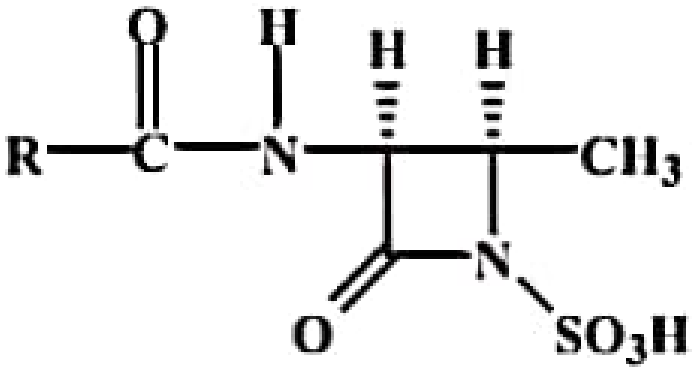
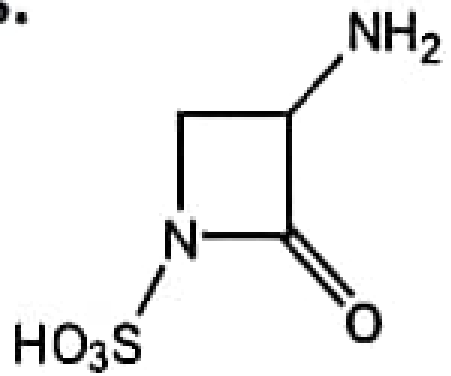
Monobactams have a monocyclic β-lactam ring and are resistant to β-lactamases.



Monobactam

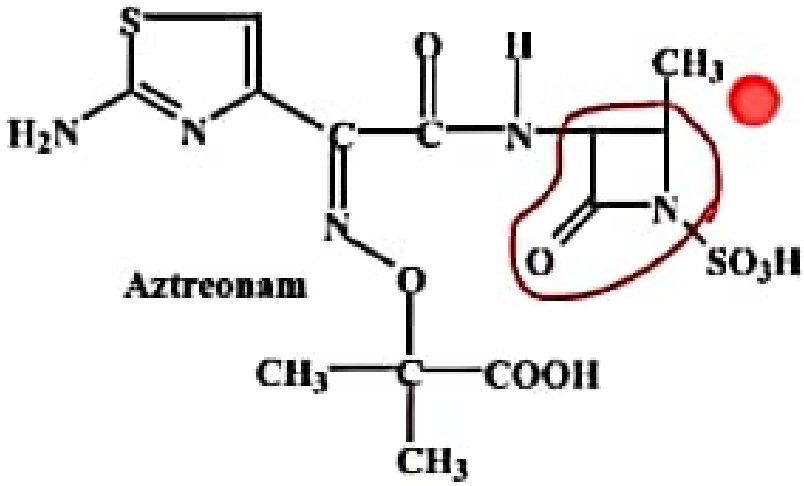


- Based on a substance produced by the bacterium *Chromobacterium violaceum* - 3-Aminomonobactamic acid
- Side chain parallels that in the cephalosporins and penicillins.
- Substitution with small polar groups such as hydroxyl, amino, carboxylic or sulphonic results in poorly active compounds- most striking divergence between the monobactam and the cephalosporins and penicillins.
- Introduction of aminothiazole oxime side chain increases antibacterial activity as the acyl substituent.

Mono bactams

- The sulfamic acid moiety attached to the β-lactam ring was unprecedented.
- Considering large size of sulfur atoms, this assembly may sufficiently spatially resemble the corresponding
- C-2 carboxyl group of the precedent β-lactam antibiotics to confuse the penicillin binding proteins.
- The strongly electron-withdrawing character of the sulfamic acid group probably also makes the β-lactam bond more vulnerable to hydrolysis.
- Monobactams demonstrate that a fused ring is not essential for antibiotic activity.
- The α-oriented methyl group at C-2 is associated with the stability of aztreonam towards β-lactamases.

