamases, enzymes that catalyze the hydrolytic opening of the β-lactam ring of penicillins to produce inactive penicilloic acids.



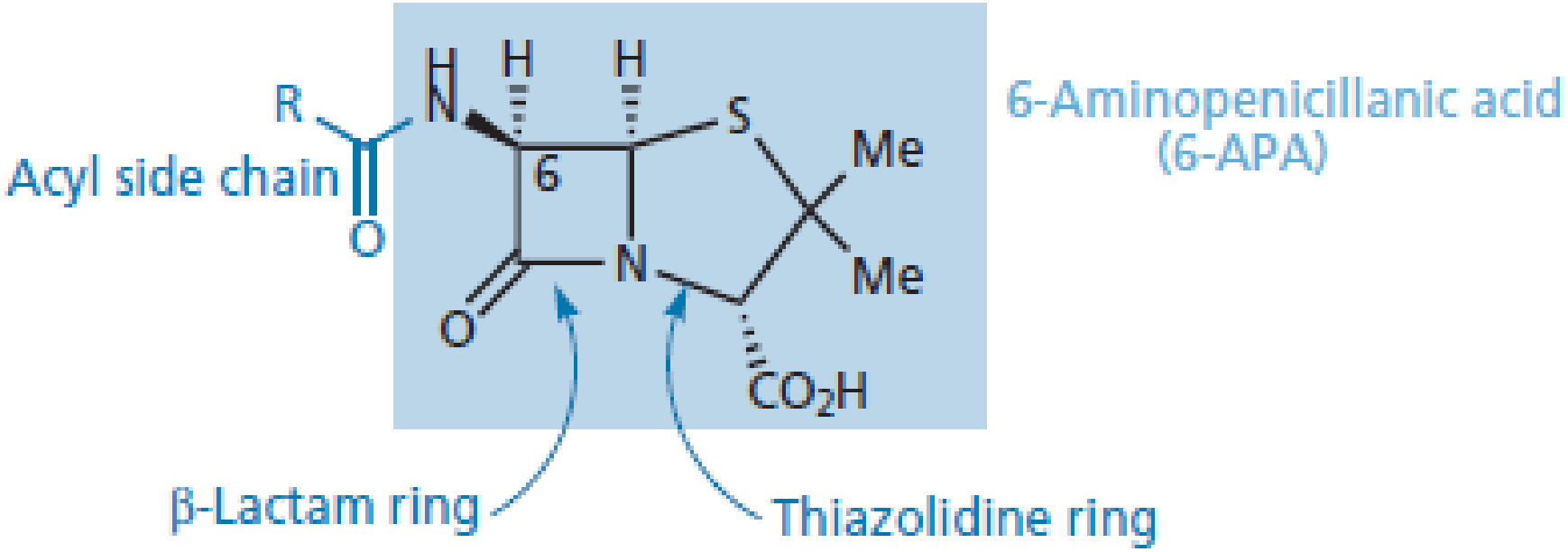
Specific acylases (enzymes that can hydrolyze the acylamino side chain of penicillins) have been obtained from several species of Gram-negative bacteria

Another important resistance mechanism, especially in Gram-negative bacteria, is decreased permeability to penicillins. Alteration of the number or nature of porins in the cell envelope also could be an important mechanism of antibiotic resistance

The penicillins

Several closely related compounds produced. These compounds differ chemically in the acid moiety of the amide side chain.

Variations in this moiety produce differences in antibiotic effect and in physicochemical properties, including stability.



Modification of β-Lactams

β-Lactam type antibiotics can be modified at various positions **to improve their ability to**:

-Be administered orally (survive acidic conditions)

-Be tolerated by the patient (allergies)

-Penetrate the outer membrane of Gram (-) bacteria

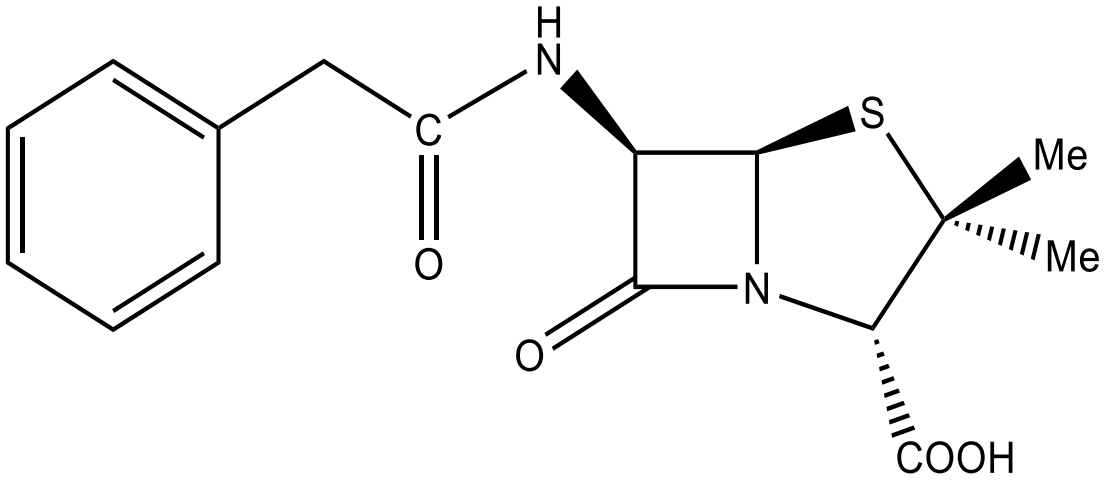
-Prevent hydrolysis by β-lactamases

-Acylate the PBPs of resistant species (there are many different PBPs) (penicillin-binding proteins)

penicillins- natural

Natural penicillins are those which can be obtained directly from the penicillium mold and do not require further modification. Many species of bacteria are now resistant to these penicillins.

Penicillin G

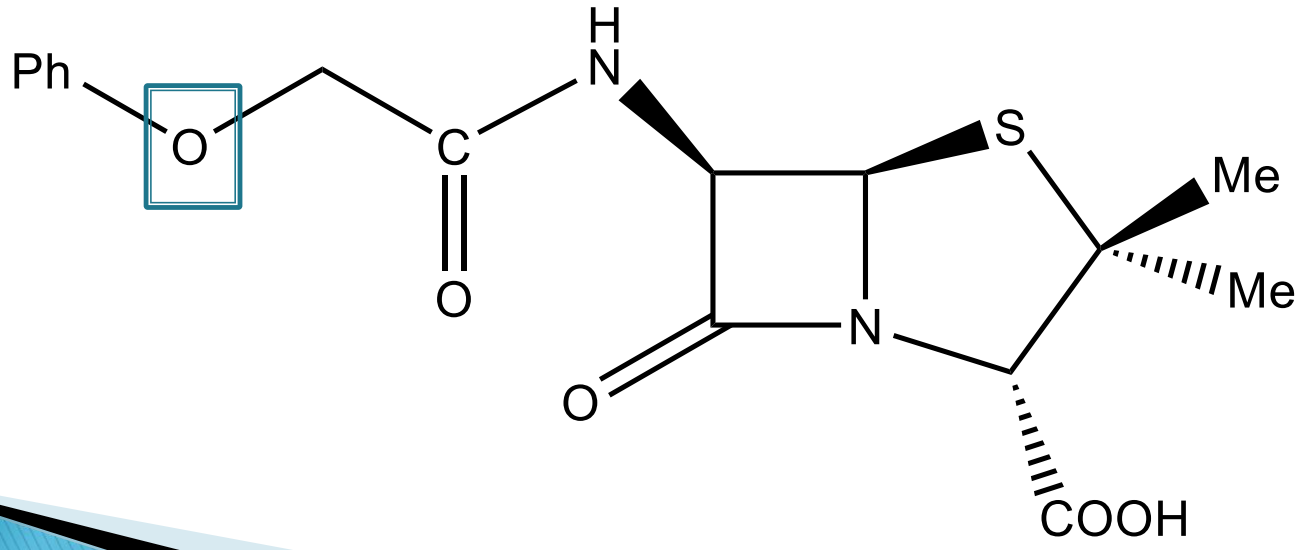


not orally active

Penicillin V

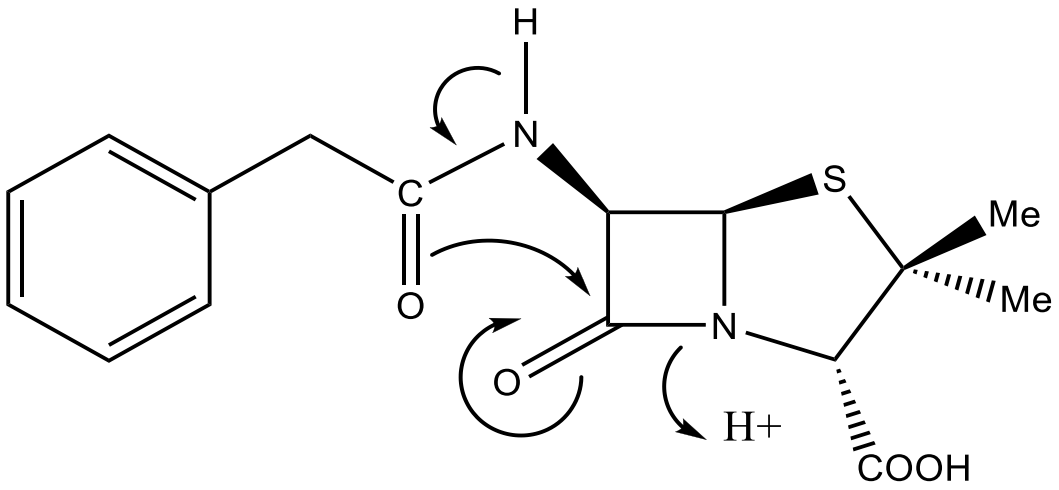
Penicillin V is produced when phenoxyacetic acid rather than phenylacetic acid is introduced to the penicillium culture.

Adding the oxygen decreases the nucleophilicity of the carbonyl group, making penicillin V acid stable and orally viable.

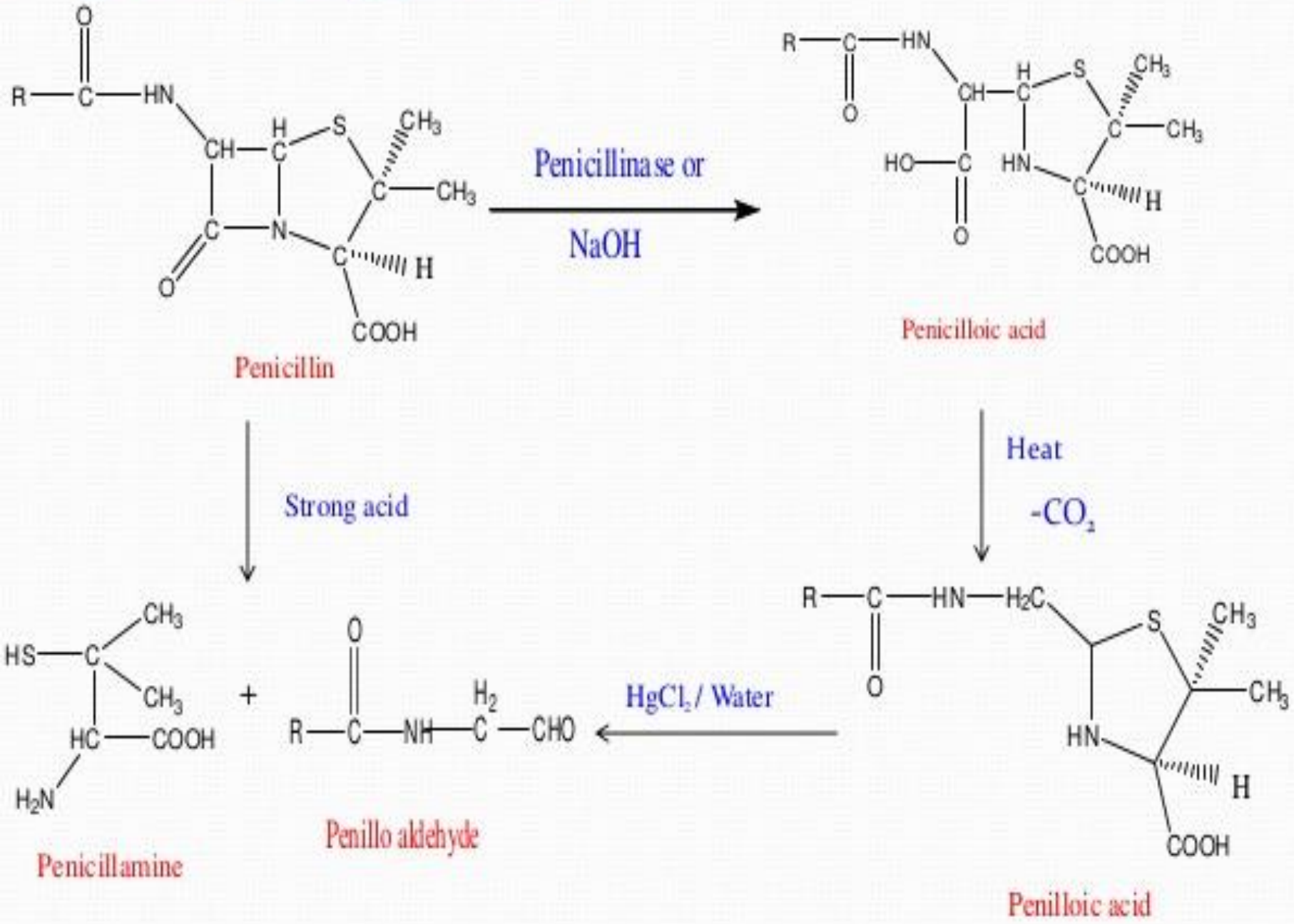


Penicillin G in acidic conditions

Penicillin G could not be administered orally due to the acidic conditions of the stomach.

