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.

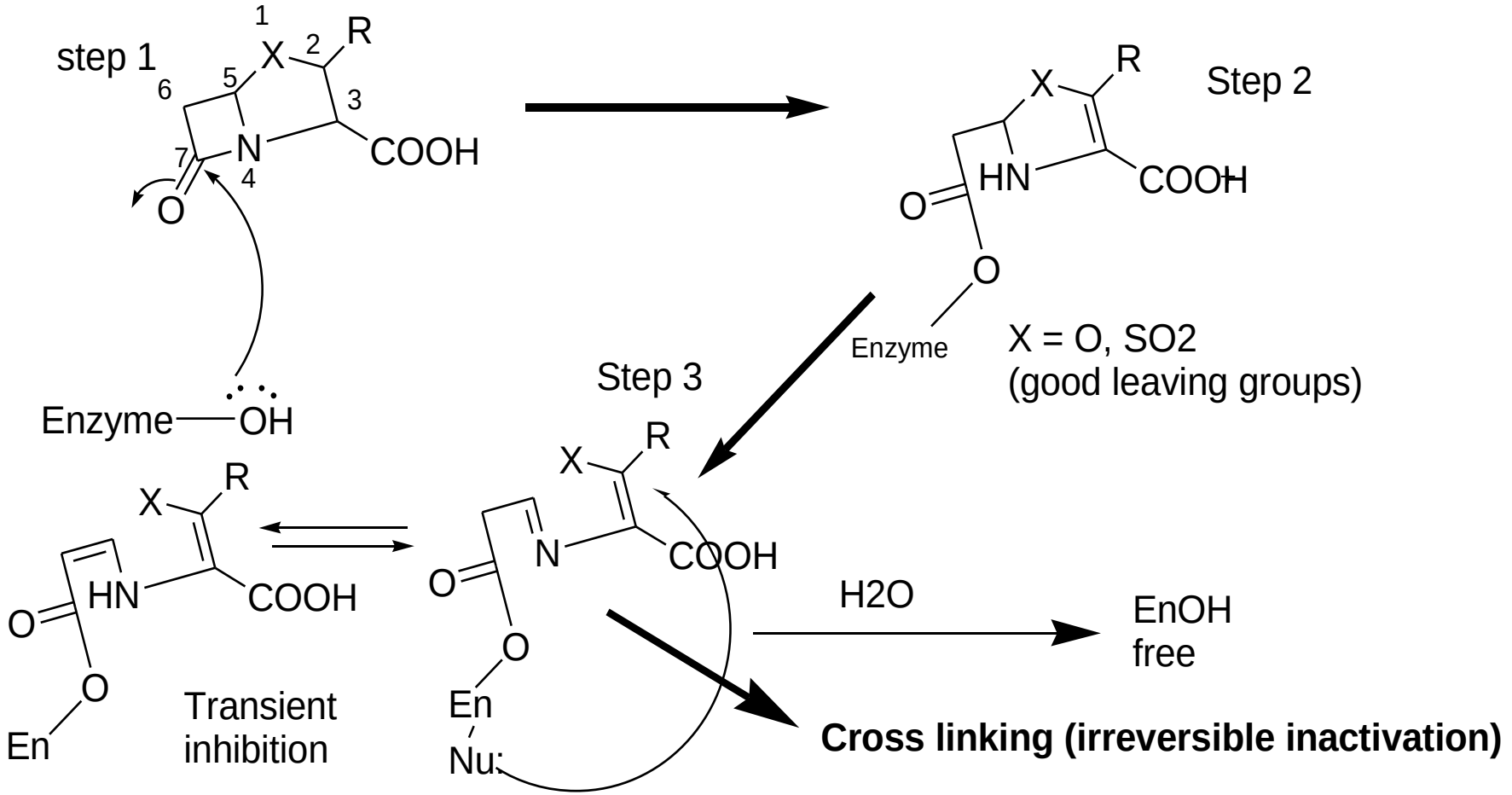
Mechanism – Based β-lactamase inhibitors

