CEPHALOSPORINS

Dr. Rand Shahin

:

Cephalosporins.

- The earliest cephalosporin was Cephalosporin C, isolated from the fungus Cephalosporium Acremonium.

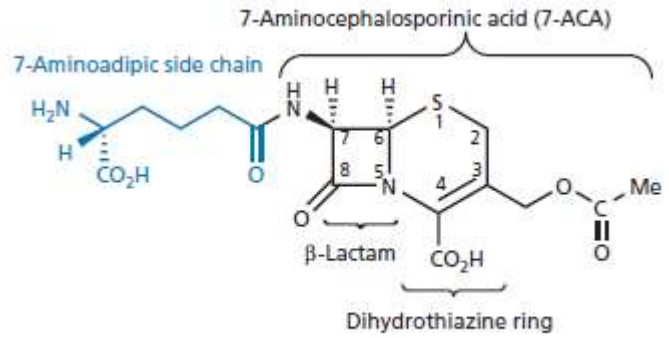
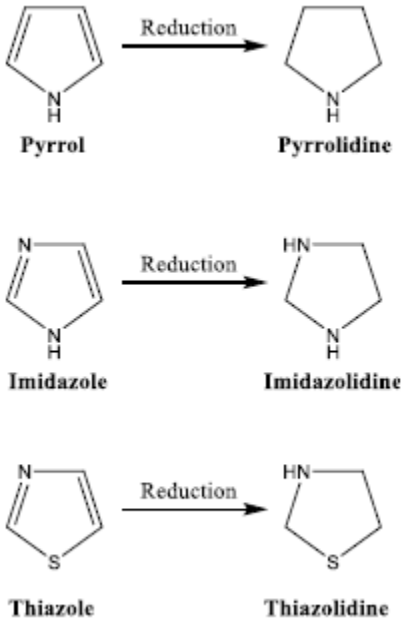
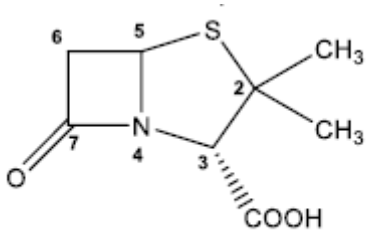


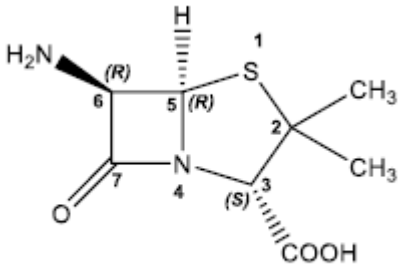
FIGURE 19.33 Cephalosporin C.

- It contains Dihydrothiazine ring instead of Thiazolidine ring in penicillins.
- Has the same mechanism of action as penicillins (inhibits cell wall cross linking).
- 7-ACA can be produces from Cephalosporin C and used semi synthetically to produce other cephalosporins
- Cephalosporin C is resistant to β-lactamases but the activity is inferior to penicillins .

Note: Beta lactamases are also called penicillinases, because they are specific to penicillins and this is the secret behind Cephalosporins being more stable







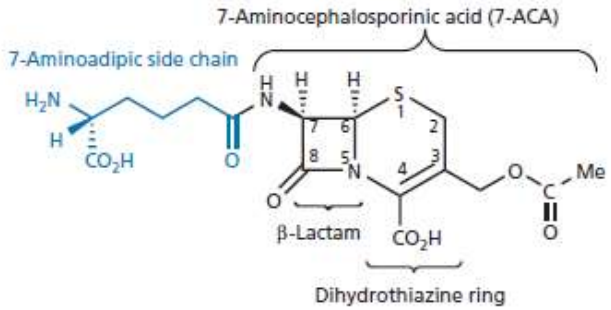
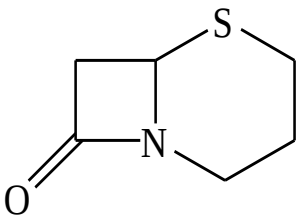


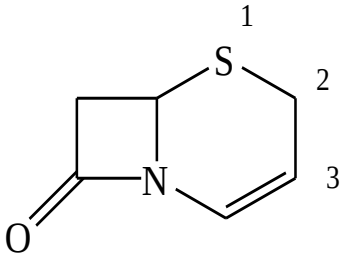
FIGURE 19.33 Cephalosporin C.

Nomenclature

- Semisynthetic derivatives of 7-amino group of 7ACA by acylation or by nucleophilic substitution or by reduction of the 3-acetoxy group

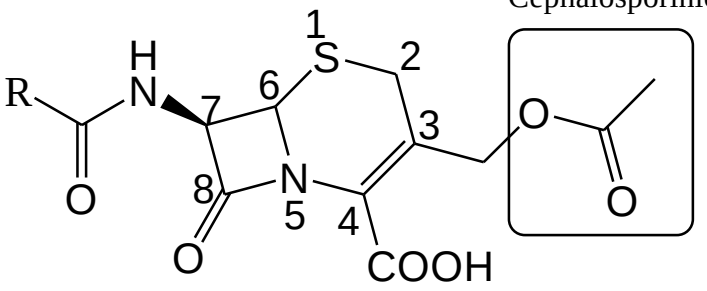


Cepham



3-Cephem, 2-Cephem are inactive

Acetoxy side chain of Cephalosporinic acid



Cephalosporins

- There is a limited number of places where modifications
- can be made, but there are more possibilities
- than with penicillins.
- These are as follows;
- variations of the 7-acylamino side chain;
- variations of the 3-acetoxymethyl side chain;
- extra substitution at carbon 7.

