بسم الله جبنا تفريغ هاد الشابتر، الله يوفقكم وييسر أموركم ☺

*جرعة الـ Penicillin تدخل كلها ع transpeptidase أو كلها كلها تتكسر بالـ B-lactamase، (بلدنه) فشو اي من الـ Penicillin يرتبطوا بشكل (لا رجعي) مع الـ B-lactams ويحمي غيرها. فقررنا نحمي الـ Penicillin عن طريق (B-lactams inhibitors)

45 محاضرة 10

34 محاضرة 11

β-lactamase inhibitors

(Semi side inhibitor) مهم 1

بمعنى انه يضحي حاله ويرتبط بطريقة لارجعية مع [B_lactams] حتى غيرو يعيش ويستمر ويوصل لل transpeptidase.

Dr. Rand Shaheen

(Methicillin)

*الميثيسلين بنحكي عنه [B-lactamse resistant]، لانه بدخل داخل الـ (binding pocket) تاعة B-lactams نتيجه الـ Methoxy group وجه الكبير بيرتد وبضل رايح لـ (transpeptidase)، اذا الـ Methicillin ما برتبط مع B-lactamse نهائيا، هي حاميه نفسها، بس مش حاميه غيرها.

شو من المنطق أخر جرعة Methicillin (هاد بحمي حاله) مع ampicillin (مركب بتأثر بالـ B-lactamse) ← مش لازم اخلطهم مع بعض

β-lactamase inhibitors

- Early attempts to combine β-lactamase inhibitors with penicillins failed (لأنه أعطيهم مع بعض فشلت نوعا ما.)
- Also, early attempts to combine penicillin β-lactamase resistant penicillins with wide-spectrum penicillinase sensitive penicillins failed to give synergistic activity (برضو فشلت)
- Example Methicillin or Oxacillin with Ampicillin or Carbencillin. (ليه فشلت)
- Reasons are:

1. Failure of lipophilic penicillinase resistant agents to penetrate cell envelopes in Gram-negative bacteria (ما بأثروا ع gram (-) بالتالي مش بيدخلوا عليها بأثروا عليها.)

2. Induction of β-lactamases by some penicillinase resistant penicillins. (هاي مركبات الي زي Methicillin قدمات ضرب B-lactams فاكرة بتخفرها وبالتالي صار أقوى)

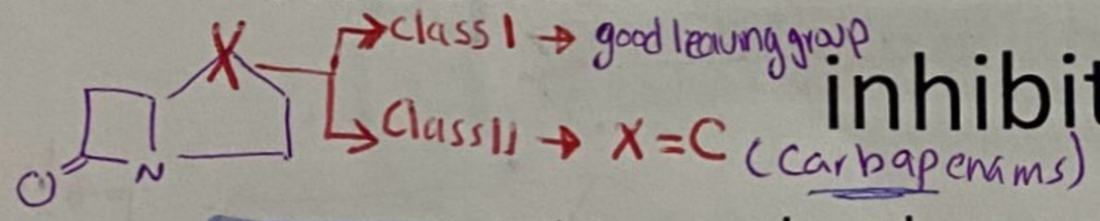
3. The reversible binding of penicillinase-resistant penicillins to β-lactamase. Higher concentration of this substance is needed to inhibit this enzyme.

(هدول لسا عم دعوا حالهم) (لا) ما يرتبطوا irreversible مع B lactamase.

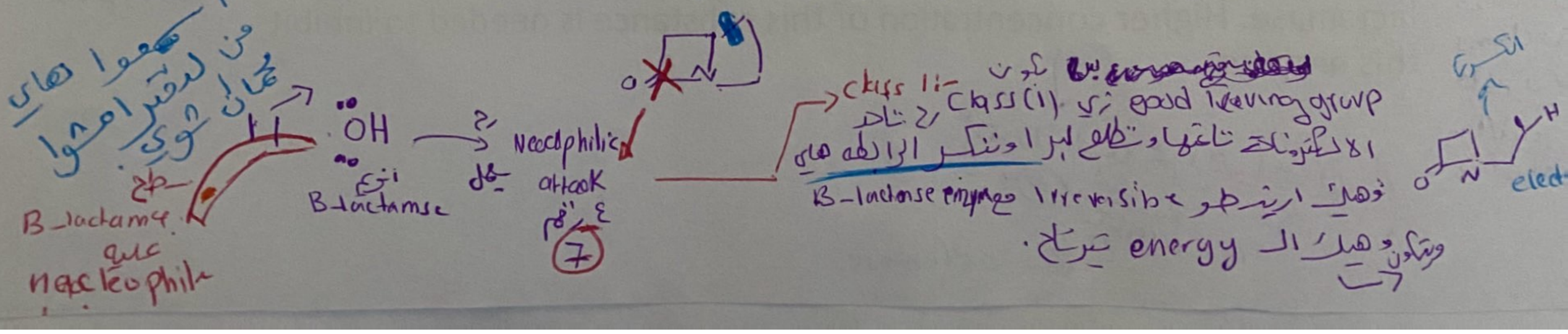
Mechanism – Based β-lactamase Inhibitors

- Examples:
- Clavulanic Acid (Natural): causes potent and progressive inactivation of β-lactamase
- Sulbactam (Synthetic)
- Tazobactam (Synthetic)
- Thienamycins: Natural, inhibit β-lactamases and bind to PBPs

