

Lec 1

4th stage

**Organic Pharmaceutical Chemistry III
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**Textbook of Organic medicinal and
pharmaceutical chemistry**

Wilson and Gisvold's

Antibacterial Antibiotics

Penicillin was discovered accidentally in 1929 by Alexander Fleming, then the numbers of antibiotics that have been added to the therapeutic application. Yet, because of:-

1. The overuse of many of these agents.
2. The biochemical fickleness of many bacteria.
3. Resistance to antibiotics has become a serious problem in the 21st century.

Indeed, there are now organisms that cannot be arrested or killed by any of the common antibiotics. Clearly, new approaches are needed.

Definition of antibiotics

Greek word:-

Anti = against , bios= life

Vuillemin define antibiosis (“against life”):- is a substance produced by microorganisms, which has the capacity of inhibiting the growth and even of destroying other microorganisms.

Antibiotic:- are defined as chemical substances or compounds produced by various species or microorganisms such as bacteria or fungi, which in low concentration destroy, kill or inhibit of other species or microorganisms.

Requirements for substance to be considered as an antibiotic

1. It should have wide spectrum of activity with the ability to destroyed or inhibit many different species of pathogenic organisms.
2. It should be eliminated completely from the body.
3. It should not produce adverse or side effects.
4. It should antagonizes the growth or survival of one or more species of microorganisms.
5. It should be highly effective in low concentrations.
6. It should be non allergenic to the host.
7. It should be not eliminate the normal flora of the host.
8. It should be able to reach the part of the human body where the infection is occurring.
9. It should be in expensive and easy to produce.
10. It should be chemically stable (have a long shelf-life).
11. It is a product of metabolism (although it may be duplicated or even have been anticipated by chemical synthesis).

Classification of antibiotic:- antibiotic are classified in many ways based on chemical structure, source, its spectrum of activity and mechanism of action.

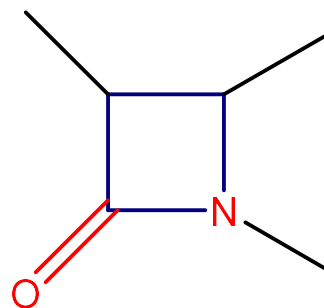
Based on chemical structure (chemical classification):-

1. β -lactam antibiotic. Penicillins, cephalosporin's, carbapenams, momobactams
2. aminoglycoside antibiotics:- streptomycin, neomycin, kanamycin, gentamycin, tobramycin, amikacin.
3. Tetracycline:- tetracycline, chlortetracycline, oxytetracycline, doxycycline, minocycline, methacycline, meclocycline.
4. Macrolide antibiotics(large conjugate double bond macrocyclic large lactone rings):- erythromycin...etc.
5. Polypeptide antibiotics:- Actinomycin...etc.
6. Antifungal antibiotics:- polyenes a) 26 membered ring polyenes Ex: natamycin
b) 38 membered macrocycles Ex:
Amphotericin B.
- 7- Antitubercular antibiotics:- Rifamycins....etc.
- 8- Antineoplastic antibiotics:- Dactinomycin.....etc.
- 9- Lincomycin:- Clindamycin.
- 10- Miscellaneous:- chloramphenicol.....etc.

β-LACTAM ANTIBIOTICS

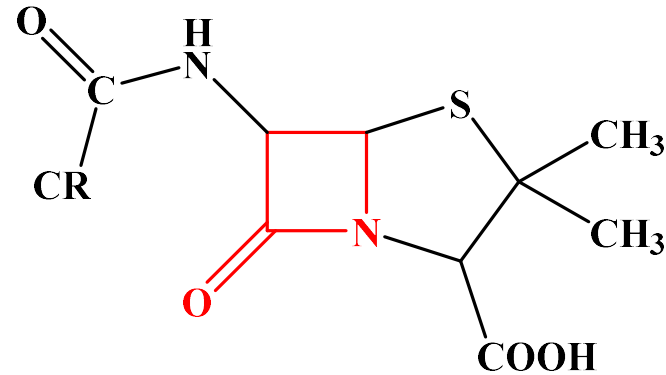
Antibiotics that possess the β-lactam (a four-membered cyclic amide) ring structure are the dominant class of agents.