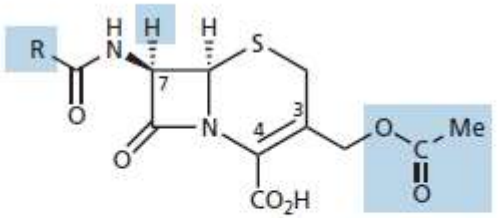


FIGURE 19.36 Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

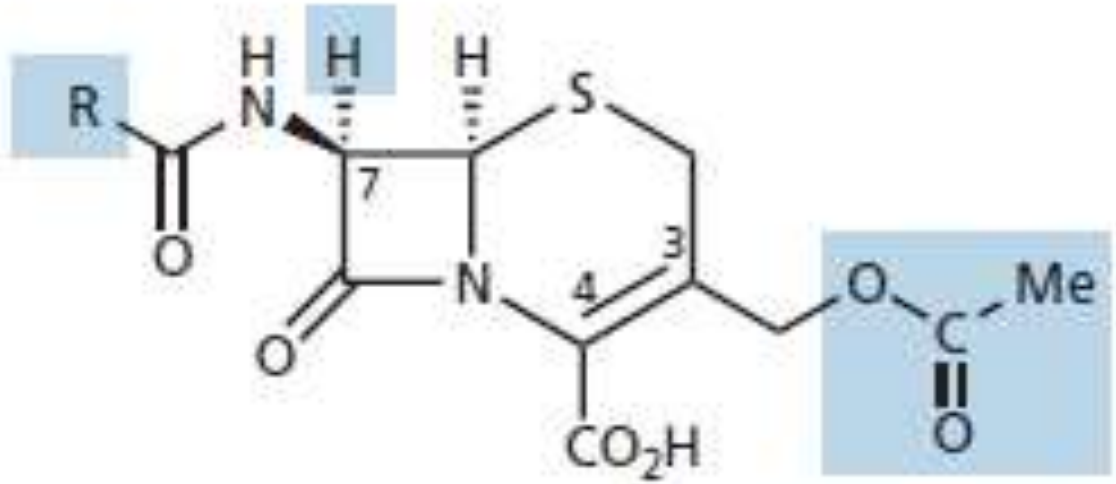
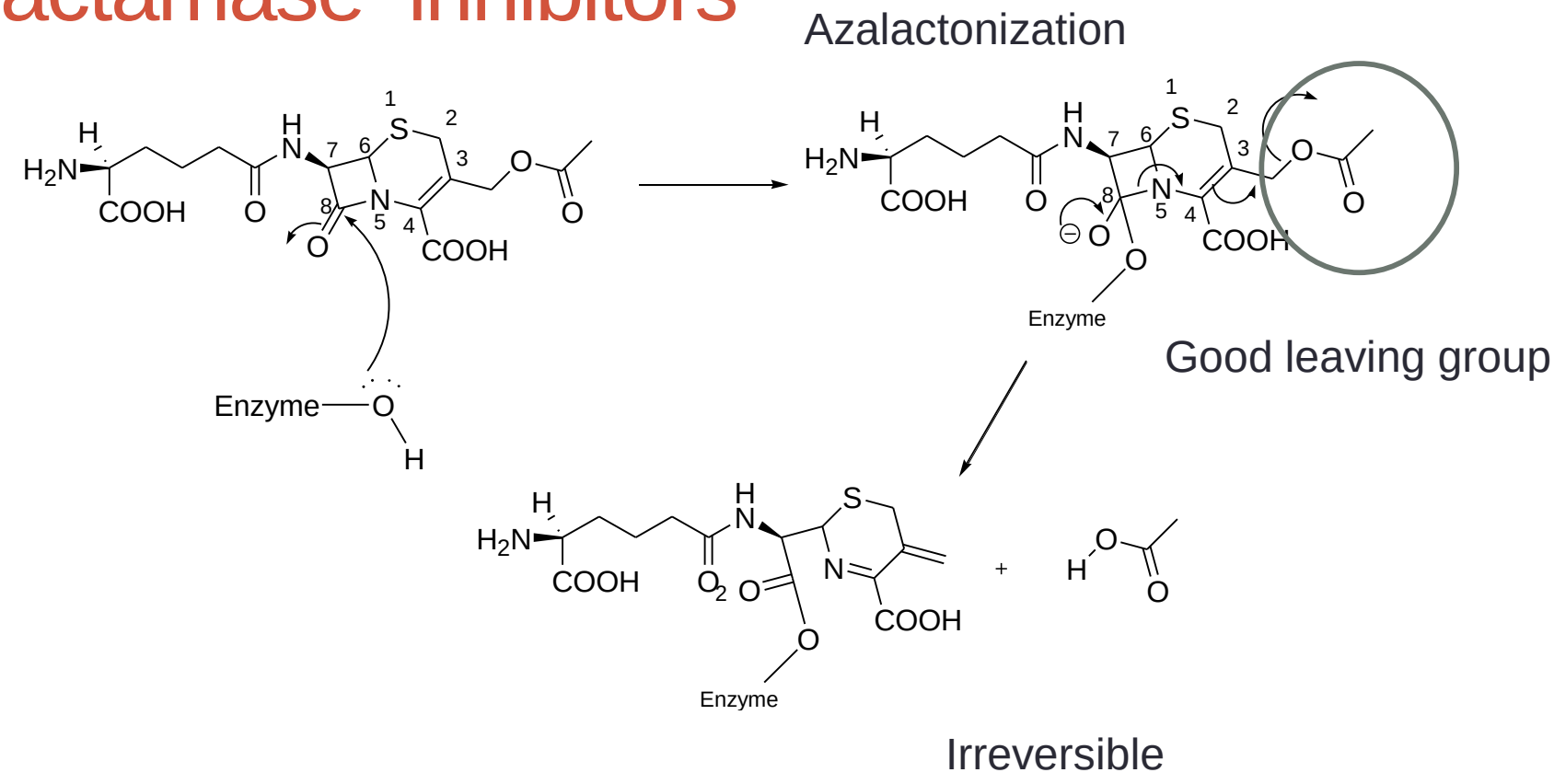


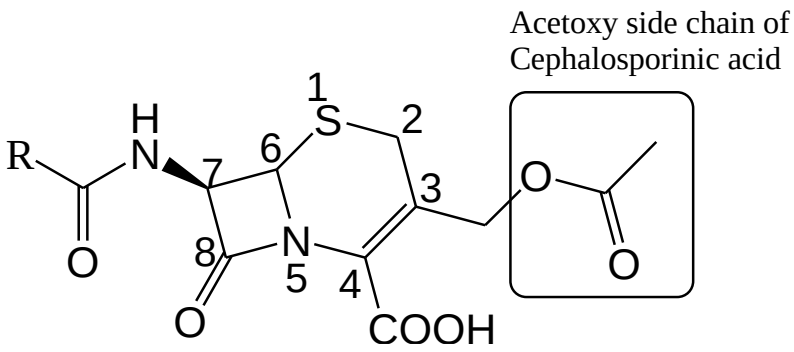
FIGURE 19.36 Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

Cephalosporins are β-lactamase resistant Cephalosporins are considered as β-lactamase inhibitors



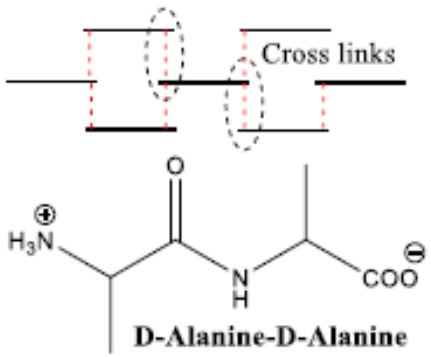
SAR of Cephalosporins

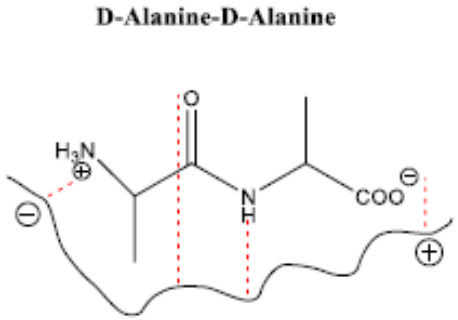
- Similar to penicillins in the 7-amino group.
- The carboxylic acid at **C_4** is essential.
- 3-Acetyoxy group at **C_3 can be easily varied** by nucleophilic substation

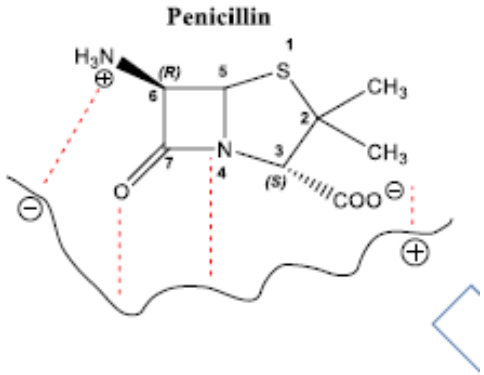


Why are the carboxylic acid and the amine group so important inhibiting the crosslinking?

