Antibacterial Antibiotics

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

1. It is a product of metabolism.

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.

In addition to the ability to combat infections or neoplastic disease, an antibiotic must possess other attributes.

First, it must exhibit sufficient selective toxicity to be effective against pathogenic microorganisms or neoplastic tissue.

Second, an antibiotic should be chemically stable enough.

Third, the rates of biotransformation and elimination of the antibiotic should be slow enough.

COMMERCIAL PRODUCTION

The general scheme may be divided into six steps:

(a) preparation of a pure culture

(b) Fermentation

(c) isolation of the antibiotic

(d) purification; ***(e)*** assays ***(f)*** formulation.

TABLE 8.1 **Mechanisms of Antibiotic Action**

Site of Action	Antibiotic	Process Interrupted	Type of Activity
Cell wall	Bacitracin	Mucopeptide synthesis	Bactericidal
	Cephalosporin	Cell wall cross-linking	Bactericidal
	Cycloserine	Synthesis of cell wall peptides	Bactericidal
	Penicillins	Cell wall cross-linking	Bactericidal
	Vancomycin	Mucopeptide synthesis	Bactericidal
Cell membrane	Amphotericin B	Membrane function	Fungicidal
	Nystatin	Membrane function	Fungicidal
	Polymyxins	Membrane integrity	Bactericidal
Ribosomes	Chloramphenicol	Protein synthesis	Bacteriostatic
50S subunit	Erythromycin	Protein synthesis	Bacteriostatic
	Lincomycins	Protein synthesis	Bacteriostatic
30S subunit	Aminoglycosides	Protein synthesis and fidelity	Bactericidal
	Tetracyclines	Protein synthesis	Bacteriostatic
Nucleic acids	Actinomycin	DNA and mRNA synthesis	Pancidal
	Griseofulvin	Cell division, microtubule assembly	Fungistatic
DNA and/or RNA	Mitomycin C	DNA synthesis	Pancidal
	Rifampin	mRNA synthesis	Bactericidal

CHEMICAL CLASSIFICATION

β-LACTAM ANTIBIOTICS

Antibiotics that possess the β-lactam (a four-membered cyclic amide). The first antibiotic to be used in therapy, and a close biosynthetic relative, phenoxy- methyl penicillin.

Mechanism of Action

The uniquely lethal antibacterial action of these agents has been attributed to a selective inhibition of bacterial cell wall synthesis. Specifically, 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-transpeptidase. Bacterial D-alanine carboxypeptidases are also inhibited by β-lactam antibiotics.

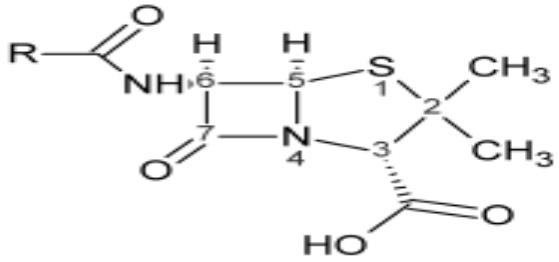
Studies in *E. coli* have revealed as many as seven different functional proteins, each with an important role in cell wall.

- PBPs 1_a and 1_b
- PBP 2
- PBP 3
- PBPs 4 through 6

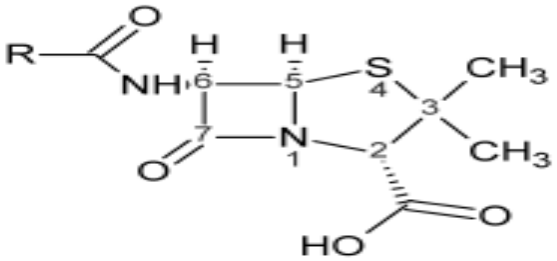
The various β-lactam antibiotics differ in their affinities for PBPs. Penicillin G binds preferentially to PBP 3, whereas the first-generation cephalosporins bind with higher affinity to PBP 1_a. In contrast to other penicillins and to cephalosporins, which can bind to PBPs 1, 2, and 3, amdinocillin binds only to PBP 2.

Nomenclature

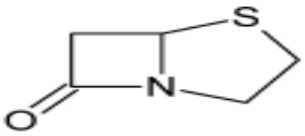
Two numbering systems for the fused bicyclic heterocyclic system exist. The *Chemical Abstracts* system and the *USP* system.



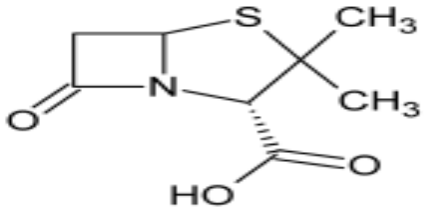
Chemical Abstracts



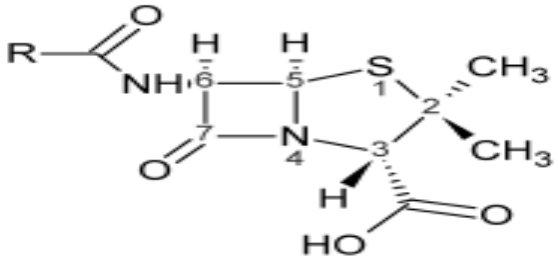
USP

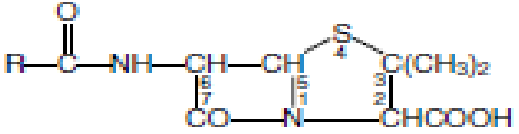


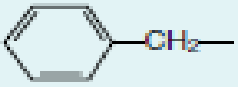
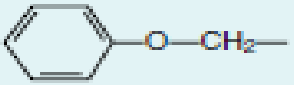
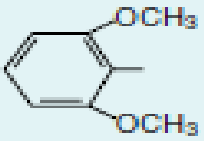
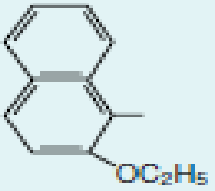
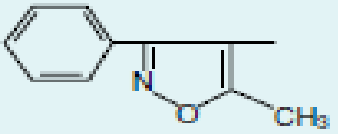
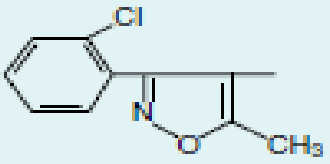
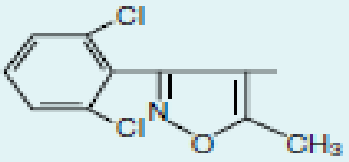
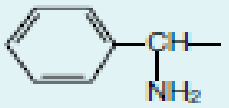
Penam

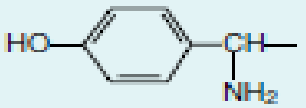
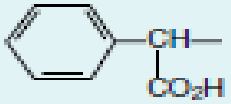
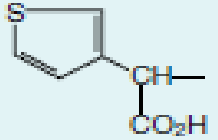
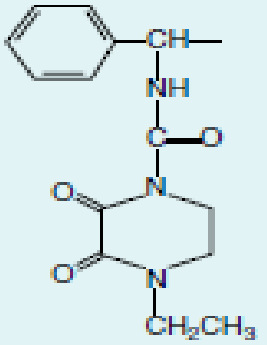
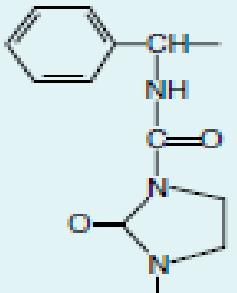


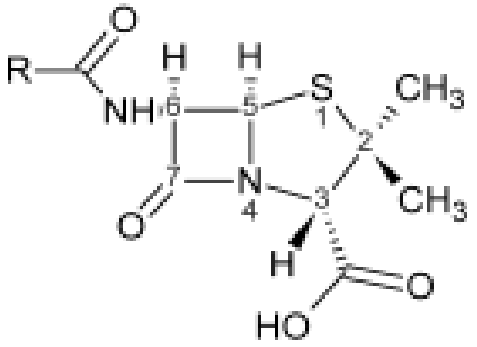
Penicillanic Acid





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	
Cloxacillin	5-Methyl-3-(2-chlorophenyl)-4-isoxazolylpenicillin	
Dicloxacillin	5-Methyl-3-(2,6-dichlorophenyl)-4-isoxazolylpenicillin	
Ampicillin	D-α-Aminobenzyl-penicillin	

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	
Mezlocillin	α-(1-Methanesulfonyl-2-oxoimidazolidino-carbonylamino)benzyl-penicillin	



Stereochemistry

The penicillin molecule contains three chiral carbon atoms (C-3, C-5, and C-6). The absolute stereochemistry of the penicillins is designated 3S:5R:6R.