Aztreonam



- Aztreonam was isolated from *Chromobacterium violaceum*
- Aztreonam is the first clinically useful monobactam.
- The antimicrobial activity of Aztreonam differs from those of other β-lactam antibiotics and more closely resembles that of an aminoglycosides in activity without the nephrotoxicity c aminoglycosides (aerobic gram negative-require oxygen).
- The protein binding is moderate (~50%), and the drug is nearly unchanged by metabolism

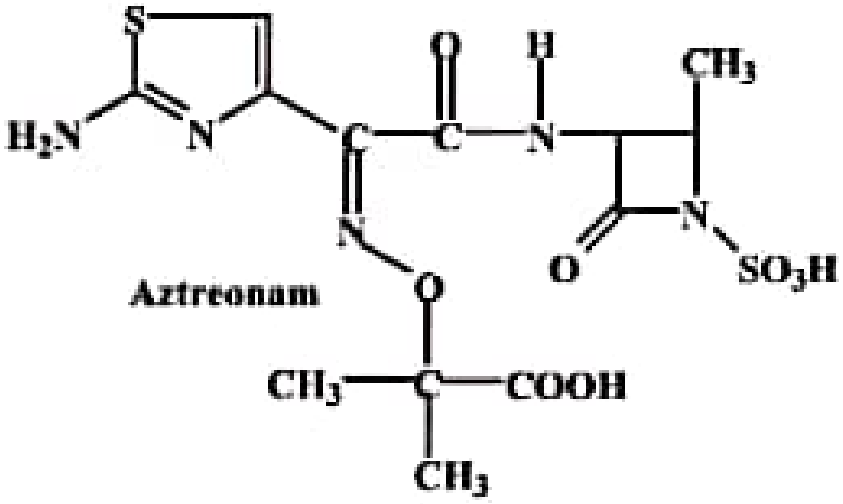
Mechanism of action
Uses

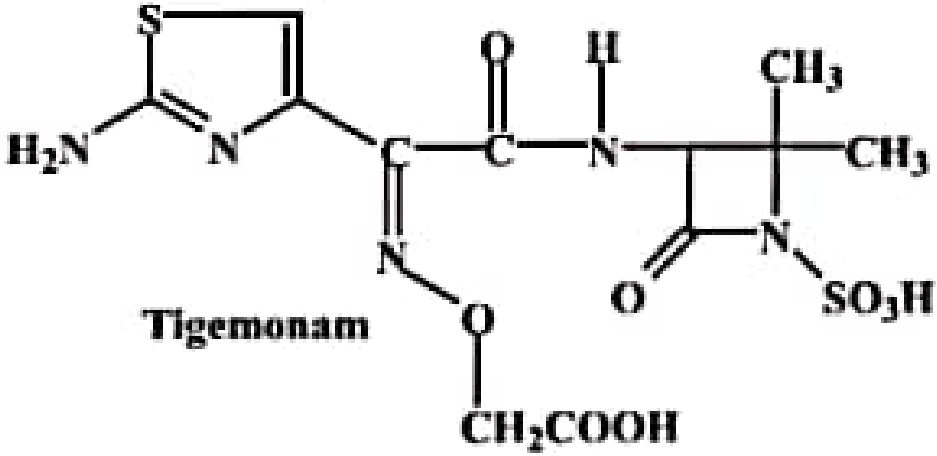
- Aztreonam is unique among the β-lactam antibiotics b/c it is active only against Gm–ve aerobes and inactive against Gm +ve and anaerobes.
- The combination of Aztreonam and Piperacillin is synergistic against some strains of *P. aeruginosa* and Enterobacter

- ***Toxicity***

  It is a safe agent with side effect similar to those of other β-lactams.

Tigemonam





It is orally active.

- It is highly resistant to β-lactamases.
- The antibacterial spectrum of activity of tigemonam resemb that of aztreonam.
- It is very active against the Enterobacteriaceae, including: *E. coli, Klebsiella, Proteus, Enterobacter* species.

Beta lactamases inhibitors

- INTRODUCTION
- SOURCE
- STRUCTURE
- MOA
- SAR

β- lactamases Classification

- These enzymes are divided as:

1) Class A contains enzymes from Gram-positive bacteria. The majority of them are transmissible, plasmid-mediated enzymes, often referred to as penicillinases because their preferred substrates are penicillins.
2) Class B contains broad-spectrum metallo-enzymes which mainly hydrolyzing carbapenams.
3) Class C contains predominately chromosomally mediated enzymes from Gram-negative bacteria whose preferred substrates are cephalosporins are thus referred to as cephalosporinases.

Beta lactamase enzymes

1) Class D includes enzymes capable of hydrolyzing the more β-lactamase stable isoxazolyl penicillins.

Two strategies have evolved to combat β- lactamases-mediated resistance.

i. Development of classes of β- lactam antibiotics with improved stability.
ii. Identification of β- lactamase inhibitors for co-administration with the other antibiotics.

