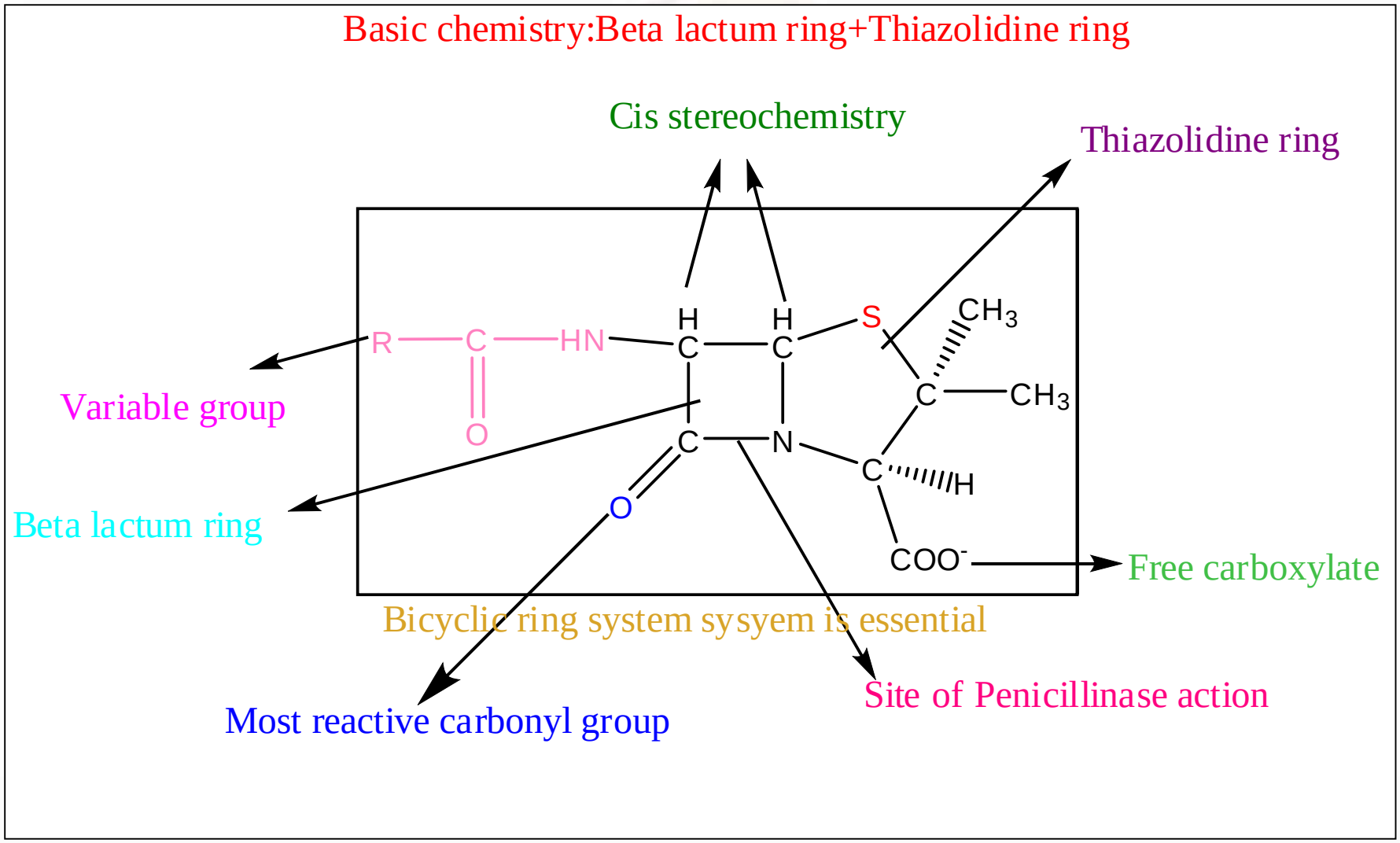
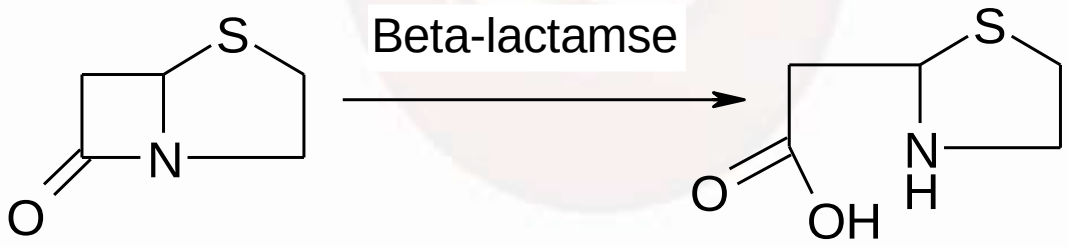
β-Lactam antibiotics

BASIC STRUCTURE OF PENICILLIN



β-LACTAMASE INHIBITORS

- Has negligible antibacterial activity.
- Given with Penicillins which increases spectrum of activity.
- Microbial resistance to beta lactam antibiotics.



