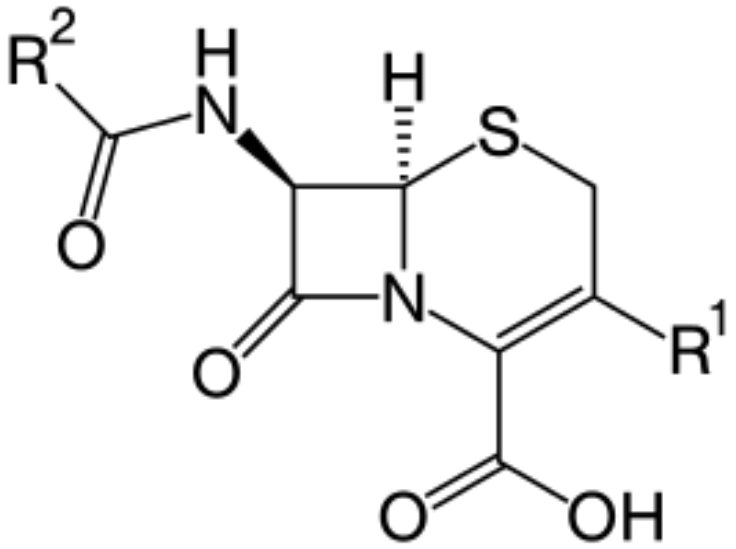
BETA LACTAM ANTIBIOTICS
CEPHALOSPORINES

PHARMACEUTICAL CHEMISTRY II

PHA387



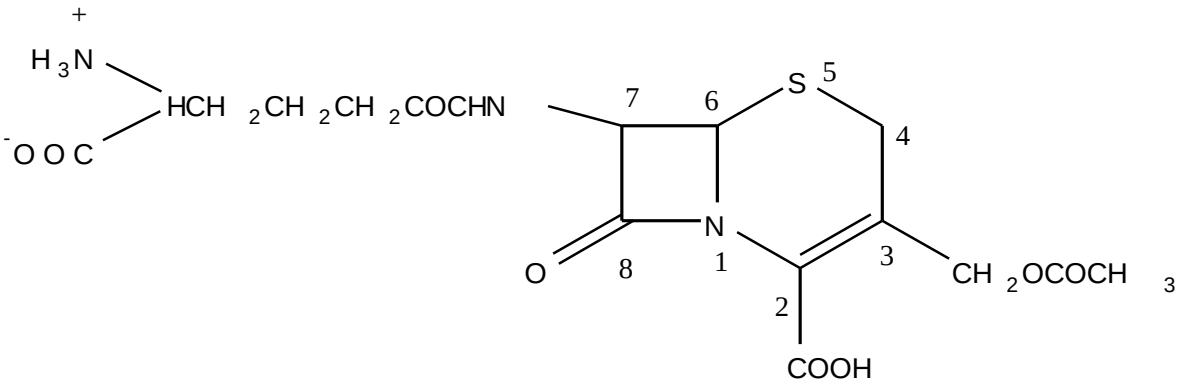
- The **cephalosporins** are a class of β-lactam antibiotics originally derived from the fungus *Acremonium*, which was previously known as "*Cephalosporium*".

- In 1945, the Italian scientist **Giuseppe Brotzu** obtained various antibiotics that inhibited the development of Staphylococcus aureus from Cephalosporium acremonium cultures.

- Cephalosporin C, which is first isolated from compounds called CEPHALOSPORINS.

- In Oxford in 1948 **three major antibiotics** were isolated from cultures of such fungi by Abraham and Newton.
- **1-** Cephalosporin P
- **2-**Cephalosporin N (Penicillin N)
- **3-**Cephalosporin C

In **cephalosporin C**, there is a **dihydrothiazine ring** instead of the thiazolidine ring in Penicillin N.



- The **main core of cephalosporins** is **7-ACA** (7-amino cephalosporanic acid).

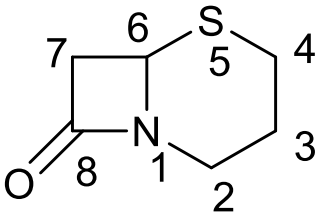
- The **7-ACA** core is **similar** to the 6-amino penicillanic acid (**6-APA**), the main structure of the penicillins, due to the presence of the **β-lactam ring**.

MECHANISM OF ACTION

- **Cephalosporins** produce **bactericidal** action, such as penicillins, by **inhibiting** the final step (transpeptidase reaction) of the synthesis of the mureine layer of the **bacterial cell wall**.

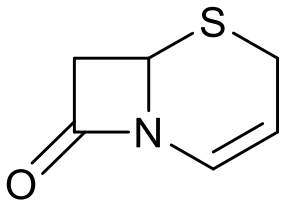
NOMENCLATURE OF CEPHALOSPORINS

CEPHAM is the saturated ring in cephalosporanic acid and has no substituent.
If it contains a double bond, it is called **CEPHEM**.