β- lactamase Inhibitors

- Although they exhibit negligible antimicrobial activity, they contain the beta-lactam ring.
- Their sole purpose is to prevent the inactivation of beta-lactam antibiotics by binding the beta-lactamases, and, as such, they are co-administered with beta-lactam antibiotics.

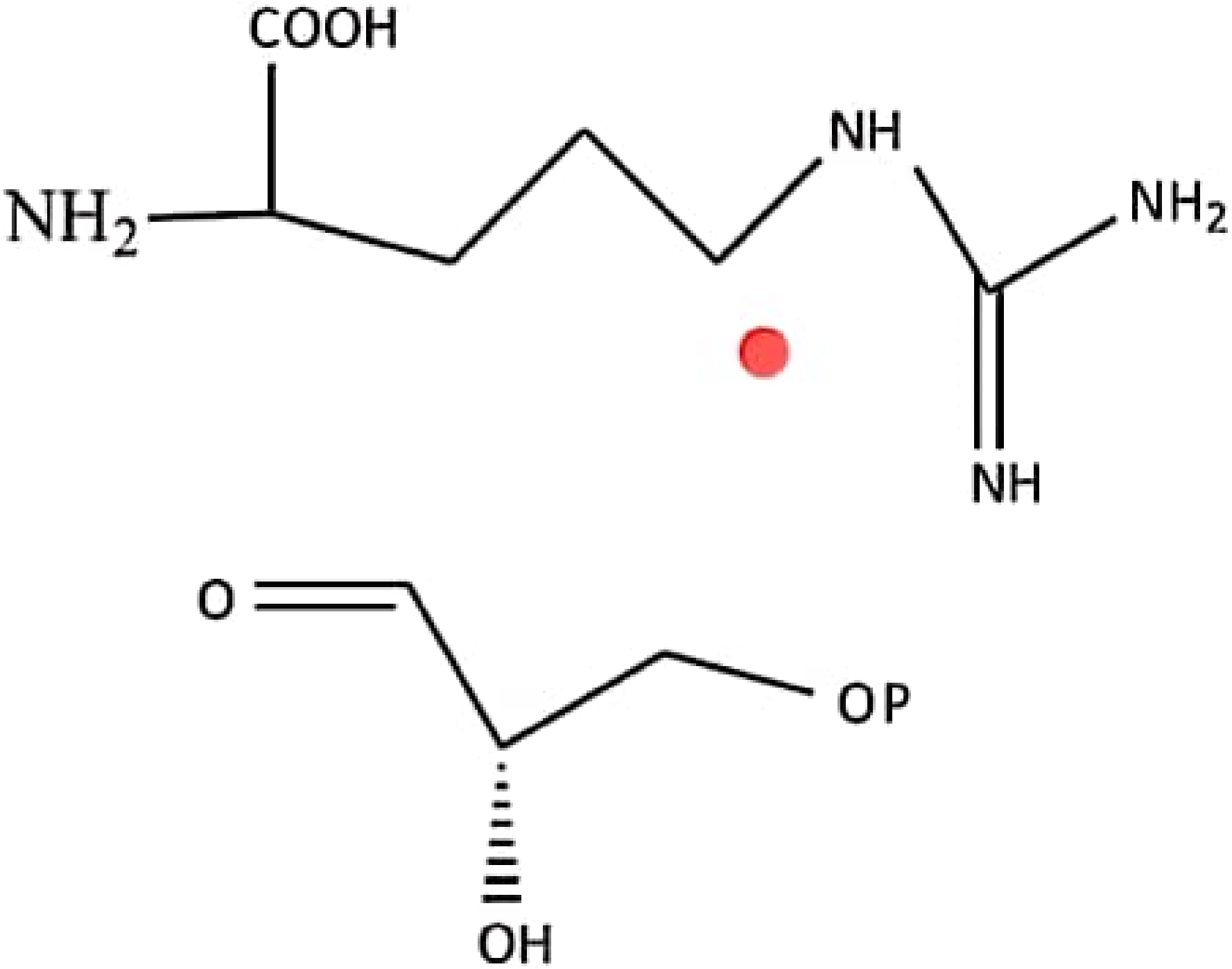
1. clavulanic acid
2. tazobactam
3. sulbactam