- 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

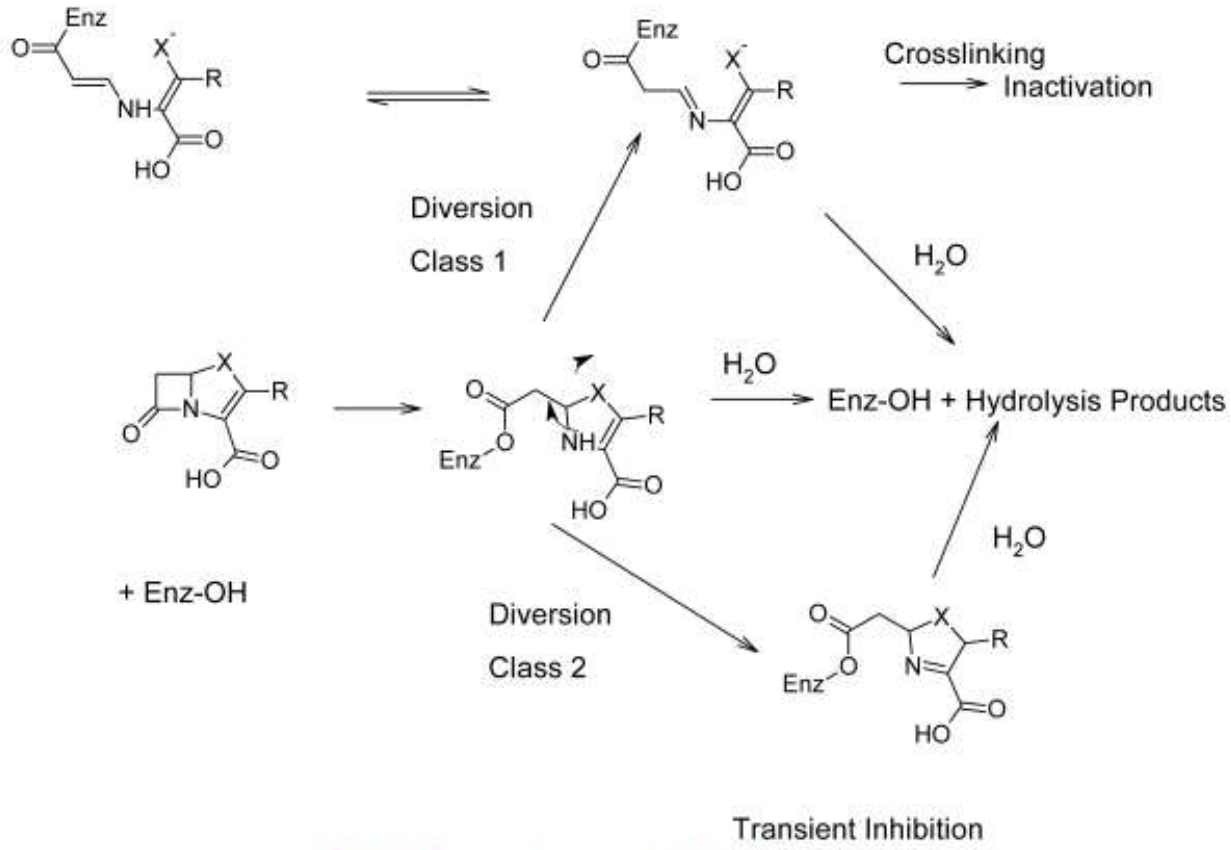
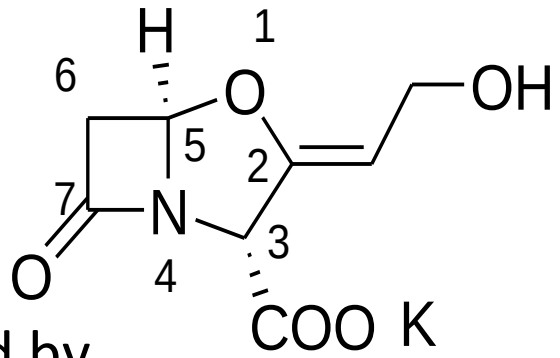


Figure 8.4 • Mechanism-based inhibition of β-lactamases.

