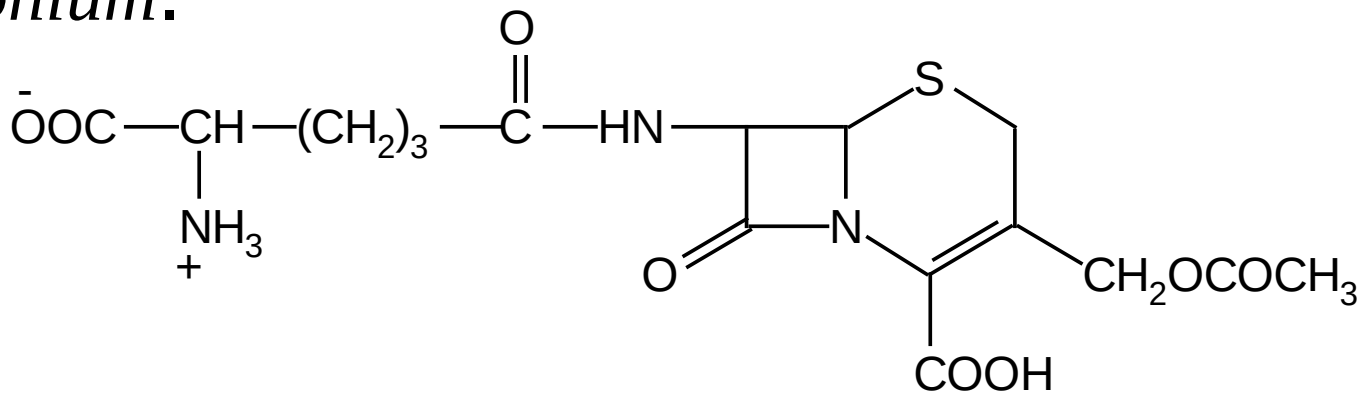
Cephalosporins

Cephalosporins are similar to penicillins in terms of mechanism of action, chemical structure, and toxicities.

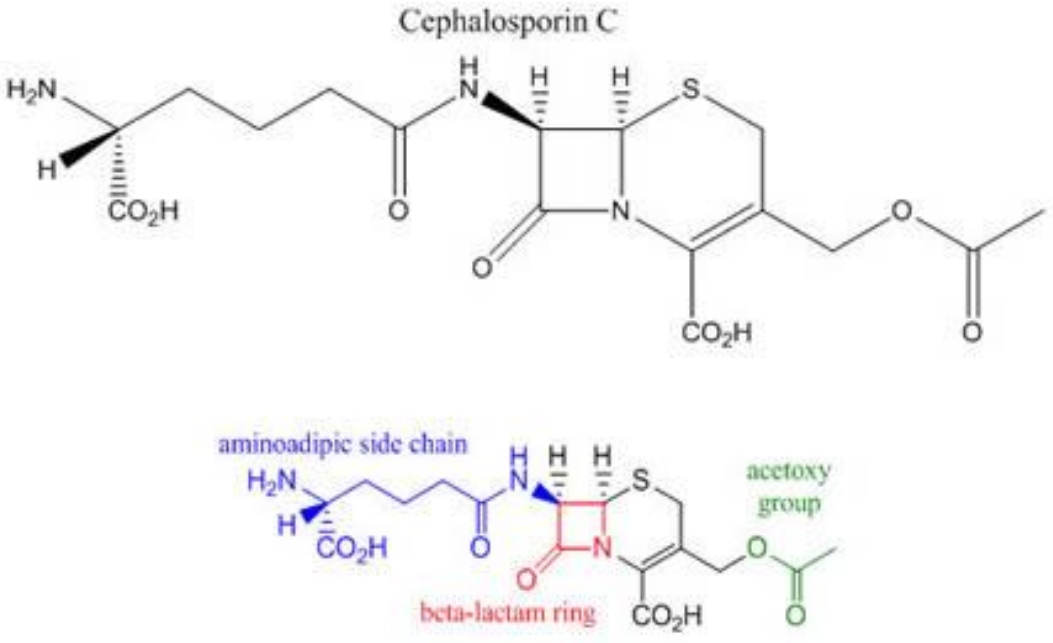
Cephalosporins are the second major group of β-lactam antibiotics to be discovered.

All cephalosporins molecules are based on cephalosporin C, which was discovered by Edward Abraham and his colleagues in Oxford as a minor component of the antibiotic complex produced by *Cephalosporium acremonium*.



The structure of cephalosporin C involves:

1. A **six membered dihydrothiazine** ring with an **acetoxymethyl group** at its 3-position. This ring is fused to four membered β-lactam ring.
2. An **α-aminoadipoyl side chain**, that on hydrolysis yields 7-aminocephalosporanic acid (7ACA).



Properties of Cephalosporin C

2. Low potency.

3. Not absorbed orally. 4. Non toxic.

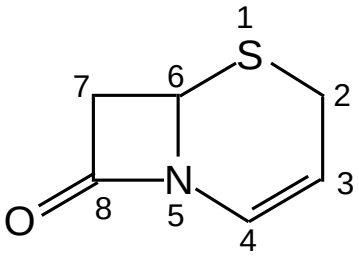
5. Relatively stable to acid hydrolysis compared to penicillins.

6. More stable to penicillinase than penicillin G.

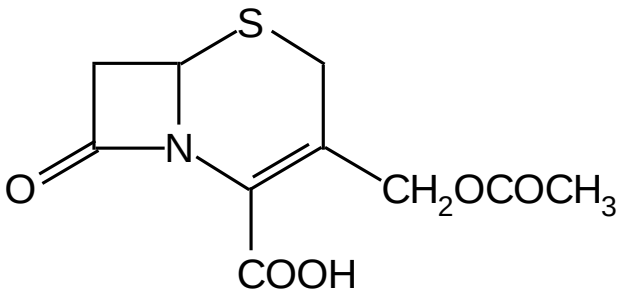
7. The 7-aminocephalosporanic acid can be modified at a number of positions to obtain the semisynthetic cephalosporins.