- **NOTES**:
- - The amine groups and carboxyl groups are ionized at neutral PH (ammonium and carboxylate).
- - Alanines in our bodies are L-alanin, but the bacteria use D-alanin (99% of the organisms use L-amino acids; rarely D-amino acids are used).
- - The enzyme that uses this D-ala-D-ala as crosslinks
- is called "**Transpeptidase**" or "**Penicillinbinding protein**".
- When we look at D-ala-D-ala at 3D view with penicillin at the other side, we will note that both have similar pharmacophoric requirements (Binding features). Both have carboxylate, ammonium, and amide linkage, which will make electrostatic attractions and hydrogen bonging with the catalytic binging pocket of the Transpeptidase enzyme. So the enzyme will confuse between the penicillin and its original substrate D-ala-D-ala due to their dimensional similarity, and both can bind to the same binging pocket.

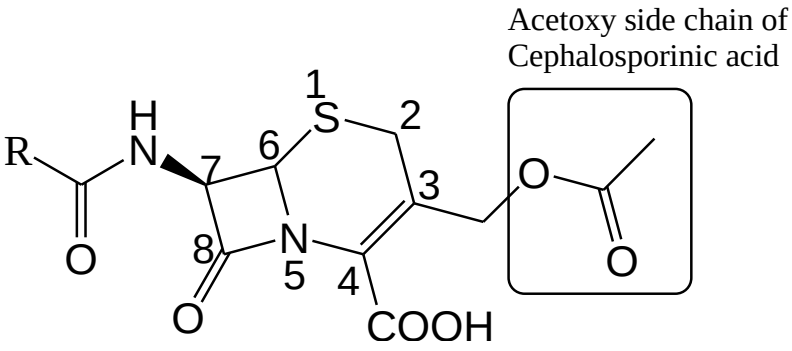


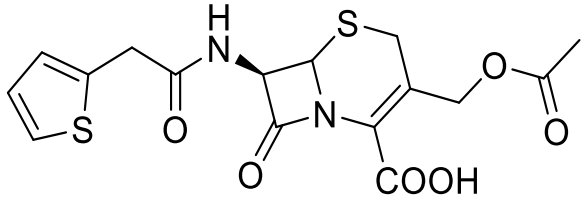




SAR of Cephalosporins

- The acetoxymethyl (position 3) can be substituted, but still substation will lead to decrease in activity.
- Cephalosporines can be easily hydrolysed by strong acidic conditions and nucleophiles.
- If COOH group at position 4 is esterified the product is inactive.
- Acylases can cleave acyl of penicillinic acid – type structures under acidic conditions at the 7-amino position
- Neutral and basic conditions lead to intramolecular aminolysis of β-lactams
- Enzymatic hydrolysis of 3-acetoxymethyl in some Cephalosporins is responsible for some loss in activity





Cephalothin One of the most commonly used fi rst-generation cephalosporins
easily hydrolysed in the blood by estarases to give the inactive alcohol metabolite
mainly given parenterally

Replacing the ester with a metabolically stable pyridinium group gives **cephaloridine**

- . The pyridine can still act as a good leaving group for the inhibition mechanism, but is not cleaved by esterases. Cephaloridine exists as a zwitterion and is soluble in water, but, like most first generation cephalosporins, it is poorly absorbed through the gut wall and has to be injected.

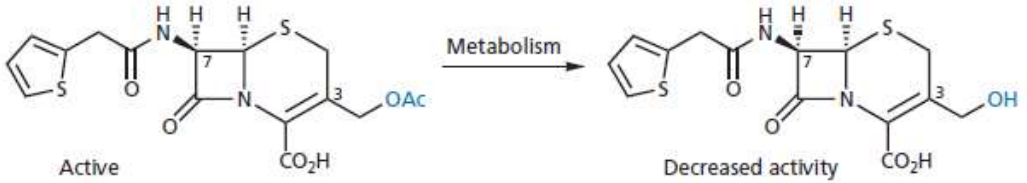


FIGURE 19.40 Metabolic hydrolysis of cephalothin.

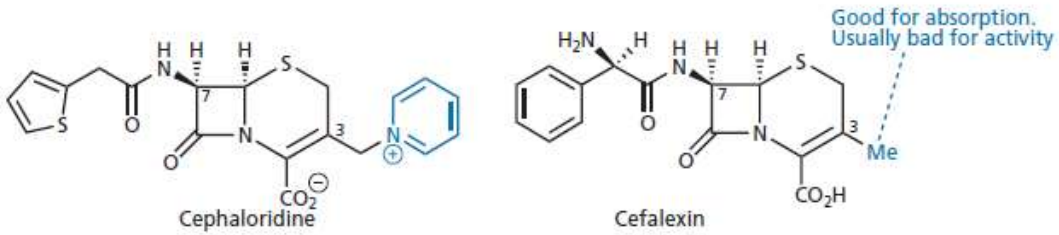


FIGURE 19.41 Cephaloridine and cefalexin.

Oral Cephalosporins

- 1. α-amino groups stabilizes the carbonyl and prevent breakdown by azalactonization
- 2. Zwitter ionic cephalosporins are dipeptides (cysteine and Valine) like and are actively transported by carriers through the GIT (just like Ampicillin and Amoxicillin)

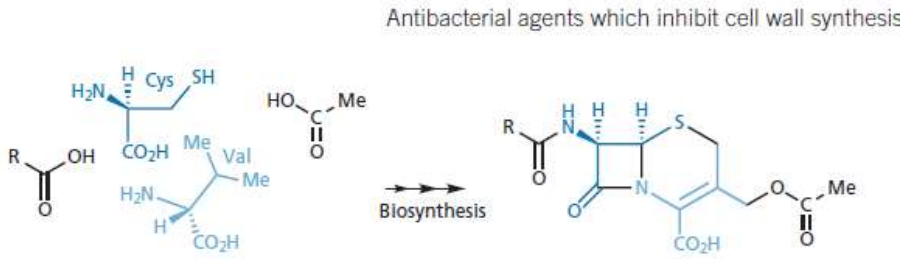
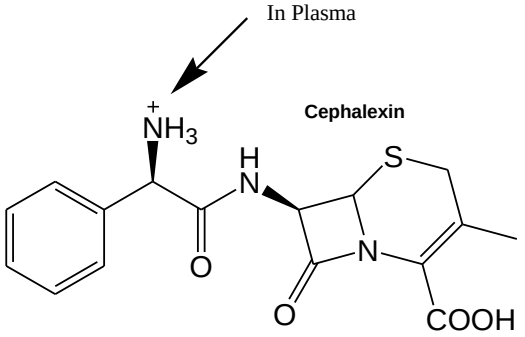
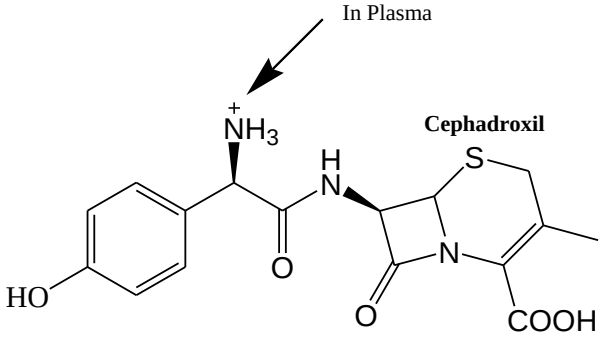


FIGURE 19.34 Biosynthetic precursors of cephalosporin C.