Synthesis

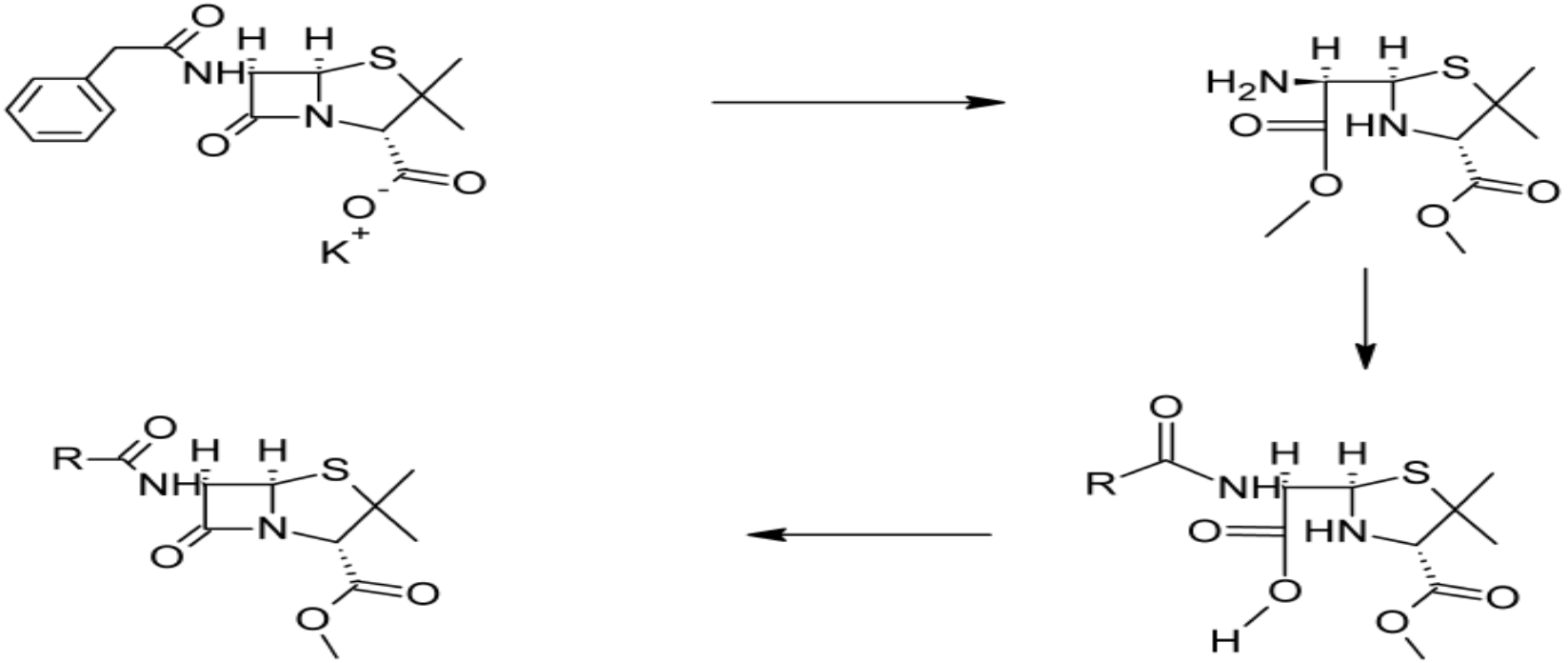


Figure 8.1 • Conversion of natural penicillin to synthetic penicillin.

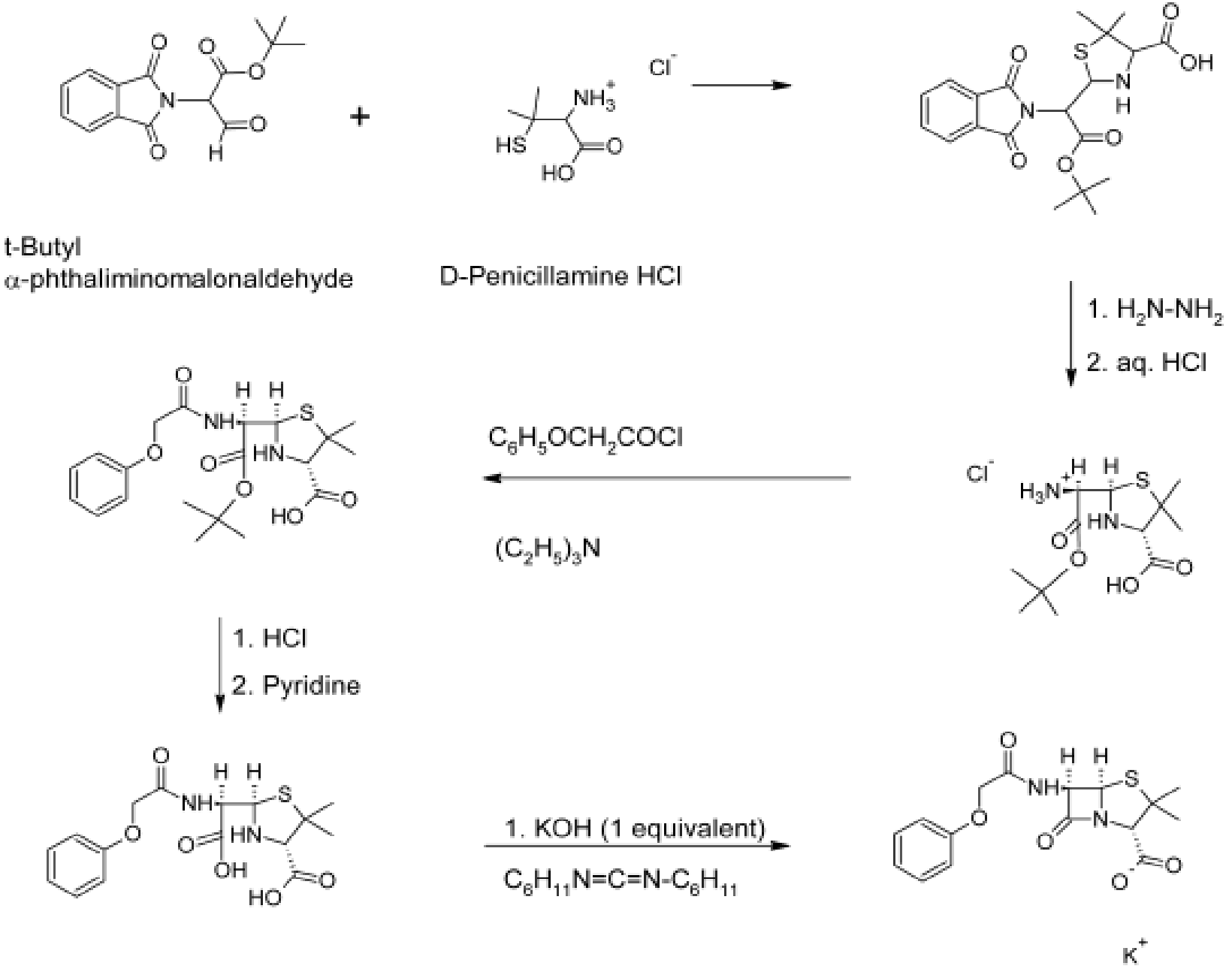


Figure 8.2 • Synthesis of phenoxymethylpenicillin.

Chemical Degradation

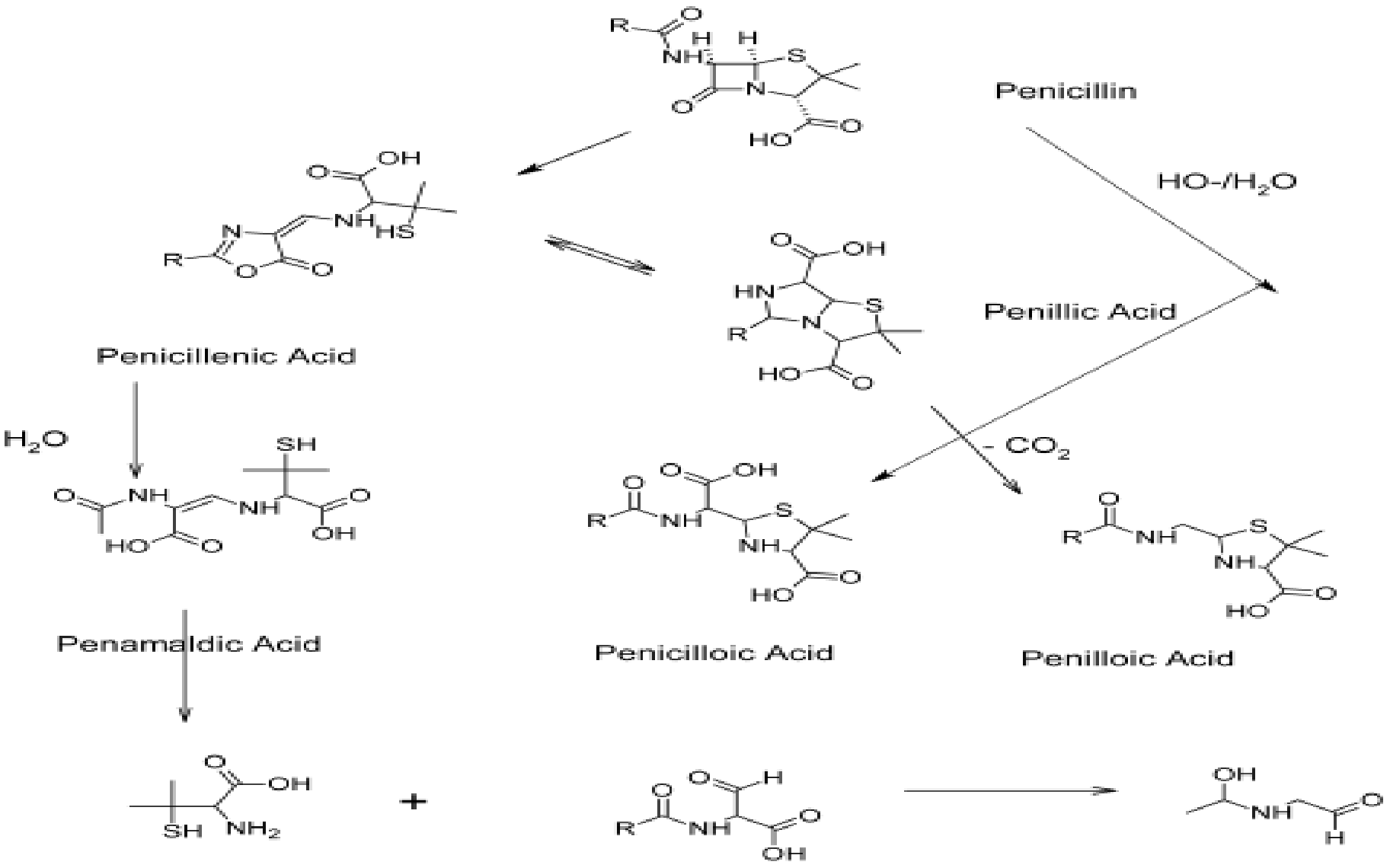


Figure 8.3 ● Degradation of penicillins.

Bacterial Resistance

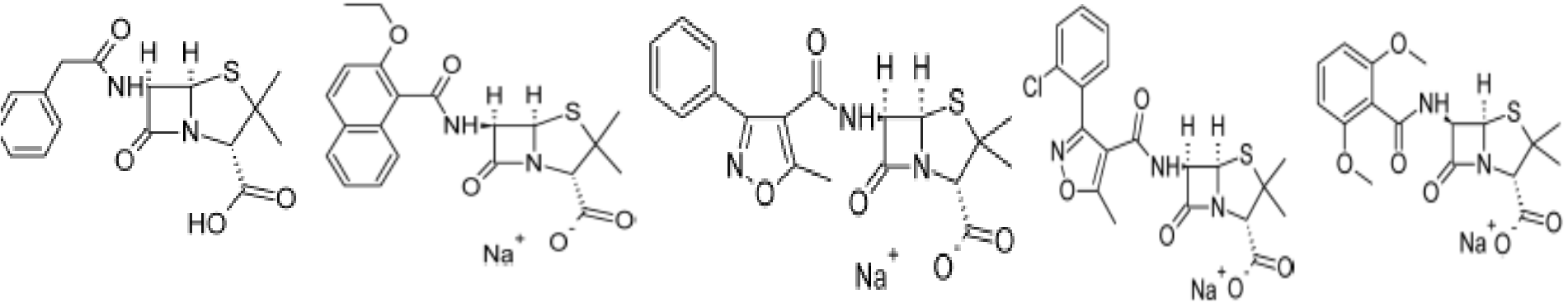
The best understood and, probably, the most important biochemical mechanism of penicillin resistance is the bacterial elaboration of enzymes that inactivate penicillins. Such enzymes, which have been given the nonspecific name *penicillinases*, are of two general types: *β*- lactamases and acylases.