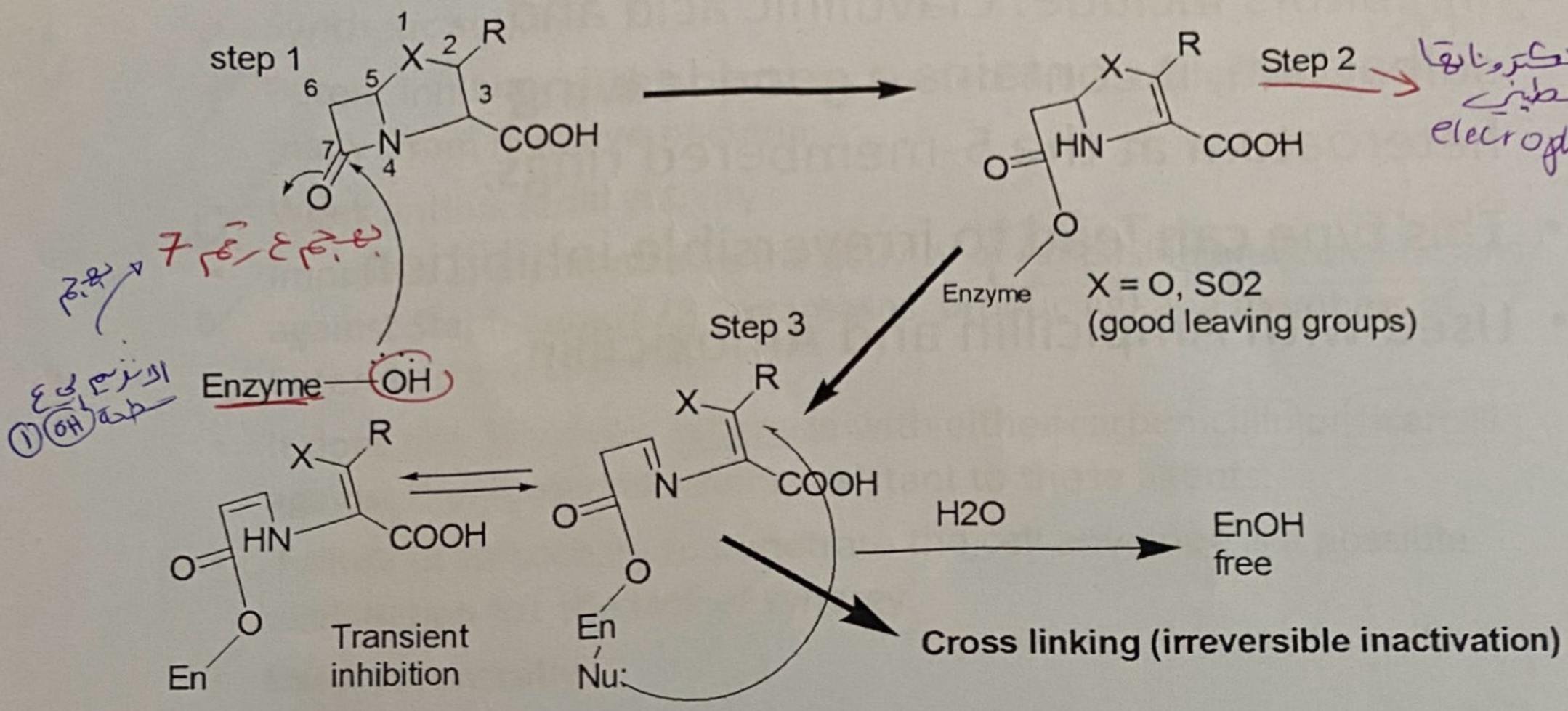
Mechanism – Based β-lactamase inhibitors



- **Class I** inhibitors that have a heteroatom leaving group at position 1 (e.g., clavulanic acid and sulbactam) and **Class II** inhibitors that do not (e.g., the carbapenems).
- Unlike competitive inhibitors, which bind reversibly to the enzyme they inhibit, mechanism-based inhibitors react with the enzyme in much the same way that the substrate does. With the -lactamases, an acyl-enzyme intermediate is formed by reaction of the -lactam with an active-site serine hydroxyl group of the enzyme.



Mechanism of inactivation Class I inhibitors the acyl-enzyme intermediate formed when a mechanism-based inhibitor is attacked by the enzyme is diverted by tautomerism to a more stable imine form that hydrolyzes more slowly to eventually free the enzyme (transient inhibition).



