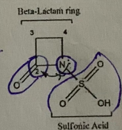
Monobactams

- Monobactams -by their name- contain β-Lactam ring only without any other cycle, and as we said previously that β-Lactam ring is too stable here because the pair of electrons on nitrogen are in resonance with the carbonyl, so to decrease the stability, monobactam have a sulfonic acid at the nitrogen.
- Which means that the β-Lactam ring has been destabilized by the sulfonic acid which
- takes away the electrons, and this will prevent the resonance to occur **–sulfonic acid destabilize the β-Lactam ring-**

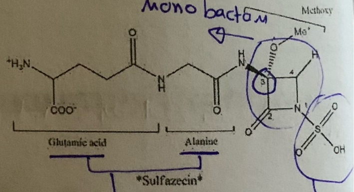


ال methoxy لما يصير protonation وبالتالي بتصير good leaving وبخرب unstable group

- Monobactams:
- **1- Sulfazecin**
- 2- Aztreonam
- 3- Tigemonam
- Sulfazecin is a natural monobactam, at carbon #3 there is dipeptide –Alanine with glutamic acid- and methoxy, attached to the monobactam

Sulfazecin is:

1. Orally inactive
2. Chemically unstable (because of the protonation at the methoxy so it becomes a good leaving

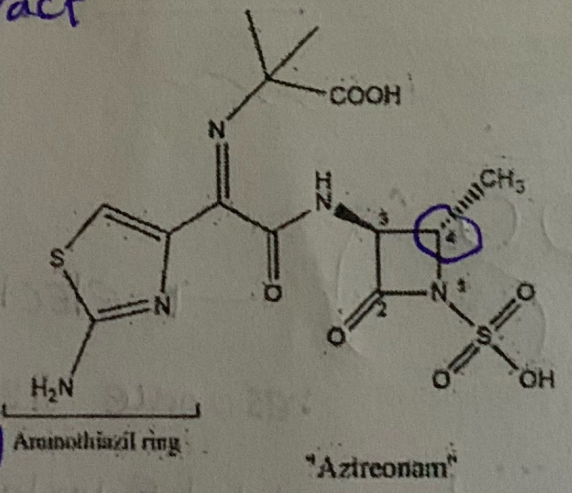


Side chains di peptide

2- Aztreonam

Aztreonam is an:

1. Acid stable (but still not orally available)
2. Used to treat local GI tract infections
3. β-Lactamase resistant
4. Gram negative antibacterial agent (only gram negative, not gram positive because Aztreonam is too hydrophilic) – have an effect on *E.coli*, and effect on pseudomonas aeruginosa, streptococcus and staphylococcus.



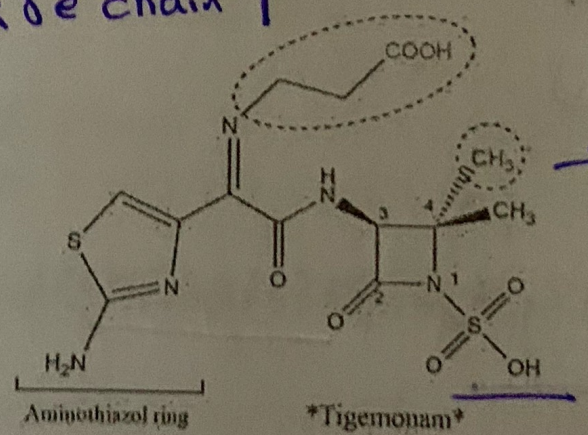
Cephalosporins

3- Tigemonam

- Tigomonam is:
- β-Lactamase resistant
- its spectrum of activity is the same as Aztreonam (against Gram –ve only except Pseudomonas) → سيليومونام
- Orally stable(due to the hydrophilicity which is balanced here)

hydrophilicity وهاي تبز

adepic acid side chain



Aminothiazol ring

Tigemonam

→ it's electrone donating group ring N stability تقوي

sulfon side chain

Cephalosporins

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

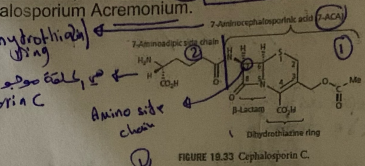


FIGURE 18.33 Cephalosporin C.

- 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 .

