

Subject : Medicinal Chemistry-III (B.Pharm, 6th Semester)

Topic : a) β -Lactam antibiotic (Penicillin, Cephalosporins)

b) β - Lactamase inhibitors

c) Monobactams

Presented by

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What is an antibiotic ?

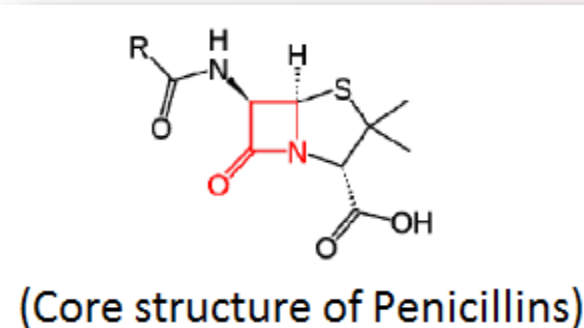
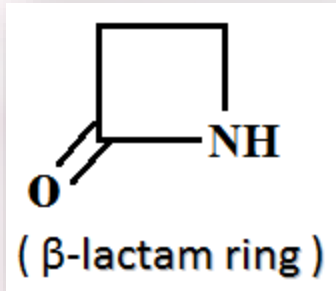
An antibiotic or an antibiotic substance is a substance produced by the microorganisms, which has the capacity of inhibiting the growth and even of destroying other micro-organisms.

Classification Antibiotics based on Chemical structure

- a) **β - lactam antibiotic:** Penicillins , Cephalosporins
- b) **Aminoglycoside antibiotics :** Streptomycin, Neomycin, Kanamycin, Amikacin, Gentamycin, Tobramycin, Netilmicin, Sisomicin, Spectinomycin, Paromomycin
- c) **Tetracyclines:** Tetracyclines, Chlorotetracycline, Rolitetracycline, Oxytetracycline, Methacycline, Doxycycline, Minocycline, Demeclocycline
- d) **Macrolide antibiotics:** Erythromycin, Clarithromycin, Azithromycin, Dirithromycin, Troleandomycin
- e) **Lincomycins:** Lincomycin, Clindamycin
- f) **Polypeptide antibiotics:** Vancomycin, Bacitracin, Polymyxin B, Colistin, Gramicidin, Teicoplanin
- g) **Miscellaneous:** Chloramphenicol, Novobiocin, Mupirocin, Fusidic acid.

β -Lactam antibiotics

- Beta-lactam antibiotics, which are named for the beta-lactam ring in their chemical structure.
- Its include penicillins, cephalosporins and related compounds.
- These agents are active against many gram-positive, gram-negative and anaerobic organisms.
- The beta-lactam antibiotics exert their effect by interfering with the structural crosslinking of peptidoglycans in bacterial cell walls.



Penicillin

- Alexander Fleming accidentally discovered penicillin. 1928, he noticed that a fungus, *Penicillium notatum*, had contaminated a culture plate of *Staphylococcus* bacteria he had accidentally left uncovered.
- The fungus had created bacteria-free zones wherever it grew on the plate. Fleming isolated and grew the mould in pure culture.
- He found that *P. notatum* proved extremely effective even at very low concentrations, preventing *Staphylococcus* growth even when diluted 800 times, and was less toxic than the disinfectants used at the time.

Classification of penicillin

1. Based on the nature:

- a) **Natural (Biosynthetic) penicillin:** Penicillin-G, Penicillin-F, Penicillin-K Penicillin-X, Penicillin-V, Penicillin-O
- b) **Semi-synthetic penicillin:** Methicillin, Amoxicillin, Ampicillin, Cloxacillin, Dicloxacillin, Carbenicillin, Piperacillin, Mezolocilin, Cyclacillin
- c) **Penicillin combination:** Procaine penicillin, Benzathine penicillin