Differences in

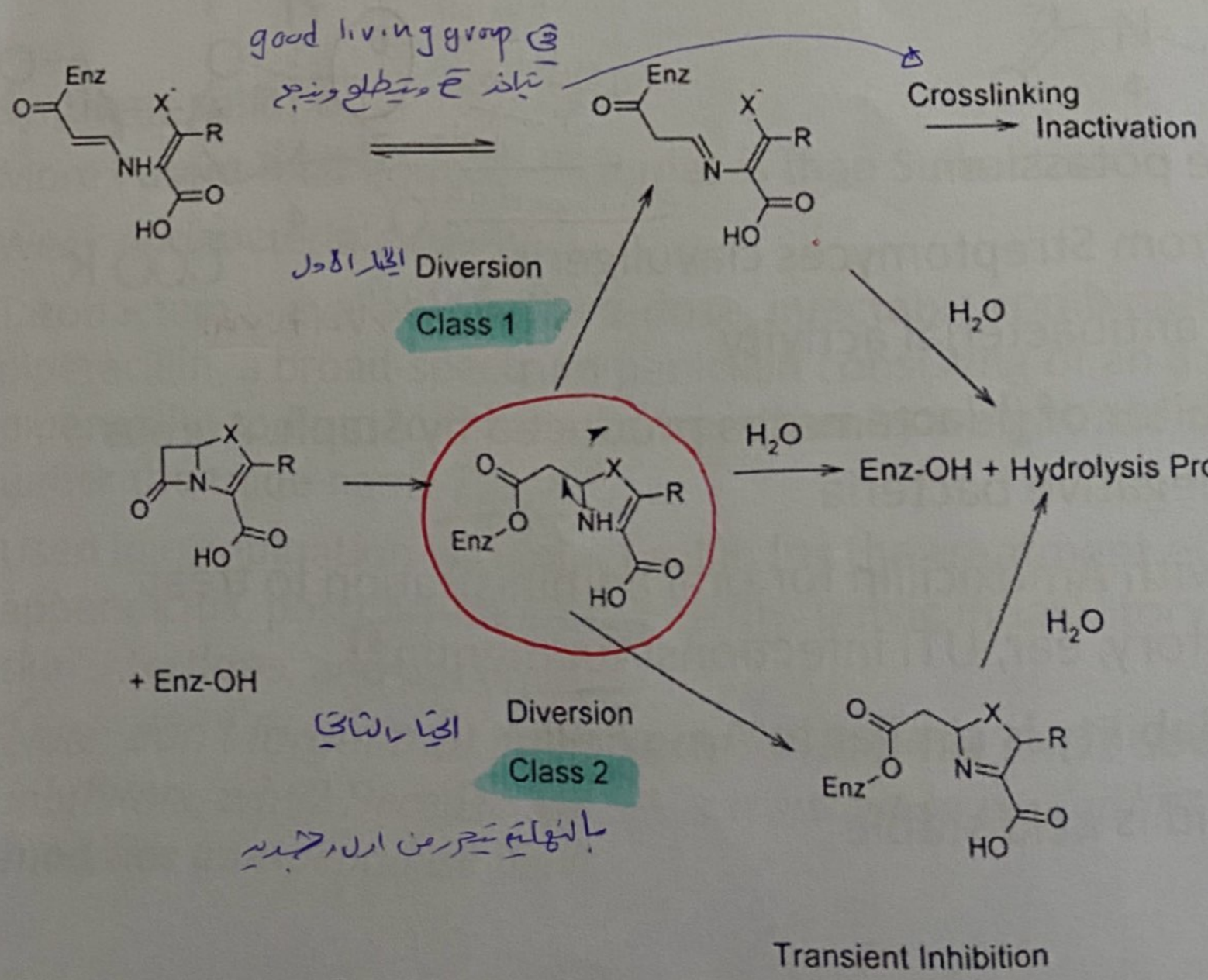
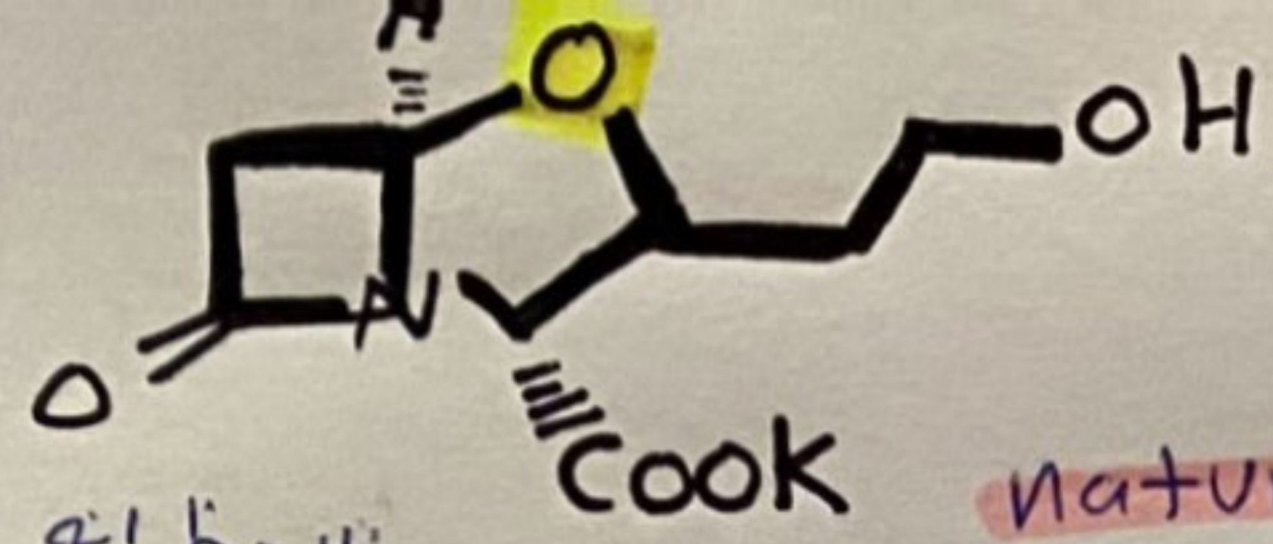


Figure 8.4 • Mechanism-based inhibition of β-lactamases.

Class *I* β-lactamase inhibitors

- Inhibitors include: Clavulinic acid and sulbactam, it contains a good leaving heteroatom at the 5-membered rings.
- This type can lead to irreversible inhibition.
- Used with Ampicillin and Amoxicillin.

من هون لنهاية الشابتر التلخيص
هاد شامل لكل السلايدات + حكي
الدكتورة رند



natural

نلاحظ انه كثير Very simple يشبه الـ Pencillin البنسلين

Clavulanate Potassium.