8-Moreover, the likelihood of causing allergic reactions is less. As a result, cephalosporin C became a useful lead compound for the development of better antibiotics

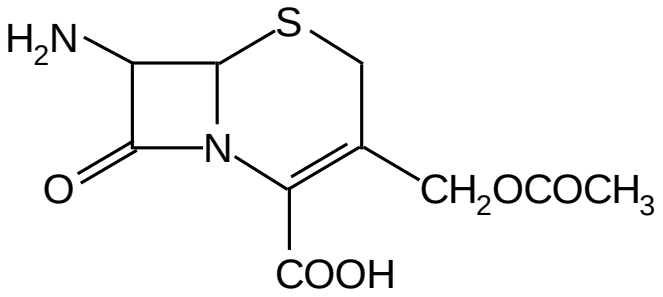
Nomenclature of the Semisynthetic Cephalosporins



3-Cephem



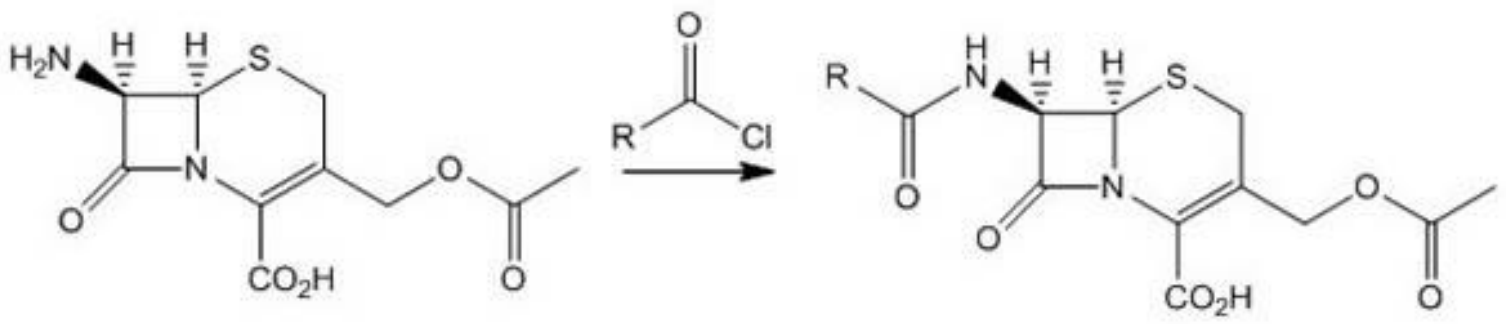
Cephalosporanic acid

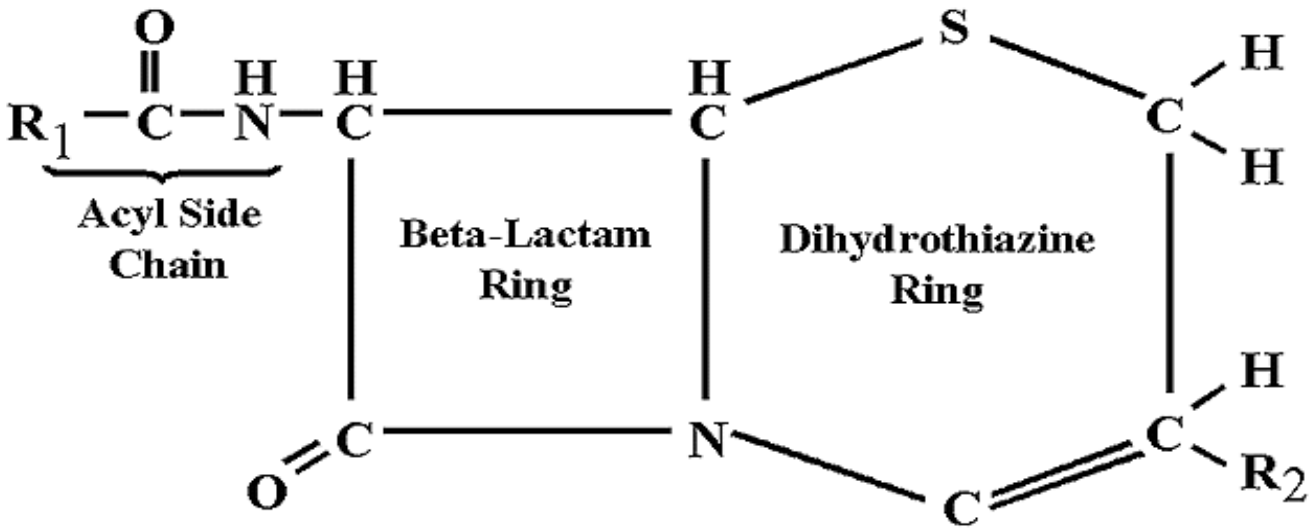


7-Aminocephalosporanicacid (7-ACA)

7-aminocephalosporinic acid (7-ACA) is used as the precursor of many cephalosporins.

Cephalosporin analogues may be formed by reacting 7-ACA with acid chlorides.





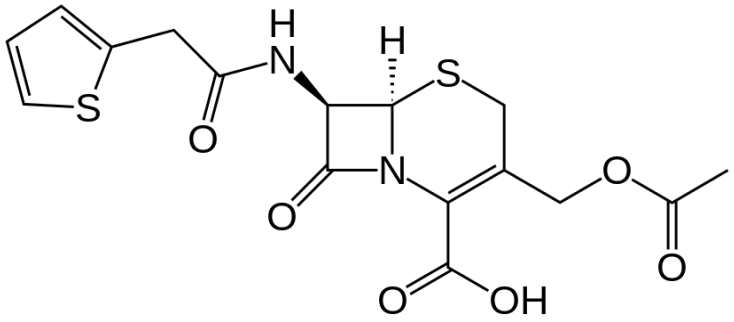
General Structure of Cephalosporins

First Generation Cephalosporins

-Produced between 1960-1970.
-Broad-spectrum activity against many Gram-positive bacteria.
-They are not significantly active against Gram-negative organisms.
-Poor ability to penetrate cerebrospinal fluid.-
-Inactive against Pseudomonas.