Classification of penicillin

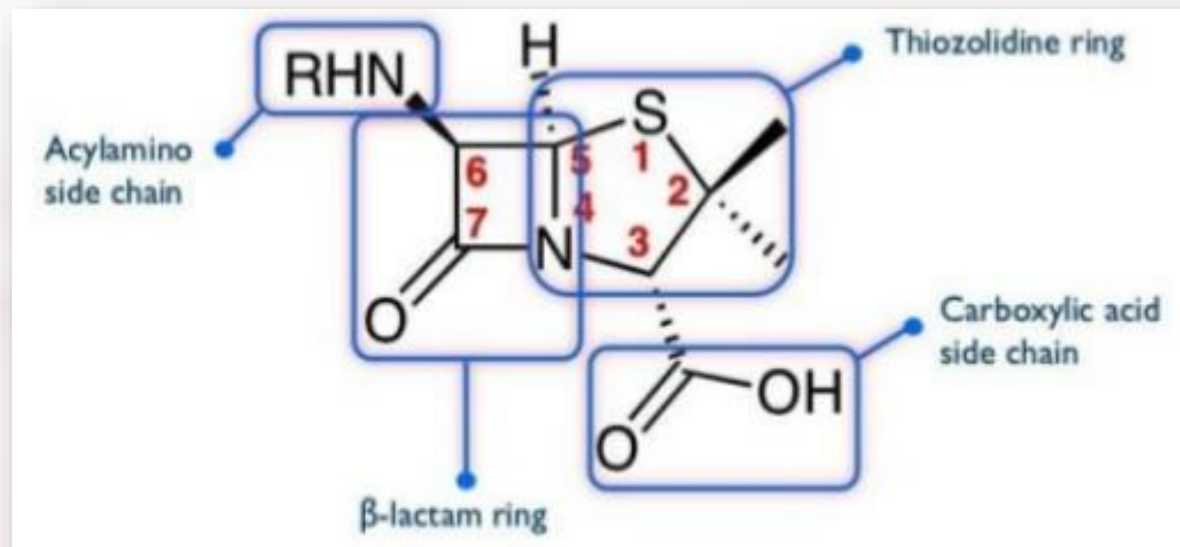
2. Based on spectrum activity:

- a) **Effective against gram +ve bacteria :** Penicillin-G, Ampicillin, Oxacillin.
- b) **Effective against gram -ve bacteria :** Temocillin
- c) **Broad spectrum Penicillin :** Ampicillin, Amoxicillin, Carbenicillin.
- d) **Penicillinase resistant penicillin:** Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, Nafacillin
- e) **Acid resistant penicillin:** Phenoxymethyl penicillin, Benzathine penicillin, Phenoxy ethyl penicillin, Phenoxy propyl penicillin.

Chemistry of Penicillin

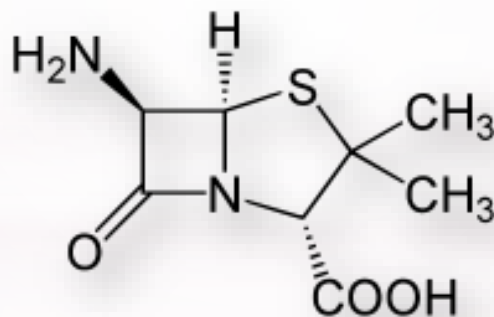
Penicillin as well as Cephalosporine are called beta-lactam antibiotics. They are characterised by three fundamental structural requirements.

- The fused beta-lactam & Thiazolidine ring structure.
- A free carboxyl acid group.
- One or more substituted amino acid side chain.



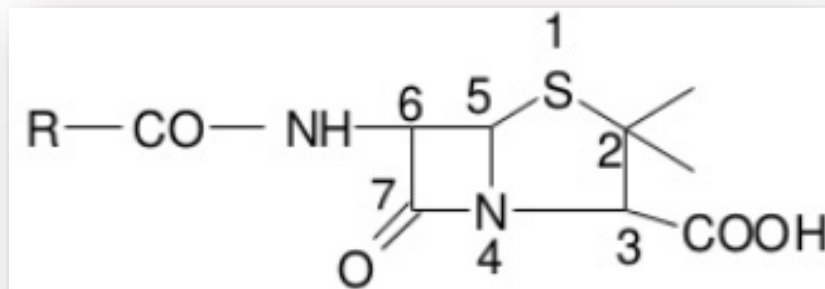
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- The structure of penicillin composed of fused 4-member beta-lactam ring with thiazolidine nucleus.
- It contains three chiral carbon atoms (C-3, C-5 & C-6)
- 6-Amino penicillanic acid (6-APA) is the basic skeleton structure of all penicillins.

