Antibacterial Antibiotics

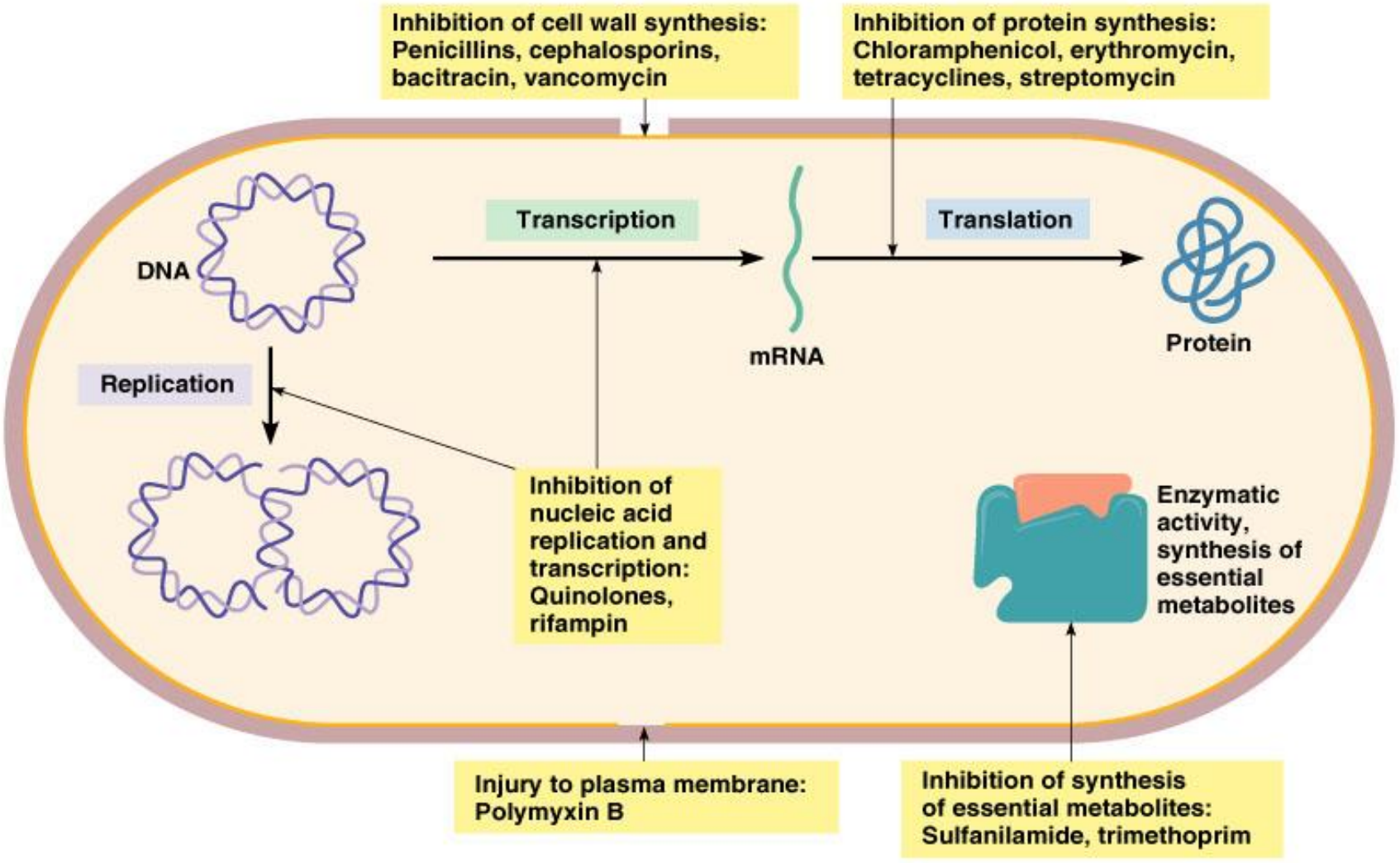
B-lactam antibiotics

Dr. Widad Abd AL-Jabbar

AL-Mustaqbal university

College of pharmacy

Mechanism of action



B-lactam antibiotics

Antibiotics that possess the β-lactam (a four-membered cyclic amide) ring structure.

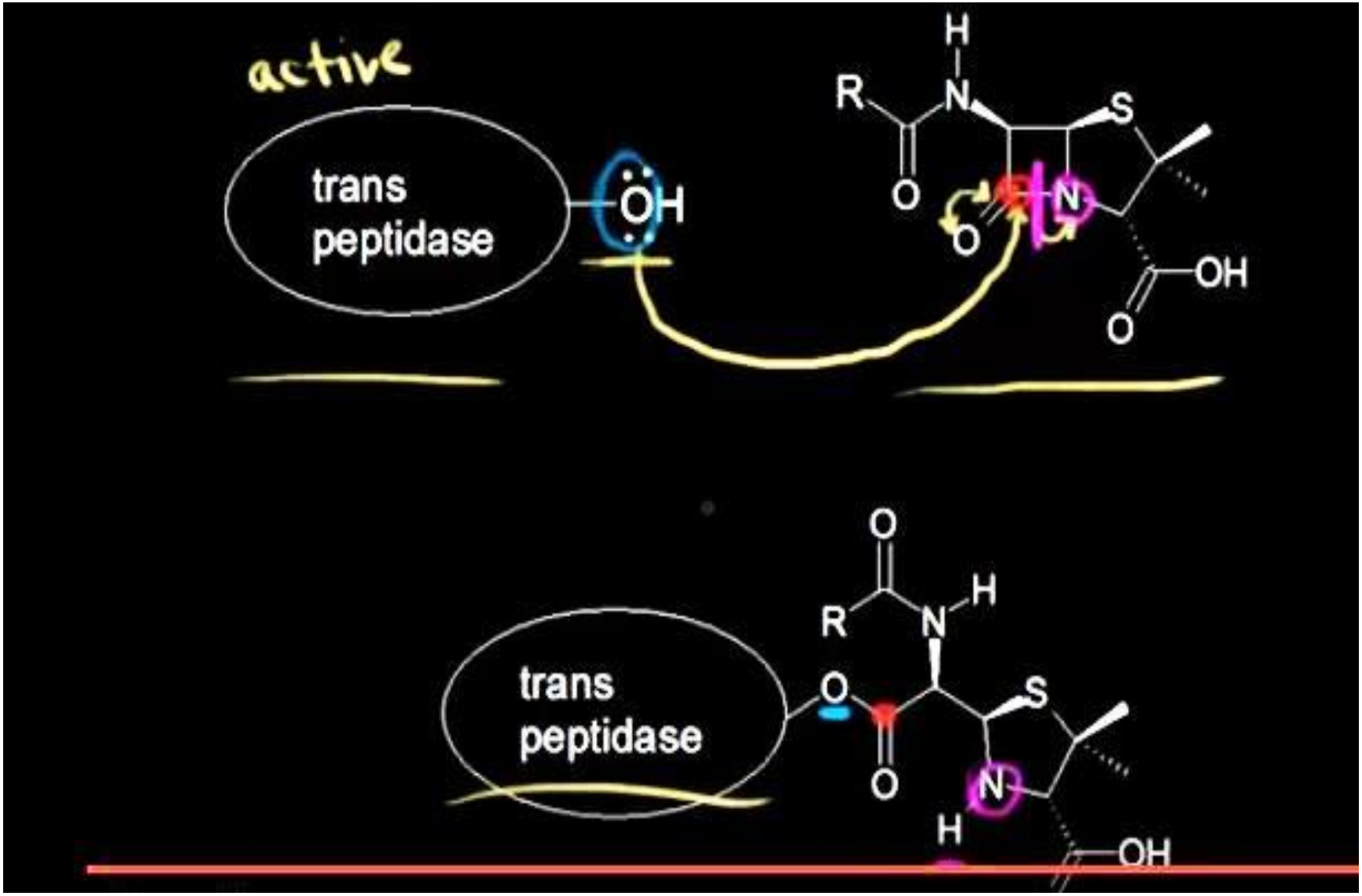
The first antibiotic to be used in therapy, penicillin (penicillin G or benzyl penicillin), and a close biosynthetic relative, phenoxy methyl penicillin (penicillin V), remain the agents of choice for the treatment of infections caused by most species of Gram-positive bacteria.

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

β-Lactams acylate the hydroxyl group on the serine residue of PBP active site in an irreversible manner.

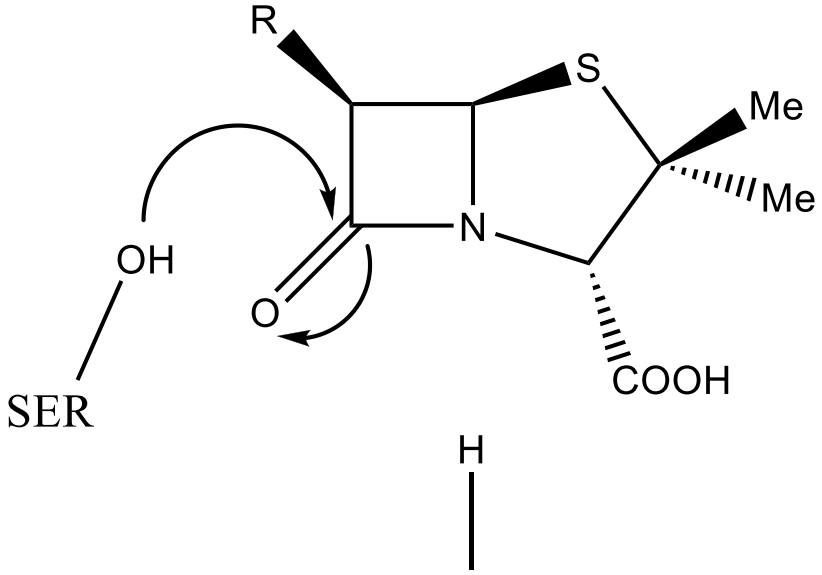
This reaction is further aided by the oxyanion hole, which stabilizes the tetrahedral intermediate and thereby reduces the transition state energy.

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


active
trans
peptidase
OH
H
N
R
S
O
N
O
OH
O
trans
peptidase
O
H
R
N
O
S
O
N
H
OH

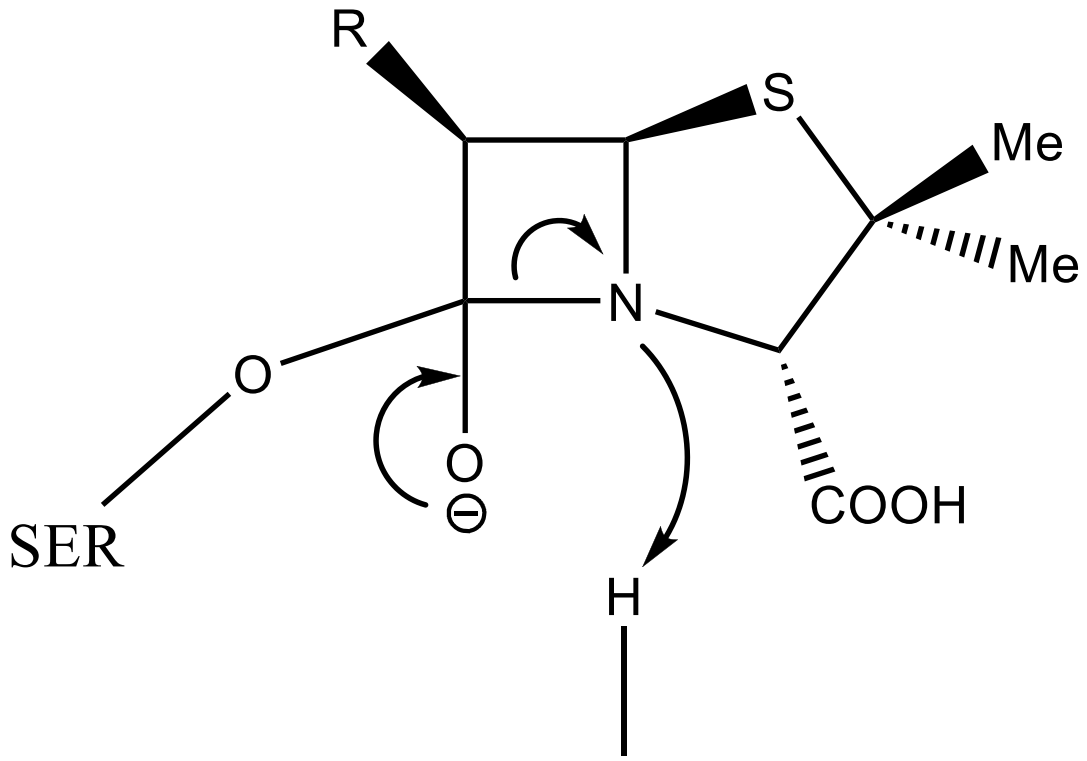
Mechanism of β-Lactam Drugs

The hydroxyl attacks the amide and forms a tetrahedral intermediate.