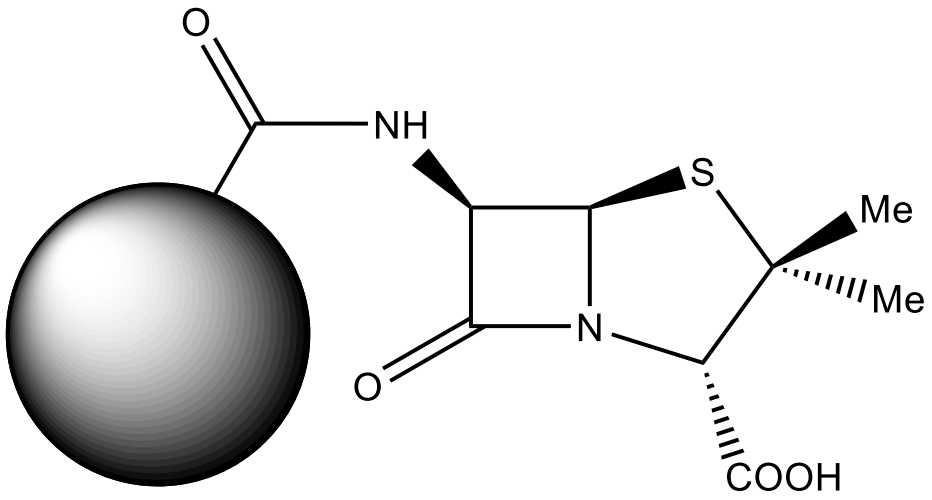


Chemical degradation:



Penicillins- Anti staphylococcal

Penicillins which have bulky side groups can block the β-Lactamases which hydrolyze the lactam ring.



Methicillin

Methicillin was the first penicillin developed with this type of modification, Methicillin sodium is particularly resistant to inactivation by the penicillinase found in staphylococci and somewhat more resistant than penicillin G to penicillinase from Bacillus cereus. The absence of the benzyl methylene group of penicillin G and the steric protection afforded by the 2- and 6-methoxy groups make this compound particularly resistant to enzymatic hydrolysis.

Methicillin is acid sensitive and has been **improved upon by** adding electron withdrawing groups, as was done in penicillin V, resulting in drugs such as **oxacillin** and **nafcillin.**

In **Oxacillin** the steric effects of the 3-phenyl and 5-methyl groups of the isoxazolyl ring prevent the binding of this penicillin to the β-lactamase active site and, thereby, protect the lactam ring from degradation in much the same way as has been suggested for methicillin.

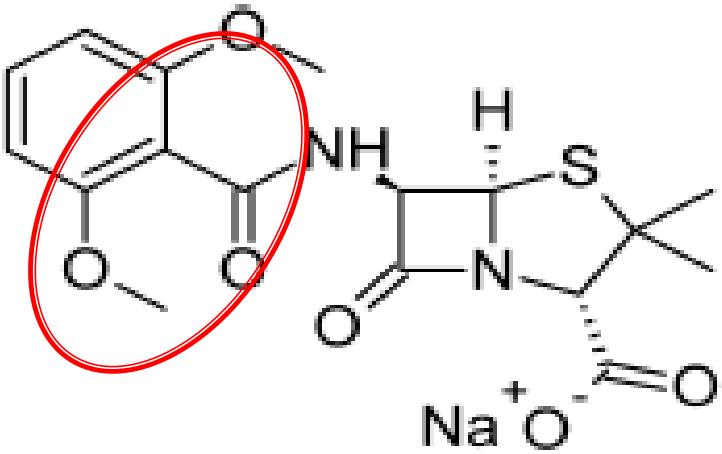
It is also relatively resistant to acid hydrolysis and, therefore, **may be administered orally** with good effect.

The substitution of chlorine atoms on ortho or on both carbons ortho to the position of attachment of the phenyl ring to the isoxazole ring enhances the activity and the stability of **Cloxacillin** , **Dicloxacillin** sodium, by enhancing its oral absorption, leading to higher plasma levels.

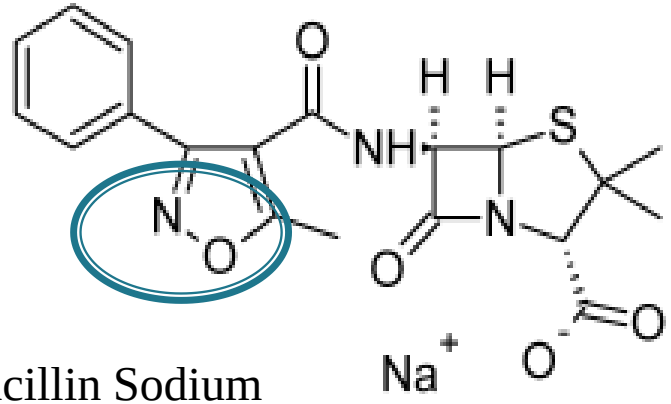
The incorporation of an isoxazolyl ring into the penicillin side chain led to orally active compounds which were stable to the β-lactamase enzyme of S. aureus . The isoxazolyl ring acts as the steric shield but it is also electron withdrawing, giving the structure acid stability.

Nafcillin sodium, 6-(2-ethoxy-1-naphthyl)penicillin sodium (Unipen), is another **semisynthetic penicillin** that resulted from the search for penicillinase-resistant compounds.

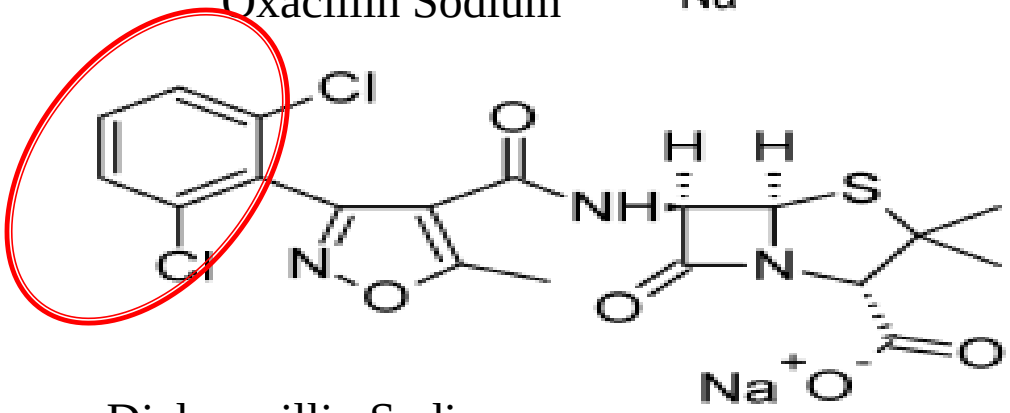
Like methicillin, nafcillin has substituents in positions ortho to the point of attachment of the aromatic ring to the carboxamide group of penicillin. No doubt, the ethoxy group and the second ring of the naphthalene group play steric roles in stabilizing nafcillin against penicillinase