β lactam antibiotics

↓

Contain β lactum ring

↓

β lactamases — Catalysing the hydrolysis of β lactum ring

↓

INACTIVE COMPOUNDS

β lactam antibiotics + β lactamase inhibitor

↓

Complex

↓

Effectiveness of β lactamase is diminished

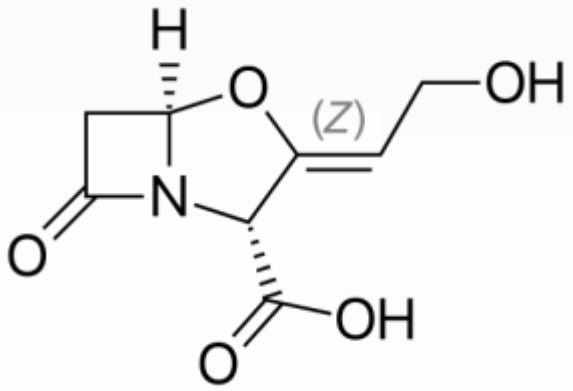
↓

Enhances the activity of β lactam antibiotics

- **Clavulanic acid:**

➢Isolated from Streptomyces clavuligerus.

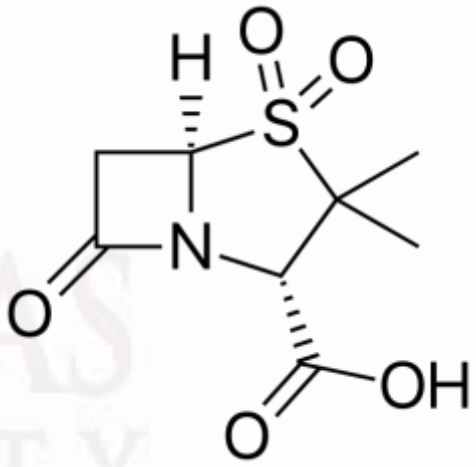
➢1st naturally occurring β-lactam ring that was not fused to a 'S' containing ring.



- **Sulbactum:**

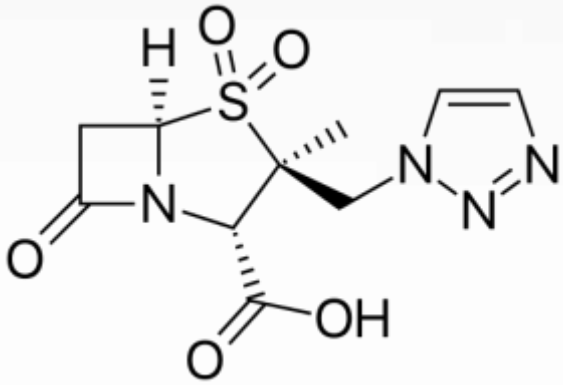
➢β-lactamase disabiling agent.

➢Prepared by partial chemical synthesis from penicillins.



Tazobactum:

- Co-administered with Piperacillin.
- Has little or no antibacterial activity.



Beta lactamase Inhibitors:

Available agents	β-lactamase binding	Potency
Clavulanic acid	++	++++
Sulbactam	++++	++
Tazobactam	++++	++++

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.
- They were isolated from cultures of Cephalosporium acremonium by italian scientist Giuseppe Brotzu in 1945.

- In 1948, Abraham and his colleagues have isolated three principle antibiotic components from cultures of fungus.

✓Cephalosporin P
✓Cephalosporin N
✓Cephalosporin C

- 1964 ,the first semi synthetic cephalosporin i.e. cefalothin was launched in the Market by Eli Lilly and company.
- Unlike penicillin, cephalosporins have two side chains which can be easily modified. Cephalosporins are also more difficult for β-lactamases to hydrolyze.

CLASSFICATION OF CEPHALOSPORINS

First Generation

1.Parenteral

- Cephalothin
- Cephaloridine
- Cefazolin

2.Oral

- Cephalexin (Keflex)
- Cephadroxil (Durecef)