A. Parenteral Agents

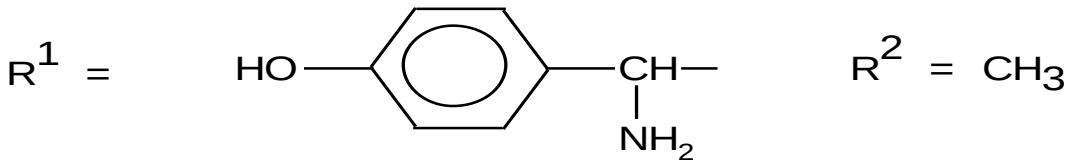
Cefalotin (Cephalothin)



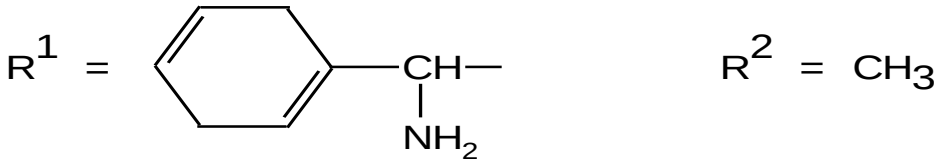
7-(2-Thienylacetamido)-3-acetoxymethyl-Δ^3-Cephem-4-carboxylic acid

B. Oral Agents

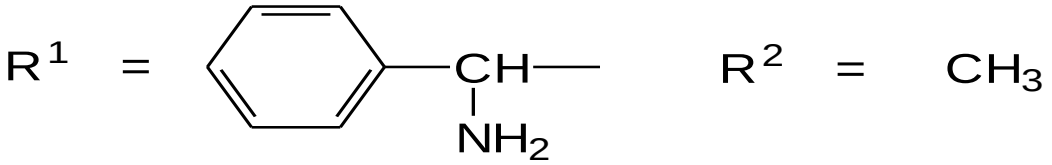
i. Cefadroxil



ii. Cephradine

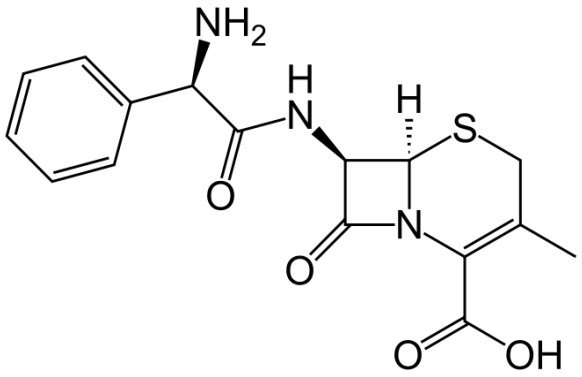


iii. Cephalexine



Cephalexine

7-[(D-α-amino-α-phenyl)acetamido]-3-methyl-Δ3- cephem-4-carboxylic acid.



Second Generation Cephalosporins

Produced between 1970-1980.

Broad-spectrum activity especially against Gram-positive bacteria and including H. influenzae and some **increased activity against Gram-negative** organisms.

Some drugs can pass the cerebrospinal fluid.

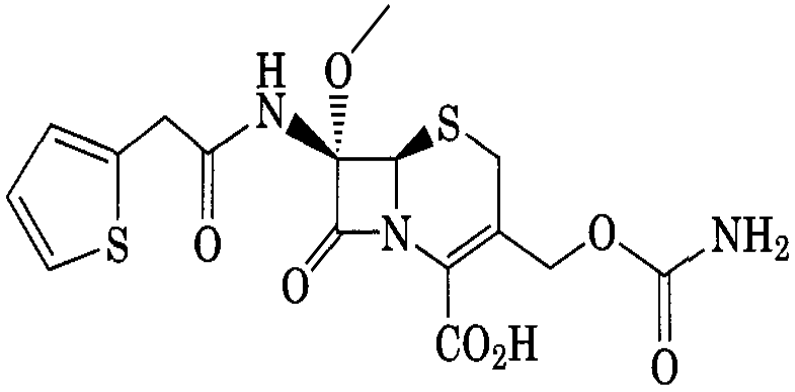
Many drugs are for parenteral use.

A. Parenteral Agents

i. Cefoxitin

7-[2-(2-Thienyl)acetamido]-7-α-methoxy-3-carbamoyloxymethyl-Δ3-cephem-4-carboxylic acid.

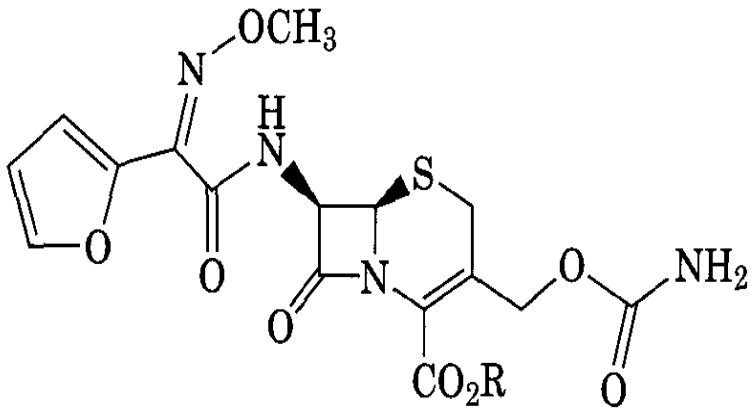
The α-Methoxy group at C-7 ⟶ steric hindrance ⟶ **high stability against β-lactamases.**