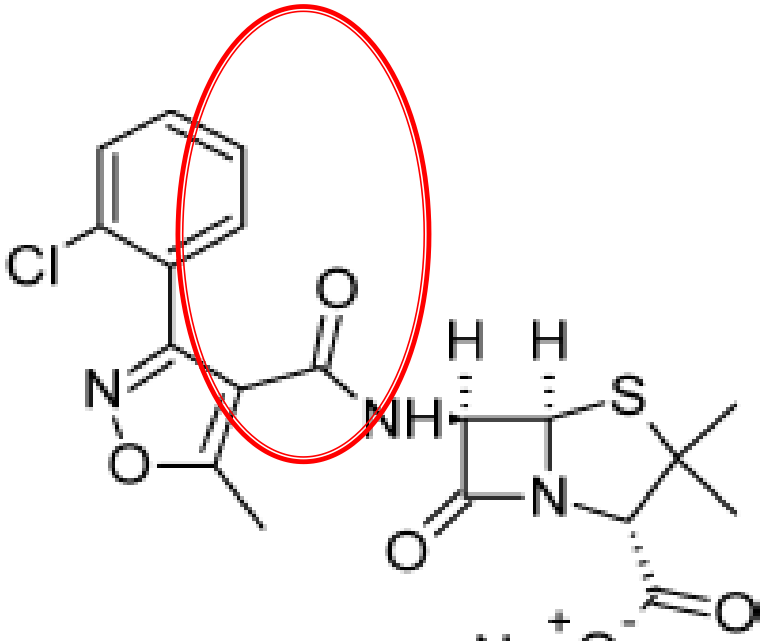
Methicillin Sodium



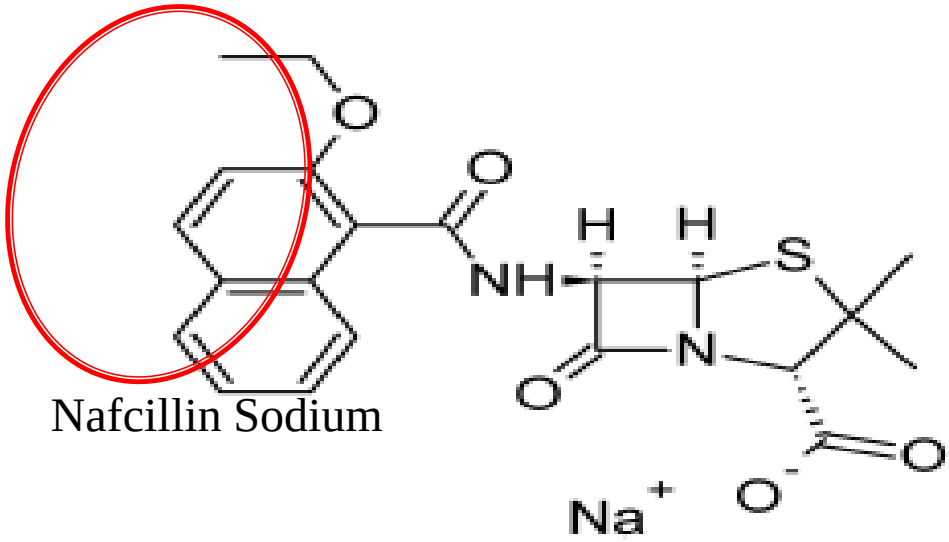
Oxacillin Sodium



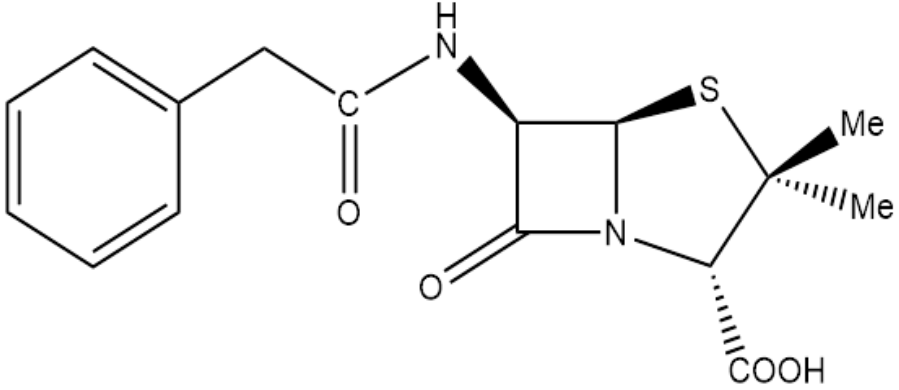
Dicloxacillin Sodium



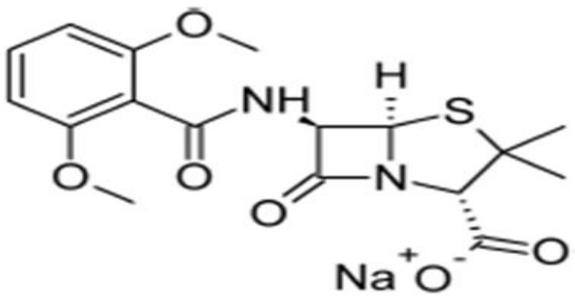
Cloxacillin Sodium



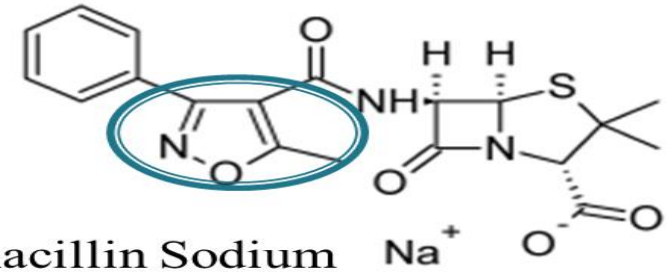
Nafcillin Sodium



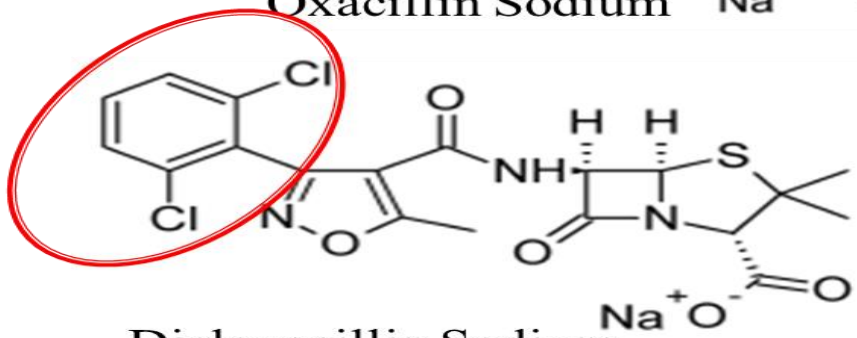
Penicillin G



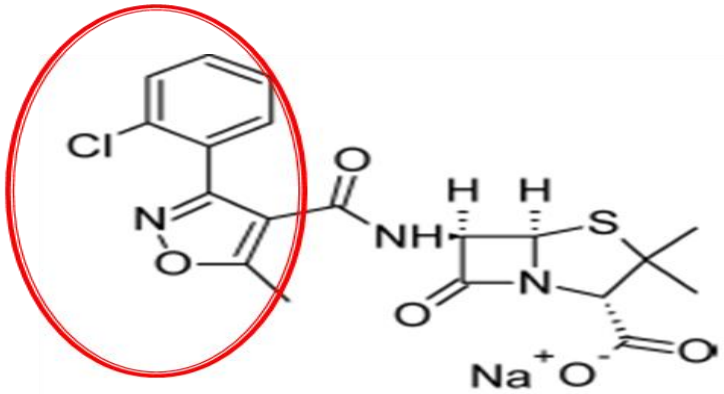
Methicillin Sodium



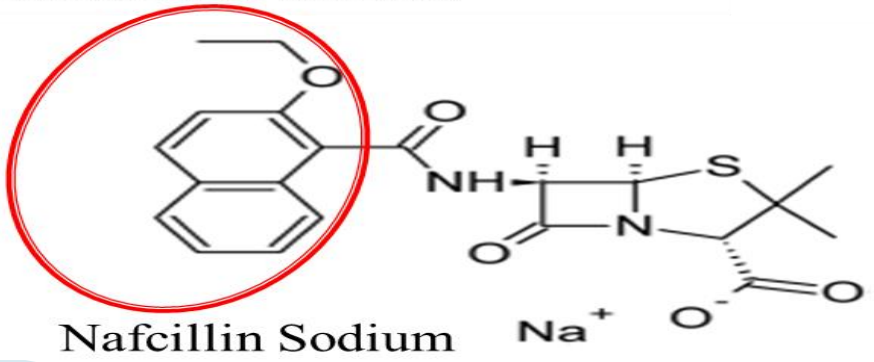
Oxacillin Sodium



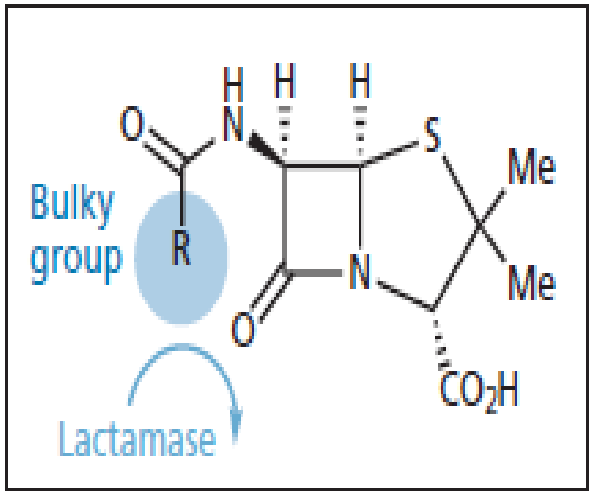
Dicloxacillin Sodium

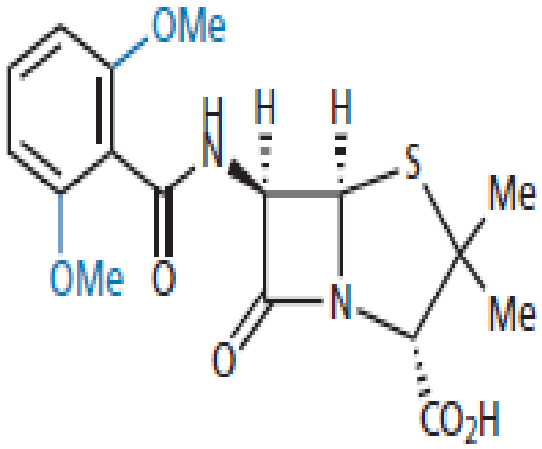


Cloxacillin sodium

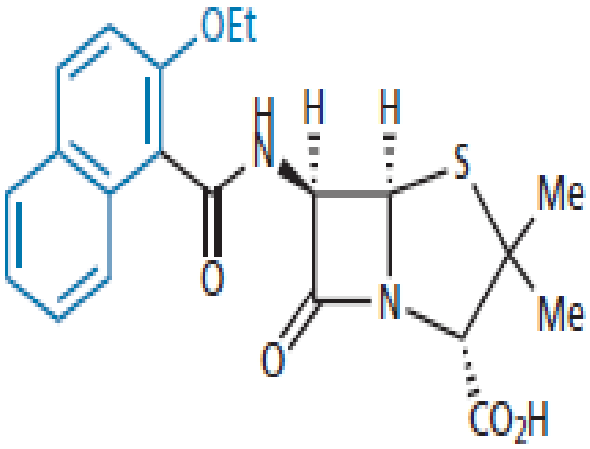


Nafcillin Sodium

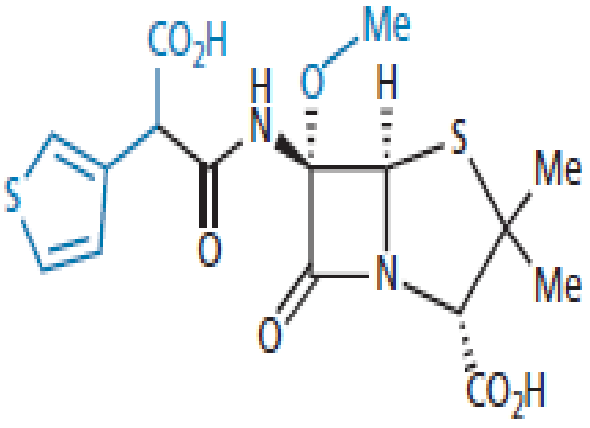




Methicillin



Nafcillin



Temocillin

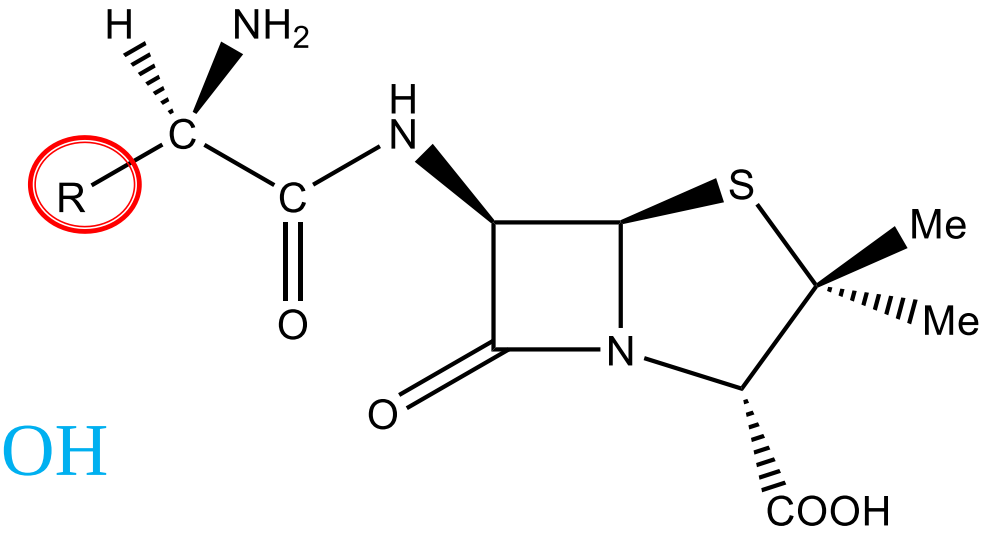
The use of steric shields to blocking penicillin from reaching the β-lactamase active site.

Penicillins- Amino penicillins

In order to increase the range of activity, the penicillin has been modified to have more hydrophilic groups, allowing the drug to penetrate into Gram (-) bacteria via the porins.

Ampicillin R=Phenyl

Amoxicillin R= Phenyl -OH



Ampicillin

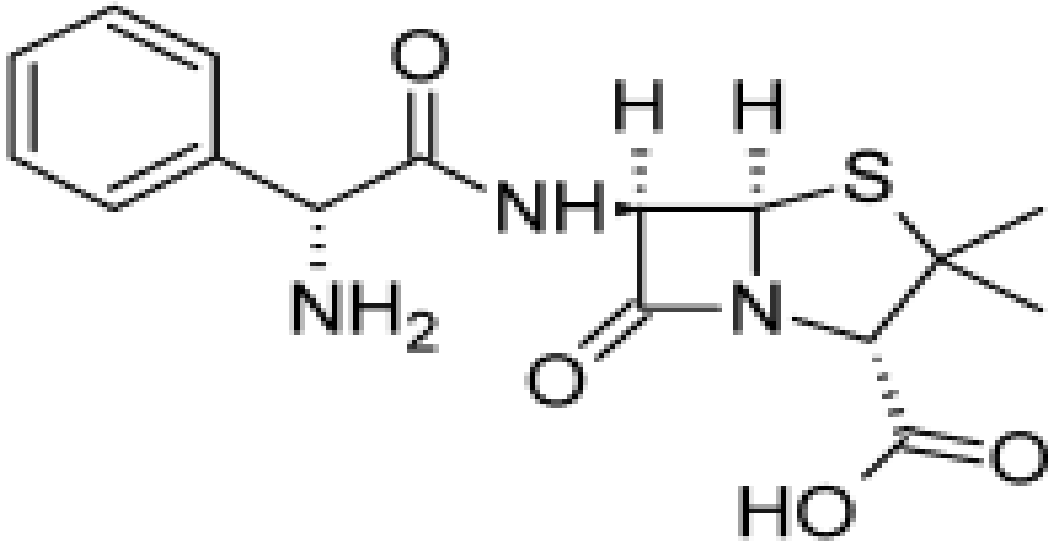
6-[D-α-amino phenyl acetamido]penicillanic acid, D-α-amino benzyl penicillin an antibacterial spectrum than that of penicillin G. Obviously, the α-amino group plays an important role in the activity, but the mechanism for its action is unknown. It has been suggested that the amino group confers an ability to cross cell wall barriers that are impenetrable to other penicillins.

D-(-)-Ampicillin more active than L-(+)-ampicillin.

Ampicillin is not resistant to penicillinase, and it produces the allergic reactions

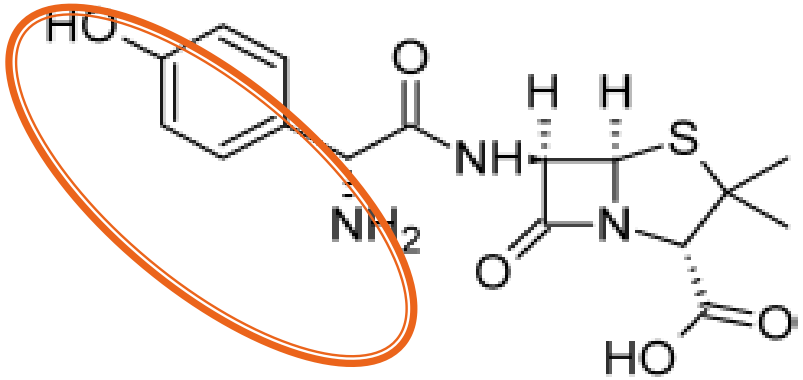
Ampicillin is water soluble and stable in acid.

The protonated α-amino group of ampicillin has a pKa of 7.3 and thus it is protonated extensively in acidic media, which explains ampicillin's stability to acid hydrolysis and instability to alkaline hydrolysis.



Ampicillin

Amoxicillin



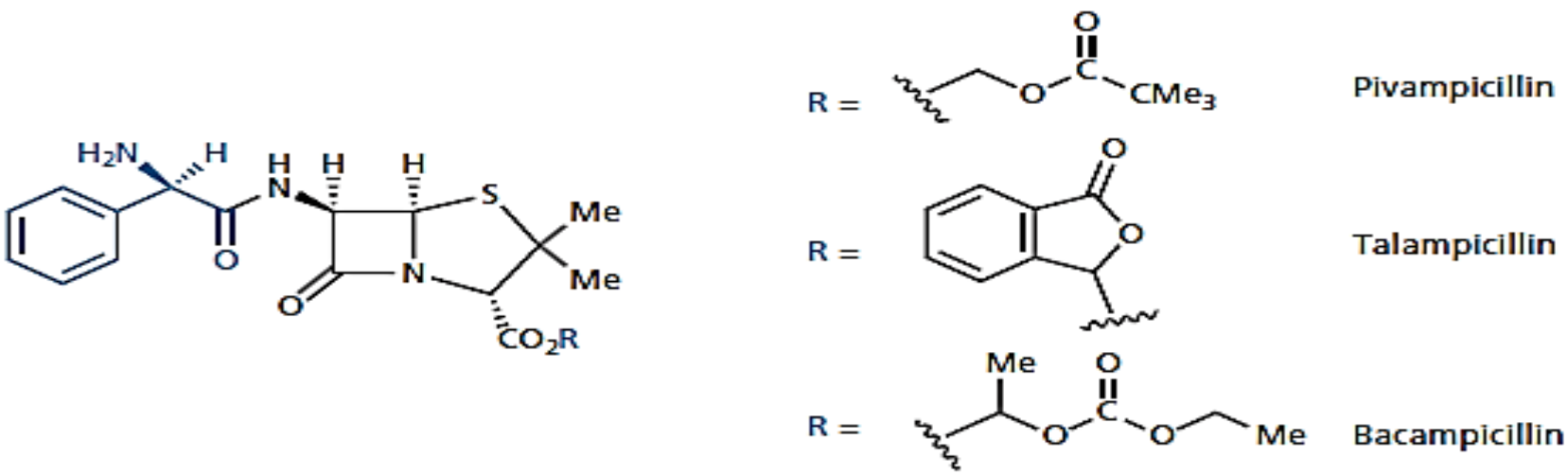
is simply the p-hydroxy analog of ampicillin, prepared by acylation of 6-APA with p-hydroxy phenyl glycine.