3.Oral & Parenteral

- Cephradine

Second Generation

1.Parenteral

- Cefamycinc
- Cefoxitin
- Cefotitan
- Cefmetazole

2.Oral

- Cefachlor
- Cefprozil

Third Generation

1.Parenteral

- Cefotaxime
- Ceftazidime
- Ceftriaxone

2.Oral

- Cefixime
- Cefdinir
- Ceftibuten

Fourth Generation

1.Parenteral

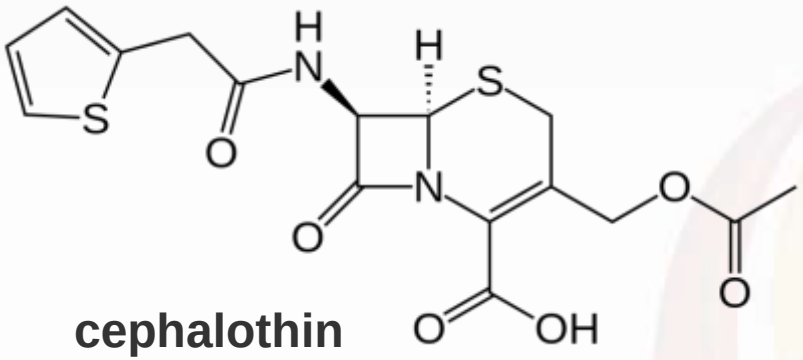
- Cefepime
- Cefpirome

Fifth Generation

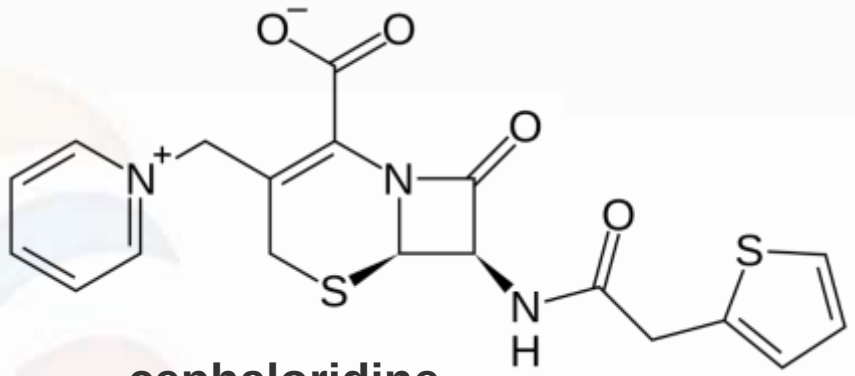
1.Parenteral

- Ceftobiprole