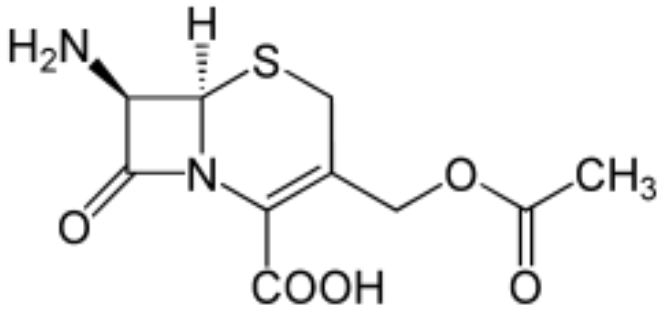


CEPHAM

5-thia-1-azabicyclo
[4.2.0]octan-8-one



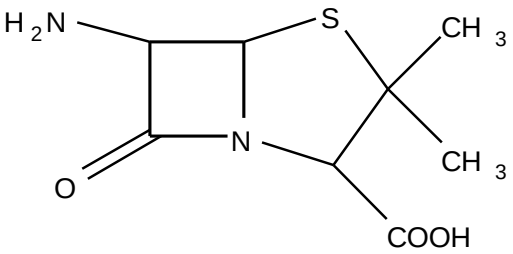
3-CEPHEM (Δ^3-CEPHEM)



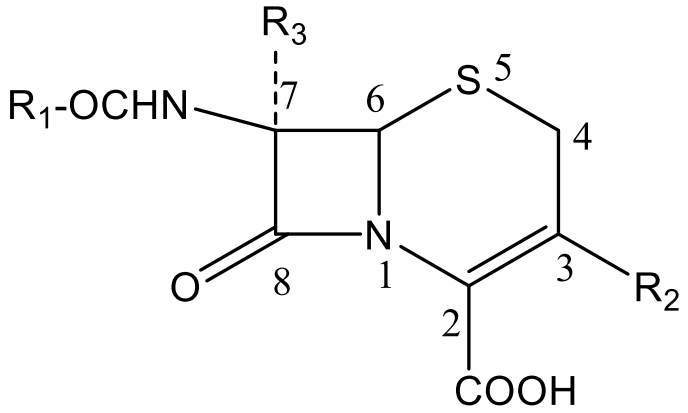
7-Aminocephalosporanic acid (7-ACA)

IUPAC name

3-(Acetyloxymethyl)-7-amino-8-oxo-5-thia-1-azabicylo[4.2.0]oct-2-ene-2-carboxylic acid



6-APA



Cephalosporin Structure

GENERAL IMPORTANCE OF CEPHALOSPORINS

- Except for broad-spectrum third-generation cephalosporins, the most important features of **cephalosporins**, mainly on the part of patients with **allergy to penicillin** or secrete **penicillinase staphylococcus aureus infections** that can **take the place of penicillins, BACTERICIDAL** drugs.

PREPARATION OF CEPHALASPORINS

- It is possible to prepare **natural cephalosporins** from the cephalosporium culture,
- **Synthetic derivatives** are derived from 7-ACA.

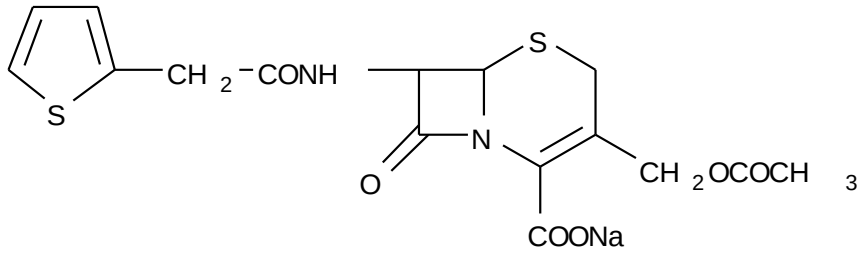
CLASSIFICATION OF CEPHALOSPORIN DERIVATIVES

Cephalosporins are grouped into "generations" by their antimicrobial properties.

1. First-generation cephalosporins (First found = Basic Cephalosporins)
2. Second generation cephalosporins (Transition cephalosporins)
3. Third generation cephalosporins (broad spectrum cephalosporins)
4. Fourth generation cephalosporins
5. Fifth generation cephalosporins