Another important resistance mechanism, especially in Gram-negative bacteria, is decreased permeability to penicillins.

Certain strains of bacteria are resistant to the lytic properties of penicillins but remain susceptible to their growth inhibiting effects. This mechanism of resistance is termed *tolerance* and apparently results from impaired autolysin activity in the bacterium.

Penicillinase-Resistant Penicillins

In general, increasing the steric hindrance at the α-carbon of the acyl group increased resistance to staphylococcal β-lactamase, with maximal resistance being observed with quaternary substitution. More fruitful from the standpoint of antibacterial potency, however, was the observation that the α-acyl carbon could be part of an aromatic (e.g., phenyl or naphthyl) or heteroaromatic (e.g., 4-isoxazoyl) system. Substitutions at the *ortho* positions of a phenyl ring (e.g., 2,6-dimethoxy [methicillin]) or the 2-position of a 1-naphthyl system (e.g., 2-ethoxyl [nafcillin]) increase the steric hindrance of the acyl group and confer more β- lactamase resistance than shown by the unsubstituted compounds or those substituted at positions more distant from the α-carbon.



Extended-Spectrum Penicillins

Introduction of an ionized or polar group into the α-position of the side chain benzyl carbon atom of penicillin G confers activity against Gram-negative bacilli.
The basis for the expanded spectrum of activity associated with the ampicillin group is not related to β-lactamase inhibition.

Incorporation of an acidic substituent at the α-benzyl carbon atom of penicillin G also imparts clinical effectiveness against Gram-negative bacilli and, furthermore, extends the spectrum of activity to include organisms resistant to ampicillin.

Carbenicillin is active against both β-lactamase– producing and non–β-lactamase producing strains of Gram negative bacteria. Because it is a derivative of phenylmalonic acid, carbenicillin readily decarboxylates to benzylpenicillin in the presence of acid; therefore, it is not active (as carbenicillin) orally and must be administered parenterally.

A series of α-acylureido–substituted penicillins, exemplified by azlocillin, mezlocillin, and piperacillin, exhibit greater activity against certain Gram-negative bacilli than carbenicillin.

Protein Binding

Penicillins with polar or ionized substituents in the side chain exhibit low-to-intermediate fractions of protein binding.

Allergy to Penicillins

Allergic reactions to various penicillins, ranging in severity from a variety of skin and mucous membrane rashes to drug fever and anaphylaxis

Evidence suggests that penicillins or their rearrangement products formed in vivo (e.g., penicillenic acids) react with lysine ε-amino groups of proteins to form penicilloyl proteins, which are major antigenic determinants.

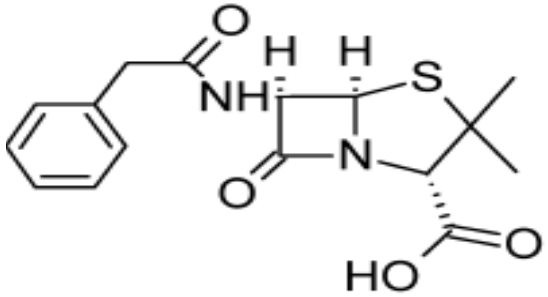
Polymeric impurities in ampicillin dosage forms have been implicated as possible antigenic determinants and a possible explanation for the high frequency of allergic reactions with this particular semisynthetic penicillin.

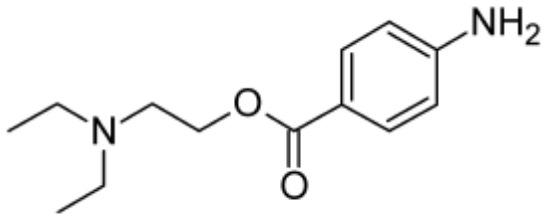
TABLE 8.3 Classification and Properties of Penicillins

Penicillin	Source	Acid Resistance	Oral Absorption (%)	Plasma Protein Binding (%)	β-Lactamase Resistance (*S. aureus*)	Spectrum of Activity	Clinical Use
Benzylpenicillin	Biosynthetic	Poor	Poor (20)	50–60	No	Intermediate	Multipurpose
Penicillin V	Biosynthetic	Good	Good (60)	55–80	No	Intermediate	Multipurpose
Methicillin	Semisynthetic	Poor	None	30–40	Yes	Narrow	Limited use
Nafcillin	Semisynthetic	Fair	Variable	90	Yes	Narrow	Limited use
Oxacillin	Semisynthetic	Good	Fair (30)	85–94	Yes	Narrow	Limited use
Cloxacillin	Semisynthetic	Good	Good (50)	88–96	Yes	Narrow	Limited use
Dicloxacillin	Semisynthetic	Good	Good (50)	95–98	Yes	Narrow	Limited use
Ampicillin	Semisynthetic	Good	Fair (40)	20–25	No	Broad	Multipurpose
Amoxicillin	Semisynthetic	Good	Good (75)	20–25	No	Broad	Multipurpose
Carbenicillin	Semisynthetic	Poor	None	50–60	No	Extended	Limited use
Ticarcillin	Semisynthetic	Poor	None	45	No	Extended	Limited use
Mezlocillin	Semisynthetic	Poor	Nil	50	No	Extended	Limited use
Piperacillin	Semisynthetic	Poor	Nil	50	No	Extended	Limited use

Penicillin G

For years, the most popular penicillin has been penicillin G, or benzylpenicillin. In fact, with the exception of patients allergic to it, penicillin G remains the agent of choice for the treatment of more different kinds of bacterial infection than any other antibiotic.





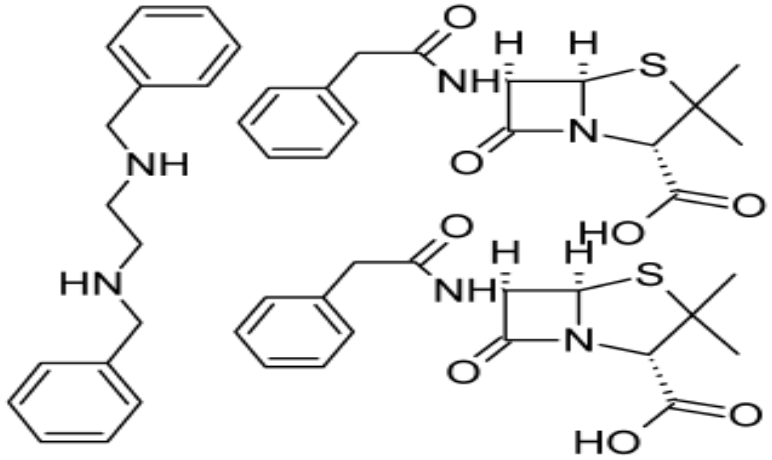
Penicillin G Procaine

The first widely used amine salt of penicillin G was made with procaine

Penicillin G Benzathine

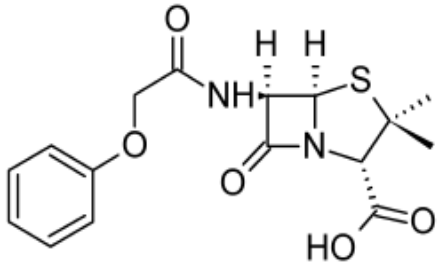
Since penicillin G benzathine, *N,N*¯-dibenzylethylenediamine dipenicillin G ,is the salt of a diamine.

At the pH of gastric juice, it is quite stable, and food intake does not interfere with its absorption. It is available in tablet form and in several parenteral preparations.



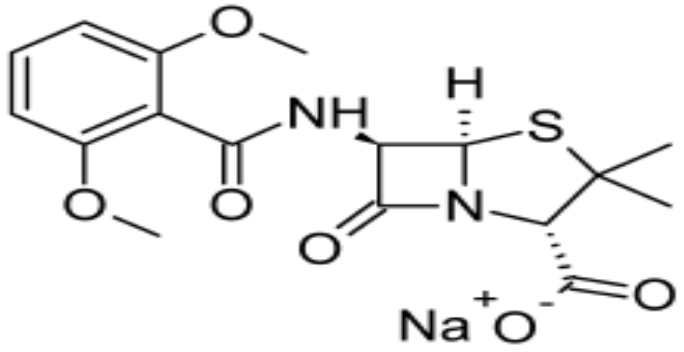
Penicillin V

Phenoxy methylpenicillin as a biosynthetic product. its resistance to hydrolysis by gastric juice For parenteral solutions, the potassium salt is usually used. This salt is very soluble in water. hydrabamineprovides a very long-acting form of this compound.



