



MIRACLE Academy

ميدسينال 2
زميلتكم ريماس الشوابكة



لجان الدفعات

قال تعالى (يَرْفَعُ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

CEPHALOSPORINS

Dr. Rand Shahin

من مضادات حيوية
تشبه الـ Penicillin
يوجد الـ
beta lactam ring

ربما سمعتموه
كقوى

Cephalosporins.

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

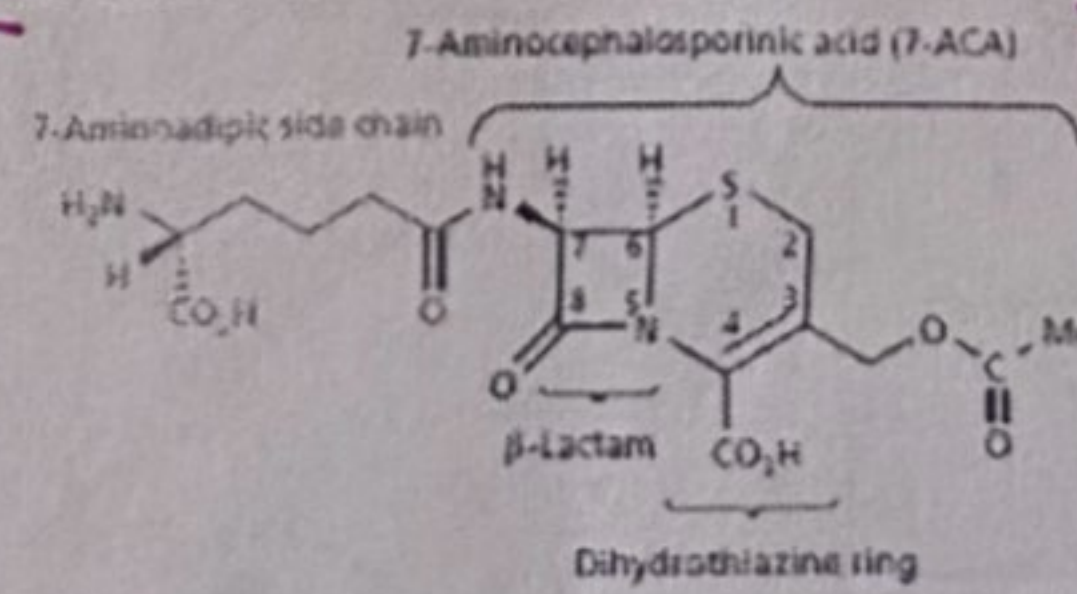


FIGURE 19.33 Cephalosporin C.

- 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.

* كل Cephalosporine
بيجواما هاد (C)
بيدين بنكر
amide
ونتم تصنع انواع
اخرى

لا يتم استعماله
كقوى

* بنمبر ال
Cephalosporin's
عن ال β -lactam
انه يكون
cephalosporins
فا عليهم resistance
كثير
صنعت ما يتكروا به
Beta lactamases

* عفان صيد
[Beta lactamase]
(Penicillinase)

الذكر لم يشاكل ال
penicillin

① ② ③

فاندا
orally
wide
spectrum

resistance
B-lactamase

ناضية هاي لينة
cephalosporins
فاندا كلها

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

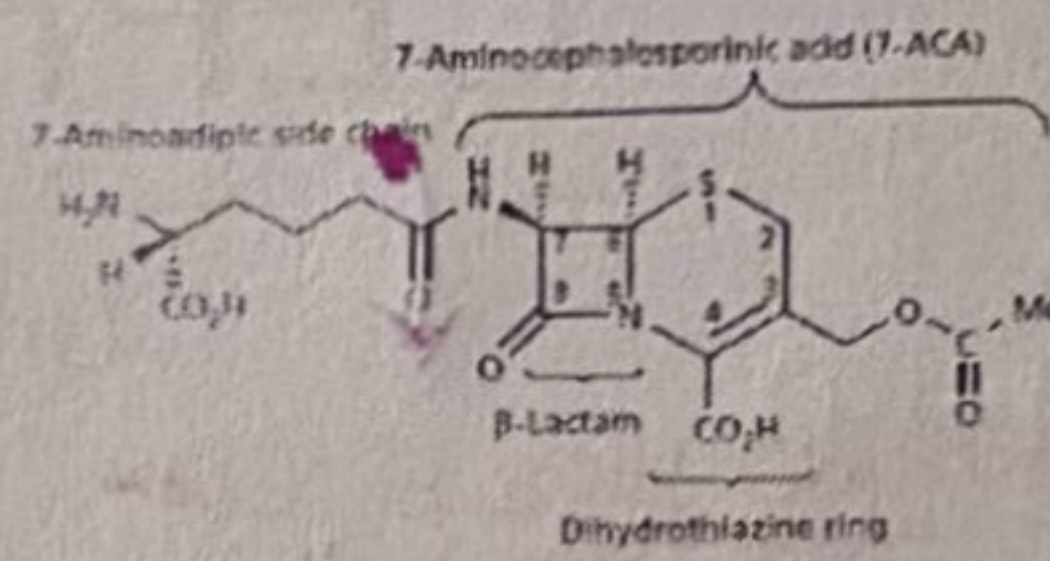
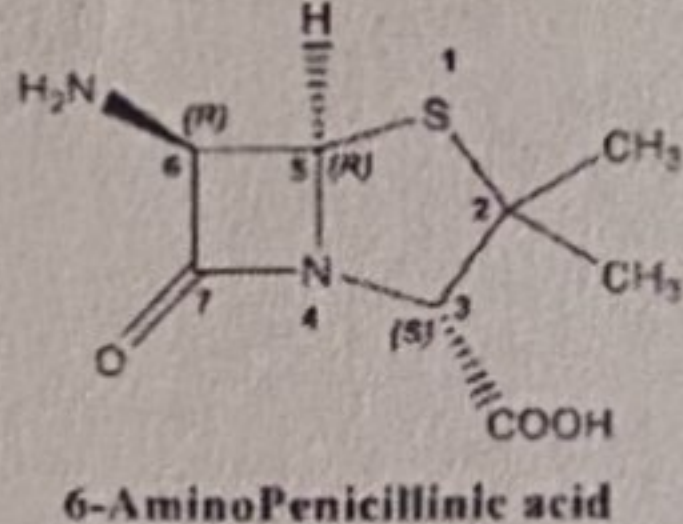
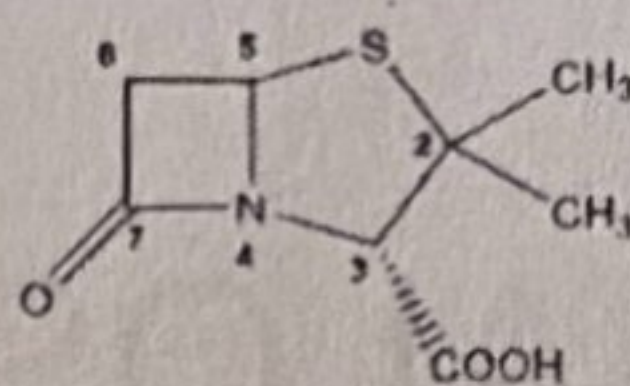
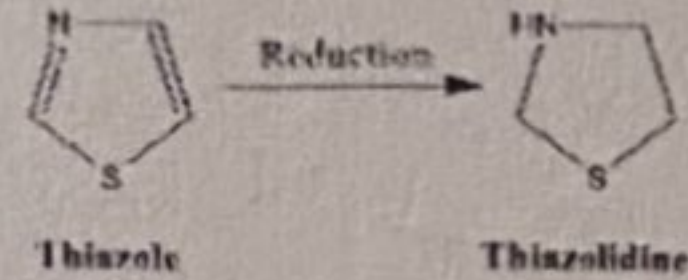
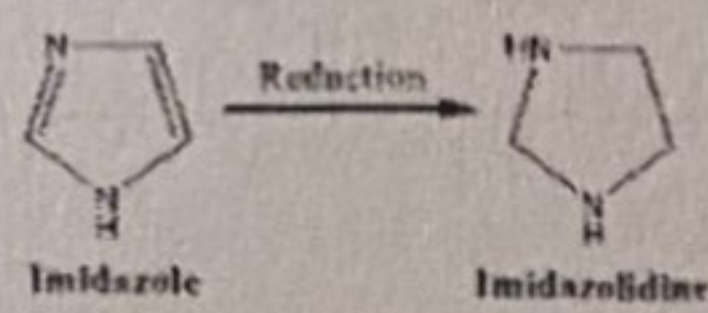
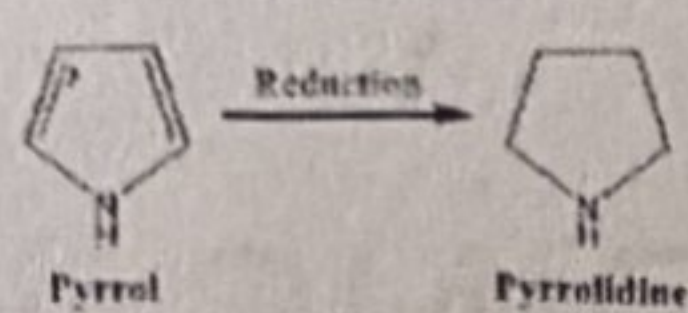
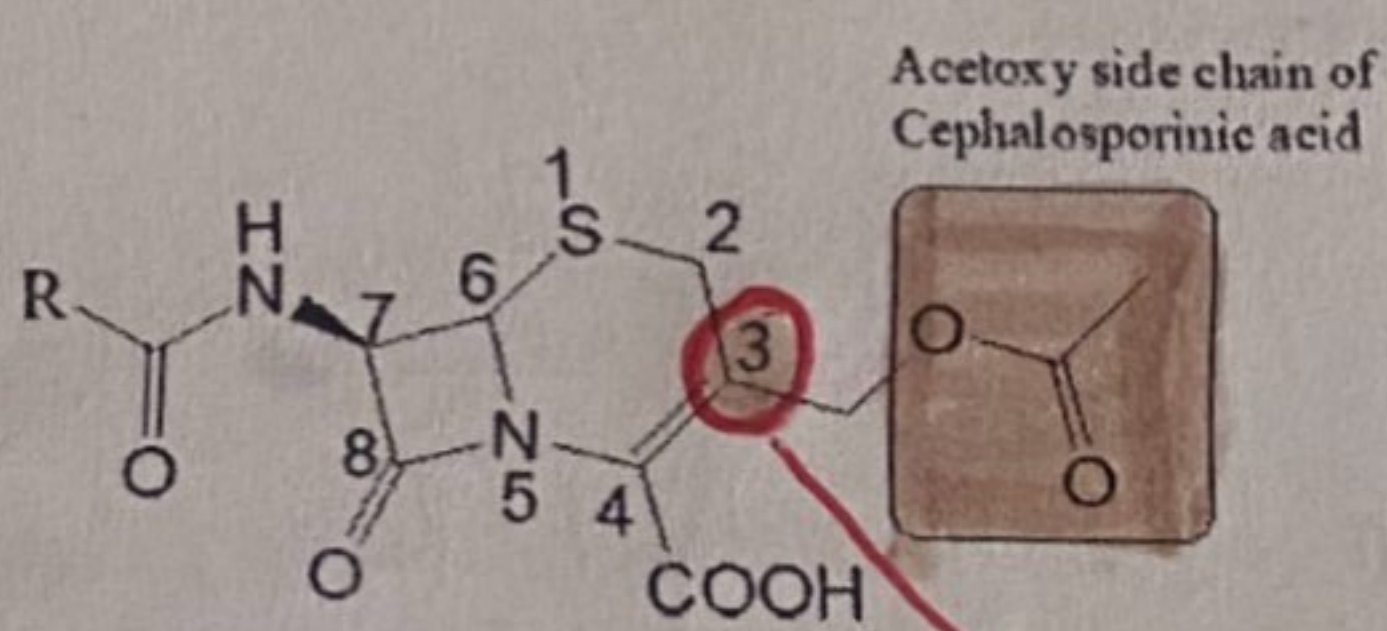
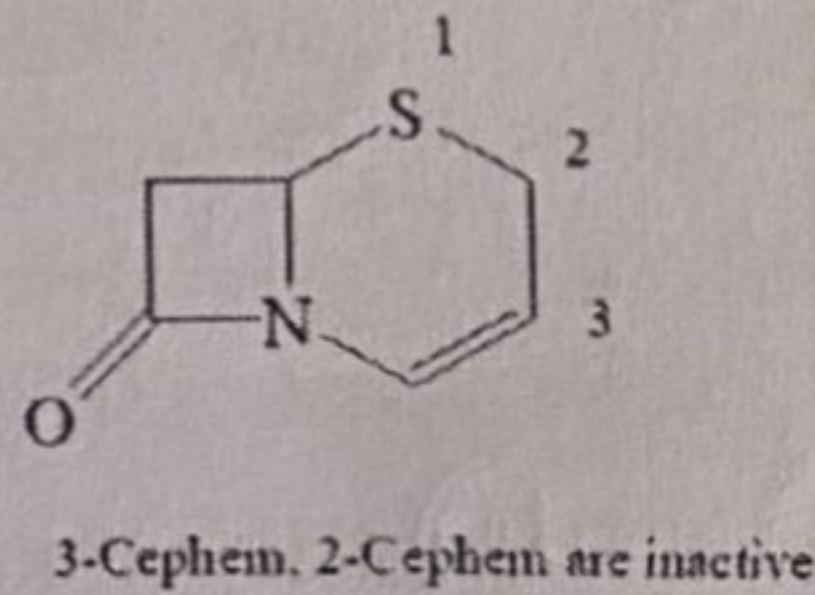
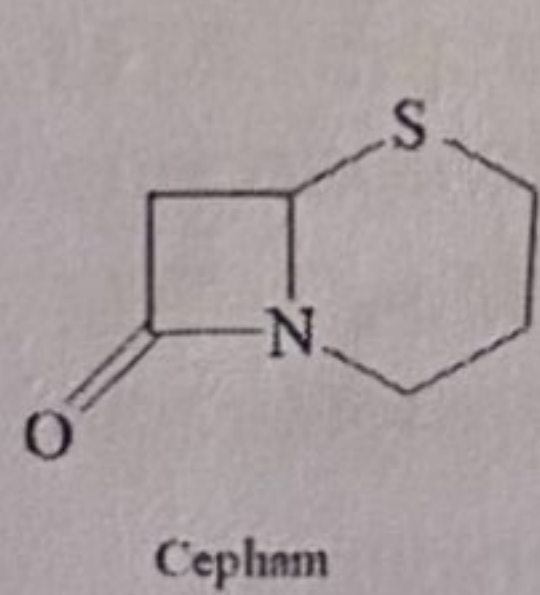


FIGURE 19.33 Cephalosporin C.

Nomenclature

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



Acetoxy group :- (كثير مهمة)

صنعت acetyl ester

وهي الى تنقسم الى
Beta lactamase

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.