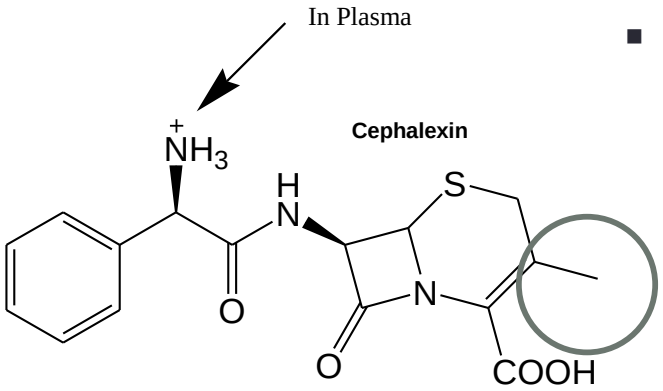


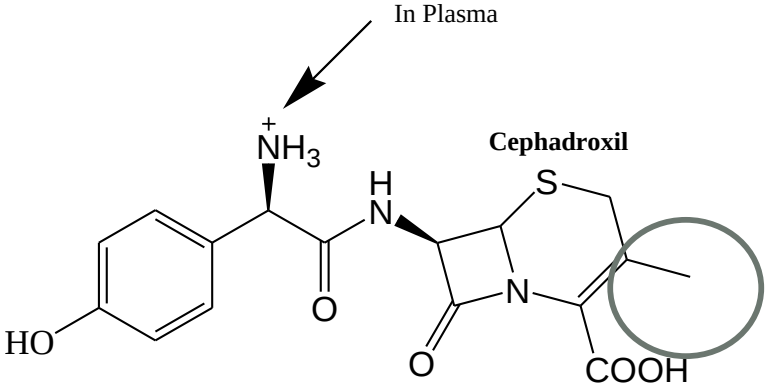


Cephalexin and **Cephadroxil**
less active than cephalothin due to the poor leaving methyl group
better oral bioavailability than cephalothin

Examples of orally active cephalosporines

- Reduction of 3-acetoxy to methyl **gives oral activity**
- Cephalosporines degrade by nucleophiles in a similar manner to penicillins by breaking the β lactam ring .





Cephalexin and **Cephadroxil**
less active than cephalothin due to the poor leaving methyl group
better oral bioavailability than cephalothin

Cefalexin (First generation Cephalosporin) has a methyl substituent at position 3 which appears to help oral absorption.
A methyl group would normally be bad for activity as it is not a good leaving group.
However, the presence of a hydrophilic amino group at the α-carbon of the 7-acylamino side chain in cefalexin helps to restore activity and cephalexin is one of the few cephalosporins which is orally active.
The mechanism of absorption through the gut wall is poorly understood and it is not clear why the 3-methyl group is so advantageous for absorption.
Cefazolin is another example of a first-generation cephalosporin.

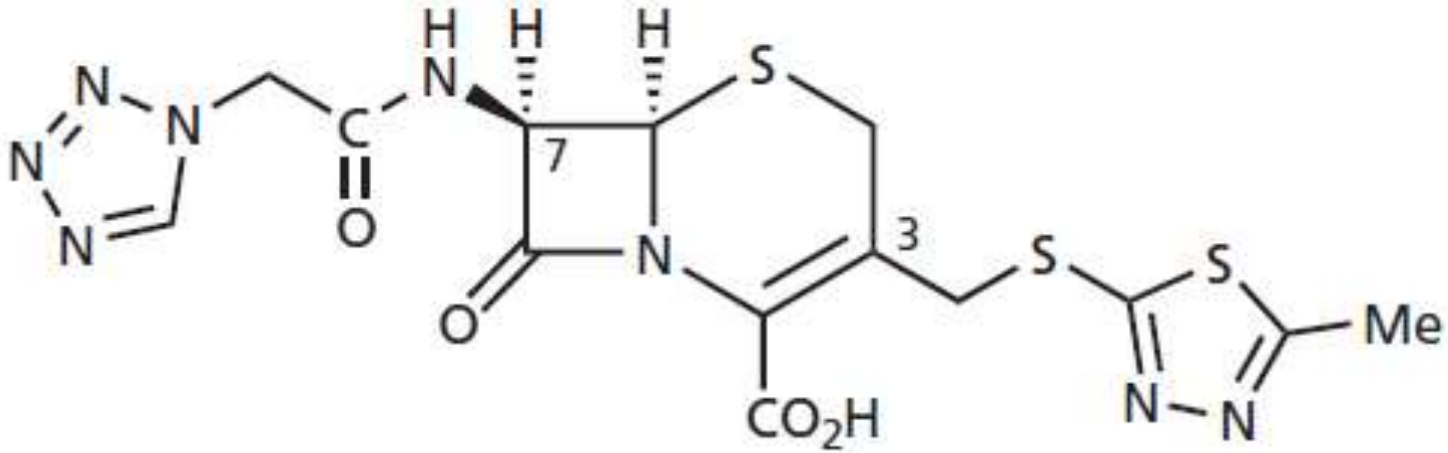
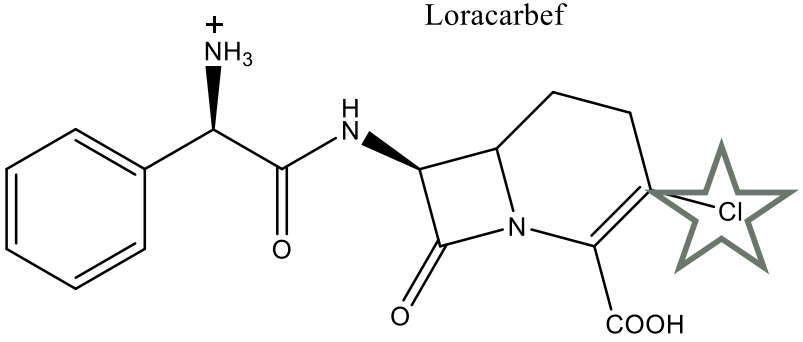


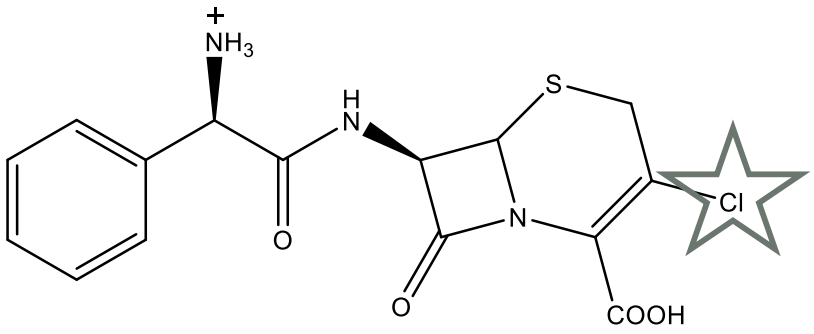
FIGURE 19.42 Cefazolin.