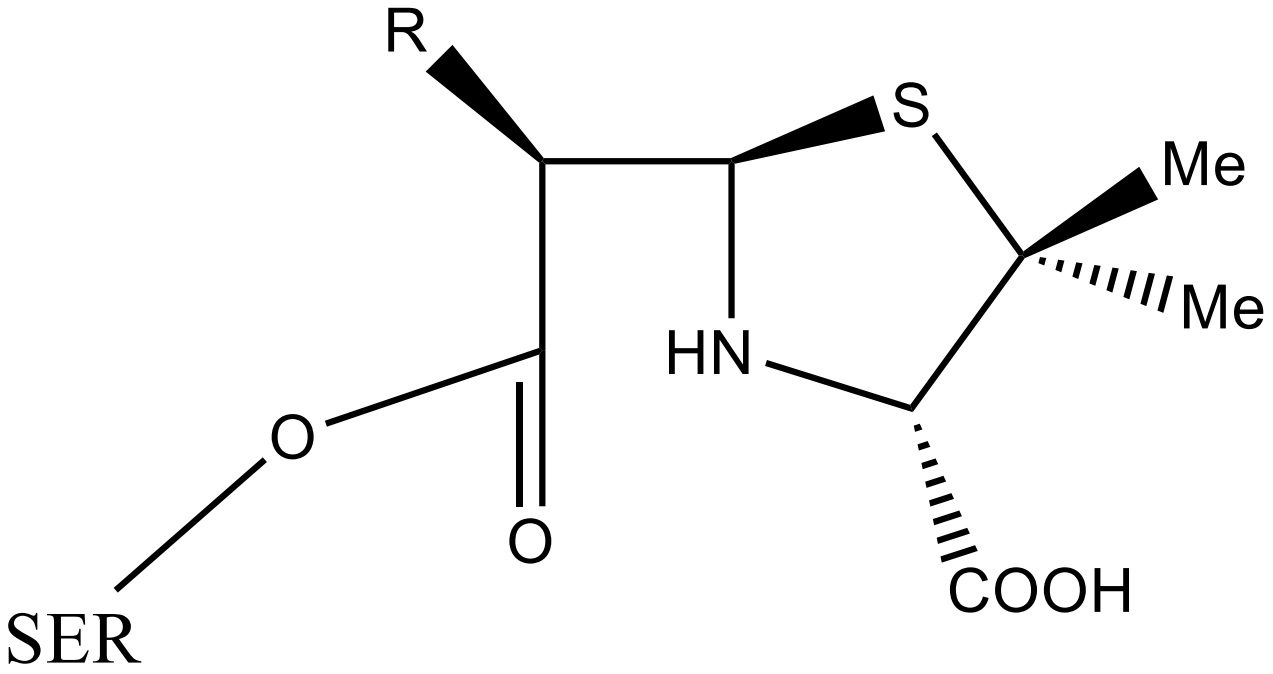
Mechanism of β-Lactam Drugs

The tetrahedral intermediate collapses, the amide bond is broken, and the nitrogen is reduced.



Mechanism of β-Lactam Drugs

The PBP is now covalently bound by the drug and cannot perform the cross linking action.



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.

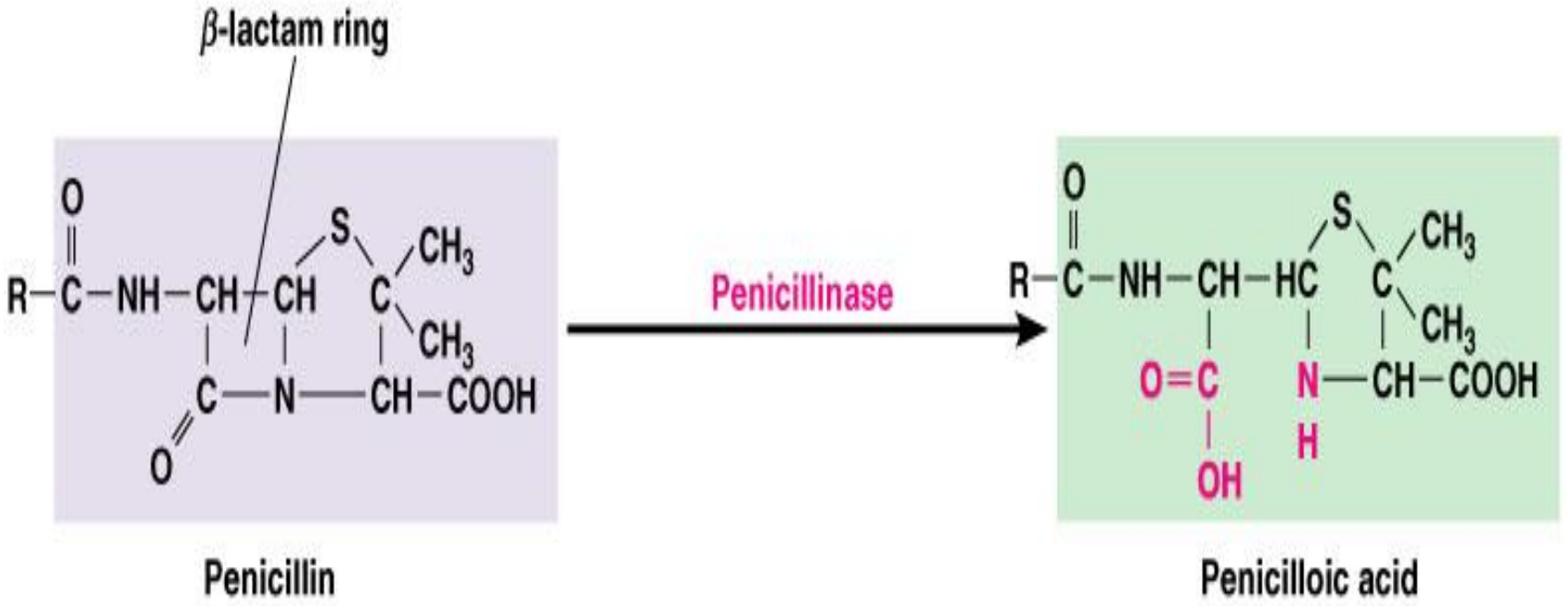
By far, the more important of these are the β-lactamases, enzymes that catalyze the hydrolytic opening of the β-lactam ring of penicillins to produce inactive penicilloic acids.

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

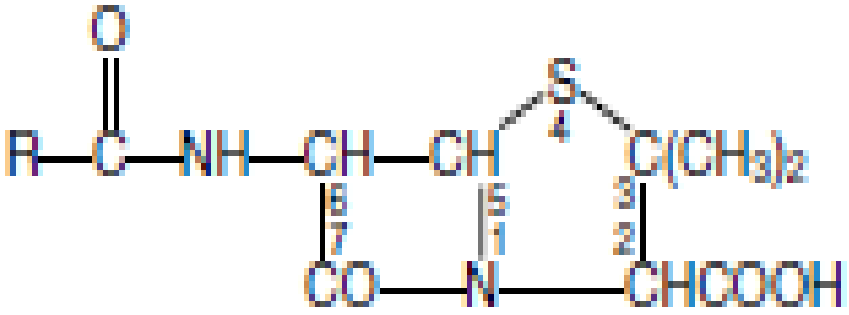
Penicillinase (β- Lactamase)



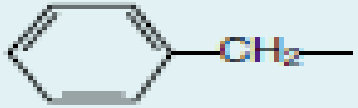
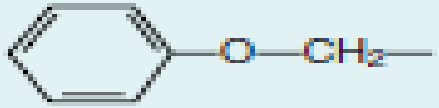
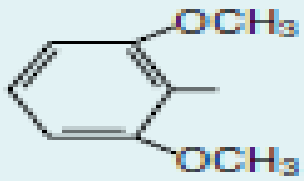
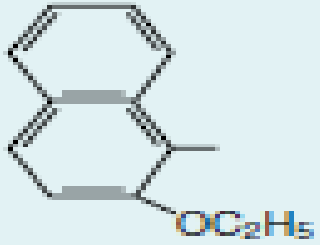
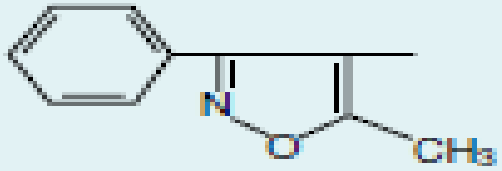
The penicillins

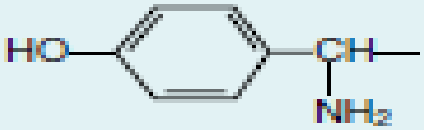
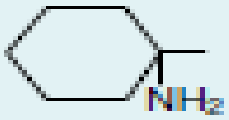
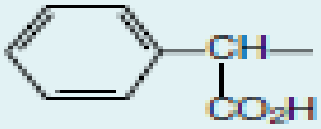
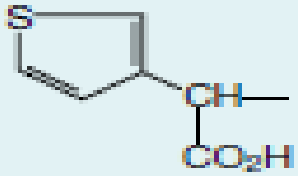
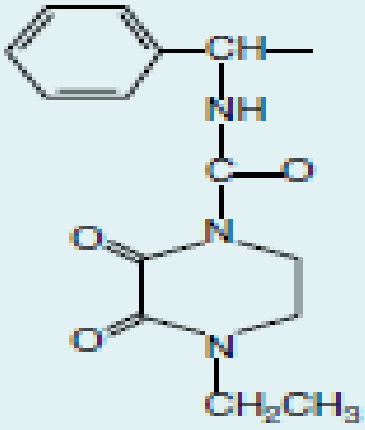
Several closely related compounds produced. These compounds differ chemically in the acid moiety of the amide side chain.

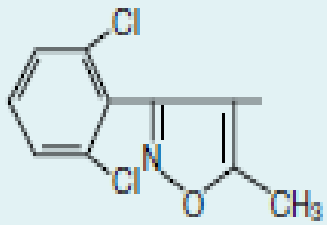
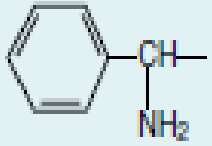
Variations in this moiety produce differences in antibiotic effect and in physicochemical properties, including stability.

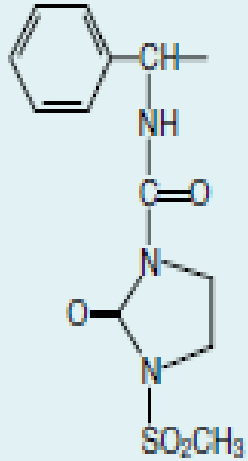


Structure of penicillins

Generic Name	Chemical Name	R Group
Penicillin G	Benzylpenicillin	
Penicillin V	Phenoxymethylpenicillin	
Methicillin	2,6-Dimethoxyphenyl-penicillin	
Nafcillin	2-Ethoxy-1-naphthyl-penicillin	
Oxacillin	5-Methyl-3-phenyl-4-isoxazolylpenicillin	

Generic Name	Chemical Name	R Group
Amoxicillin	D-α-Amino-p-hydroxybenzylpenicillin	
Cyclacillin	1-Aminocyclohexyl-penicillin	
Carbenicillin	α-Carboxybenzyl-penicillin	
Ticarcillin	α-Carboxy-3-thienyl-penicillin	
Piperacillin	α-(4-Ethyl-2,3-dioxo-1-piperazinylcarbonyl-amino)benzylpenicillin	

Generic Name	Chemical Name	R Group
Dicloxacillin	5-Methyl-3-(2,6-dichlorophenyl)-4-isoxazolylpenicillin	
Ampicillin	D-α-Aminobenzyl-penicillin	

Generic Name	Chemical Name	R Group
Mezlocillin	α-(1-Methanesulfonyl-2-oxoimidazolidino-carbonylamino)benzyl-penicillin	

Nomenclature

The Chemical Abstracts system initiates the numbering with the sulfur atom and assigns the ring nitrogen the 4-position. Thus, penicillins are named as 4-thia-l-azabicycloheptanes, according to this system. The numbering system adopted by the USP is the reverse of the Chemical Abstracts procedure, assigning number 1 to the nitrogen atom and number 4 to the sulfur atom. The name "penam" used for the unsubstituted bicyclic system, including the amide carbonyl group, with one of the foregoing numbering systems

Thus, penicillins generally are designated according to the Chemical Abstracts system as 5- acylamino-2,2-dimethylpenam-3-carboxylic

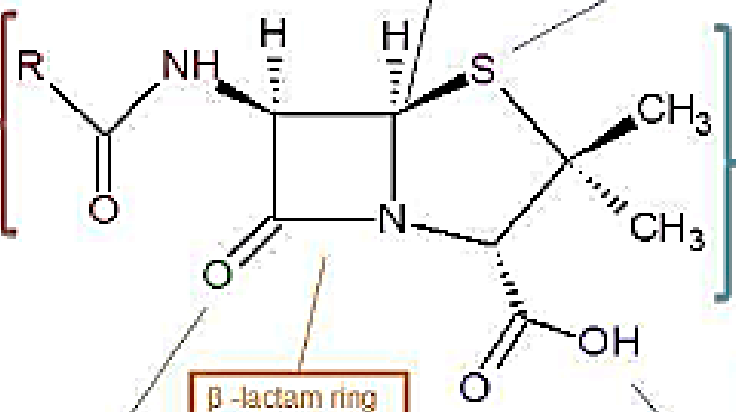
Uses the name “penicillanic acid” to describe the ring system with substituents that are generally present (i.e., 2,2-dimethyl and 3-carboxyl).