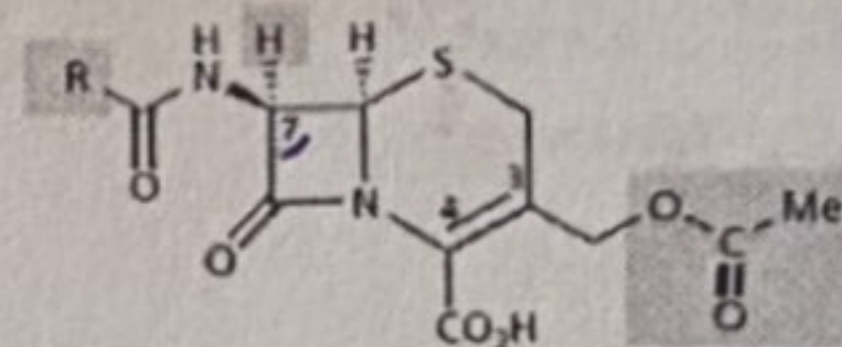


FIGURE 19.36 Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

الأماكن التي يمكن
الجلايد في تحت هاي
توضيح
3 → acetoxymethyl side chain
7 → amino side chain
extra substitution
ال hydrogen ال
تكون ع (7) carbon

مكتوب

* ليه بيت اختل من Generation إلى Generation ال Cephalosporins :-

حتى نوع ال Spectrum ال gram (-) وجون عن beta lactamase → stase

* ممكن نلعب ب 3 أماكن واضحة هون :-

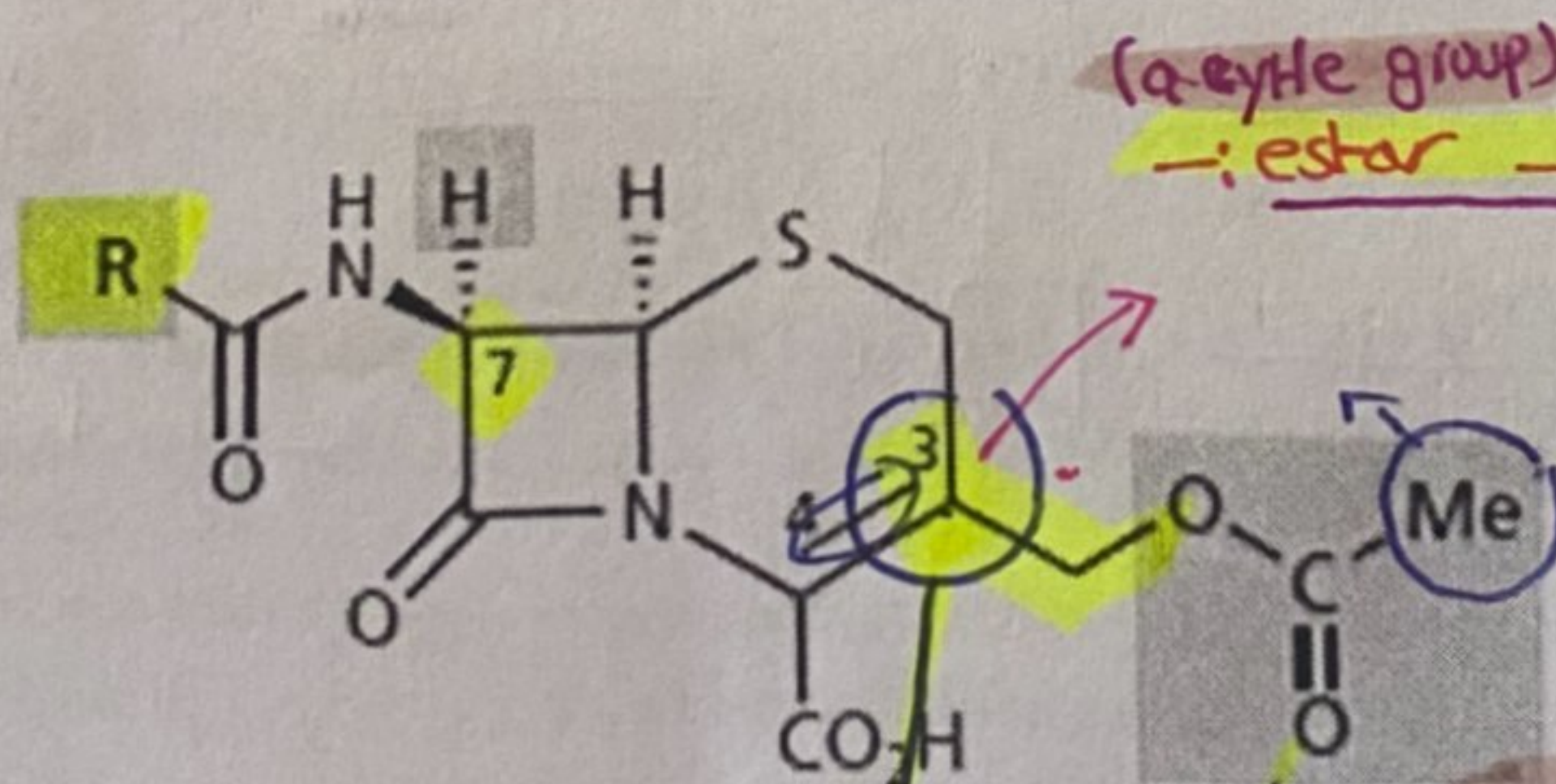


FIGURE 19.36 Positions for possible modification of cephalosporin C. The shading indicates positions which can be varied.

ال B-lactame penicillin
كان في هون (carboxylic acid)

(acetyl group)
لا أهمية ال ester :-

من جرعة ال Cephalosporins
روح يروح ال Beta lactamase
ويرتبط (irreversible)
بسبب
good leaving group ع رقم 3
بقية الجرعة تبقى
intact وتتدخل
ال (transpeptidase)
ولتستغل هونها
good leaving group ع رقم 3 مهمة

هون في acetyl group و methyl

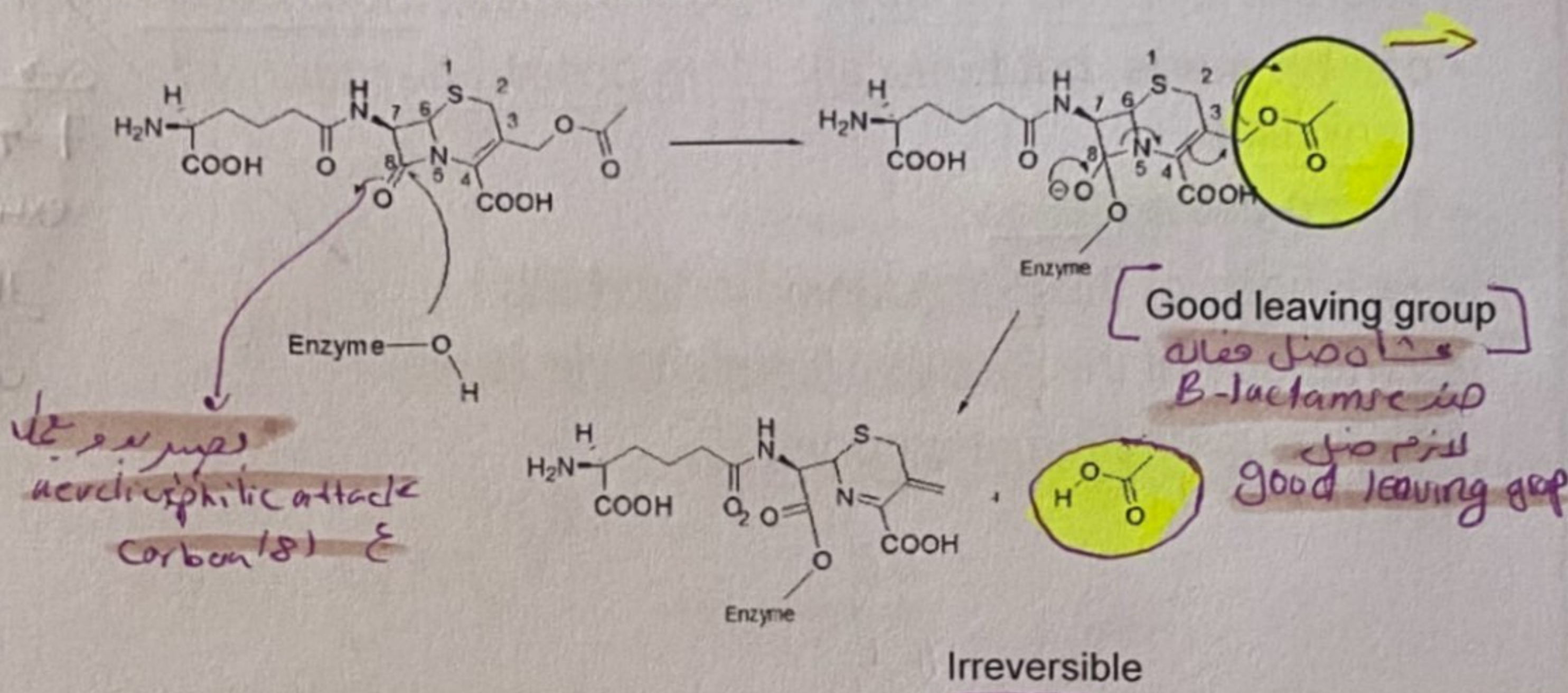
إذا ما فهمتوا
حكي هون
افتحوا السلام
اي جدهاي

جزء متفاعل مع الـ
Beta lactamase
ويتسببها

جزء تخرت جدار الخلية
وتفاعل مع
(transpeptidase)

وليفوا انه هاد الـ دور في
تكوين جدار الخلية وبن اقصى عليه نقصي
ع بكتيريا

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



هون بكتيريا
عالة وطلع الـ
acetoxy group
ليبر، يفتت
ماخلي غدار رواب
انفاونه بدابقوا
وتزلت الـ
energy
تاي الميك

* الـ صبار الـ :-

جزء من جزيء العلاجية الـ cephalosporine يرتبط الـ Irreversible مع
ويتحسب الـ بقتة جزيء العلاجية الـ تدخل الـ transpeptidase ويطالع

فترنا جزء من جزيء العلاجية الـ Beta lactamase الـ بالمقابل الـ Beta lactamase الـ صبار الـ (لا) ربي

SAR of Cephalosporins

- (Similar) to penicillins in the 7-amino group. ^{بالـ Penicilline} 6-amino group
- The carboxylic acid at C_4 is essential.
- 3-Acetoxy group at C_3 can be easily varied by nucleophilic substitution

ممكن طابقت بالـ
Penicilline
مع الـ C_3

على اهورا

الـ مجموعيات

اخرى

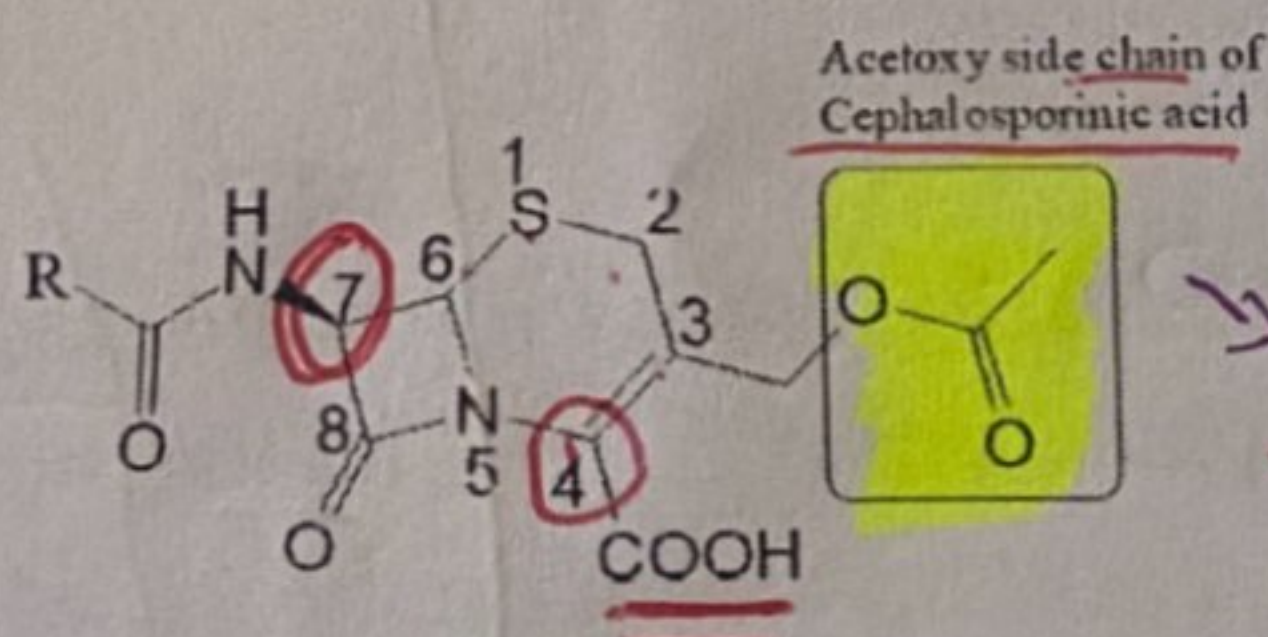
صبار اذا

نفتت

الـ activity

تاي لرون

نقل



ممكن
تاي
orally

مقاومة البكتيريا

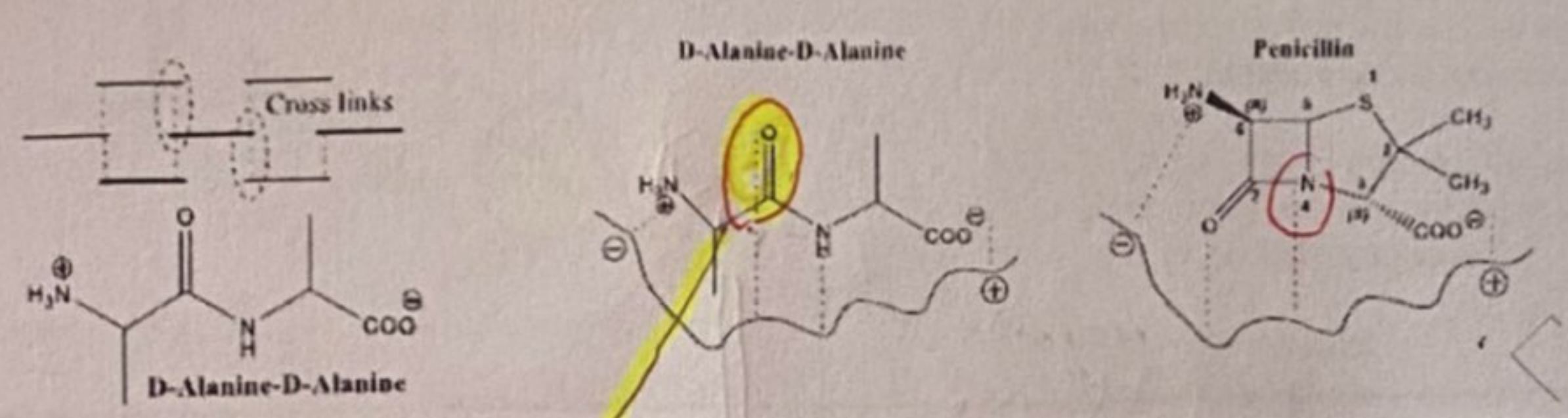
Beta lactamase
تفعل

sub state + transph base → D-ala Dala
 target enzyme → transpeptidase. 10/26/2024

