Pharmaceutical chemistry
Antibacterial Antibiotics
B-lactam antibiotics **Cont.**
Aminoglycosides

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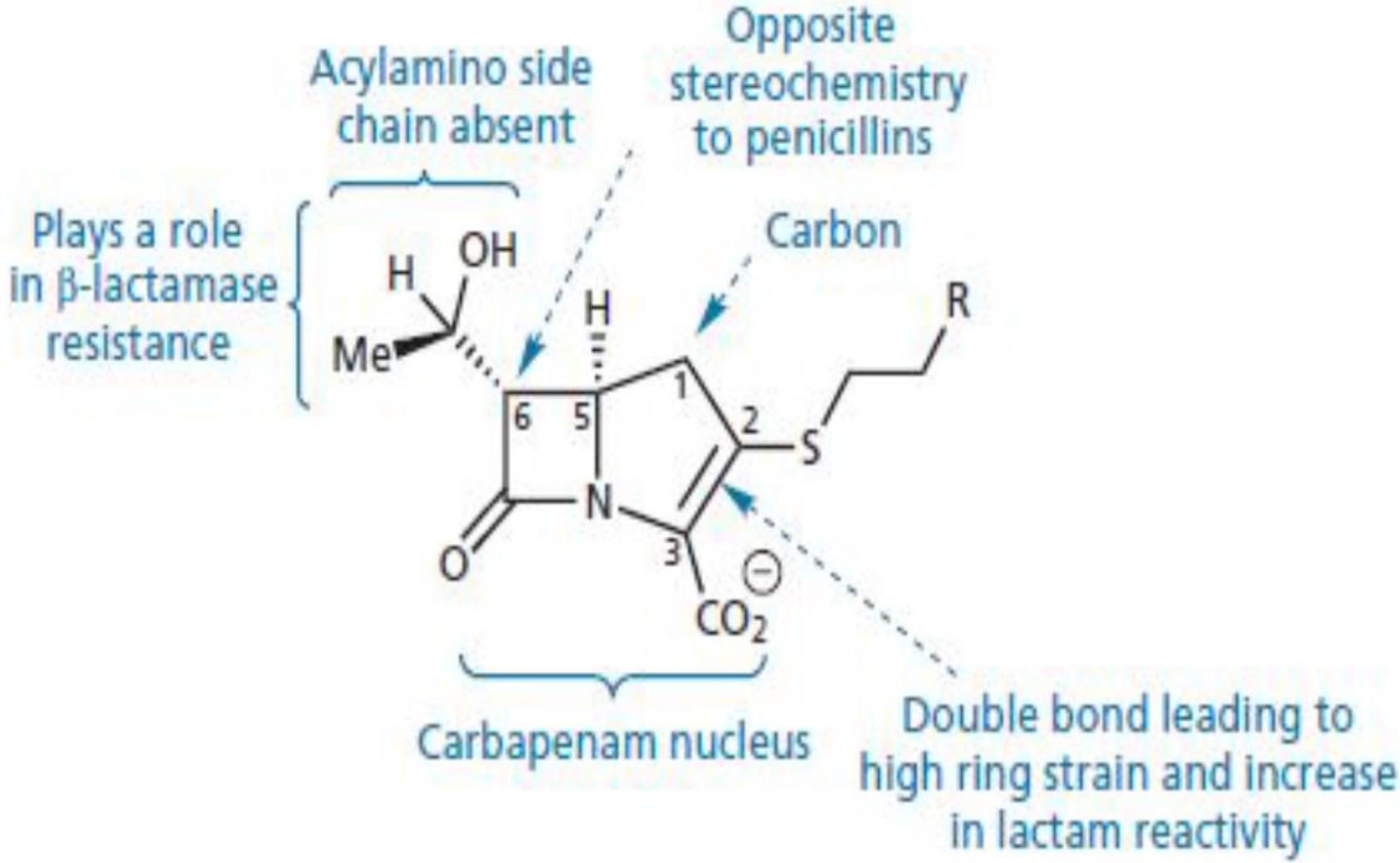
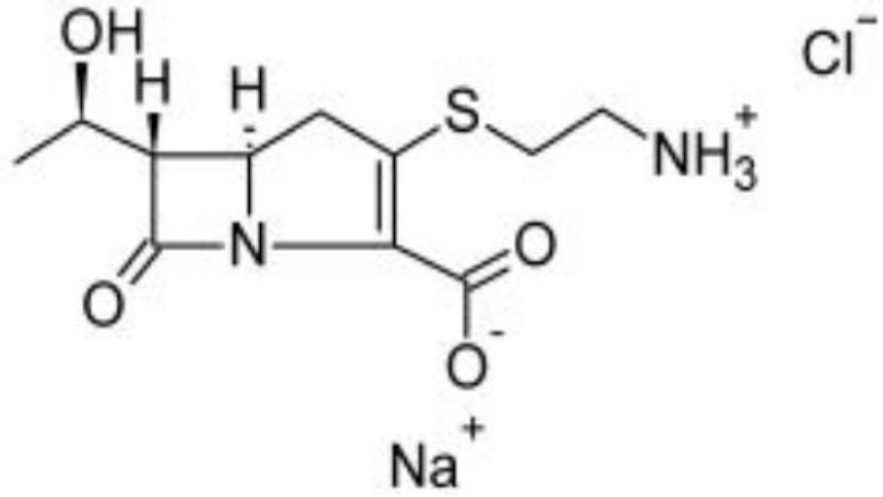
Carbapenems

- Carbapenems are a potent class of β-lactams which attack a wide range of PBPs, have low toxicity, and are much more resistant to β-lactamases than the penicillins or cephalosporins.
- Carbapenems contain a β-lactam ring (cyclic amide) fused to a five-membered ring.
- Carbapenems differ in structure from penicillins in that within the five-membered ring a sulfur is replaced by a carbon atom (C1) and an unsaturation is present between C2 and C3 in the five-membered ring.


Acylamino side chain absent
Opposite stereochemistry to penicillins
Plays a role in β-lactamase resistance
Carbon
OH
H
Me
H
R
6
5
1
2
S
N
O
3
$CO_2^{\ominus}$
Carbapenam nucleus
Double bond leading to high ring strain and increase in lactam reactivity

Thienamycin

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

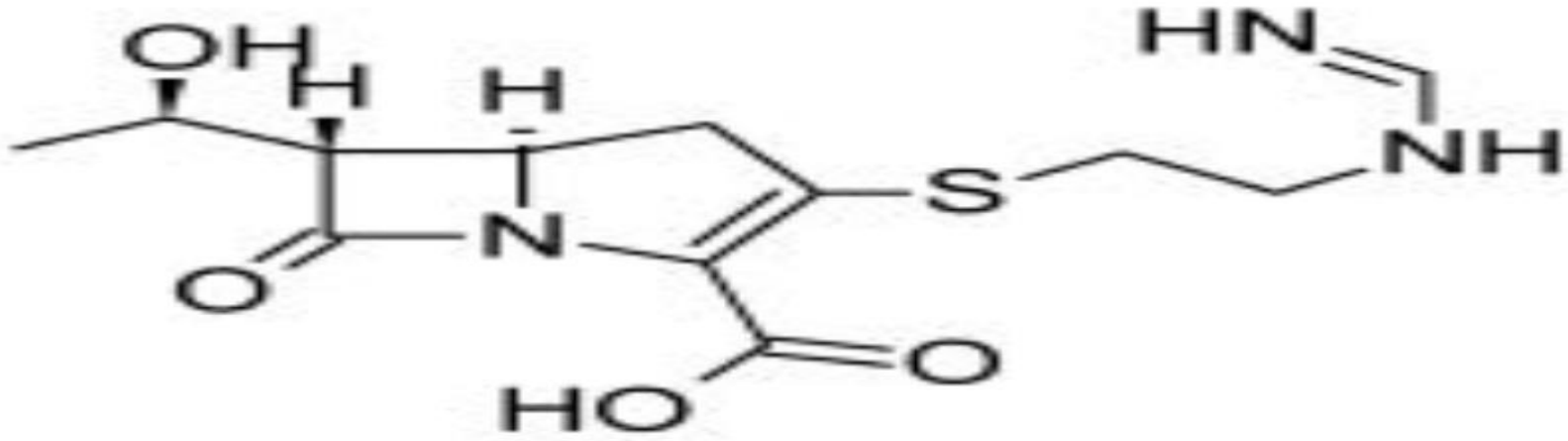
1- Hydroxyethyl group instead of the familiar acylamino side chain, and it is oriented to the bicyclic ring system rather than having the usual orientation of the penicillins and cephalosporins.

2- Amino ethyl thioether 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 position of the double bond

2. The 3-carboxyl group

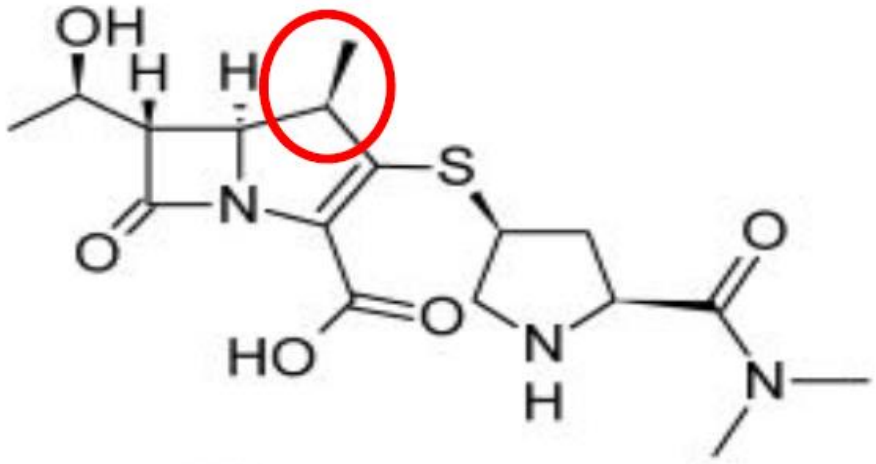
3. The 6-α-hydroxy ethyl side chain for both broadspectrum antibacterial activity and β-lactamase stability in Carbapenems. Modifications, therefore, have concentrated on variations at positions 1 and 2 of the carbapenem nucleus.