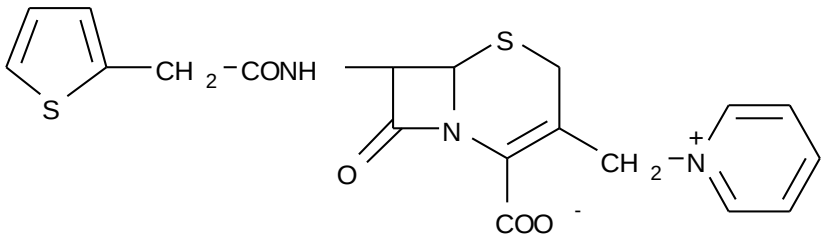
FIRST-GENERATION CEPHALOSPORINS

CEFALOTIN SODIUM



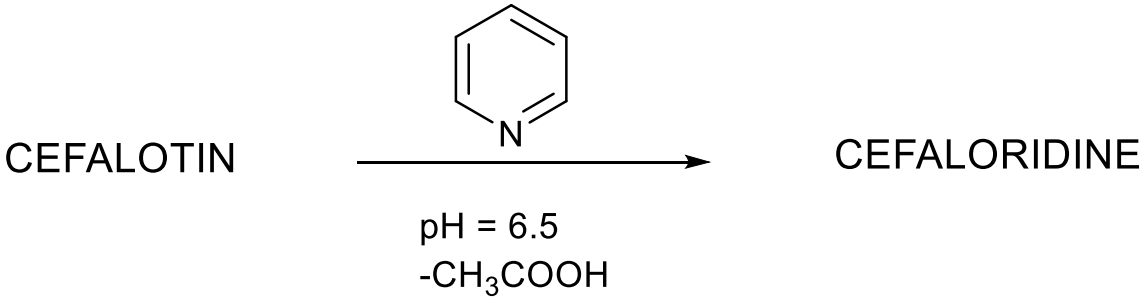
7-(2-Thienylacetamido)-
cephalosporanic acid sodium salt

CEFALORIDINE

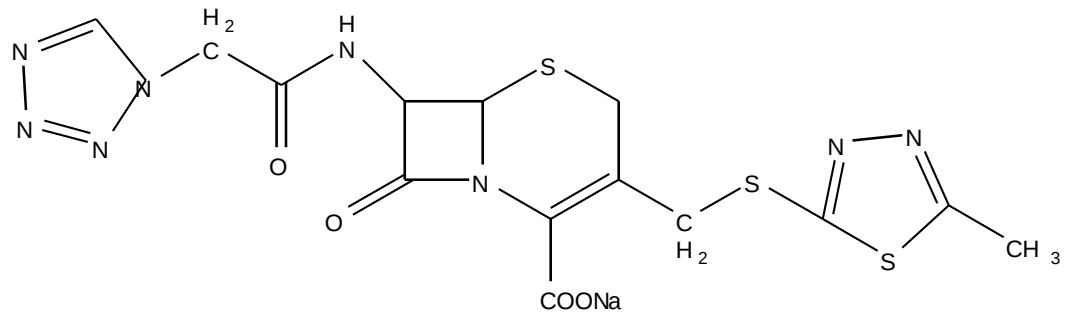


3-Pyridinomethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate

Synthesis: It is prepared start from 7-ACA.