Four groups beta-lactam antibiotics including:-

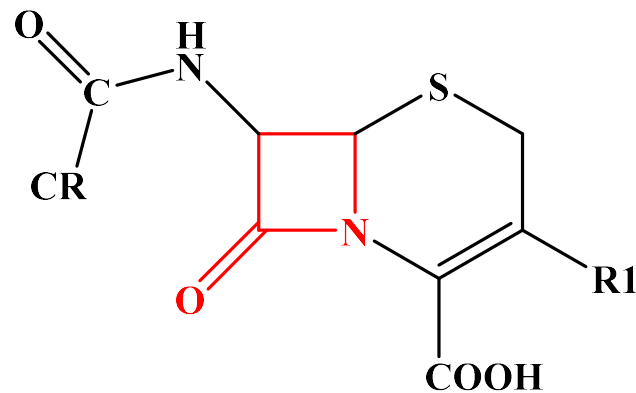


It is named as such because the nitrogen atom is attached to the β-carbon atom relative to the carbonyl

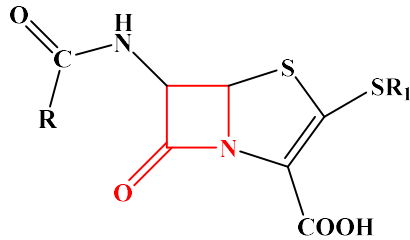
Penicillins:- The beta lactam ring is joined to a five-membered thiazolidine ring.



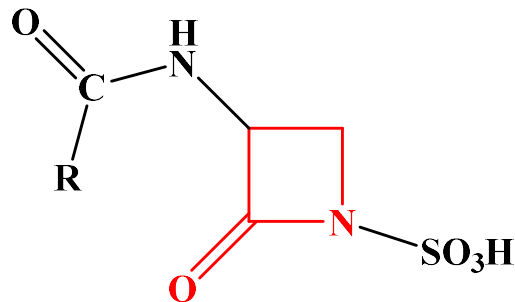
cephalosporin's:- The beta lactam ring is joined to a six-membered dihydrothiazine ring.



carbapenams-:- The beta lactam ring is also joined to a five-membered ring although it is carboxylic



Momobactams:- have a monocyclic beta- lactam structure, and a side sulfo-group is joined to a nitrogen atom.



All of these contain a four-membered beta-lactam ring, which is necessary for exhibiting antibacterial activity.

Penicillins

Penicillins:- is a group of antibiotics that are commonly used to treat different types of gram positive and gram negative bacterial infections. In their structure, beta-lactam ring is located due to this reason these drugs are also called as beta-lactam antibiotics.

HISTORY

Penicillin was discovered in 1928 by Alexander Fleming, who noticed that one of his experimental cultures of staphylococcus was contaminated with mold, which caused the bacteria to lyse. Since mold belonged to the family penicillium, he named the antibacterial substance penicillin.

About a decade later, a group of researchers at Oxford University isolated a crude substance made up of a few low molecular substances, which were penicillins (F, G, K, O, V, X).