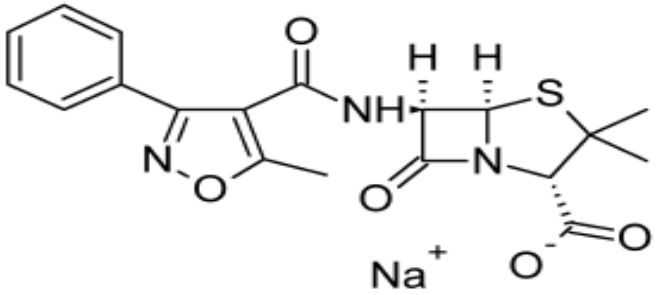
Methicillin Sodium

Reacting 2,6-dimethoxybenzoyl chloride with 6-APA forms 6-(2,6-dimethoxybenzamido) penicillanic acid. 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*. Methicillin and many other penicillinase resistant penicillins induce penicillinase formation



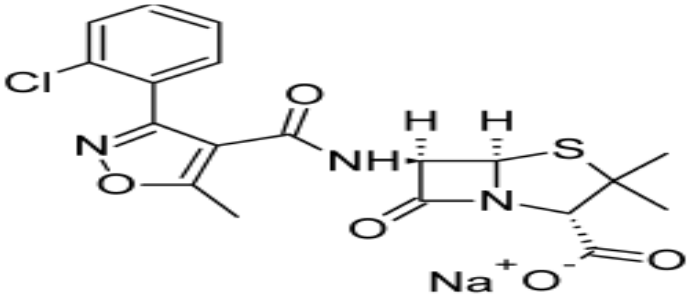
Oxacillin Sodium

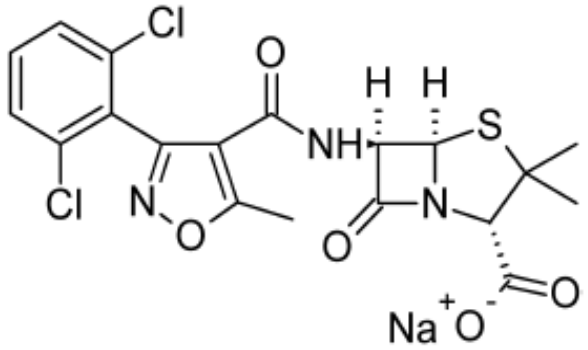
Oxacillin sodium, (5-methyl3-phenyl-4-isoxazolyl)penicillin sodium monohydrate, is the salt of a semisynthetic penicillin that is highly resistant to inactivation by penicillinase.



Cloxacillin Sodium

[3-(*o*-chlorophenyl)-5-methyl-4-isoxazolyl] penicillin sodium monohydrate



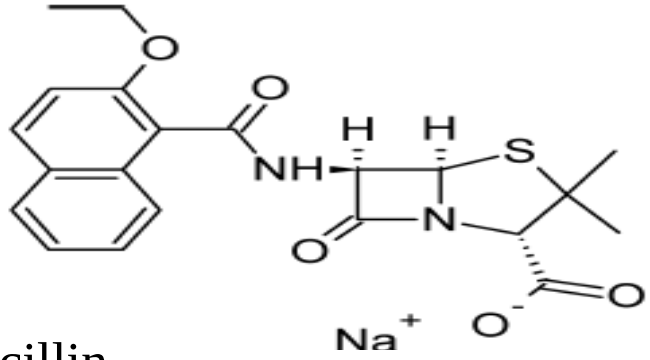


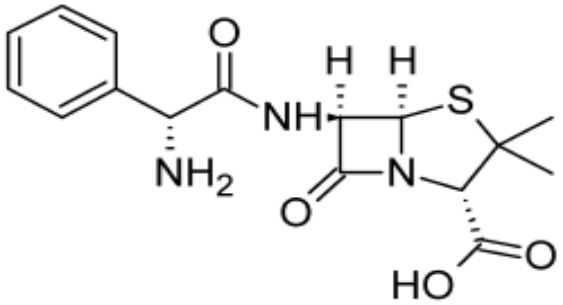
Dicloxacillin Sodium

[3-(2,6- dichlorophenyl)-5-methyl-4-isoxazolyl]penicillin sodium monohydrate

Nafcillin Sodium

Nafcillin sodium, 6-(2-ethoxy-1-naphthyl) penicillin sodium, is another semisynthetic penicillin



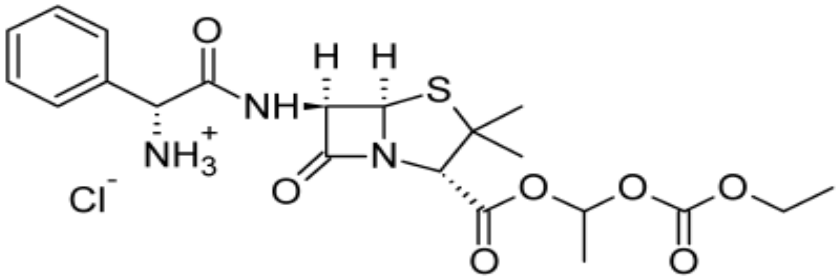


Ampicillin

D-α-amino benzyl-penicillin. This product is active against the same Gram-positive organisms that are susceptible to other penicillins, and it is more active against some Gram-negative bacteria and enterococci than are other penicillins.

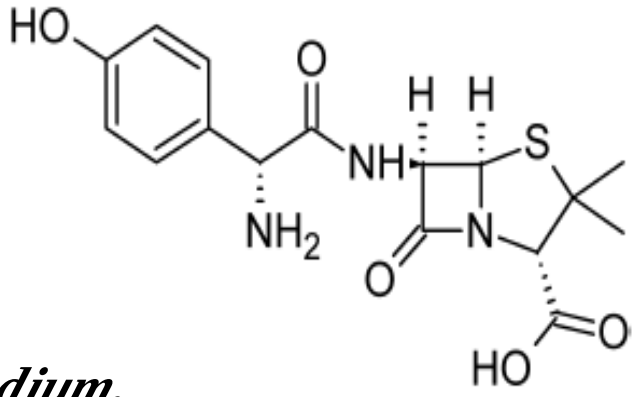
Bacampicillin Hydrochloride

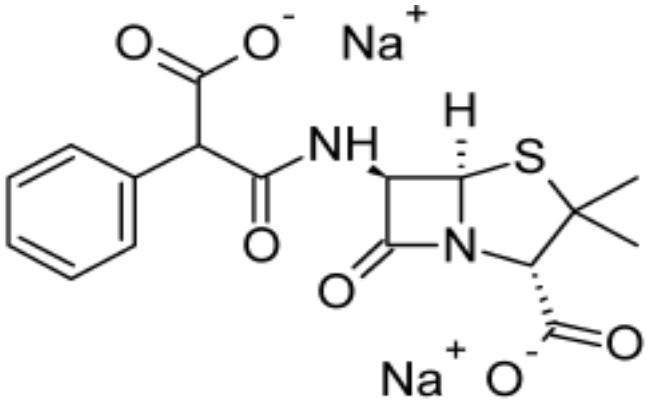
Bacampicillin hydrochloride After oral absorption. Oral absorption of bacampicillin is more rapid and complete than that of ampicillin and less affected by food. Effective plasma levels are sustained for 12 hours, allowing twice-a-day dosing.



Amoxicillin

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. orally administered amoxicillin possesses significant advantages over ampicillin, including more complete GI absorption to give higher plasma and urine levels, less diarrhea, and little or no effect of food on absorption.



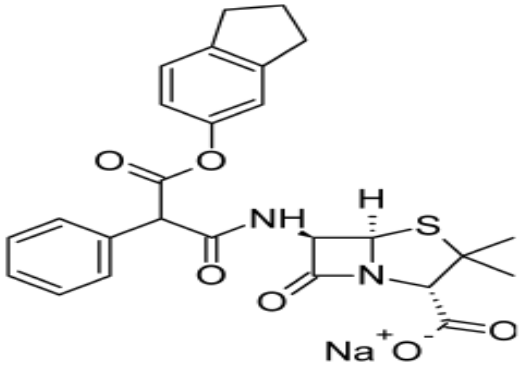


Carbenicillin Disodium,

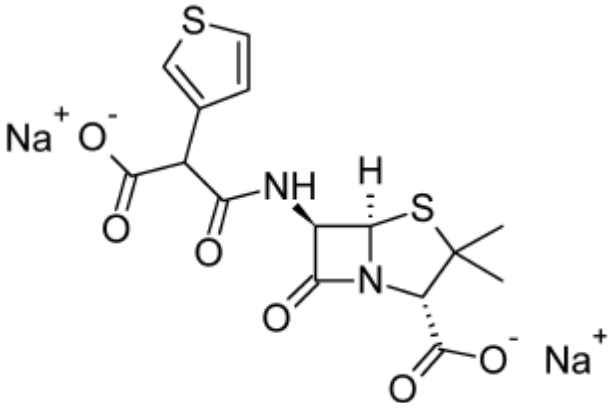
Carbenicillin disodium, disodium α-carboxybenzylpenicillin , is a semisyntheti penicillin. Examination of its structure shows that it differs from ampicillin in having a ionizable carboxyl group rather than an amino group substituted on the α-carbon atom o the benzyl side chain. Carbenicillin has been effective in the treatment of systemic an urinary tract infections caused by *P. aeruginosa*, indole-producing *Proteus* spp., an *Providencia* spp., all of which are resistant to ampicillin.

Carbenicillin Indanyl Sodium

Efforts to obtain orally active forms of carbenicillin led to the eventual release of the 5-indanyl ester carbenicillin.



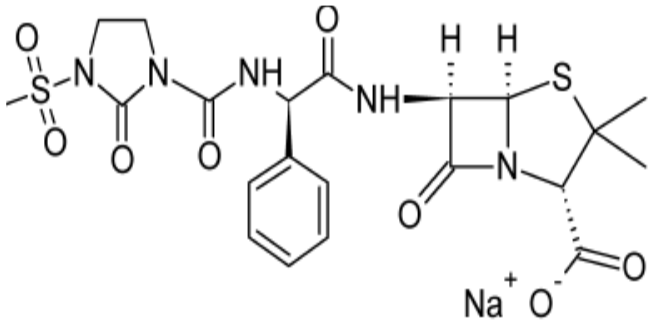
Ticarcillin Disodium

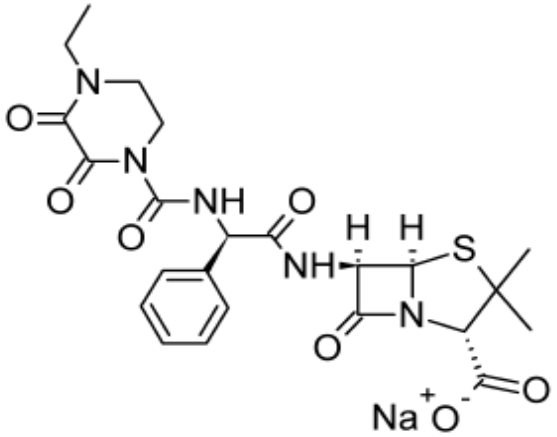


Ticarcillin disodium, α-carboxy-3-thienylpenicillin is an isostere of carbenicillin. It is similar to carbenicillin in antibacterial spectrum and pharmacokinetic properties. Two advantages for ticarcillin are claimed: (a) slightly better pharmacokinetic properties, including higher serum levels and a longer duration of action; and (b) greater in vitro potency against several species of Gramnegative bacilli, most notably *P. aeruginosa* and *Bacteroides fragilis*.