SOURCE AND STEROCHEMISTRY

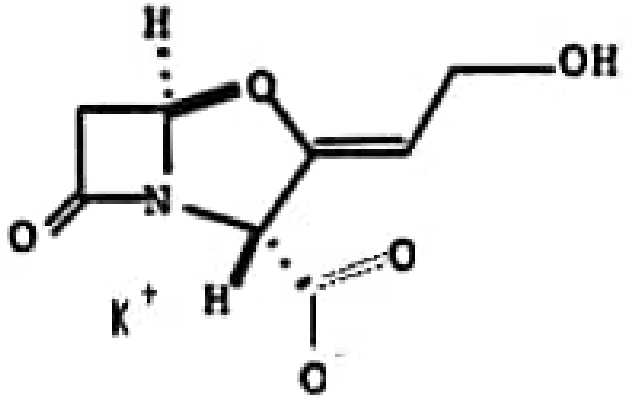
Clavulanic acid is a secondary metabolite produced by Streptomyces clavuligerus.

It possesses a clavam structure and a characteristic 3R,5R stereochemistry essential for action as a beta-lactamase inhibitory molecule.

t is produced from glyceraldehyde-3-phosphate and arginine in an eight step biosynthetic pathway.

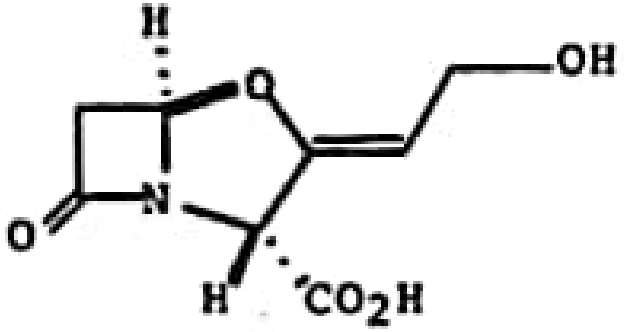


Clavulanic Acid



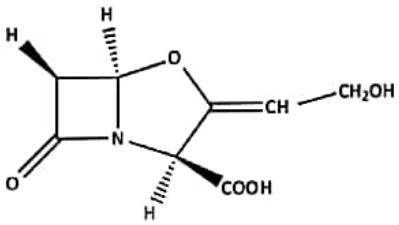
Clavulanate Potassium

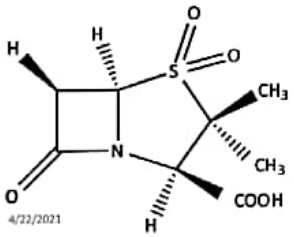
Clavulanic Acid

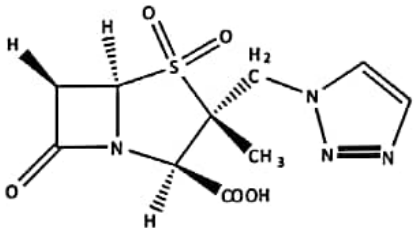


- Clavulanic acid can be considered as the most important & representive among the inhibitors of β- lactamases.
- It is first clinically useful β- lactamase inhibitor was identified as a natural product from a strain of *Streptomyces clavuligerus*.
- Structurally it is a 1-oxopenam lacking the 6-acyl amino side chain of penicillins but possessing a 2-hydroxy ethylidene moiety at C-2