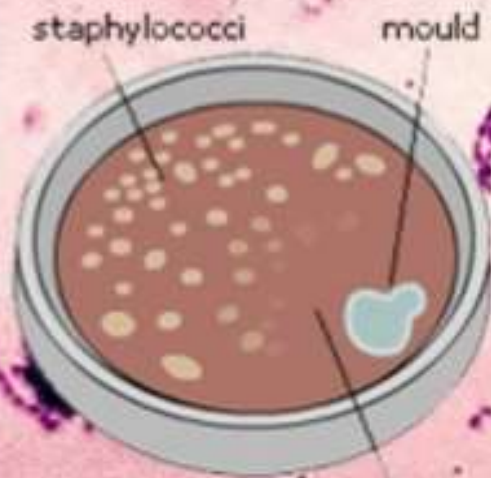


Alexander Fleming



Science

Penicillium



staphylococci

mould

no growth close to mould

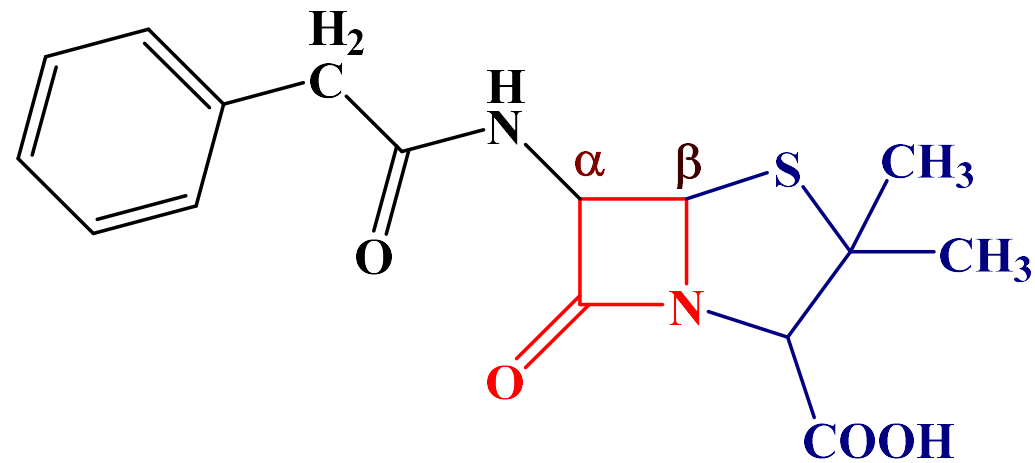
Staphylococcus Bacteria

Penicillium mould
(penicillium notatum)



Penicillin

The first antibiotic to be used in therapy, penicillin (penicillin G or benzylpenicillin), was obtained by fermentation of fungus *penicillium notatum*.



Penicillin G (Benzylpenicillin)

Mechanism of Action

There are many properties contribute to the importance of β -lactam antibiotics in chemotherapy:-

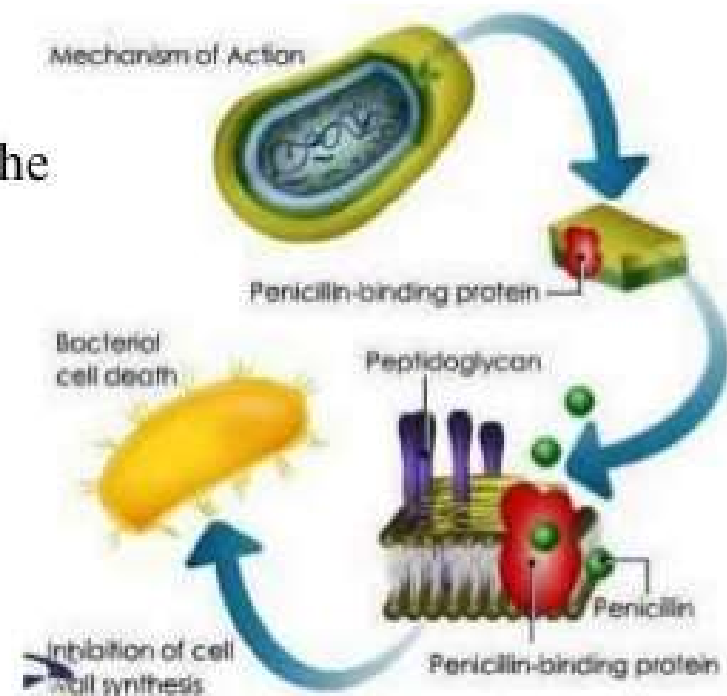
1. A broad spectrum of antibacterial action.
2. A potent and rapid bactericidal action against bacteria in the growth phase.
3. A very low frequency of toxic and other adverse reactions in the host.