Class I β-lactamase inhibitors

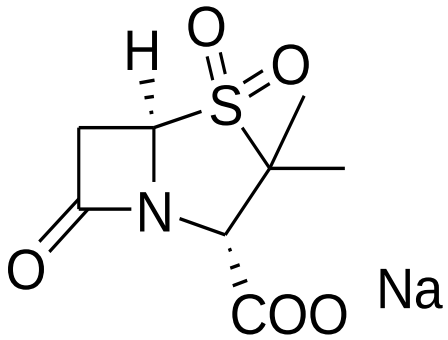
- Inhibitors include: Clavulinic acid and sulbactam, it contains a good leaving heteroatom at the 5-membered rings.
- This type can lead to irreversible inhibition.
- Used with Ampicillin and Amoxicillin.

Products
Clavulanate potassium



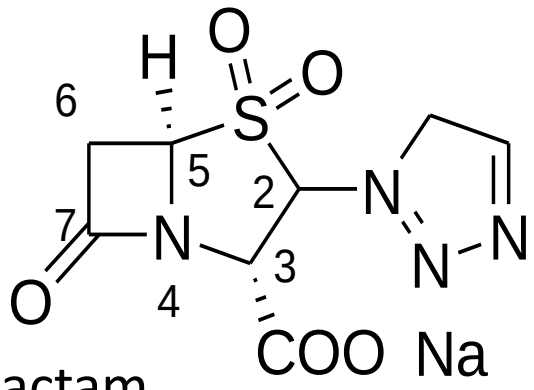
- Clavulanate potassium
- Antibiotic from Streptomyces clavuligeris
- Very week antibacterial activity
- Potent inhibitor of β-lactamases produced by
- Staph. Aureus and Gram negative bacteria
- Combined with Amoxicillin for oral administration to treat skin, respiratory, ear, UTI infections Augmentin®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

Products
Sulbactam



- Synthetic sulfone
- Potent inhibitor of β-lactamases produced by Staph aureus and many Gram negative bacteria
- Week antibacterial activity
- Improves and potentiates the activity of Ampicillin and Carbencillins against Staph aureus (β-lactamases producing) and members of Enterobacteracia family,
- 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**

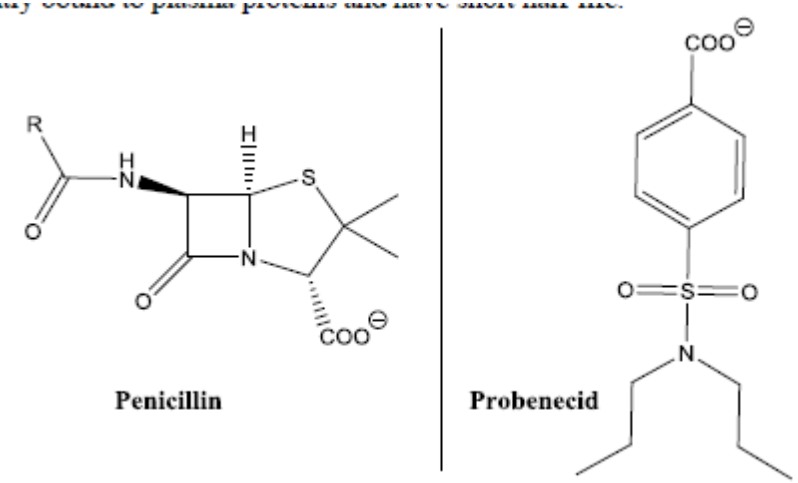
Products
Tazobactam



- 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 ®*.
- Used in combination with piperacillin for the treatment of appendicitis, postpartum endometritis, pelvic inflamatory 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.*