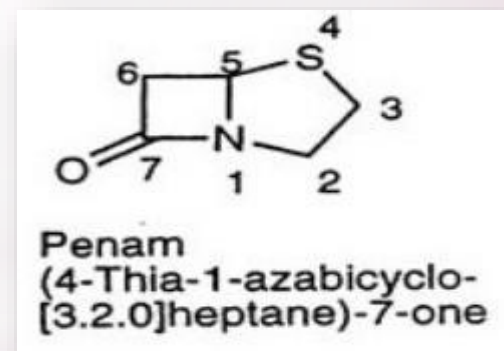
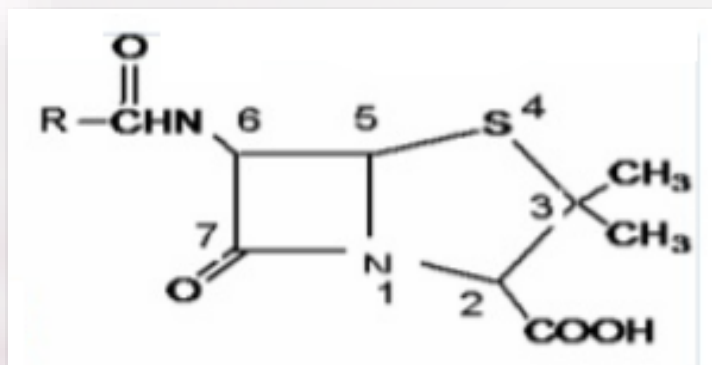


Nomenclature

Chemical abstract system (CAS):

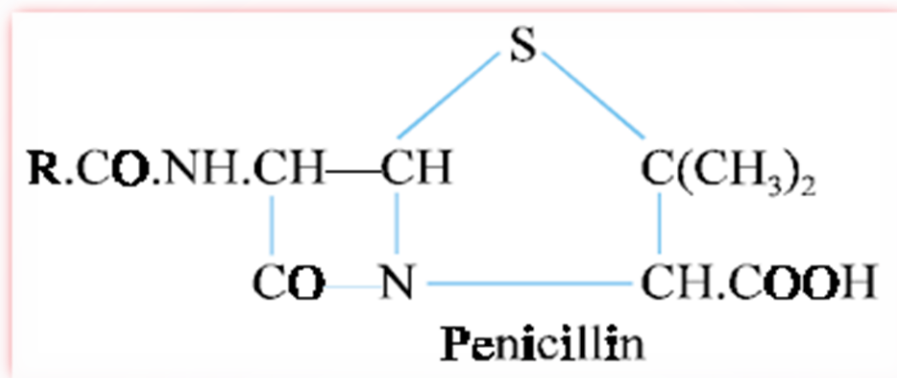



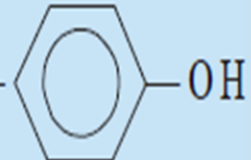
United state Pharmacopoeia (USP) :