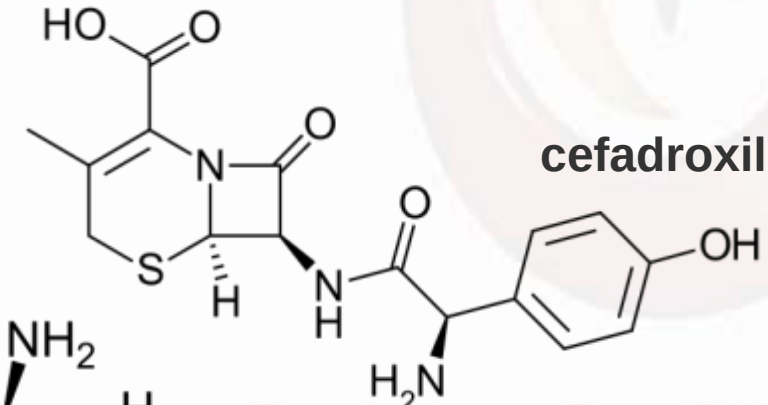
1ST Generation Cephalosporins



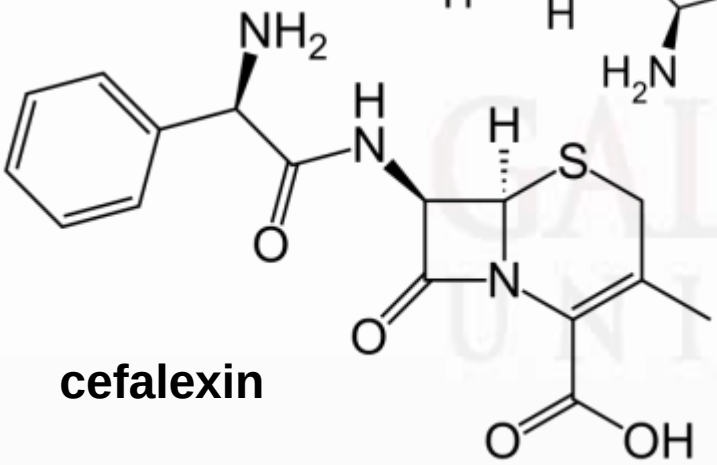
cephalothin



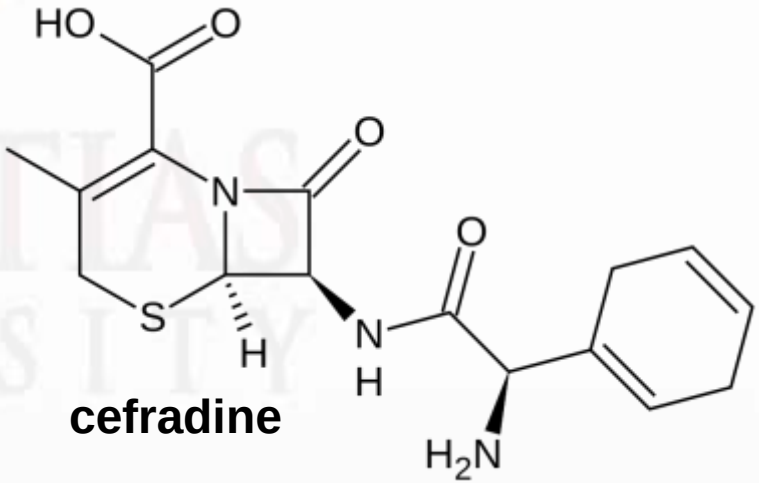
cephaloridine



cefadroxil



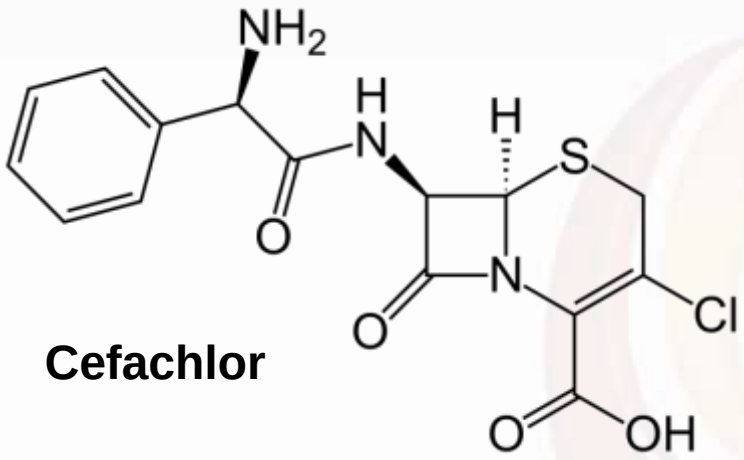
cefalexin



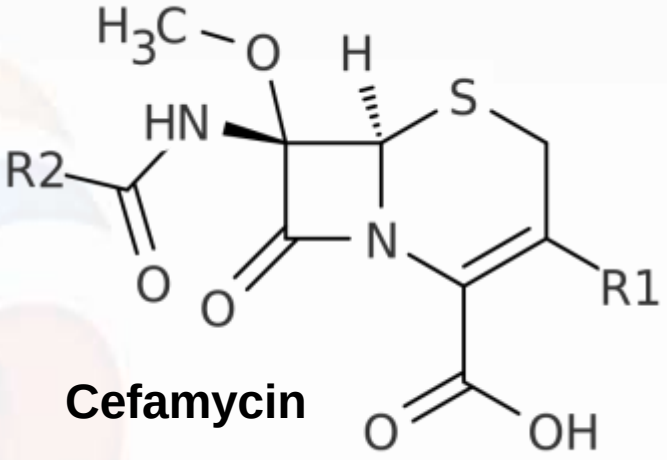
cefradine

- These drugs are very active against Gram-positive cocci (such as Pneumococci, Streptococci, and Staphylococci).
- ***They do not cross BBB***.