- acid stable

antibiotic → Strepromyces clavulgeris

antibacteril activity → very week

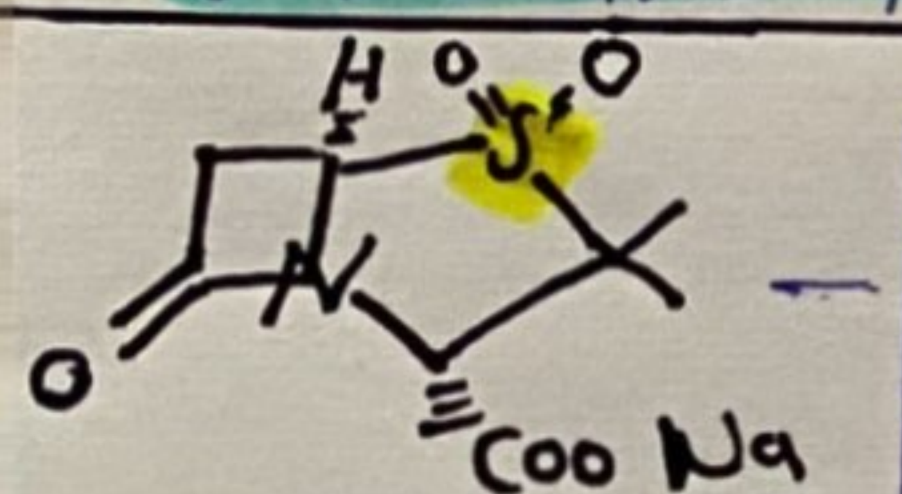
Potent inhibitor of B-lactamase

Produced by → Staph. Aureus. (and) G(-) bacteria

بعطى مع Amoxicillin oral للعلاج → - Skin - respiratory - ear - UTI infection

Augmentin الخيار الاول لعلاجه

- oral bioquibality is simelar → Amoxicillin



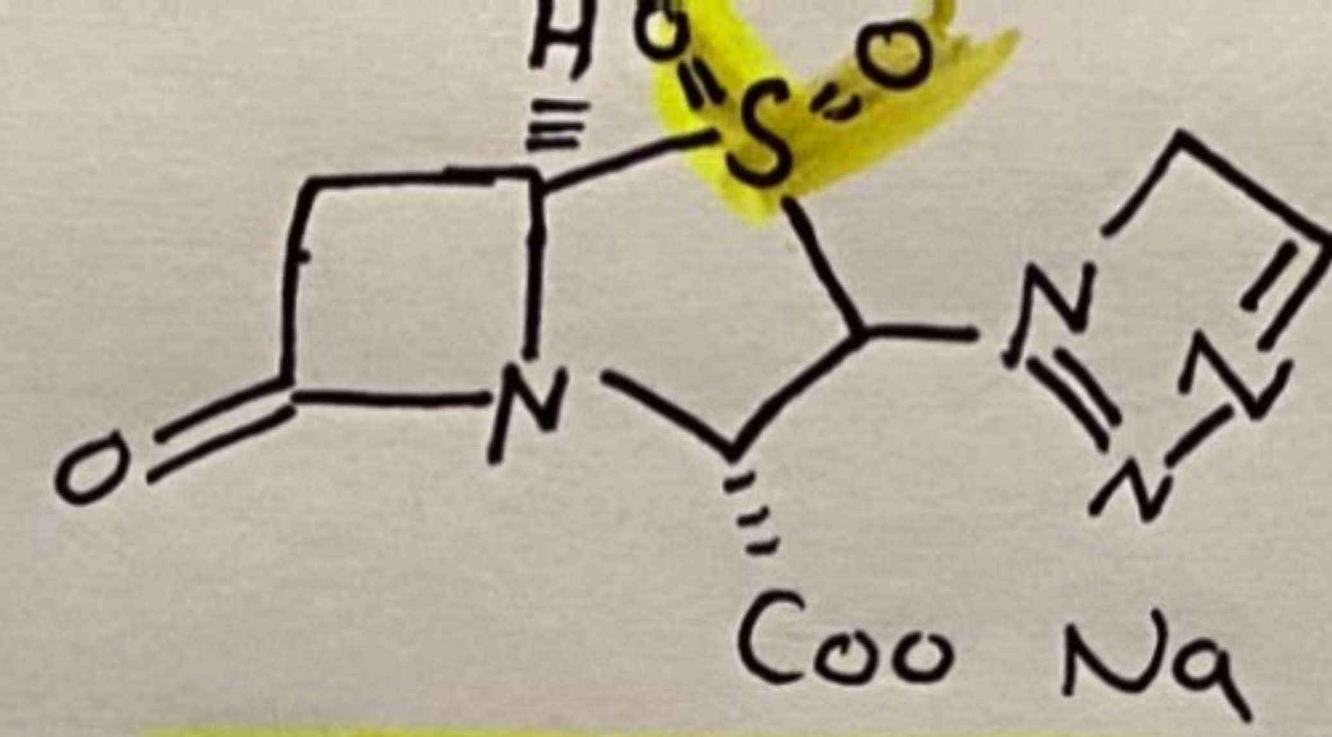
Sulbactam [Parentally]

→ Synthetic Sulfone
→ ضعيف → Staph Aorevs G-
→ Week antibacteril activity
→ يعطى مع ... → Ampicillin + Carbencilline

Enterbacteria + staph Aoures

* Does not [synergize] → Carbenicillin (or) ticarcillin.

failre ?? Sulbactan ما يقدر Pentrate الـ cell



Tazobactam. (Zosyn)

(synthetic)

→ Sulbactam أقوى من

→ activity → week antibacteril.

Tazobactam + Piperacillin

- injectable.
- fixed dose

8:1 ratio. of piperacillin sodium to tazobactan sodium by weight

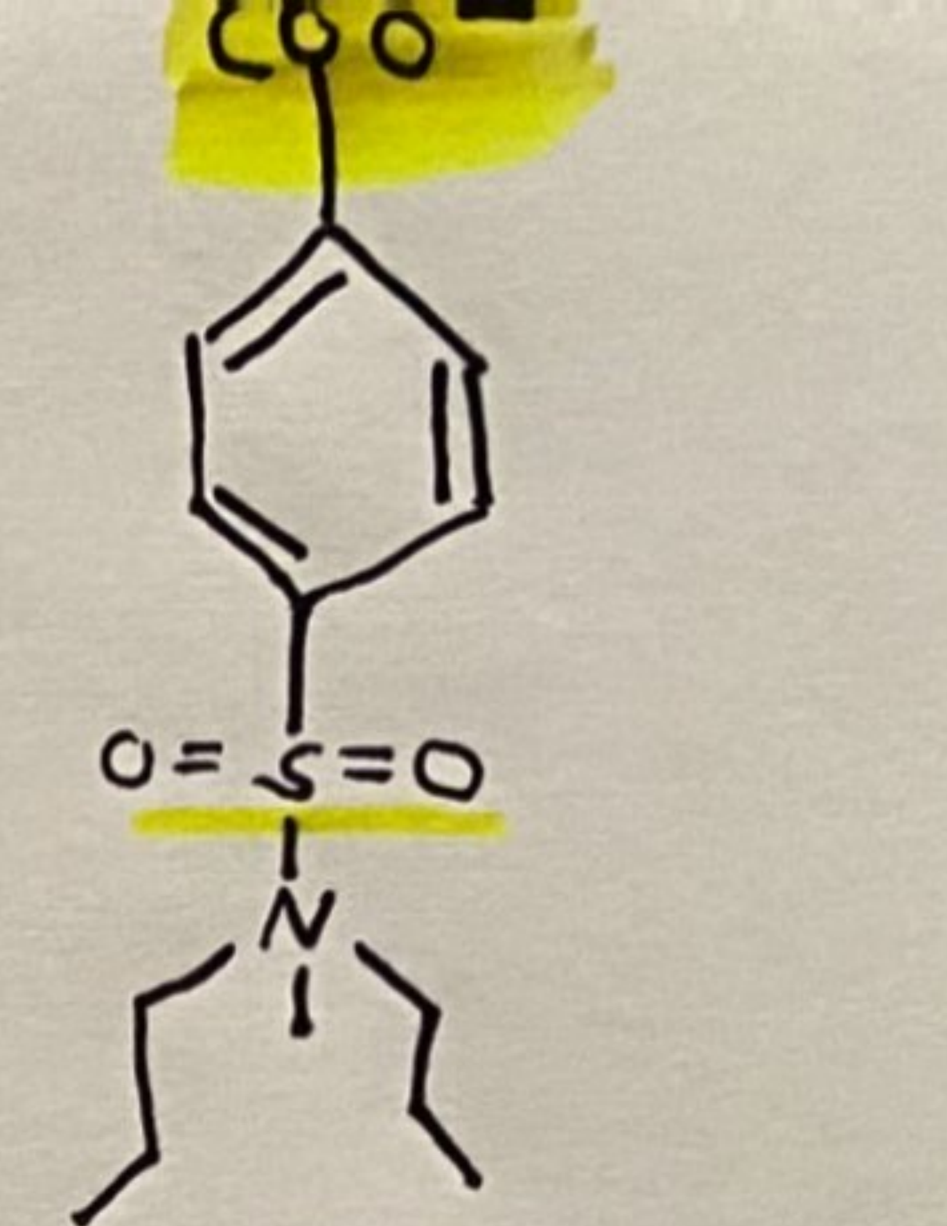
العلاج 1 → Appendicitis التهاب الزائدة الدودية

2 → Postapartum endometeritis التهاب بطانة الرحم بعد الولادة

3 → Skin infections

3 → Pneomonia.

