β-lactamase inhibitors

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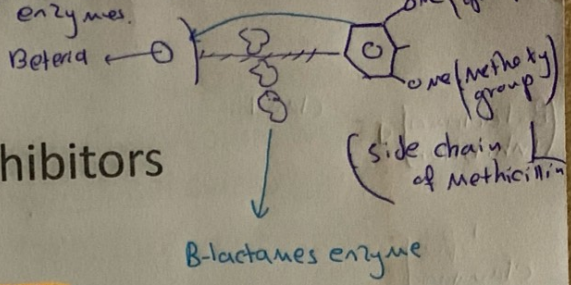


[β-lactamase inhibitors]

- Early attempts to combine β-lactamase inhibitors with penicillins failed
- Also early attempts to combine penicillin β-lactamase resistant penicillins with wide-spectrum penicillinase sensitive penicillins failed to give synergistic activity
- Example Methicillin or Oxacillin with Ampicillin or Carbencillin.
- Reasons are:

1. Failure of lipophilic penicillinase resistant agents to penetrate cell envelopes in Gram negative bacteria
2. Induction of β-lactamases by some penicillinase resistant penicillins.
3. The reversible binding of penicillinase-resistant penicillins to β-lactamase.. Higher concentration of this substance is needed to inhibit this enzyme.

class 1 + class 2 → اختلفوا في التركيز وفي mechanism of action

Mechanism - Based β-lactamase inhibitors

- Examples:
  - (β-lactamase inhibitor) class I Clavulanic Acid (Natural): causes potent and progressive inactivation of β-lactamase
  - Sulbactam (Synthetic) (يشبه clavulanic acid)
  - Tazobactam (Synthetic)
  - class II 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.

class 1 + class 2 → يرتبطوا مع الانزيم ويكونوا acyl-enzyme intermediate

← ممكن يصير cross linkage ممكن يصير الانزيم بس acyl enzyme مش نشط وباشكال بصير بدي

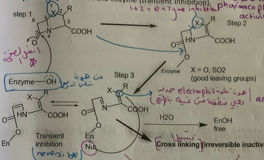
Mechanism-based-β-lactamase-inhibition

hetero atom (oxygen)

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).

acyl side chain

(clavulanic acid)



ال Side chain هنا هو ethylen brig على الكحول

لازم يكون في acyl side chaine at carbone Number 6

∴ clavulanic acid is not active antibiotic

it's mechanism b-lactamases class 1 inhibition

∴ it's not active as a drug

Carboxyl ... sid chain

cross linking

(reversible acyl side chain ... enzyme)

Differences in

* The hetero atom in class 2 it's not a good leaving group

it's a carbon that's mean X = C

cross linking

Transient inhibition

B-lactamase

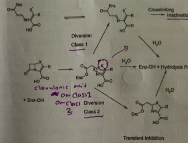


Figure 8.4 • Mechanism-based inhibition of β-lactamases.

side chain

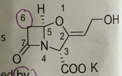
Nu attack ... side chain ... acyl chain (7)

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.

Clavulanic acid ← بعمل Covelent bond مع Beta lactamases وبروح بثبطه
فالتالي لما نعطي مع Amoxacillin بروح ال Amoxa بوصل إلى B penicillin biding protien (PBP)

Products
Clavulanate potassium



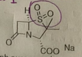
- Clavulanate potassium
- Antibiotic from Streptomyces clavuligeris
- Very week antibacterial activity
- Potent inhibitor of β-lactamases produced by
- Staph. Aureus and Gram negative bacteria
- Combined with Amoxicillin for oral administration to treat skin, respiratory, ear, UTI infections Augmentin®
- Oral bioavailability is similar to Amoxicillin
- Clavulinic acid is acid stable

(not given orally and it's a synthetic product)

Products

class 1 — sulfoxid

Sulbactam



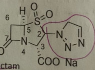
Sulfoxid

- Synthetic sulfone
- Potent inhibitor of β-lactamases produced by Staph aureus and many Gram negative bacteria
- Week antibacterial activity (because not have a pharmacophore of penicillin)
- Improves and potentiates the activity of Ampicillin and Carbencillins against Staph aureus (β-lactamases producing) and members of Enterobacteracia family, (G-ve)
- It does not, however, synergize with either carbenicillin or ticarcillin against *P. aeruginosa* strains resistant to these agents. Failure of sulbactam to penetrate the cell envelope is a possible explanation for the lack of synergy.
- Failure to penetrate cell envelop may be the reason
- **Used parentrally**