(Dala Dala) → Penicilline
 زي ما كونا باد ~~cephalosporine~~

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

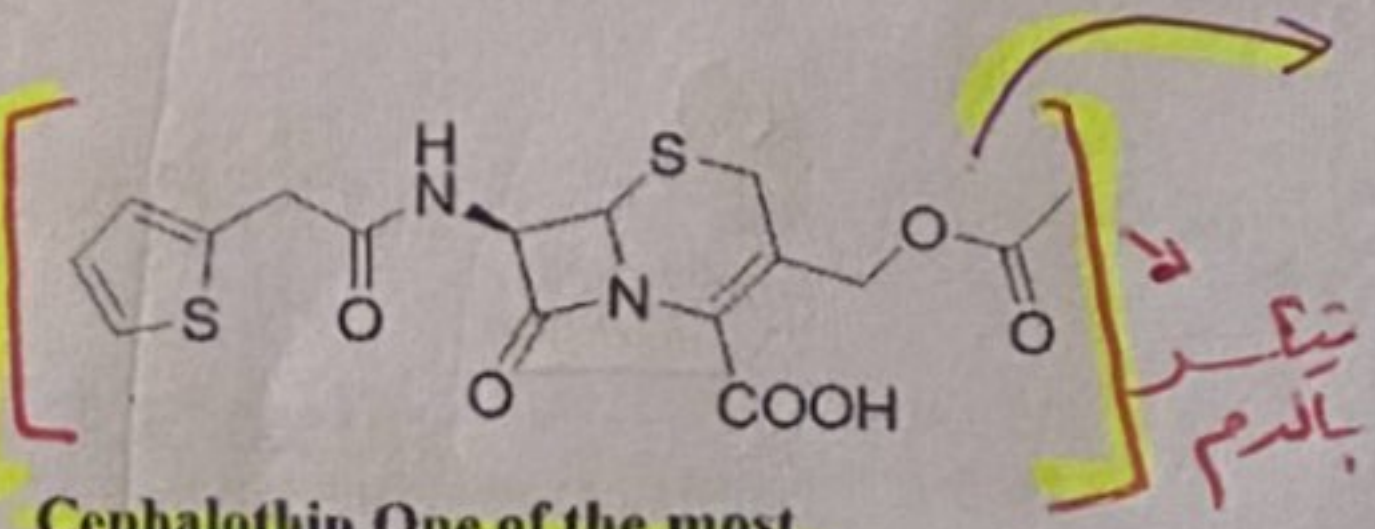
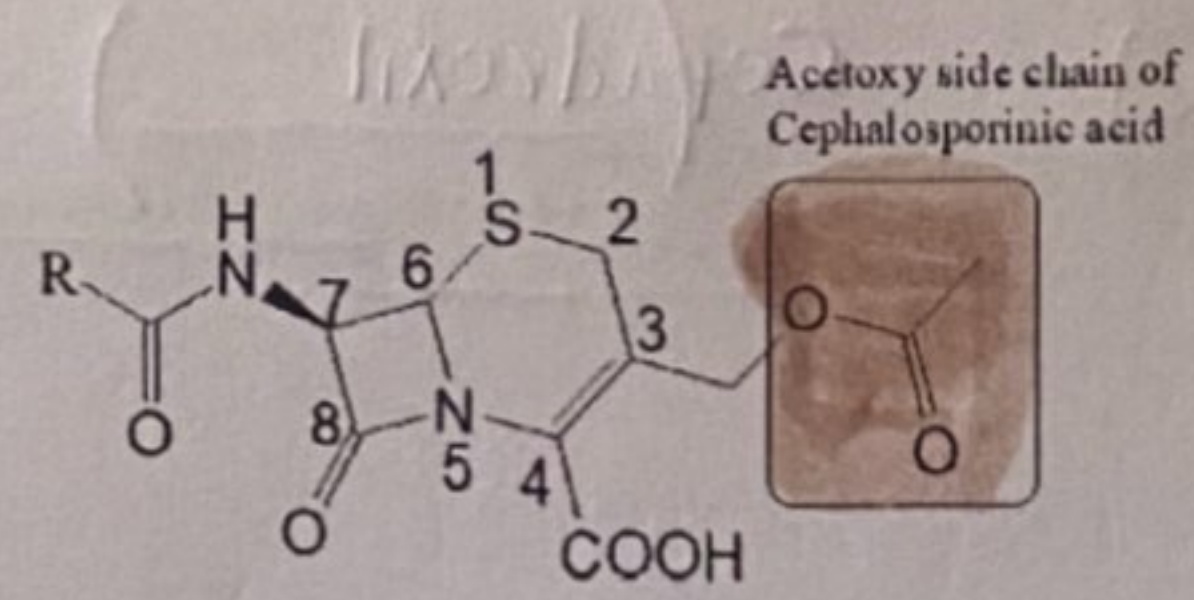
- **NOTES:**
- - The amine groups and carboxyl groups are ionized at neutral PH (ammonium and carboxylate).
- - Alanine in our bodies are L-alanine, but the bacteria use D-alanine (99% of the organisms use L-amino acids; rarely D-amino acids are used).
- - The enzyme that uses this D-ala-D-ala as crosslinks is called "**Transpeptidase**" or "**Penicillin binding protein**".
- When we look at D-ala-D-ala at 3D view with penicillin/ cephalosporins 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 bonding with the catalytic binding pocket of the transpeptidase enzyme. So, the enzyme will confuse between the penicillin/ cephalosporin and its original substrate D-ala-D-ala due to their 3-dimensional similarity, and both can bind to the same binding pocket.



(هاي كثير مهمه)

SAR of Cephalosporins

- The acetoxymethyl (position 3) can be substituted, but still substitution 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.
- (Acyases) can cleave acyl of penicillanic acid – type structures under acidic conditions at the 7-amino position
- Neutral and basic conditions lead to intramolecular amino-lysis 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 first-generation cephalosporins easily hydrolysed in the blood by esterases to give the inactive alcohol metabolite mainly given parenterally

قربنا
 تشيل
 ال
 ester
 زكوا ال
 Pyridine

هاي النقطة مهمة
 تسبب كادي بنقد نلعب
 خيها
 لاهل الون من كفرن
 ع كمال Powder جديليج
 لافرح يطر بيضه
 Data Dala
 زي ال acylases
 ما باثر على Penicillina
 رح ياتروا ع cephalosporine
 لكن اهميتهم محدودة
 لانه لا تفرم الاله
 Beta lactamase
 هاي

Beta lactame Backbone
 - Basic
 - Neutral
 لعينه لازم يكون المركب ع مثل
 Powder

ليه جانا صك
وهاد عشان
ماتنا بالدم

ester → Pyridinium

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.

+ (N)
- (Carboxyl)

Pyridine على حلقه

لباسا هيك صافيد
orally →

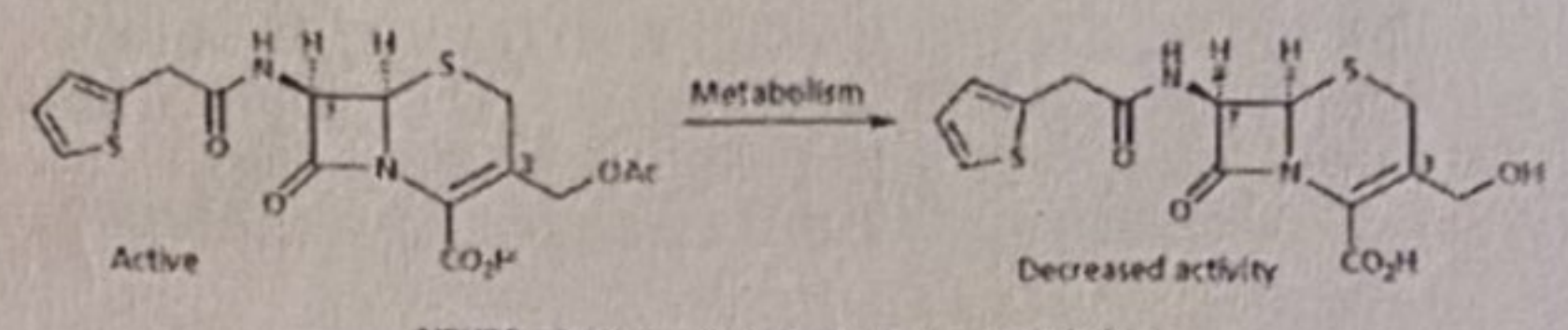


FIGURE 19.40 Metabolic hydrolysis of cephalothin.

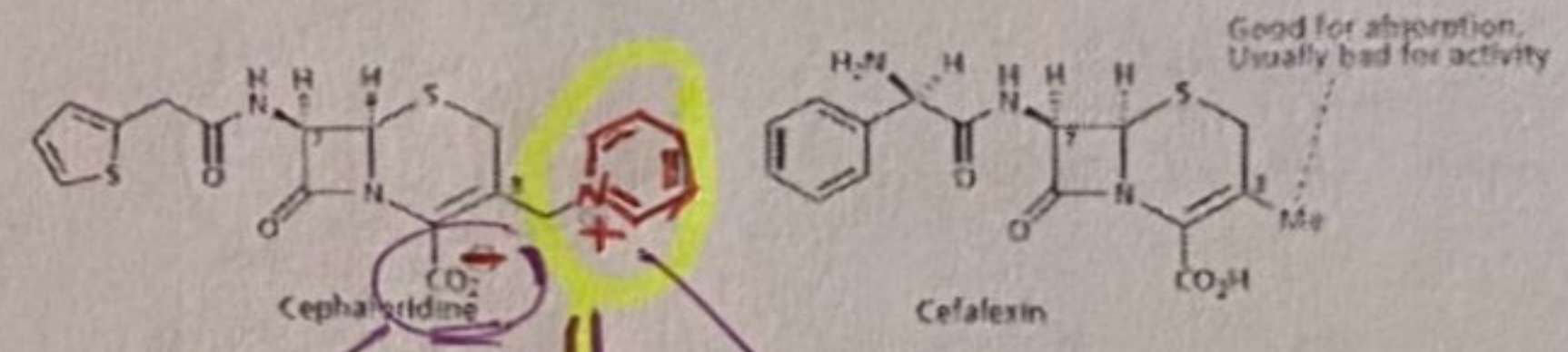


FIGURE 19.41 Cephaloridine and cephalexin.

Negative charge
(good leaving group) pyridine
Positive charge

اي مركب تحتوي
على ال-
acetoxy
ما جمل absorbed
orally

Methyl group ← Acetoxy ← لازم اسيل كل عشان اقدر اعطي orally

Oral Cephalosporins (less active)

amine penicilline.

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)

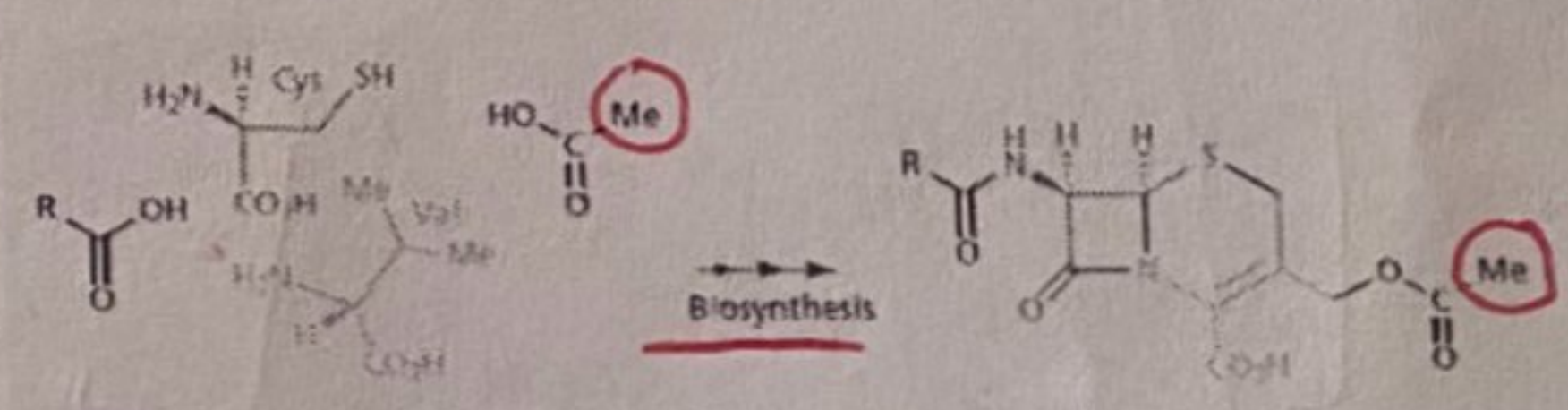
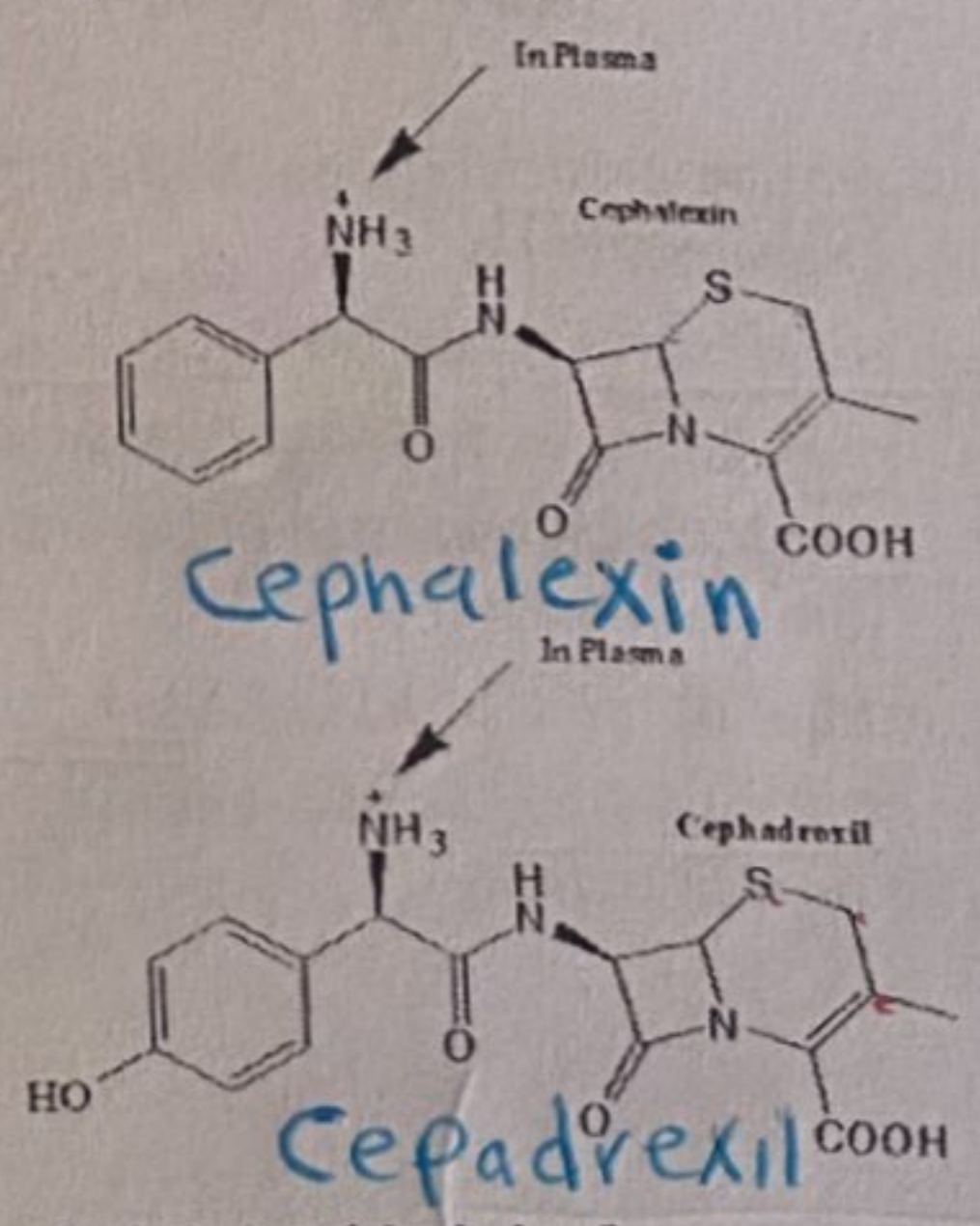


FIGURE 19.34 Biosynthetic precursors of cephalosporin C.