ما نستعمله مع/اذا في MRSA ⇒ Becouse is resistant to Penicillins becouse it modification transpeptidase it self.



Probenceid.

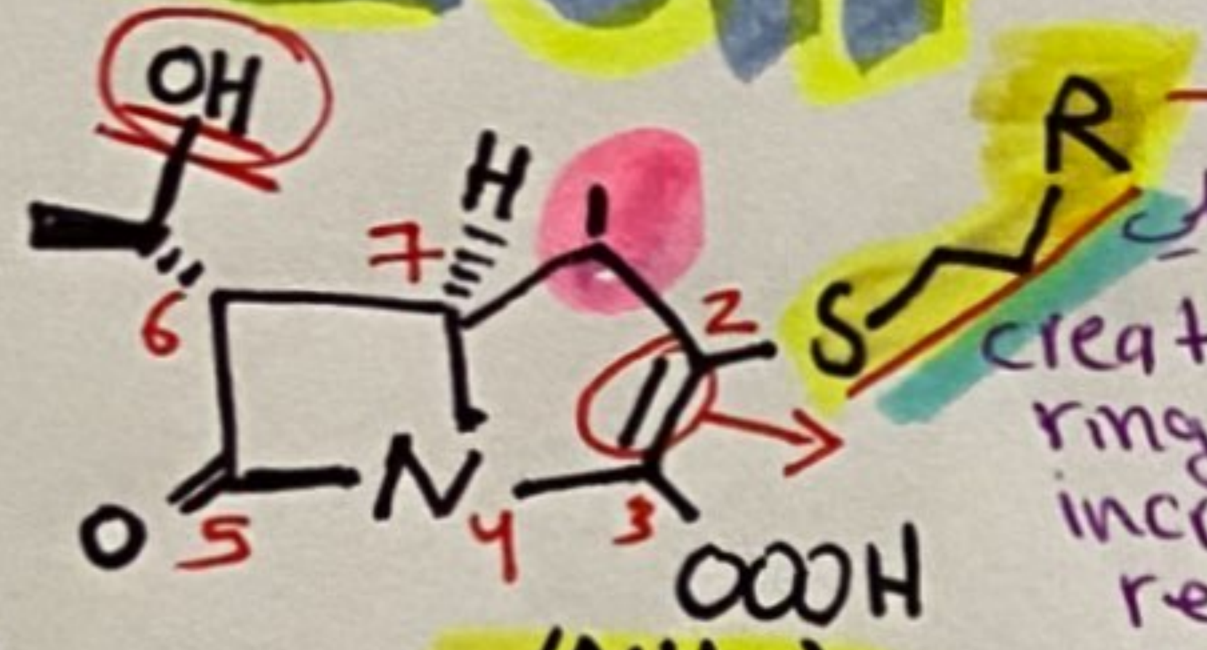
يحتوي Carboxylic acid

بالبلازما plasma [carboxylate]

يرتبط (highly bound to plasm protein) الـ albumin's شحنة [positive]

* also penicillins are candidate for renal secrtion by anionic pump (which pumps carboxylic acid in the urine) thats why sometimes they add probencid (adjuvant contains carboxylic acid) to compete with penicilline of the pump so probencid reduce elimintion rate of penicillin remain longer in the body

Carbapenems



R → cystamine side

يعمل إجهاد للحلقة/ وبزيد في تفاعلاتها

creates considerable ring strain and increases the reacativity of the lactam to ring opning reation

(NH2)

" Thienamycin "

Solated → "Streptomycess Cattleya"

على

(1) → NO (S)

* orally → inactive.
* Broad spectrum.
* optimum stability 6-7PH
* [Two Rings] (strained)

↓

↓ chemical stability

↓ acid stability

[instability]

وهاد الاشي خلى اكثر عرضة

Hydrolysis in both acidic + alkline solutions.

* Sterochemistry → 5R:6S:8S.

Very potent B-lactamse inhibitors

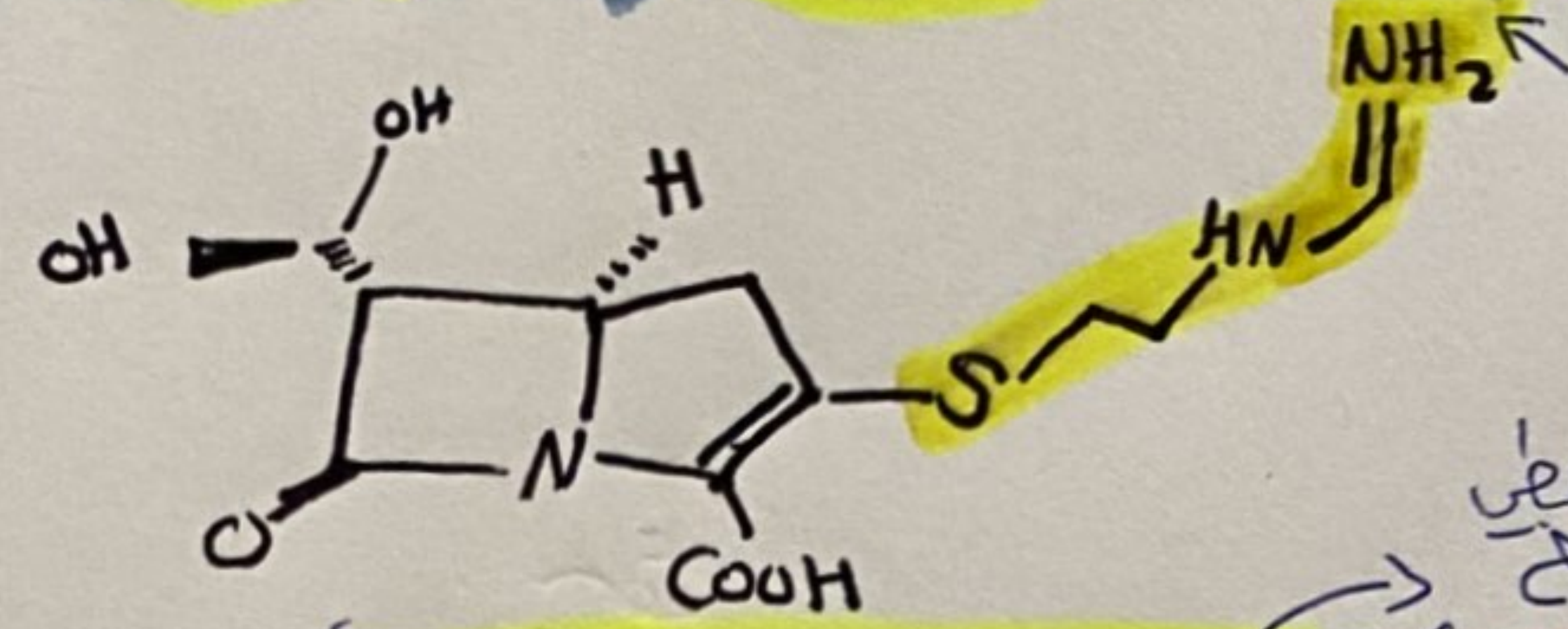
[Outstanding spectrum]