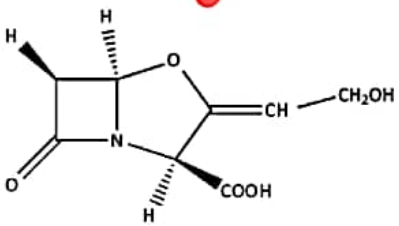
Beta-lactamase inhibitors

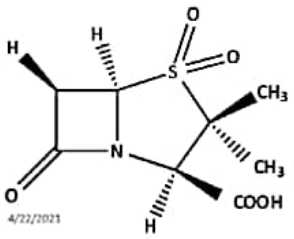


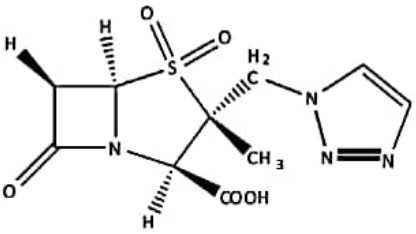




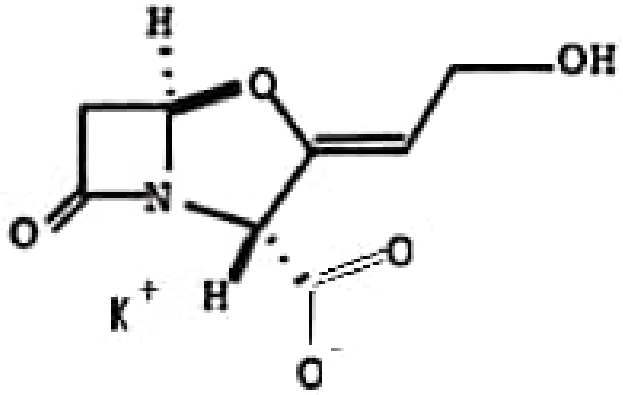
Beta-lactamase inhibitors



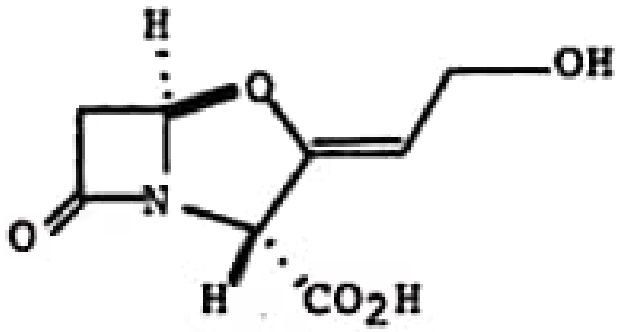




Clavulanic Acid



Clavulanic Acid



Clavulanate Potassium

- It was the first clinically useful β- lactamase inhibitor identified as a natural product from a strain of *Streptomyces clavuligerus.*

Structurally it is a 1-oxopenam lacking the 6-acyl amino side chain of penicillins but possessing a 2-hydroxy ethylidene moiety at C-2

Mechanism of action

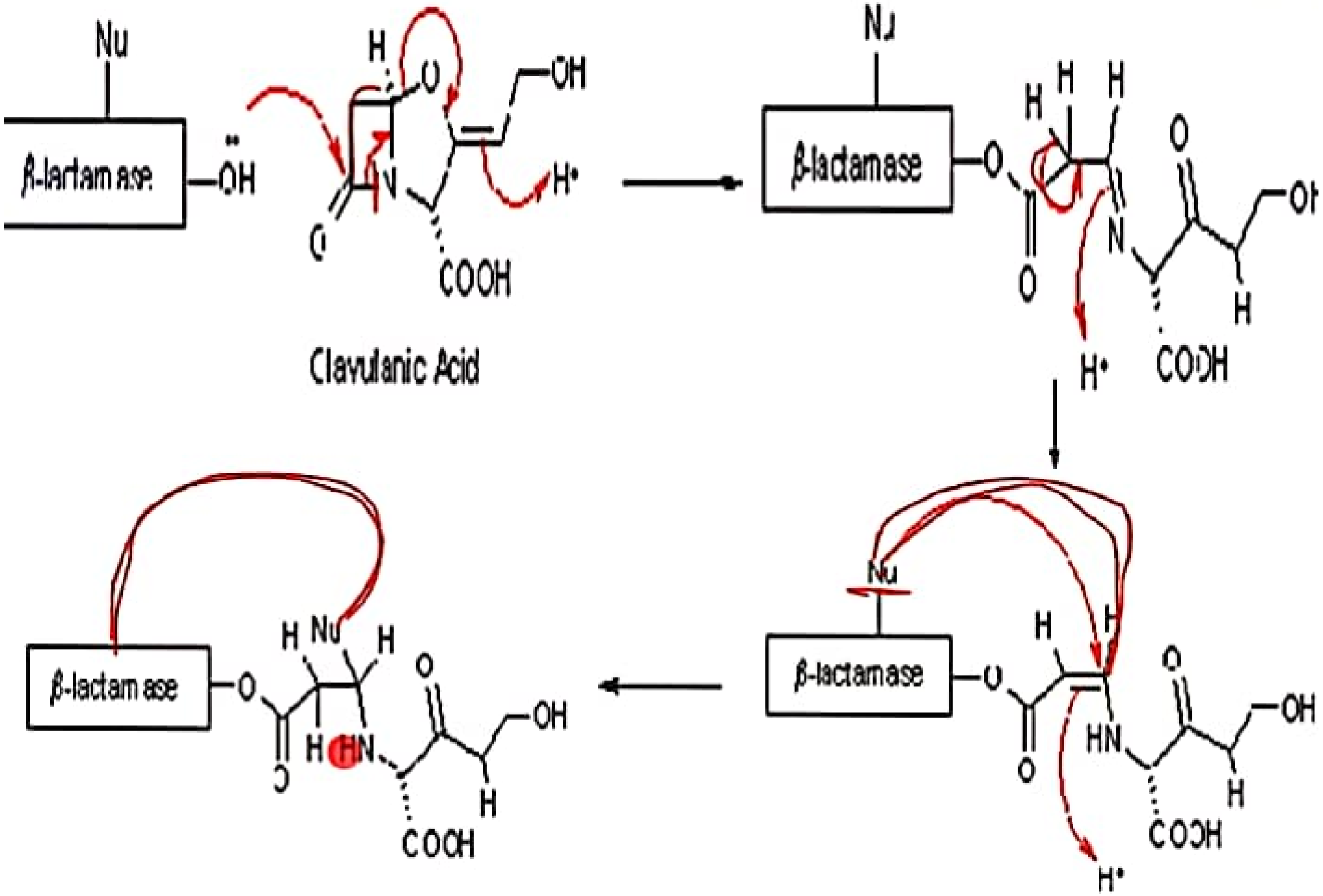
- Have negligible intrinsic antimicrobial activity, despite sharing the β-lactam ring that is characteristic of beta-lactam antibiotics.
- Exhibits very weak antibacterial activity, comparable with that of 6- amino penicillanic acid therefore is not useful as an antibiotic- lacks 6-acyl amino group.
- However, the similarity in chemical structure allows the molecule to act as a competitive inhibitor of beta-lactamases secreted by certain bacteria to confer resistance to beta- lactam antibiotics.