- The incorporation of a α-methyl group at the1position gives the carbapenem stability to hydrolysis by renal DHP-I.

- 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 is a second-generation carbapenem that, to date, has undergone the most extensive clinical evaluation. 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.



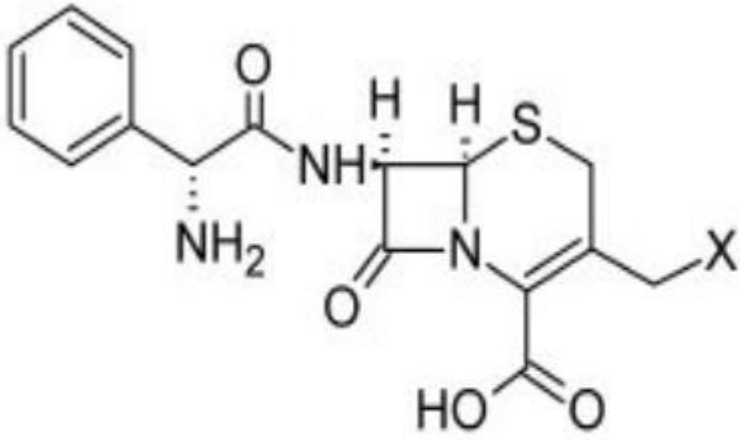
Meropenem

Cephalosporins

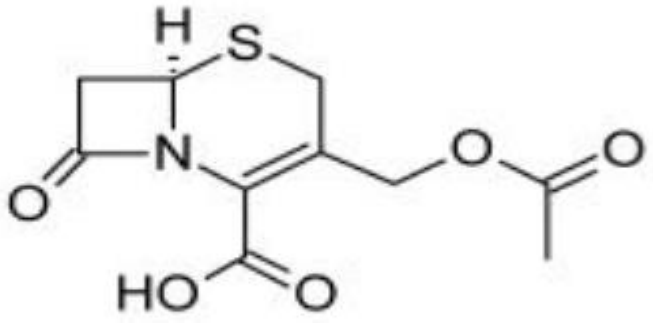
- Cephalosporins were discovered shortly after penicillin entered into widespread product, but not developed till the 1960's.
- Cephalosporins are similar to penicillins but have a 6 member dihydrothiazine ring instead of a 5 member thiazolidine ring.
- 7-aminocephalosporanic acid (7-ACA) can be obtained from bacteria, but it is easier to expand the ring system of 7-APA because it is so widely produced.

Cephalosporins

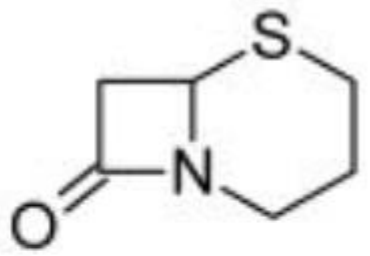
- Unlike penicillin, cephalosporins have two side chains which can be easily modified. Cephalosporins are also more difficult for β-lactamases to hydrolyze.



Cephalosporin



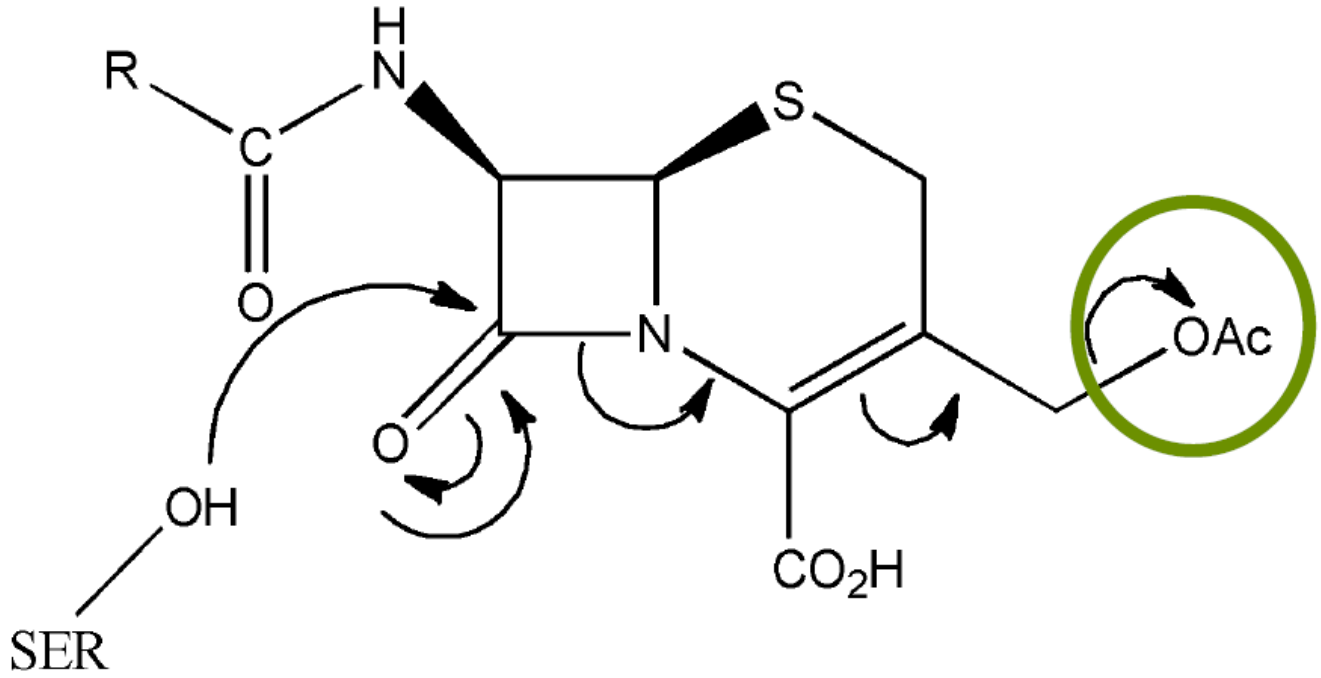
Cephalosporanic Acid



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:

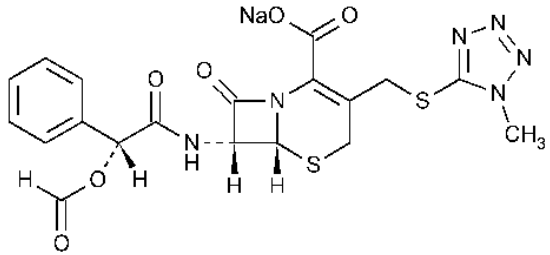
1. increased acid stability?
2. improved pharmacokinetic properties, particularly better oral absorption,
3. broadened antimicrobial spectrum
4. increased activity against resistant microorganisms (as a result of resistance to enzymatic destruction, improved penetration, increased receptor affinity, etc.)
5. decreased allergenicity?
6. increased tolerance after parenteral administration.

β-Lactamase Resistance

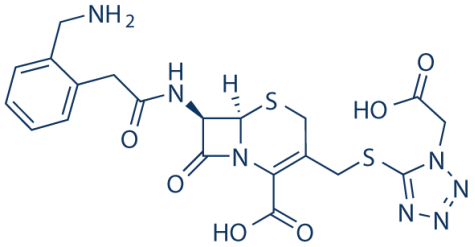
- The susceptibility of cephalosporins to various lactamases varies considerably with the source and properties of these enzymes.
- Cephalosporins are significantly less sensitive than all but the β-lactamase–resistant penicillins to hydrolysis by the enzymes from S. aureus and Bacillus subtilis.
- The“penicillinase”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

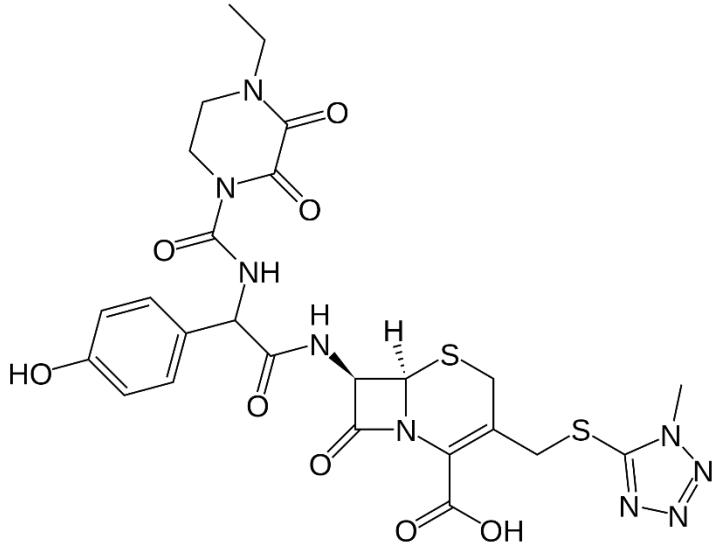
Cefamandole



Ceforanide



Cefoperazone



- 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 cepham nucleus having stereochemistry.