Stereochemistry

- The penicillin molecule contains three chiral carbon atoms (C-3, C-5, and C-6). All naturally occurring and microbiologically active synthetic and semisynthetic penicillins have the same absolute configuration about these three centers.
- 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. Thus, the acylamino and carboxyl groups 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 (6-APA) portion of the structure are derived biosynthetically from two amino acids, L-cysteine and L-valin. The absolute stereochemistry of the penicillins is designated 3S:5R:6R

STRUCTURE ACTIVITY RELATIONSHIP OF PENICILLIN



Cis-stereochemistry -essential

No substitution allowed

Sulphur is usual but not essential

Acylamino side chain
Electron withdrawing group render amide oxygen less nucleophilic.
Bulky group provides steric hindrance to β-lactamase.
Incorporation of polar group makes it more hydrophilic.

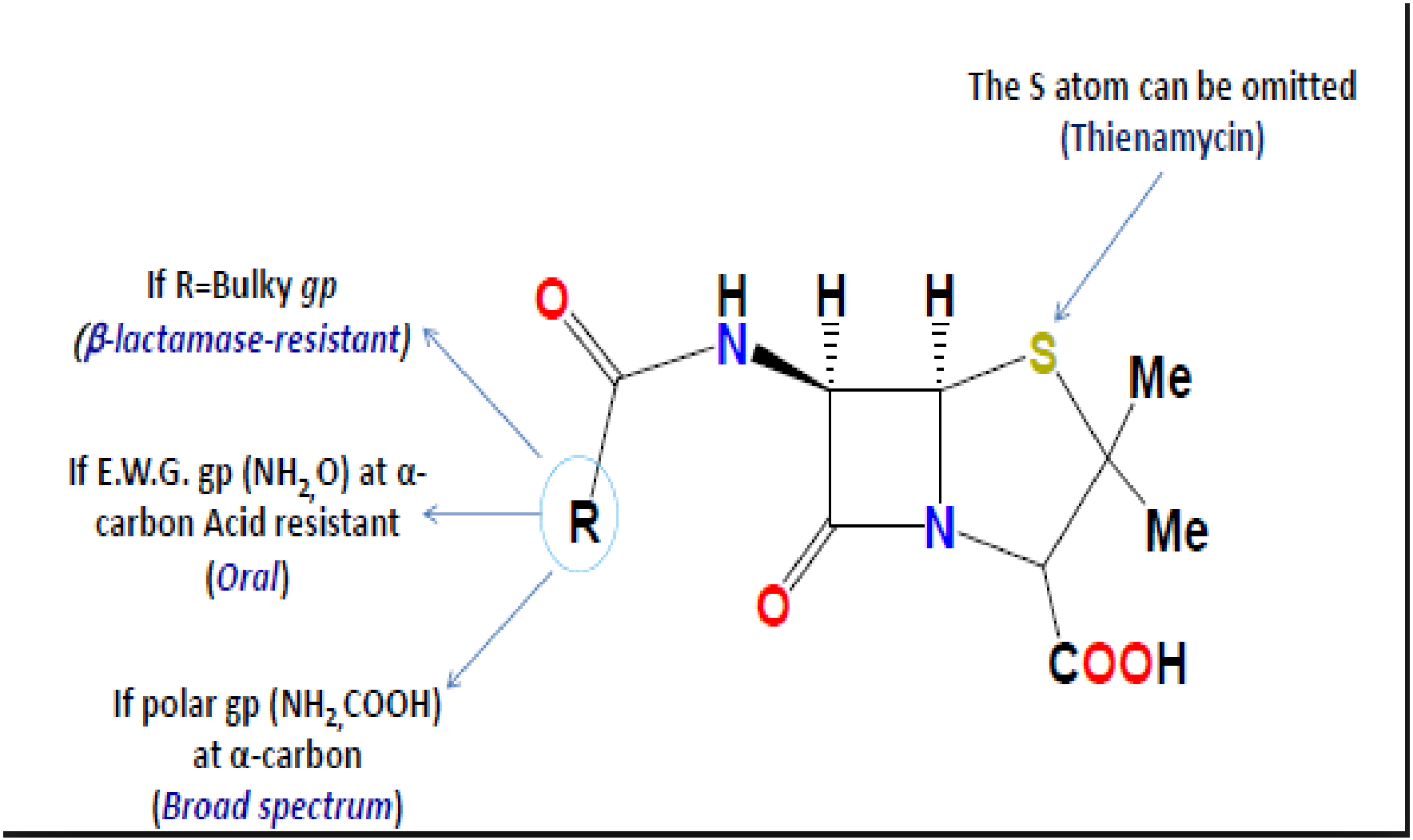
Thiazolidine ring
-5-membered nitrogen saturated ring

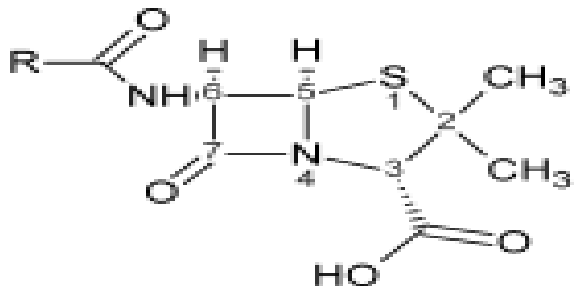
β -lactam ring
-strained

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

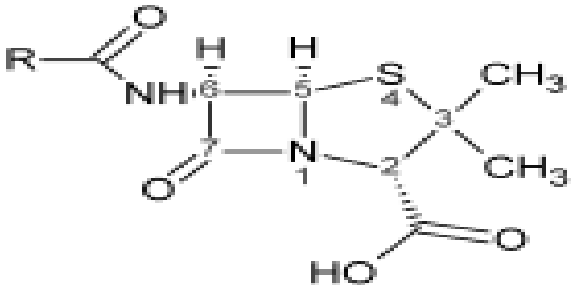
Bicyclic system
-confers further strain on β -lactam ring.
-the greater the strain, the greater the activity, the greater the instability of the molecule to other factors.

Carboxylic acid
-Usually ionized and administered as sodium/potassium salt
-Carboxylate ions bind to charged nitrogen of a lysine residue in the binding site.
-Activity reduces when modified to alcohol/ ester.

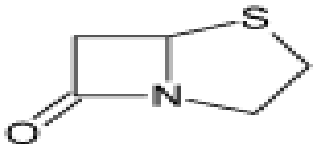

The S atom can be omitted
(Thienamycin)
If R=Bulky gp
(β-lactamase-resistant)
If E.W.G. gp (NH2,O) at α-carbon Acid resistant
(Oral)
If polar gp (NH2,COOH) at α-carbon
(Broad spectrum)
O
H
H
H
N
S
Me
Me
R
N
O
COOH



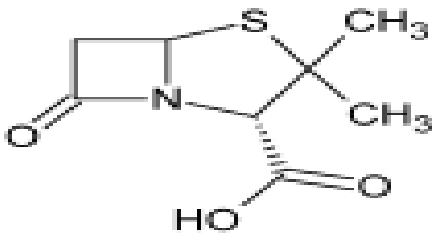
Chemical Abstracts



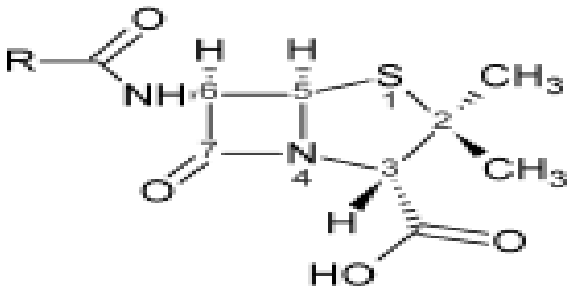
USP



Penam



Penicillanic Acid



Chemical Abstracts

Modification of β-Lactams

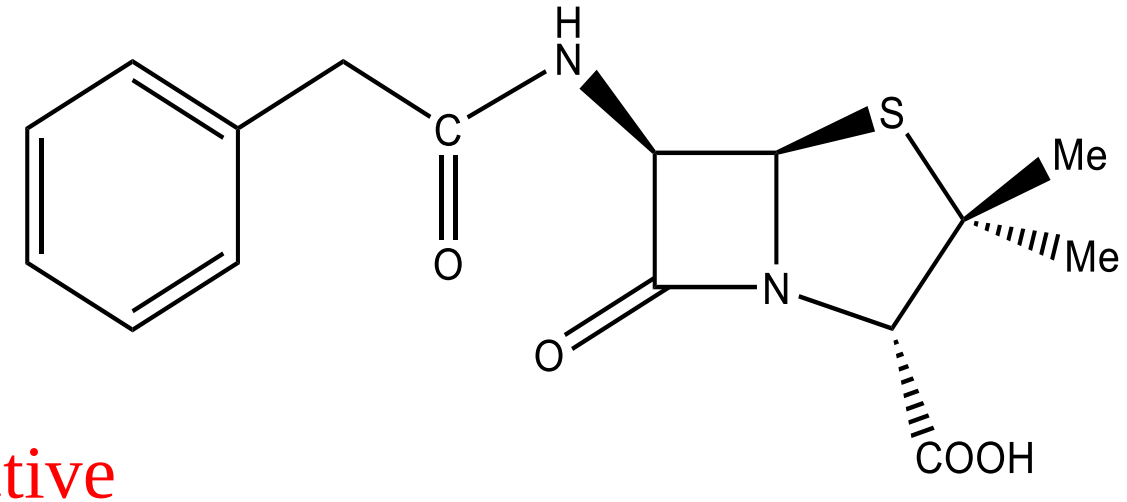
β-Lactam type antibiotics can be modified at various positions to improve their ability to:

-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)

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.

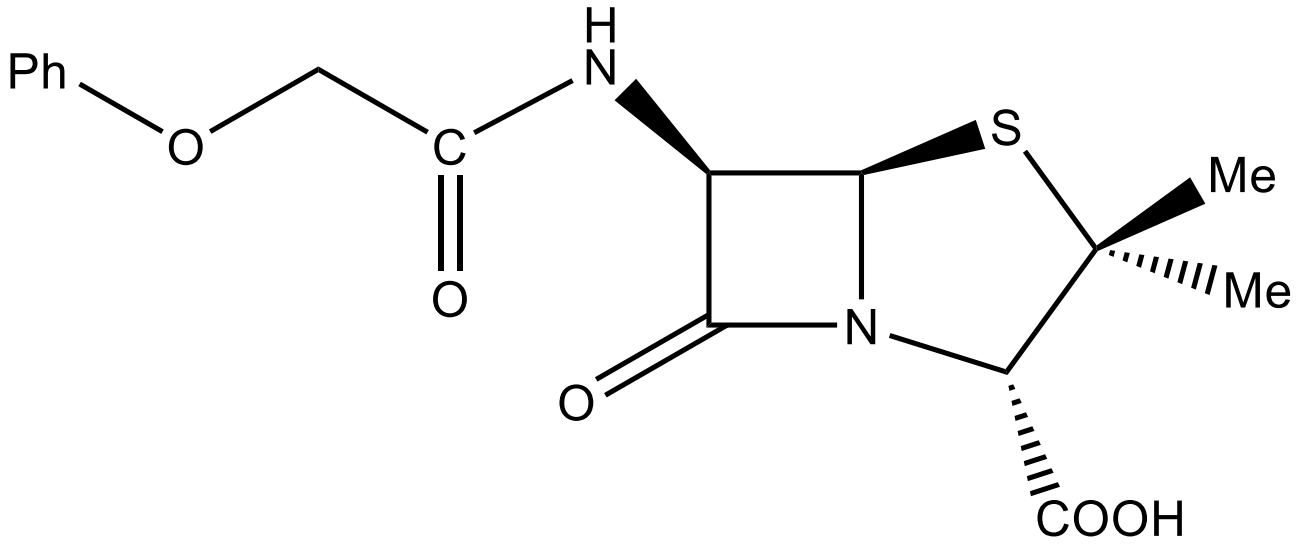
Penicillin G



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.