Continue....

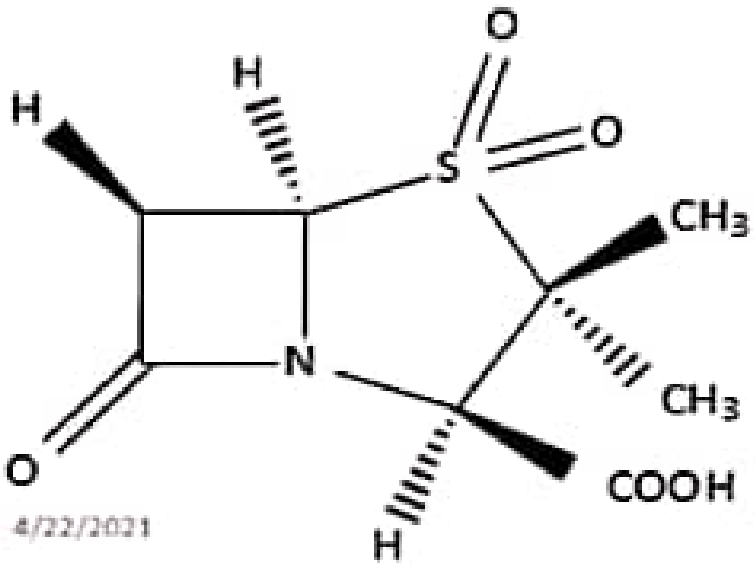
- This inhibition restores the antimicrobial activity of beta-lactam antibiotics against a lactamase-secreting resistant bacteria.
- Despite this, some bacterial strains have emerged that are even resistant to such combinations.

Clavulanic acid

- Clavulanic acid is a potent inhibitor of bacterial β-lactamase enzyme
- This enzyme is a serine protease and can hydrolyze β -lactams, such as the penicillin antibiotics.
- It is the principal enzyme responsible for penicillin-resistant bacteria.
- Clavulanic acid itself is a β -lactam and, if given in combination with penicillin, is preferentially taken up by β -lactamase and hydrolyzed.
- During the process of hydrolysis, however, the molecule undergoes a cleavage, leading to the formation of a "Michael acceptor," which subsequently alkylates a nucleophilic residue on b-lactamase, causing irreversible inhibition.
- Clavulanic acid is an excellent irreversible inhibitor of most β-lactamases. It is believed to acylate the active site serine by mimicking the normal substrate