Oral Cephalosporins

- The oral activity conferred by the phenyl glycyl substituent is attributed to increased acid stability of the lactam ring, resulting from the presence of a protonated amino group on the 7-acylamino portion of the molecule.
- Carrier mediated transport of these dipeptide-like, zwitterionic cephalosporins is also an important factor in their excellent oral activity. The situation, then, is analogous to that of the α-amino benzylpenicillins (e.g., ampicillin).
- Also important for high acid stability (and, therefore, good oral activity) of the cephalosporins is the absence of the leaving group at the 3-position.

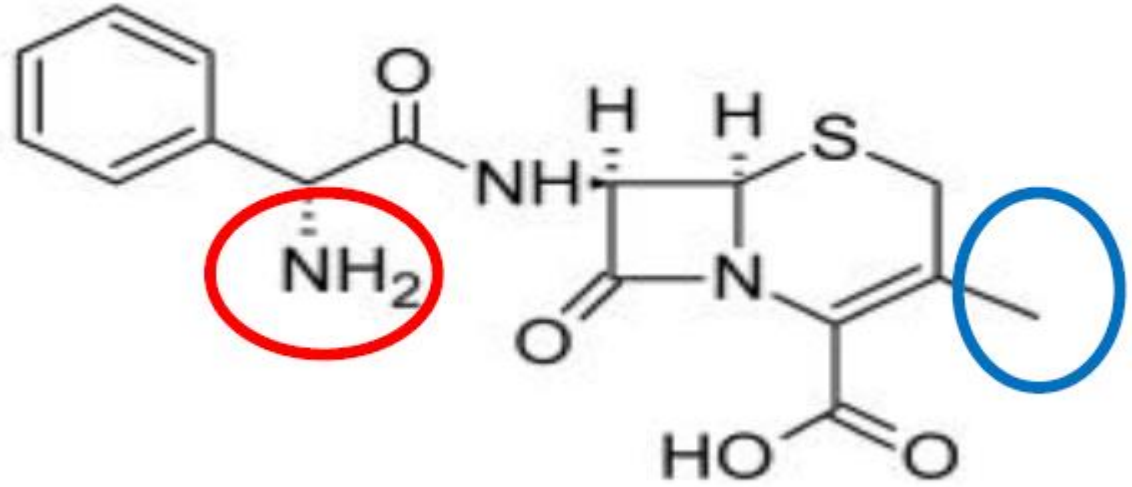
Parenteral Cephalosporins

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

Classification

- Cephalosporins are divided into first-, second-, third-, and fourth-generation agents, based roughly on their time of discovery and their antimicrobial properties.
- In general, progression from first to fourth generation is associated with a broadening of the Gram-negative antibacterial spectrum, some reduction in activity against Gram-positive organisms, and enhanced resistance to β- lactamases.
- Individual cephalosporins differ in their pharmacokinetic properties, especially plasma protein binding and half-life, but the structural bases for these differences are not obvious.

Products



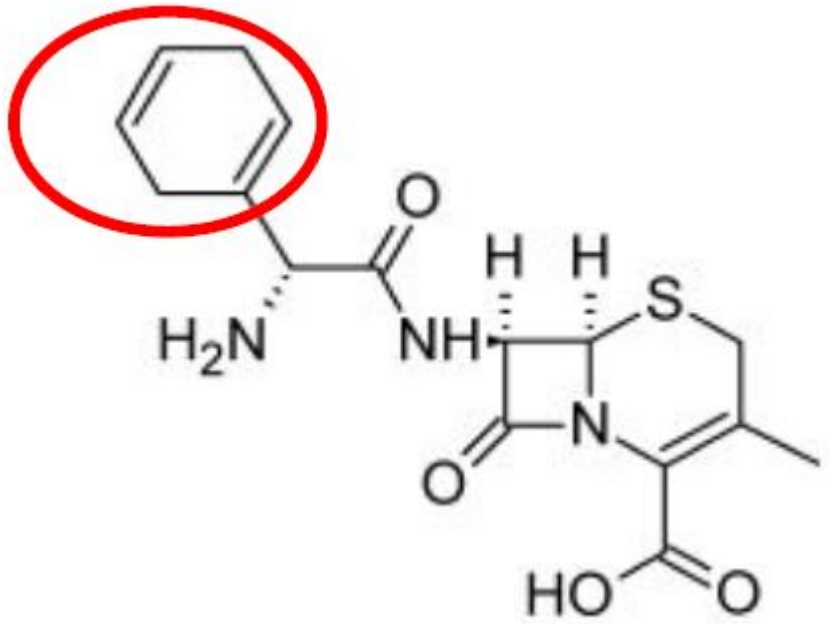
❖ First Generation

Cephalexin

- Cephalexin,7α-(D-amino-α-phenylacetamido)-3-methyl cephemcarboxylic acid (Keflex), 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.

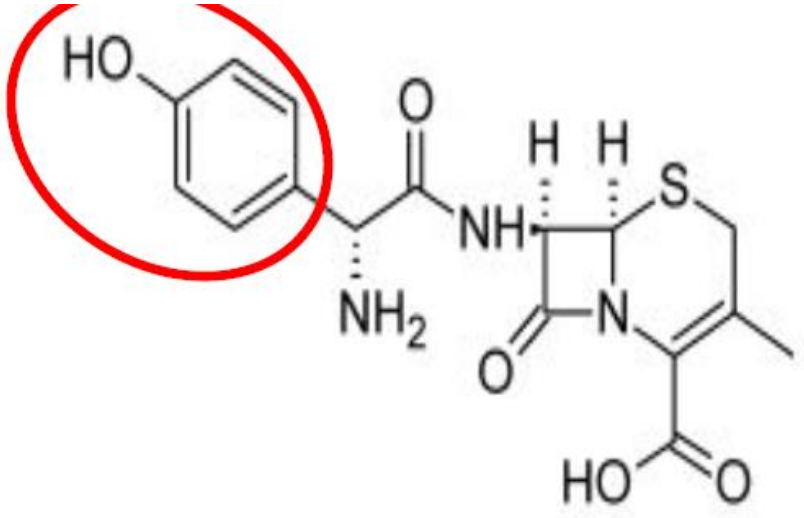
Cephradine

- 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



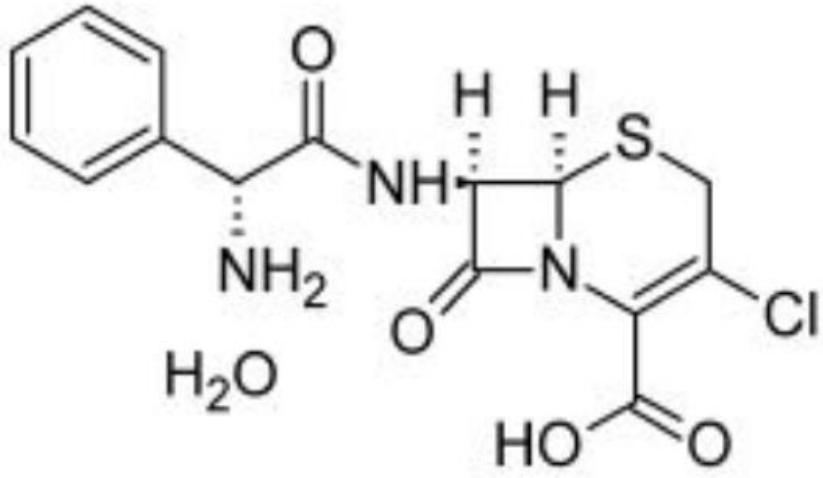
Cefadroxil

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



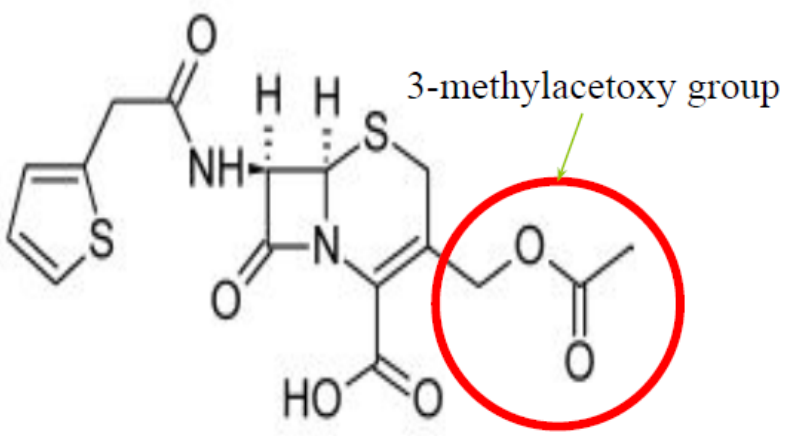
Cefaclor

- 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).