2nd Generation Cephalosporins

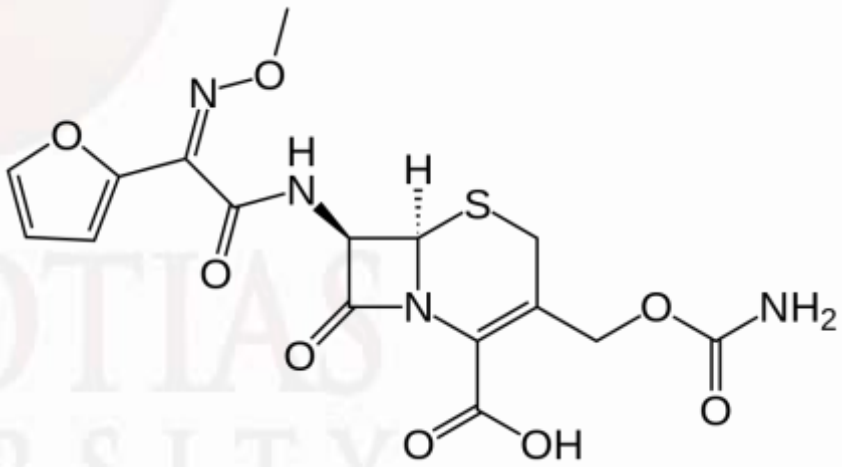


Cefachlor



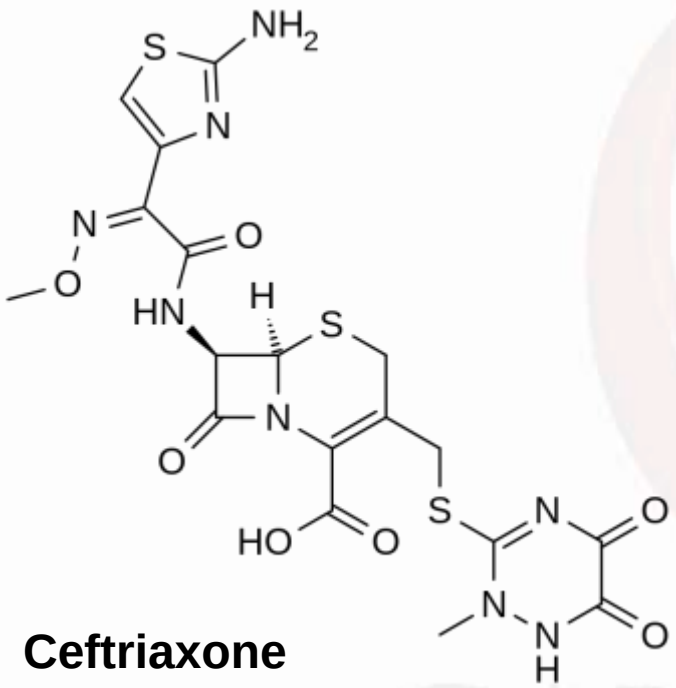
Cefamycin

- They have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria.
- They are also more resistant to *β-lactamase.*
- **No BBB Penetration.**

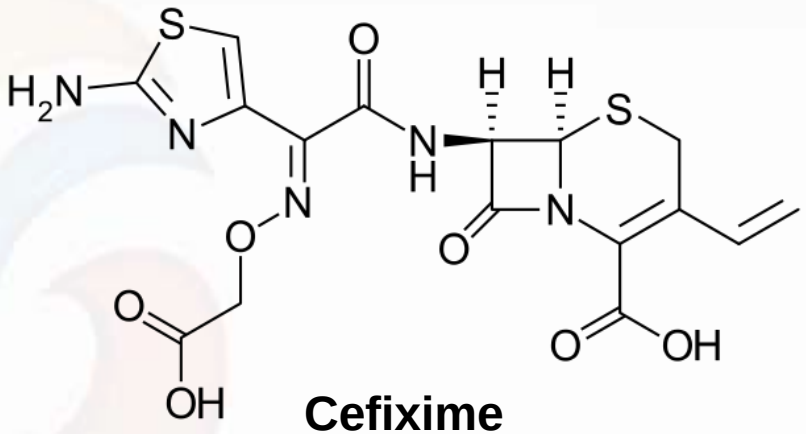


Cefuroxime

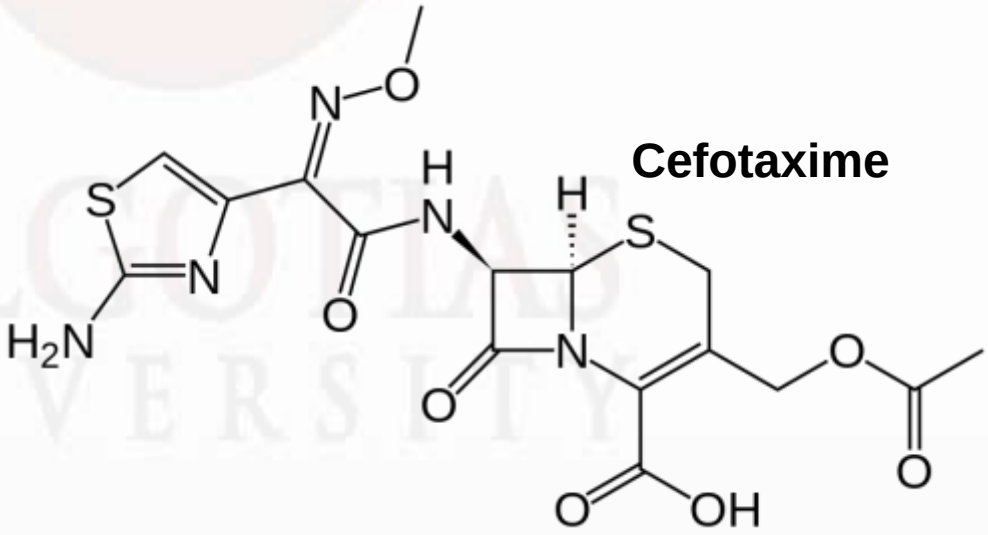
3rd Generation Cephalosporins



Ceftriaxone



Cefixime



Cefotaxime

Third-generation drugs exhibit the lest activity against gram-positive bacteria, but most potent activity against gram-negative bacteria :

(a) Extended antibacterial spectrum, include Pseud. aeruginosa;

(b) Less activity on gram-positive bacteria than first and second generation;