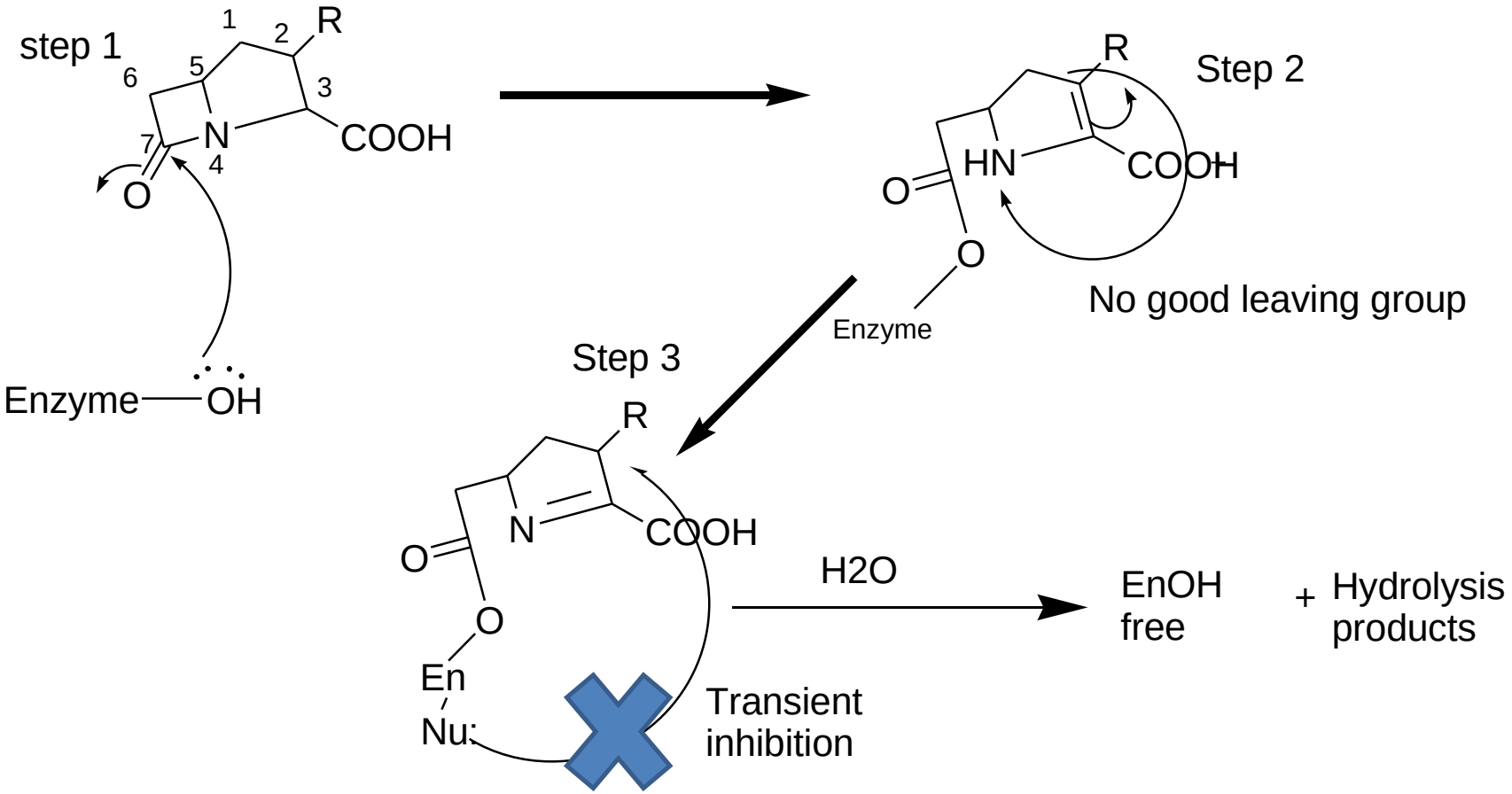
probenecid

- 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.