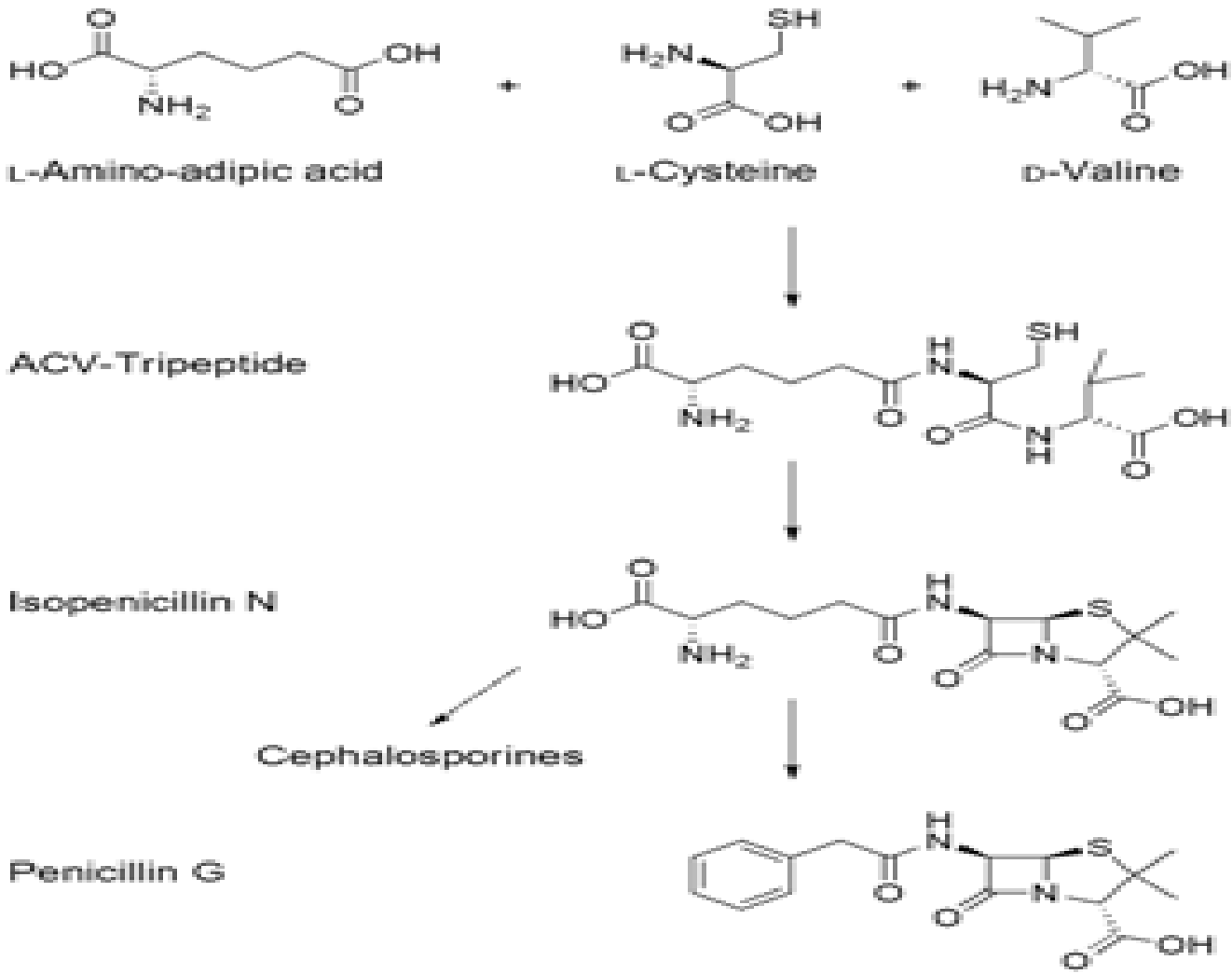


Production

All commercially available β-lactams are initially produced through the fermentation of bacteria.

Bacteria assemble the penicillin molecule from L-AAA, L-valine, and L-cysteine in three steps using ACV synthase, IPN synthase, and acyl transferase.

Penicillin Biosynthetic Pathway



Chemical Degradation

1. The solubility and other physicochemical properties of the penicillins are affected by the nature of the acyl side chain and by the cations used to make salts of the acid. Most penicillins are acids with pKa values in the range of 2.5 to 3.0, but some are amphoteric.
2. The free acids are not suitable for oral or parenteral administration. The sodium and potassium salts of most penicillins, however, are soluble in water and readily absorbed orally or parenterally.

3. β-lactam carbonyl group of penicillin readily undergoes nucleophilic attack by water or (especially) hydroxide ion to form the inactive penicilloic acid, which is reasonably stable in neutral to alkaline solutions but readily undergoes decarboxylation and further hydrolytic reactions in acidic solutions.

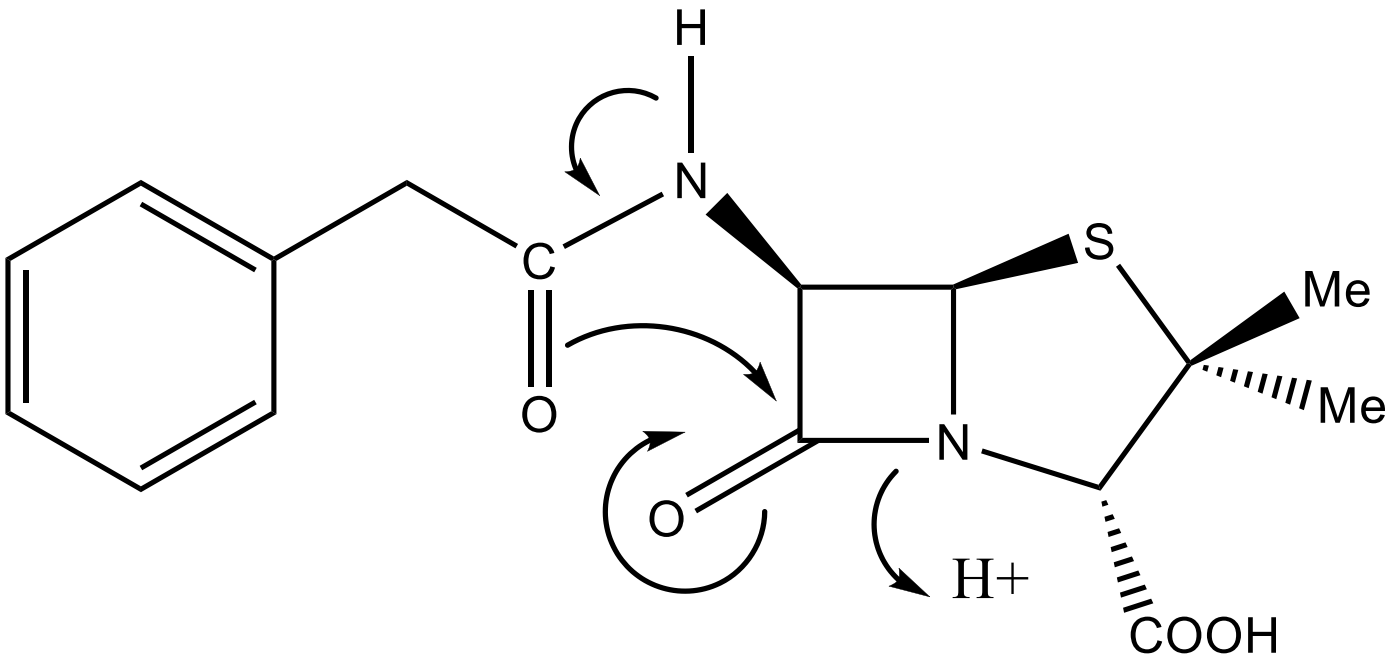
4. Other nucleophiles, such as hydroxylamines, alkylamines, and alcohols, open the β-lactam ring to form the corresponding hydroxamic acids, amides, and esters. It has been speculated that one of the causes of penicillin allergy may be the formation of antigenic penicilloyl proteins in vivo by the reaction of

nucleophilic groups (e.g., Ɛ-amino) on specific body proteins with the β-lactam carbonyl group.

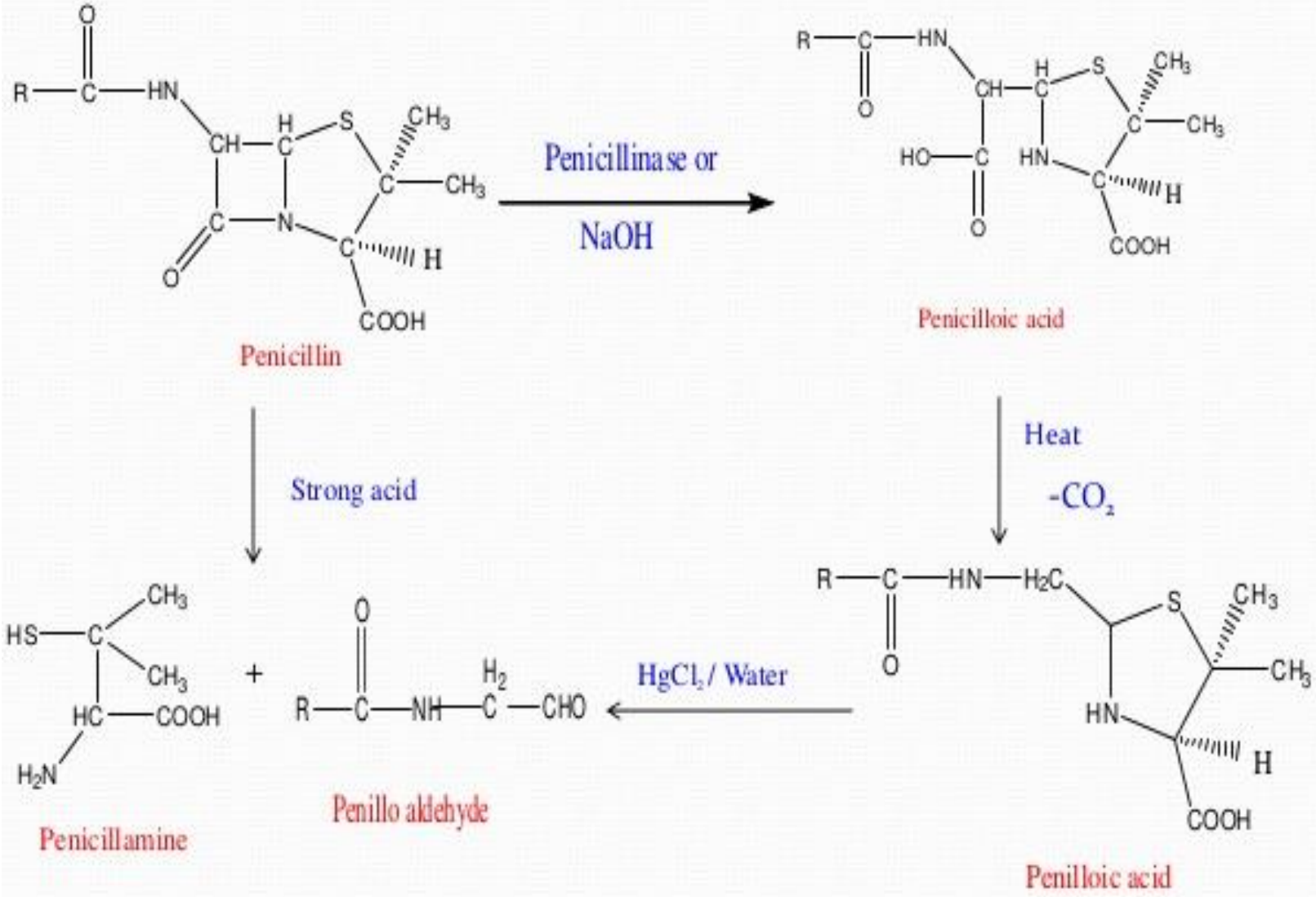
5. In strongly acidic solutions (pH 3), penicillin undergoes a complex series of reactions leading to various inactive degradation products .The first step appears to involve rearrangement to the penicillanic acid. This process is initiated by protonation of the β-lactam nitrogen, followed by nucleophilic attack of the acyl oxygen atom on the β-lactam carbonyl carbon. The subsequent opening of the β -lactam ring destabilizes the thiazoline ring, which then also suffers acid-catalyzed ring opening to form the penicillanic acid.

Penicillin G in acidic conditions

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



Chemical degradation:



Acid-catalyzed degradation

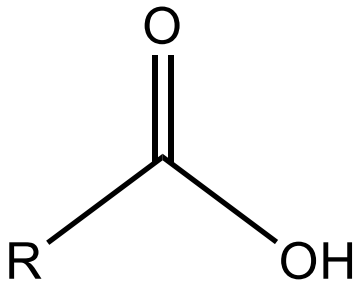
In the stomach contributes strongly to the poor oral absorption of penicillin. Thus, efforts to obtain penicillins with improved pharmacokinetic and microbiological properties have focused on acyl functionalities that would minimize sensitivity of the β-lactam ring to acid hydrolysis while maintaining antibacterial activity.

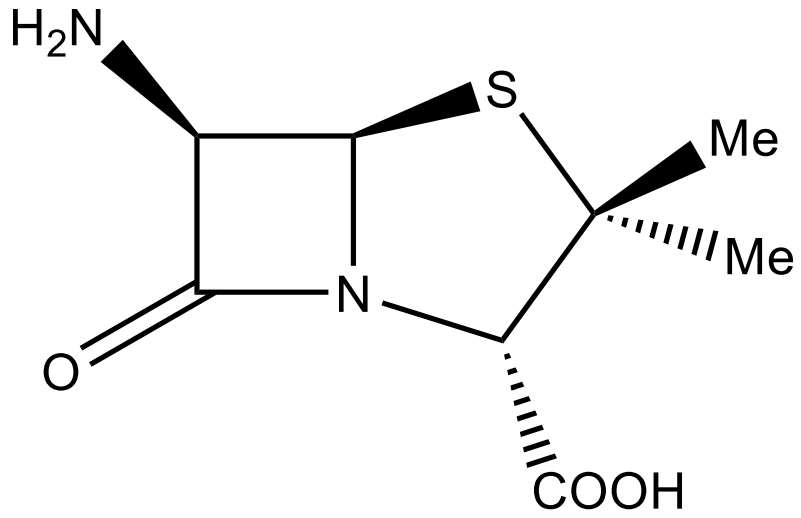
Substitution of an electron-withdrawing group in the α-position of benzylpenicillin markedly stabilizes the penicillin to acid-catalyzed hydrolysis.