ii. Cefuroxime

Other parenteral drugs include Cefamandole and Cefonicid. Cefuroxime R = H

Cefuroxime axetil **R** = CH(CH3)0Ac

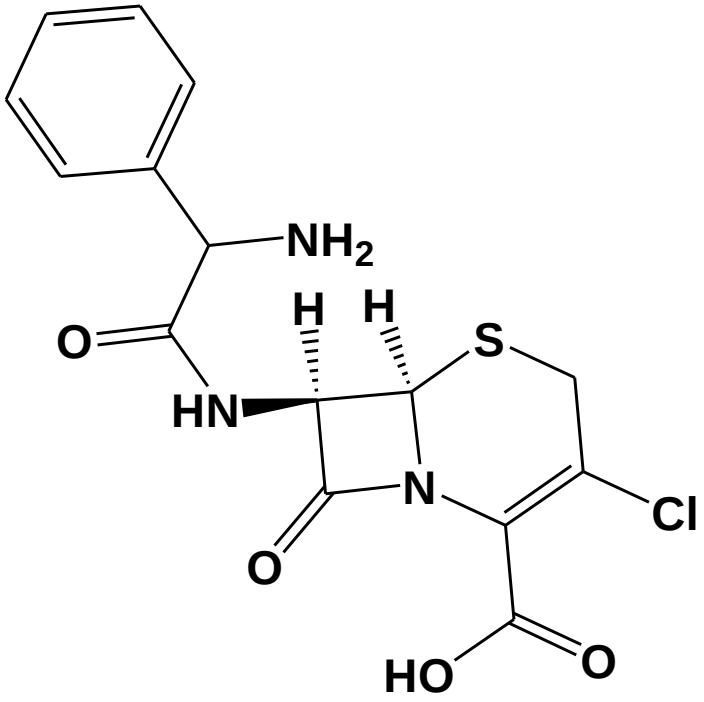


The oxime group increases the stability against β-lactamases

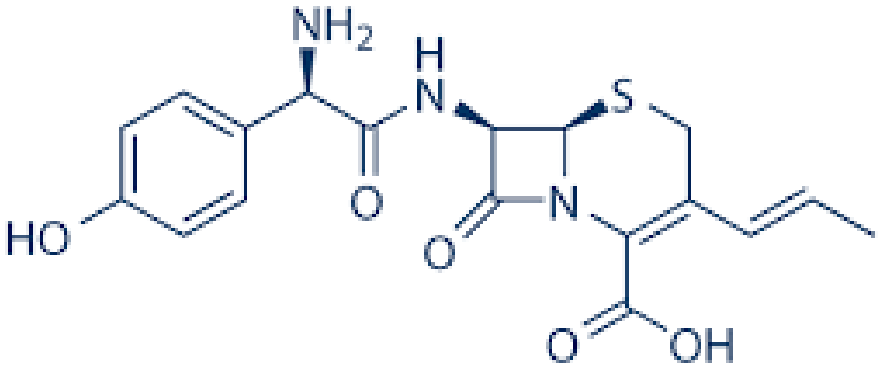
B. Oral Agents

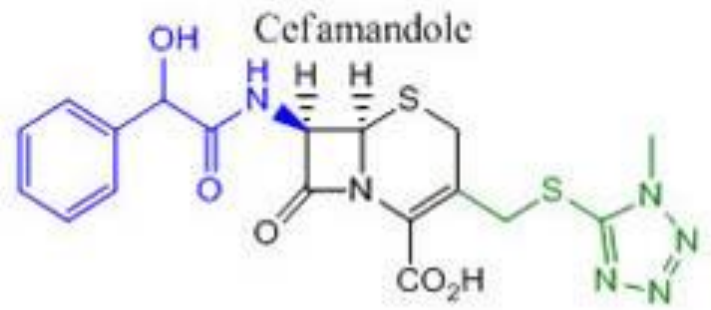
i. Cefaclor

7-[(D-α-amino-α-phenyl)acetamido]-3-chloro-Δ3-cephem-3-carboxylic acid.



Cefprozil





The presence of the iminomethoxy group appears to increase stability against certain β-lactamases

Third Generation Cephalosporins

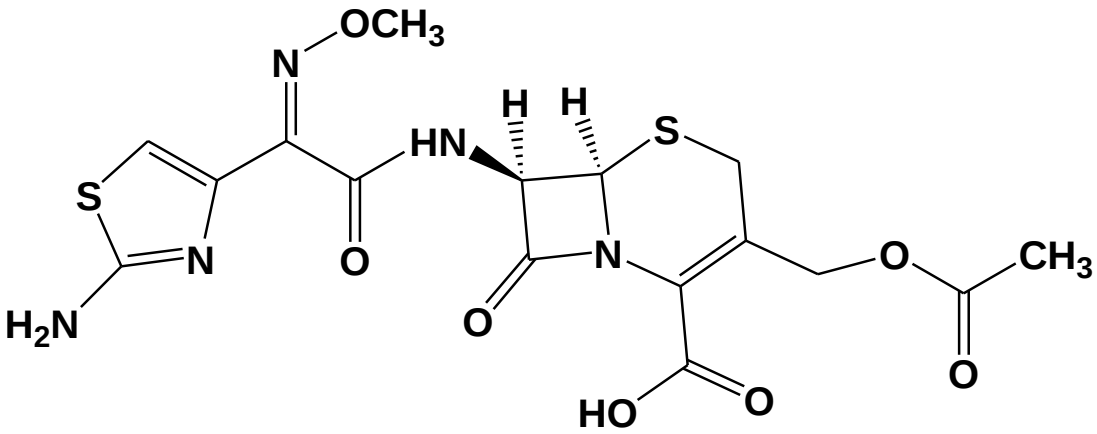
- Produced after1980.
- **Broader spectrum** against Gram-negative organisms on the expense of their Gram-positive activity. They are effective in treating a large variety of infections resistant to many other drugs.
- Some drugs have **high activity** against Pseudomonas aeruginosa.
- Many drugs are for **parenteral use**.
- **More resistance** to β-lactamases.
- They are **very expensive**.