Its antibacterial spectrum is nearly identical with that of ampicillin, and like ampicillin, it is resistant to acid, orally administered amoxicillin possesses significant advantages over ampicillin, including more complete GI absorption.

Ampicillin prodrugs

Pivampicillin, **talampicillin**, and **bacampicillin** are prodrugs of ampicillin .In all three cases, the esters used to mask the carboxylic acid group seem rather elaborate and one may ask why a simple methyl ester is not used. The answer is that methyl esters of penicillins are not metabolized in humans.

The bulky penicillin skeleton is so close to the ester that it acts as a steric shield and prevents the esterase enzymes that catalyse this reaction from accepting the penicillin ester as a substrate.

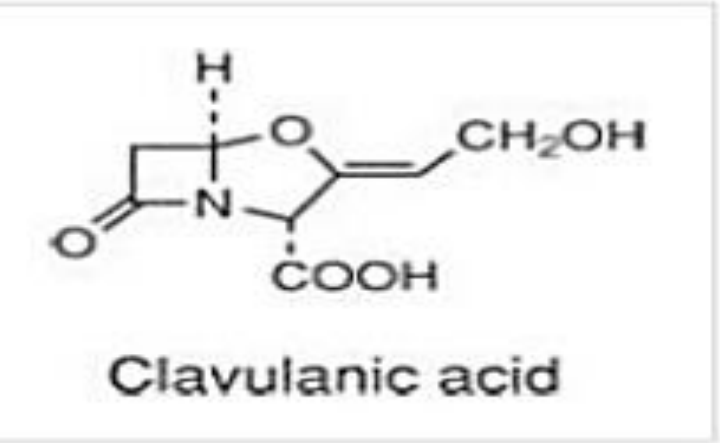


Prodrugs used to aid absorption of ampicillin through the gut wall.

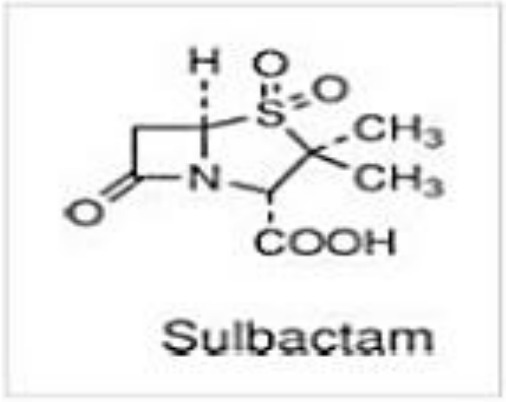
B-lactamase inhibitors

The discovery of the naturally occurring, mechanism based inhibitor **Clavulanic acid**, which causes potent and progressive inactivation of β-lactamases has created renewed interest in **β-lactam combination therapy.**

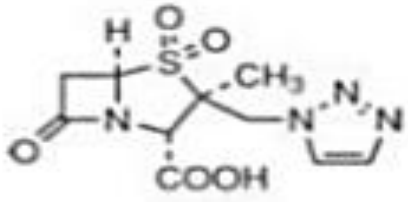
This interest has led to the design and synthesis of additional mechanism-based β-lactamase inhibitors, such as **Sulbactam** and **Tazobactam,** and the isolation of naturally occurring β-lactams, such as the **Thienamycins,** which both inhibit β-lactamases and interact with PBPs.



Clavulanic acid



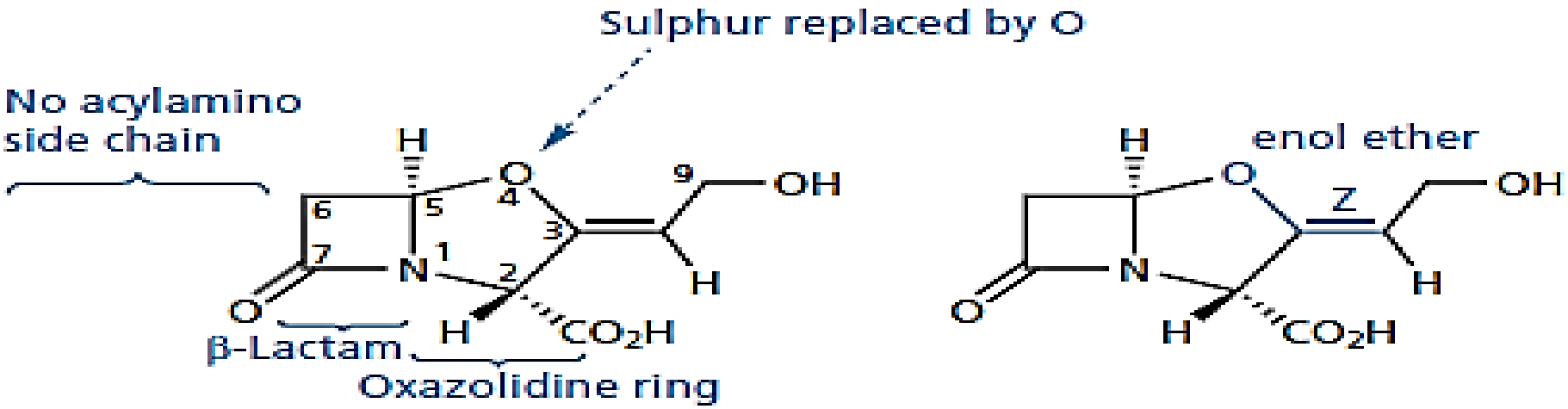
Sulbactam



Tazobactam

Clavulanate Potassium

Clavulanic acid is an antibiotic isolated from Streptomyces clavuligeris. Structurally, it is a 1-oxopenam lacking the 6-acylamino side chain of penicillins but possessing a 2- hydroxyethylidene moiety at C-2. Clavulanic acid exhibits very weak antibacterial activity, comparable with that of 6-APA and, therefore, is not useful as an antibiotic. It is, however, a potent inhibitor of S. aureus β-lactamase and plasmid-mediated β-lactamases elaborated by Gram negative bacilli.



Clavulanic acid.

Many analogues have now been made and the essential requirements for β-lactamase inhibition are:

- A strained β-lactam ring
- The enol ether
- The Z configuration for the double bond of the enol ether (activity is reduced but not eliminated if the double bond is E)
- No substitution at C-6
- (R)-stereochemistry at positions 2 and 5
- The carboxylic acid group.

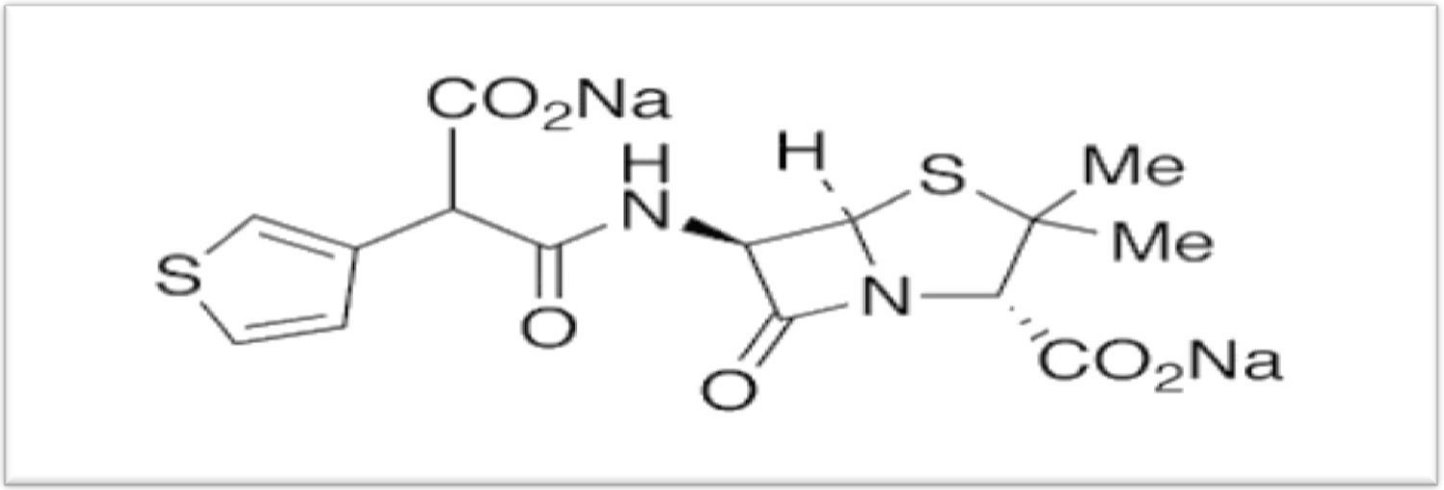
It is also thought that the 9-hydroxyl group is involved in a hydrogen bonding interaction with the active site of the β-lactamase enzyme. Clavulanic acid is a mechanism-based irreversible inhibitor and can be classed as a suicide substrate .

Clavulanic acid is acid-stable. It cannot undergo penicillanic acid formation because it lacks an amide side chain.

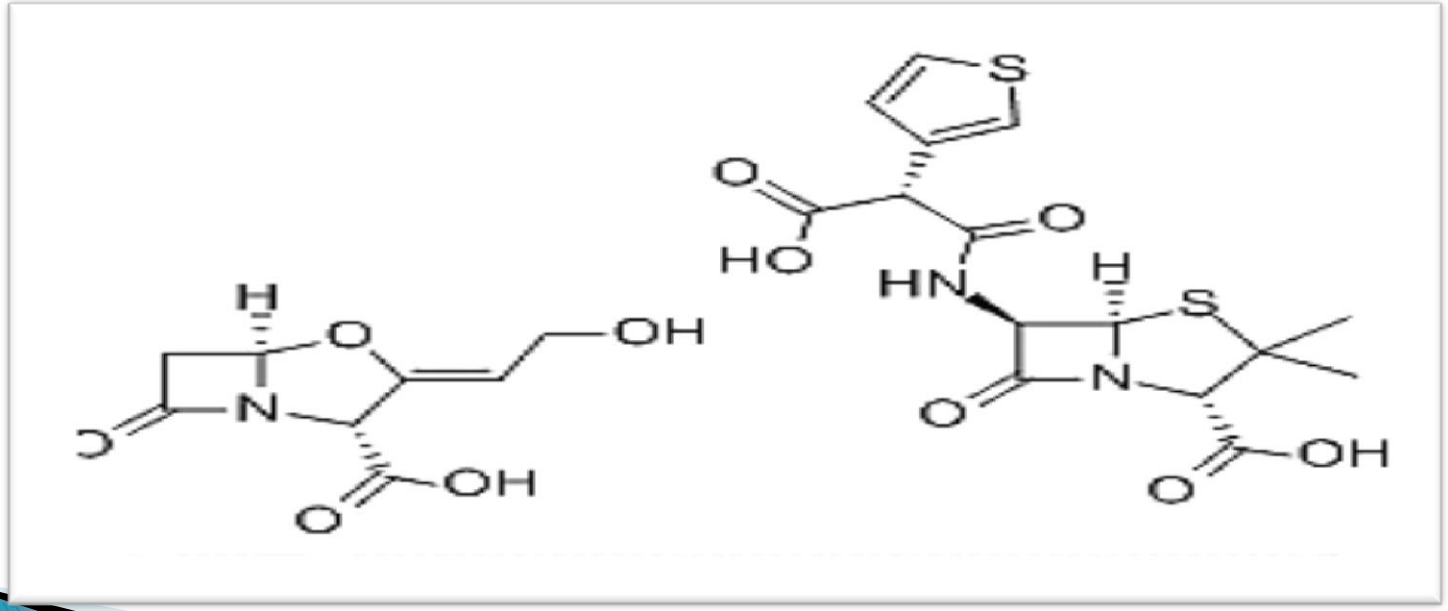
Combinations of amoxicillin and the potassium salt of clavulanic acid are available (**Augmentin**) in various fixed-dose oral dosage forms intended for the treatment of skin, respiratory, ear, and urinary tract infections caused by β-lactamase–producing bacterial strains.

Clavulanic acid is also administered intravenously with **ticarcillin** as **Timentin**.

Timentin is a prescription medicine used to treat the symptoms of bacterial infections such as Septicemia, Lower Respiratory Infections, Bone and Joint Infections, Urinary Tract Infections, Intra-abdominal Infections, and Gynecologic Infections. Timentin may be used alone or with other medications.



Ticarcillin

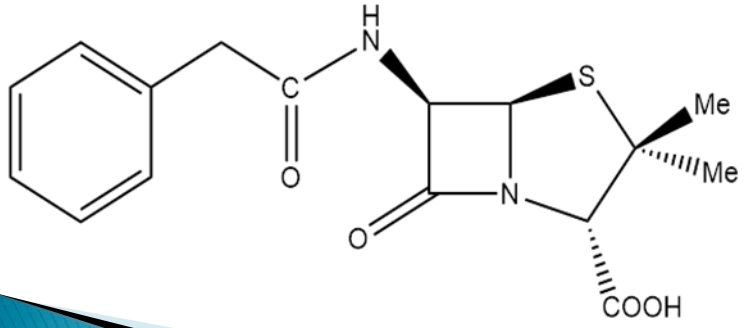


Timentin

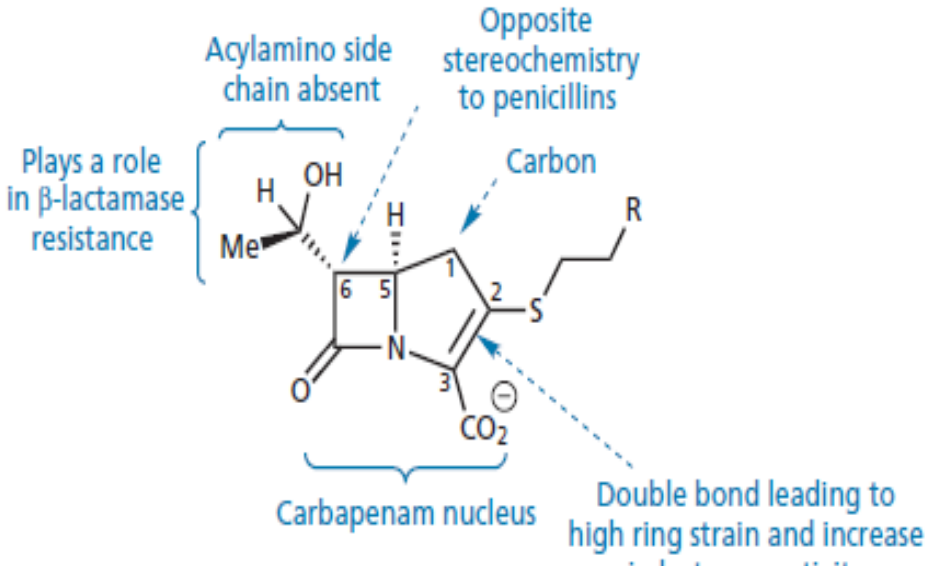
Carbapenems

Carbapenems are a potent class of β-lactams which attack a wide range of PBPs, have low toxicity, and are much more resistant to β-lactamases than the penicillins or cephalosporins.