D-alanine-D-alanin

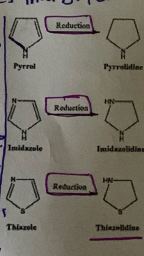
① Cephalosporin → it's intrinsicly (intrinsic activity of beta lactames and antibacterial activity (مثل البنسلين)

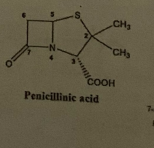
② pencillin → amoxacillin and ampicillin

sulbactam, claculanic acid → beta lactamase inhibitor

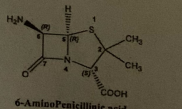
Note: Beta lactamases are also called penicillinases because they are specific to penicillins and this is the secret behind Cephalosporins being more stable

Beta lactames inhibitors





Penicillinic acid



6-AminoPenicillinic acid

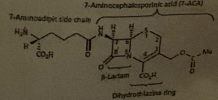


FIGURE 18.33 Cephalosporin C.

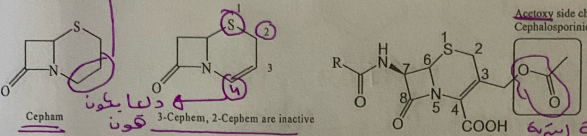
Transpeptidase inhibitors

B-L-inhibitors

Trans peptidase inhibitor.

Nomenclature

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



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.

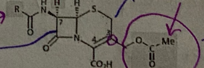
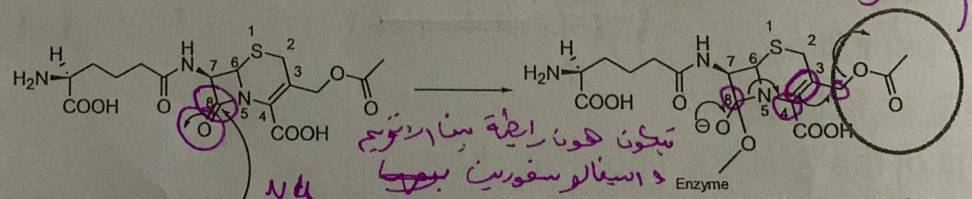


FIGURE 19.36 Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

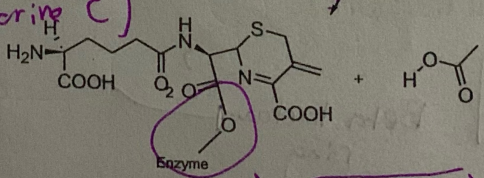
inhibition, covalent بينا تدرس كيف β-lactames
Cross linking with cephalosporine bond

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

(stable) تفاعل انعكاسي
Azalactonization
good leaving groups



β-lactames enzyme
proto type cephalosporine C



acyle ⇒ linking

Irreversible

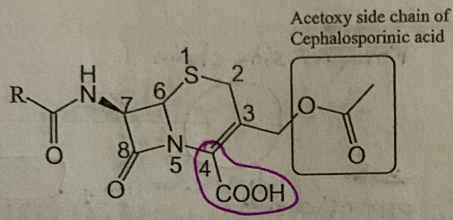
covalent bond

Nuclophilic attack

acetuty group

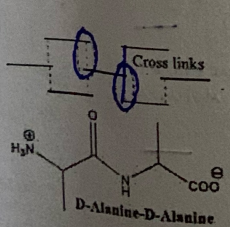
SAR of Cephalosporins

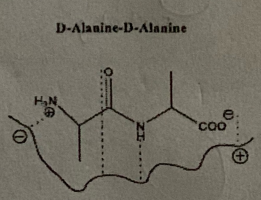
- Similar to penicillins in the 7-amino group.
- The carboxylic acid at C_4 is essential.
- 3-Acetyoxy group at **C_3 can be easily varied** by nucleophilic substation

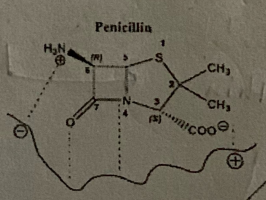


Why are the carboxylic acid and the amine group so important inhibiting the crosslinking?

- **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.