Mezlocillin Sodium, Sterile

Mezlocillin is an acylureidopenicillin with an antibacterial spectrum similar to that of carbenicillin and ticarcillin; however, there are some major differences. It is much more active against most *Klebsiella* spp., *P. aeruginosa*, anaerobic bacteria, and *H. influenza.* Mezlocillin is not generally effective against *β*- lactamase–producing bacteria, nor is it active orally.



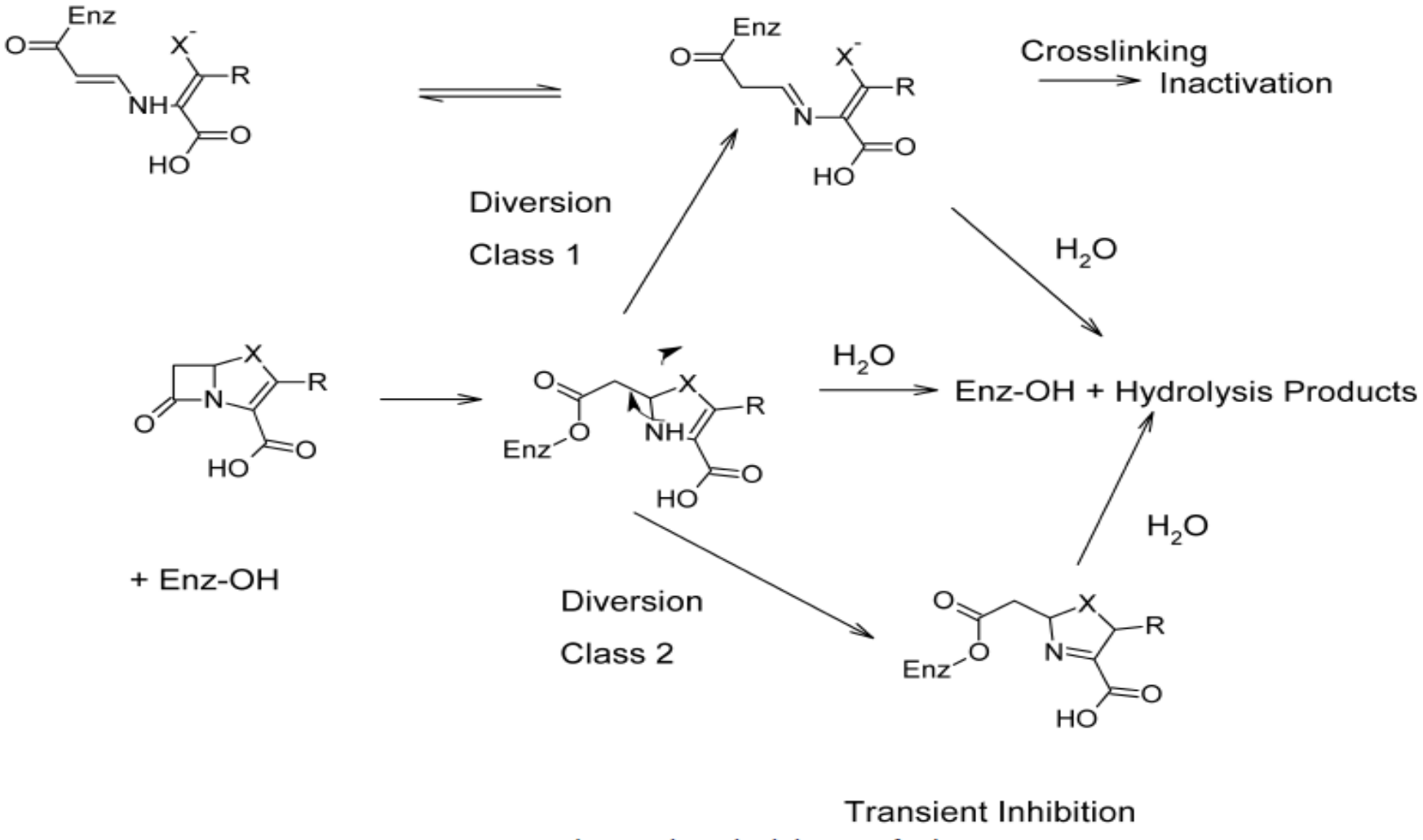


Piperacillin Sodium, Sterile

Piperacillin is the most generally useful of the extended- spectrum acylureidopenicillins. The *β*- lactamase susceptibility of piperacillin is not absolute because *β*-lactamase–producing, ampicillin-resistant strains of *N. gonorrhoeae* and *H. influenzae* are susceptible to piperacillin.

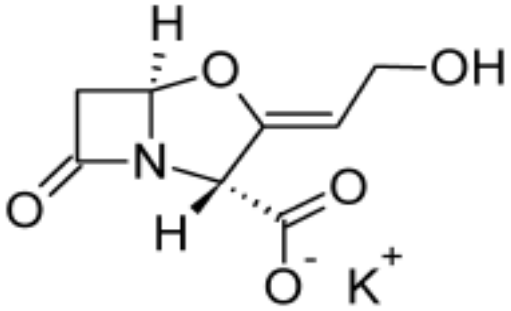
β-LACTAMASE INHIBITORS

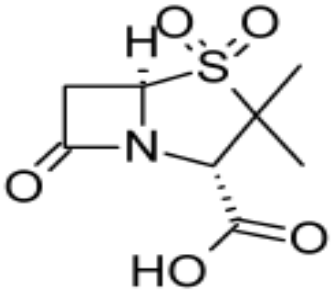
Early attempts to obtain synergy against β-lactamase–producing bacterial strains by using combinations consisting of a β- lactamase–resistant penicillin (e.g., methicillin or oxacillin) as a competitive inhibitor and a β-lactamase– sensitive penicillin (e.g., ampicillin or carbenicillin) to kill the organisms, met with limited success.



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.



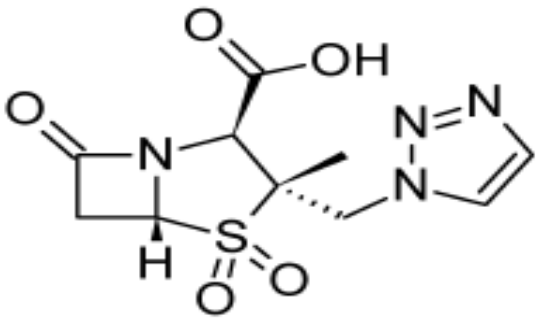


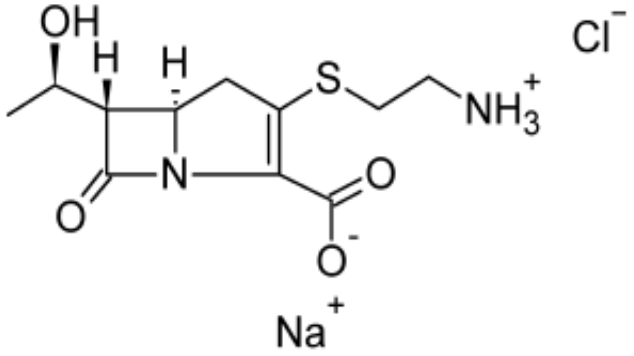
Sulbactam

Sulbactam is penicillanic acid sulfone or 1,1-dioxopenicillanic acid. This synthetic penicillin derivative is a potent inhibitor of *S. aureus* β-lactamase as well as many β-lactamases elaborated by Gram-negative bacilli.

Tazobactam

Tazobactam is a penicillanic acid sulfone that is similar in structure to sulbactam. It is a more potent *β*-lactamase inhibitor than sulbactam and has a slightly broader spectrum of activity than clavulanic acid. Approved indications for the piperacillin–tazobactam combination include the treatment of appendicitis, postpartum endometritis, and pelvic inflammatory disease , skin and skin structure infections and pneumonia caused by *β*-lactamase–producing strains of *H. influenzae*.



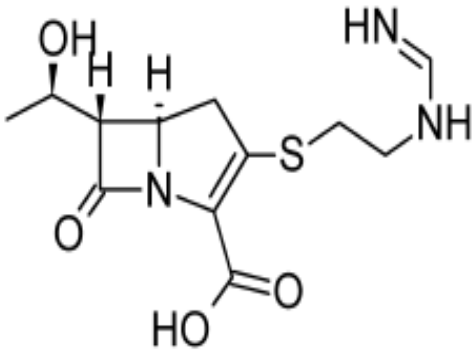


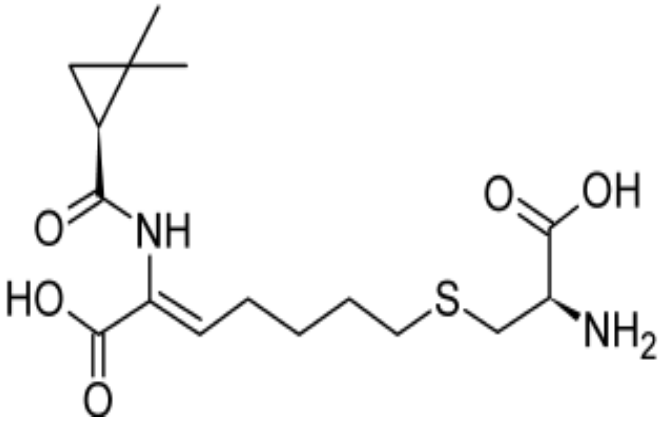
Thienamycin

Two structural features of thienamycin are shared with the penicillins and cephalosporins: a fused bicyclic ring system containing a *β*-lactam and an equivalently attached 3-carboxyl group. It is highly active against most aerobic and anaerobic Gram-positive and Gram negative bacteria, including *S. aureus*, *P. aeruginosa.* thienamycin undergoes concentration-dependent inactivation. inactivation by renal dehydropeptidase-I (DHP-I),

Imipenem–Cilastatin

Imipenem is *N*-formimidoylthienamycin, the most successful of a series of chemically stable derivatives of thienamycin in which the primary amino group is converted to a nonnucleophilic basic function. Its bactericidal activity results from the inhibition of cell wall synthesis . Imipenem is very stable to most β-lactamases. It is an inhibitor of β-lactamases from certain Gram-negative bacteria resistant to other β-lactam antibiotics.