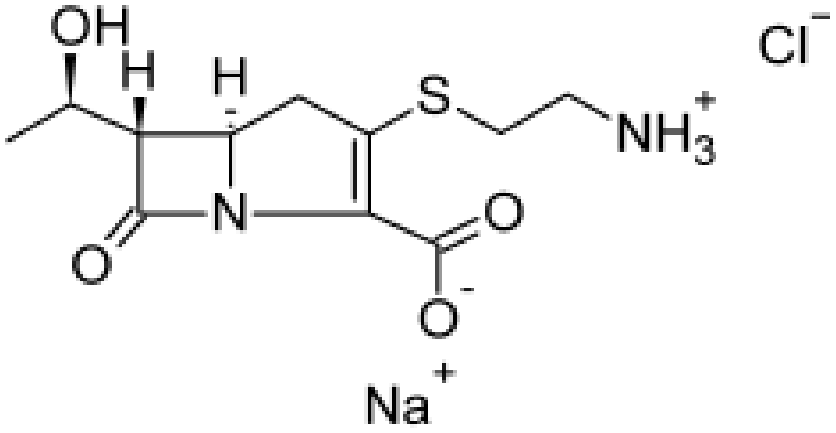
Carbapenems contain a β-lactam ring (cyclic amide) fused to a five-membered ring. Carbapenems differ in structure from penicillins in that within the five-membered ring a sulfur is replaced by a carbon atom (C1) and an unsaturation is present between C2 and C3 in the five-membered ring.



Penicillin G



Thienamycin



It is potent, with an extraordinarily broad range of activity against Gram-positive and Gram negative bacteria, including P. aeruginosa . It has low toxicity and shows a high resistance to β-lactamases.

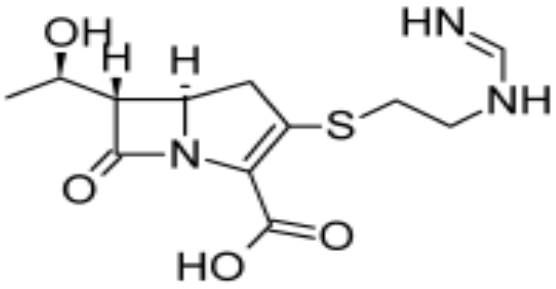
This resistance has been ascribed to the presence of the hydroxy ethyl side chain. Unfortunately, it shows poor metabolic and chemical stability, and is not absorbed from the gastrointestinal tract.

The surprising features in thienamycin are the missing sulphur atom and acylamino side chain, both of which were thought to be essential to antibacterial activity.

The side chain is unique in two respects:

- 1- Hydroxyethyl group instead of the familiar acylamino side chain, and it is oriented to the bicyclic ring system rather than having the usual orientation of the penicillins and cephalosporins.
- 2- Aminoethylthioether function at C-2.
- An unfortunate property of Thienamycin is its chemical instability in solution. It is more susceptible to hydrolysis in both acidic and alkaline solutions than most β-lactam antibiotics, because of the strained nature of its fused ring system containing an endocyclic double bond

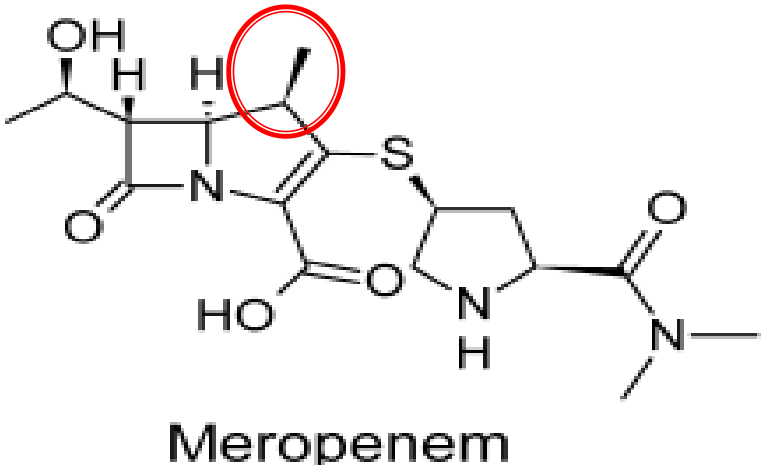
Imipenem– Cilastatin



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 retains the extraordinary broad-spectrum antibacterial properties of Thienamycin.

Its bactericidal activity results from the inhibition of cell wall synthesis associated with bonding to PBPs.

Imipenem is very stable to most β-lactamases. It is an inhibitor of β-lactamases from certain Gram-negative bacteria resistant to other -lactam antibiotics



Meropenem

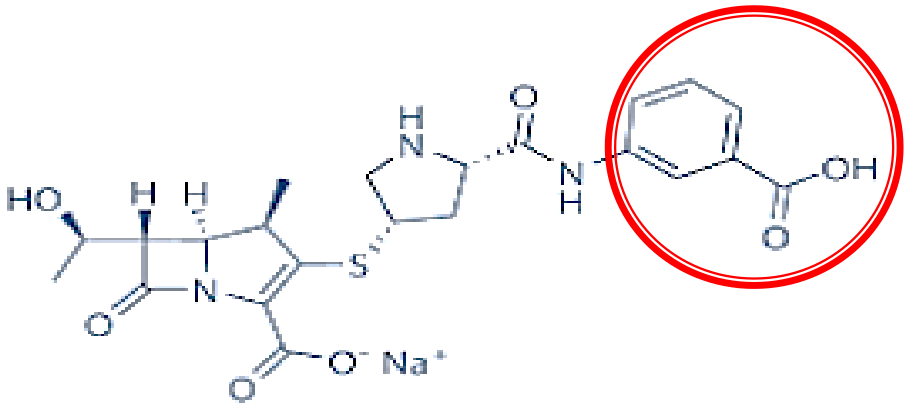
Newer Carbapenems

Meropenem

Meropenem is a second-generation carbapenem. Like imipenem, Meropenem is not active orally. Meropenem exhibits greater potency against Gram-negative and anaerobic bacteria than does imipenem, but it is slightly less active against most Gram-positive species. Both meropenem and imipenem penetrate the outer membrane of Gram-negative bacteria through porins, but meropenem enters more efficiently, resulting in higher activity against these bacteria.

Ertapenem was approved in 2002 and is similar in structure to meropenem.

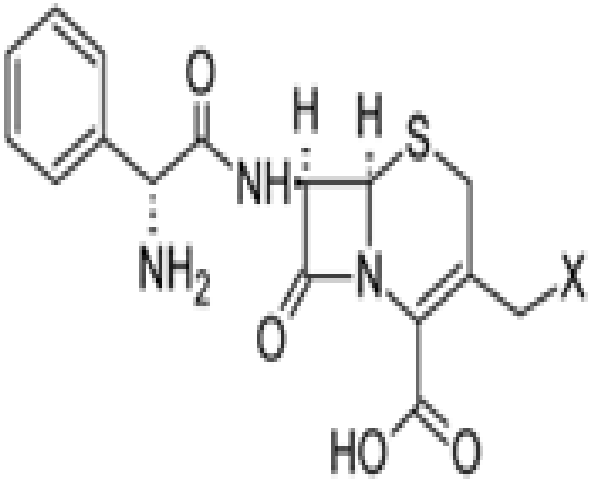
It has an extra substituent on the carbapenem ring (R 1 = Me) which provides further stability against dehydropeptidases, while the ionized benzoic acid contributes to high protein binding and prolongs the half life of the drug such that once-daily dosing is feasible.



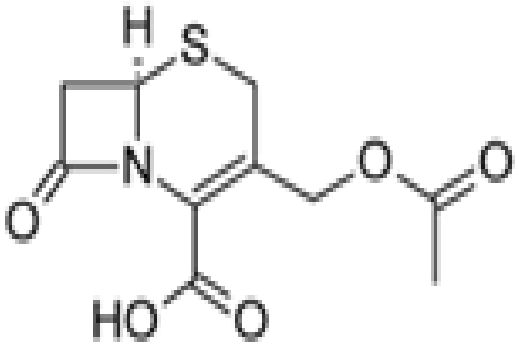
Cephalosporins

Cephalosporins are similar to penicillins but have a 6 member dihydrothiazine ring instead of a 5 member thiazolidine ring.

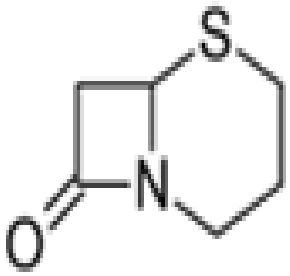
Unlike penicillin, cephalosporins have two side chains which can be easily modified. Cephalosporins are also more difficult for β-lactamases to hydrolyze.



Cephalosporin



Cephalosporanic Acid



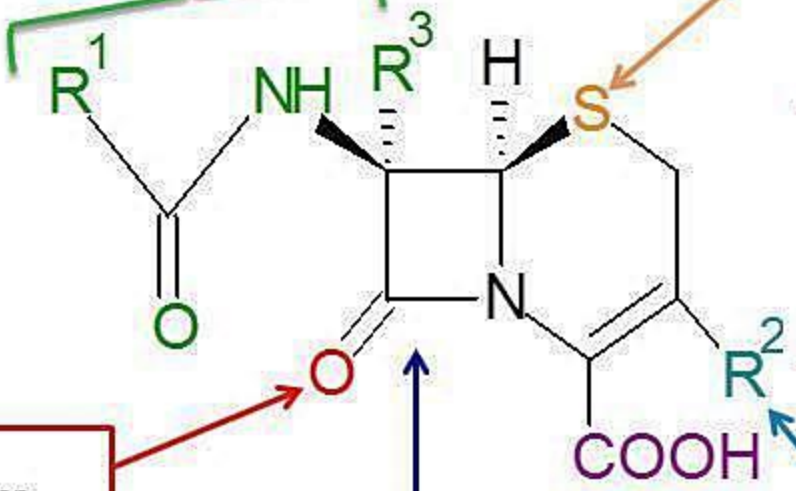
Cepham

STRUCTURE ACTIVITY RELATIONSHIP OF CEPHALOSPORIN

7-position substituent
- Semi-synthetic incorporation
- Influence the antibacterial activity
- Affects binding of β-lactamase

Cis-stereochemistry - essential

Exchange S with:
O = oxacepham
C = carbacepham



6 membered dihydrothiazine ring

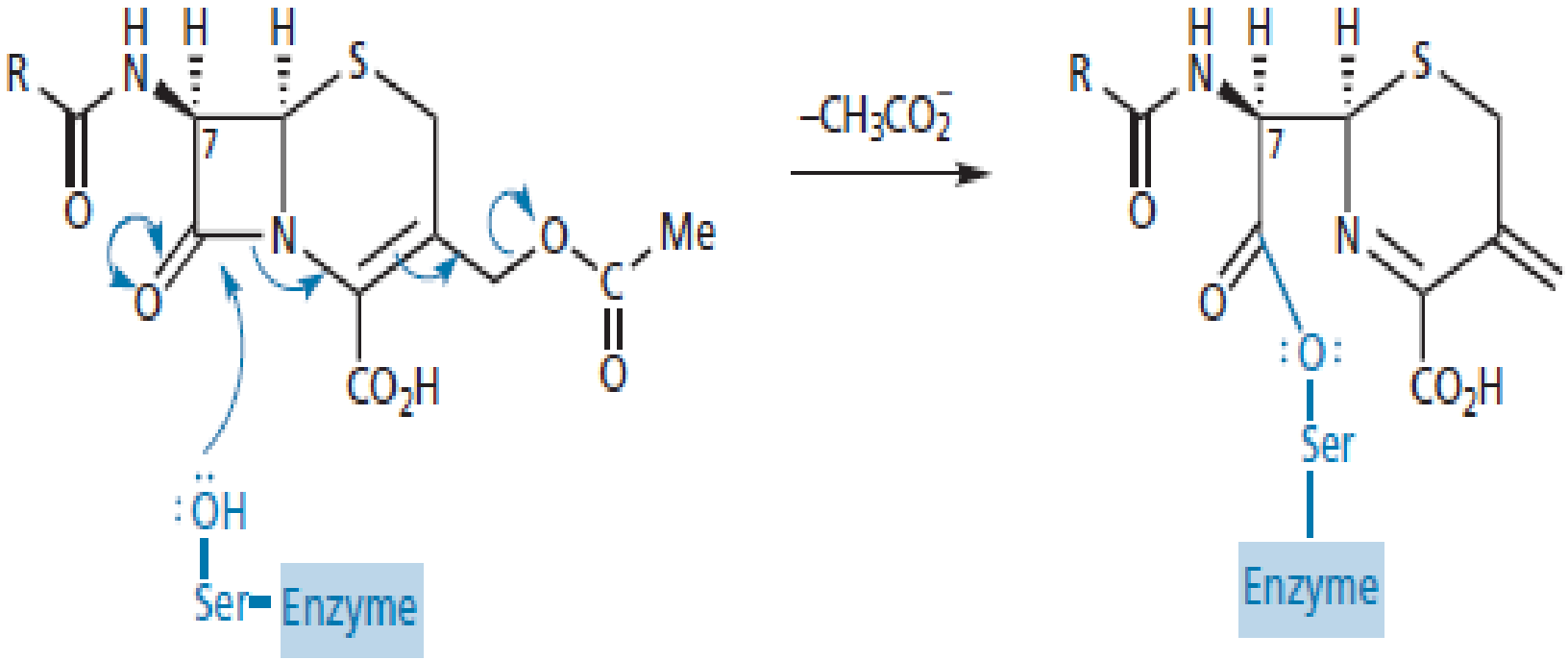
Carbonyl group
- Lone pair electron located on nitrogen atom not fed to carbonyl group to form a stabilized resonance structure, thus more electrophilic for nuclephilic attack.