Sulbactam

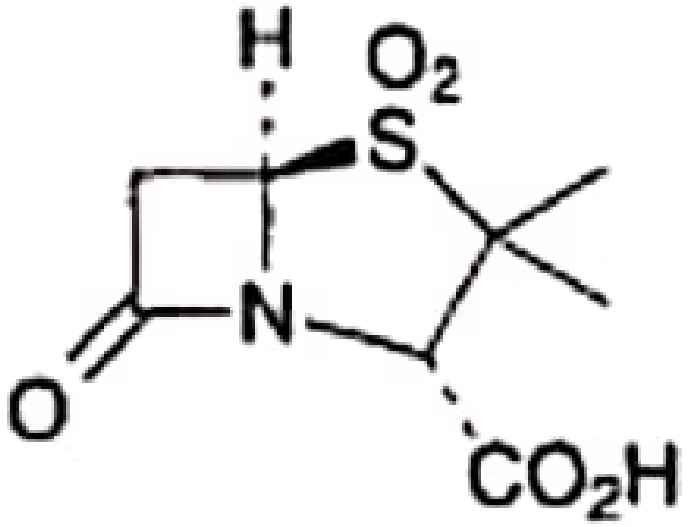


4/22/2021

- The oxidation of the sulfur atom to a sulfone greatly enhances the potency of Sulbactam.
- Sulbactam and ampicillin have enhanced antibacterial activity.

Sulbactam semi synthesis

- Sulbactam is prepared by partial chemical synthesis from penicillins.
- Diazotization/ bromination of 6-APA followed by oxidation, gave the 6,6-dibromopenicillanic acid sulfone which on catalytic hydrogenation provided sulbactam.
- It is an irreversible inhibitor of several β- lactamases,.
- compared with Clavulanic acid sulbactam has a broader spectrum of activity but is less potent.