- Core ring present in penicillin is 4-thia-1-aza-bicyclo [3.2.0] heptan-7-one

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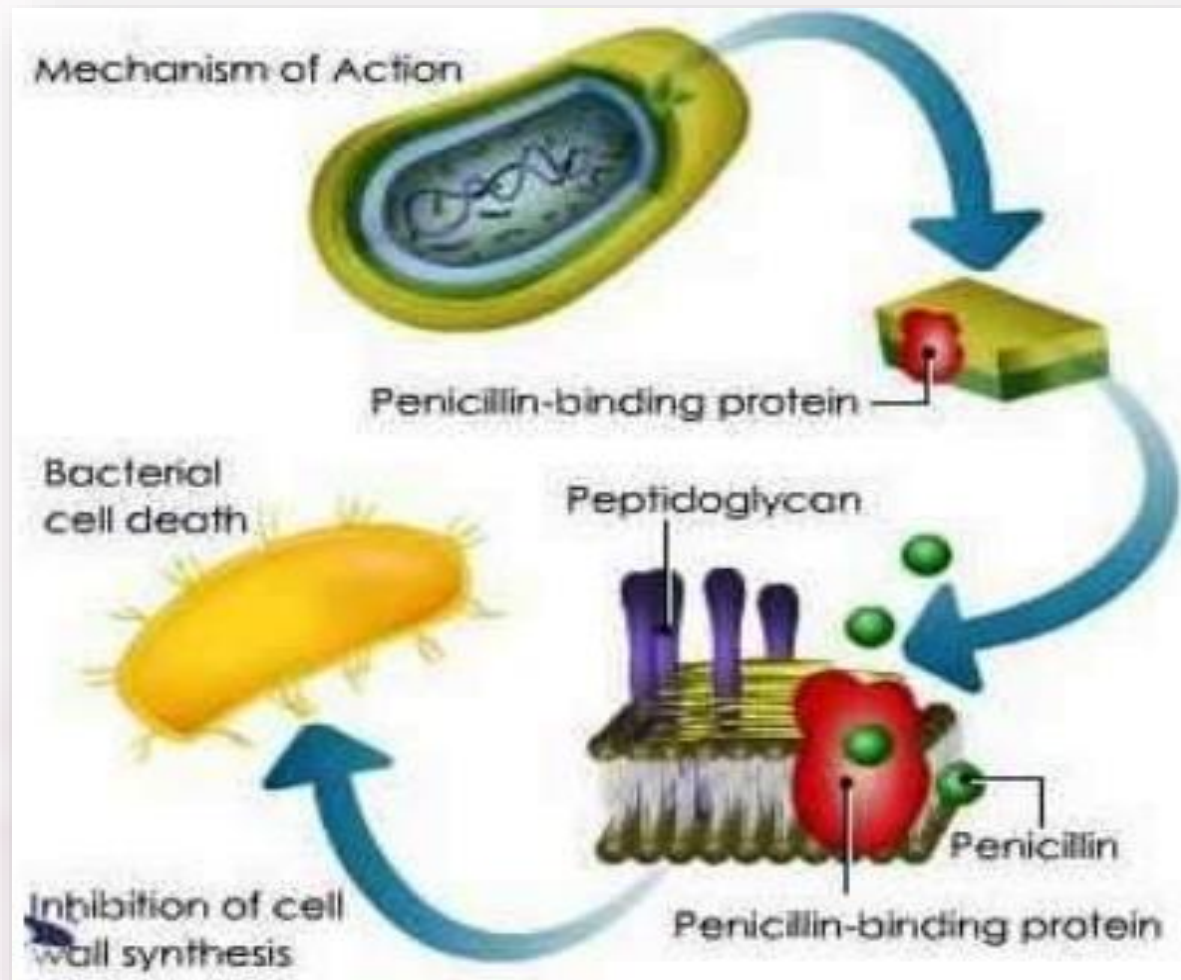


S. No.	Chemical Name	Other Names	—R
1	Pent-2-enylpenicillin	Penicillin-1 or F	—CH ₂ .CH = CH.CH ₂ CH ₃
2	Benzylpenicillin	Penicillin-II or G	—CH ₂ — 
3	<i>p</i> -Hydroxybenzyl-penicillin	Penicillin-III or X	—CH ₂ —  —OH
4	<i>n</i> -Heptylpenicillin	Penicillin-IV or K	—(CH ₂) ₆ .CH ₃
5	<i>n</i> -Amylpenicillin	Dihydro-F-penicillin	—(CH ₂) ₄ .CH ₃
6	Phenoxymethyl-penicillin	Penicillin-V	—CH ₂ —O—C ₆ H ₅