Another examples on orally active Cephalosporins

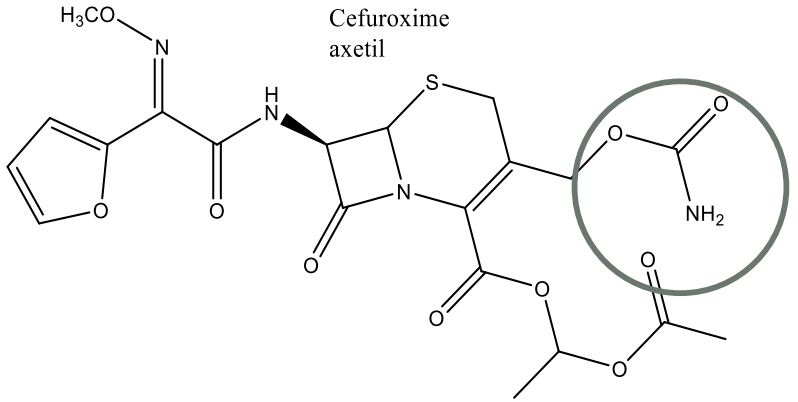
Loracarbef



Cefaclor

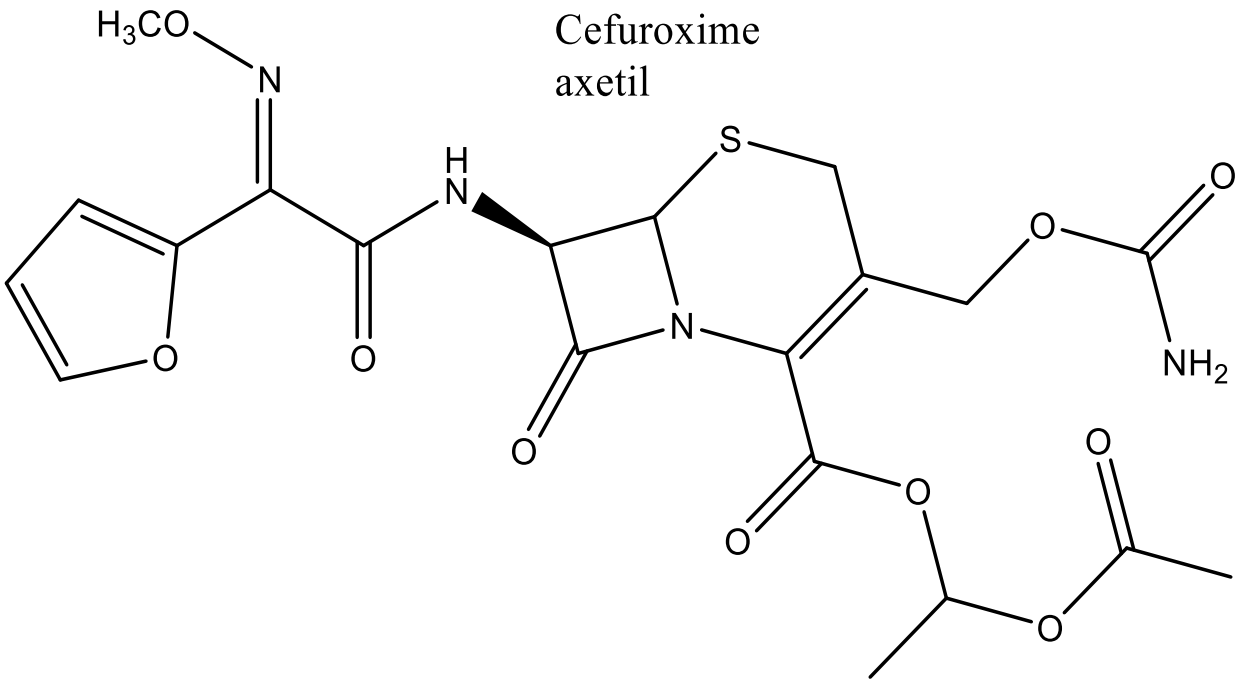


- If the 3-acetoxymethyl was replaced by lipophilic acid-resistant ester then it gives oral activity.



Acid stable ester

Orally active ester prodrug of cefuroxime that release the drug in plasma by esterases Carbamate is a bad leaving group.has an increased resistance to â-lactamases and mammalian esterases.(Second generation cephalosporin)



Cefuroxime axetil

Acid stable ester

Orally active ester prodrug of cefuroxime that release the drug in plasma by esterases
Carbamate is a bad leaving group.has an
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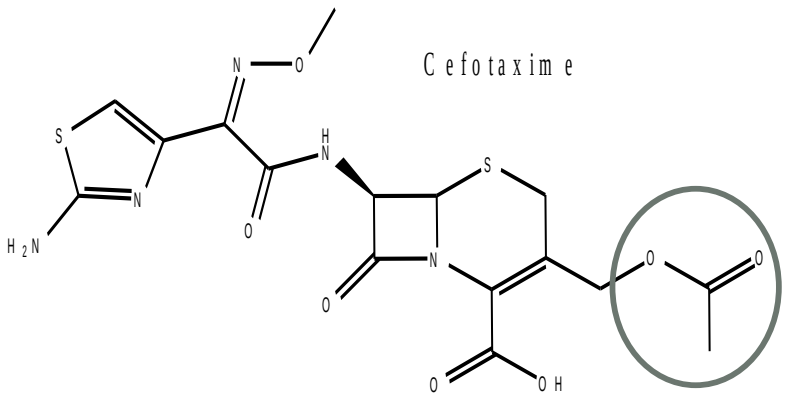
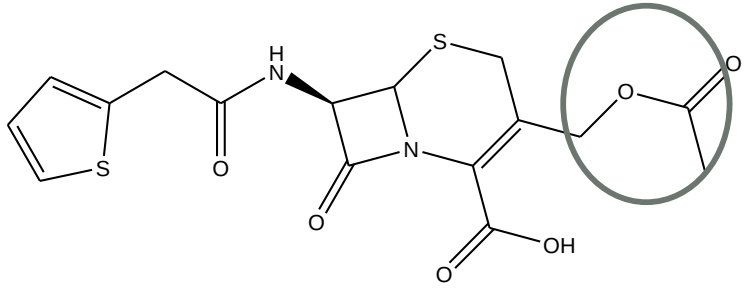
Parentral Cephalosporins