Semi-Synthetic Penicillins

The acyl side chain of the penicillin molecule can be cleaved using enzyme or chemical methods to produce 6-APA, which can further be used to produce semi-synthetic penicillins or cephalosporins

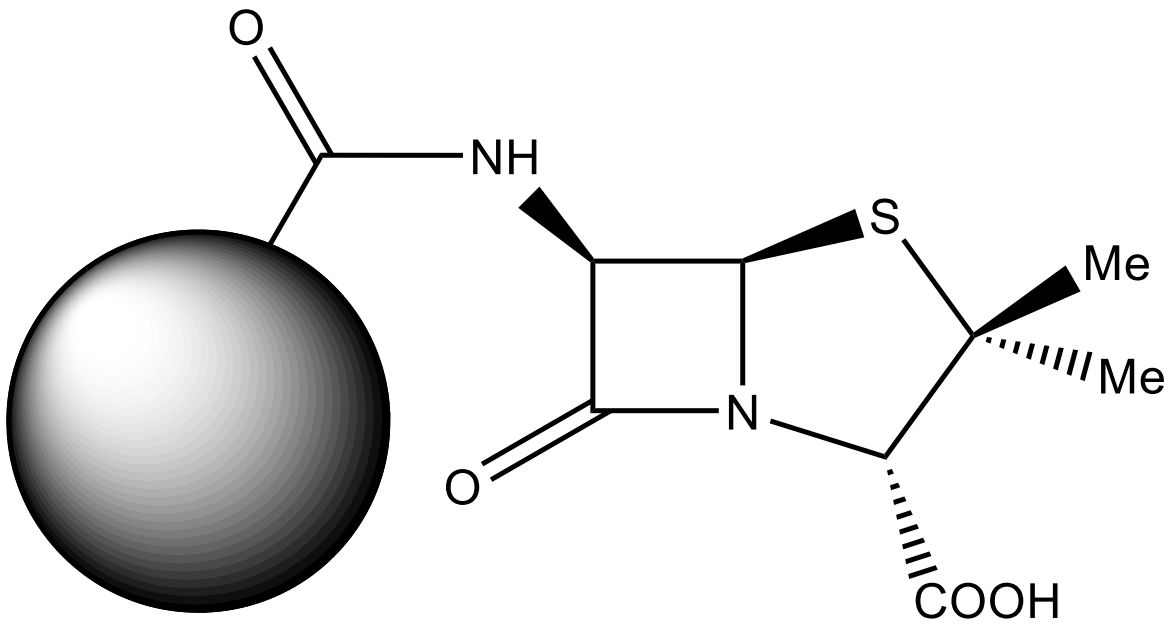
75% of the penicillin produced is modified in this manner





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.

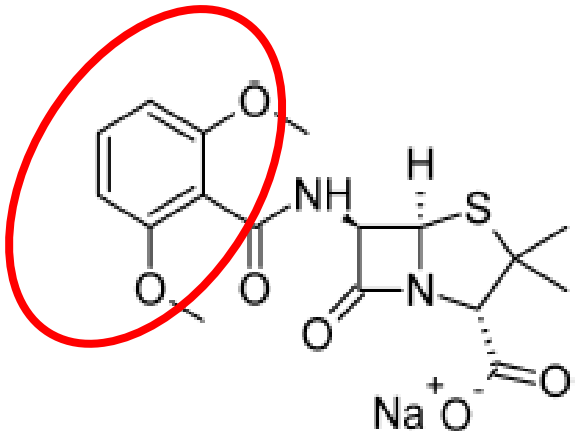
Methicillin is acid sensitive and has been improved upon by adding electron withdrawing groups, as was done in penicillin V, resulting in drugs such as oxacillin and nafcillin.

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.

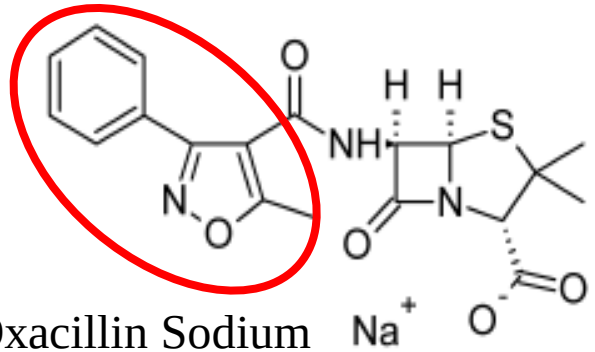
It is also relatively resistant to acid hydrolysis and, therefore, may be administered orally with good effect.

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.

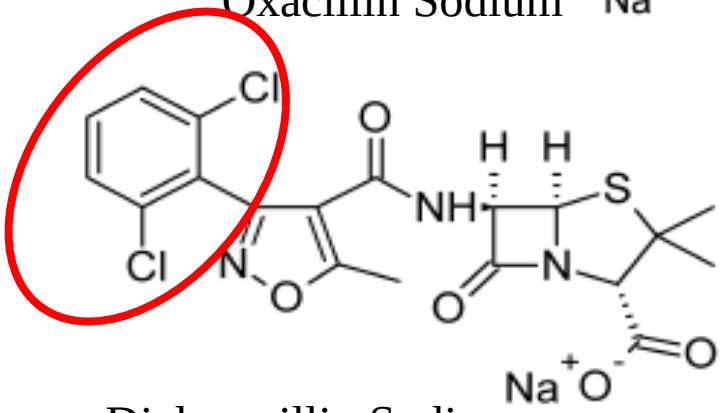
Nafcillin sodium, 6-(2-ethoxy-1-naphthyl)penicillin sodium (Unipen), is another semisynthetic penicillin that resulted from the search for penicillinase-resistant compounds. Like methicillin, nafcillin has substituents in positions ortho to the point of attachment of the aromatic ring to the carboxamide group of penicillin. No doubt, the ethoxy group and the second ring of the naphthalene group play steric roles in stabilizing nafcillin against penicillinase



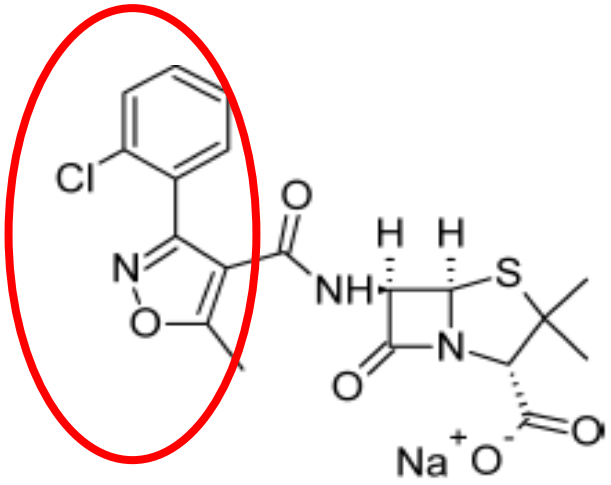
Methicillin Sodium



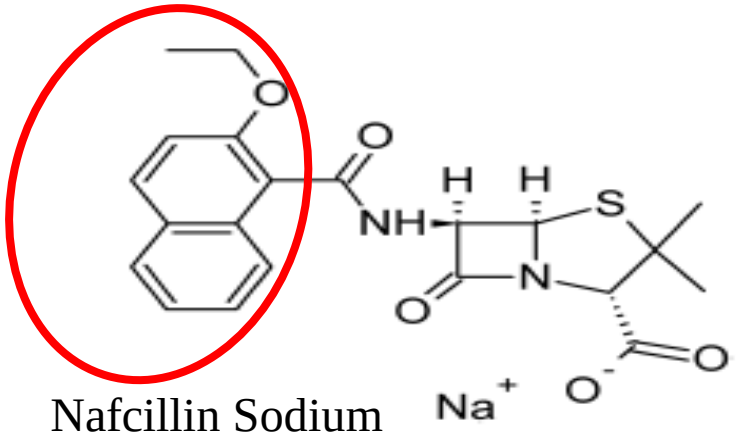
Oxacillin Sodium



Dicloxacillin Sodium



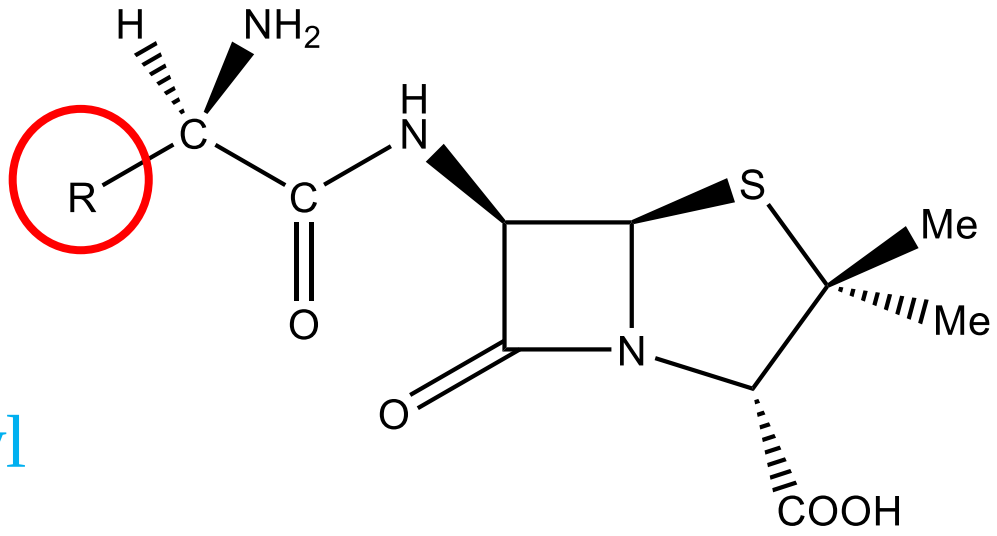
Cloxacillin sodium



Nafcillin Sodium

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

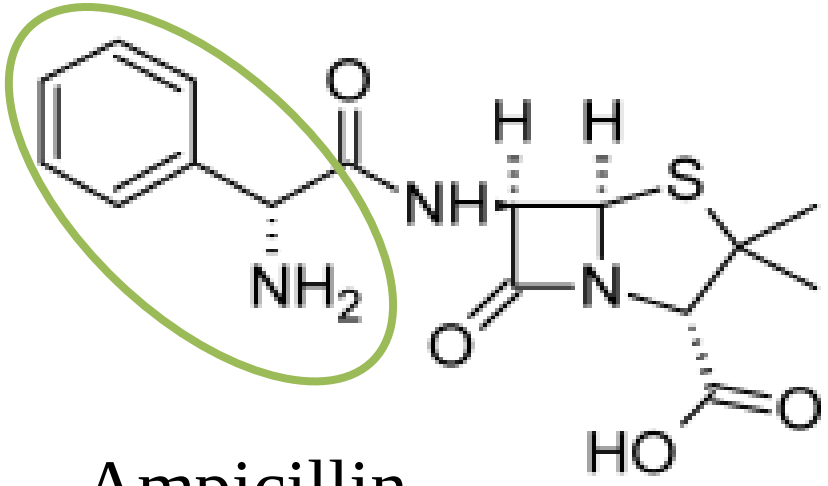
6-[D-α-aminophenylacetamido]penicillanic acid, D-α-aminobenzylpenicillin an antibacterial spectrum broader than that of penicillin G. Obviously, the α-amino group plays an important role in the broader activity, but the mechanism for its action is unknown. It has been suggested that the amino group confers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

D-(-)-Ampicillin, prepared from D-(-)-α-amino phenylacetic acid, is significantly more active than L-(+)-ampicillin.

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

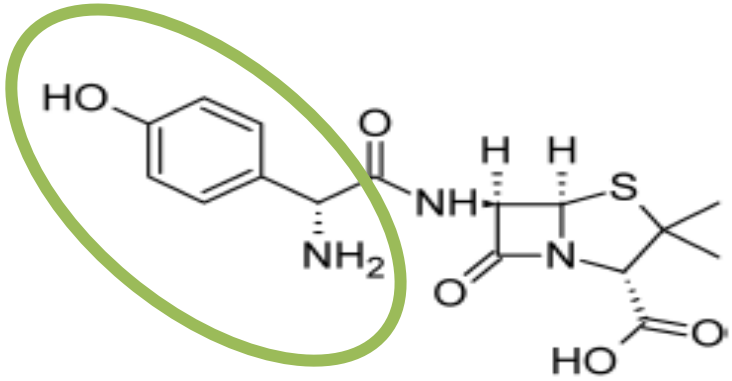
Ampicillin is water soluble and stable in acid.

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, susceptible to alkaline and β-lactamase hydrolysis, and weakly protein bound. Early clinical reports indicated that orally administered amoxicillin possesses significant advantages over ampicillin, including more complete GI absorption

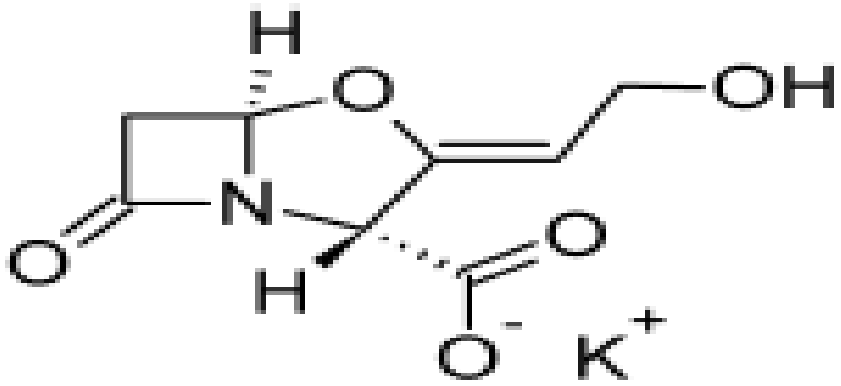
B-lactamase inhibitors

The discovery of the naturally occurring, mechanism based inhibitor Clavulanic acid, which causes potent and progressive inactivation of β-lactamases. 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.