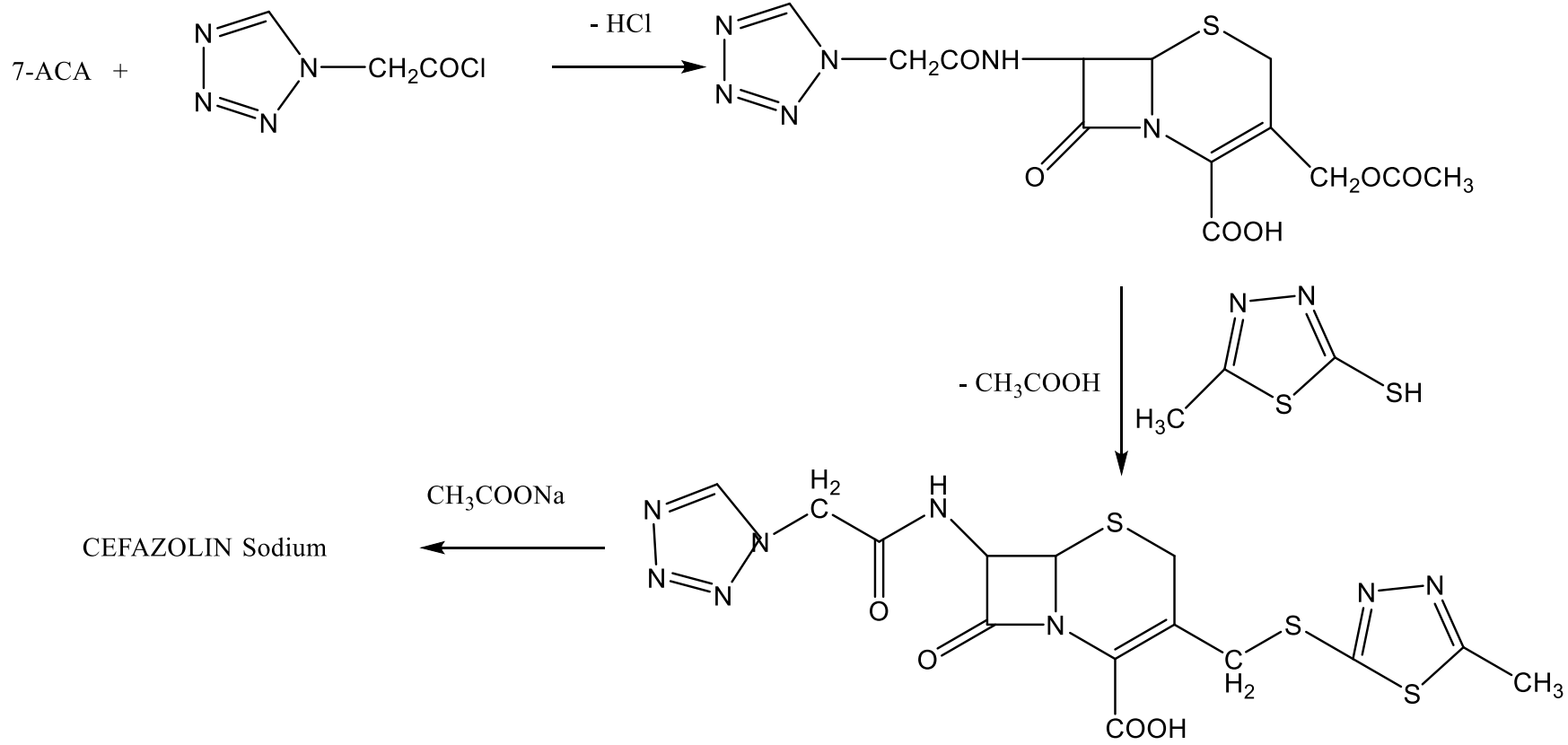
CEFAZOLIN SODIUM



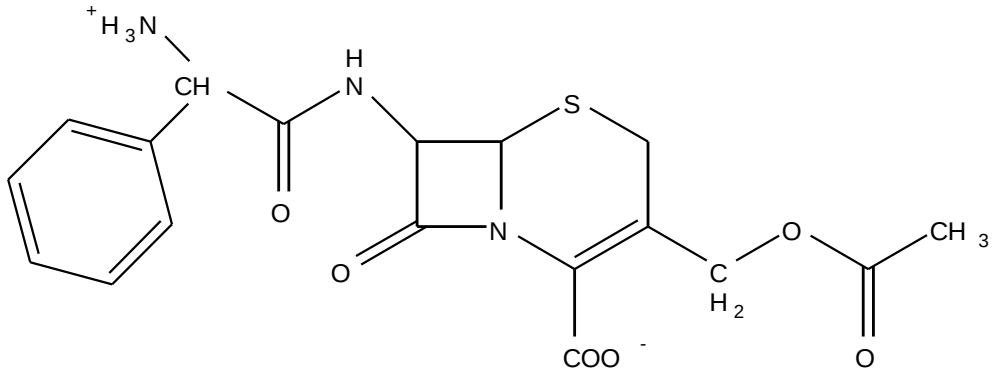
3-((5-Methyl-1,3,4-thiadiazol-2-yl)thio)methyl)-7-(1[H]-tetrazol-1-yl-acetamido)-3-**sefem-**4-sodiumcarboxylate

(6*R*,7*R*)-3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-7-[(1*H*-tetrazol-1-ylacetyl)amino]-**8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-**2-carboxylic acid

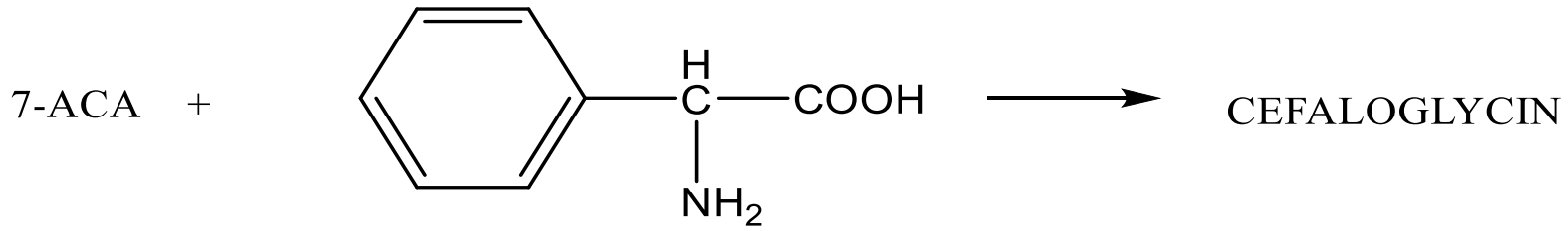
Synthesis:



CEFALOGLYCIN

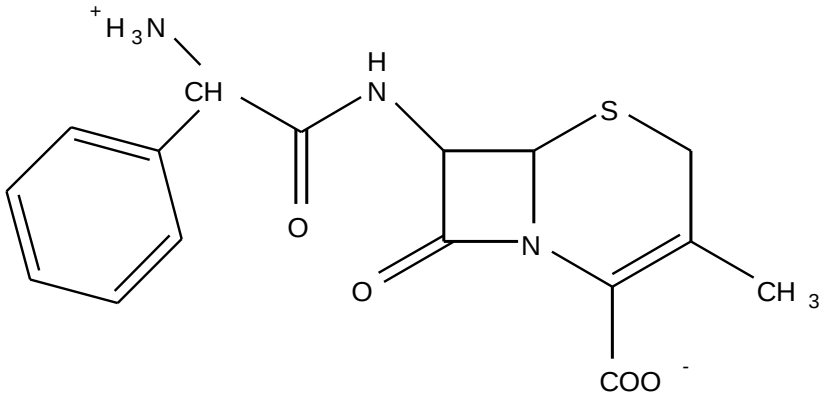


- 7-(D-α-aminophenylacetamido)**cephalosporanic acid**
- (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-{[(2*R*)-2-amino-2-phenylacetyl]amino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