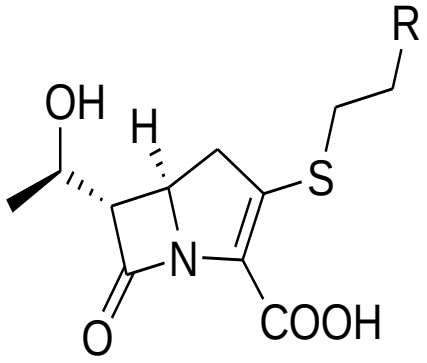
Penicillin **Probenecid**

Class II inhibitors



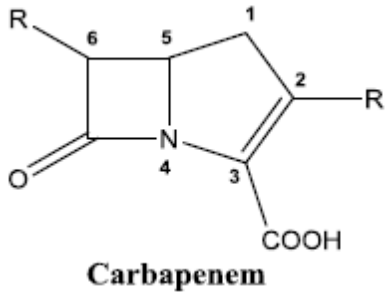
Class II inhibitors

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



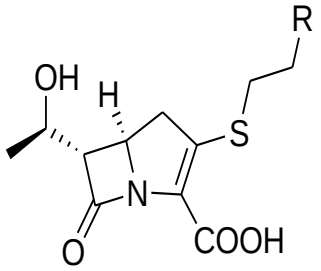
R = NH_2 Thienamycin

R = NHCH=NH imipenem



Carbapenem

Carbapenems Thienamycin



$R = NH_2$ Thienamycin

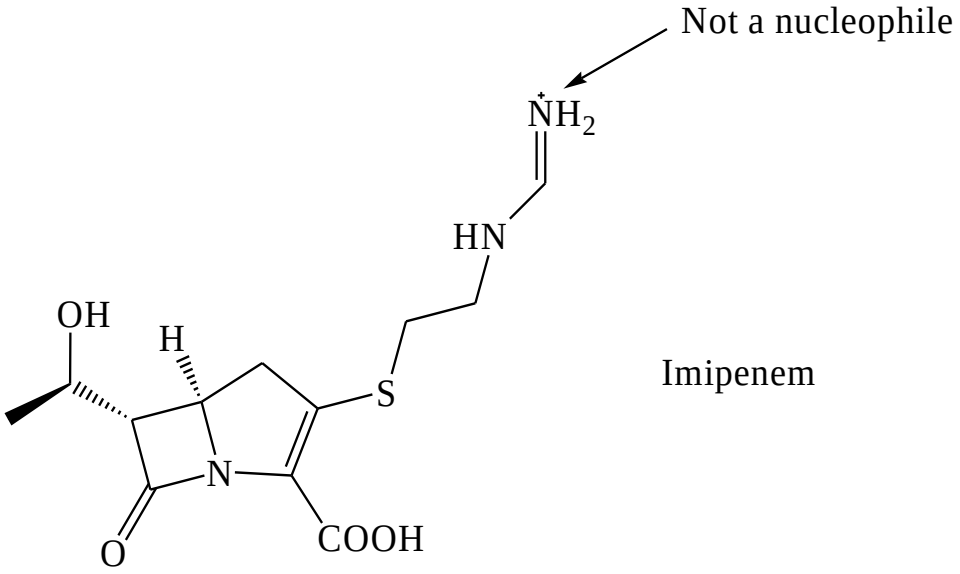
R = NHCH=NH imipenem

- 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.

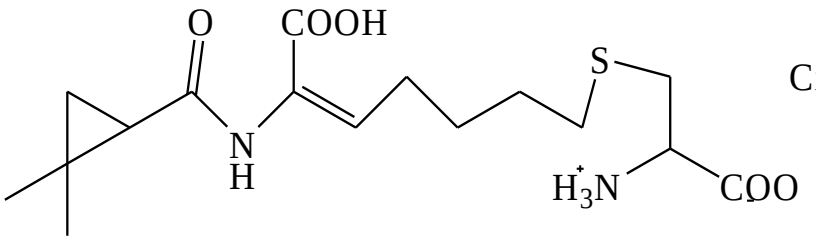
Thienamycin properties:

- - 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



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.

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
- Synergestic action with Aminoglycosides , but 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.*

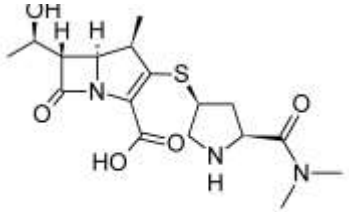
NEWER CARBAPENEMS

- 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.