β-lactam ring

3-position substituent
Chemical/ metabolic instability
< effect on antibacterial activity

Carboxylic acid
Useful during formulation
Prodrug development

Mechanism of Cephalosporins

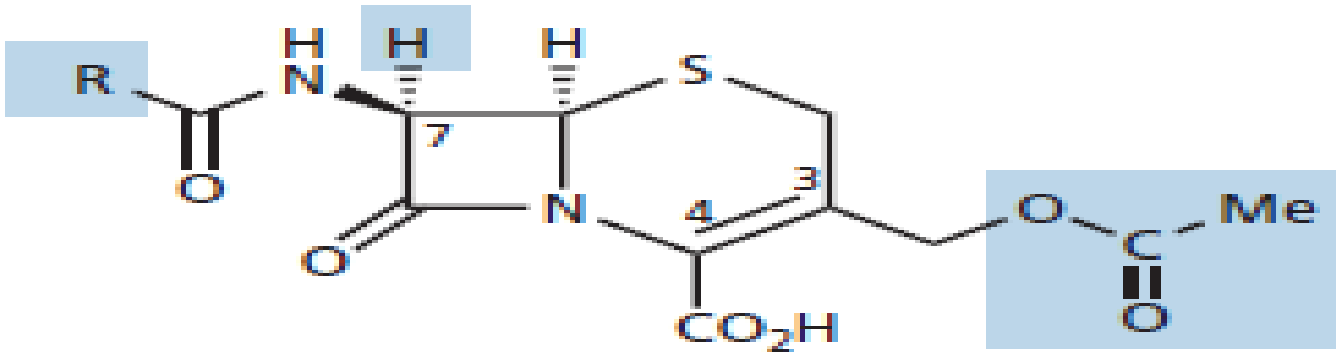


Mechanism by which cephalosporins inhibit the transpeptidase enzyme.

Semisynthetic Derivatives

There is a limited number of places where modifications can be made but there are more possibilities than with penicillins. These are as follows;

- variations of the 7-acylamino side chain;
- variations of the 3-acetoxymethyl side chain;
- extra substitution at carbon 7.



Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

In the preparation of semisynthetic cephalosporins, the **following improvements are sought:**

(a) increased acid stability

(b) improved pharmacokinetic properties, particularly better oral absorption,

(c) broadened antimicrobial spectrum

(d) increased activity against resistant microorganisms (as a result of resistance to enzymatic destruction, improved penetration, increased receptor affinity, etc.)

(e) decreased allergenicity

(f) increased tolerance after parenteral administration.

β-Lactamase Resistance

- Cephalosporins are significantly less sensitive than all but the β-lactamase–resistant penicillins to hydrolysis by the enzymes from S. aureus and Bacillus subtilis.
- The“penicillinase” resistance of cephalosporins appears to be a property of the bicyclic cephem ring system rather than of the acyl group.
- The different cephalosporins exhibit considerable variation in rates of hydrolysis by the enzyme:
- **cephalothin** and **cefoxitin** are the most resistant, and **Cephaloridine** ,**cefazolin** are the least resistant.

- The introduction of polar substituents in the aminoacyl moiety of cephalosporins appears to confer stability to some β-lactamases.
- Steric shields are successful in protecting cephalosporins from these β-lactamases, but also prevent them from inhibiting the transpeptidase target enzymes.

.

Oral Cephalosporins

The oral activity conferred by the phenyl glycyl substituent is attributed to increased acid stability of the lactam ring, resulting from the presence of a protonated amino group on the 7-acylamino portion of the molecule. Carrier mediated transport of these dipeptide-like, zwitterionic cephalosporins is also an important factor in their excellent oral activity.

The situation, then, is analogous to that of the α-amino benzylpenicillins (e.g., ampicillin).

Also important for high acid stability (and, therefore, good oral activity) of the cephalosporins is the absence of the leaving group at the 3-position.

Parenteral Cephalosporins

Hydrolysis of the ester function, catalyzed by hepatic and renal esterases, is responsible for some in vivo inactivation of parenteral cephalosporins containing a 3-acetoxymethyl substituent (e.g., **cephalothin, cephapirin**, and **cefotaxime)**.

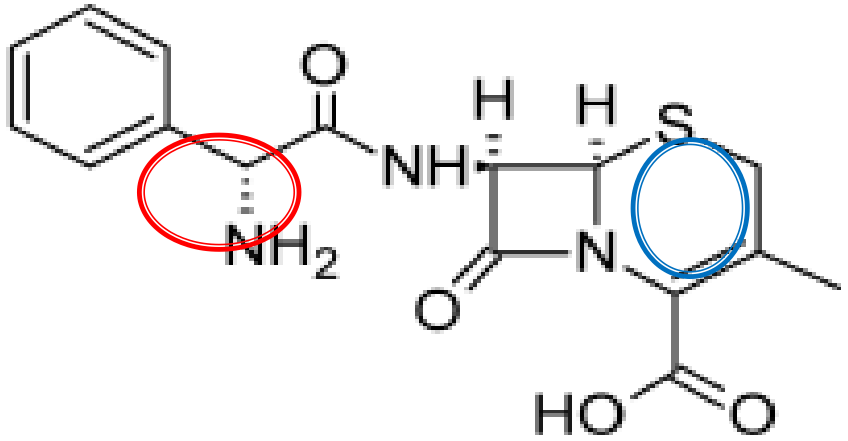
Parenteral cephalosporins lacking a hydrolyzable group at the 3-position are not subject to hydrolysis by esterases. **Cephradine** is the only cephalosporin that is used both orally and parenterally.

Classification

Cephalosporins are divided into first-, second-, third-, and fourth-generation agents, based roughly on their time of discovery and their antimicrobial properties

In general, progression from first to fourth generation is associated with a broadening of the Gram-negative antibacterial spectrum, some reduction in activity against Gram-positive organisms, and enhanced resistance to β- lactamases.

Products



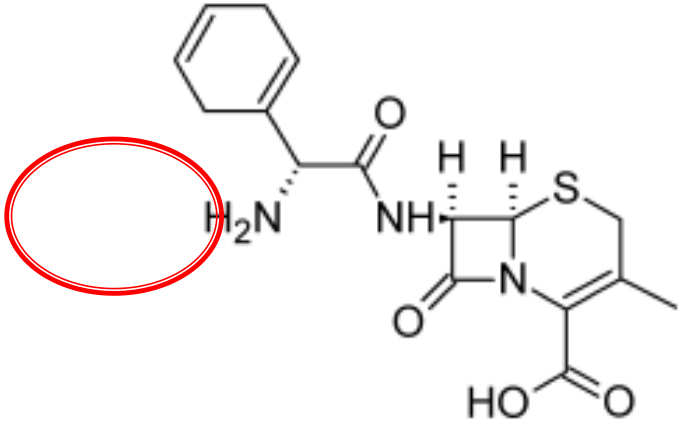
- **First Generation**

Cephalexin

Cephalexin,7α-(D-amino-α-phenyl acetamido)-3-methyl cephem carboxylic acid (**Keflex**, **Keforal**), was designed purposely as an orally active, semisynthetic cephalosporin.

The α-amino group of cephalexin renders it acid stable, . It is freely soluble in water, resistant to acid, and absorbed well orally. Food does not interfere with its absorption. A methyl group would normally be bad for activity as it is not a good leaving group. The presence of a hydrophilic amino group at the α-carbon of the 7-acylamino side chain in cephalexin helps to restore activity

Cephradine



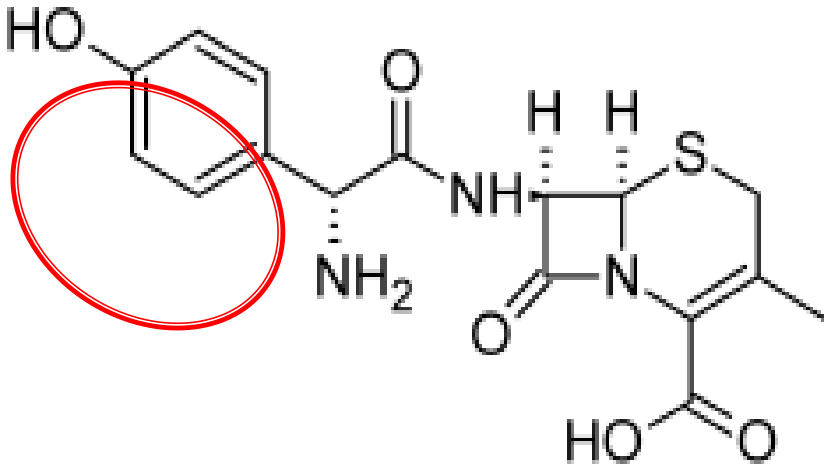
Cephradine (Anspor**, Velosef**)

is the only cephalosporin derivative available in both oral and parenteral dosage forms.

It closely resembles cephalexin chemically (it may be regarded as a partially hydrogenated derivative of cephalexin) and has very similar antibacterial and pharmacokinetic properties.

Cephradine is stable to acid and absorbed almost completely after oral administration

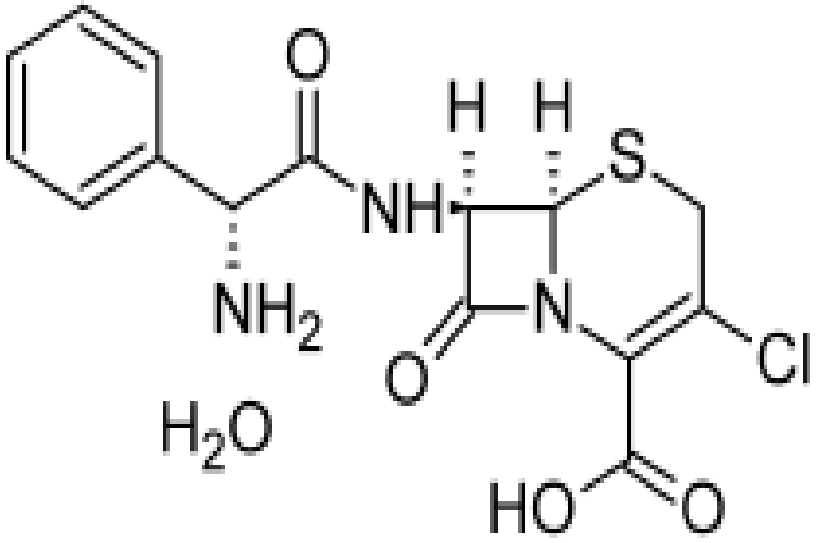
Cefadroxil



Cefadroxil (**Duricef**) is an orally active semisynthetic D-hydroxyl phenyl glycyl moiety. The main advantage claimed for Cefadroxil is its somewhat prolonged duration of action, which permits once-a-day dosing.

The prolonged duration of action of this compound is related to relatively slow urinary excretion of the drug compared with other cephalosporins,

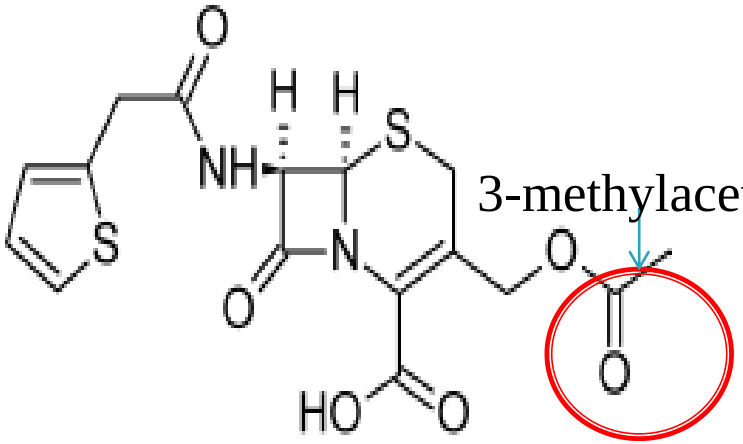
Cefaclor

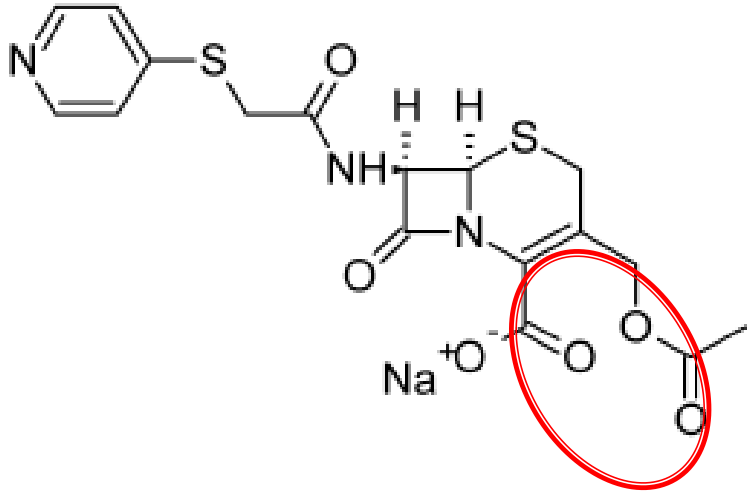


Cefaclor (**Ceclor**) is an orally active semisynthetic Cephalosporin.