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

-amoxicillin
-ampicillin

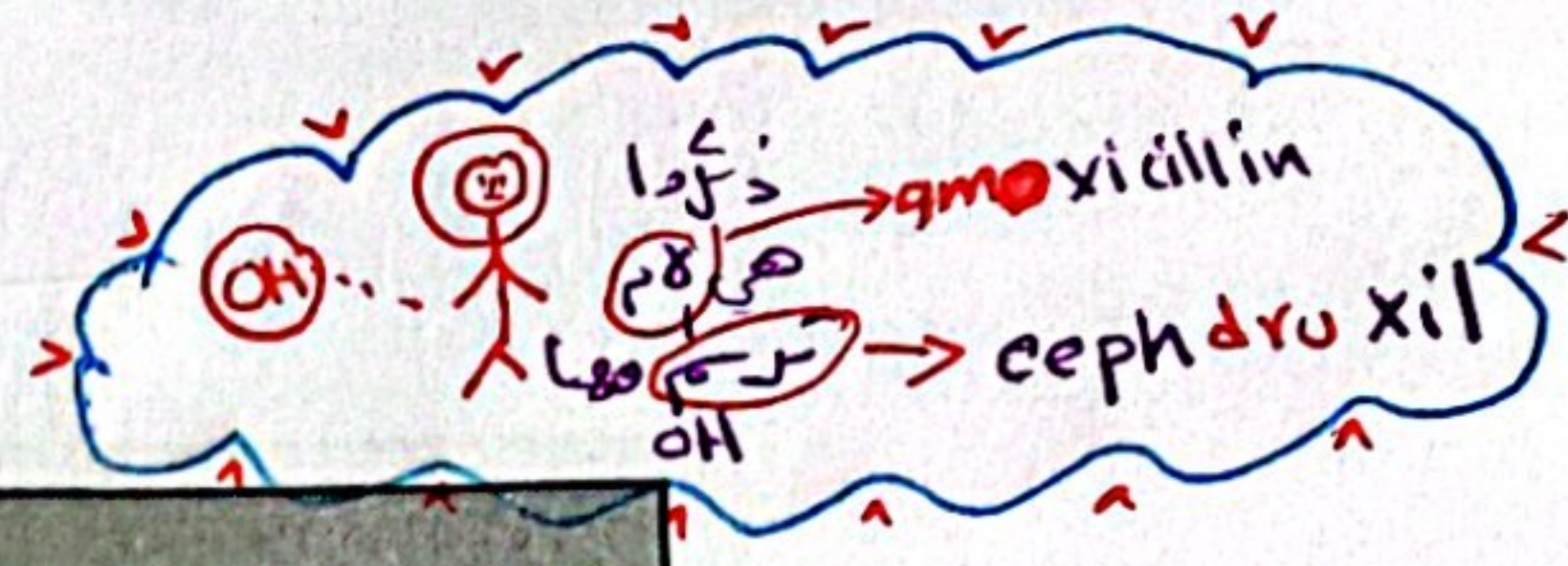
Cephalexin + Cephadroxil

لبس هدرع في
Methyl group

لبرطوا هندن
بسيه مينه
تأليف واخراج
رياحه

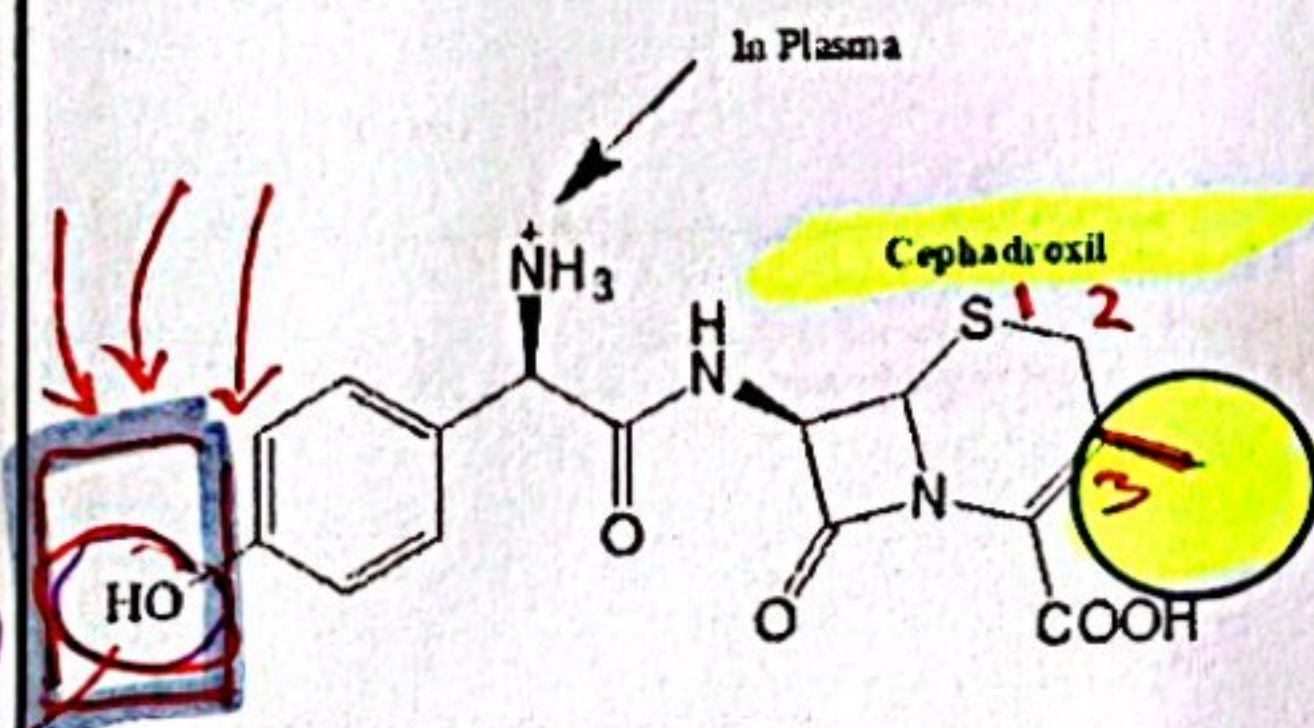
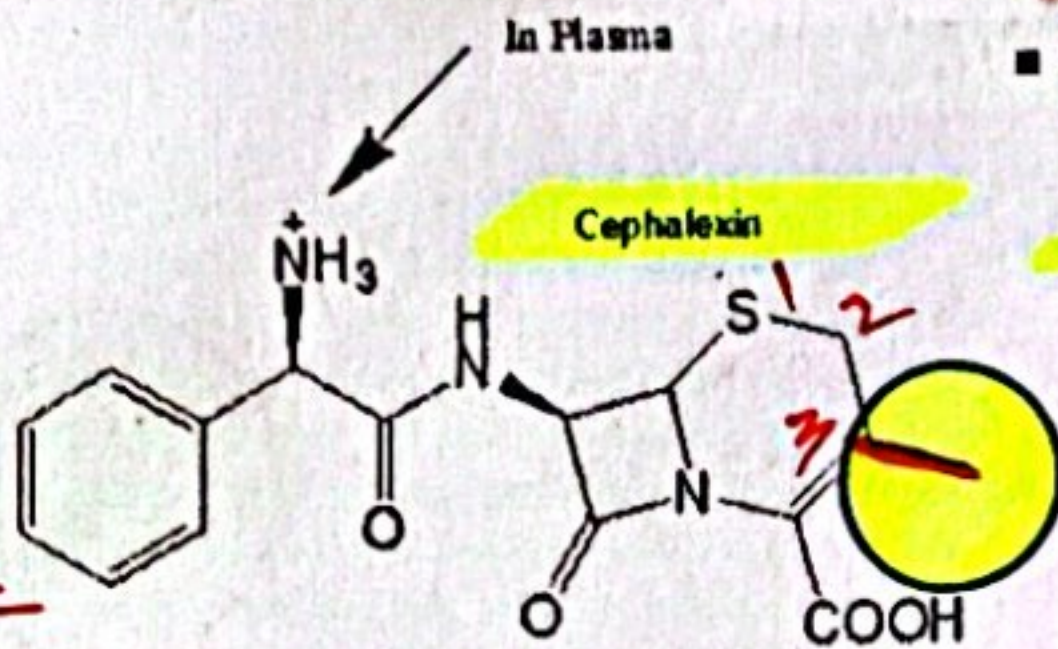
(ampicillin) $\xrightarrow{\text{بسيه}}$ cephalexin $\xrightarrow{\text{عالي}}$ ampi
(amoxicillin) $\xrightarrow{\text{بسيه}}$ cephadroxil $\xrightarrow{\text{OH}}$

(الام رسم) جدول بشبهوا بعض



Examples of orally active cephalosporines

- Reduction of 3-acetoxy to methyl gives oral activity $\rightarrow$ acetoxy $\rightarrow$ methyl $\rightarrow$ oral
- (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 cefalexin 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.

acetoxy $\rightarrow$ methyl $\rightarrow$ oral

لبيك بيتم تصنيف
على Suspension

ليس خبيثه اد
methyl
بالاصحاب عن طريقه
مع انه اد
bad activity
not a good leaving group

ولكن وجود ال
Carbon of the
7-acylamino
side.

الهدية (الهدية)

Cephalexin $\rightarrow$ Cephalothin
Cephadroxil $\rightarrow$ Cephalothin

less active

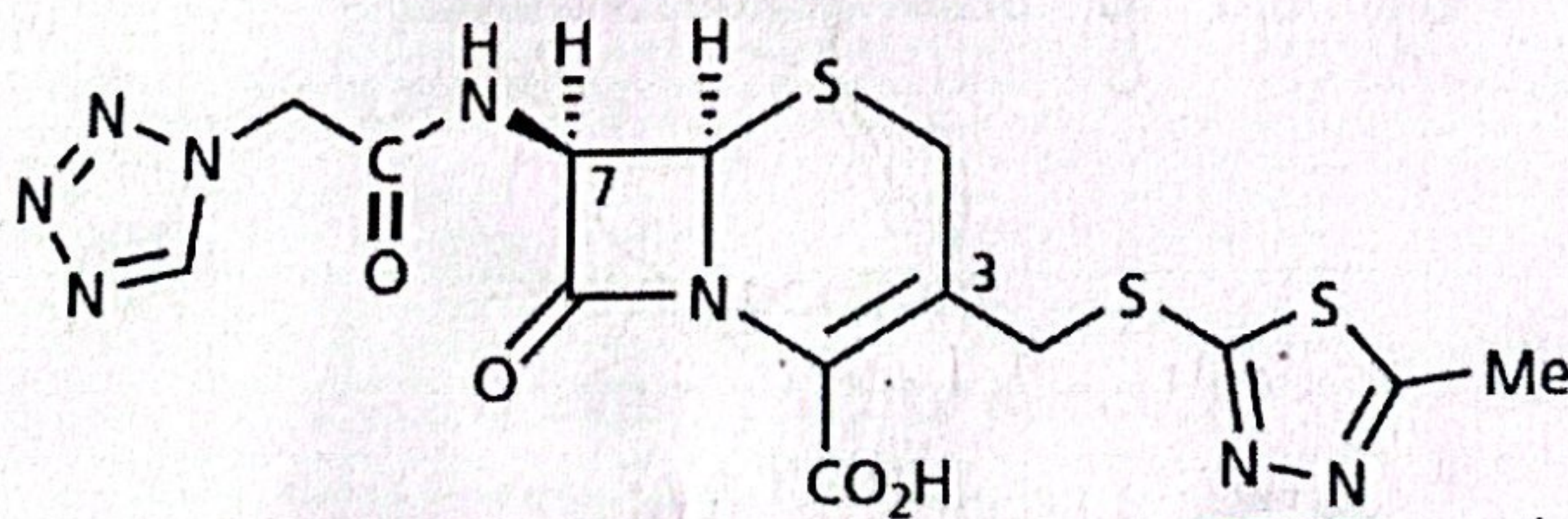


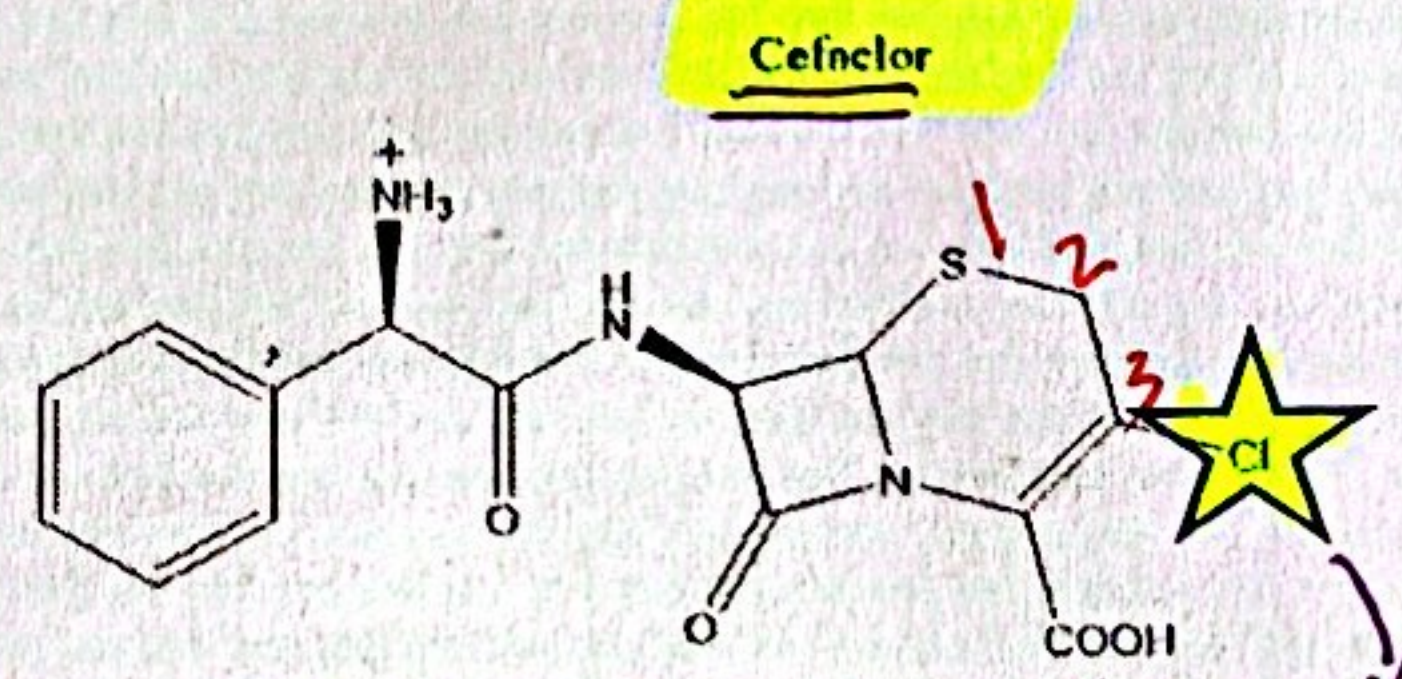
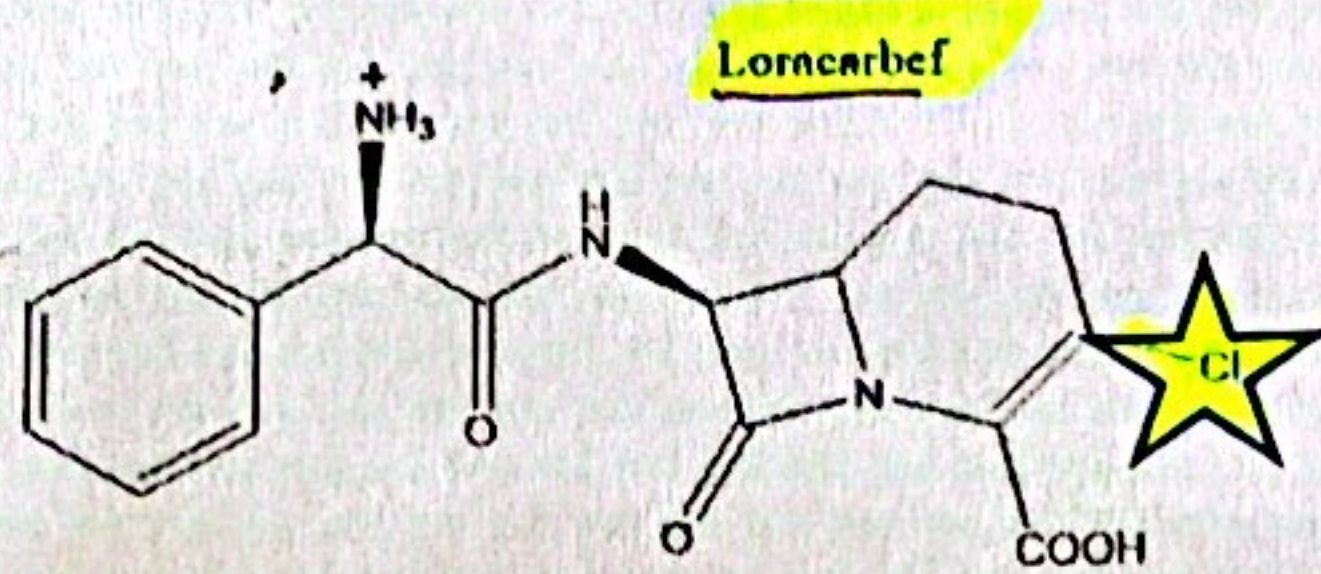
FIGURE 19.42 Cefazolin.