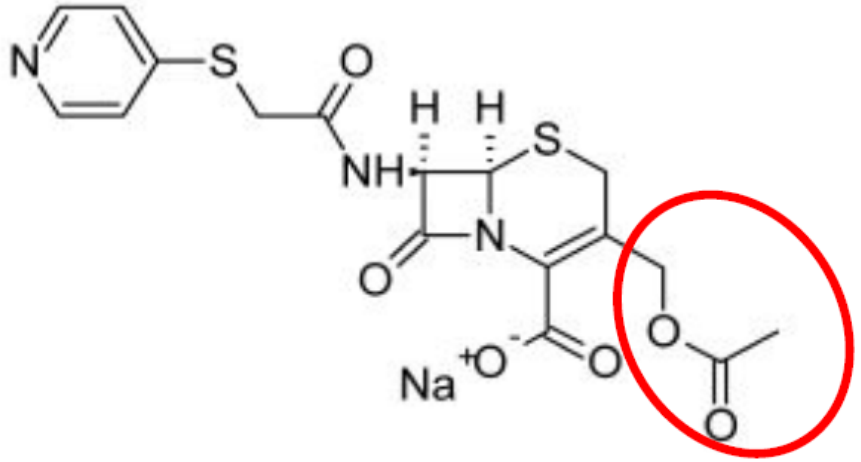


Parenterally products

- 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).



cephalothin

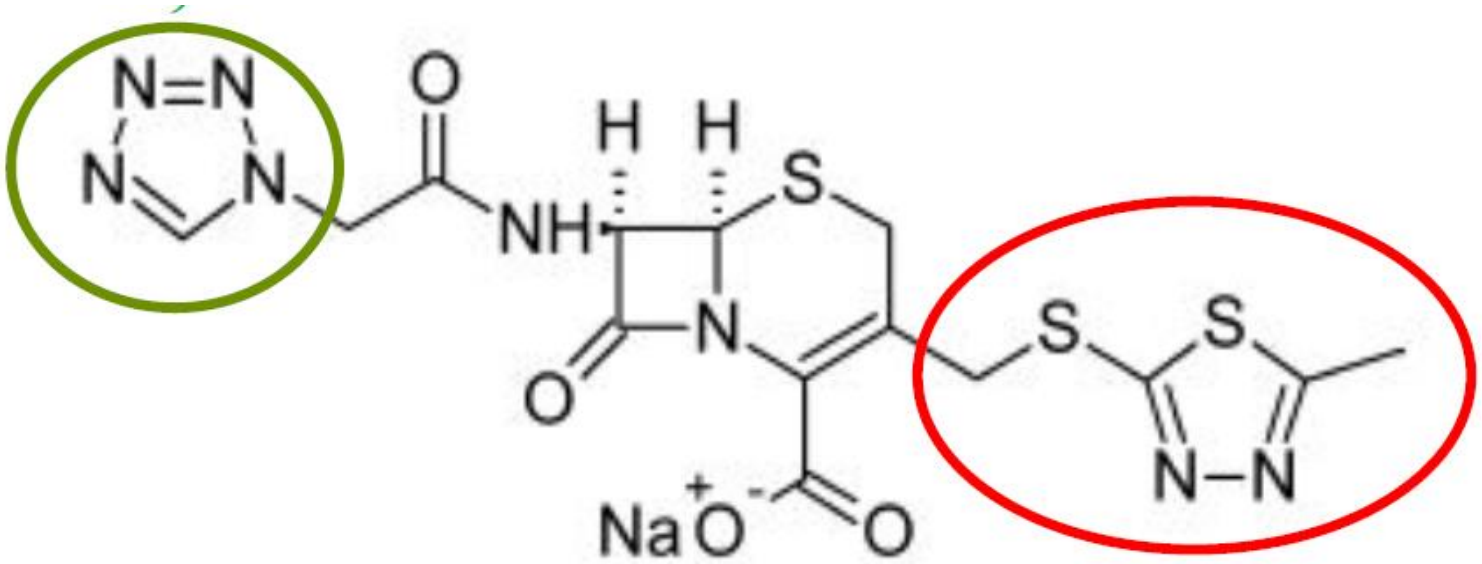


cephaloridine

- 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.

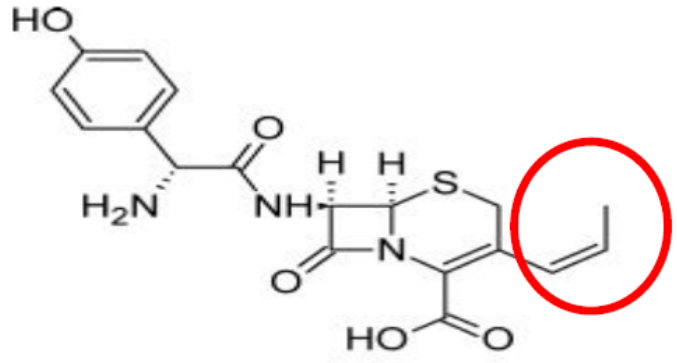
Cefazolin Sodium, Sterile

- 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. It also contains the somewhat unusual tetrazolylacetyl acylating group. It is active only by parenteral administration

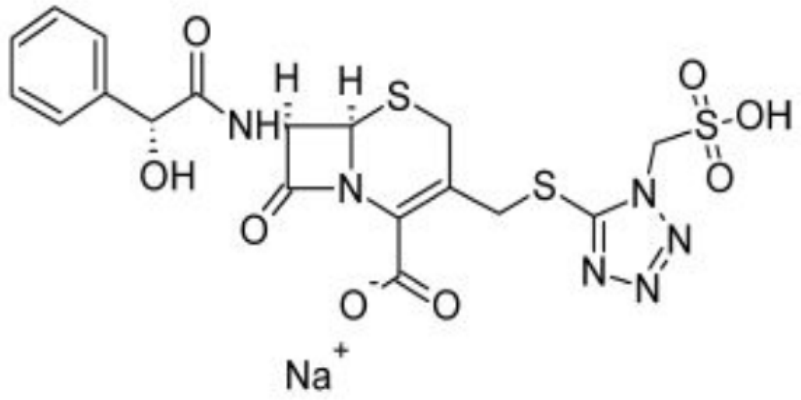


Second-generation

- 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



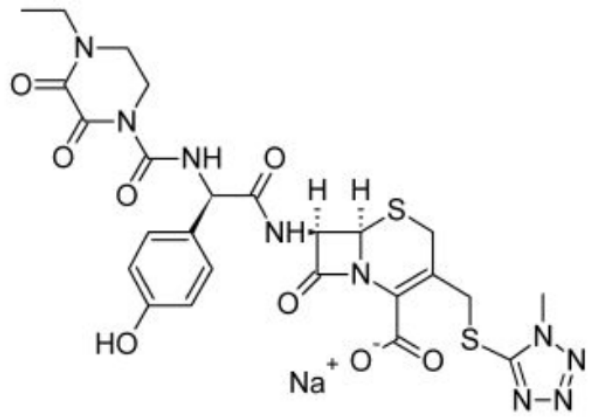
Cefprozil



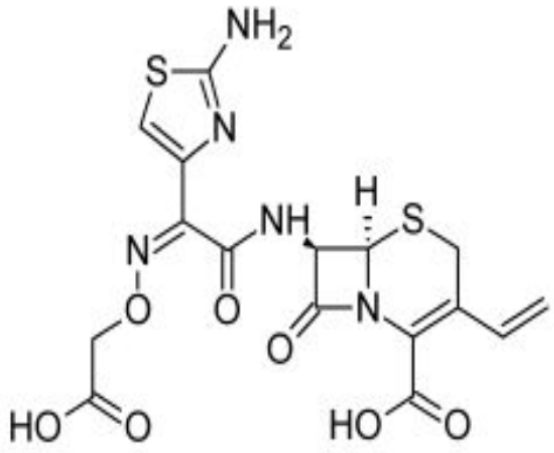
Cefonicid Sodium

Third-generation

- 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.



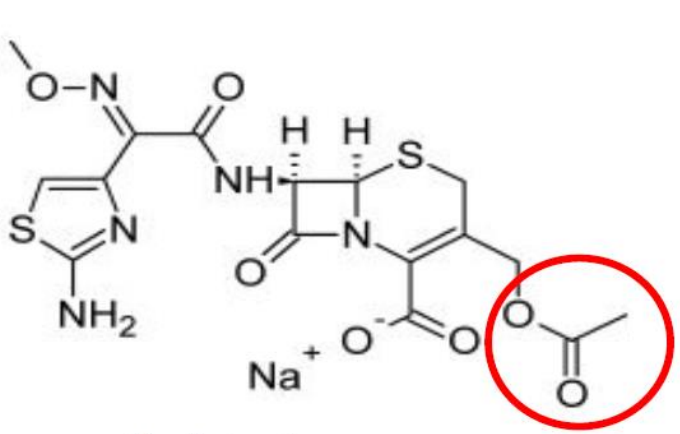
Cefoperazone



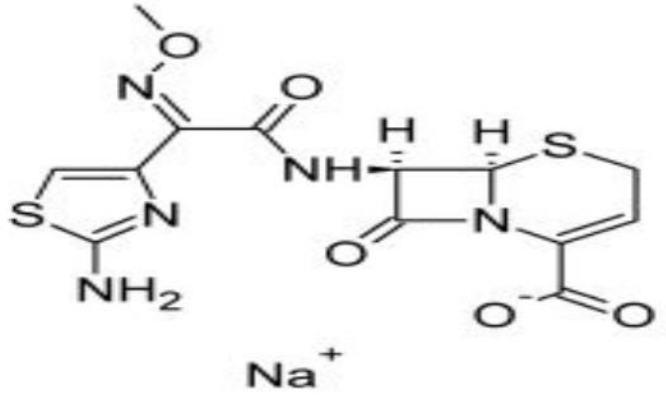
Cefixime

Cefotaxime Sodium and 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.