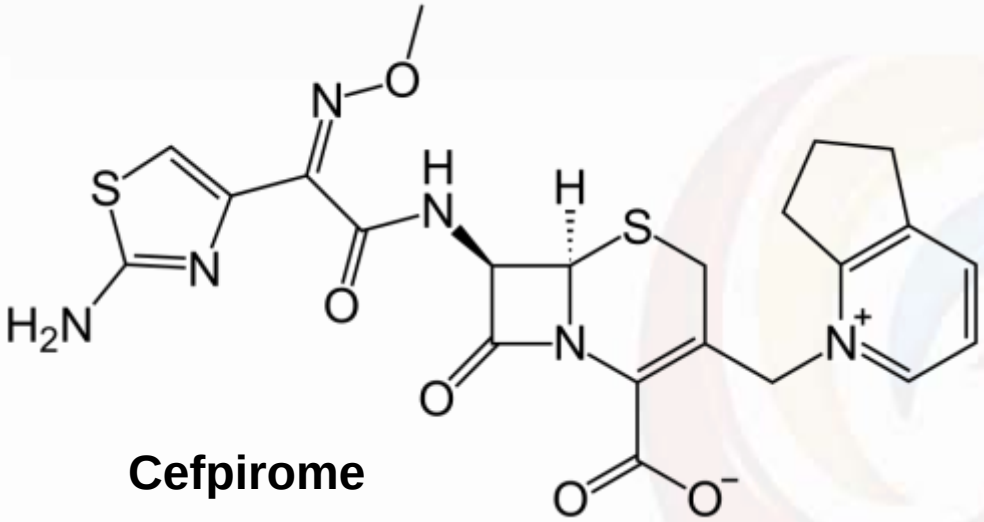
(c) Most active on gram-negative bacteria;

(d) High stability with β-lactamase;

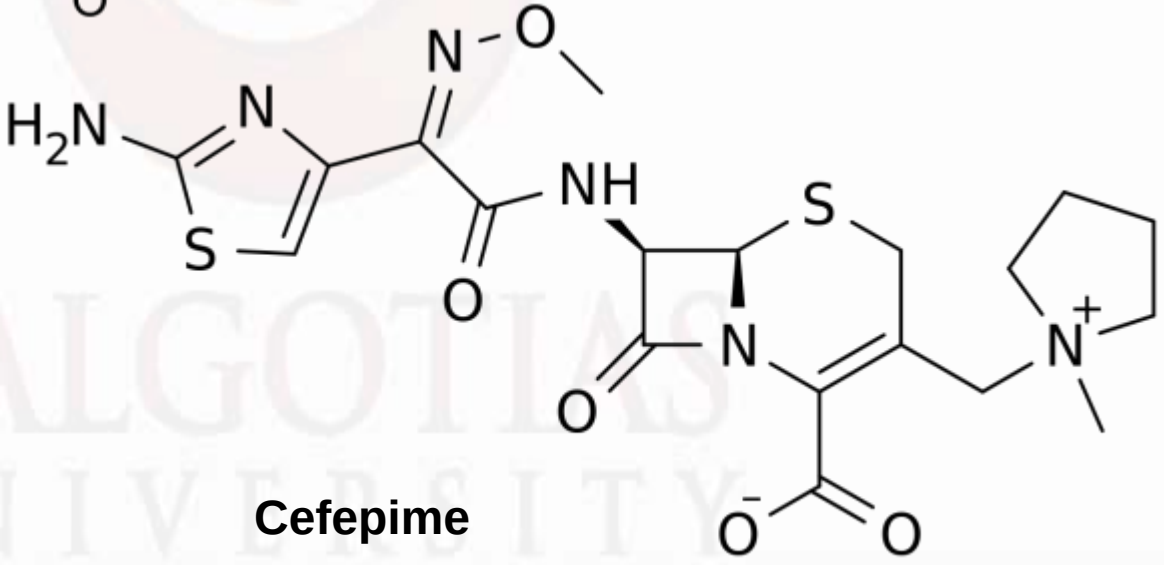
(e) Easy penetrate to different tissues, and then have broad distribution;

(f) Little kidney toxicity.