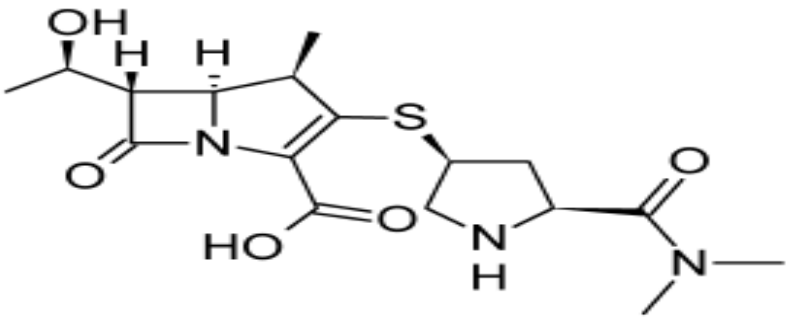


NEWER CARBAPENEMS

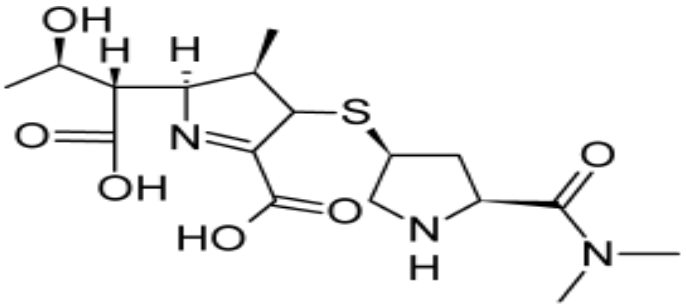
Improvements that are particularly desired include stability to hydrolysis catalyzed by DHP-I, stability to bacterial metallo-β-lactamases, activity against MRSA, and increased potency against *P. aeruginosa*, especially imipenem-resistant strains.

Meropenem

Meropenem is a second-generation carbapenem that, to date, has undergone the most extensive clinical evaluation. It has recently been approved as Merrem for the treatment of infections caused by multiply-resistant bacteria and for empirical therapy for serious infections.



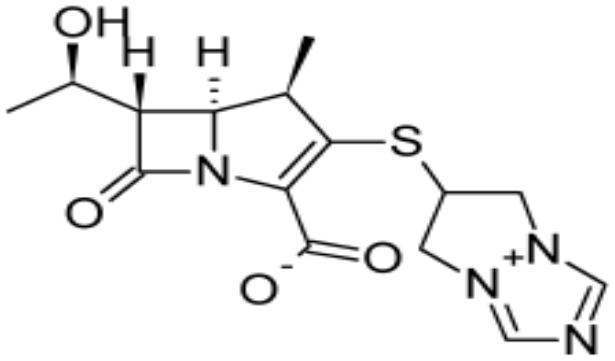
Meropenem



Meropenem metabolite

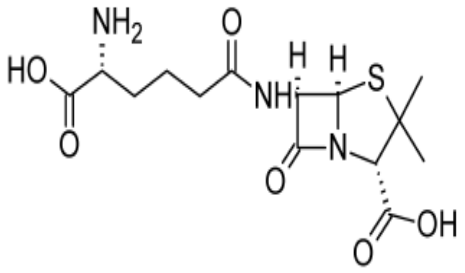
Biapenem

Biapenem is a newer second-generation carbapenem with chemical and microbiological properties similar to those of meropenem. Thus, it has broad-spectrum antibacterial activity that includes most aerobic Gram-negative and Gram positive bacteria and anaerobes

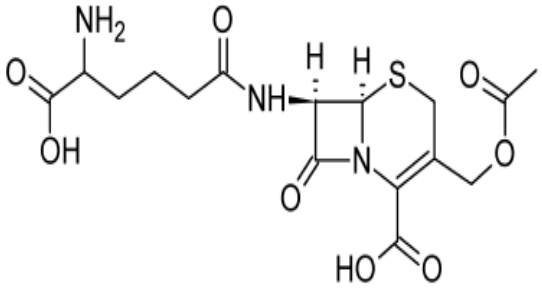


CEPHALOSPORINS

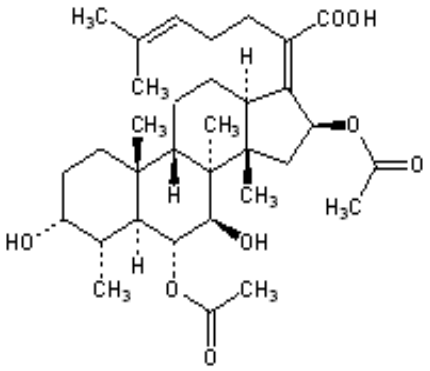
The cephalosporins are β-lactam antibiotics isolated from *Cephalosporium* spp. or prepared semisynthetically.



Penicillin N

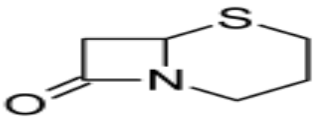


Cephalosporin C

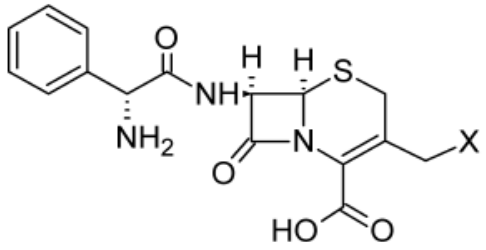


Nomenclature

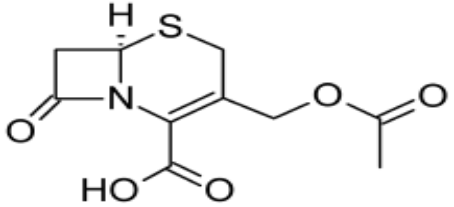
Chemical Abstracts as 5-thia-1-azabicyclo[4.2.0]oct-2-ene. A simplification that retains some of the systematic nature of the *Chemical Abstracts* procedure names the saturated bicyclic ring system with the lactam carbonyl oxygen *cepham* (cf., *penam* for penicillins). According to this system, all commercially available cephalosporins and cephamycins are named *3-cephems* (or Δ^3-cephems) to designate the position of the double bond.



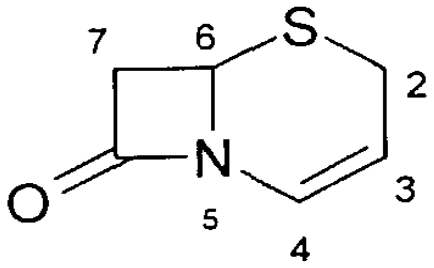
Cepham

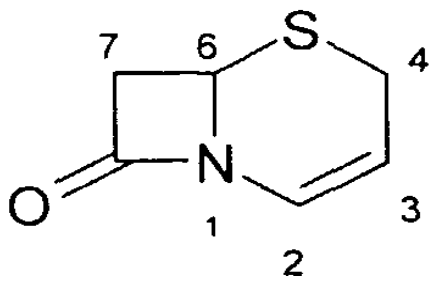


Cephalosporin



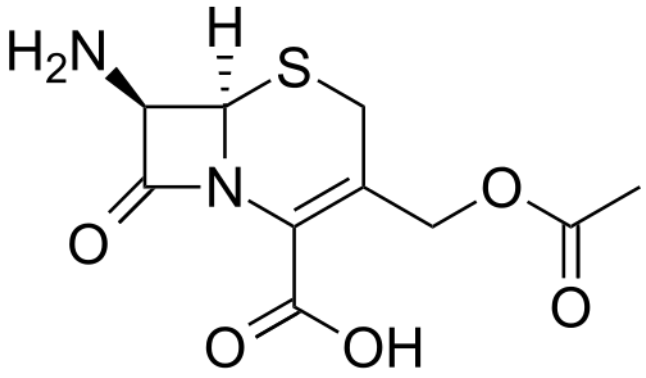
Cephalosporanic Acid

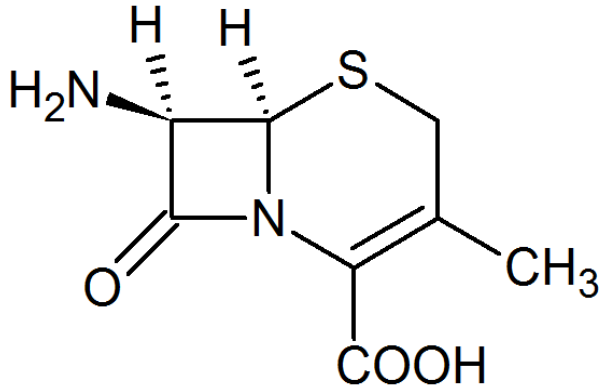




Semisynthetic Derivatives

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.





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, and (f) increased tolerance after parenteral administration.

Chemical Degradation

Cephalosporins experience various hydrolytic degradation reactions whose specific nature depends on the individual structure