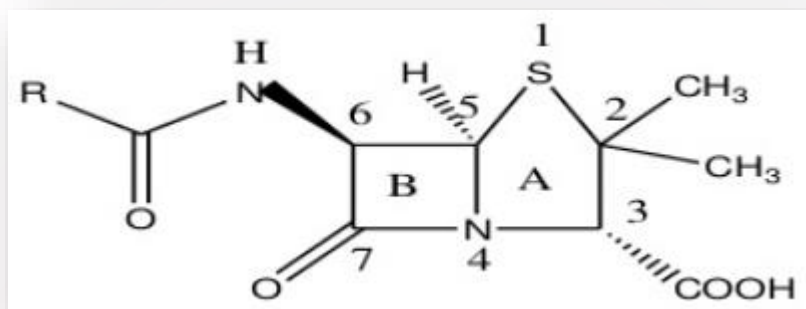
Mechanism of action of penicillin

- Bacteria cells are surrounded by a protective envelope called the cell wall.
- One of the primary components of the bacterial cell wall is peptidoglycan, a structural macromolecule with a net-like composition that provides rigidity and support to the outer cell wall.
- In order to form the cell wall, a single peptidoglycan chain is cross-linked to other peptidoglycan chains through the action of the enzyme DD transpeptidase (also called a penicillin binding protein—PBP).
- Penicillin kills bacteria through binding to DD-transpeptidase, inhibiting its cross-linking activity and preventing new cell wall formation. Without a cell wall, a bacterial cell is vulnerable to outside water and molecular pressures, and quickly dies.

Mechanism of action of penicillin



SAR of penicillin



Position-1: The sulfur atom of the Thiazolidine ring is oxidized to sulfone or sulfoxide, it improves acid stability, but decrease the activity of the agent.

Position-2: No substitution allow at this position, any change will lower activity, Methyl groups are necessary

Position-3: The carboxylic acid of the Thiazolidine is required for activity. If it is changed to an alcohol or ester, activity is decreased.

Position-4: The nitrogen is must.

Position-5: No substitution allowed.

Cont.

Position-7: The carbonyl on the beta-lactam ring is must

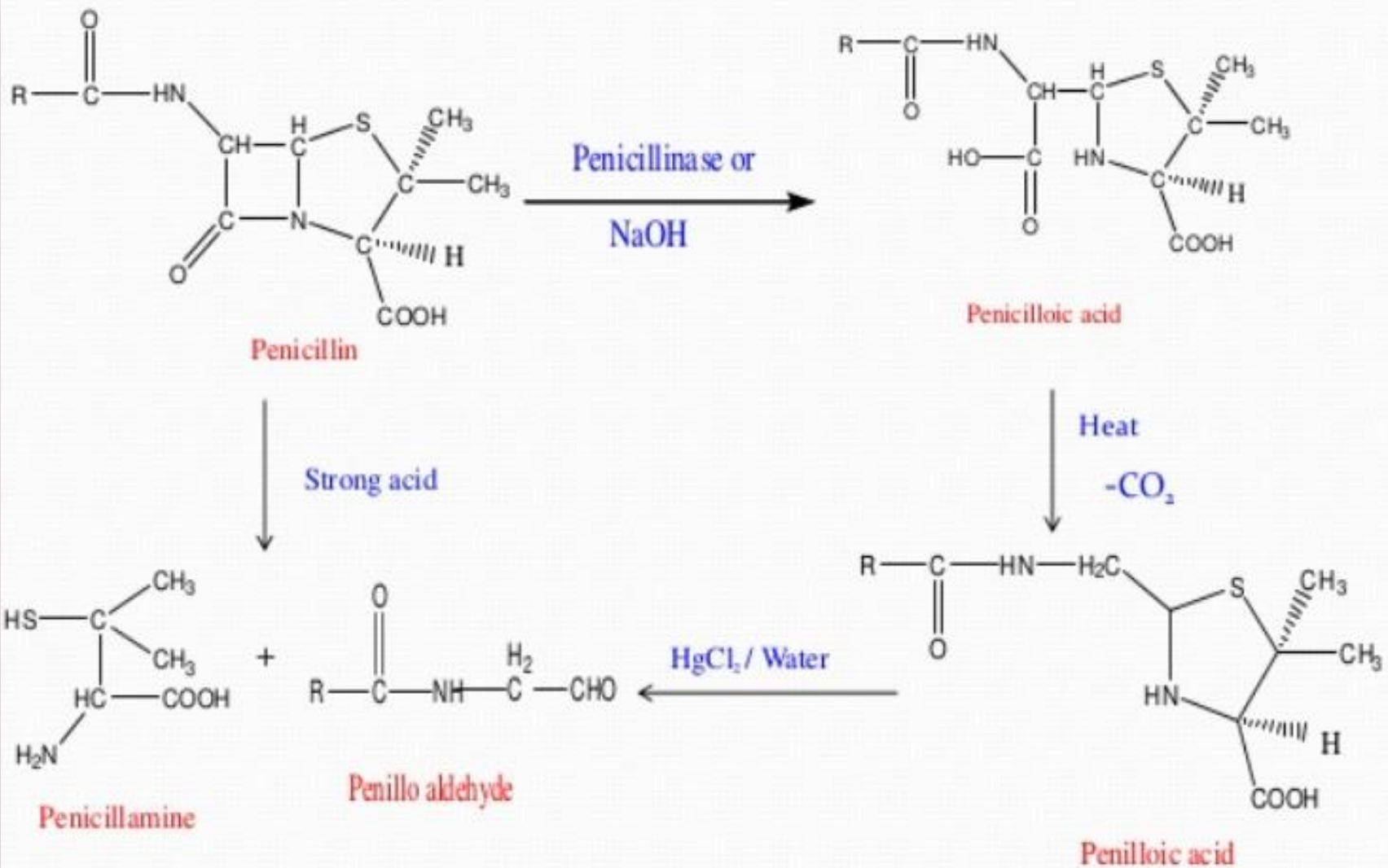
Position-6: Substitution are allowed on the side chain of the amide.