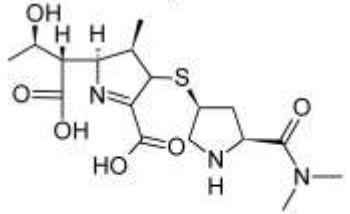
1. Improvements that are particularly desired include stability to hydrolysis catalyzed by DHP-I,
2. stability to bacterial metallo--lactamases (“carbapenemases”) that hydrolyze imipenem, activity against MRSA.
3. increased potency against *P. aeruginosa*, especially imipenem-resistant strains.
4. Enhanced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

NEWER CARBAPENEMS

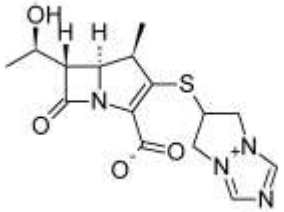
- Refer to your book to read more about these compunds



Meropenem



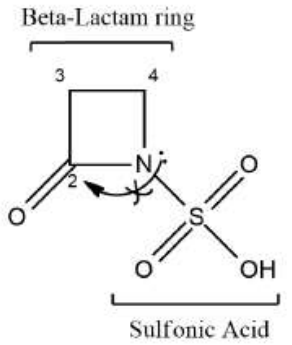
Meropenem metabolite



Biapenem

Monobactams

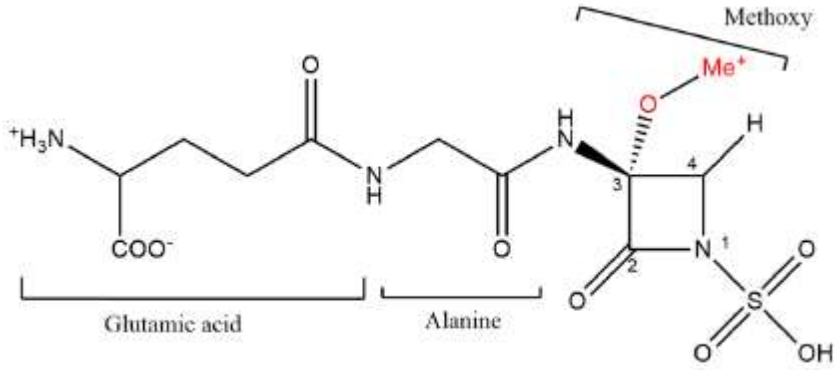
- Monobactams –by their name- contain β-Lactam ring only without any other cycle, and as we said previously that β-Lactam ring is too stable here because the pair of electrons on nitrogen are in resonance with the carbonyl, so to decrease the stability, monobactam have a sulfonic acid at the nitrogen.
- 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-**



- 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:

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

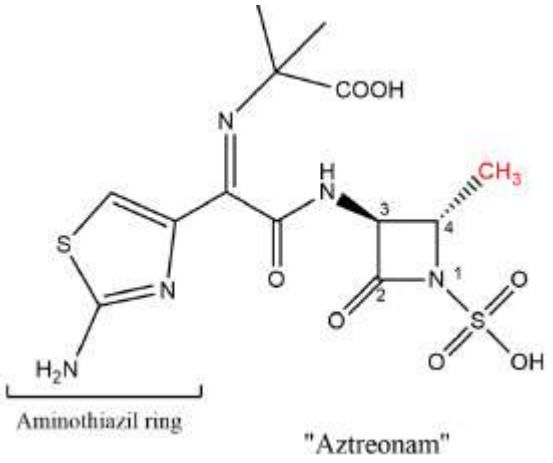


Sulfazecin

2- Aztreonam

Aztreonam is an:

- Acid stable (but still not orally available)
- Used to treat local GI tract infections
- β-Lactamase resistant
- Gram negative antibacterial agent (only gram negative, not gram positive
- because Aztreonam is too hydrophilic) – have an effect on *E.coli, and* no effect
- on pseudomonas aeruginosa, streptococcus and staphylococcus.



3- Tigemonam

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