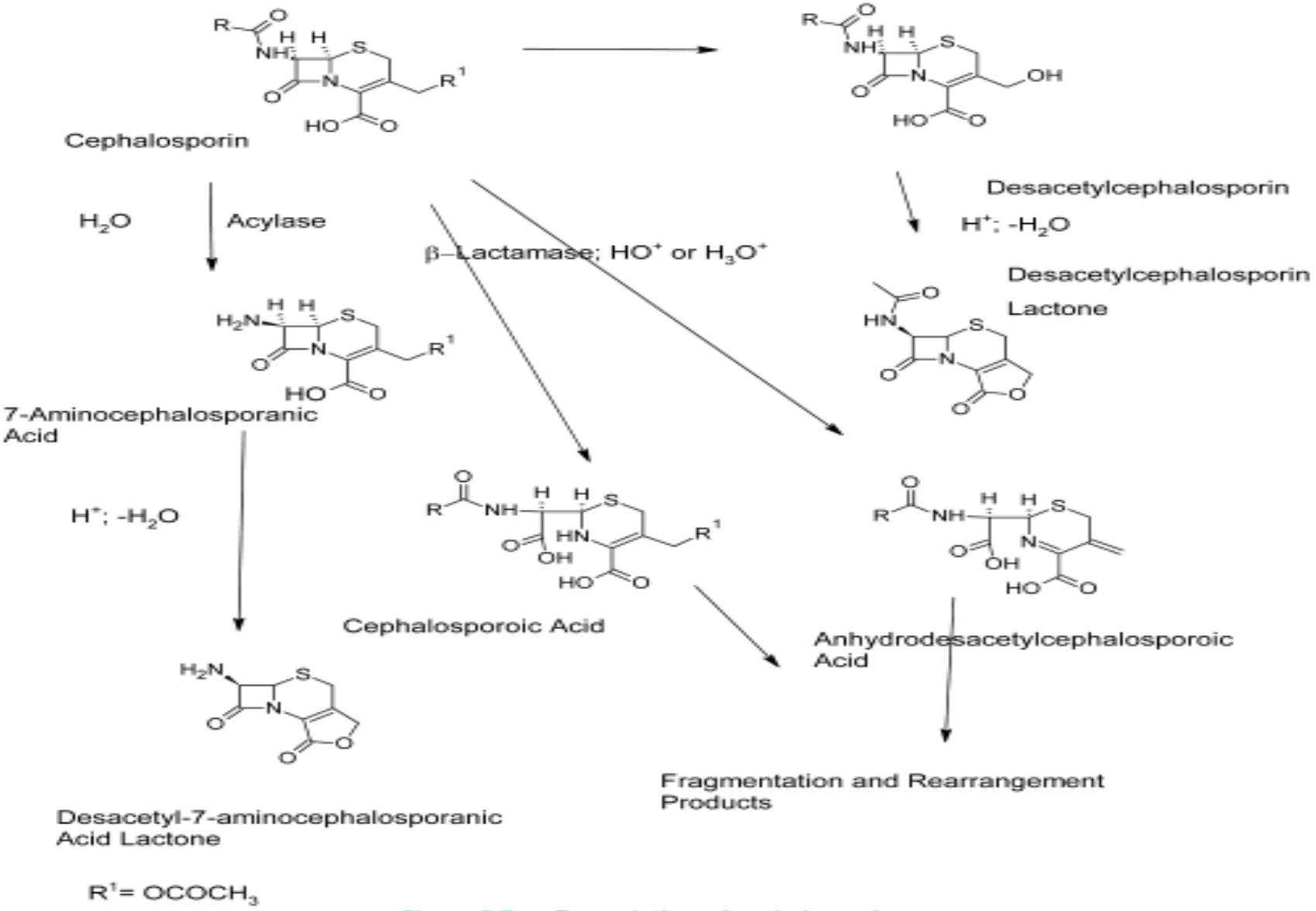
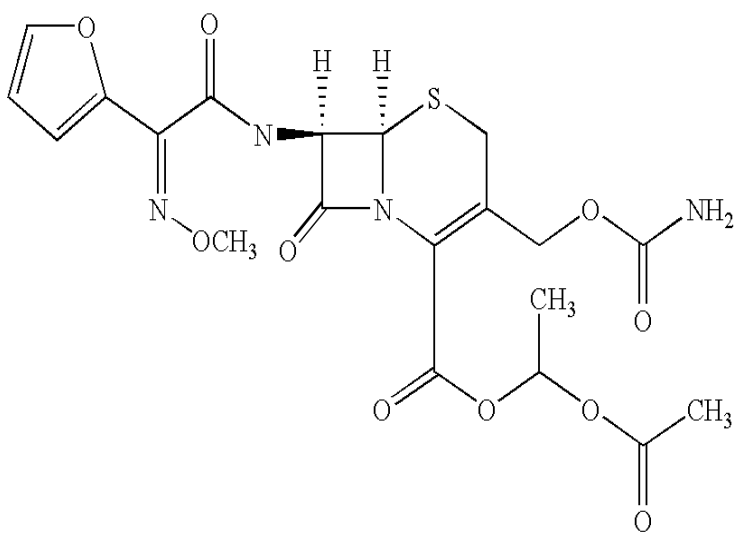


Figure 8.5 • Degradation of cephalosporins.

Oral Cephalosporins

The oral activity conferred by the phenylglycyl 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.

Oral activity can also be conferred in certain cephalosporins by esterification of the 2-carboxylic acid group to form acid-stable, lipophilic esters



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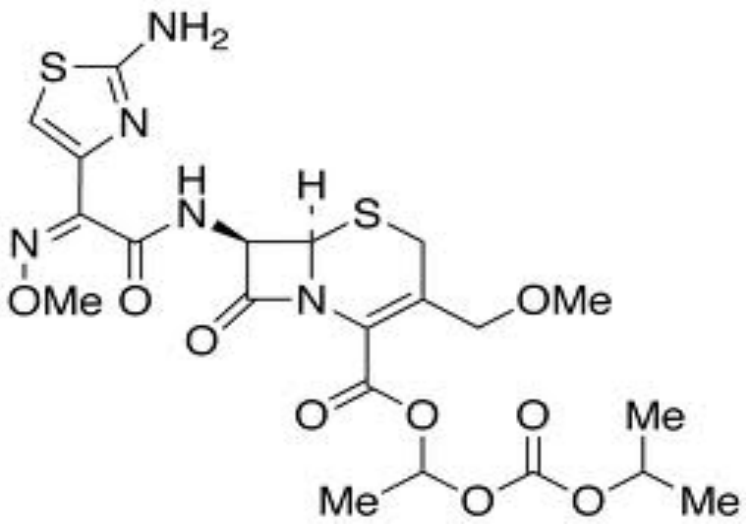
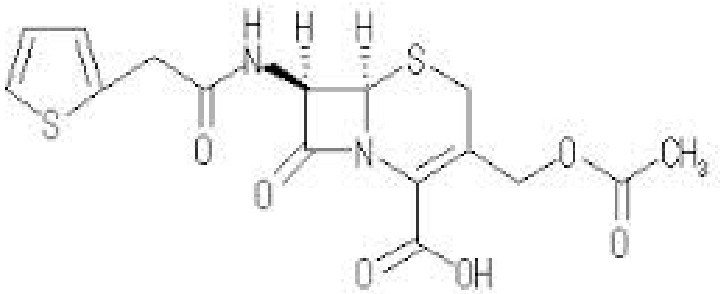
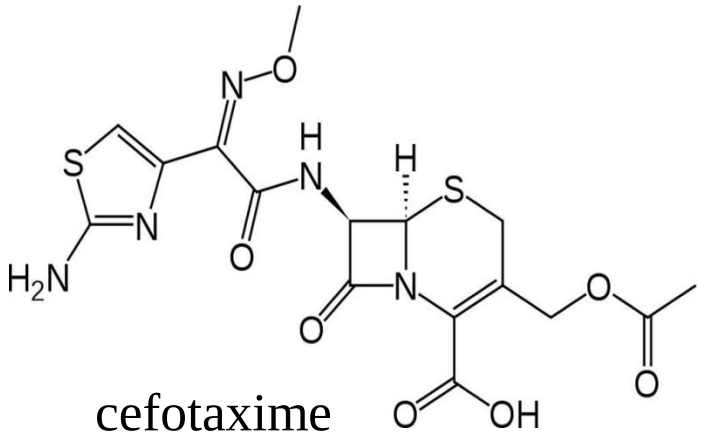


Parenteral Cephalosporins

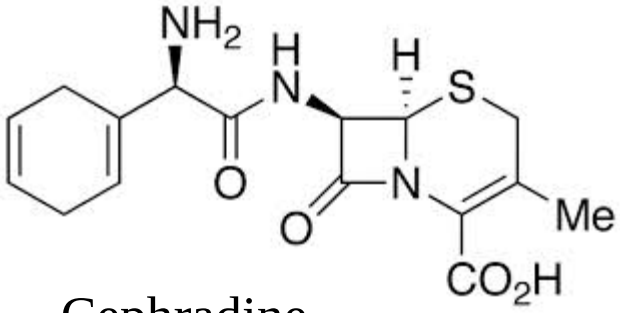
Hydrolysis of the ester function, catalyzed by hepatic and renal esterases, is responsible for some in vivo inactivation of parenteral cephalosporins containing a 3-acetoxymethyl substituent (e.g., cephalothin, cephapirin, and cefotaxime). Parenteral cephalosporins lacking a hydrolyzable group at the 3-position are not subject to hydrolysis by esterases. Cephradine is the only cephalosporin that is used both orally and parenterally.



Cephalothin



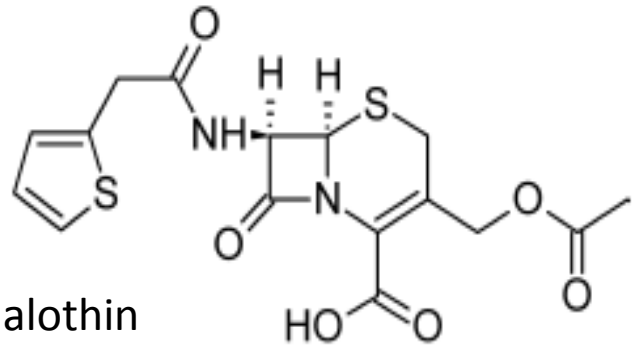
cefotaxime



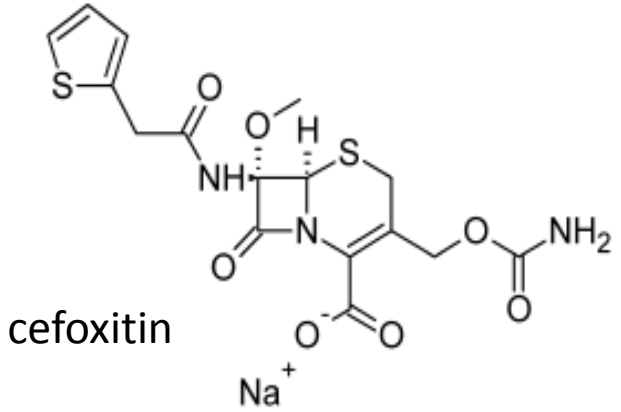
Cephradine

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. cephalothin and cefoxitin are the most resistant, and cephaloridine and cefazolin are the least resistant. The same acyl functionalities that impart β-lactamase resistance in the penicillins unfortunately render cephalosporins virtually inactive against S. aureus and other Gram-positive bacteria.