covers

(G+) ← arobic + aneobic bacteria → (G−)

المضادات الي تعمل ع هاي محدود كثيرا

high resistane.



NH2 ← not a neulcphi...

أو Imipenem (NHCH=NH) → يعطى مع (Cilastatin) وهاد اخلاس مع Imipenem.

- class II

- more stable than thienamycin

- T1/2 = 1hr (short) ع renal section of penc...

Imipenem [wide spectrum]

على → G(+) ✗

- P. aeruginosa
- S. marcescens
- Enterobacter spp

على

* Pseudomonas spp

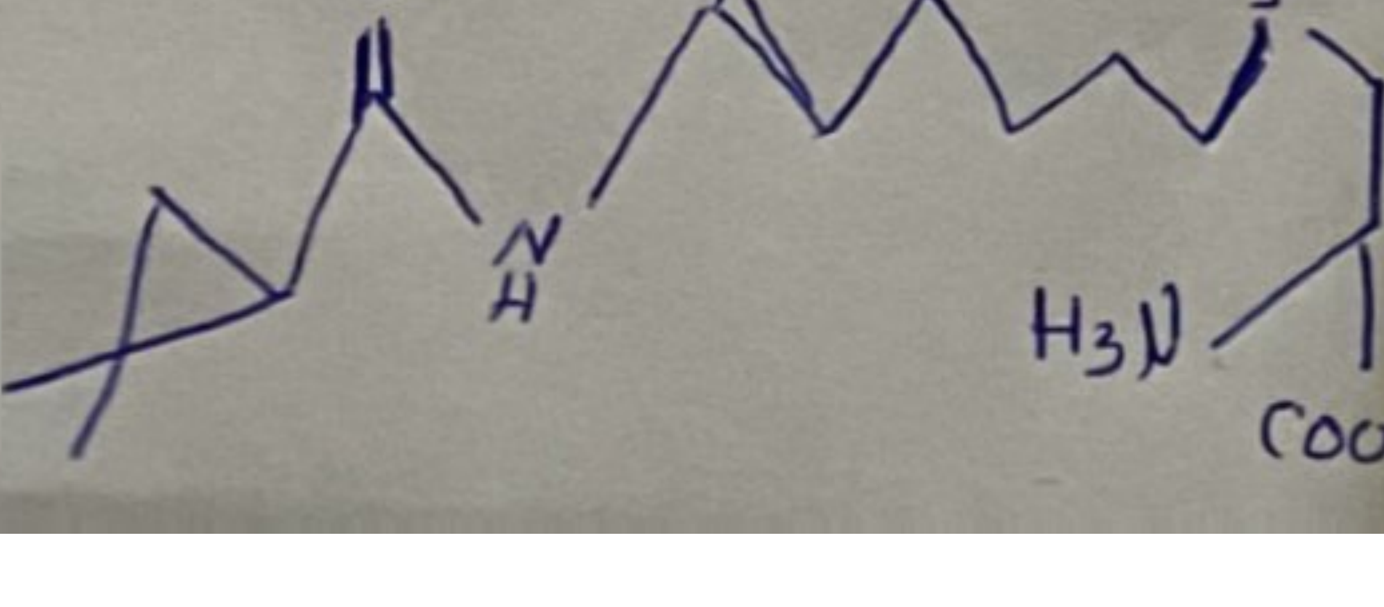
- P. maltophilia
- P. cepacia
- Methicillin resistant staphylococci

على

non lactamase producing strains of these and additional bacterial species.

- but other less expensive & equally effective antibiotic are prefored for the treatment of infection caused by these organisms.

(Cilastatin)



Imipenem → يستعمل لعلاج.

① bacterial infections.

[skin/tissues/ lower respiratory tract bones/ Joints/ genitourinary]

عظمه بكلب بيرو جيري

② Septicemia [هي تتصير هاي لعدوى عشان مش بالجسم تروح للدم]

③ Endocarditis

طبقة لغشاء لداخلي للقلب تصير عليها التهاب ناتج من عدوى بكتيرية

Imipenen – cilastatin

هاي إبرة عشان هلأ مثلاً تتذكروا هون في إبرة

- Sterile powder [injection]

Solution stable → 4hr 25°C

Synergestic action مع → Aminoglycoside AGCs

Chemically → incompatible

* Cilstatin.

is inhibitor of (~~dehydrogenase~~ (dehydropeptidase −1)

IMIPENEM

- → A reserved antibiotic
- → out standing in spectrum
- → adminstration ε- Parentally ✓
- Stable under neutral conditions
- → Very short half life (1 hour)

السبب !! :
- Carbuxylic acid تكثير → secrtion & because it's unstable
- → Imipenem + Cilastatin. (تحوي COOH)
  - ⇒ ↑ duration of imipnem remaning in the body
  - ⇒ Protects the Kidneys from toxic metabolites of impenem.
- → لازم يضل → hospitals بسبب → risistance tisses.