A. Parenteral Agents

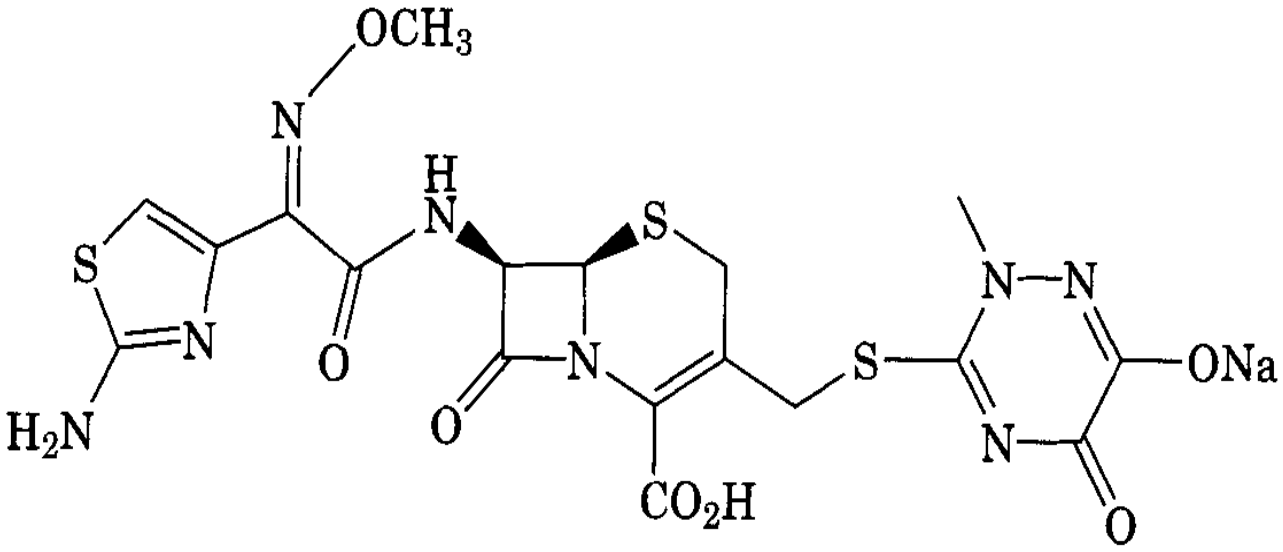
Cefotaxime

7-[(2-Amino-4-thiazolyl)-2-methoxyimino)-acetamido]-3-acetylyloxy-methyl-Δ3-cephem-4-carboxylic acid.

It has an excellent broad spectrum activity against Gram -ve and Gram +ve aerobic and anaerobic bacteria.

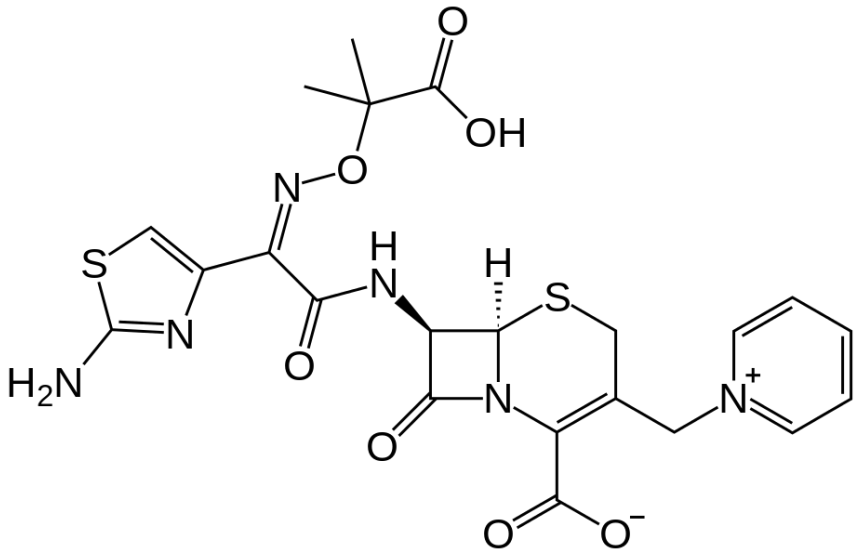


Ceftriaxone



Ceftazidime

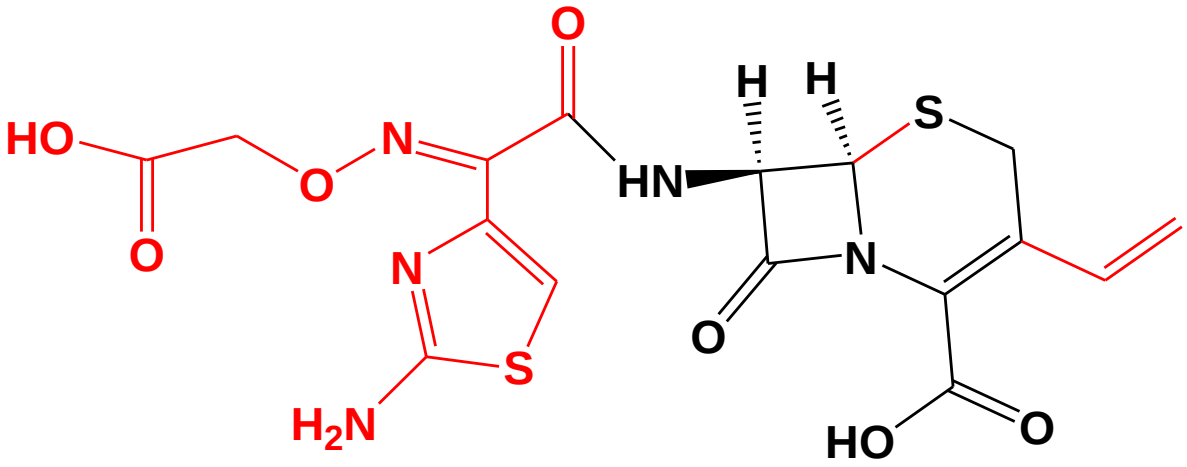
More pronounced β-lactamase stability, greater anti–pseudomonal activity, and increased activity against some Gram-positive organisms like *S. pneumonia* and *S. yogenes*.