MECHANISM OF ACTION

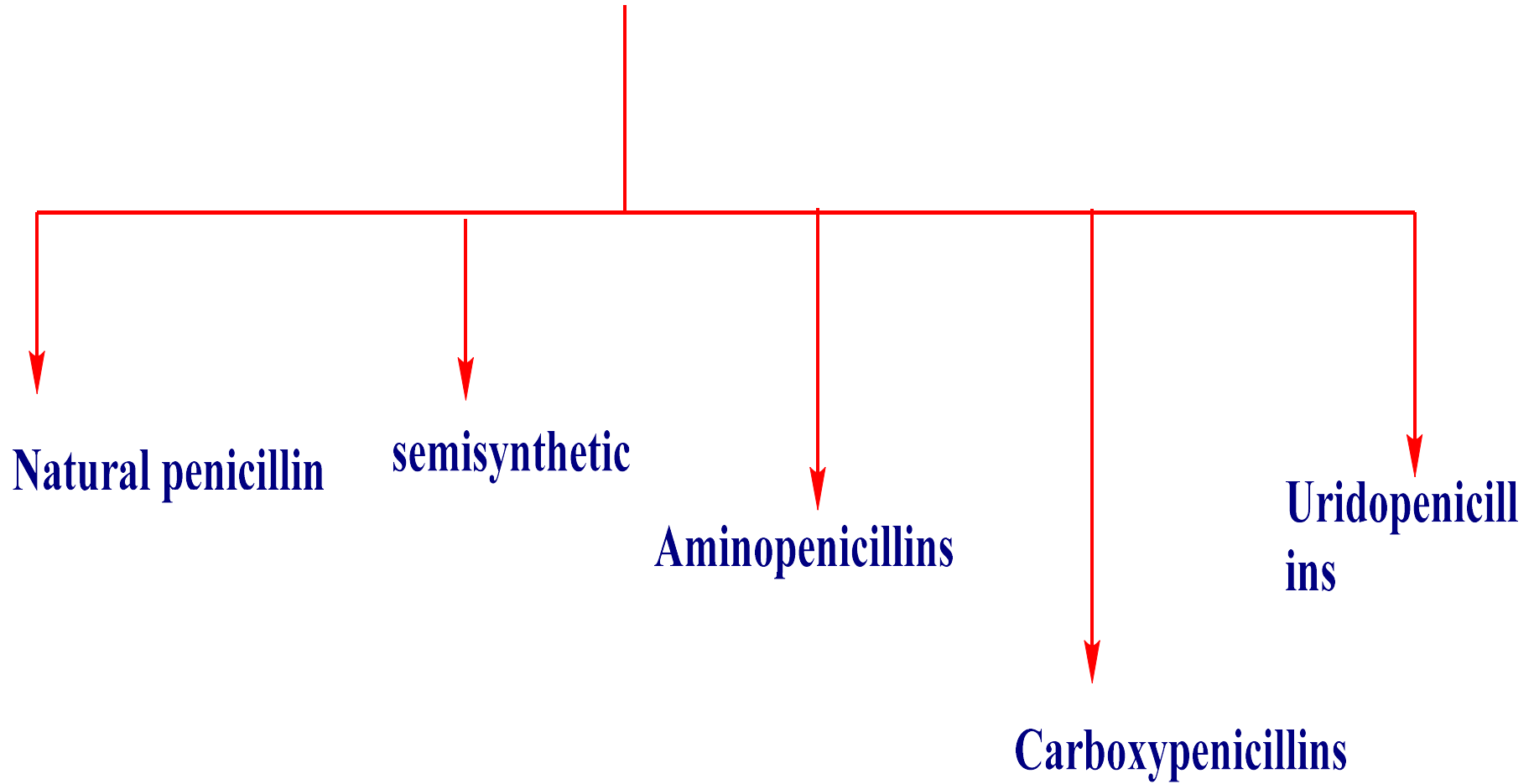
- ❖ Penicillins are **bactericidal** antibiotics as they kill the microorganisms when used at therapeutic dose.
- ❖ The synthesis of cell wall of bacteria is completely depended upon an enzyme named as **transpeptidase**.
- ❖ Primarily, Penicillin inhibits the cell wall of bacteria by blocking transpeptidase after binding to **penicillin-binding protein (PBP)** and prevents its synthesis.