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.

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.



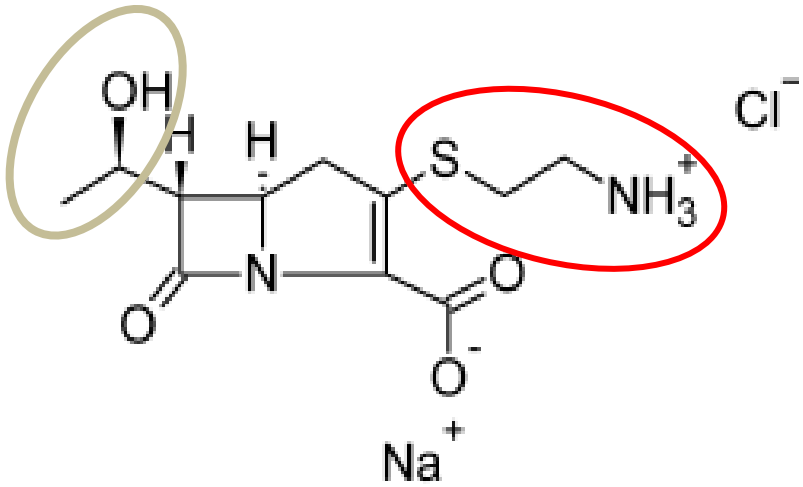
potassium salt of Clavulanic acid

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 (C_1) and an unsaturation is present between C_2 and C_3 in the five-membered ring.

Thienamycin



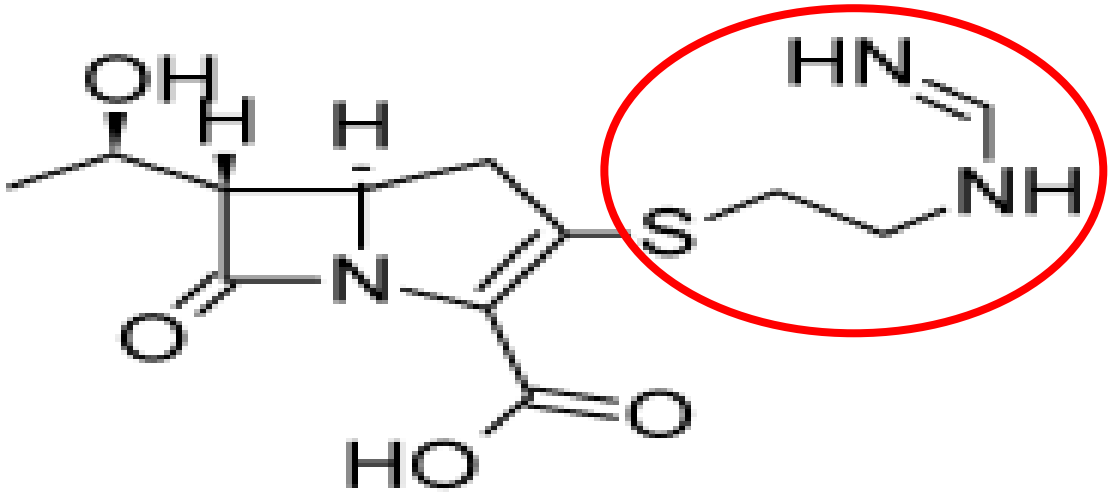
Thienamycin is a novel β-lactam antibiotic first isolated and identified by researchers from fermentation of cultures of Streptomyces cattleya.

It is resistant to inactivation by most β-lactamases elaborated by Gram-negative and Gram positive bacteria and, therefore, is effective against many strains resistant to penicillins and cephalosporins. Due to its highly unstable nature this drug and its derivatives are created through synthesis, not bacterial fermentation.

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.
- The absolute stereochemistry of Thienamycin has been determined to be 5R:6S:8S.
- 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 1b and 2.

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

Newer Carbapenems

structure–activity studies established the critical importance of:

1. The Δ^2position of the double bond
2. The 3-carboxyl group
3. The 6-α-hydroxy ethyl side chain for both broad spectrum antibacterial activity and β-lactamase stability in Carbapenems. Modifications, therefore, have concentrated on variations at positions 1 and 2 of the carbapenem nucleus.

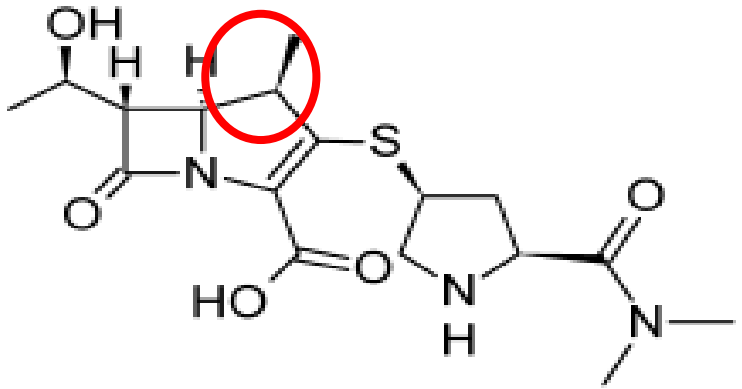
The incorporation of a α-methyl group at the1position gives the carbapenem stability to hydrolysis by renal DHP-I (de hydro peptidase inhibitor).

Substituents at the 2-position, however, appear to affect primarily the spectrum of antibacterial activity of the Carbapenem by influencing penetration into bacteria.

The capability of Carbapenems to exist as zwitterionic structures resulting from the combined features of a basic amine function attached to the 2-position and the 3-carboxyl group, may enable these molecules to enter bacteria via their charged porin channels.

Newer Carbapenems

Meropenem



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.

Cephalosporins

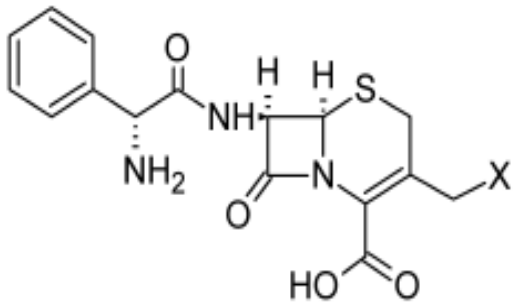
Cephalosporins were discovered shortly after penicillin entered into widespread product, but not developed till the 1960's.

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

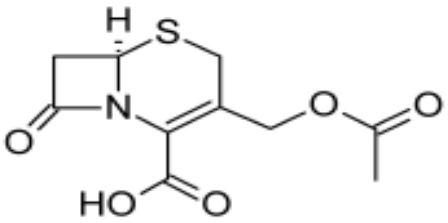
7-aminocephalosporanic acid (7-ACA) can be obtained from bacteria, but it is easier to expand the ring system of 7-APA because it is so widely produced.

Cephalosporins

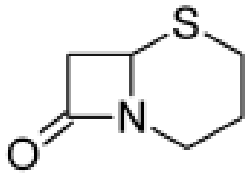
Unlike penicillin, cephalosporins have two side chains which can be easily modified. Cephalosporins are also more difficult for β-lactamases to hydrolyze.



Cephalosporin



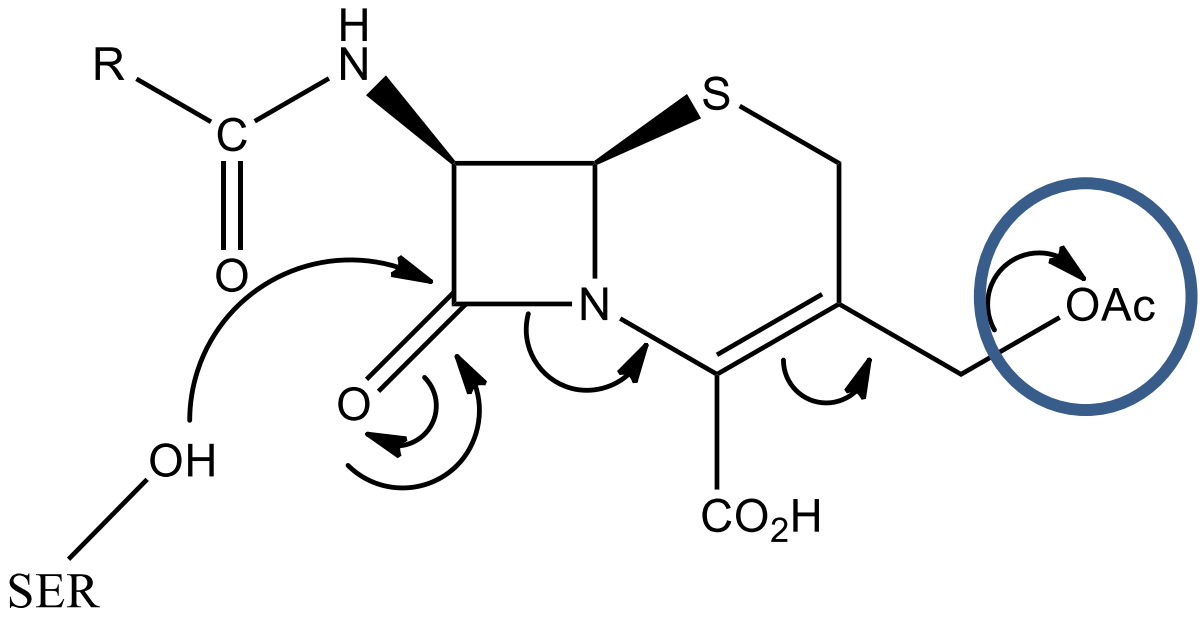
Cephalosporanic Acid



Cepham

Mechanism of Cephalosporins

The acetoxy group (or other R group) will leave when the drug acylates the PBP.



Semisynthetic Derivatives

To date, the more useful semisynthetic modifications of the basic 7-ACA nucleus have resulted from acylations of the 7- amino group with different acids or nucleophilic substitution or reduction of the acetoxyl group.

Structure–activity relationships

The presence of an allylic acetoxyl function in the 3-position, however, provides a reactive site at which various 7-acylaminocephalosporanic acid structures can easily be varied by nucleophilic displacement reactions.

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

(a) increased acid stability

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

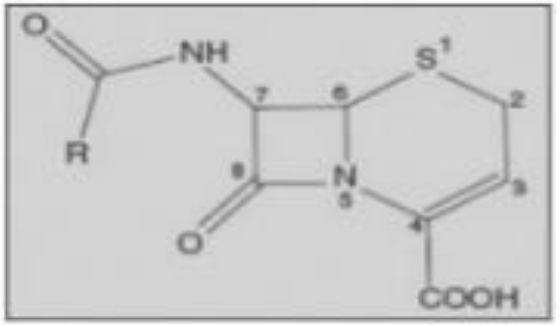
(c) broadened antimicrobial spectrum

(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.

SAR of cephalosporins



1. 7-Acylamino substituents:

a) Acylation of amino group generally increases the potency against gram-positive bacteria, but it is accompanied by a decrease in gram-negative potency.

b) High antibacterial activity is observed only when the new acyl groups are derived from carboxylic acids for gram-positive bacteria.

c) Substituents on the aromatic ring that increases 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, and these include thiophene, tetrazole, furan, pyridine, and aminothiazoles

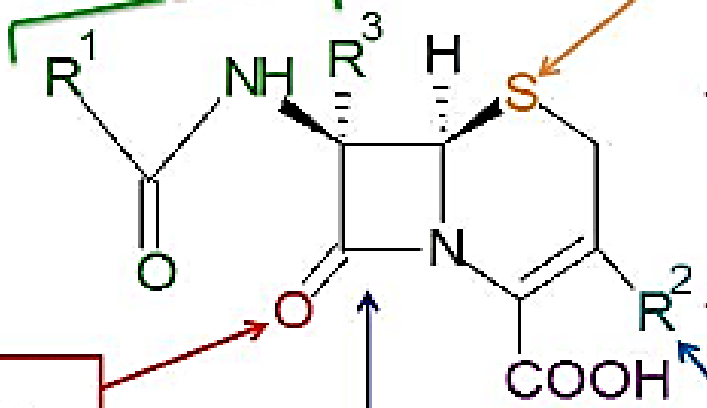
2. C-3 substituents: The nature of C-3 substituents influences pharmacokinetic and pharmacological properties as well as antibacterial activity. Modification at C-3 position has been made to reduce the degradation (lactone of desacetyl cephalosporin) of cephalosporins.

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

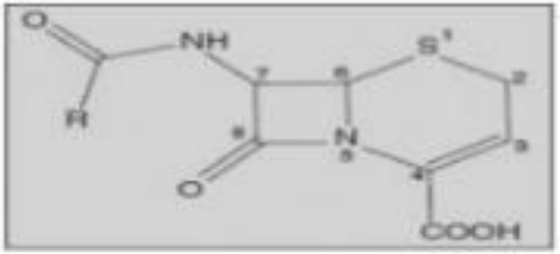
Carbonyl group
- Lone pair electron located on nitrogen atom not fed to carbonyl group to form a stabilized resonance structure, thus more electrophilic for nuclephilic attack.