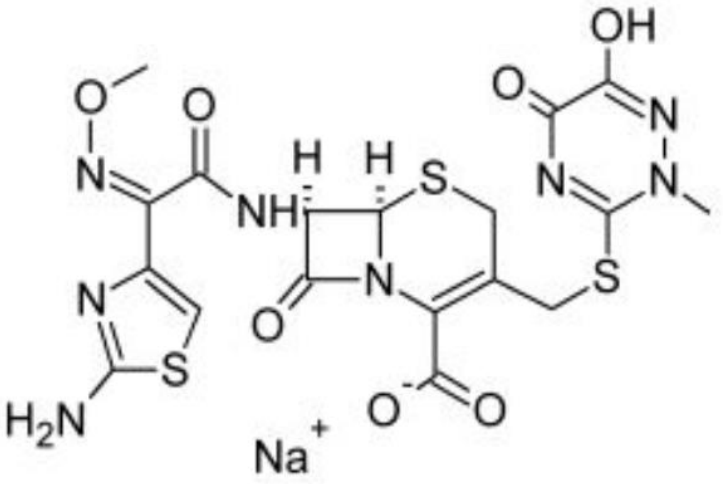
Cefotaxime



Ceftizoxime

Ceftriaxone Disodium, Sterile

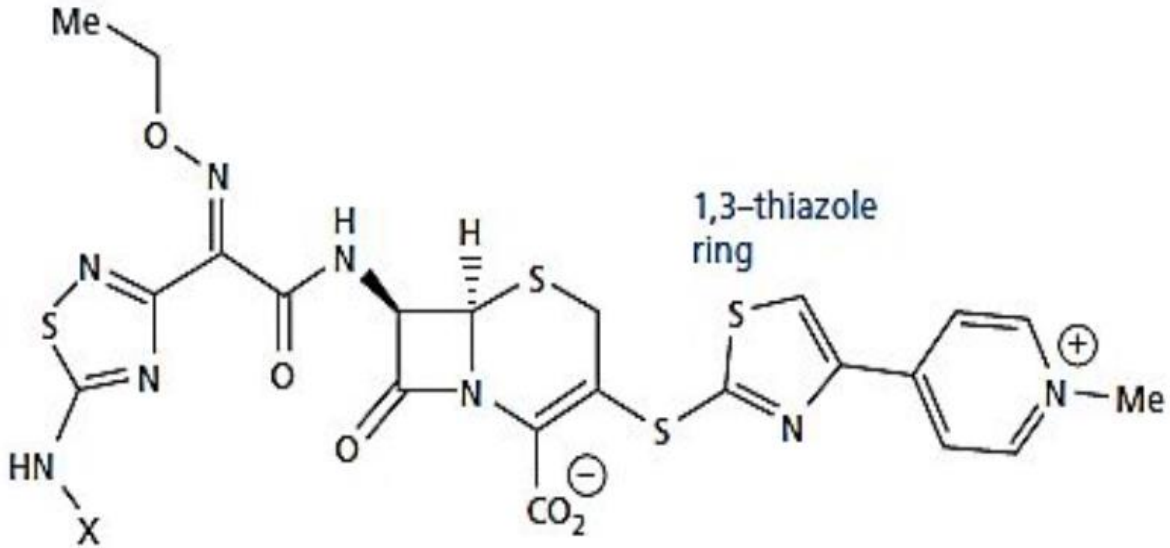
- Ceftriaxone (Rocephin) is a β-lactamase–resistant cephalosporin with an extremely long serum half-life.
- Once-daily dosing suffices for most indications. Two factors contribute to the prolonged duration of action of ceftriaxone: high protein binding in the plasma and slow urinary excretion.



Ceftriaxone

Fifth-generation cephalosporins

- Ceftaroline fosamil is a fifth-generation cephalosporin that has activity against various strains of MRSA methicillin resistant Staphylococcus aureus and multi-resistant Streptococcus pneumonia (MDRSP). It acts as a prodrug for ceftaroline , and the 1,3-thiazole ring is thought to be important for its activity against MRSA.



Ceftaroline and ceftaroline fosamil.

Aminoglycosides

- Streptomycin, first aminoglycoside antibiotic, isolated from the genus Streptomyces. Among the many antibiotics isolated from that genus, several compounds closely related in structure to streptomycin. Six of them—kanamycin, neomycin, paromomycin, gentamicin, tobramycin, and netilmicin are marketed in the United States.
- Amikacin, a semisynthetic derivative of kanamycin A, has been added, and it is possible that additional aminoglycosides will be introduced in the future.
- All aminoglycoside antibiotics are absorbed very poorly following oral administration, and some of them (kanamycin, neomycin, and paromomycin) are administered by that route for the treatment of GI infections. Because of their potent broad spectrum antimicrobial activity,

Chemistry

- Aminoglycosides are so named because their structures consist of amino sugars linked glycosidically.
- All have at least one aminohexose, and some have a pentose lacking an amino group (e.g., streptomycin, neomycin, and paromomycin).
- Additionally, each of the clinically useful aminoglycosides contains a highly substituted 1,3-diaminocyclohexane central ring; in kanamycin, neomycin, gentamicin, and tobramycin, it is deoxystreptamine, in streptomycin, it is streptadine.

- The aminoglycosides are thus strongly basic compounds that exist as polycations at physiological pH
- Aminoglycosides are apparently not metabolized in vivo.
- Their inorganic acid salts are very soluble in water.
- All are available as sulfates.
- Solutions of the aminoglycoside salts are stable to autoclaving.
- The high water solubility of the aminoglycosides no doubt contributes to their pharmacokinetic properties.
- They distribute well into most body fluids but not into the central nervous system, bone, or fatty or connective tissues.

Spectrum of Activity

- Although the aminoglycosides are classified as broad spectrum antibiotics, their greatest usefulness lies in the treatment of serious systemic infections caused by aerobic Gram-negative bacilli.

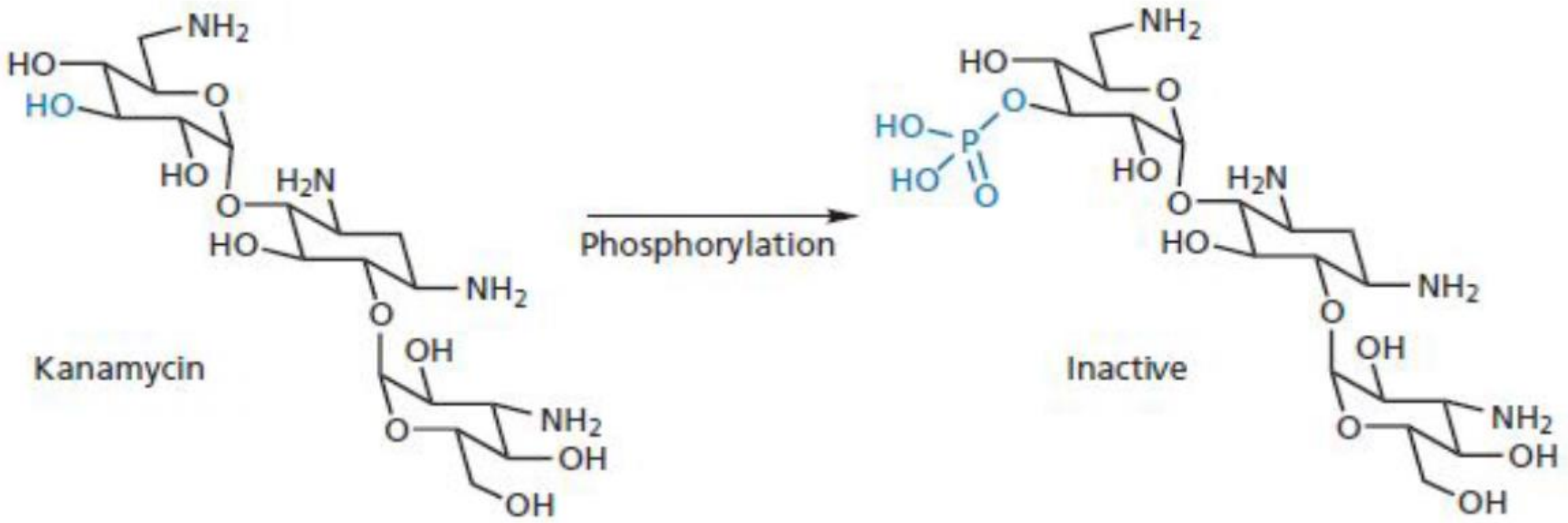
Mechanism of Action

- The aminoglycosides act directly on the bacterial ribosome to inhibit the initiation of protein synthesis. They bind to the 30S ribosomal subunit to form a complex that cannot initiate proper amino acid polymerization.
- The binding of streptomycin and other aminoglycosides to ribosomes also causes misreading mutations of the genetic code, and hence incorporation of improper amino acids into the peptide chain.