2-Phenylglycin

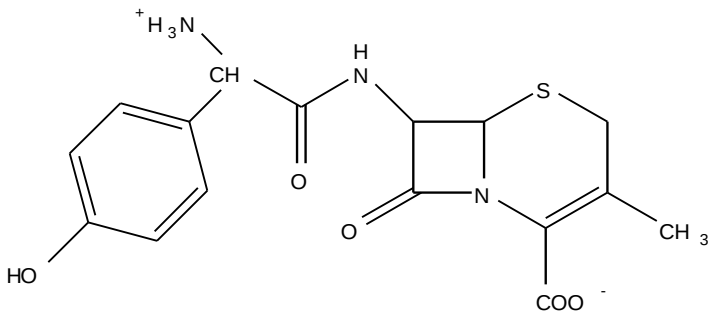
CEFALEXIN



- 7-(D-α-Aminophenylacetamido)-3-methyl-3-**sefem**-4-carboxylic acid
- (6*R*,7*R*)-7-{[(2*R*)-2-Amino-2-phenylacetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

CEFALOGLYCIN $\xrightarrow[\text{Red.}]{\text{Pd / } H_2}$ CEFALEXIN

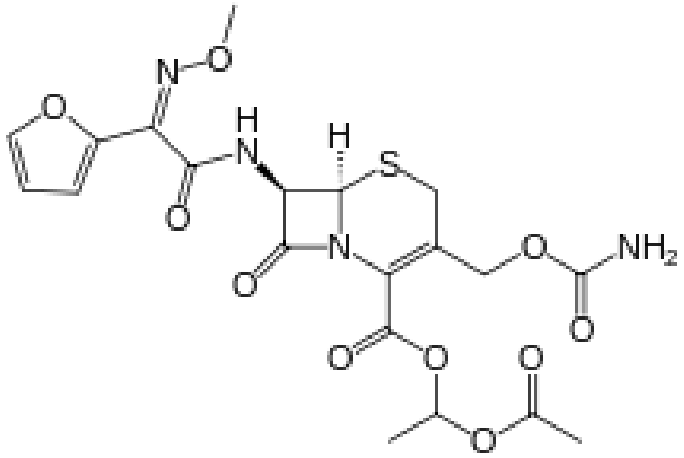
CEFADROXIL



(6*R*,7*R*)-7-{[(2*R*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

SECOND-GENERATION CEPHALOSPORINS

CEFUROXIME Axetil

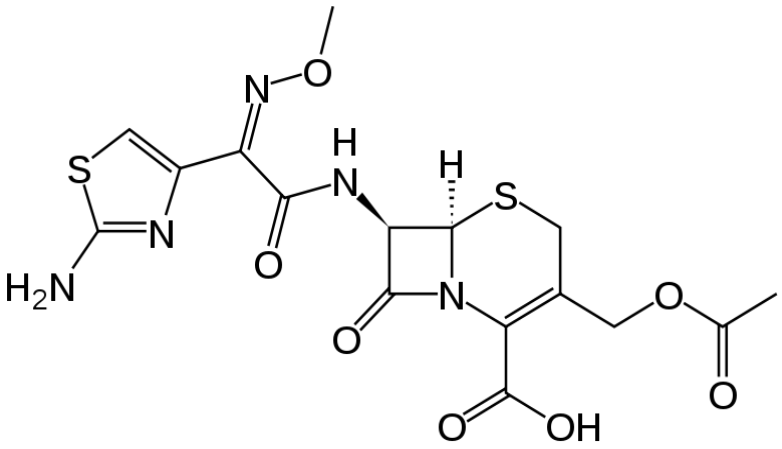


- **Cefuroxime** 1-acetoxyethyl ester
- (6*R*,7*R*)-3-{[(aminocarbonyl)oxy]methyl}-7-{[(2*Z*)-2-(2-furyl)-2-(methoxyimino) acetyl]amino}-**8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid**

- It is an **acetoxyethyl ester** prodrug of cefuroxime which is effective orally. The activity depends on *in vivo* hydrolysis and release of cefuroxime tablets.

THIRD-GENERATION CEPHALOSPORINS

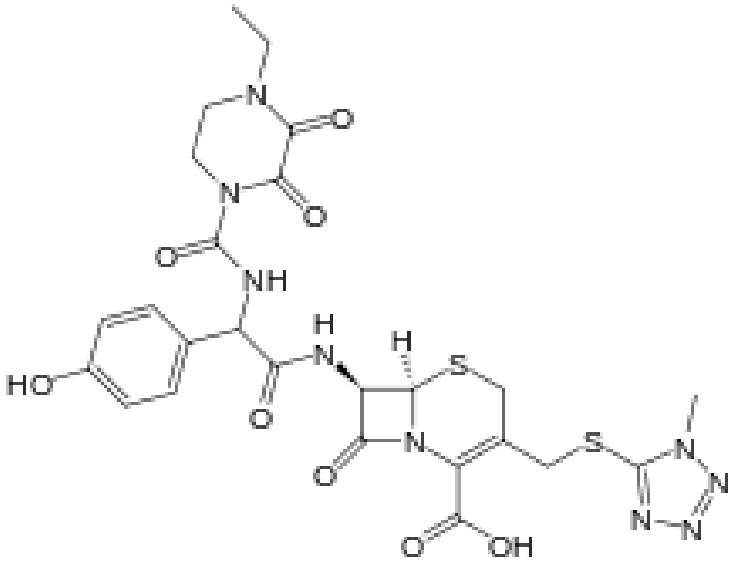
CEFOTAXIME



Systematic (IUPAC) name

(6*R*,7*R*,*Z*)-3-(acetoxymethyl)-7-(2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