4th Generation Cephalosporins



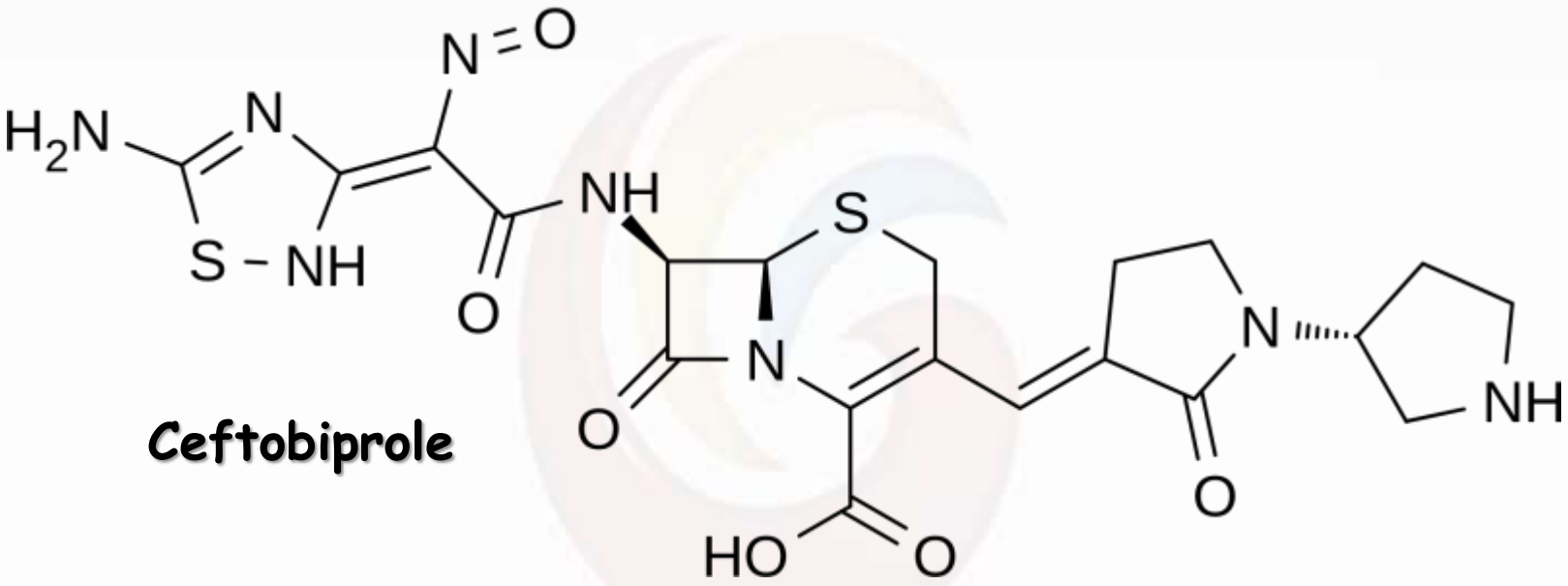
Cefpirome



Cefepime

- Zwitterionic compounds.
- Good affinity for the transpeptidase enzyme.
- Low affinity for some β-lactamases.
- Cross BBB and effective in *meningitis.*

5th Generation Cephalosporins



Ceftobiprole

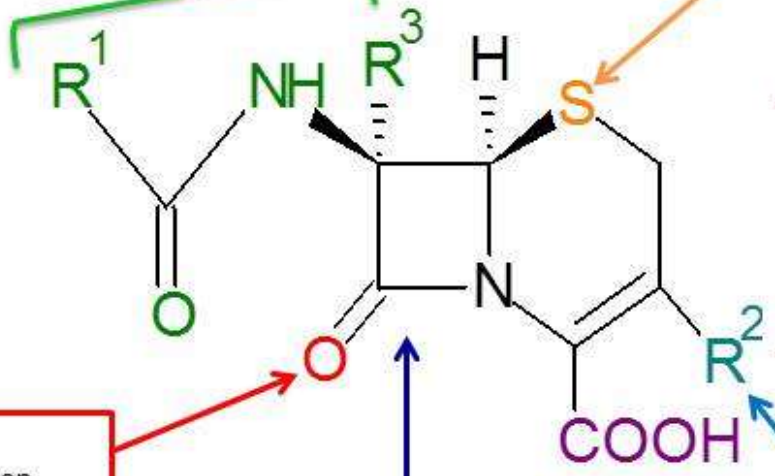
- Active against
  - **Methicillin-resistant** -*Staphylococcus aureus*
  - **Penicillin-resistant** - *Streptococcus pneumoniae*

STRUCTURE ACTIVITY RELATIONSHIP OF CEPHALOSPORIN

7-position substituent
- Semi-synthetic incorporation
- Influence the antibacterial activity
- Affects binding of β-lactamase

Cis-stereochemistry - essential

Exchange S with:
O = oxacepham
C = carbacepham



6 membered dihydrothiazine ring

Carbonyl group
- Lone pair electron located on nitrogen atom not fed to carbonyl group to form a stabilized resonance structure, thus more electrophilic for nuclephilic attack.

β-lactam ring

Carboxylic acid
Useful during formulation
Prodrug development

3-position substituent
Chemical/ metabolic instability
< effect on antibacterial activity

Cephalosporins advantages over penicillins

- Increased ***acid stability*** compare to penicillins.
- Most of the drugs have ***better absorption*** than penicillins.
- ***Broad*** antimicrobial spectrum.
- Increased activity against ***resistant*** microorganisms.
- Decreased ***allergenicity.***
- Increased ***tolerence*** than penicillins.