It differs structurally from cephalexin in that the 3-methyl group has been replaced by a chlorine atom.).

Parenterally products

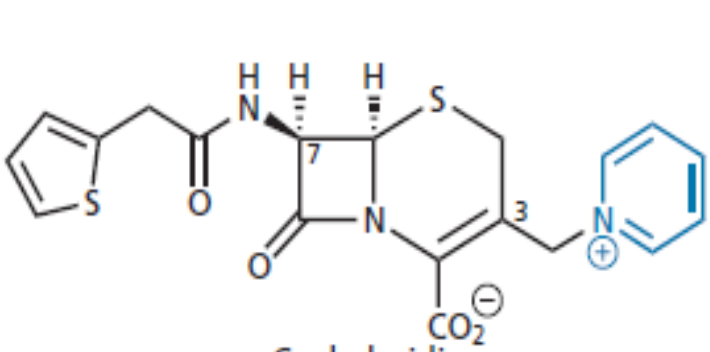




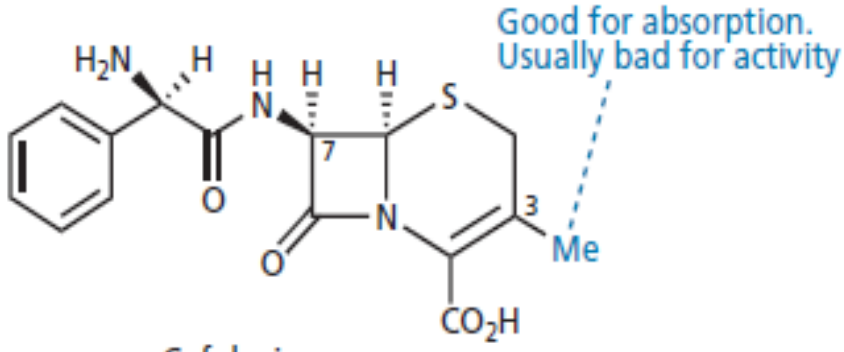
The oral inactivation of cephalosporins has been attributed to two causes: instability of the β-lactam ring to acid hydrolysis (**cephalothin** and **cephaloridine**) and solvolysis or microbial transformation of the 3-methylacetoxy group (**cephalothin, cephaloglycin**). The acetyloxy group is important to the mechanism of inhibition and acts as a good leaving group,

Cephalothin is resistant to penicillinase produced by S. aureus and provides an alternative to the use of penicillinase-resistant penicillins for the treatment of infections caused by such strains. Cephalothin is absorbed poorly from the GI tract and must be administered parenterally for systemic infections.

Replacing the ester with a metabolically stable pyridinium group gives **cephaloridine.** The pyridine can still act as a good leaving group for the inhibition mechanism, but is not cleaved by esterases. Cephaloridine exists as a zwitterion and is soluble in water, but unlike most first generation cephalosporins, it is poorly absorbed through the gut wall and has to be injected.



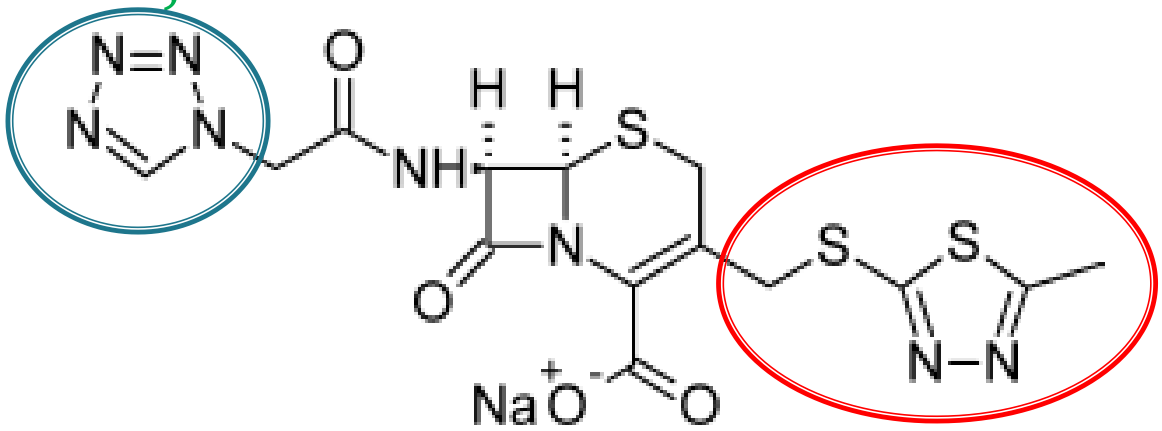
Cephaloridine



Cefalexin

Cephaloridine and cefalexin.

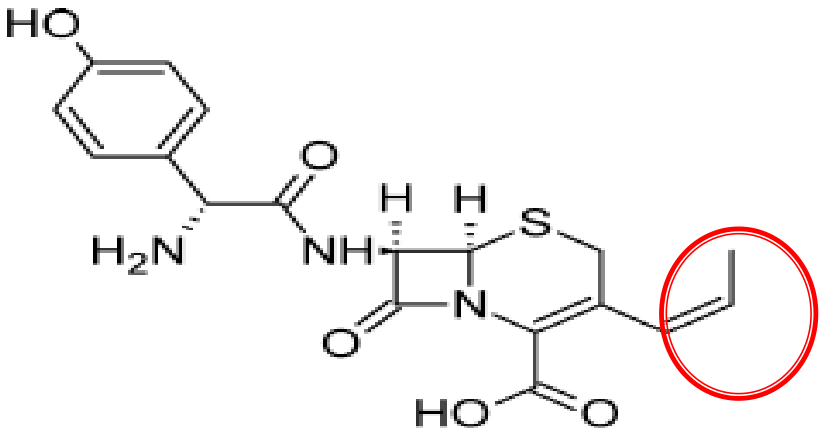
Cefazolin Sodium, Sterile



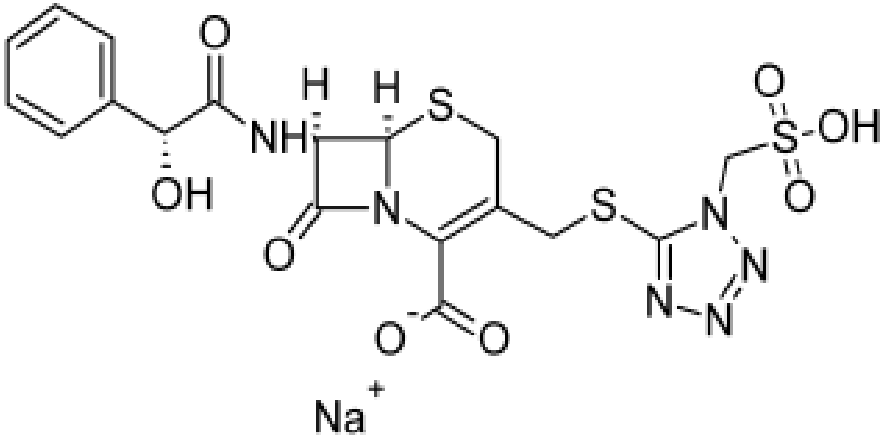
Cefazolin (Ancef, **Kefzol)**

is one of a series of semisynthetic cephalosporins in which the C-3 acetoxy function has been replaced by a thiol-containing heterocycle. It is active only by parenteral administration

Second-generation



Cefprozil



Cefonicid Sodium

Cefprozil (**Cefzil)** is an orally active second-generation cephalosporin that is similar in structure and antibacterial spectrum to cefadroxil.

Cefonicid is unique among the second-generation cephalosporins in that it has an unusually long serum half life of approximately 4.5 hour

Cephamycins

Eg. Cefoxitin, Cefotetan, Latamoxef

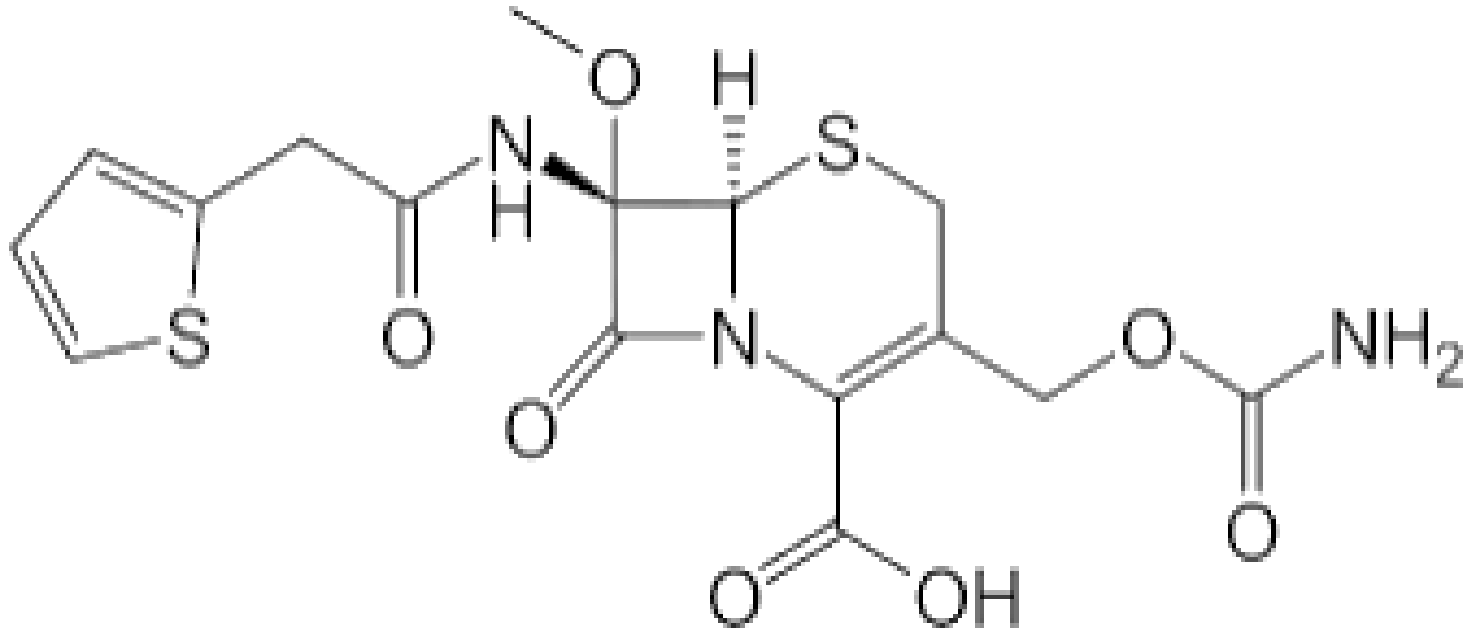
- Often grouped with 2nd generation cephalosporins.
- Natural product is cephamycin, isolated from a culture of *Streptomyces clavuligerus.*
- Semisynthetic derivatives are in clinical use.
- 7- methoxy analogues of cephalosporins.
- It has similar antibacterial activity with second-generation cephalosporins and good activity to anaerobe.
- It is used for mixed infection of aerobe and anaerobe.
- Have anaerobic activity (in particular Bacteroides)
- Also in-vitro activity against ESBL bacteria, but up-regulation of efflux mechanisms limits clinical use for these organisms.
- Clinically useful in Surgical Prophylaxis for Colorectal Surgery.

Cefoxitin

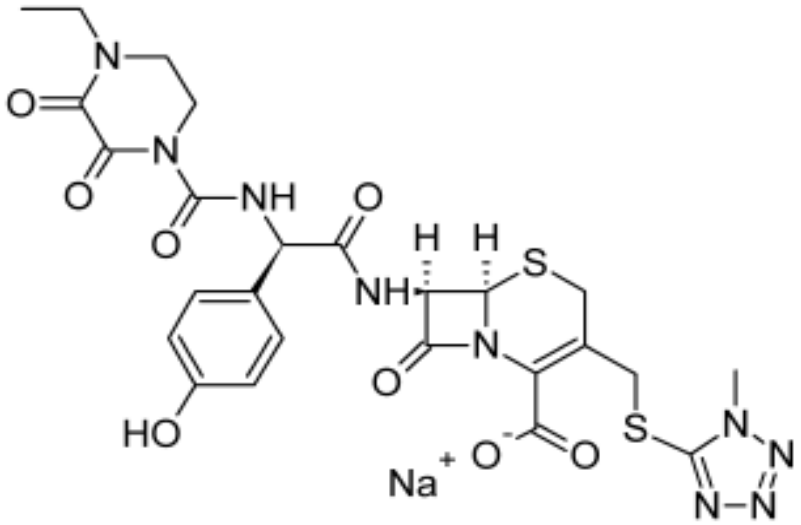
Cephamycin C

- Semisynthetic cephamycin
- Presence of methoxy group broader spectrum of activity than most first generation cephalosporins
- Greater resistance to β-lactamase enzymes
- The 7-methoxy group may act as a steric shield
- Broad range of gram-negative and gram-positive bacteria including anaerobes.