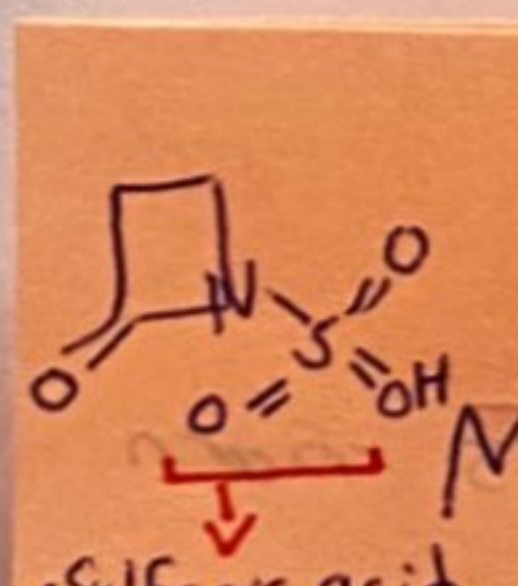
/ لانه Reserved → لازم يضل

شو يعني (Reserved antibiotic) ?!

يعني تحتفظ فيها بالمستشفيات وهم قوات الإحتياط ، لانه احنا ما بدنا يصير عليهم resistanse ، لانه كان صار ، الماجيني واحد معه endcarditis ليش احيانا بي تكون أدوات الأسنان ملوثة ، غير الصلاحيات اعطيهم (Imipenem)

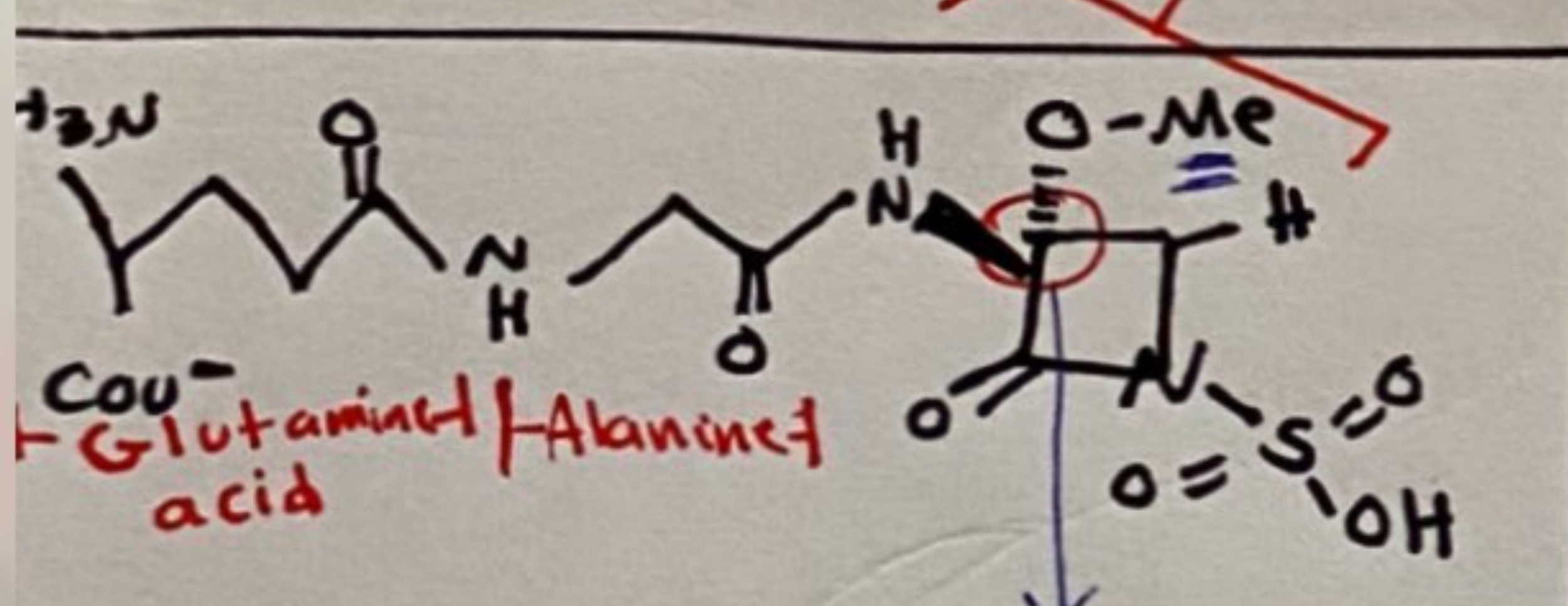
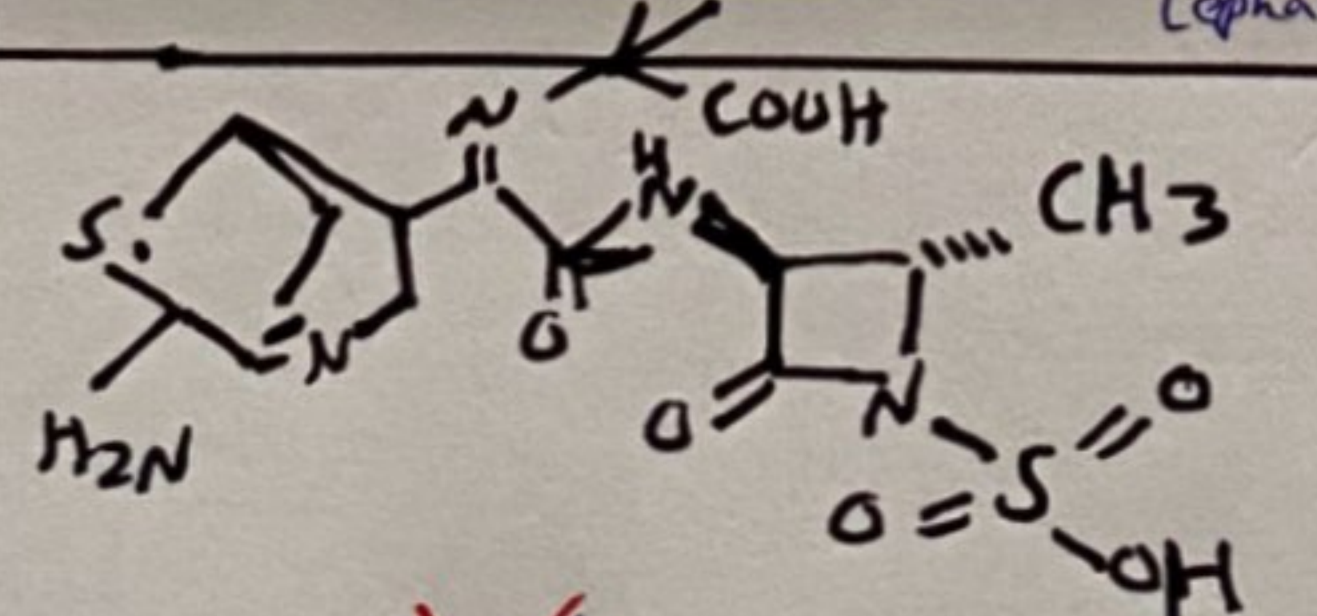
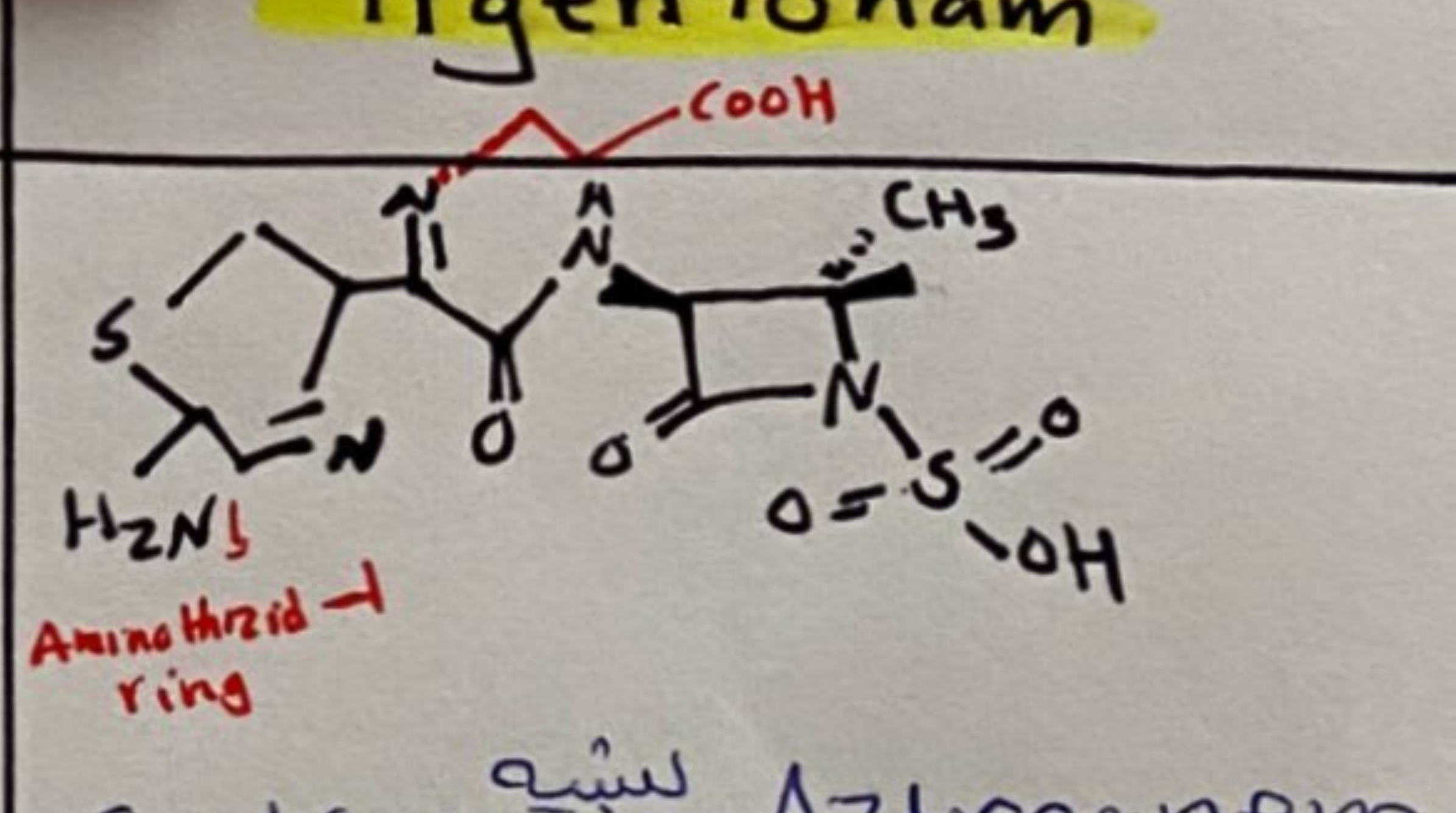
Newer Carbapenems