First generation.

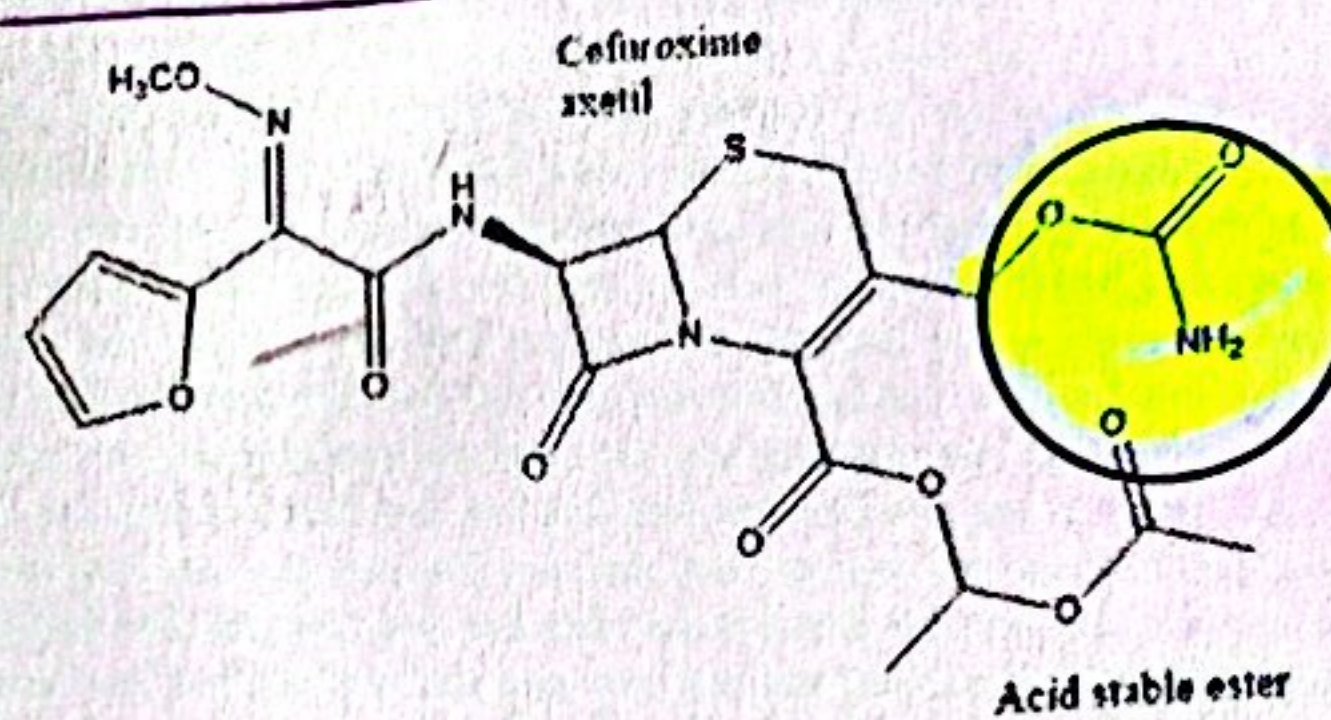
(thiazole)

Other examples of orally active Cephalosporins

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

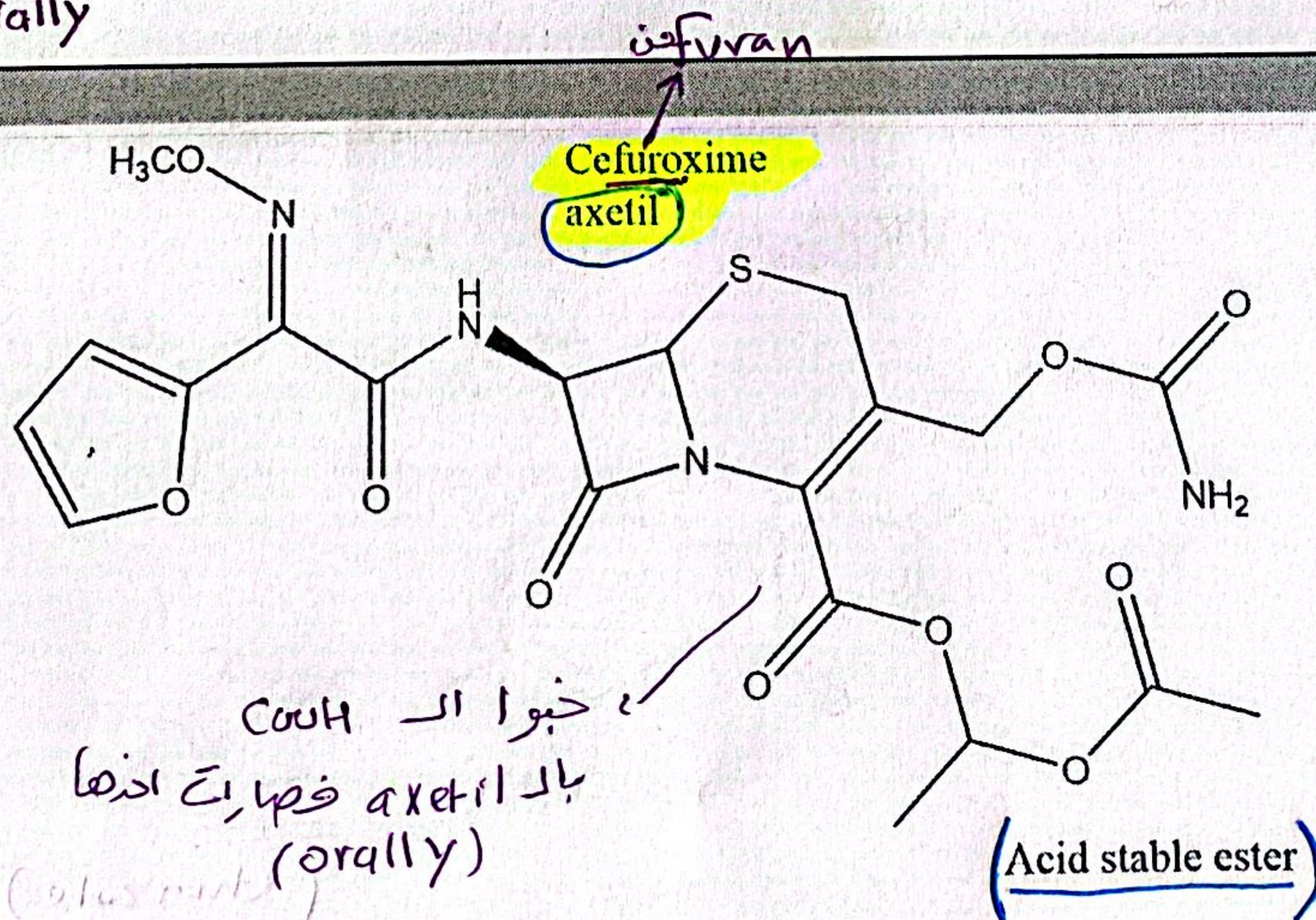


(orally) وجود كلور ع 3



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 β -lactamases and mammalian esterases (Second generation cephalosporin).

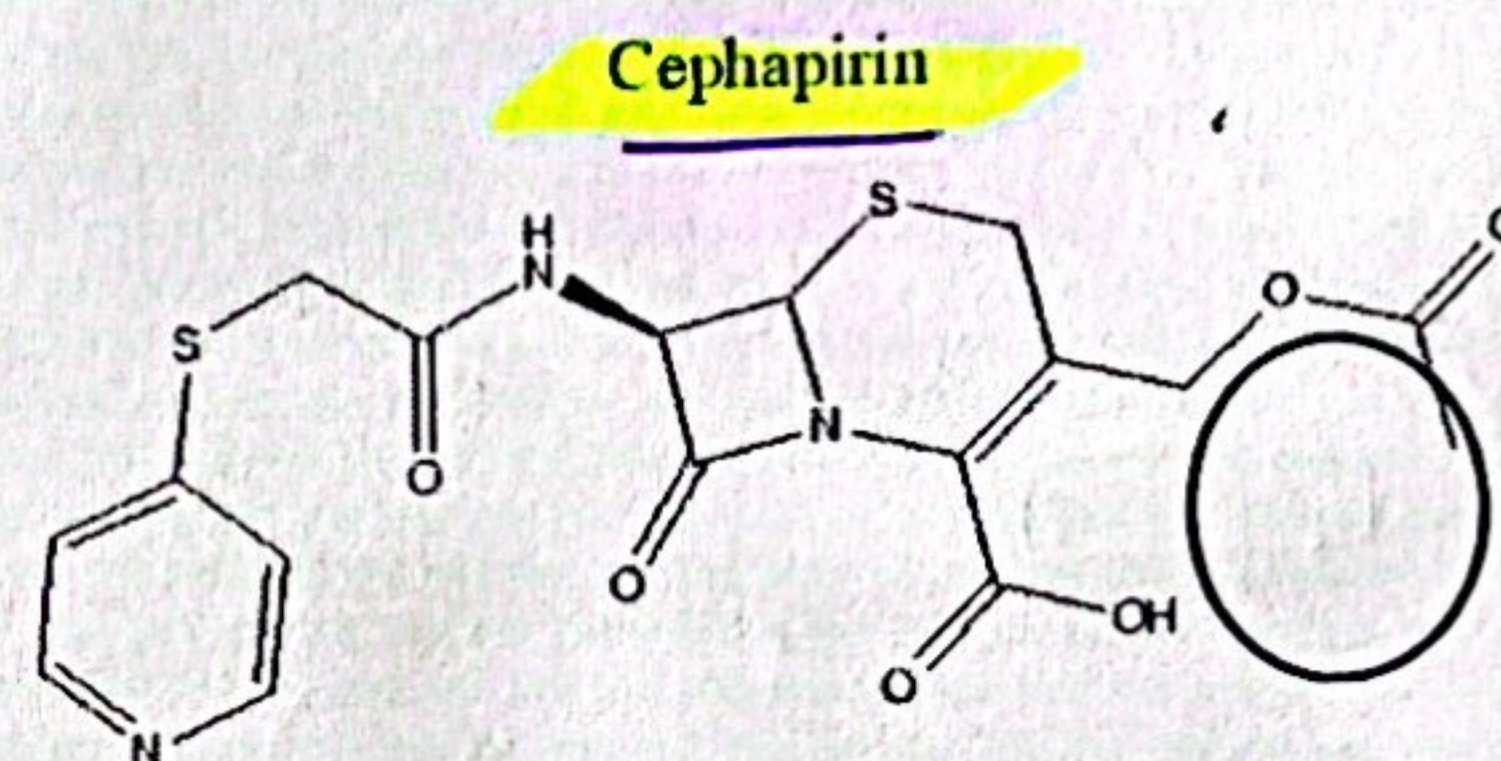
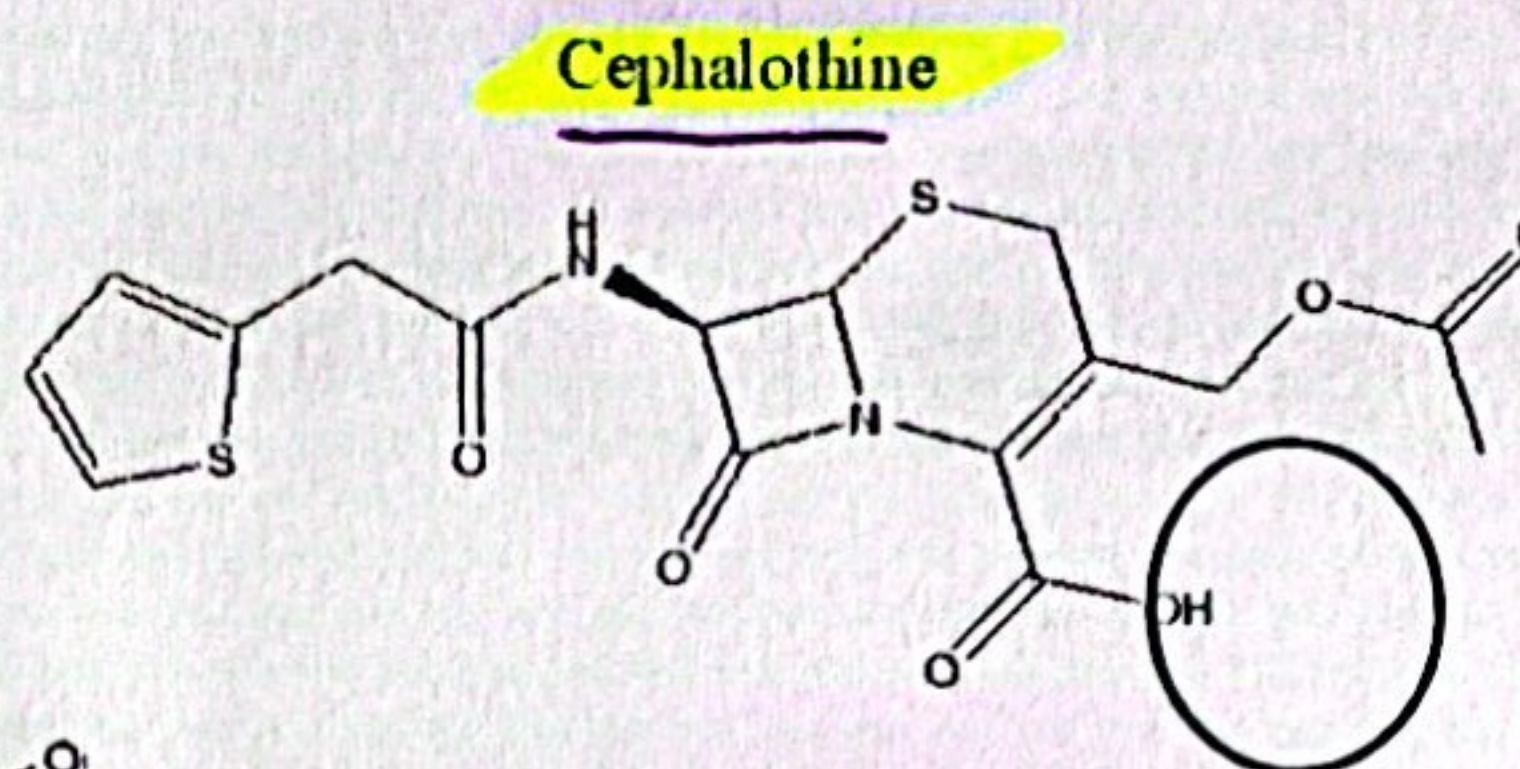
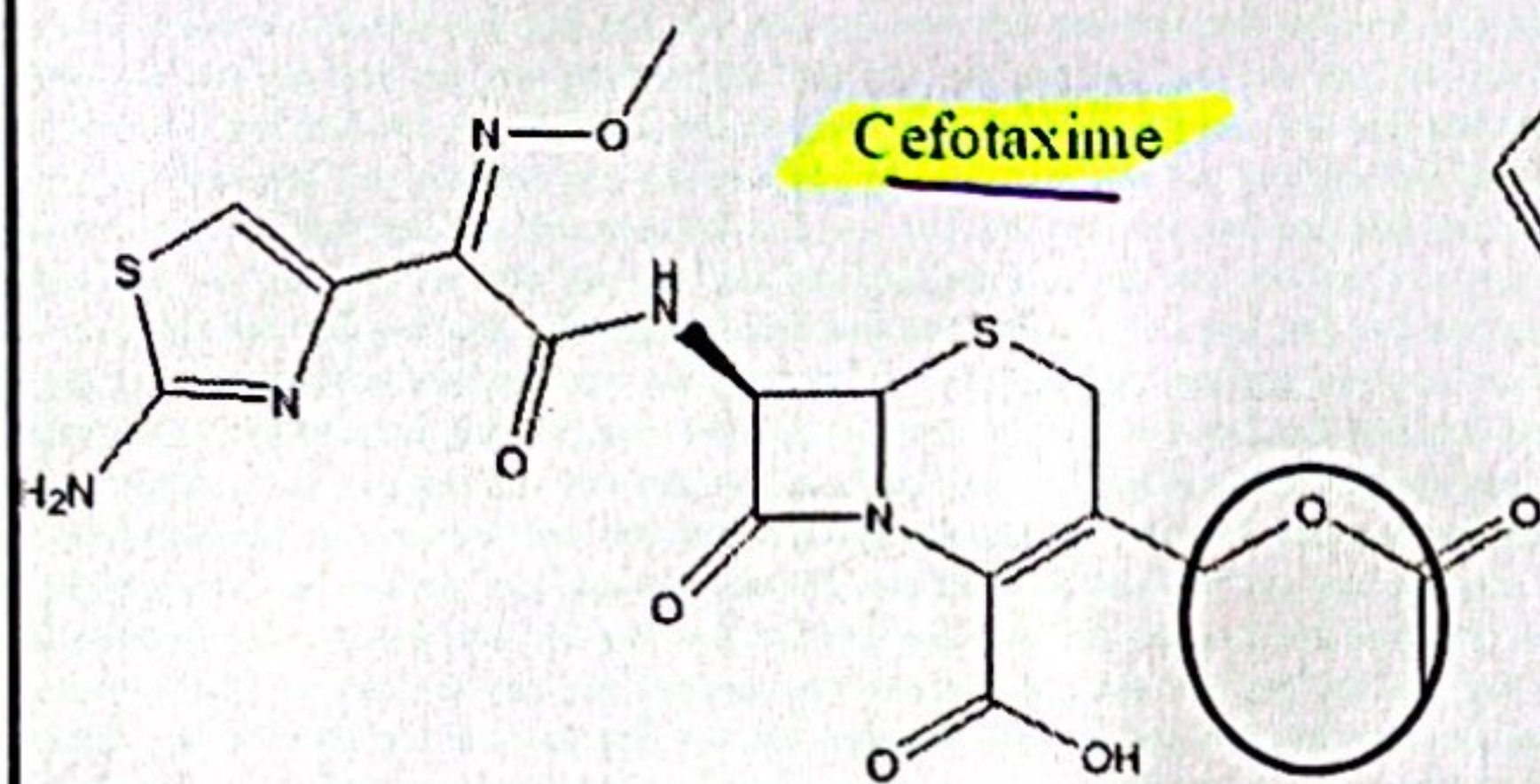
Cefuroxime $\rightarrow$ Parental
Cefuroxime axetil $\rightarrow$ orally