Products

Tazobactam

Sulbactam من أقوى



Triazolen

- Synthetic sulfone
- More Potent inhibitor of β-lactamases than Sulbactam
- Week antibacterial activity
- Tazobactam is available in fixed-dose, injectable combinations with piperacillin, a broad-spectrum penicillin consisting of an 8:1 ratio of piperacillin sodium to tazobactam sodium by weight and marketed under the trade name *Zosyn* ® (Tazobactam + piperacillin)
- Used in combination with piperacillin for the treatment of appendicitis, postpartum endometritis, pelvic inflammatory disease, skin infections, and pneumonia.
- *Note: don't forget that if we have MSRA, we can't use these inhibitors, why? Because MRSA is resistant to penicillins because it modifies transpeptidase itself.*

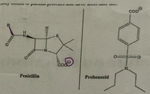
MRSA — B-lactamase inhibitors Traspeptidase enzyme

Biding

MRSA ← B-lactamase

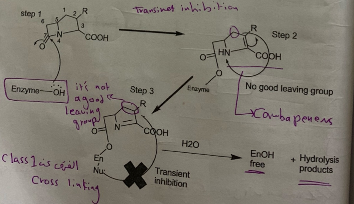
بنافس البنسلين على excretion **probenecid**

- Note: penicillins has carboxylic acid, so it becomes carboxylate in plasma, so tightly bound to plasma proteins (because albumin's charge is positive) (−)
- also penicillins are candidate for renal secretion by **anionic pump** (which pumps carboxylic acids in the
- urine), that's why sometimes they add **probenecid** (adjuvant contains carboxylic acid) to compete with penicillin on the pump, so probenecid reduces elimination rate of penicillin and penicillin remains longer in the body.



anionic pump ← اذا عملت inhibition او بعطي
مركب بنافس البنسلين عليه وبالتالي البنسلين رح يظله
فترة اطول بالجسم لانه ما صير له secretion بسهولة ومن
~~probecid~~ الادوية هاي بكونوا عليها (−) هي
probenecid

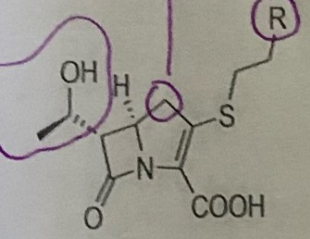
Class II inhibitors



Class II inhibitors

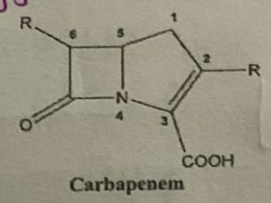
- This class include Carbapenams, Imipenem
- Both have β-lactamase inhibition activity and antibacterial activity.

good leaving group (not sulfur, oxygen ....)



① $R = NH_2$ Thienamycin

② $R = NHCH=NH$ imipenem



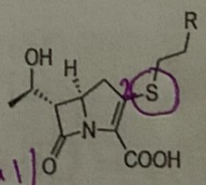
Carbapenem

spectrum of activity واسع

antibaterial activity

Carbapenems

Thienamycin



(natural)

$R = NH_2$ Thienamycin

$R = NHCH=NH$ imipenem

(not stable under any pH)

- Thienamycin solated from "Streptomyces cattleya"
- No (S atom) at position 1
- Double bond at C2-C3 (The double bond in the bicyclic structure creates considerable ring strain and increases the reactivity of the -lactam to ring opening reactions.
- Cystamine side chain at C2
- Simple alcohol side chain at position 6
- Stereochemistry is 5R:6S:8S
- They have two strained rings which decrease the chemical stability as well as acid stability. An unfortunate property of thienamycin is its chemical instability in solution. It is more susceptible to hydrolysis in both acidic and alkaline solutions
- Optimum stability pH 6-7
- Have broad spectrum activity.

pH = acidic or alkaline

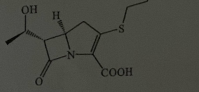
Thienamycin properties:

- - Very potent β -lactamase inhibitor
- Outstanding spectrum of activity that covers gram +ve, gram –ve bacteria (including pseudomonas aeruginosa), aerobic and anaerobic bacteria.
- *Note: antibiotics that work on anaerobic bacteria is limited due to its high resistance.*
- - Orally inactive.