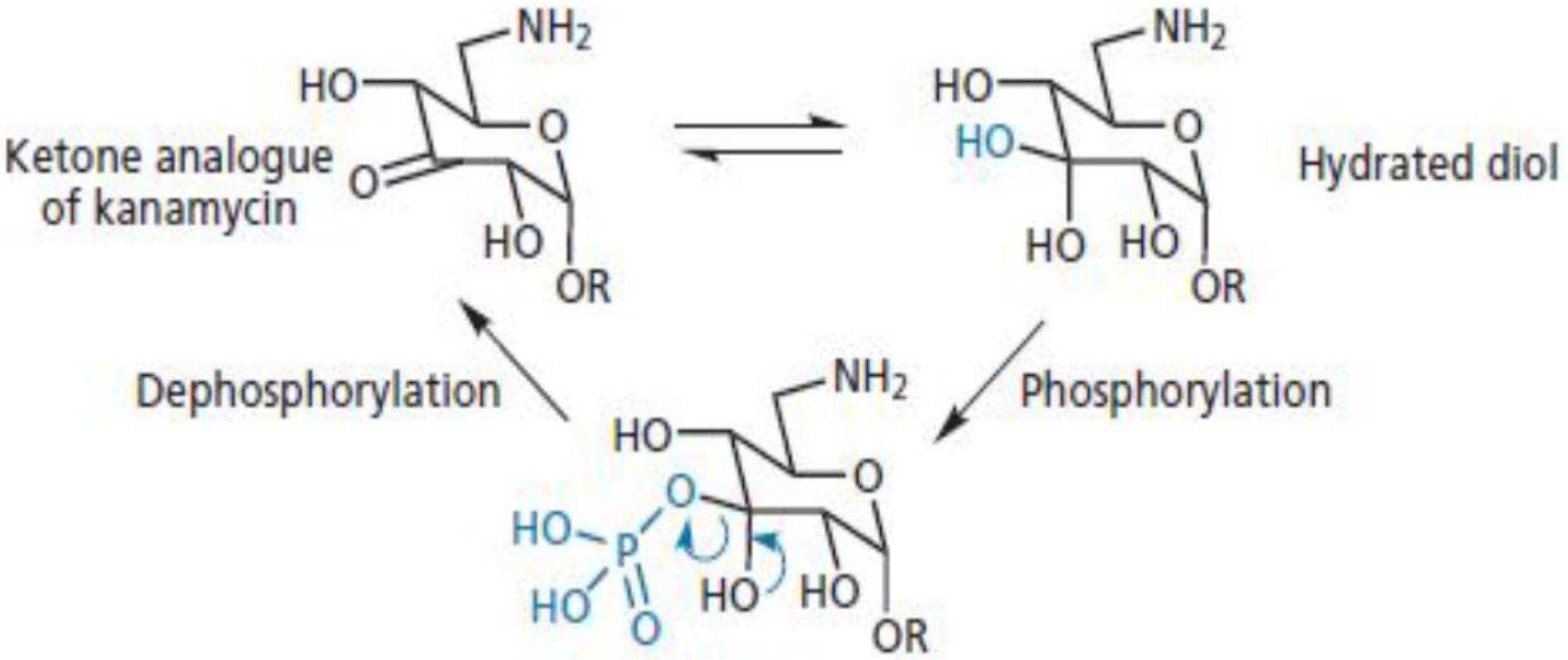
Microbial Resistance

- A pattern of bacterial resistance to each of the aminoglycoside antibiotics, however, has developed as their clinical use has become more widespread.
- Consequently, there are bacterial strains resistant to streptomycin, kanamycin, and gentamicin.
- Strains carrying R factors for resistance to these antibiotics synthesize enzymes that are capable of acetylating, phosphorylating, or adenylylating key amino or hydroxyl groups of the aminoglycosides.

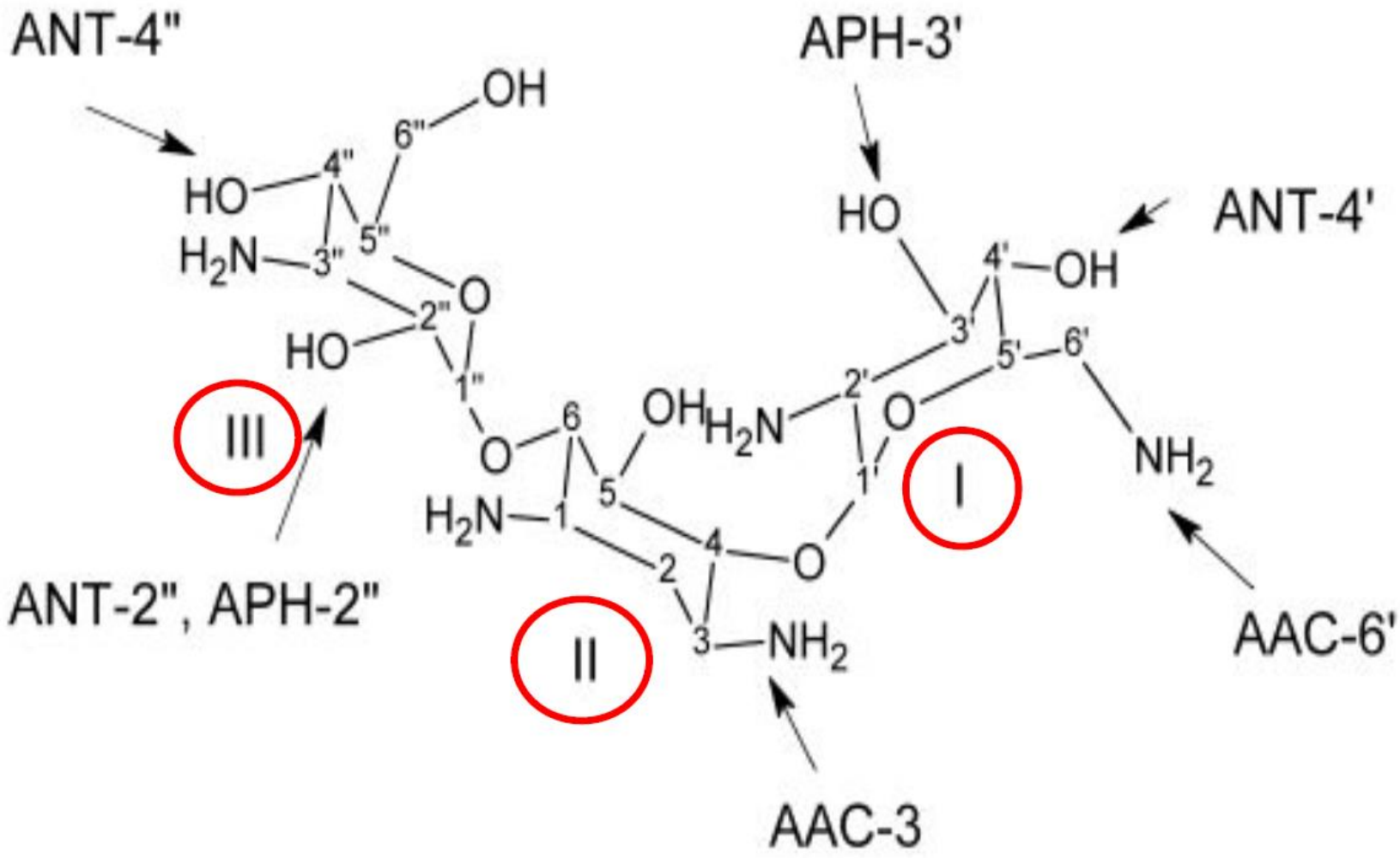
- Resistance of individual aminoglycosides to specific inactivating enzymes can be understood, in large measure, by using chemical principles.
- First, one can assume that if the target functional group is absent in a position of the structure normally attacked by an inactivating enzyme, then the antibiotic will be resistant to the enzyme.
- Second, steric factors may confer resistance to attack at functionalities otherwise susceptible to enzymatic attack.



- The phosphorylation reaction causing resistance to kanamycin



- Analogue of kanamycin which is resistant to phosphorylation



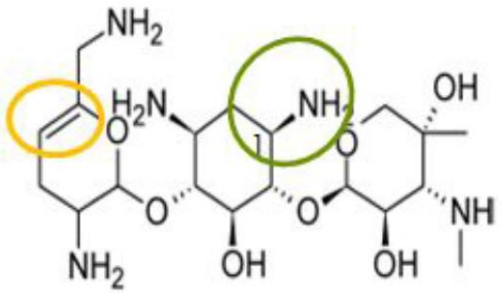
- Inactivation of kanamycin B by bacterial enzymes.

Structure–Activity Relationships

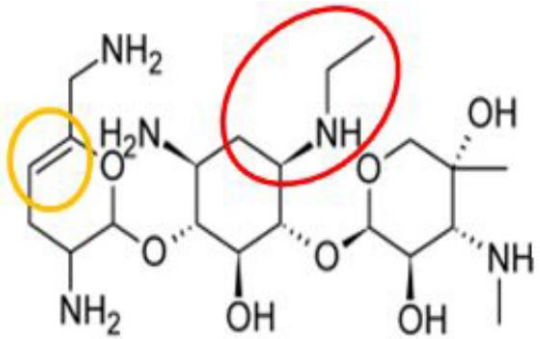
- It is convenient to discuss sequentially aminoglycoside SARs in terms of substituents in rings I, II, and III.
- Ring I is crucially important for characteristic broad spectrum antibacterial activity, and it is the primary target for bacterial inactivating enzymes.
- Amino functions at 6` and 2` are particularly important as kanamycin B (6`amino, 2`-amino) is more active than kanamycin A (6`-amino, 2`-hydroxyl), which in turn is more active than kanamycin C (6`-hydroxyl, 2`amino).

- Methylation at either the 6`-carbon or the 6`-amino positions does not lower appreciably antibacterial activity and confers resistance to enzymatic acetylation of the 6`-amino group.
- Removal of the 3`-hydroxyl or the 4`-hydroxyl group or both in the kanamycins (e.g., 3`,4`- dideoxykanamycin B or dibekacin) does not reduce antibacterial potency.
- The gentamicins also lack oxygen functions at these positions, as do sisomicin and netilmicin, which also have a 4`5`-double bond.