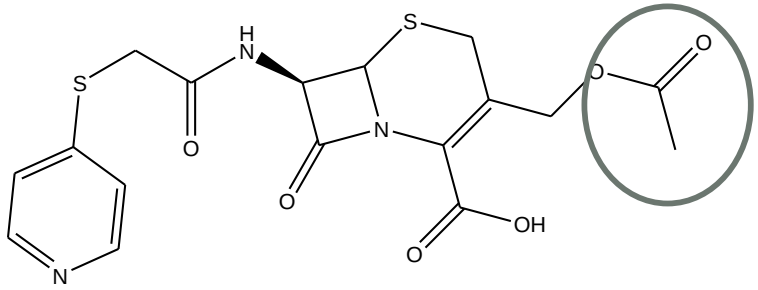
- Examples :



Cephalothine



Cephapirin

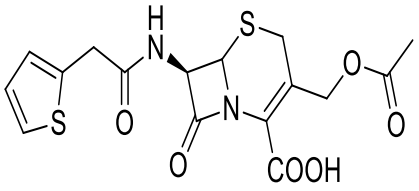


Classification of Cephalosporins

- Divided into first, second, third, fourth, and fifth generations based on their time of discovery and antimicrobial properties.
- From first to third :
- 1. broader gram negative spectrum
- 2. some reduction in gram positive spectrum
- 3. enhanced resistance to β-lactamase

1st Generation Cephalosporins

- Have lower activity than penicillin but they have broader spectrum action.
- Still susceptible to β-lactamase degradation.



Cephalothin
easily hydrolysed to give the inactive alcohol metabolite
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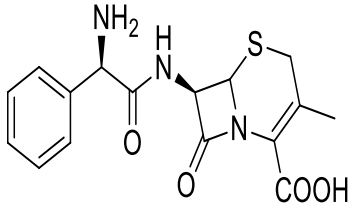


Cephalexin
less active than cephalothin due to the poor leaving methyl group
better oral bioavailability than cephalothin

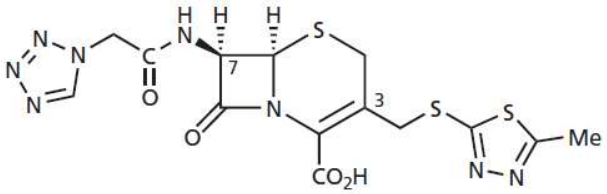
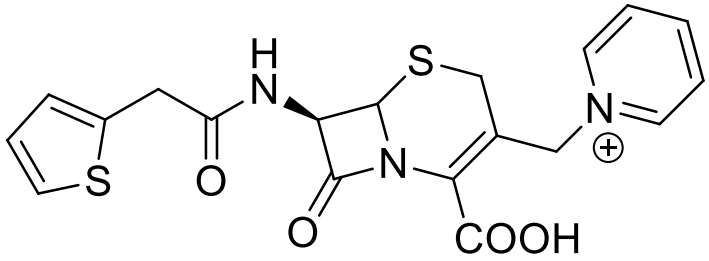


FIGURE 19.42 Cefazolin.

1st Generation Cephalosporins



Cephaloridine

- Have the good leaving group, pyridinium ion.. This improves the activity.
- This group is not hydrolysable compared to the acetyloxy group found in cephalothin.
- Poorly absorbed from the gut because it will be ionized all the time.
- Only given parenterally.

Second-generation cephalosporins
Cephamycins

- **Cephamycins** contain a methoxy substituent at position 7, which has proved advantageous.
- The parent compound **cephamycin C** was isolated from a culture of *Streptomyces clavuligerus* and was the first β-lactam to be isolated from a bacterial source
- N.B: The functional groups that β-lactamase resistance at α-carbon group of penicillins lead to complete loss of activity for the cephosporins against Staph aureus and other gram positive bacteria.

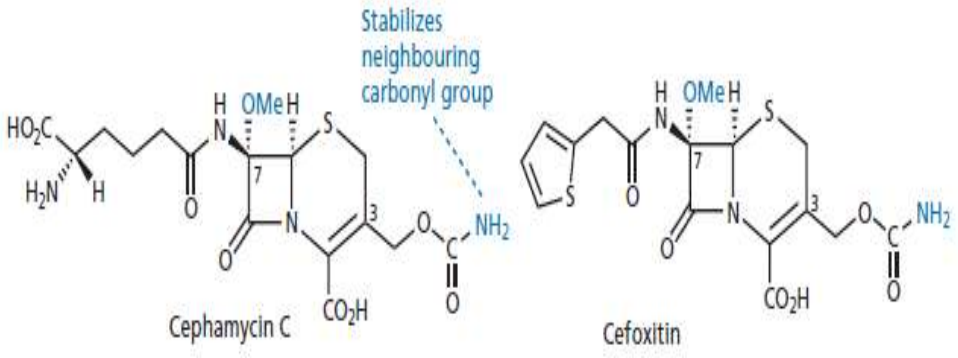


FIGURE 19.43 Cephamycin C and cefoxitin.

methoxy group gave **cefoxitin**, which showed a broader spectrum of activity than most first-generation cephalosporins.
This is due to greater resistance to β-lactamase enzymes, which may be due to the steric hindrance provided
by the methoxy group.
Cefoxitin shows good metabolic
stability to esterases owing to the presence of the **urethane** group at position 3, rather than an ester

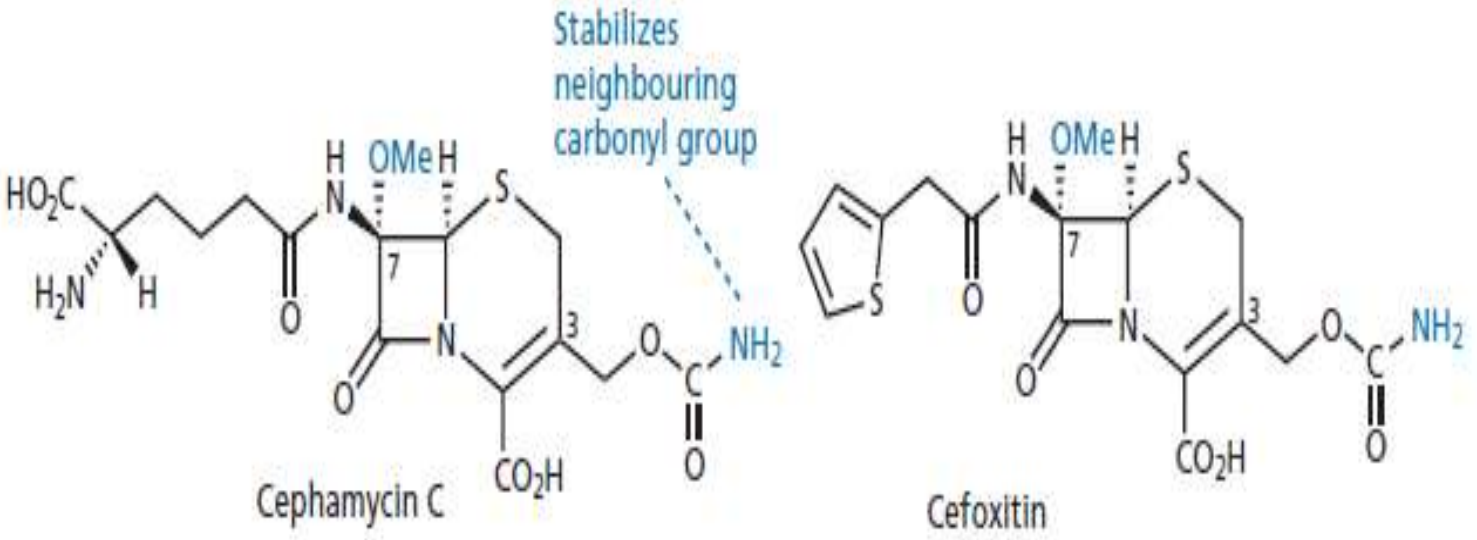


FIGURE 19.43 Cephamycin C and cefoxitin.