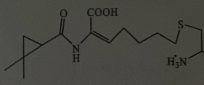
Carbapenems

Imipenem – Cilastatin

Not a nucleophile



Imipenem



Cilastatin

Imipenem is indicated for the treatment of a wide variety of bacterial infections of the skin and tissues, lower respiratory tract, bones and joints, and genitourinary tract, as well as of septicemia and endocarditis caused by lactamase–producing strains of susceptible bacteria

Carbapenems
Imipenem – Cilastatin

- Chemically more stable than Thienamycin
- Cilastatin is inhibitor of (dehydropeptidase- 1)
- Cilastatin give enzymatic stability for Imipenem
- $T_{1/2}$ = 1 hour (short) due to renel secretion of penicillin
- Imipenem is extraordinary wide-spectrum antibacterial agent It is an inhibitor of -lactamases from certain Gram-negative bacteria resistant to other -lactam antibiotics (e.g., *P. aeruginosa*, *S.marcescens*, and *Enterobacter* spp.).
- Some *Pseudomonas* spp. are resistant such as *P. maltophilia* and *P. cepacia*, as are some methicillin-resistant staphylococci. Imipenem is effective against non-- lactamase-producing strains of these and additional bacterial species, but other less expensive and equally effective antibiotics are preferred for the treatment of infections caused by these organisms.

not chemical stability
- enzymatic stability

Carbapenems
Imipenem – Cilastatin

- β-lactamases resistant and class II inhibitor
- Imipenem – Cilastatin are available as sterile powder for injection, in solution its stable for 4 hours at 25 C

Stable بدون Cilastatin بتكون for 1 hours

- Synergestic action with Aminoglycosides , but chemically incompatible (+)

Chemically incompatible

Imipenem is:

A **reserved** antibiotic, outstanding in spectrum, parenterally administered and stable under neutral conditions.

Imipenem has very short half-life (1 hour) , because it has carboxylic acid which makes it candidate for active secretion and because it's unstable .

- So imipenem is coadministered with **cilastatin** (that contains COOH in its structure) , so increases the duration of imipenem remaining in the body and protects the kidneys from toxic metabolites of imipenem.
- *Note: **reserved antibiotic** means that these antibiotics which are broad spectrum can*
- *be only available at hospitals due to resistance issues.*

Carbapenems → extended spectrum of activity and they denoted to anaerobic bateria and B.lactames resistance

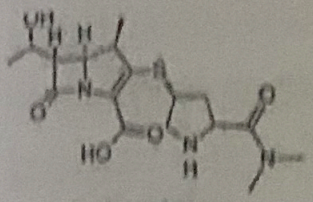
NEWER CARBAPENEMS

- The extended spectrum of antibacterial activity associated with the carbapenems together with their resistance to inactivation by most -lactamases make this class of –lactams an attractive target for drug development.
- In the design of new carbapenems, structural variations are being investigated
- with the objective of developing analogs with advantages
- over imipenem.

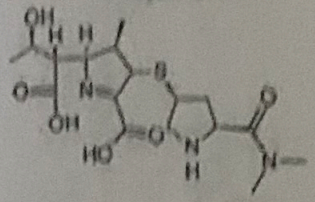
1. Improvements that are particularly desired include stability to hydrolysis catalyzed by DHP-I,
2. stability to bacterial metallo--lactamases ("carbapenemases") that hydrolyze imipenem, activity against MRSA.
3. increased potency against *P. aeruginosa*, especially imipenem-resistant strains.
4. Enhanced pharmacokinetic properties, such as oral bioavailability and a longer duration of action, have heretofore received little emphasis in carbapenem analog design.

NEWER CARBAPENEMS

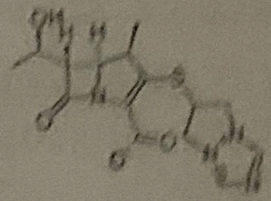
- Refer to your book to read more about these compunds



Meropenem



Meropenem metabolite



Biapenem

هدول مطلوبين بناءاً على الصفات اللي بدي اياهم