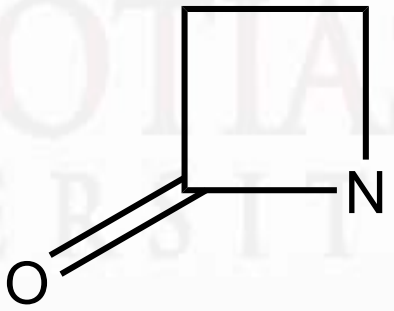
β-Lactam antibiotics

Disclaimer

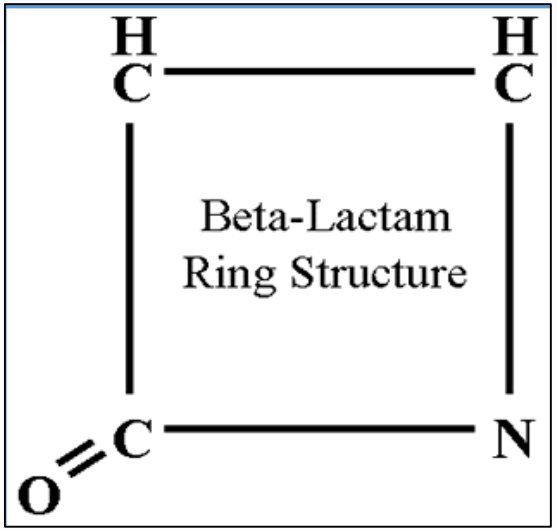
All the content material provided here is only for teaching purpose.

Introduction

- The name "Lactam" is given to cyclic amides and is analogous to the name "Lactone" which is given to cyclic esters .
- Antibiotics that contains the β-lactam (a four membered cyclic amide) ring structure constitute the dominant class of agent currently employed for the chemotherapy of bacterial infections.
- β-Lactam antibiotics are the most widely produced and used antibacterial drugs in the world, and have been ever since their initial clinical trials in 1941.



HISTROICAL BACKGROUND



- The first synthetic β-Lactam was prepared by HERMANN STAUDINGER in 1907 by reaction of the schiff base of aniline and benzaldehyde with diphenylketone in a cycloaddition.
- Upto 1970, most β-Lactam research was concerned with the penicillin and cephalosporin groups, but since then a wide variety of structures have been described.

History

1928- Alexander Fleming discovers a mold which inhibits the growth of staphylococcus bacteria

1940- penicillin is isolated and tested on mice by researchers at Oxford

1941- penicillin mass produced by fermentation for use by US soldiers in WWII

1950's- 6-APA is discovered and semi-synthetic penicillins are developed.

1960's to today- novel β-lactams/ β-lactamase inhibitors are discovered and modified from the natural products of bacteria

BETA-LACTAM ANTIBIOTICS
(inhibitors of cell wall synthesis)

- **Their structure contains a beta-lactam ring.**

The major subdivisions are:

(a) **penicillins** whose official names usually include or end in "cillin"