Oximinocephalosporins

- The development of **oximinocephalosporins** has been a major advance in cephalosporin research.
- These structures contain an **iminomethoxy group** at the α-position of the acyl side chain, which significantly increases the stability of cephalosporins against the β-lactamases produced by some organisms (e.g. ***Haemophilus influenza***).
- The first useful agent in this class of compounds was **cefuroxime** which, like cefoxitin (mentioned in the previous slide), has an increased resistance to β-lactamases and mammalian esterases. Unlike cefoxitin, cefuroxime retains activity against streptococci and, to a lesser extent, staphylococci.

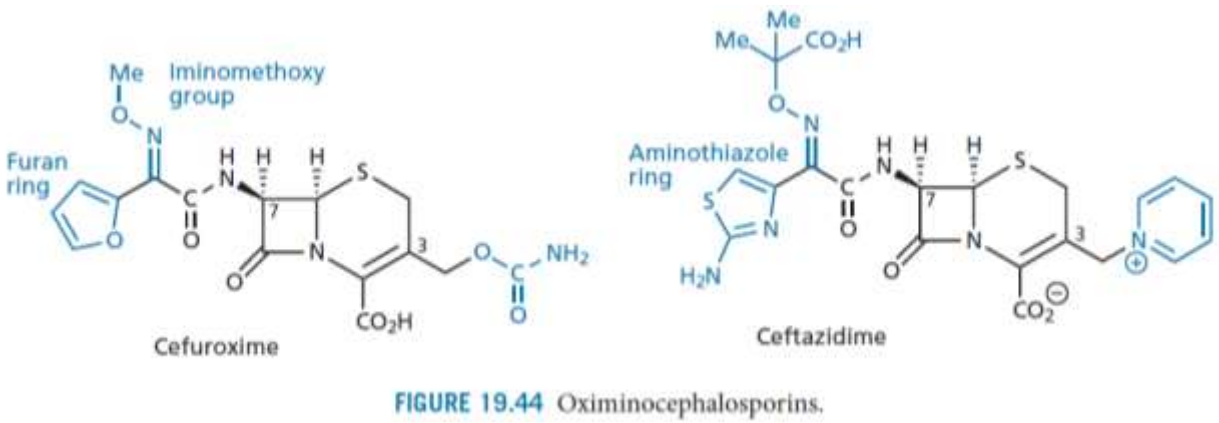
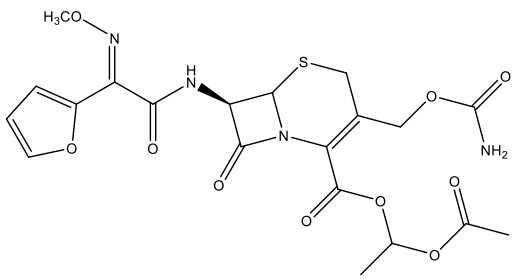


FIGURE 19.44 Oximinocephalosporins.



Cefuroxime axetil

Third-generation cephalosporins

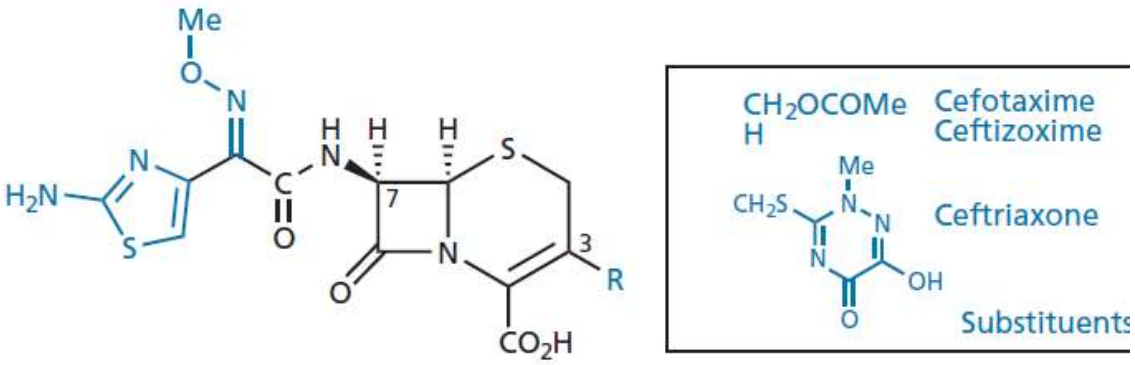


FIGURE 19.45 Third- and fourth-generation oximinocephalos

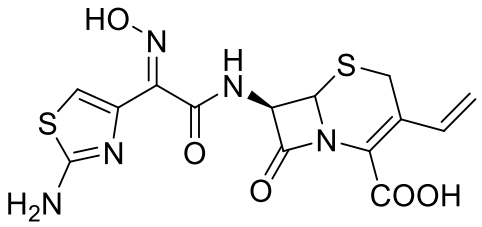
Replacing the furan ring of the aforesaid oximinocephalosporins with an **aminothiazole ring** enhances the penetration of cephalosporins through the outer membrane of Gram-negative bacteria, and may also increase affinity for the transpeptidase enzyme.

Third-generation cephalosporins

- As a result, third-generation cephalosporins containing this ring have a marked increase in activity against t Gram-negative bacteria bacteria. A variety of such structures have been prepared, such as **ceftazidime** , **cefotaxime** ,
- **ceftizoxime** , and **ceftriaxone**
- With different substituents at **position 3** to vary the pharmacokinetic properties. They play a major role in antimicrobial therapy because of their activity against Gram-negative bacteria, many of which are resistant to other β-lactams. As such infections are uncommon outside hospitals, physicians are discouraged from prescribing these drugs routinely and they are viewed as ‘reserve troops’ to be used for
- troublesome infections which do not respond to the more commonly prescribed β-lactams.