β-lactam ring

Carboxylic acid
Useful during formulation
Prodrug development

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

SAR of cephalosporins



3. Pyridine and imidazole-replaced acetoxy groups show improved activity against *P. aeruginosa*. Displacement of acetoxy group by azide ion yields derivatives with relatively low gram-negative activity.
4. Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.
5. Replacement of acetoxy group at C-3 position with $-CH_2Cl$ has resulted in orally active compounds.
6. Oxidation of ring sulphur to sulphoxide or sulphone greatly diminishes or destroys the antibacterial activity.
7. Replacement of sulphur with oxygen leads to oxacepam (latamoxef) with increased antibacterial activity, because of its enhanced acylating power.
8. Similarly, replacement of sulphur with methylene group (loracarbef) has greater chemical stability and a longer half-life.
9. The carboxyl group of position-4 has been converted into ester prodrugs to increase bioavailability of cephalosporins, and these can be given orally as well. Examples include cefuroxime axetil and cefodoxime proxetil
10. Olefinic linkage at C 3-4 is essential for antibacterial activity. Isomerization of the double bond to 2-3 position leads to great losses in antibacterial activity.

β-Lactamase Resistance

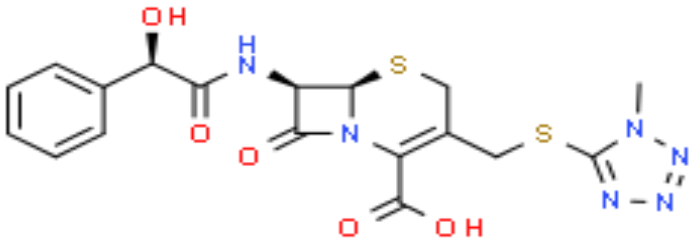
- The susceptibility of cephalosporins to various lactamases varies considerably with the source and properties of these enzymes.
- Cephalosporins are significantly less sensitive than all the β-lactamase–resistant penicillins to hydrolysis by the enzymes from S. aureus and Bacillus subtilis.
- The“penicillinase” 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 and cefazolin are the least resistant.

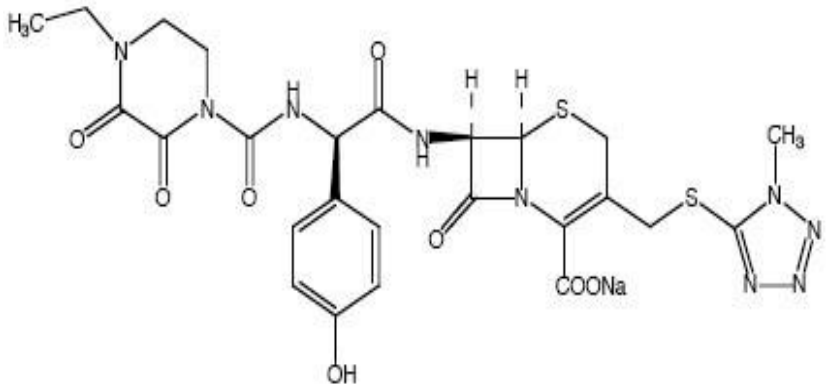
- The introduction of polar substituents in the aminoacyl moiety of cephalosporins appears to confer stability to some β-lactamases.

Cefamandole which contain an hydroxy phenyl acetyl (or mandoyl) group and Ceforanide, which has an o-amino phenyl acetyl group, are resistant to a few β-lactamases.

- Steric factors also may be important because Cefoperazone, an acylureido cephalosporin that contains the same 4-ethyl-2,3-dioxo-1 piperazinyl carbonyl group present in piperacillin, is resistant to many β- lactamases.

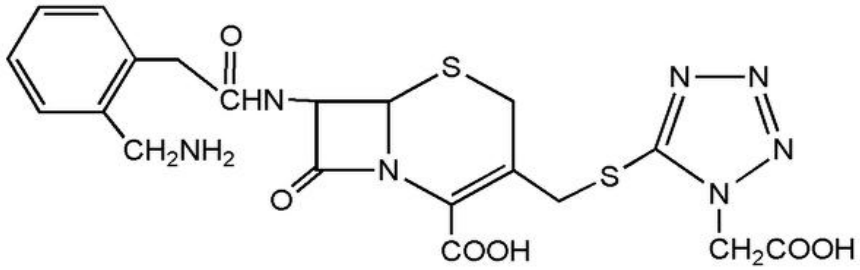
- Cefamandole





- Cefoperazone

- Ceforanide



Oddly enough, piperacillin is hydrolyzed by most of these enzymes.β-lactamases

Two structural features confer broadly based resistance to β-lactamases among the cephalosporins:

(a) an alkoximino function in the aminoacyl group and

(b) a methoxyl substituent at the 7-position of the cephem nucleus having stereochemistry.

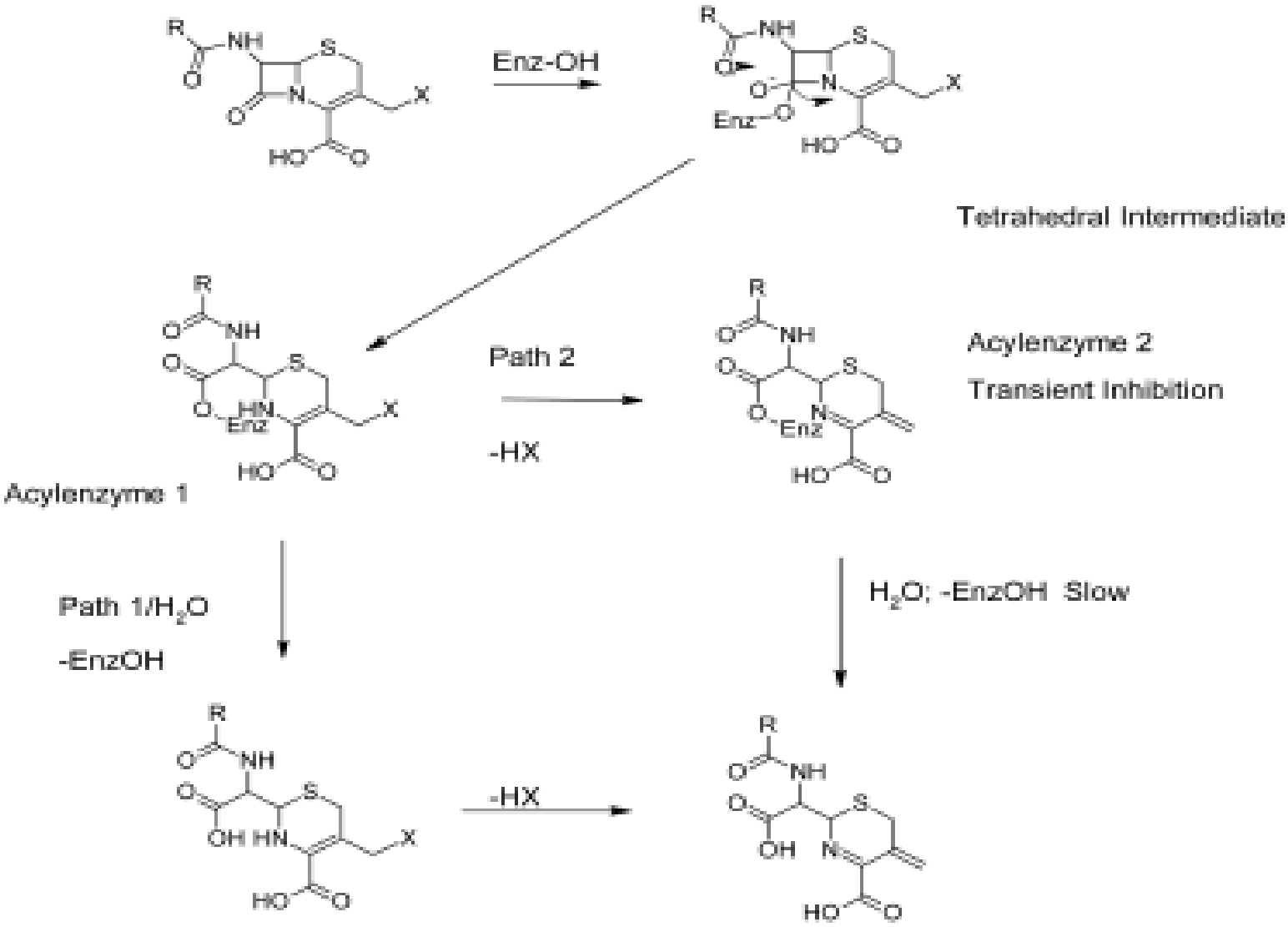


Figure 8.6 • Inhibition of β-lactamases by cephalosporins.

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)

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).

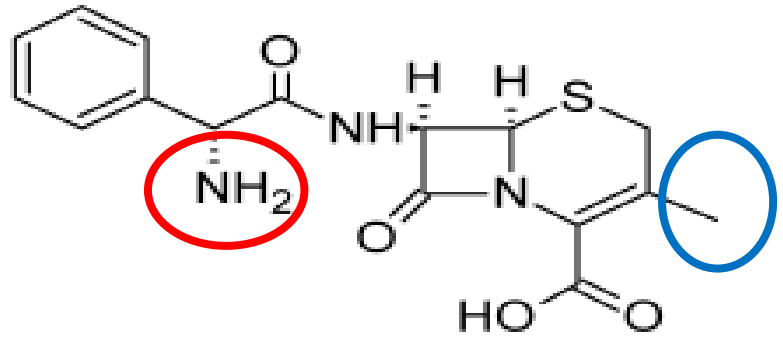
Parenteral cephalosporins lacking a hydrolyzable group at the 3-position are not subject to hydrolysis by esterases. Cephradine is the only cephalosporin that is used both orally and parenterally.

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. Individual cephalosporins differ in their pharmacokinetic properties, especially plasma protein binding and half-life, but the structural bases for these differences are not obvious.

Pro



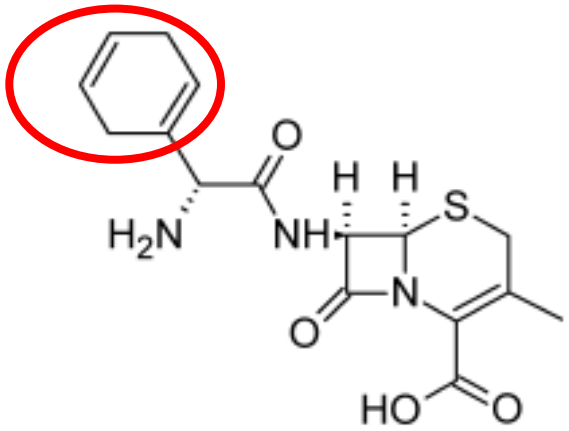
❖ First Generation

Cephalexin

Cephalexin,7α-(D-amino-α-phenylacetamido)-3-methylcephemcarboxylic acid (Keflex, Keforal), was designed purposely as an orally active, semisynthetic cephalosporin.

The α-amino group of cephalexin renders it acid stable, and reduction of the 3-acetoxymethyl to a methyl group circumvents reaction at that site. It is freely soluble in water, resistant to acid, and absorbed well orally. Food does not interfere with its absorption.

Cephradine



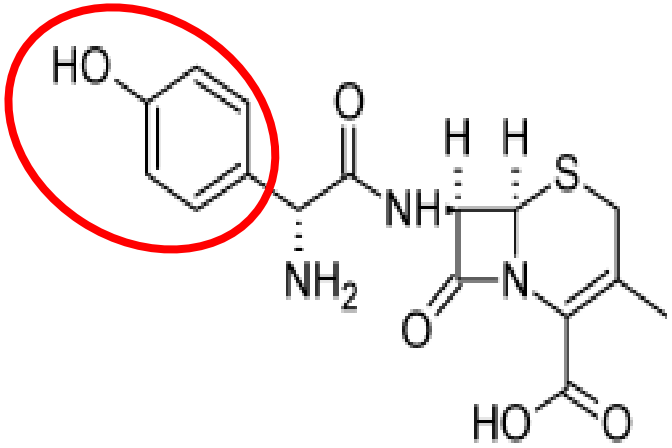
Cephradine (Anspor, Velosef)

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.