An electron withdrawing group added at this position will give the compound better acid stability because this substitution will make the amide oxygen less nucleophilic.

- A bulky group added close to the ring will make the compound more resistant to beta-lactamases.
- Steric hindrance provides protect to the beta-lactam ring.

Chemical degradation of penicillin

- The beta lactam carbonyl group of penicillin undergoes nucleophilic attack by water or hydroxide ion to form the inactive penicilloic acid.
- Penicilloic acid on decarboxylation produces penilloic acid.
- On treatment with strong acid the ultimate product formed is penicillamine & penilloaldehyde.
- On subject to pH 2.0 & 4.0 give rise to penillic acid & penicillenic acid.



Adverse effects

Common adverse drug reactions ($\geq 1\%$ of people) associated with use of the penicillins includes:

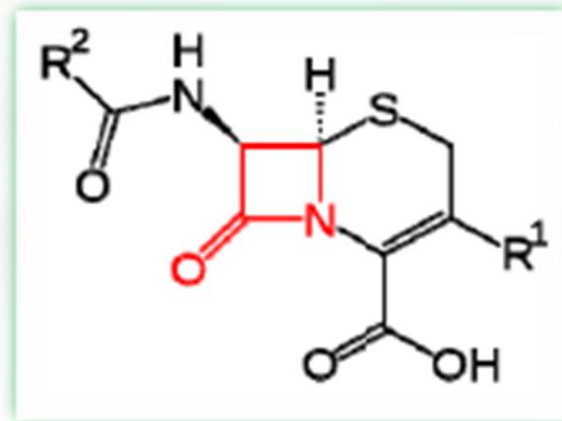
- Diarrhea
- hypersensitivity,
- Nausea
- Rash
- neurotoxicity.
- Life threatening effect includes Anaphylaxis and Seizures.

Uses

- Penicillin is effective against Streptococci (including *Streptococcus pneumoniae*), *Listeria*, *Neisseria gonorrhoeae*, *Clostridium* and *Peptococcus*.
- However, most staphylococci now are resistant to penicillin.
- Penicillin antibiotics are also effective against *H. influenzae*, *E. coli*, *pneumococci*, certain strains of staphylococci.
- Penicillin antibiotics are used to treat many types of infections caused by susceptible bacteria.
- They are used to treat infections of the middle ear, sinuses, stomach and intestines, bladder, and kidney. They also are used for treating pneumonia, blood infections (sepsis) and uncomplicated gonorrhea.