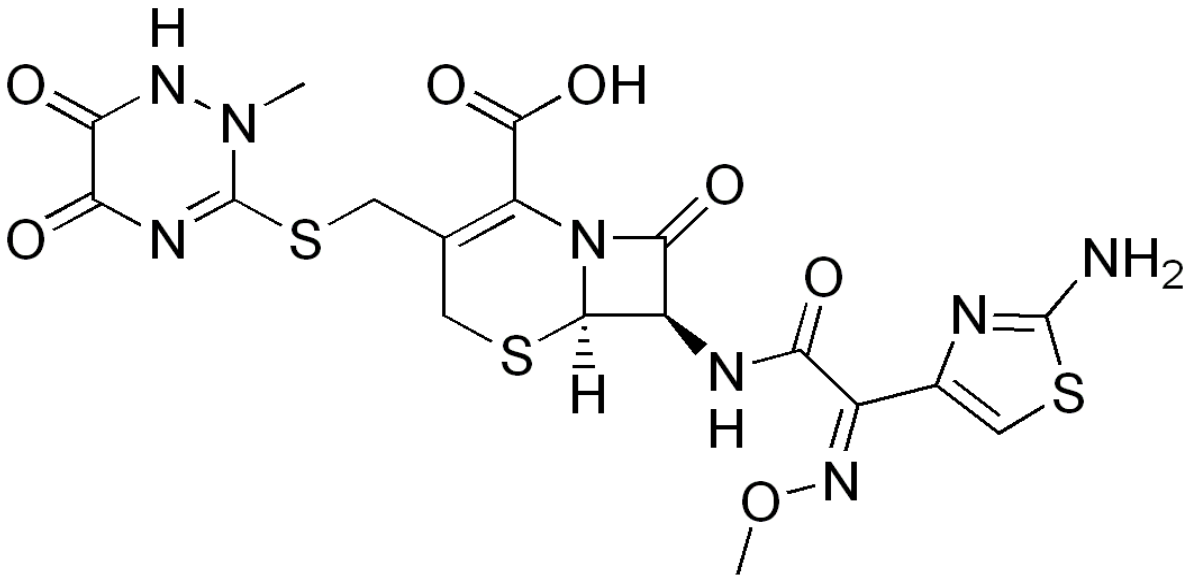
CEFOPERAZONE



- 7-[2-(4-ethyl-2,3-dioxo-1-piperazinyl carbonylamino)-2-(p-hydroxy-phenyl) acetamido]-3-(1-methyl-1[H]tetrazol-5-thiomethyl)-3-**cephem**-4-carboxylic acid

- (6*R*,7*R*)-7-[(2*R*)-2-{[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino}-2-(4-hydroxyphenyl)acetamido]-3-{[(1-methyl-1H-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}-**8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid**

CEFTRIAXONE

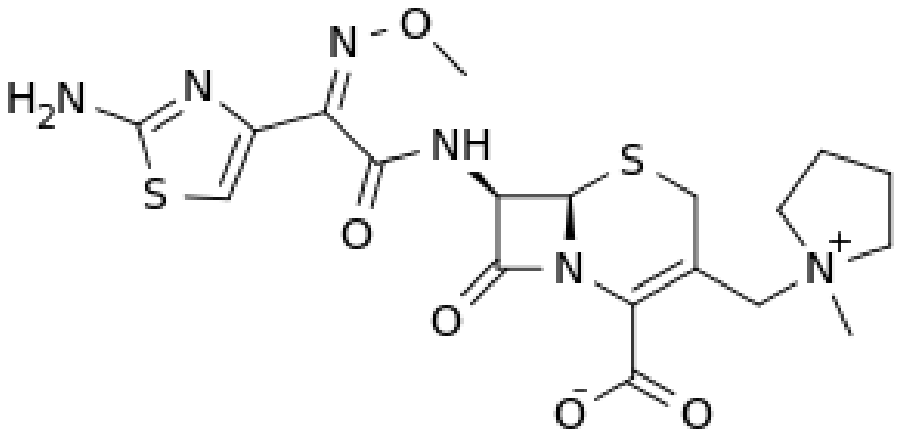


(6*R*,7*R*)-7-{[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetyl]amino}-3-{[(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-1,2,4-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

FOURTH-GENERATION CEPHALOSPORINS

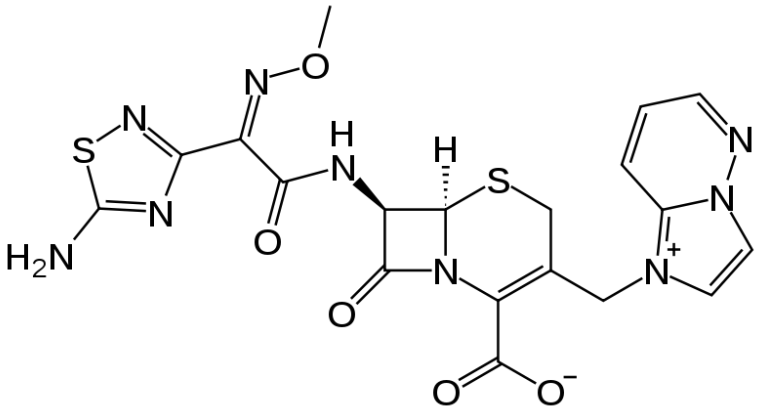
- Fourth generation cephalosporins are effective in a broad spectrum of gram (+) microorganisms such as first generation cephalosporins.
- They have more resistance to beta-lactamases than third-generation cephalosporins.
- They cross the blood-brain barrier and are effective in meningitis.