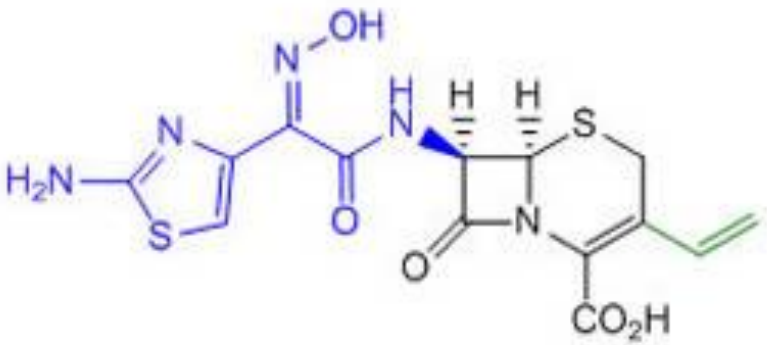
B. Oral Agents

Cefixime

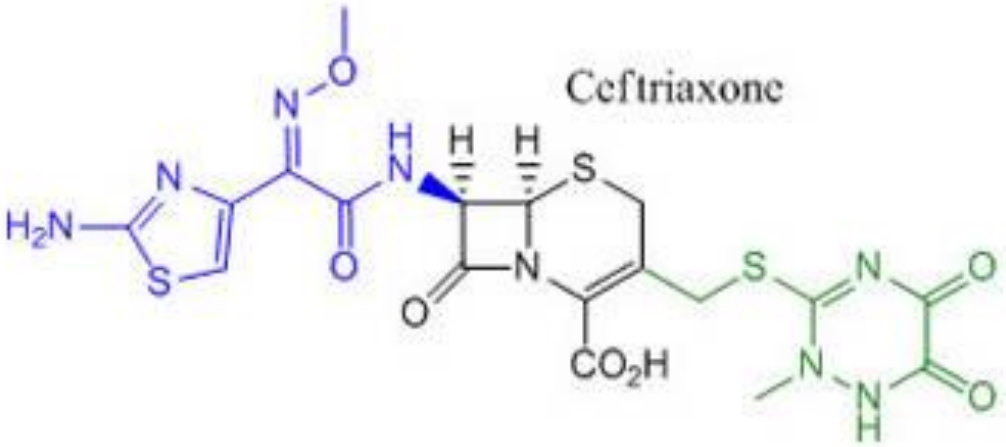
7-[(2-Amino-4-thiazolyl)-2-acetoxyimino)acetamido]-3-ethinyl-Δ3-cephem-4-carboxylic acid.



Cefdinir



Ceftriaxone



During 2008, cefdinir was one of the highest-selling cephalosporins. Ceftriaxone is marketed by Hoffmann-La Roche under the trade name Rocephin®.

Fourth Generation Cephalosporins

They are recent drugs.

Broader spectrum against Gram -ve organisms and low activity against Gram +ve

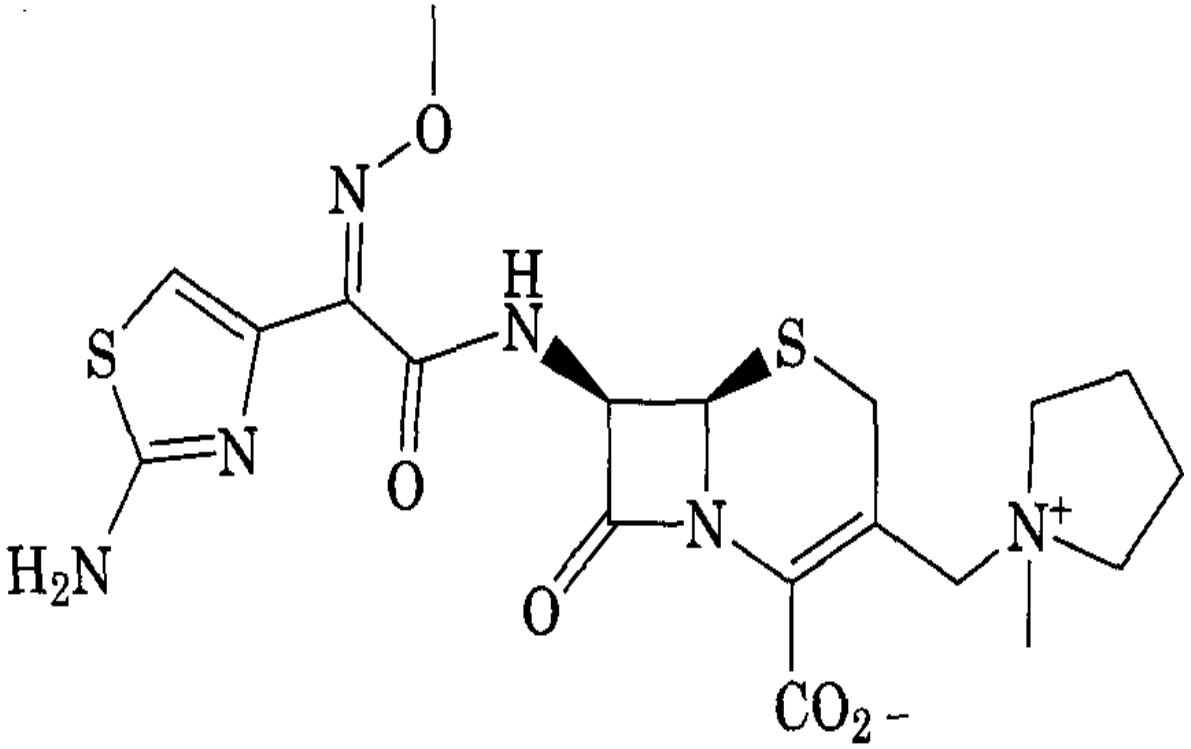
Some drugs have **high activity** against Haemophilus and Neiseria.

Mostly for **parenteral** use.

More resistance to β-lactamases.

High penetration into cerebrospinal fluid and very active against meningitis.