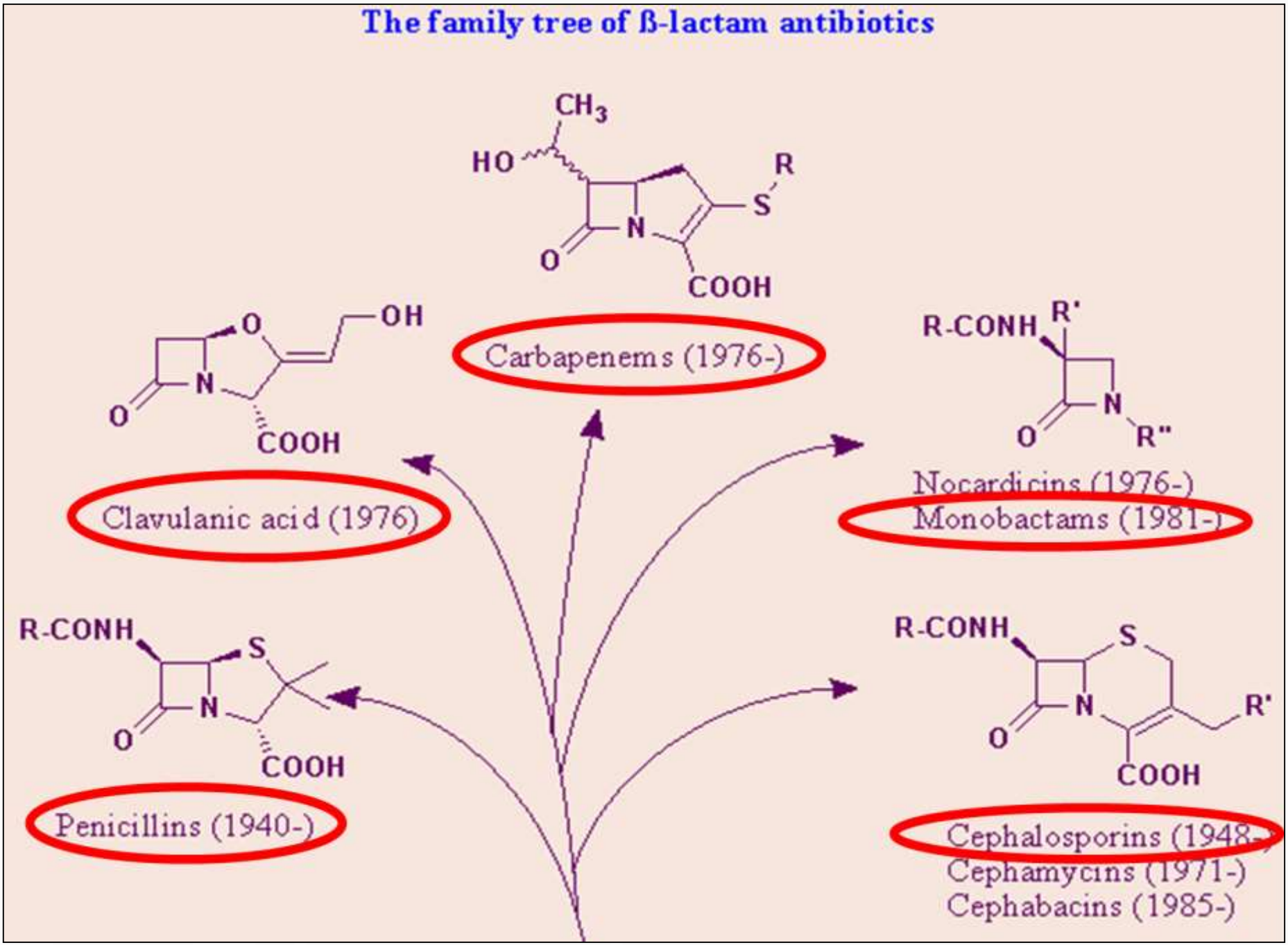
(b) **cephalosporins** which are recognized by the inclusion of "cef" or "ceph" in their official names.

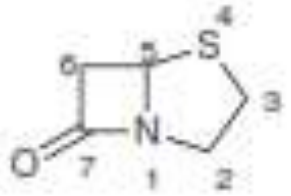
(c) **carbapenems** (e.g. meropenem, imipenem)

(d) **monobactams** (e.g. aztreonam)

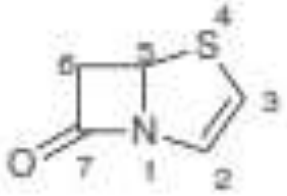
(e) **beta-lactamase inhibitors** (e.g. clavulanic acid, sulbactam).