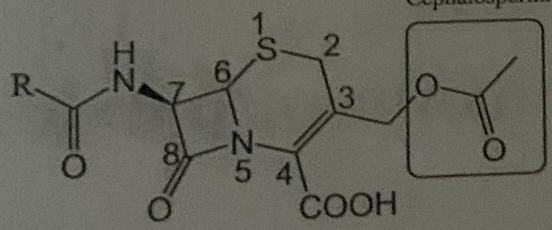


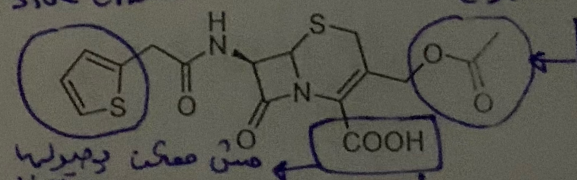




SAR of Cephalosporins

- 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

orally inactive

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

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.

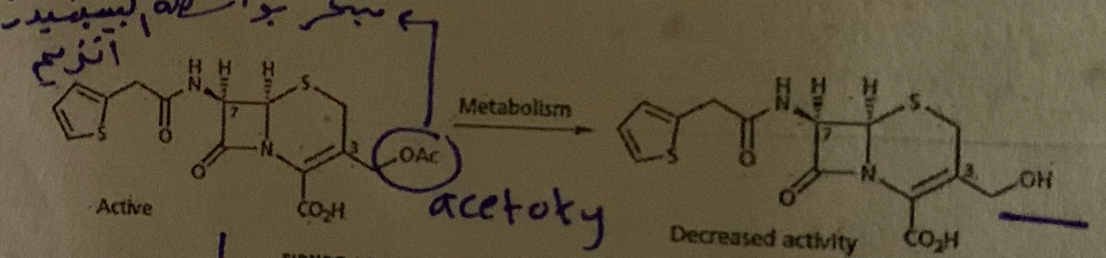


FIGURE 19.40 Metabolic hydrolysis of cephalothin.

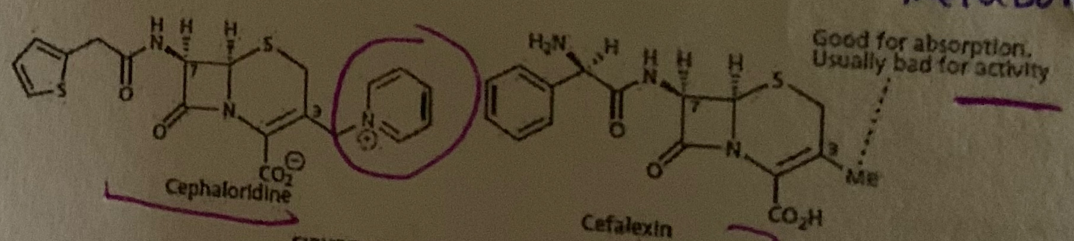


FIGURE 19.41 Cephaloridine and cefalexin.

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)

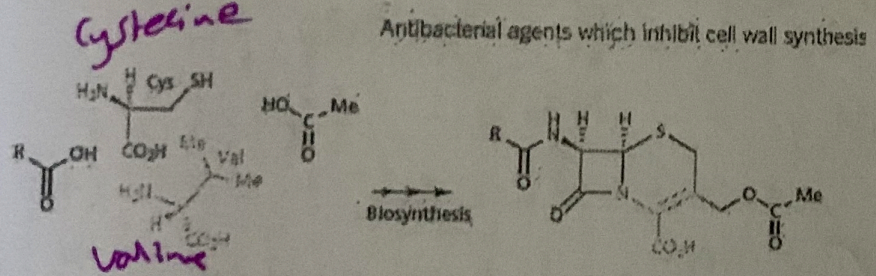
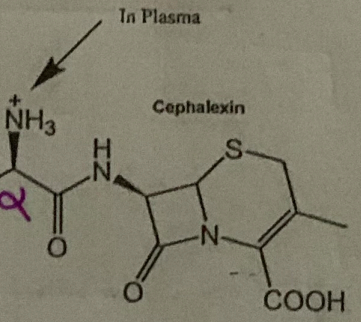
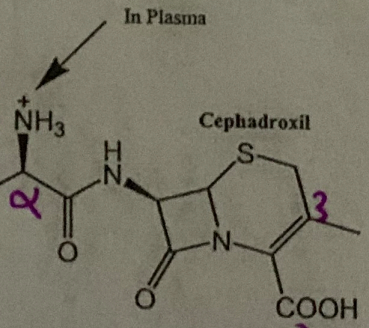


FIGURE 19.34 Biosynthetic precursors of cephalosporin C.





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