6 A PA

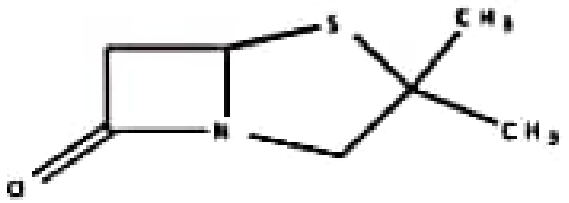
↓ Diazotization

Diazoderivative of 6 A PA

↓ Bromination

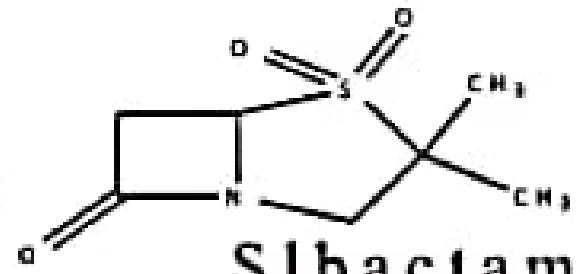
6,6-Dibromoaminopenicillanic acid

↓ Hydrgenolysis



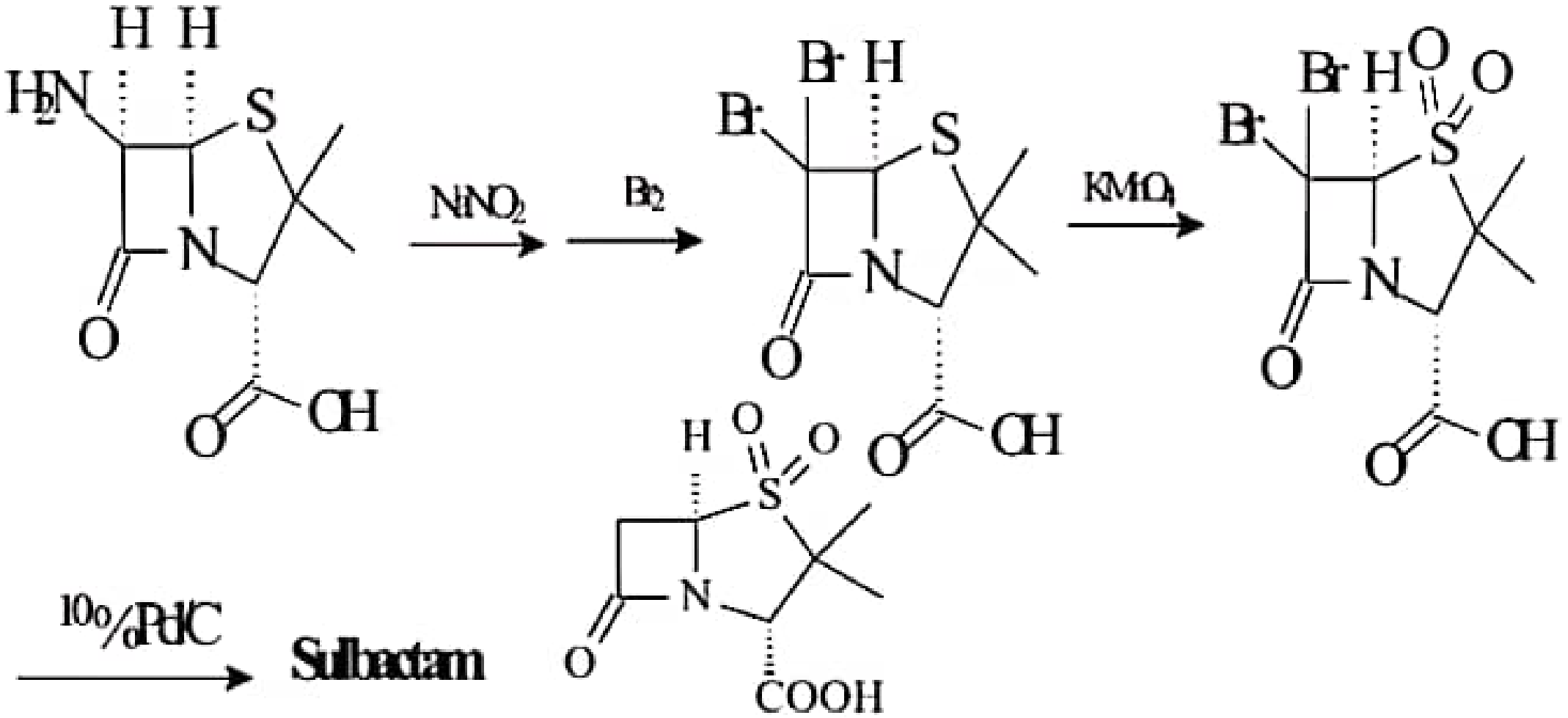
Penicillanic acid

Oxidation of sulphur to sulfone

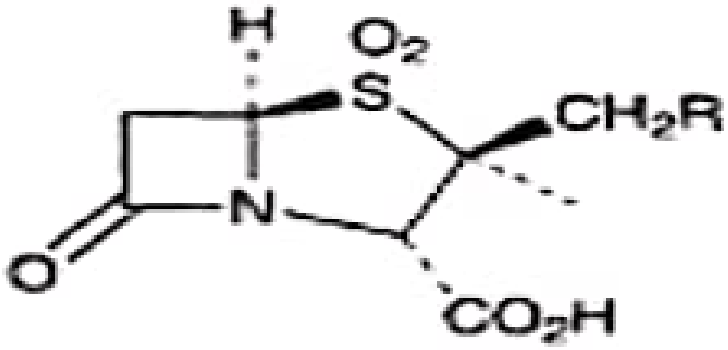


Slbactam

Synthesis



Tazobactam



132 R = Cl

134 R = 

- Tazobactam is a penicillanic acid sulfone that is similar in structure to sulbactam.
- It is a more potent β- lactamase inhibitor than sulbactam & has slightly broader spectrum of activity than Clavulanic acid.
- It has very weak antibacterial activity.

SAR of the beta lactamase inhibitors

- Bicyclic system is important for activity
- Intact beta lactam ring is essential for activity
- Free carboxylate is essential for activity
- Heteroatom nitrogen is necessary for activity
- Clavams where oxygen is the heteroatom in position one are active clavulanic acid
- Carbonyl at position seven is necessary for activity
- Beta lactamases inhibitors should irreversibly bind with enzyme and inactivate it.
- Oxidation of the Sulphur to sulfone enhances the activity
- Rate and extent of formation of inhibitor-enzyme complex determines potency.

Marketed Combinations

- Most commonly, the potassium salt potassium clavulanate is combined with amoxicillin (co- amoxiclav)
- Timetin (potassium clavulanate plus ticarcillin)
- Tazobactam is available in injectable combination with Piperacillin

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Clavulanicacid-MOA

- This leads to its classification as a mechanism-based inhibitor (or so-called suicide substrate).
- Clavulanic acid is added to ampicillin and amoxicillin preparations, the potency against β-lactamase–producing strains is markedly enhanced.
- It is a potent inhibitor of *S. aureus* β- lactamase & plasmid- mediated β- lactamases elaborated by Gram negative bacilli.