The family tree of ß-lactam antibiotics

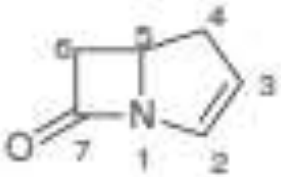




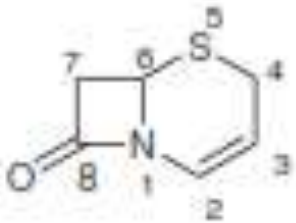
Penam
(4-Thia-1-azabicyclo-
[3.2.0]heptane)-7-one



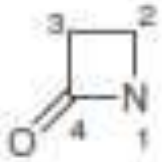
Penem
(4-Thia-1-azabicyclo-
[3.2.0]hept-2-ene)
-7-one



Carbapenem
(1-Azabicyclo[3.2.0]-
hept-2-ene)-7-one



Celem
(5-Thia-1-azabicyclo-
[4.2.0]oct-2-ene)-8-one



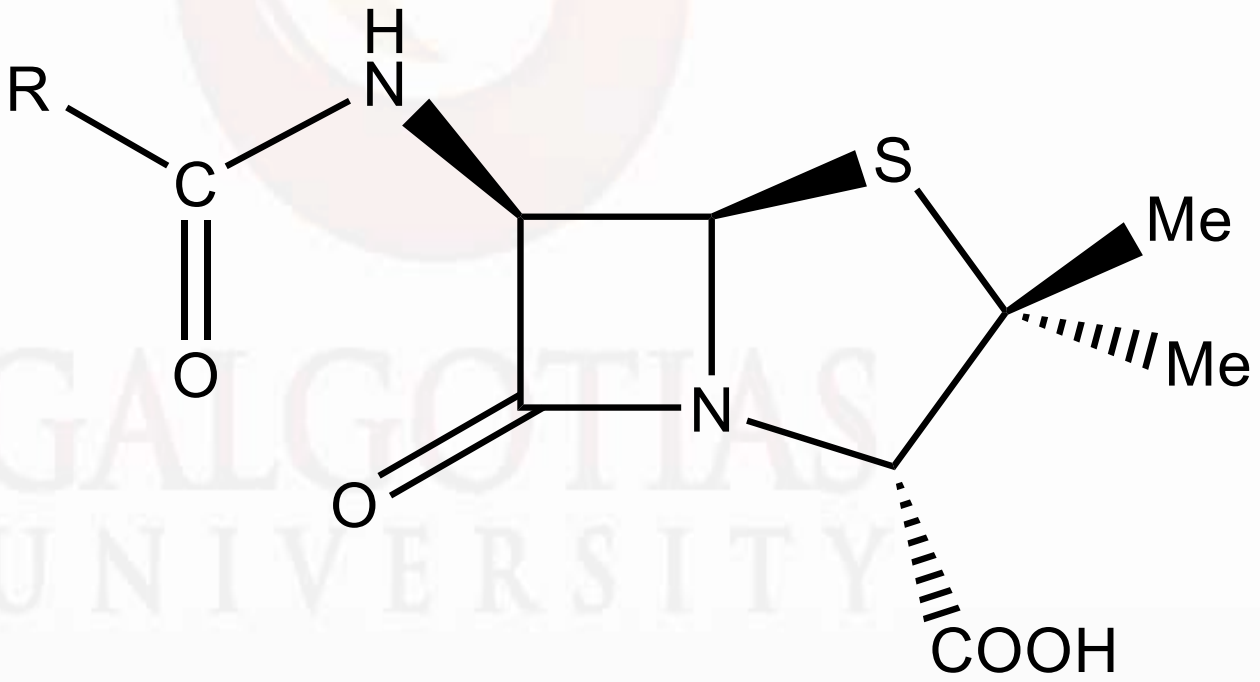
Monobactam
(1-Azacyclobutan-4-one)

FIGURE 33.12 Ring and numbering systems of clinically available β-lactam antibiotic types.

Classes of β-Lactams

The classes of β-lactams are distinguished by the variation in the ring adjoining the β-lactam ring and the side chain at the α position.