3rd Generation Cephalosporins

- Cefdinir (Omnicef®):
  - It has a broad spectrum activity.
  - More active on gram –ve bacterial infections such as respiratory, skin and soft tissues infections.
  - Estimated oral bioavailability is 20-25%
  - LogP = 0.02
  - pKa = 3.27



Fourth-generation cephalosporins

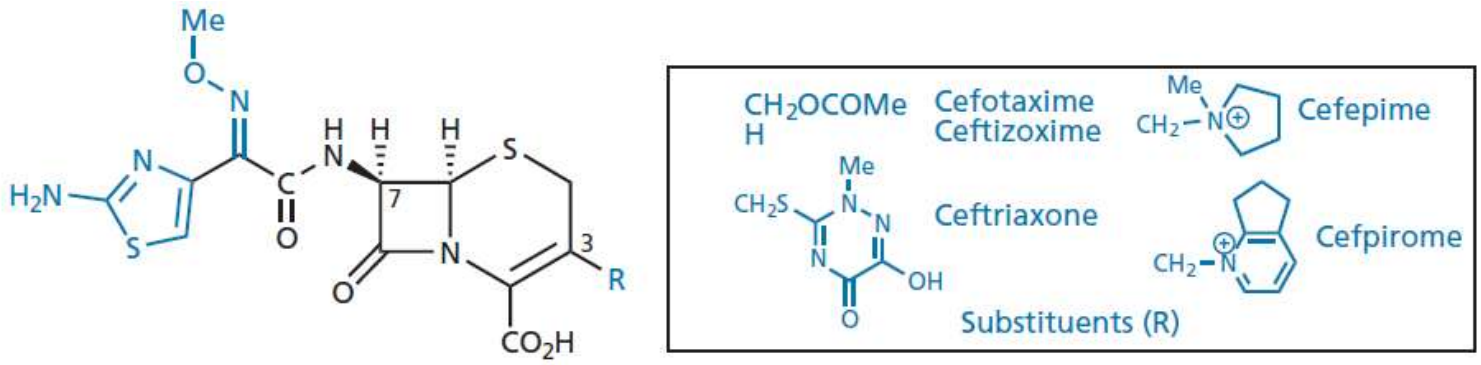
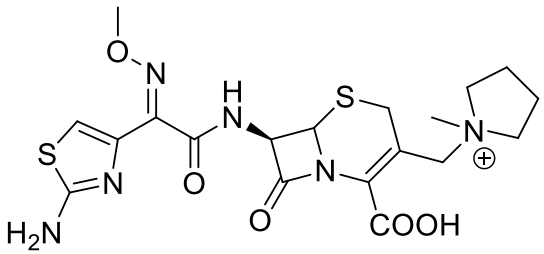


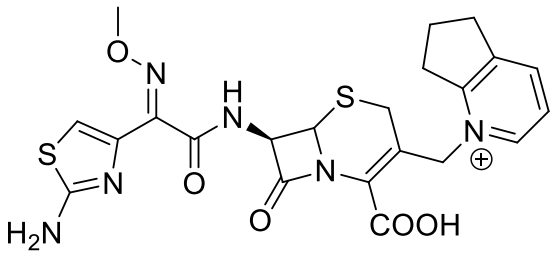
FIGURE 19.45 Third- and fourth-generation oximinocephalosporins.

Cefepime and **cefpirome** are oximinocephalosporins which have been classed as fourth-generation cephalosporins. They are zwitterionic compounds having a positively charged substituent at position 3 and a negatively charged carboxylate group at position 4. This property appears to radically enhance the ability of these compounds to penetrate the outer membrane of Gram negative bacteria.
They are also found to have a good affinity for the transpeptidase enzyme and a low affinity for a variety of β-lactamases.

4th Generation Cephalosporins



Cefipime

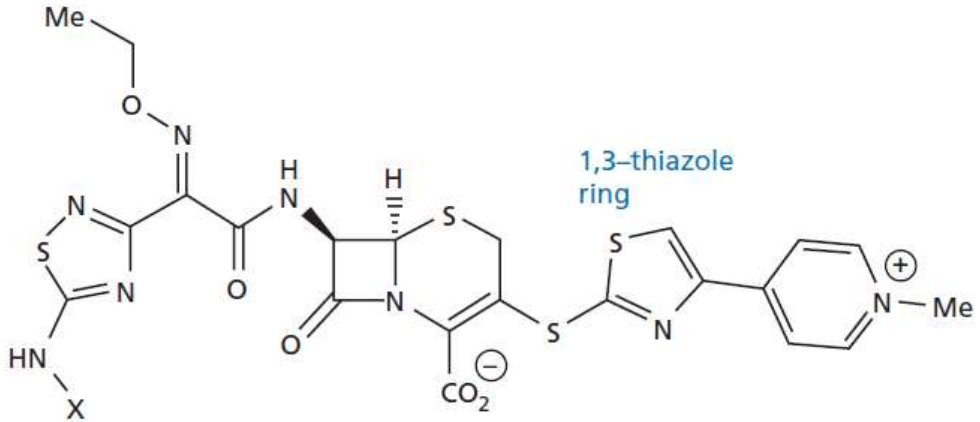


Cefpirome

- They have a positively charged group at C_3 which become a good leaving group during the binding with transpeptidase.
- They are more polar than the old generation, better penetration for the outer membrane of gram –ve bacteria.
- More stable toward β-lactamase.

Fifth-generation cephalosporins

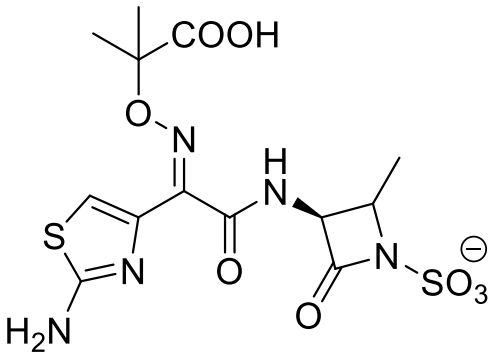
- **Ceftaroline fosamil** is a fifth-generation cephalosporin that has activity against various strains of MRSA and multi-resistant *Streptococcus pneumonia* (MDRSP).
- It acts as a prodrug for **ceftaroline** , and the 1,3-thiazole ring is thought to be important for its activity against MRSA.



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

FIGURE 19.46 Ceftaroline and ceftaroline fosamil.

Monobactams



Aztreonam

- It has a limited activity against gram +ve bacteria.
- Because it does not have the fused ring system, Aztreonam is believed to have different mechanism of action..
- highly polar structure which reduce the oral bioavailability… it is recommended to be given parenterally

Side effects and drugs interactions

- Comperatively non-toxic and selective action to bacterial cell wall by inhibiting cell-wall cross linking enzymes similar to penicillins
- Most common side effect is hypersensitivity
- Allergic reactions are believed to be less frequent in cephalosporins than penicillins
- Cross – allergy between penicillins and cephalosporins is very low (3%-7%) only.

Side effects and drugs interactions

- Cephalosporins containing N-methyl-5-thiotetrazole (MTT) such as: Cefamandol, Cefotetan, Cefmetazol, Moxalactam, and Cefoperazone have been implicated in hypoprothrombinemia, might lead to severe bleeding in some cases, The bleeding is reversed by vit. K administration (weakly).
- MTT cephalosporin are contraindicated with heparin and oral anticoagulants therapy.
- MTT Cephalosporins inhibit aldehyde dehydrogenase which oxidizes acetaldehyde to acetic acid leading to alcohol intolerance.