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 β -lactamases and mammalian esterases. (Second generation cephalosporin)

Parental Cephalosporins ^{(axetil) پروتن}

• Examples :



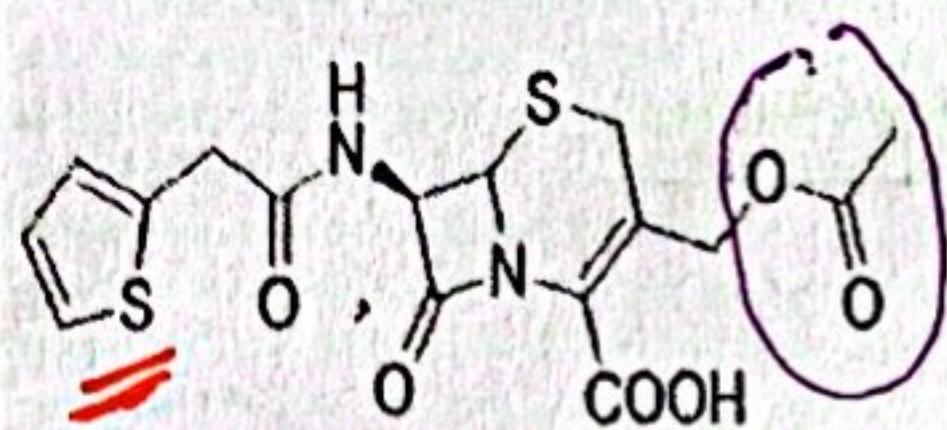
Classification of Cephalosporins

- 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**

گرم مثبتی کم
generation → گرم مثبتی → gram (+) اکثر

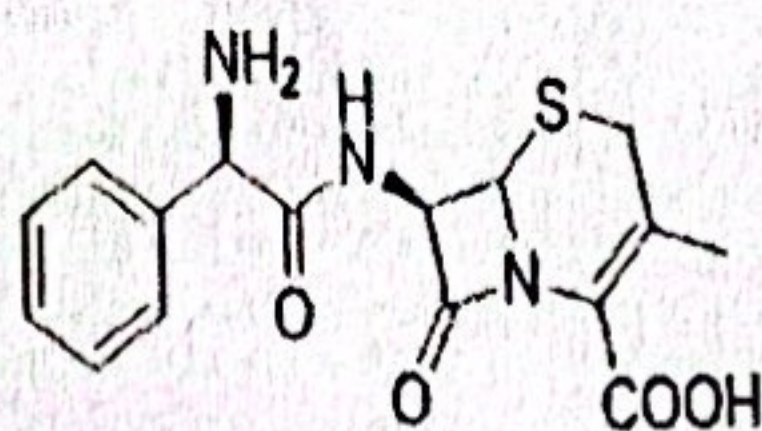
1st Generation Cephalosporins

- 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 mainly given parenterally



Cephalexin

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

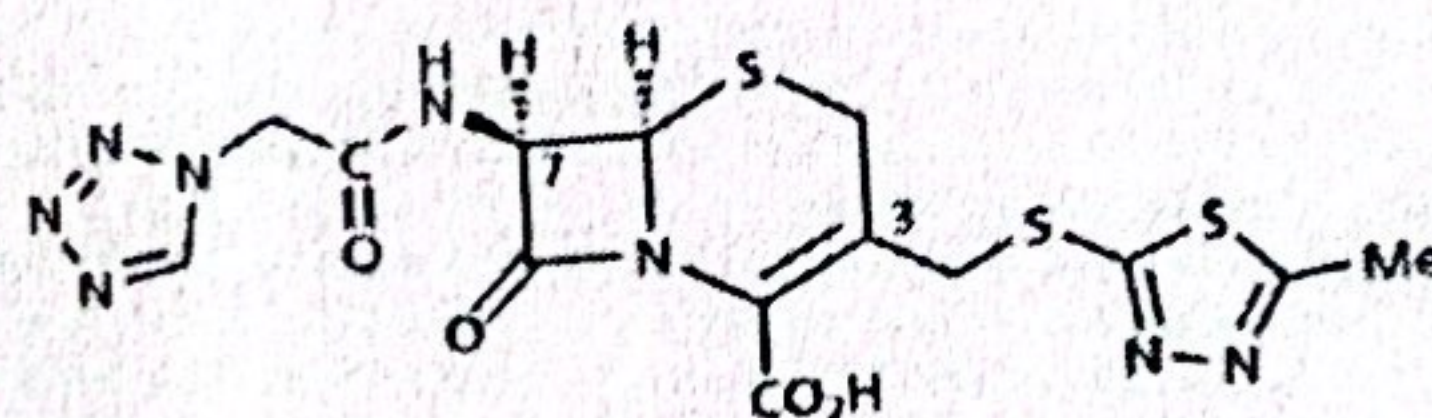
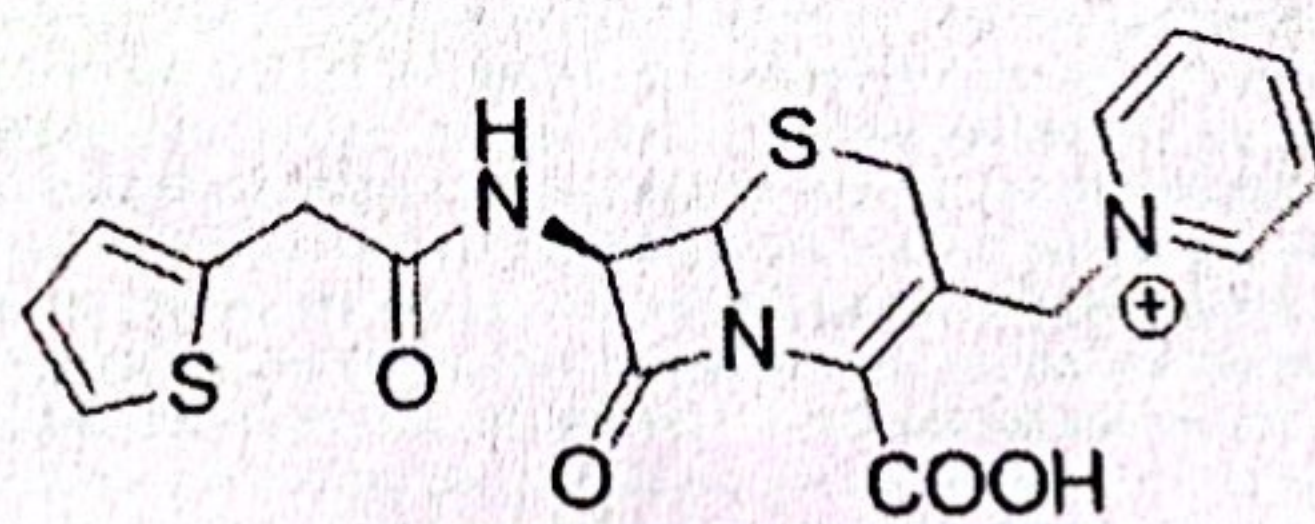


FIGURE 19.42 Cefazolin.

1st Generation Cephalosporins



Cephaloridine

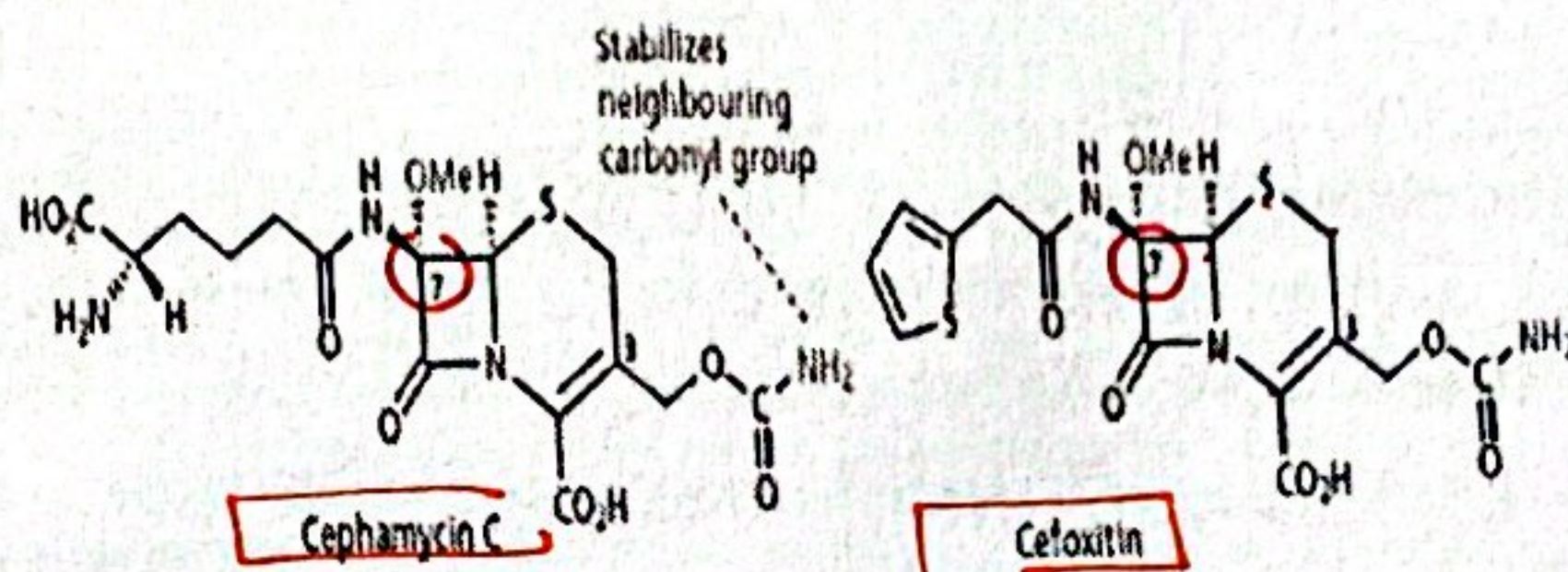
- Have the good leaving group, pyridinium ion. This improves the activity.
- This group is not hydrolysable compared to the acetyloxy group found in cephalothin.
- Poorly absorbed from the gut because it will be ionized all the time.
- Only given parenterally.

penicillin G
أكثر الفعالية
لأنه يتناصت
أحد مضادات
الحل تقوية

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 cephalosporins against Staph. aureus and other Gram-positive bacteria.



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

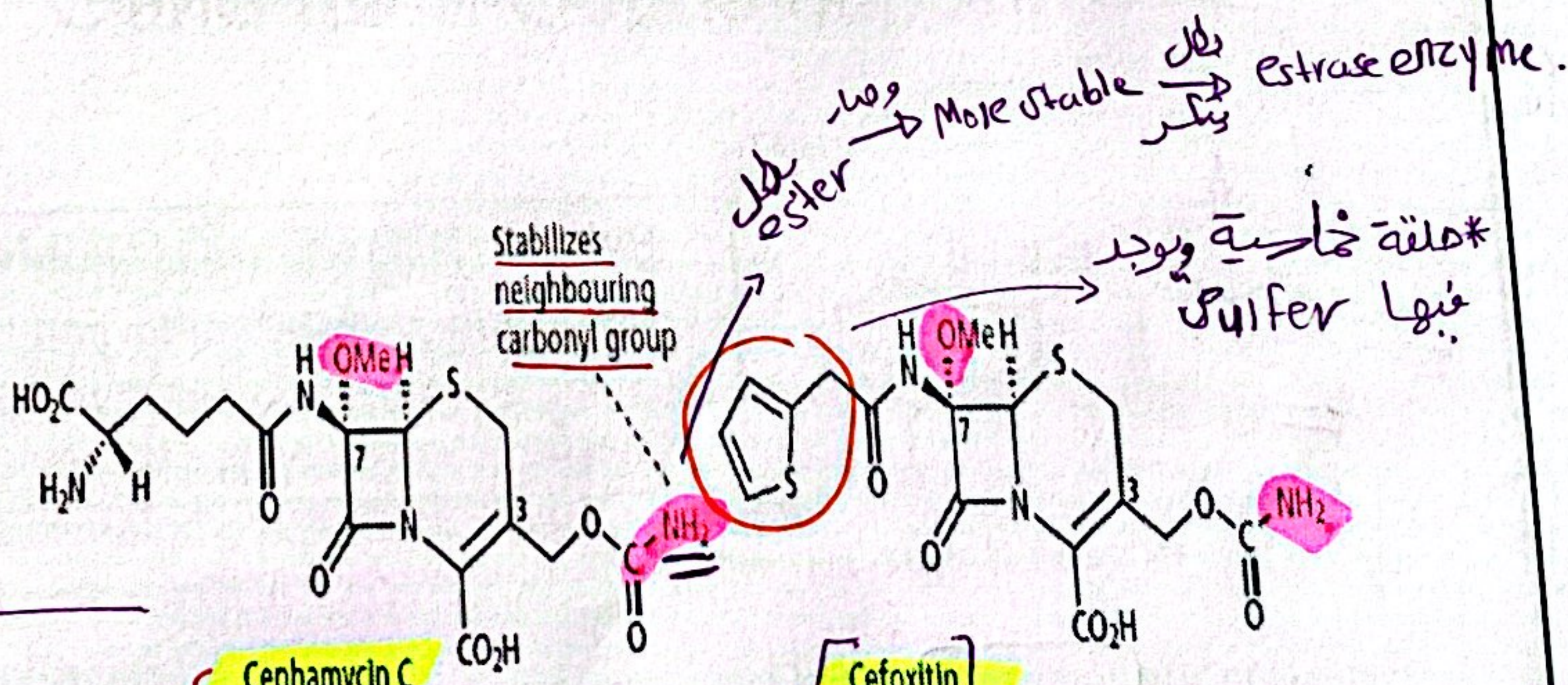


FIGURE 19.43 Cephamycin C and cefoxitin.