cephalothin



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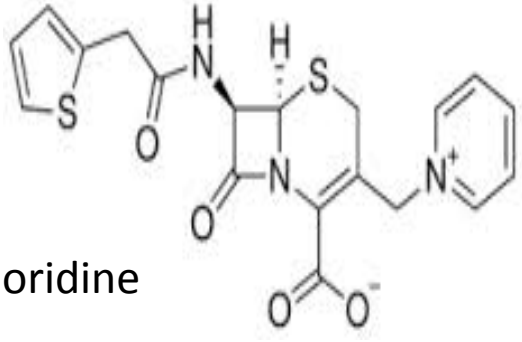
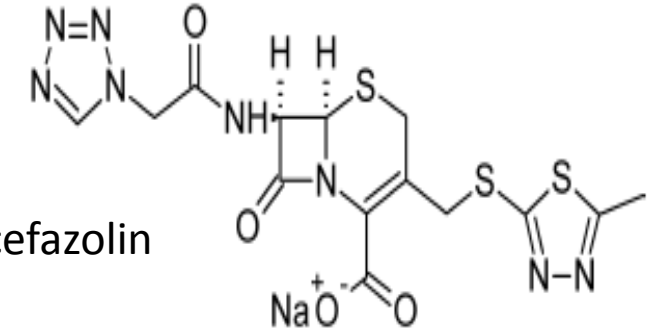
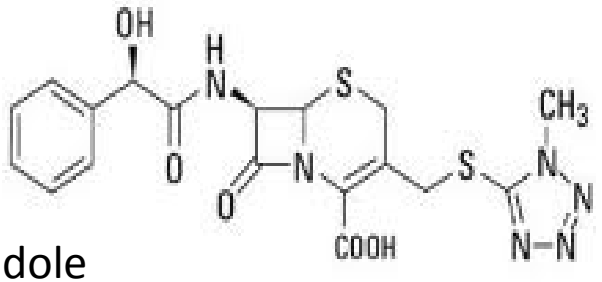


cephaloridine

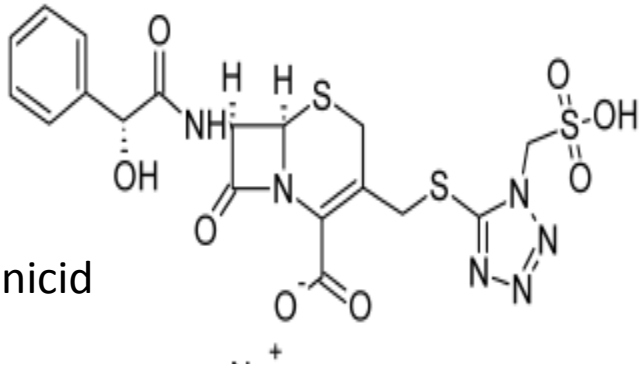


cefazolin

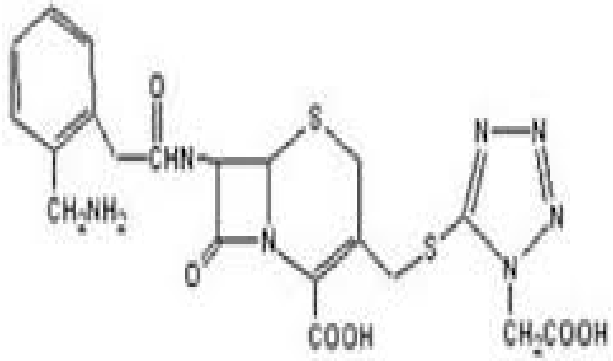
The introduction of polar substituents in the aminoacyl moiety of cephalosporins appears to confer stability to some β-lactamases. Thus, cefamandole and cefonicid, which contain an α-hydroxyphenylacetyl (or mandoyl) group, and ceforanide, which has an o-aminophenyl acetyl group, are resistant to a few β-lactamases. Steric factors also may be important because cefoperazone, an acylureidocephalosporin



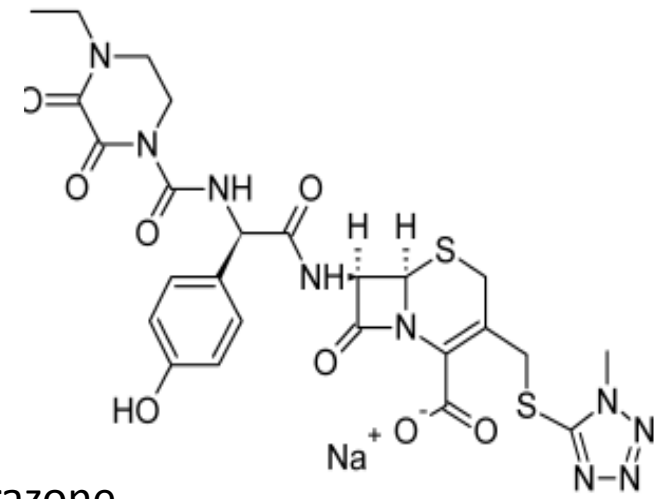
cefamandole



cefonicid

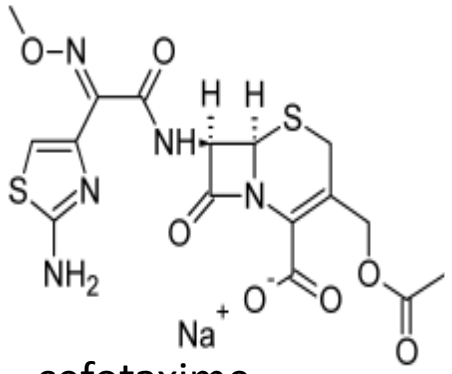


ceforanide

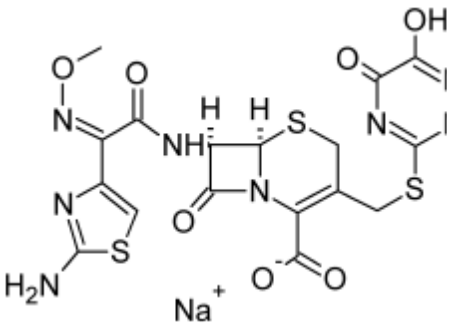


cefoperazone

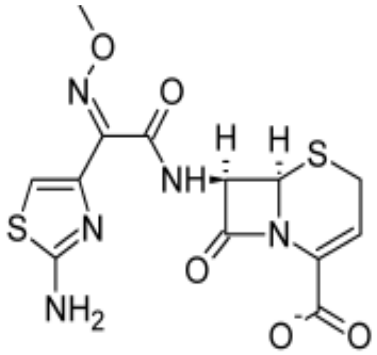
Two structural features confer broadly based resistance to β-lactamases among the cephalosporins: (a) an alkoximino function in the aminoacyl group and (b) a methoxyl substituent at the 7-position of the cephem nucleus having α stereochemistry.



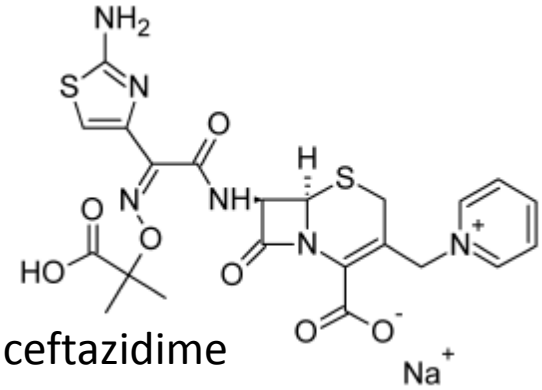
cefotaxime



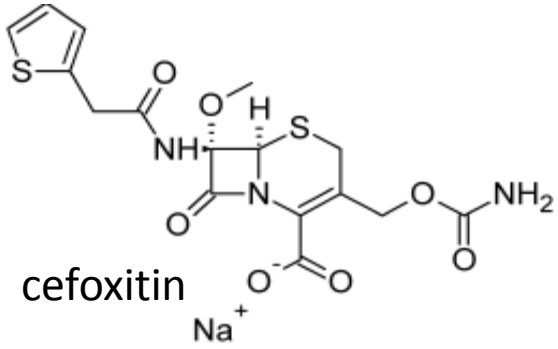
ceftriaxone



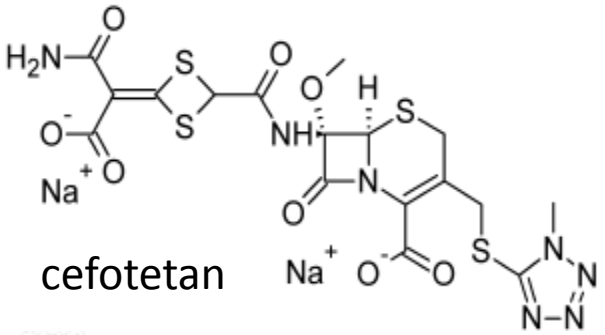
ceftizoxime



ceftazidime



cefoxitin



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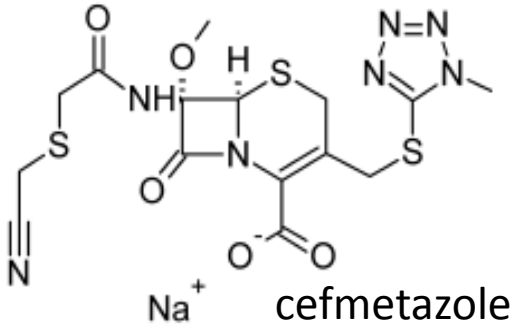
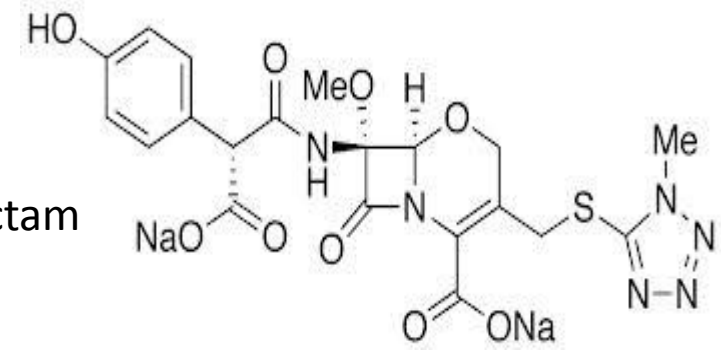


cefmetazole



moxalactam

Adverse Reactions and Drug Interactions

The most common adverse reactions to the cephalosporins are allergic and hypersensitivity reactions. These vary from mild rashes to life-threatening anaphylactic reactions.
Cephalosporins containing an N-methyl-5-thiotetrazole (MTT) moiety at the 3-position (e.g., cefamandole, cefotetan, cefmetazole, moxalactam, and cefoperazone) have been implicated in a higher incidence of hypoprothrombinemia than cephalosporins lacking the MTT group.

disulfiram-like reactions, attributed to the accumulation of acetaldehyde and resulting from the inhibition of aldehyde dehydrogenase–catalyzed oxidation of aldehyde by MTT-containing cephalosporins, may occur in patients who have consumed alcohol before, during, or shortly after the course of therapy.