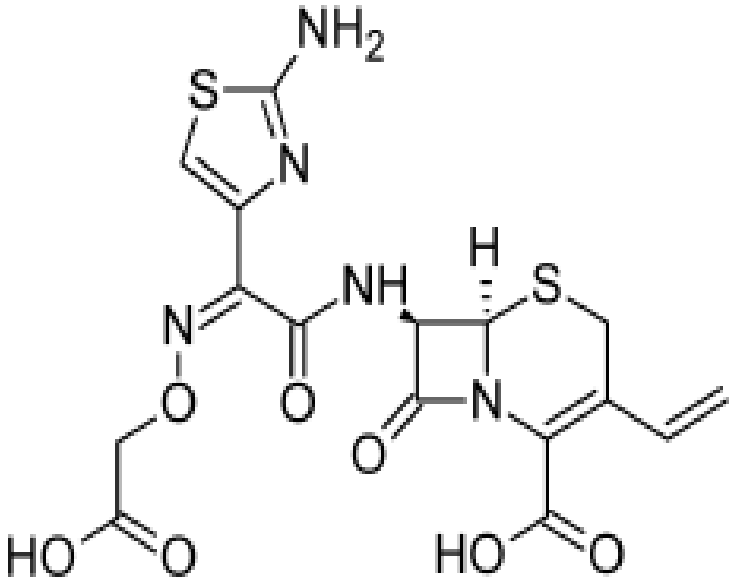
CEFOXITIN



Third-generation



Cefoperazone

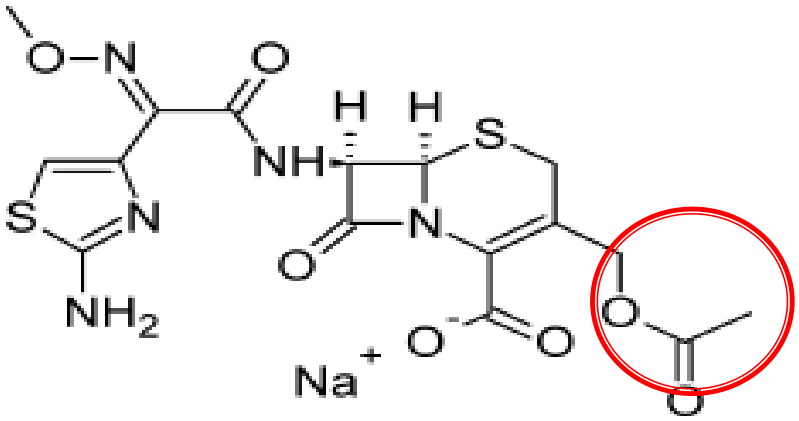


Cefixime

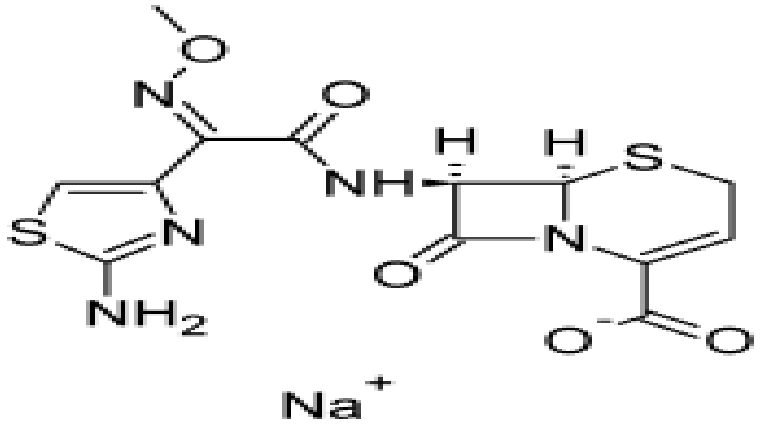
Cefoperazone (**Cefobid**) is a third-generation anti pseudomonal cephalosporin that resembles piperacillin chemically and microbiologically.

Cefixime (Suprax) is the first orally active, third-generation cephalosporin.

Cefotaxime Sodium and Ceftizoxime



Cefotaxime



Ceftizoxime

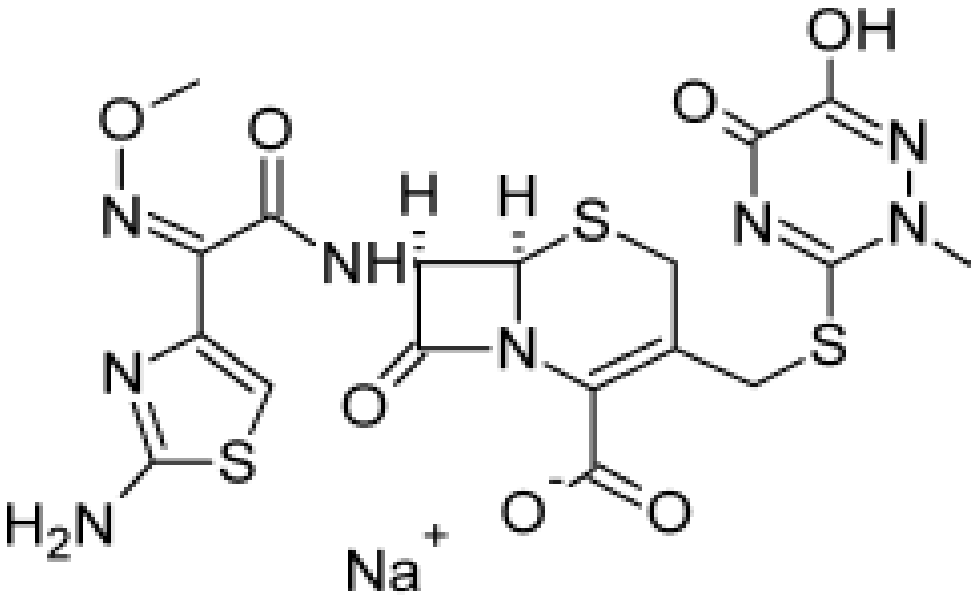
Cefotaxime (**Claforan**) was the first third-generation cephalosporin to be introduced.

It possesses excellent broad-spectrum activity against Gram-positive and Gram negative aerobic and anaerobic bacteria.

Ceftizoxime (**Cefizox**) is a third-generation cephalosporin that was introduced in 1984. It must be administered on a three-daily dosing schedule because of its relatively short half-life.

Ceftriaxone Disodium, Sterile

Ceftriaxone (**Rocephin)** is a β-lactamase–resistant cephalosporin with an extremely long serum half-life. Once-daily dosing suffices for most indications. Two factors contribute to the prolonged duration of action of ceftriaxone: high protein binding in the plasma and slow urinary excretion.

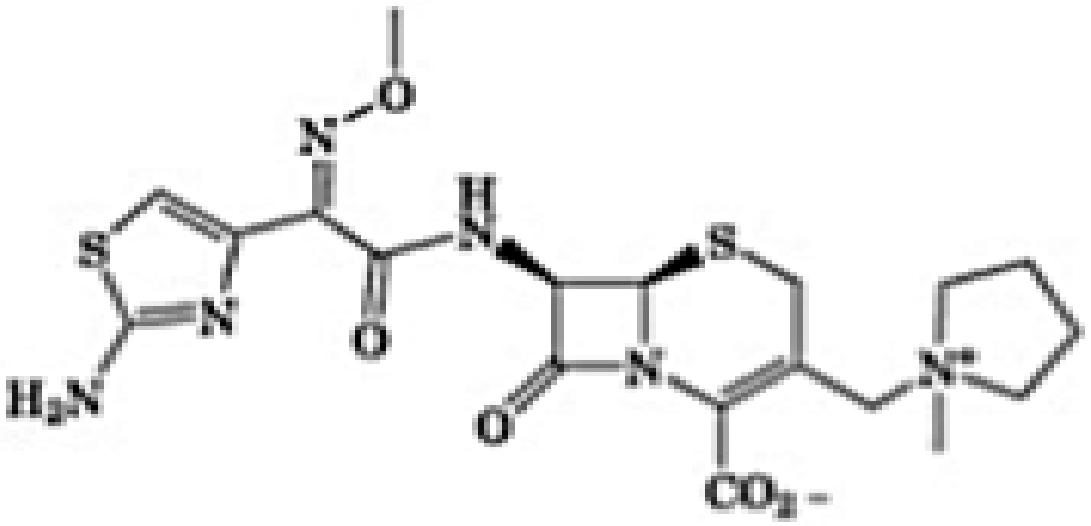


Ceftriaxone

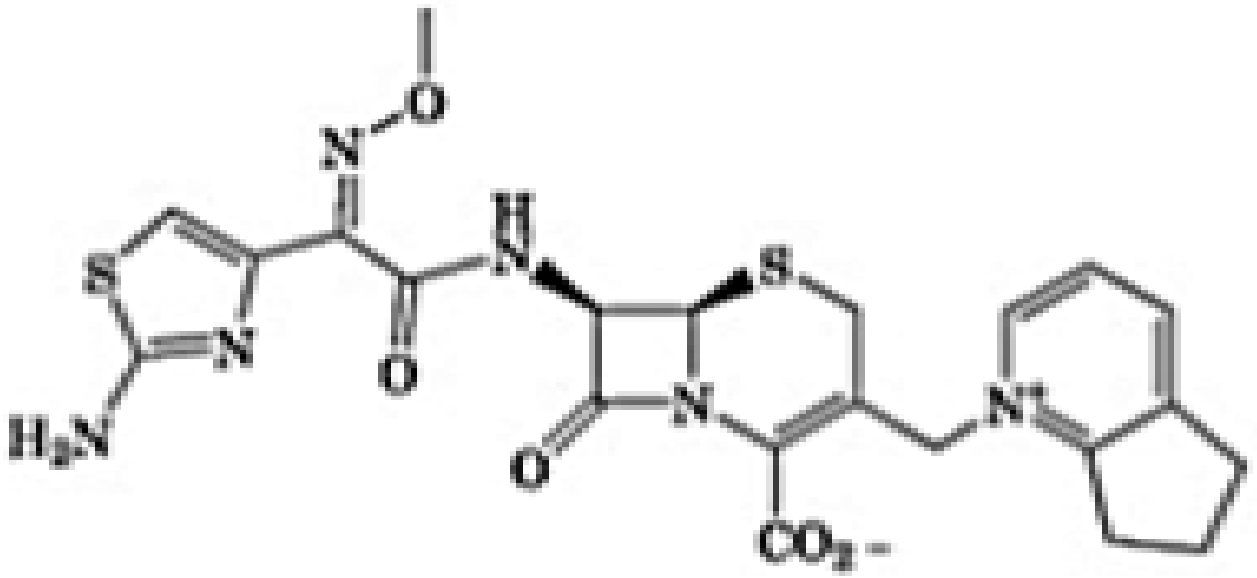
The fourth generation cephalosporins

Cefepime and **cefpirome** are zwitterionic compounds having a positively charged substituent at position 3 and a negatively charged carboxylate group at position 4.

This property appears to radically enhance the ability of these compounds to penetrate the outer membrane of Gram negative bacteria. They are also found to have a good affinity for the transpeptidase enzyme and a low affinity for a variety of β-lactamases.



Cefepime



cefpirome

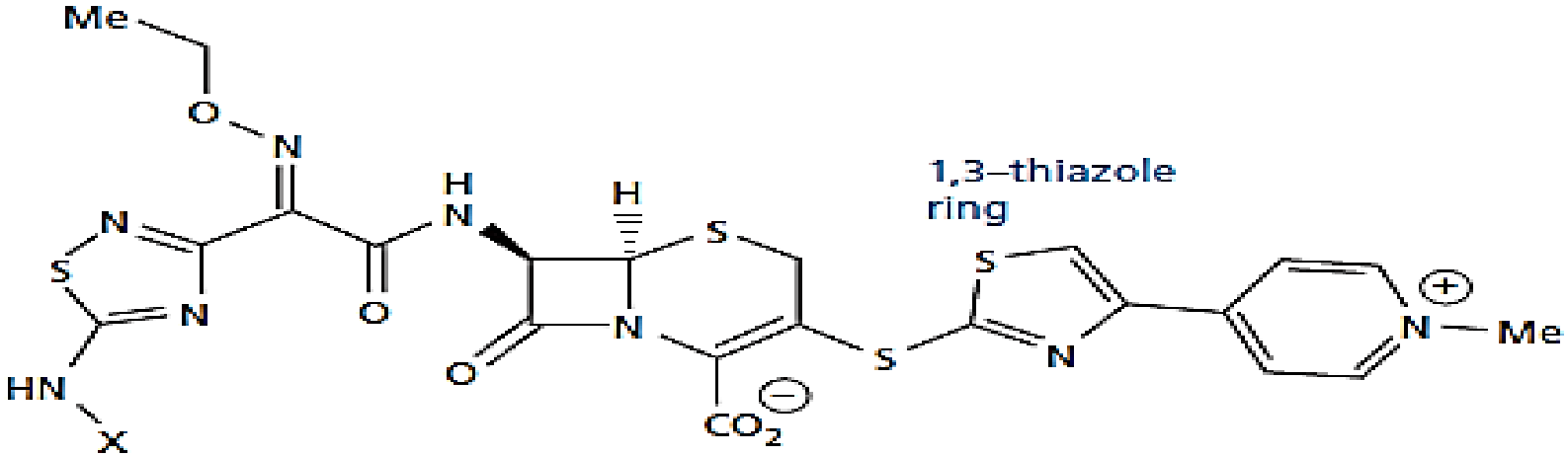
Methicillin-Resistant Staph.Aureus

- Cefipime and Cefpirom
  - Wide spectrum, active against streptococci and staphylococci but Not MRSA.
  - Effective against *Pseudomonas*.
  - Enhanced activity against certain Gram negative bacilli, including *Enterobacter, Citrobacter* and *Serratia*.
  - Uses: Severe Community Acquired Pneumonia requiring Intensive Care.
  - Not effective against ESBL producing organisms.

Fifth-generation cephalosporins

Ceftaroline fosamil is a fifth-generation cephalosporin that has activity against various strains of MRSA methicillin resistant Staphylococcus aureus and multi-resistant Streptococcus pneumonia (MDRSP).

It acts as a prodrug for ceftaroline , and the 1,3-thiazole ring is thought to be important for its activity against MR



Ceftaroline; X = H
Ceftaroline fosamil; X = P(=O)(OH)$_2$

Ceftaroline and ceftaroline fosamil.