CEFEPIME



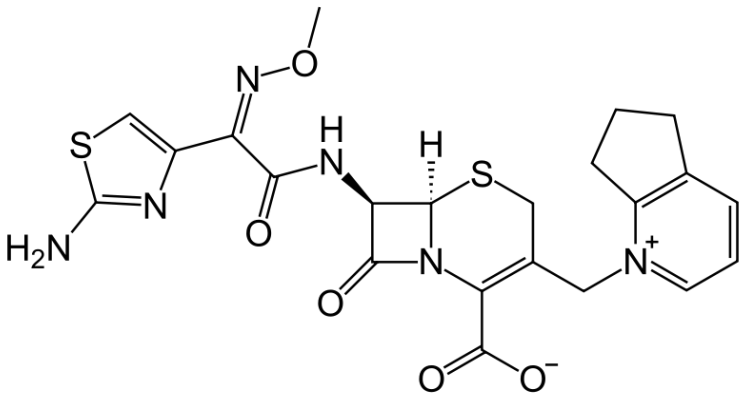
(6*R*,7*R*,*Z*)-7-(2-(2-aminotiazol-4-yl)-2-(methoxyimino)acetamido)-3-((1-methyl-pyrolydinium-1-yl)methyl)-8-oxo-5-thia-1-aza-bicylo[4.2.0]oct-2-ene-2-carboxylate

CEFOZOPRAN



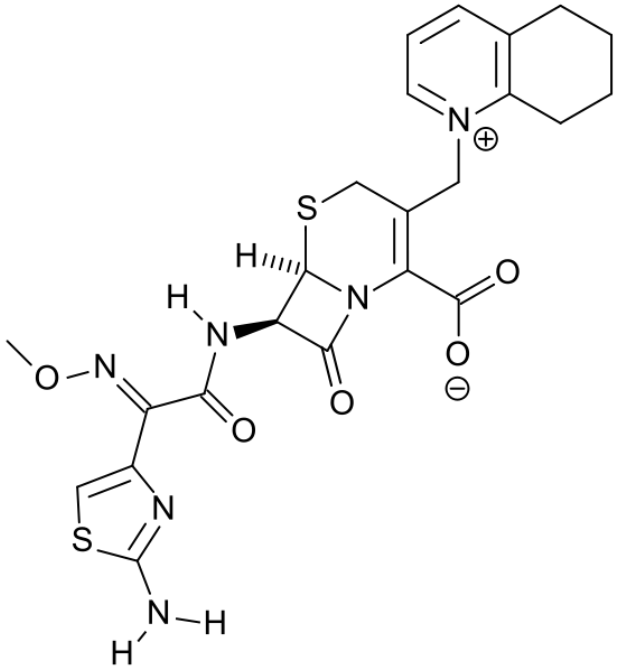
- It is used for treatment of pulmonary infections, urinary system infections, chronic respiratory system infections with IV.

CEFPIROME:



- It is effective against both Gram (-) and Gram (+) microorganisms and **broad-spectrum antibiotic**.