Cephalosporin

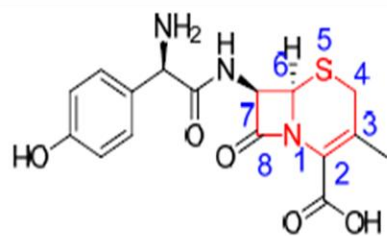
- It was isolated from fungus *Cephalosporium acremonium* in 1948 by an Italian scientist Giuseppe Brotzu.
- Cephalosporins are new and improved derivatives of the penicillins, They were actually discovered as naturally occurring substances separate from the penicillins.



Classification of Cephalosporin

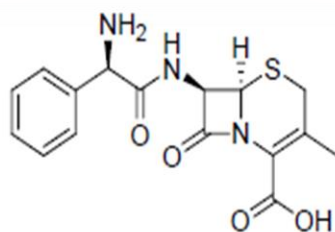
Based on generation:

- a) **First generation** : cefazoline, cefradine, cephalexin, cefadroxil, cefaclor, cefuroxime, cefprozil, ceftriaxone, cefepime
- b) **Second generation** : cefuroxime, ceftiofur, cefprozil, cefaclor, cefotiam, cefminox, cefotetan, cefoxitin.
- c) **Third generation** : ceftiofur, ceftazidime, ceftazidime avopate, ceftazidime avopate, ceftazidime avopate, ceftazidime avopate
- d) **Fourth generation**: cefepime, cefoselis, ceftazidime, ceftazidime avopate, ceftazidime avopate, ceftazidime avopate
- e) **Yet to be classified** : cefaloram, cefempidone, cefetrol, ceftriaxone, cefvitrol.



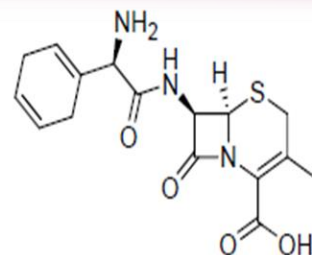
Cefadroxil

(6R,7R)-7-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



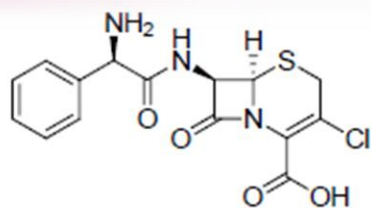
Cephalexin

(6R,7R)-7-[(2R)-2-amino-2-phenylacetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



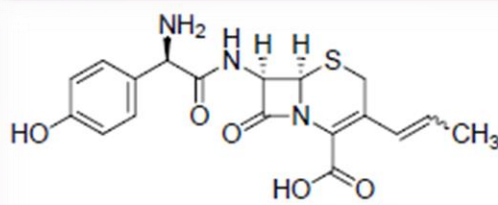
Cephadrine

(6R,7R)-7-[(2R)-2-amino-2-(cyclohexa-1,4-dien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



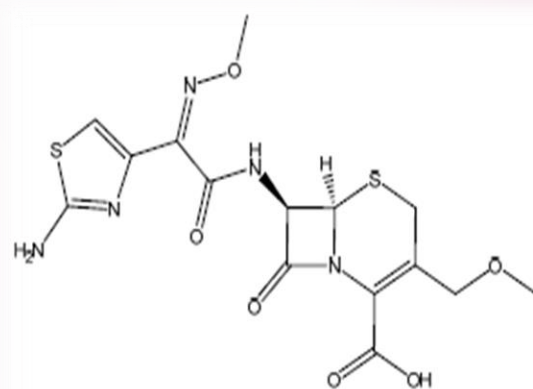
Cefaclor

(6R,7R)-7-[(2R)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



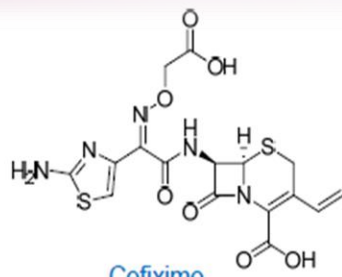
Cefprozil

(6R,7R)-7-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-(prop-1-en-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