Result: bacteria cells die from cell lysis.

- ❖ Penicillins do not kill other cells in the body.



Five classes of penicillins



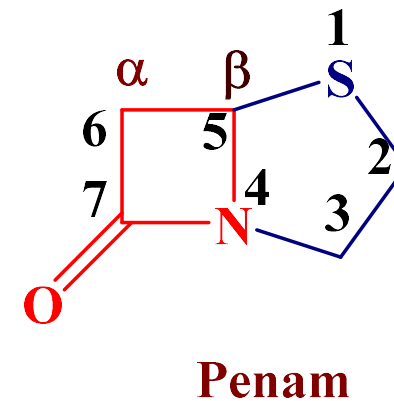
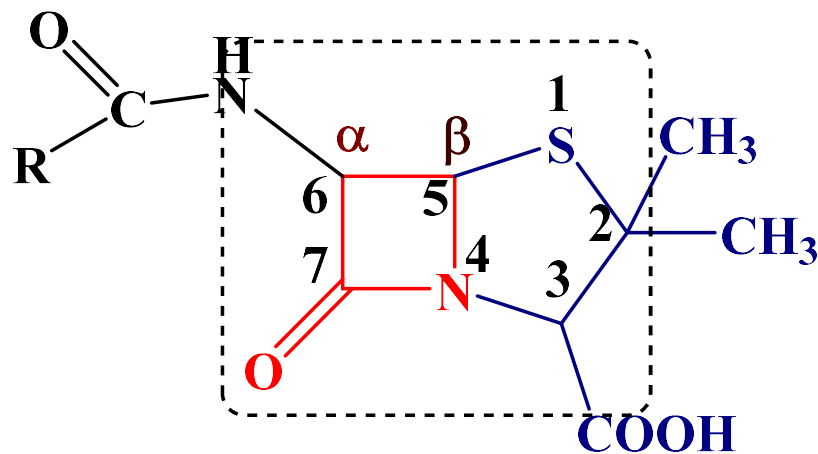
Nomenclature

Nomenclature of penicillins is done to different systems:-

- **Chemical abstract system(CAS):-**

- According to this system penicillins are numbered starting from "S" atom.

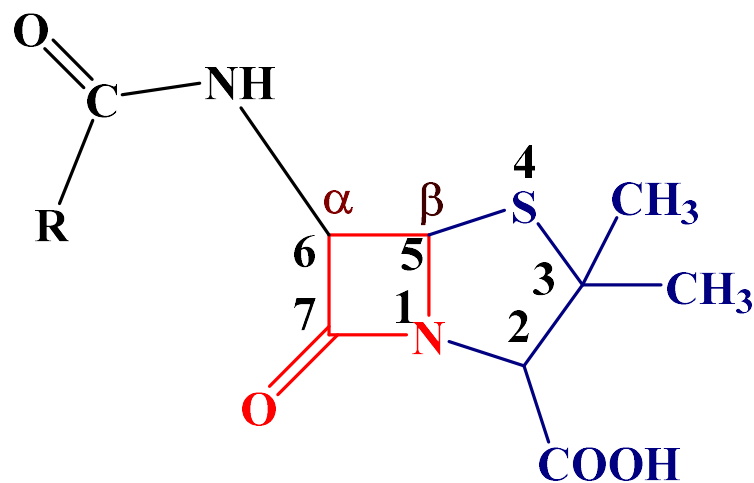
- Sulfur atom is assigned the 1st position and "N" atom is assigned number 4th position and is called 6-acylamino-2,2-dimethyl penam-3-carboxylic acid.