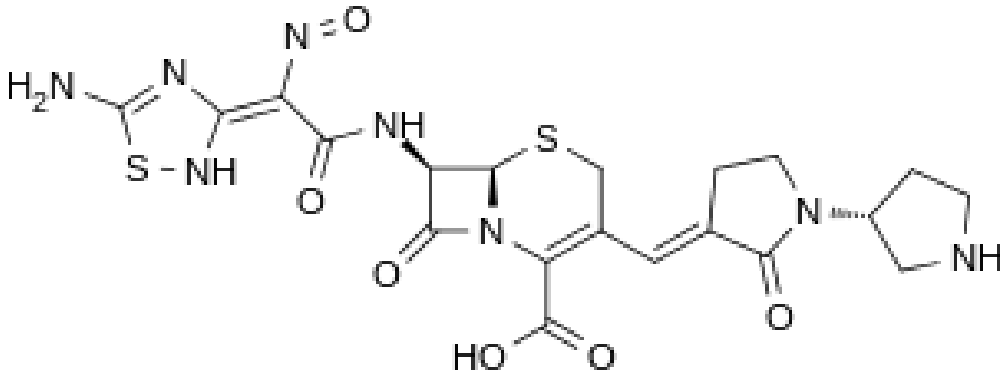
CEFQUINOME



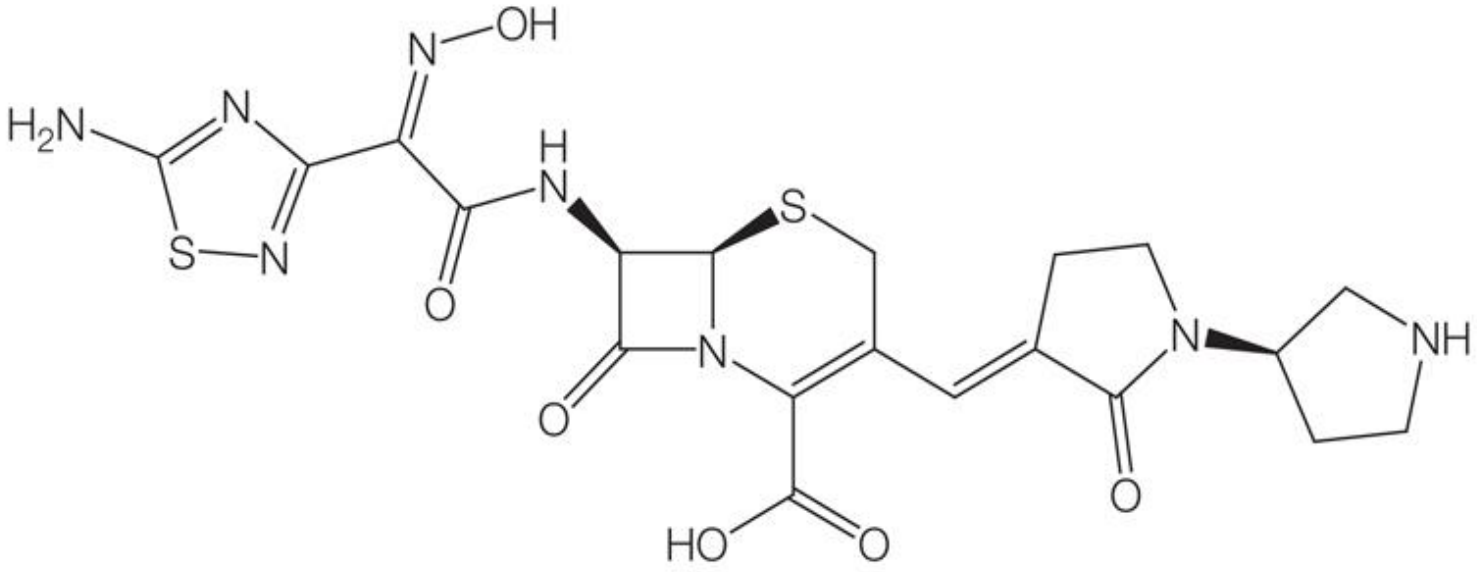
- It is used in **veterinary medicine** via IV.
- **Not approved for human use.**

FIFTH-GENERATION CEPHALOSPORINS

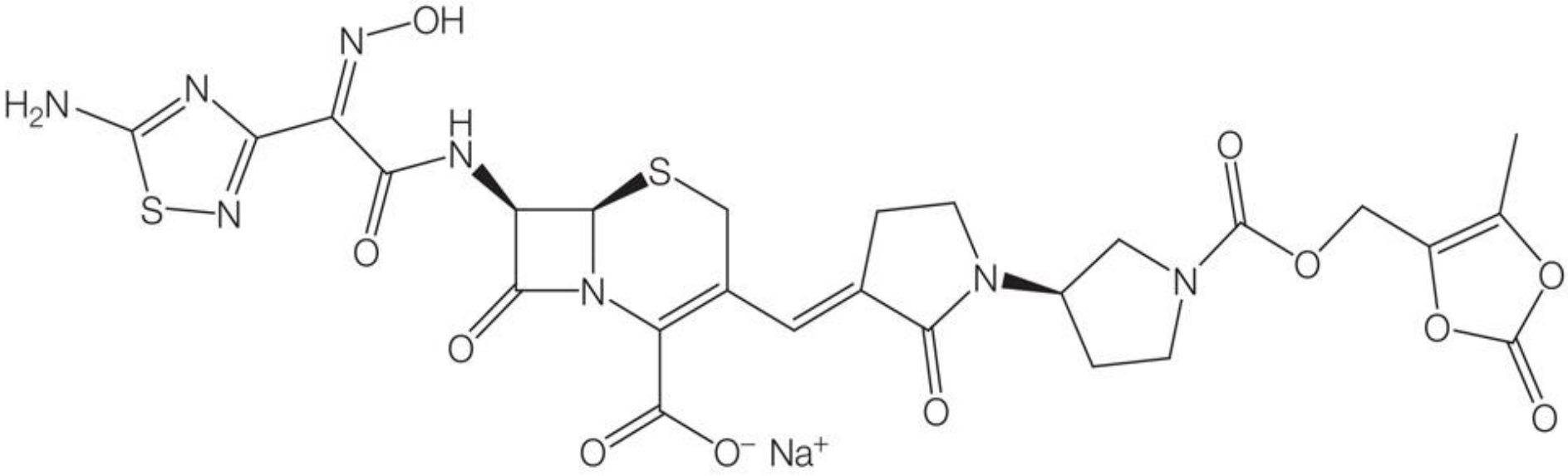
CEFTOBIPROLE



- Ceftobiprole is the active moiety of the **prodrug ceftobiprole medocaril** and is available for i.v. treatment only.



(a) Ceftobiprole



(b) Ceftobiprole medocaril