- → ليش [extended spectrum + resistance to inactivation by most lactamases] ما ازالوه هدفها → target for drug development.
- → (1) Stability to hydrolysis catalyzed by DHP4
  - تشمل التحسينات التي بدي اياها ٢ يله بالأخص الواخصنا ثقي
  - لانو بدي اطلع مقاومتها لل DHPH و اقوى
- بدي يصير كتير activity ضد MRSA
  (2) Stability to bacterial metallo-lactamases (carpenamases) that hydrolyzine impenem activity agenist MRSA
- (3) increased potency agenst P.aerginosa especially imipneem resistant strain
- (4) Enhanced pharmcokinetic properties, such as oral bioavibility and longer duration of action have heretofore recived little emphasis in Cebapnem analog design.



Monobactam → هدول ال 3

(لبسبب Protaintion - good leaving grp) stability → لل المهمة Methoxy

Sulfazecin	Aztreonam (هو زي خليط بين monobactam و Cephalosporine)	Tigemonam
		
- Natural - orally - chemical unstable [dipeptide: alanine + Glutamine acid + Methoxy]	- not orally (لانه لا تتم امتصاصه) - Chemical stable. لعلاج local (GI) tract infection → B-lactamase resistance Not G(+) و على G(-) له تأثير → E. coli. ليس لها تأثير → Pseudomonas aerginosa → Strpto coccus → Staphylo coccus	Spectrum تشبه → Aztreonem على (G-) ما عدا → Pseudomonas - B-lactamase ristantant - orally (✓) (hydrophilicty بسبب which is balanced here)

Monobactam :- by their name Contain B-lactam. ring only without any other cycle, and as we said previously that B-lactam ring, it (too stable) here because the pair of electrons on nitrogen are in resonane with the carbonyl, so to decrease the stability Monobactam have a sulfonic acid at the nitrogen!!

شو يعني هاد الحكي !!

الـ B-lactan بس بتكون لحالها عادي بتكون

تمام Stable

بس برتبط معها الـ Sulfonic acid زي هون

بتصير unstable