Cefepime

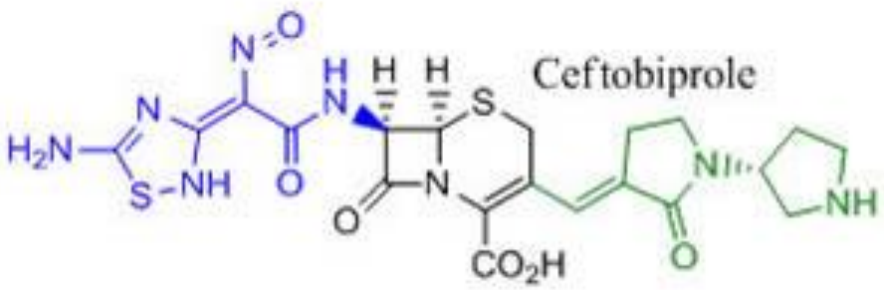


Fifth Generation Cephalosporins

Currently, members of the scientific community have not reached agreement with regards to the use of the term 'fifth generation cephalosporins' Nevertheless, compounds that are regarded by some as fifth generation will be briefly mentioned.

Ceftobiprole has been described as a fifth-generation cephalosporin. this compound possesses good anti-*Pseudomonal* activity. Ceftaroline fosamil is also another example of a cephalosporin that has been described as fifth-generation.

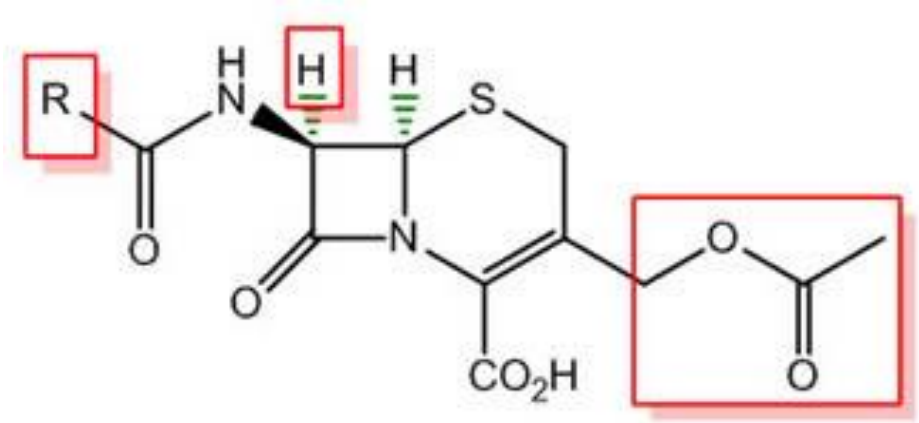
Fifth Generation Cephalosporins



Structure-Activity Relationship of Cephalosporins

The β-lactam ring is crucial for activity Bicyclic ring system important in increasing ring strain The *cis*-stereochemistry at the positions highlighted in green is important

Site of modification



Site of modification

1. **Acylation of amino** group of 7-ACA ⟶ Different Cephalosporins.
2. **Acetoxy group** at position 3 is easily leaving group in acid medium ⟶ **inactive lactone ring.**
3. **Δ3-Cephem** ⟶ inactive.
4. Removal of **-COOH at C4** ⟶ inactive.
5. **Saturation of the double bond** of cephem ⟶ inactive.
6. **A methoxy** group at **7 α-position** ⟶ increase in **resistance** against β-lactamases.

7. Replacement of S with O or CH2 of cephem at position 1⟶ No change in activity.

8. Substitution of acetoxy group at position 3

leads to:

a. Increase acid stability.

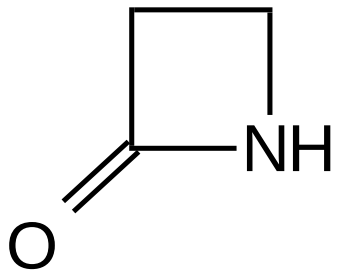
b. Broadening of the antibacterial activity.

c. Increase penetration ⟶ increase in activity against resistant bacteria.

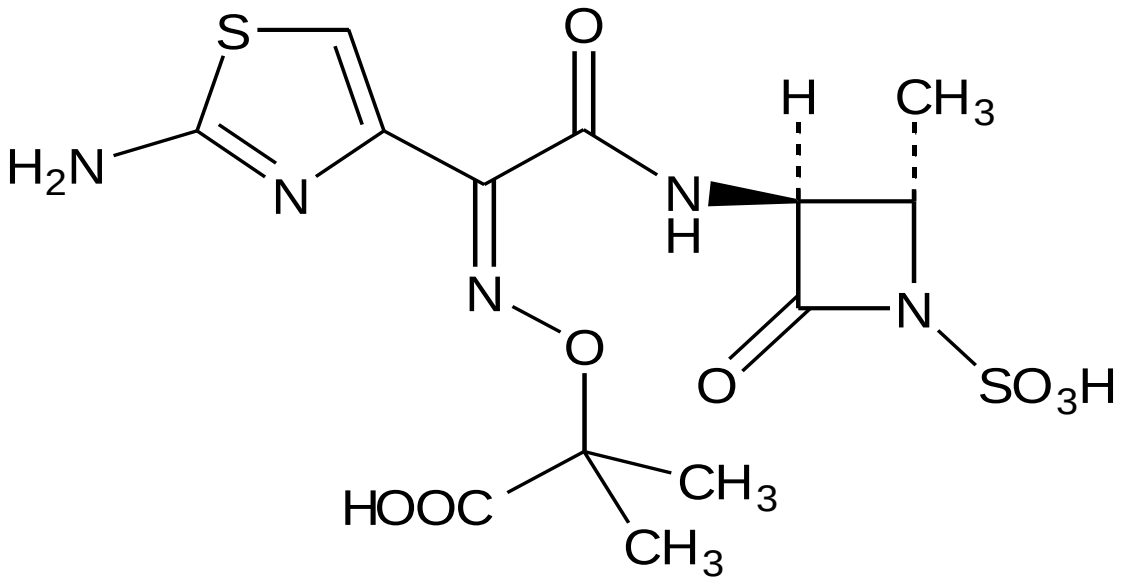
d. Decrease in allergenicity.