- None of these derivatives is inactivated by phosphotransferase enzymes that phosphorylate the 3 hydroxyl group.
- Evidently, the 3`-phosphorylated derivatives have very low affinity for aminoglycoside-binding sites in bacterial ribosomes.
- Few modifications of ring II (deoxystreptamine) functional groups are possible without appreciable loss of activity in most of the aminoglycosides.
- The 1-amino group of kanamycin A can be acylated (e.g., Amikacin), however, with activity largely retained. Netilmicin (1-N-ethylsisomicin) retains the antibacterial potency of sisomicin and is resistant to several additional bacteria-inactivating enzymes.



sisomicin

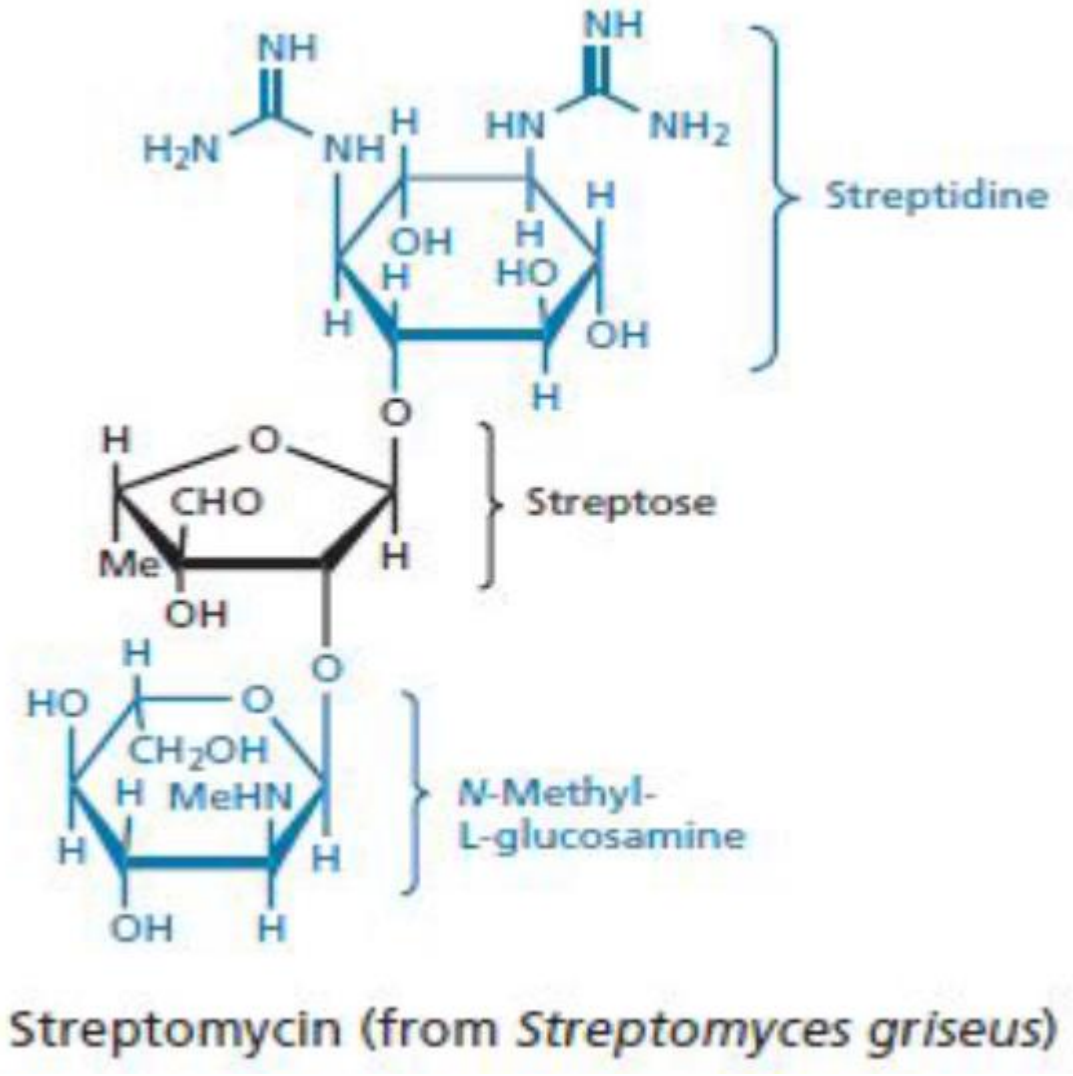


Netilmicin

- Ring III functional groups appear to be somewhat less sensitive to structural changes than those of either ring I or ring II.
- Although the 2``-deoxygentamicins are significantly less active than their 2``-hydroxyl counterparts, the 2``-amino derivatives (seldomycins) are highly active.
- The 3``-amino group of gentamicins may be primary or secondary with high antibacterial potency. Furthermore, the 4``- hydroxyl group may be axial or equatorial with little change in potency.

Products

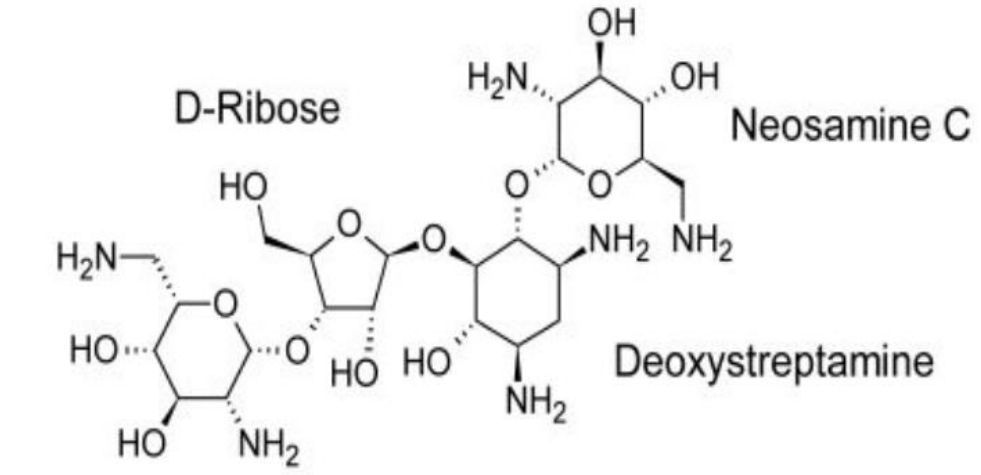
- Streptomycin Sulfate, Streptomycin acts as a triacidic base through the effect of its two strongly basic guanidino groups and the more weakly basic methylamino group
- Acid hydrolysis yields streptidine and streptobiosamine,



Streptomycin (from *Streptomyces griseus*)

Neomycin Sulfate

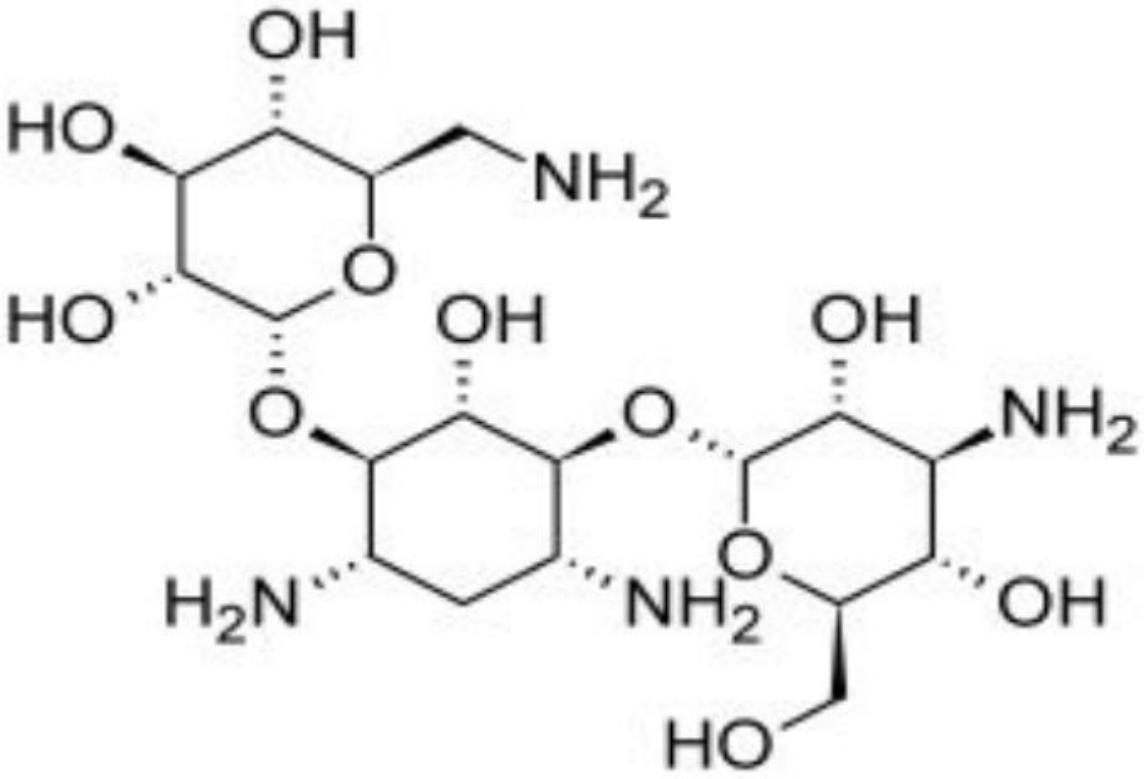
- It is considered one of the most useful antibiotics for the treatment of GI infections, It has broad-spectrum activity against various organisms and shows a low incidence of toxic and hypersensitivity reactions. It is absorbed very slightly from the digestive tract, so its oral use ordinarily does not produce any systemic effect.