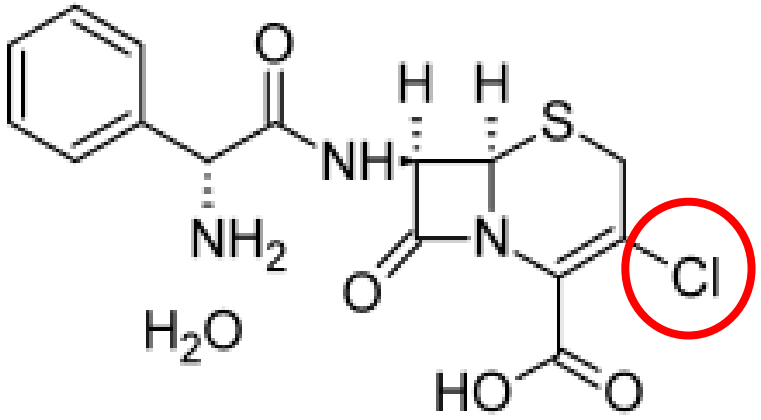
Cephradine is stable to acid and absorbed almost completely after oral administration

Cefadroxil



Cefadroxil (Duricef) is an orally active semisynthetic D-hydroxyl phenylglycyl 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,

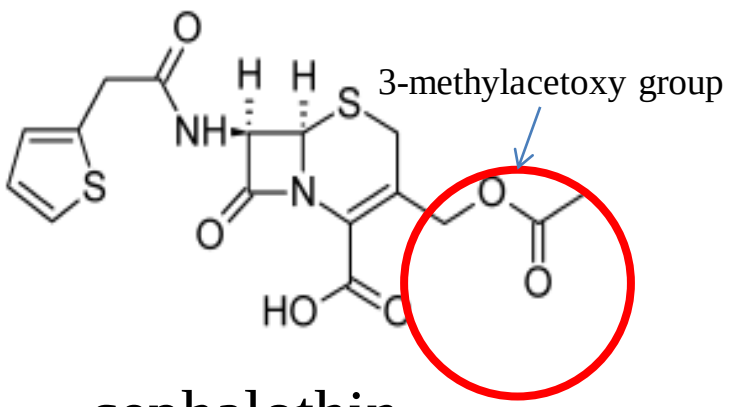
Cefaclor



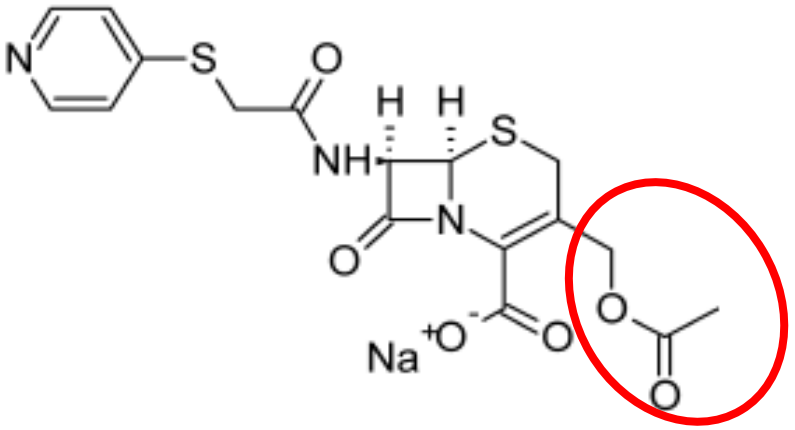
Cefaclor (Ceclor) is an orally active semisynthetic Cephalosporin.

It differs structurally from cephalexin in that the 3-methyl group has been replaced by a chlorine atom. Cefaclor is moderately stable in acid and achieves enough oral absorption to provide effective plasma levels (equal to about two-thirds of those obtained with cephalexin).

Parenterally products



cephalothin

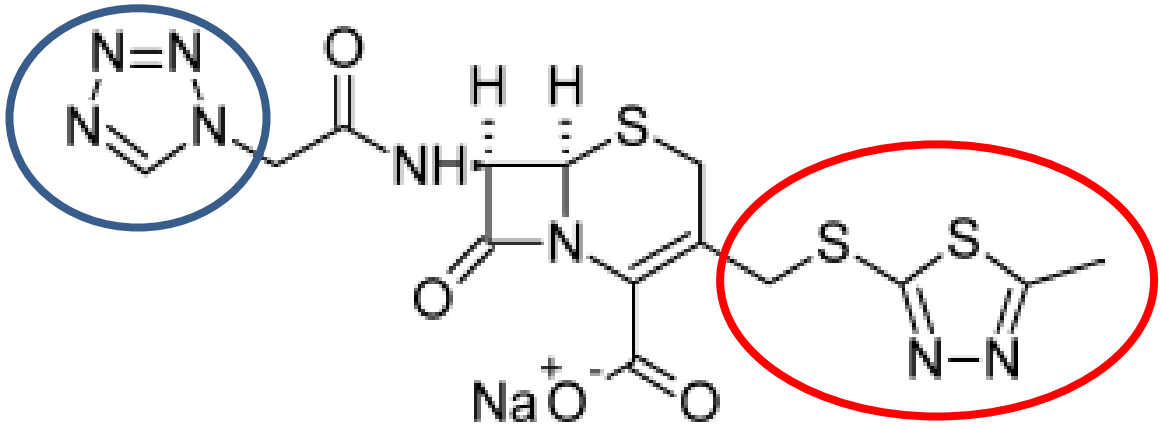


The oral inactivation of cephalosporins has been attributed to two causes: instability of the β-lactam ring to acid hydrolysis (cephalothin and cephaloridine) and solvolysis or microbial transformation of the 3-methylacetoxy group (cephalothin, cephaloglycin).

Its spectrum of activity is broader than that of penicillin G and more similar to that of ampicillin. Unlike ampicillin, 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.

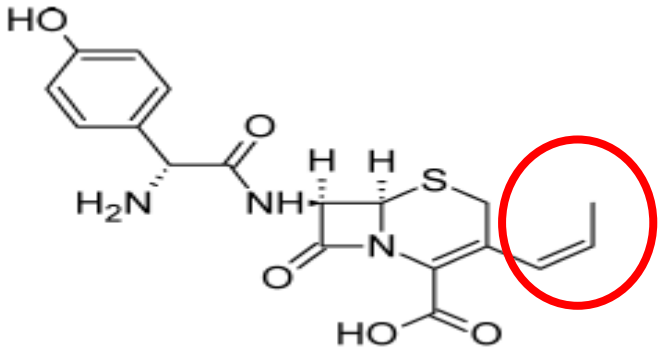
Cefazolin Sodium, Sterile

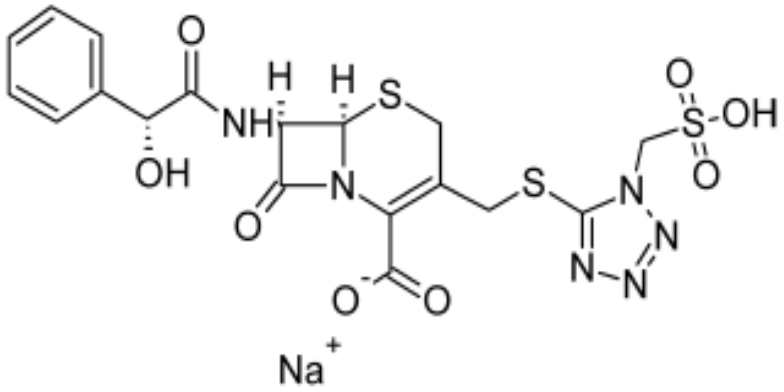


Cefazolin (Ancef, Kefzol)

is one of a series of semisynthetic cephalosporins in which the C-3 acetoxy function has been replaced by a thiol-containing heterocycle—here, 5-methyl-2-thio-1,3,4-thiadiazole. It also contains the somewhat unusual tetrazolylacetyl acylating group. It is active only by parenteral administration

Second-generation



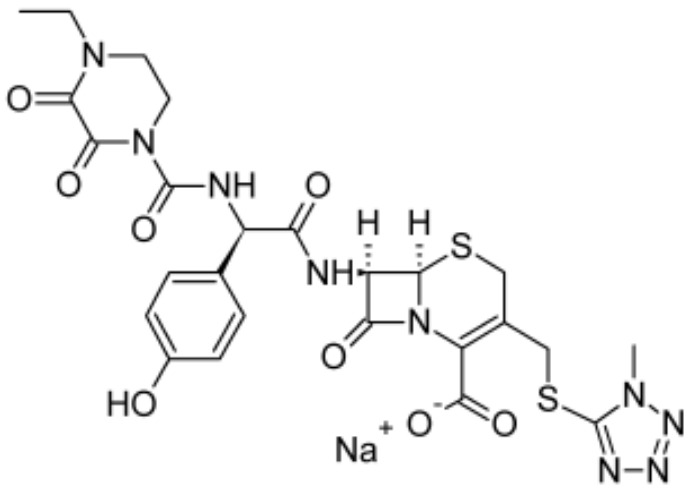


Cefprozil Cefonicid Sodium

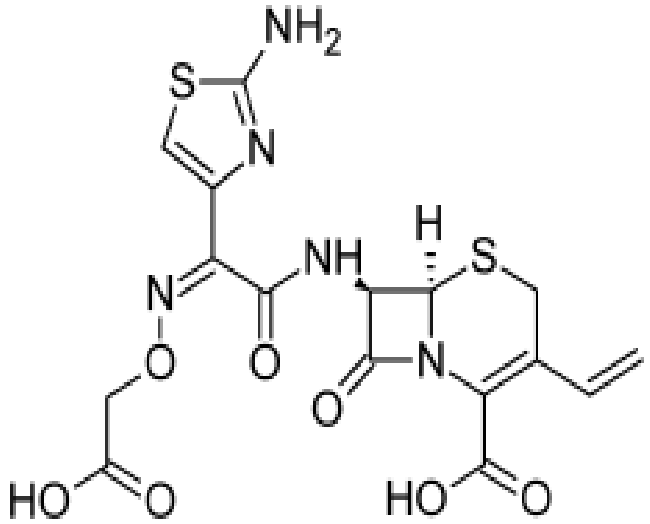
Cefprozil (Cefzil) is an orally active second-generation cephalosporin that is similar in structure and antibacterial spectrum to cefadroxil.

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

Third-generation



Cefoperazone

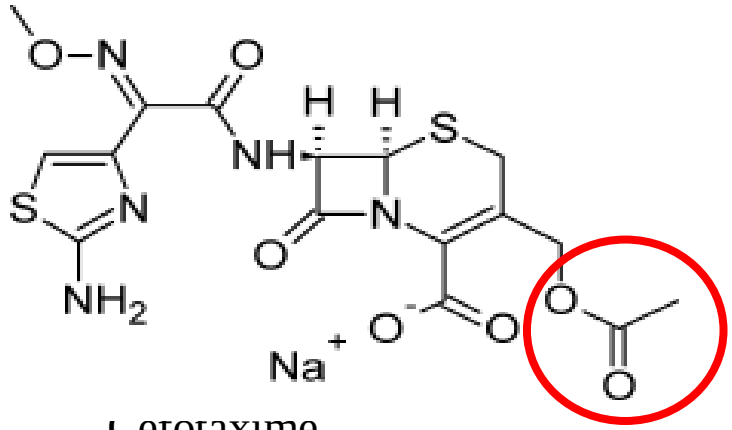


Cefixime

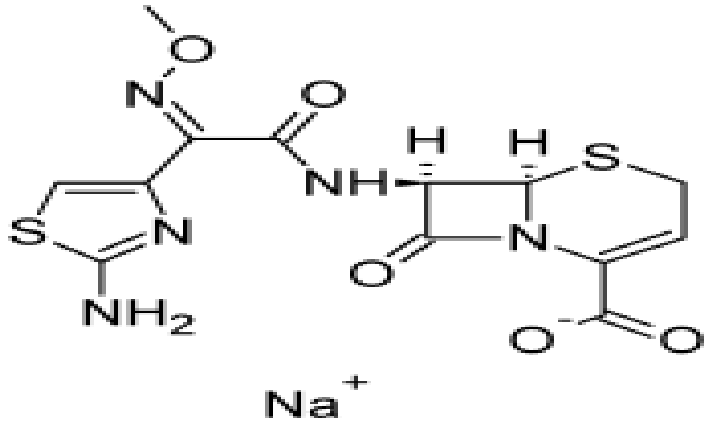
Cefoperazone (Cefobid) is a third-generation anti pseudomonal cephalosporin that resembles piperacillin chemically and microbiologically.

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.

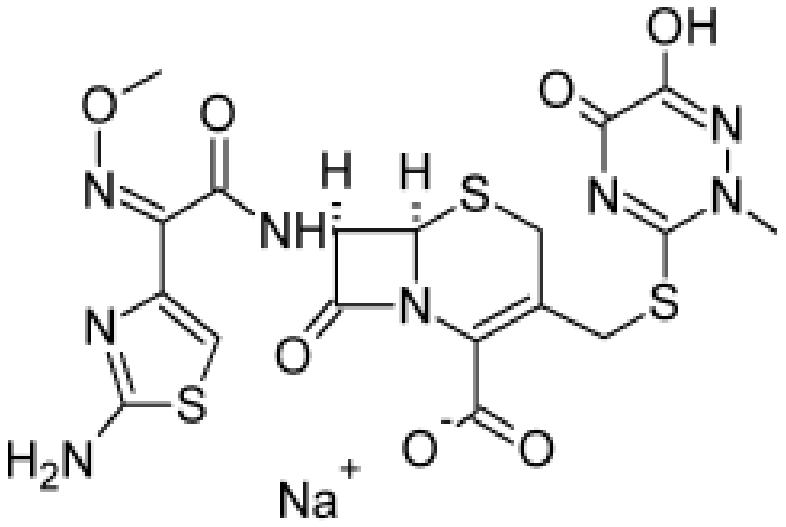
Ceftizoxime (Cefizox) is a third-generation cephalosporin that was introduced in 1984. It must be administered on a thrice-daily dosing schedule because of its relatively short half-life.

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



Ceftriaxone contains a highly acidic heterocyclic system on the 3-thiomethyl group. This unusual dioxotriazine ring system is believed to confer the unique pharmacokinetic properties of this agent.

Ceftriaxone exhibits excellent broad-spectrum antibacterial

activity against both Gram-positive and Gram-negative

organisms. It is highly resistant to most chromosomally and

plasmid-mediated -lactamases. The presence of the iminomethoxy group appears to increase stability against certain lactamases