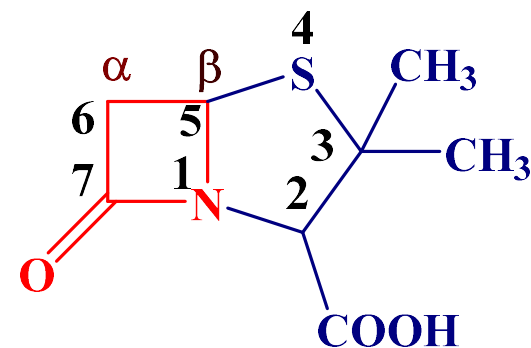
**(4-aza-thiabicyclo[3,2,0]heptane)-7-one
6-acylamino-2,2-dimethylpenam-3-carboxylic acid**

Nomenclature United states Pharmacopoeia (USP system):-

The USP system of naming penicillins is the reverse of CA system. According to this system the nitrogen atom is given the 1st position and "S" atom is assigned the 4th position and is called 4-thia-1-azabicycloheptane.

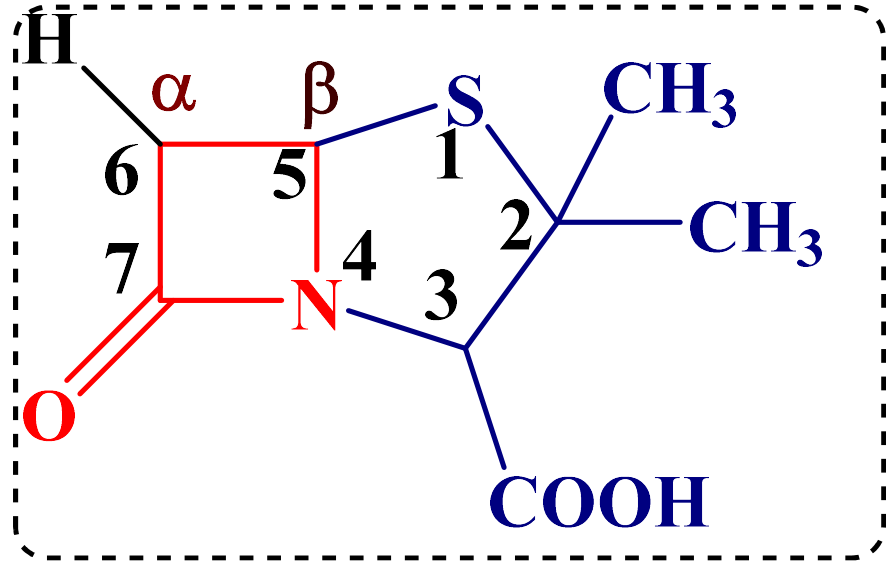


**(4-thia-1-azabicyclo[3,2,0]heptane)-7-one
6-acylamino-3,3-dimethylpenam-2-carboxylic acid**



Penicillanic acid

As a derivatives of penicillanic acid:- According to this method of nomenclature penicillind consists of penicillanic acid ring system with 2,2-dimethyl and carboxyl groups as substituents at positions 2 and 3 respectively.



Penicillanic acid

As derivatives of penicillins (On the basis of R group) This is most trivalof all the naming system.

In this system the entire 6-carboxylamino penicillanic acid (6-carboxyl-APA) portion of the molecule is named as penicillin and the different penicills are distinguished on the basis of the R group on the amino acyl side chain.