- neomycin B differs from neomycin C by the nature of the sugar attached terminally to D-ribose. That sugar, called neosamine B, differs from neosamine C in its stereochemistry.

Kanamycin Sulfate

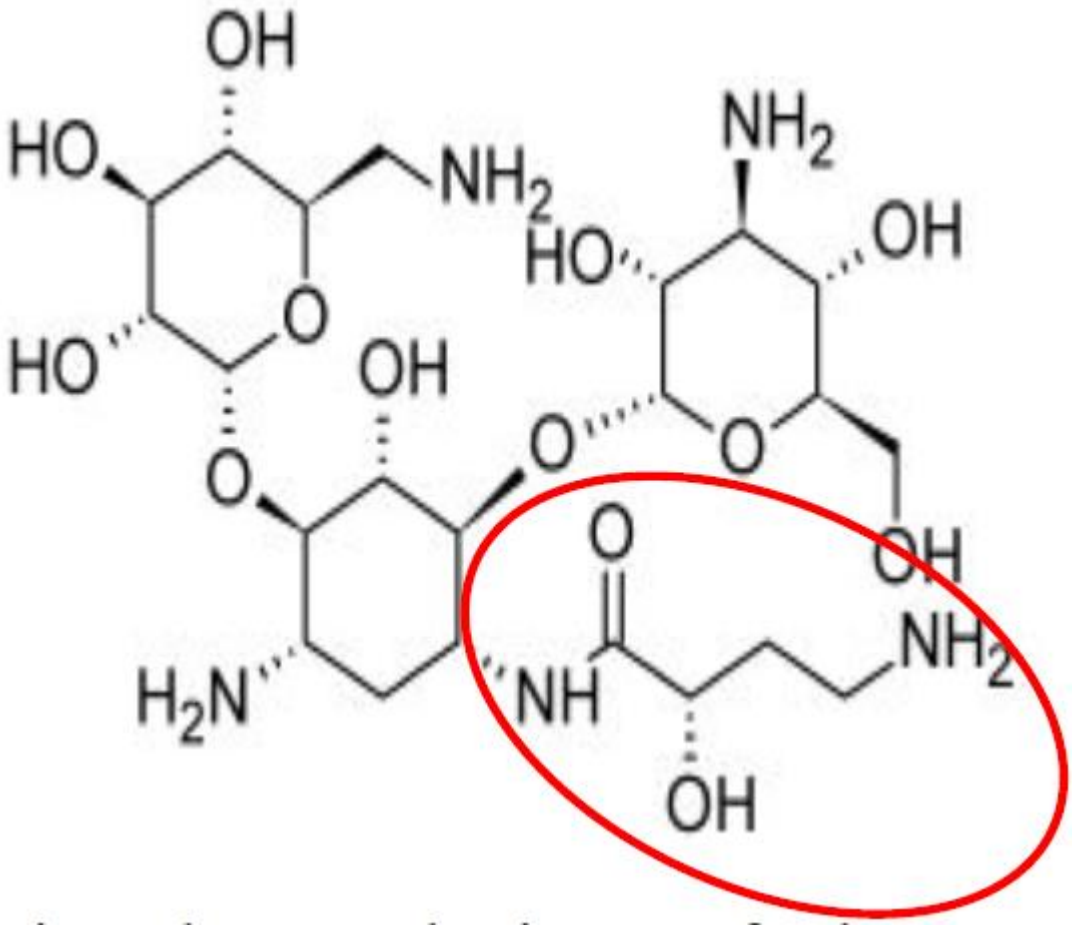
- Three closely related structures: kanamycins A, B, and C.
- Commercially available kanamycin is almost pure kanamycin A, the least toxic of the three forms.
- The kanamycins differ only in the sugar moieties attached to the glycosidic oxygen on the 4- position of the central deoxystreptamine



- The kanamycins do not have the D-ribose molecule that is present in neomycins and paromomycins. Perhaps this structural difference is related to the lower toxicity observed with kanamycins.
- The use of kanamycin in the United States usually is restricted to infections of the intestinal tract (e.g., bacillary dysentery) and to systemic infections arising from Gram negative bacilli.

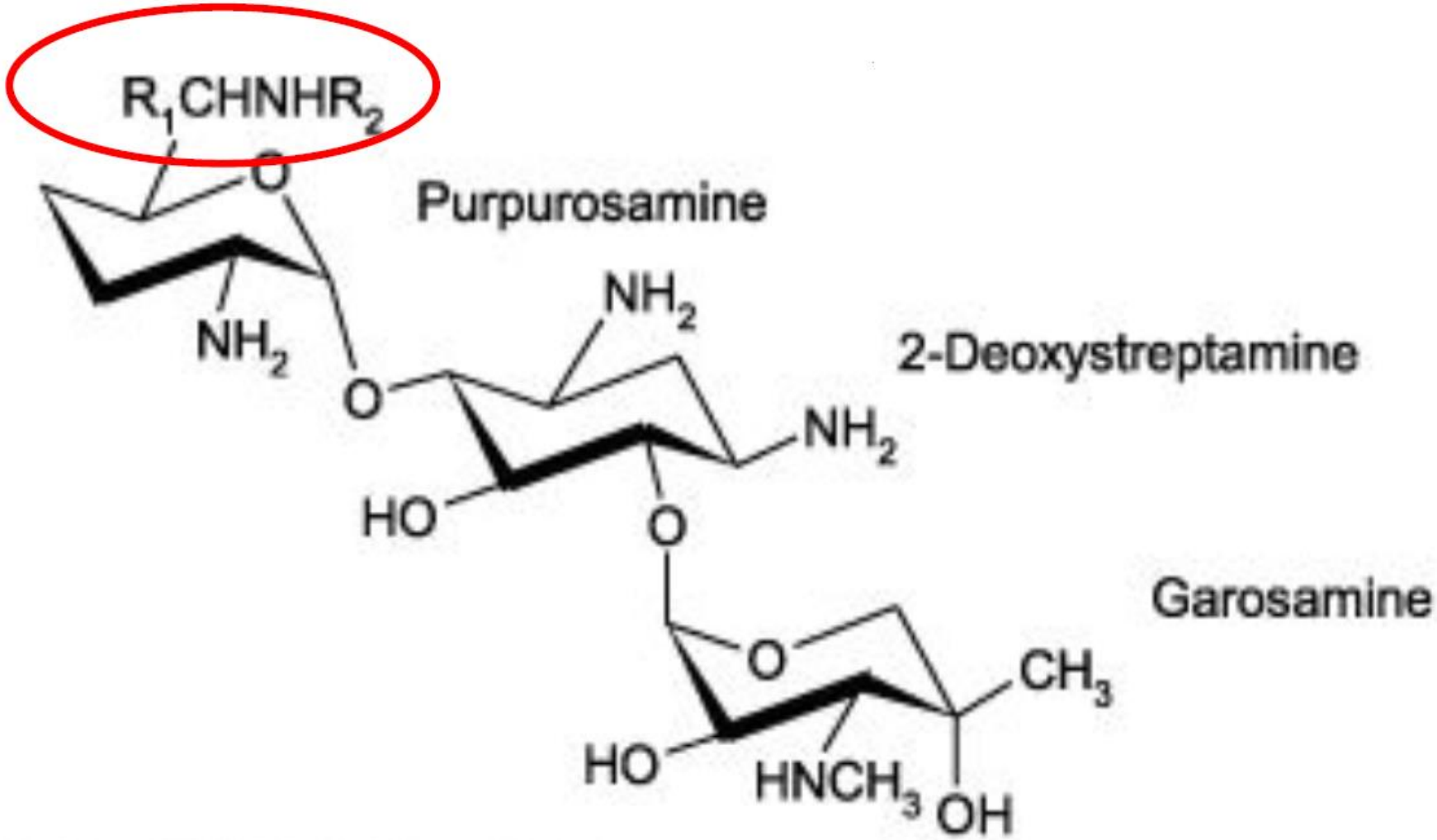
Amikacin

- 1-N-amino-α-hydroxy butyryl kanamycin A(Amikin), is a semisynthetic aminoglycoside first prepared in Japan.
- The synthesis formally involves simple acylation of the 1 amino group of the deoxystreptamine ring of kanamycin A.
- The remarkable feature of Amikacin is that it resists attack by most bacteria-inactivating enzymes and, therefore, is effective against strains of bacteria that are resistant to other aminoglycosides, including gentamicin and tobramycin.



Gentamicin Sulfate

- Gentamicin is composed of a number of related gentamicin components and fractions which have varying degrees of antimicrobial potency. The main components of gentamicin include members of the gentamicin C complex: gentamicin C1, gentamicin C1a, and gentamicin C2 which compose approximately 80% of gentamicin and have been found to have the highest antibacterial activity. Gentamicin A, B, X, and a few others make up the remaining 20% of gentamicin and have lower antibiotic activity than the gentamicin C complex



Gentamicin C_1 : $R_1 = R_2 = CH_3$

C_2 : $R_1 = CH_3$; $R_2 = H$

C_{1a} : $R_1 = R_2 = H$

THANK YOU

- ANY QUESTIONS??