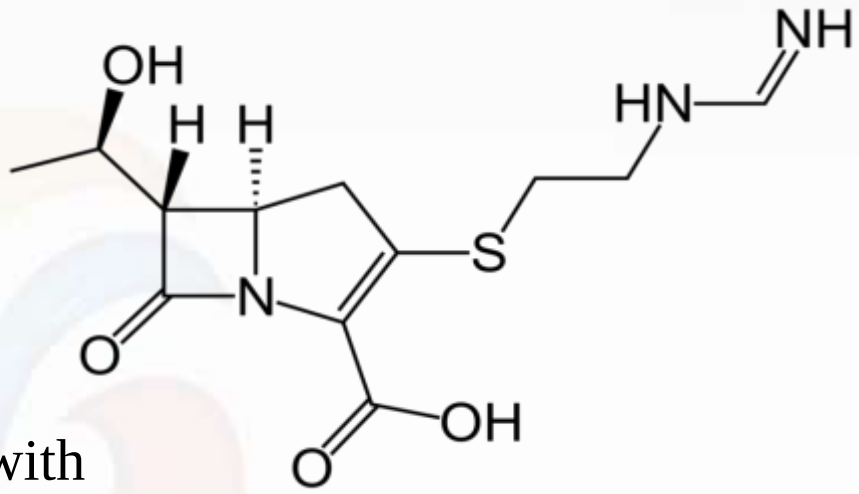
Carbapenam

- **Introduction**

- Carbapenems are a class of β-lactam antibiotics with a broad spectrum of antibacterial activity.
- They have a structure that renders them highly resistant to most β-lactamases.
- Carbapenem antibiotics were originally developed from the carbapenem thienamycin, a naturally derived product of *Streptomyces cattleya*

  Examples: **Imipenem, Meropenem, Ertapenem**

IMIPENEM:

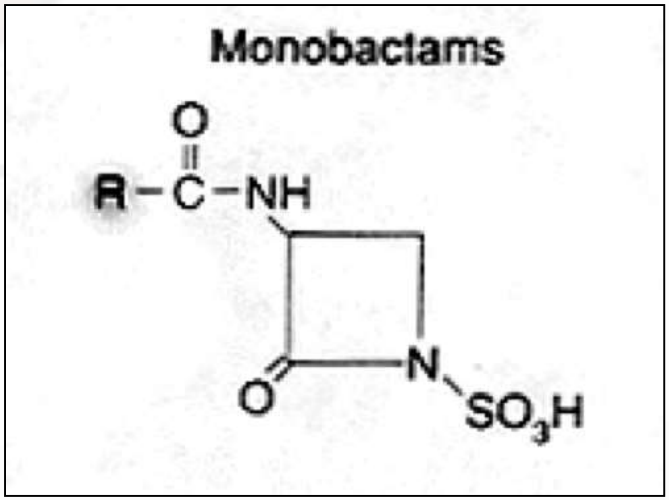


- IMIPENEM has a wide spectrum with good activity many gram negative rods incluiding P.aeruginosa, gram positive organisms and anaerobes.
- Imipenem is inactivated by dehydropeptidases in renal tubules, result in low urinary concentrations.

Monobactam

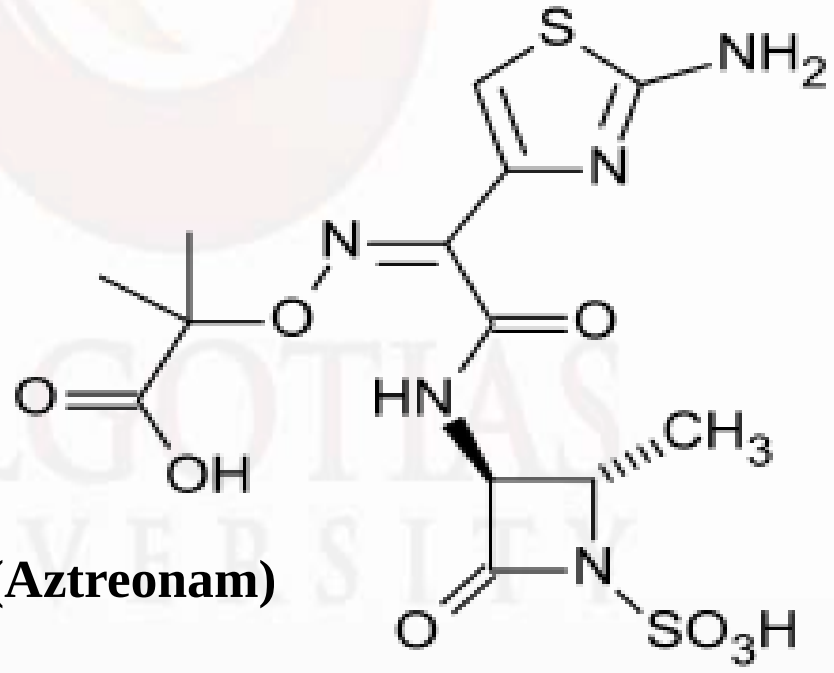
- **Introduction:**
- Monobactams are drugs with a monocyclic β-lactam ring.
- They are relatively resistant to beta-lactamases and active aganist Gram-negative rods (including Pseudomonas and Serratia).
- They have no activity against Gram-positive bacteria or anaerobes.

Examples: Aztreonam, Tigemonam.



Aztreonam

- Aztreonam is given i.v.
- The half-life is 1–2 hours and is greatly prolonged in renal failure.
- Penicillin-allergic patients tolerate aztreonam without reaction



(Aztreonam)

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