Cefpodoxime

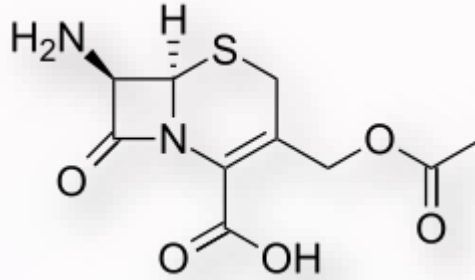
(6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



Cefixime

(6R,7R)-7-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-[(carboxymethoxy)imino]acetamido]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Chemistry of Cephalosporin



- The core of the basic cephalosporin molecule consists of a two ring system which includes a β -lactam ring condensed with dihydrothiazine ring.
- Basic nucleus is made up of 7-amino cephalosporanic acid (7-ACA).
- Core ring present in cephalosporins 5-thia-1-aza-bicyclo [4.2.0] octanes.

Mechanism of action of Cephalosporin

- Cephalosporins have same mode of action as other beta lactam antibiotics.
- It disrupt the synthesis of peptidoglycan layer of bacterial cell wall.
- The peptidoglycan layer is important for cell wall structural integrity.
- The final transpeptidation step in the synthesis of peptidoglycan is facilitated by transpeptidase known as penicillin binding protein.
- Prevents new cell wall formation in bacteria

Adverse effect

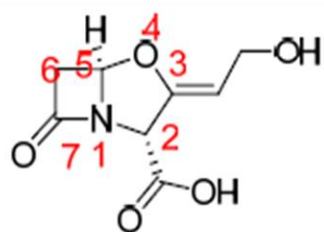
- Stomach upset
- Nausea
- Vomiting
- Diarrhea
- Dizziness

Uses

- Skin or soft tissue infections
- Urinary tract infections (UTIs)
- Strep throat
- Ear infections
- Pneumonia
- Sinus infections
- Meningitis
- Gonorrhoea

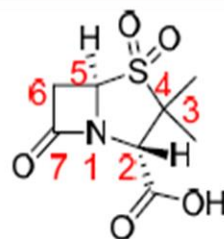
β -lactamase inhibitor

- These are a family of enzymes involved in bacterial resistance to beta-lactam antibiotics.
- They act by breaking the beta-lactam ring that allows penicillin-like antibiotics to work.
- Drug substance that inhibit the enzyme Beta-lactamases are called betalactamase inhibitors.
- β -lactamase inhibitors have little antibiotic activity of their own
- They are co-administered with beta-lactam antimicrobials to prevent antimicrobial resistance.
- Beta-lactamase inhibitors are primarily indicated for infections by gram negative bacteria, as they produce this enzyme.



Clavulanic acid

(2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

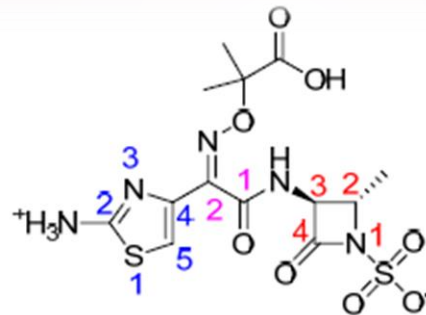


Sulbactam

(2S,5R)-3,3-dimethyl-4,4,7-trioxo-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Monobactam

- Monobactams are monocyclic β -lactam antibiotics.
- The β -lactam ring is not fused to another ring, in contrast to most other β -lactams.
- Monobactams are effective only against aerobic Gram-negative bacteria (e.g., *Neisseria*, *Pseudomonas*).



Aztreonam

(2S,3S)-3-[(2Z)-2-(2-azaniumyl-1,3-thiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetamido]-2-methyl-4-oxoazetidine-1-sulfonate

Mechanism of action of Monobactam

The antibacterial activity of monobactam is due to inhibition of penicillin binding protein 3 (PBP3), interfering with peptidoglycan synthesis and cell wall formation.

Uses

- It is used primarily to treat infections caused by gram-negative bacteria such as *Pseudomonas aeruginosa*.
- This may include bone infections, endometritis, intra abdominal infections, pneumonia, urinary tract infections, and sepsis.

Adverse effects

- Skin rash and occasional abnormal liver functions.

THANK YOU