اهم اتيه من الجيل الثاني [7 ← OMe] Second

[3 ← NH₂]

Cefoxitin

↓

Cephalosporin

↓

Methoxy group

↓

Carbonyl ester

تم اكتشافه (Bacteria)

مشتق من فطريات

كل الـ β -lactam كانوا موجودين بالقرن

بدل
H
↓
OMe

تم إيجاده بالبكتريا
استخلص منه الـ 7
التي يمكن ان تسمى الـ 7
Second
التي موجودة

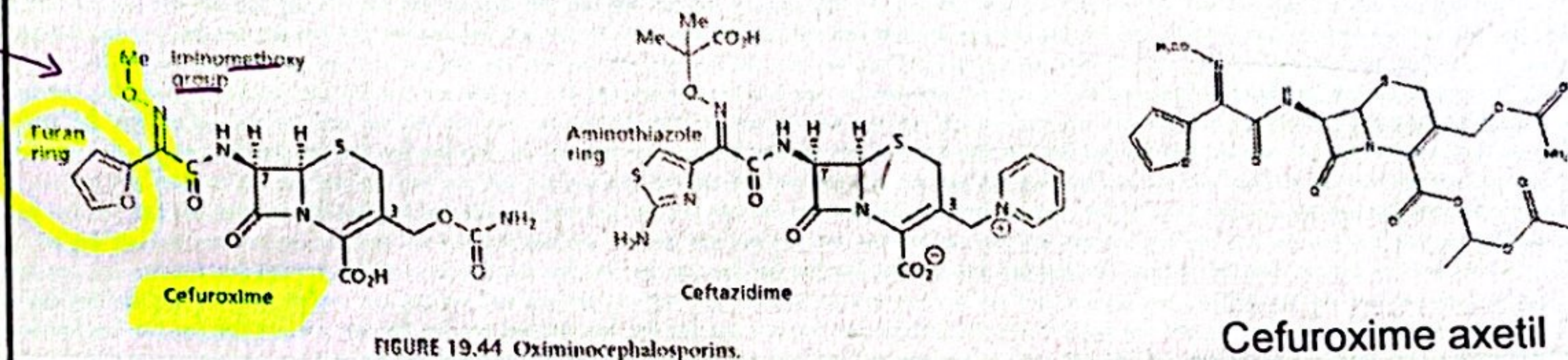
7/3

oxime, مستبدل
 يكون
 موجود
 First
 Second

Oximinocephalosporins

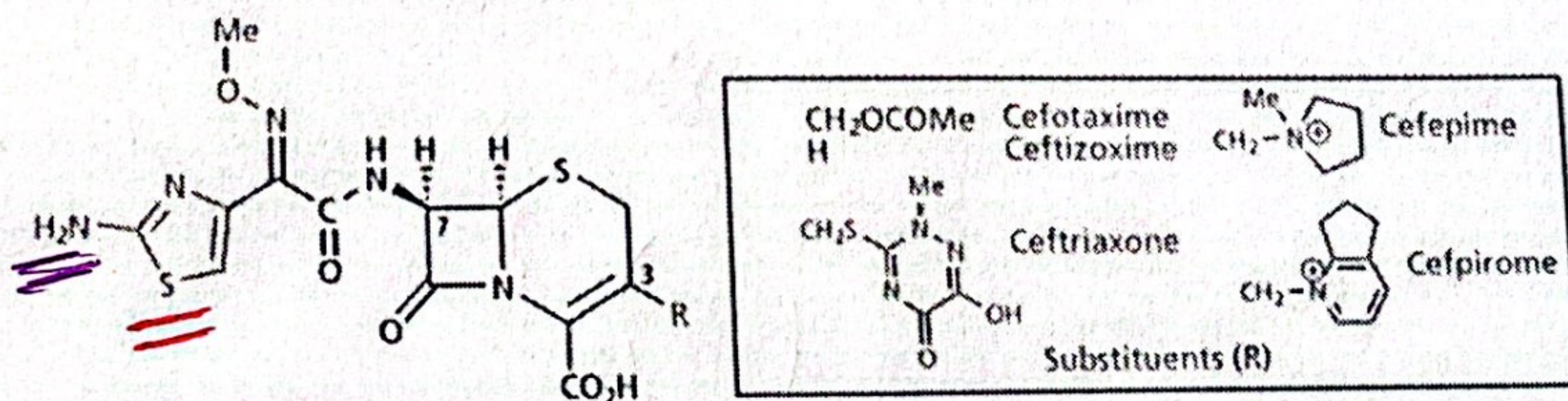
- The development of **oximinocephalosporins** has been a major advance in cephalosporin research.
- These structures contain an **iminomethoxy group** at the α -position of the acyl side chain, which significantly increases the stability of cephalosporins against the β -lactamases produced by some organisms (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.

من هون لما بنصير
 نشوف الـ
 (oximinogroup)
 وصلنا لـ
 spectrum
 صاكن او اهلين
 الـ قبل



Third-generation cephalosporins

Ceftriaxone



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

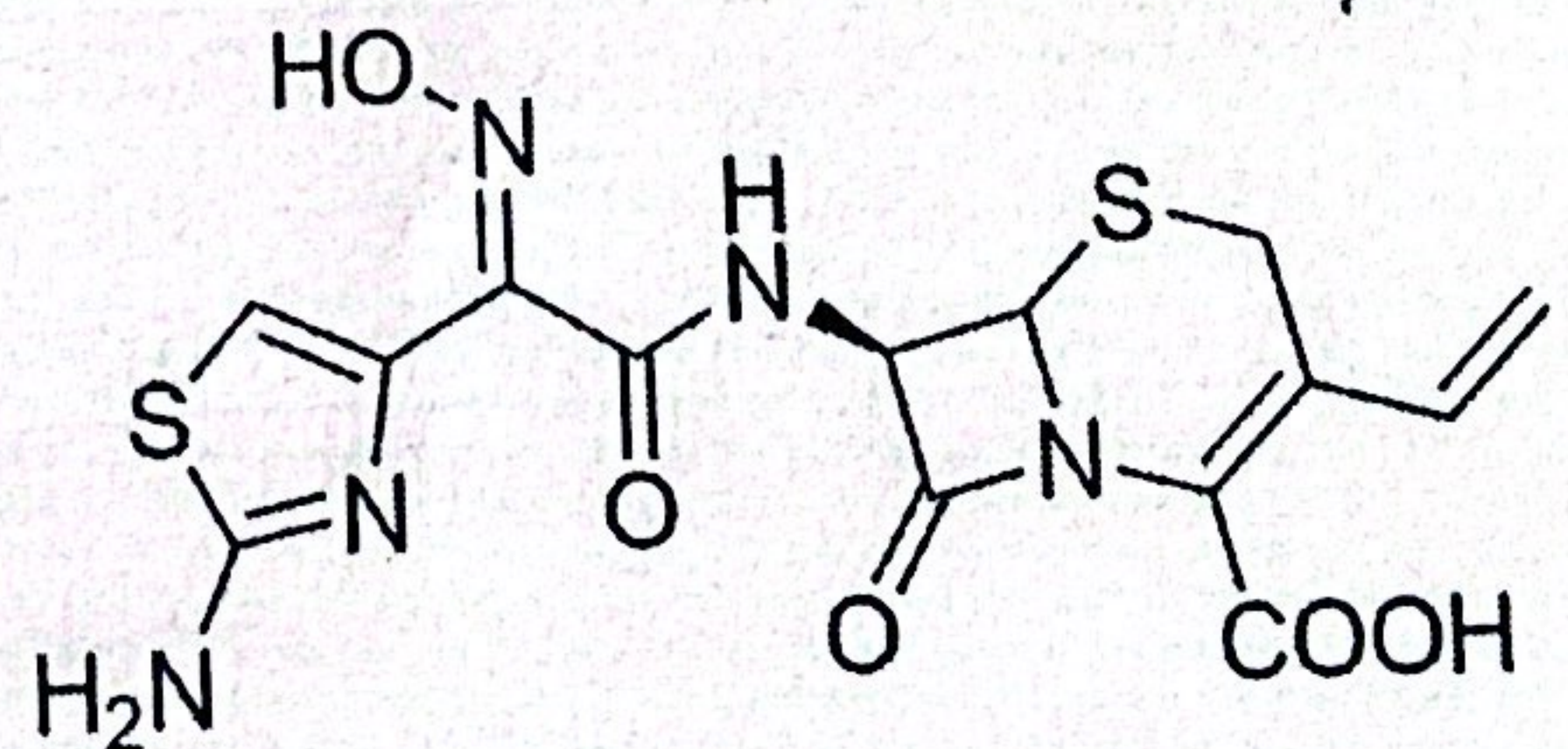
- As a result, third-generation cephalosporins containing this ring have a marked increase in activity against Gram-negative bacteria. A variety of such structures have been prepared, such as ceftazidime, cefotaxime, ceftizoxime, and ceftriaxone
- With different substituents at position 3 to vary the 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.

صفحه دهرضا لستو
برالستقی!

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



فصلهم صرف "p" Fourth-generation cephalosporins

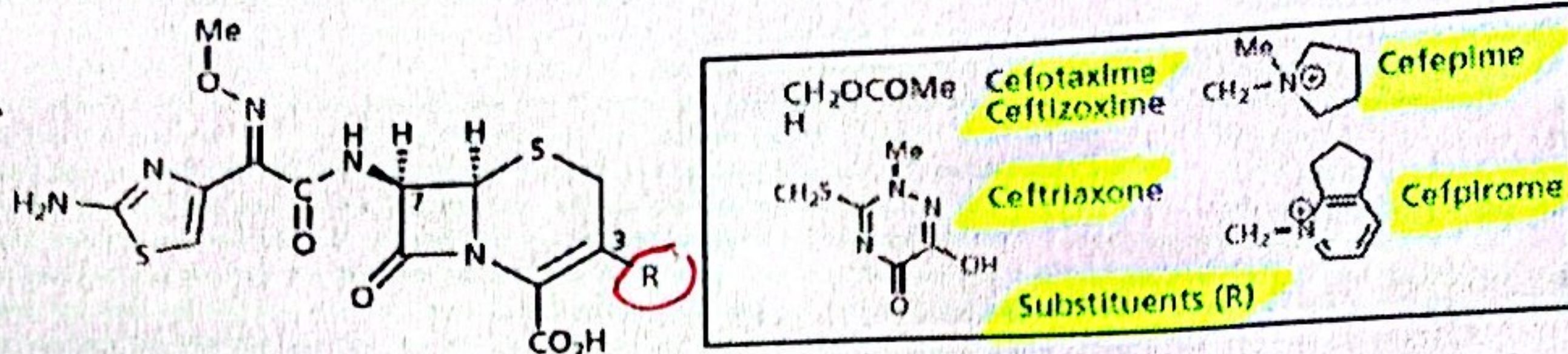


FIGURE 19.45 Third- and fourth-generation oximinocephalosporins.

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 to the transpeptidase enzyme and a low affinity to a variety of β -lactamases.

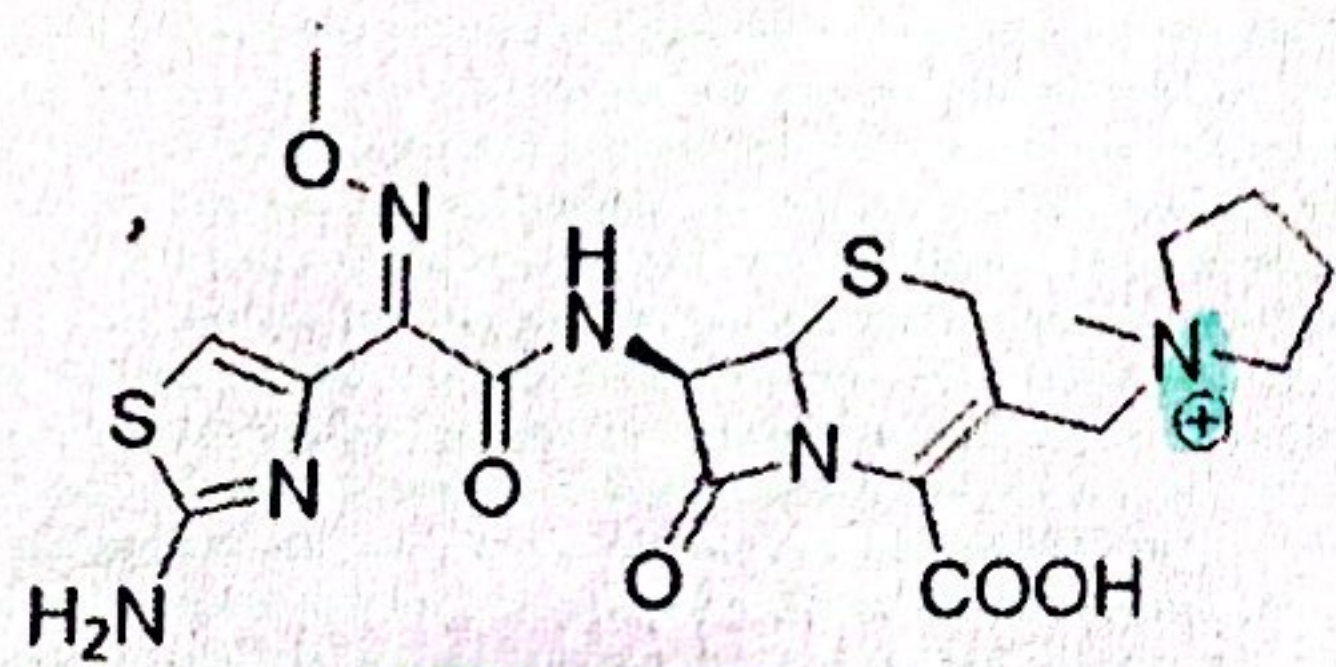
بہ نسبت زیادہ
نک (positive charge)
زادہ سے لگائی ہے۔

ہا۔ اس ربط کا target انجیل
واریتہ β -lactamase اقل (لہذا)

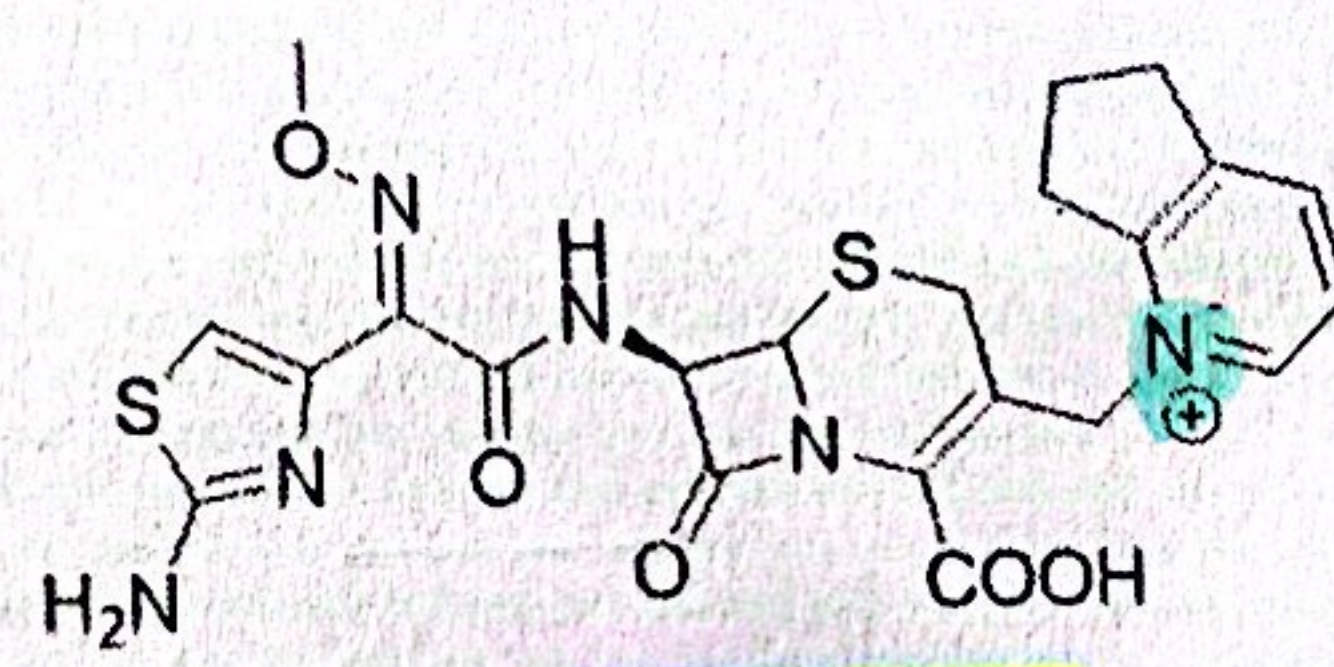
منی صا اقل
resistance

affinity
کے اعلیٰ
transpeptidase.