OTHER β-LACTAM ANTIBIOTICS

1. Monobactams



Aztreonam



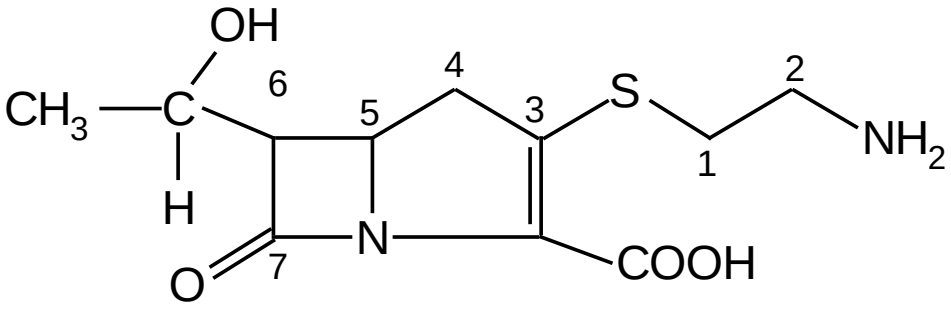
Aztreonam (Azactam) is a synthetic **monobactam** antibiotic, having a **monocyclic**, rather than a bicyclic nucleus.

- This agent inhibits synthesis of bacterial cell wall by high-affinity binding to penicillin-binding protein (PBP_3) which is found primarily in aerobic, Gram-negative microbes.
- **Aztreonam (Azactam)** is highly resistant to ß-lactamases.

- Spectrum of activity includes aerobic, Gram-negative bacteria and is similar in activity to aminoglycosides **without causing ototoxicity or nephrotoxicity**
- **Aztreonam (Azactam)** is effective in treating Gram-negative urinary tract infections, lower respiratory tract, skin, intraabdominal, gynecologic infections and septicemia.

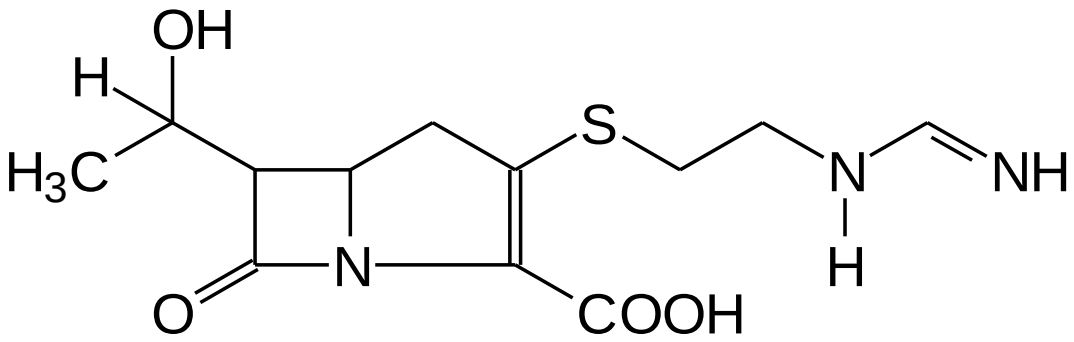
2. Carbapenem

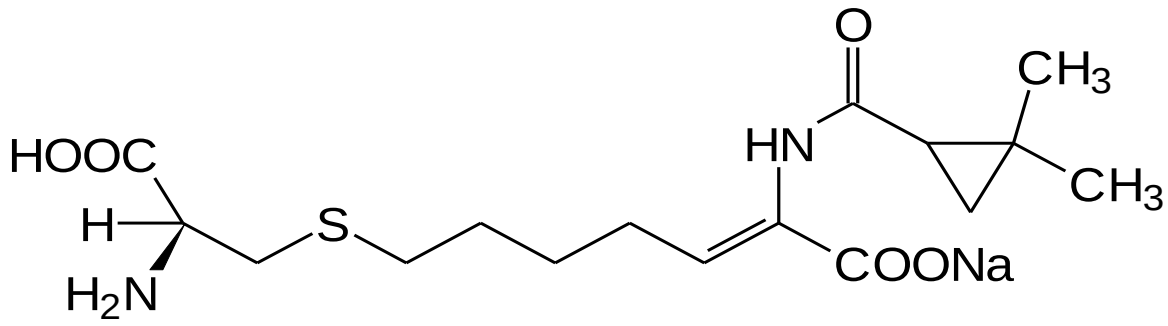
- **i. Thienamycin**
- 3-β-[(2-Aminoethyl)thio]-6-(1-hydroxyethyl)-7-oxo-1-azabicyclo[3,2.0]hept-2-ene-2-carboxylic acid
- The terminal NH2 in the side chain is a nucleophile which attacks β-lactam ring and decreases stability.
- The double bond at C2 increases the reactivity of β-lactam ring opening (More susceptible to hydrolysis in acid and alkaline solutions). **Thienamycin** is resistant to inactivation by most β-lactamases elaborated by Gram -ve and Gram +ve bacteria and therefore, is effective against many strains that are resistant to penicillins and cephalosporins.



Imipenem

It 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 non nucleophilic basic function. **Imipenem** is hydrolyzed by the renal enzyme **dehydropeptidase (DHP-1),** so it is protected by being coadministered with **Cilastatin which is an inhibitor for DHP-1.**





Cilastatin Na

■**Imipenem** inhibits bacterial cell wall mucopeptide synthesis and is bactericidal, very wide spectrum among the ß-lactams, providing good coverage of Gram-negative rods, Gram-positive bacteria, and anaerobes.

Meropenem

A semisynthetic carbapenem that has been formulated as the trihydrate for IM infusion. The β-methyl group at C4 confers increased stability to hydrolysis by dehydropeptidase 1 enzyme, thereby eliminating the need for a dehydropeptidase inhibitor in the dosing regimen.