4th Generation Cephalosporins



Cefipime

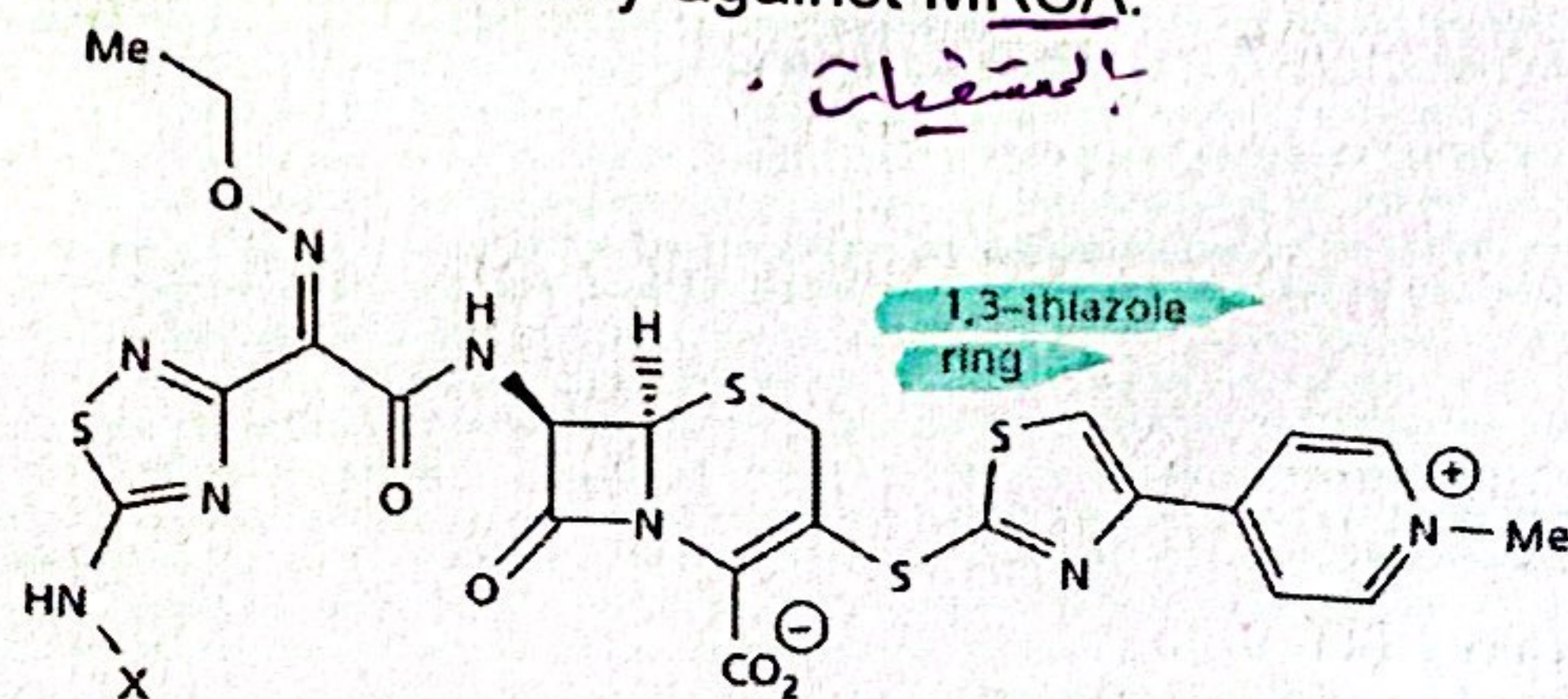


Cefpirome

- They have a positively charged group at C₃ 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 pneumoniae* (MDRSP).
 (Handwritten: "Phosphate group" وجود)
- 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

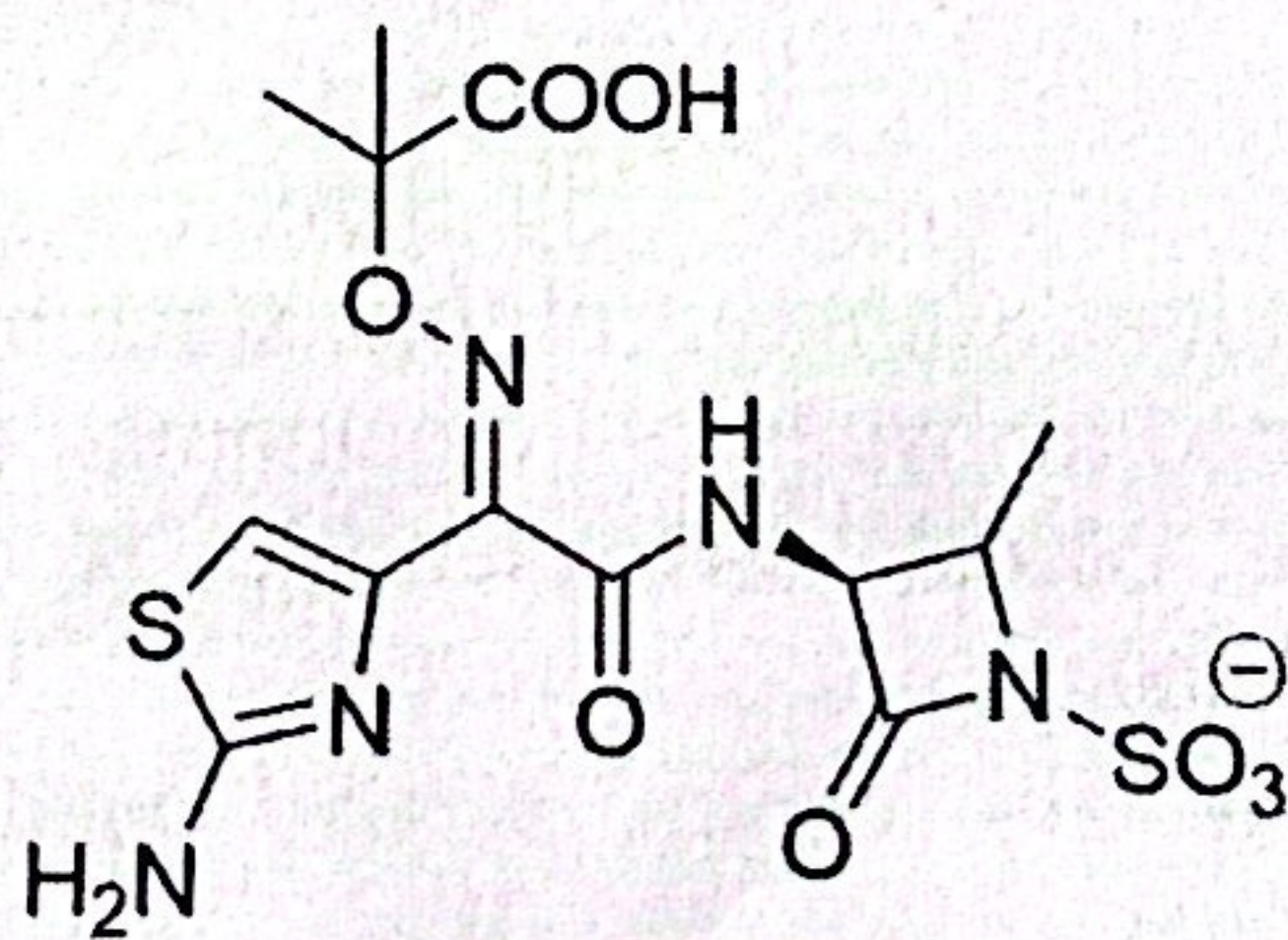
FIGURE 19.46 Ceftaroline and ceftaroline fosamil.

مقاومتهم
 المضادات
 الحيوية
 ليس أكثر من
 MRSA

MRSA :-

كثير خطورة
 لا سمح الله لو صار مع حدا
 اصابه فيلب اصبه
 ممكن توصل لدرجة
 انه مات قد يتخلص
 منها الا بقطع لا يصح

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**.

أضواء
 cephalosporins

Side effects and drugs interactions

- Comparatively **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.

↓
ممكن شرط لا عنزي سايه
Penicillins
ليكون عنزي حساسيه
Cephalosporins.

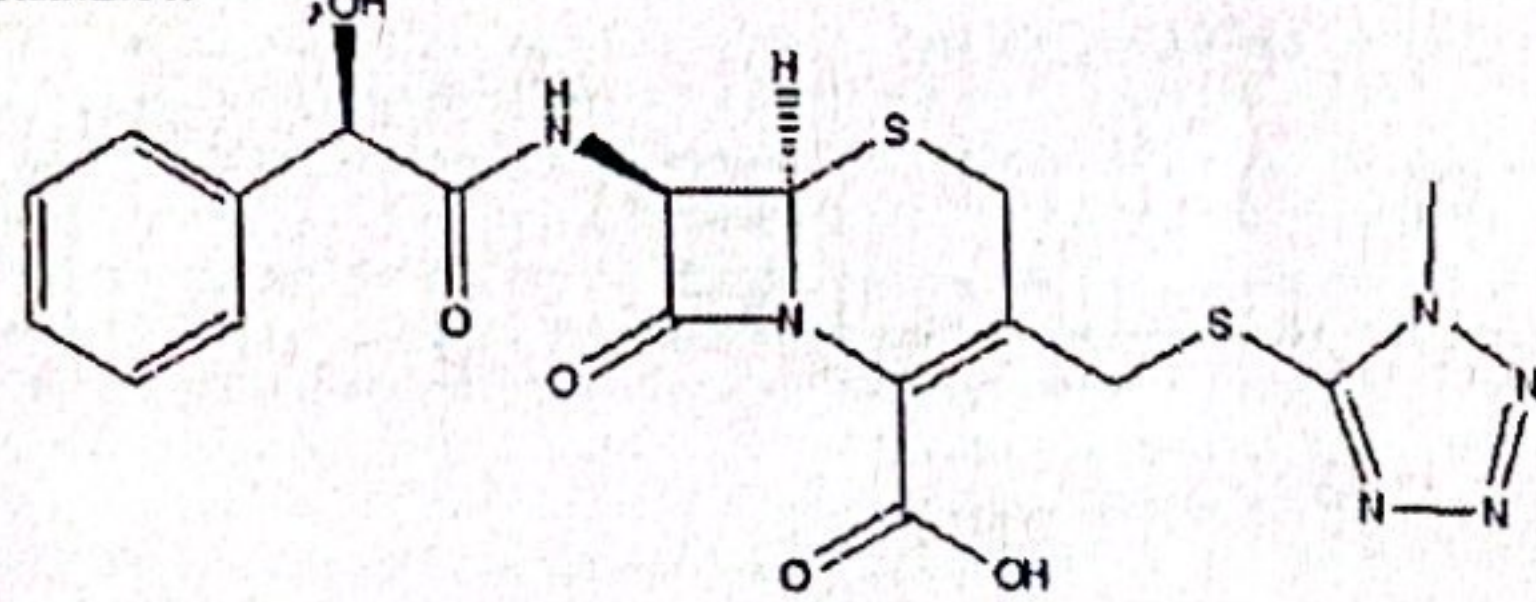
(نقص) واذا انوضع عنزي عنزي في
حساسيه هاد لا عنزي ليصير
لبنسبة (3% - 7%)

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).

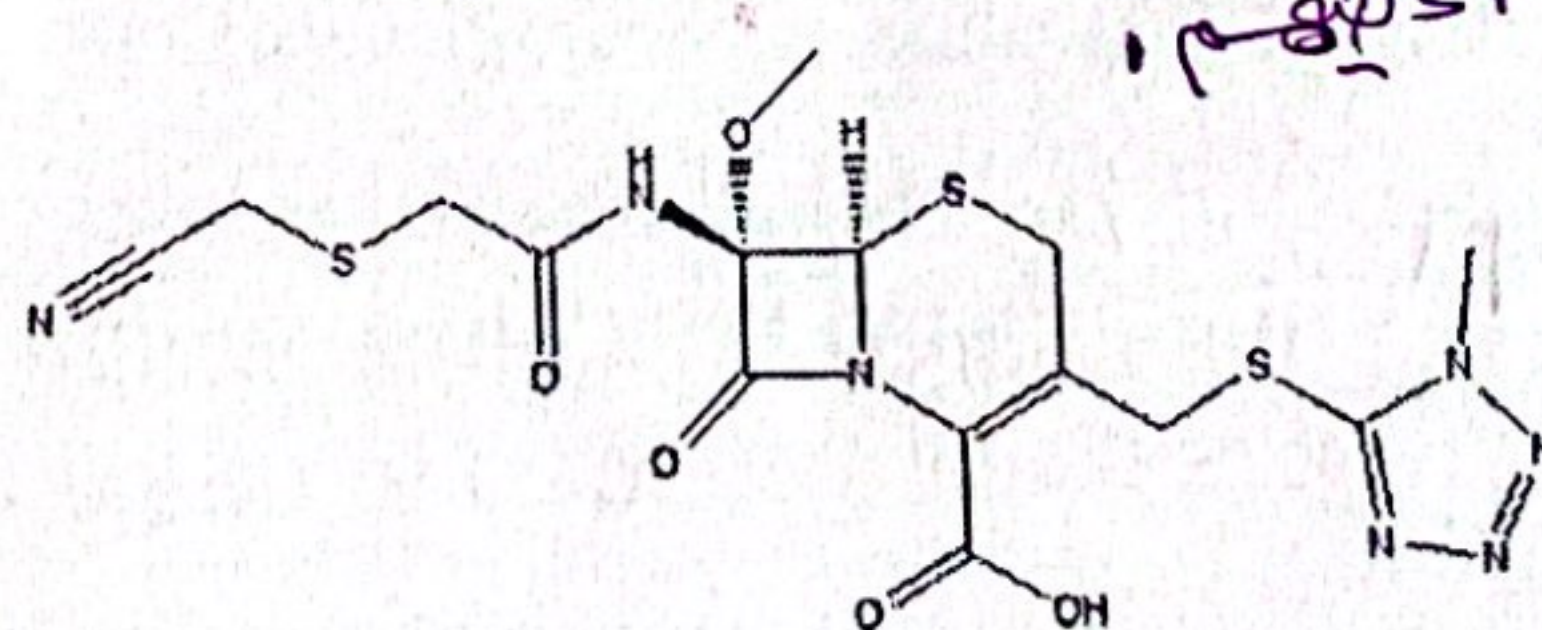
- **MTT cephalosporin** are contraindicated with **heparin** and oral anticoagulants therapy.
- **MTT Cephalosporins** inhibit aldehyde dehydrogenase which oxidizes acetaldehyde to acetic acid leading to alcohol intolerance.

Cefamandol



MTT

cefmetazol



مارعفينه
Heparin

الى باءوا
هدوك لدم يكون
عنزم بب طك
يتحط بصر
عنزي
bleeding.
ببطهم
(Vitamin K)

التيحاف ضلهم لانا

اد [MTT] بتخلي

الحم بعل
reaction

عريبه، انه بطل

لصيح ال

hypoprothrombin.

وهو مريب تحط لدم

وحتى الى باءوا
كحول ما بيل
أعطاهم