Penicillin



Modification of β-Lactams

β-Lactam type antibiotics can be modified at various positions to improve their ability to:

-be administered orally (survive acidic conditions)

-be tolerated by the patient (allergies)

-penetrate the outer membrane of Gram (-) bacteria

-prevent hydrolysis by β-lactamases

-acylate the PBPs of resistant species (there are many different PBPs)

PENICILLINS

- The penicillins were the first antibiotics discovered as natural products from the mold Penicillium.
- 1928 - Sir Alexander Fleming, professor of bacteriology at St. Mary's Hospital in London, was culturing Staphylococcus aureus. He noticed zones of inhibition where mold spores were growing. He named the mold *Penicillium rubrum*. It was determined that a secretion of the mold was effective against Gram-positive bacteria.
- It was isolated from fungus Penicillium notatum.
- Florey and Chain isolated penicillin by freeze drying and chromatography.
- Penicillin was effective even when it is diluted up to 800 times.

Science

Penicillium mould
(penicillium notatum)

www.sciencepradeep.com

Historical background of penicillins

- It was in 1928 when Alexander Fleming observed while experimenting on influenza virus that a common fungus inhibiting the growth of organism.
- It was a Serendipitous observation(fortuitous accident) i.e (happening by chance) in his laboratory in the basement of St. Mary's Hospital in London (now part of imperical college).
- On Friday, September 28, in 1928, Fleming left the lid off of one of his Petri dishes for several weeks, and a fungal spore landed on it (the culture became contaminated). After returning from vacation, Fleming noticed that his *Staphylococcus* culture was contaminated with this fungus but instead of throwing the Petri dish away, he **carefully examined it first**.
- There was an inhibited bacterial growth around the mould. Fleming concluded that the mould (fungal colony) was releasing a antibacterial substance which was spreading into the surrounding area where the bacterial colonies were dying. i.e. lysing the bacteria.

Historical background of Penicillins

- He grew a pure culture and discovered that it was a *Penicillium* mould, now known to be *Penicillium notatum.*
- Penicillium mould must be secreting an antibacterial substance, which he isolated first in crude form of the active substance and named it as penicillin.
- Unfortunately, the substance was also **unstable and Fleming was unable to isolate and purify the compound**. He therefore came to the conclusion that penicillin was too unstable to be used clinically.
- **Florey and Chain in 1938** by using processes such as **freeze-drying and chromatography** which allowed isolation of pure form of penicillins.
- Fleming, Florey, and Chain shared the **1945 Nobel Prize** for their medicinal work on penicillin.
- In june 1942 availability of penicillin was just to treat 10 patients.
- After fermentation research 2.3 million doses had been increased in U.S.

Chemistry

- Penicillin nucleus consists of
  - Thiazolidine ring (Ring A) - Sulphur containing with COOH (Carboxyl group).
  - Beta lactam ring (Ring B) – **(Broken by Beta-lactamase)**

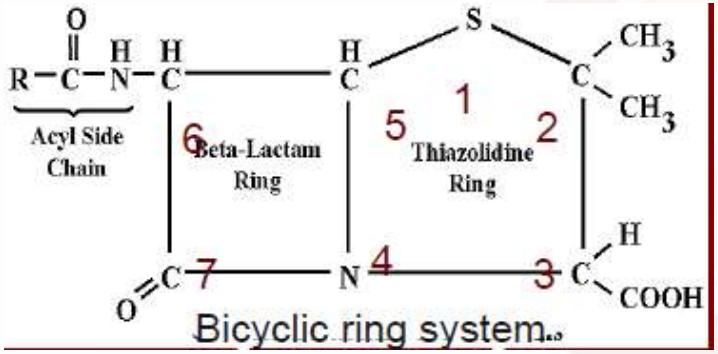
    Side chain is attached at position – 6- (NHCOR)
  - Side chains attached through amide linkage. **(Broken by Amidase)**
  - Beta Lactam ring is broken by –
    - Penicillinase (Beta Lactamase), and by gastric acid.
    - Resultant Product is Penicilloic acid with **No anti-bacterial activity but Acts as antigenic determinant (Major determinant)**

Nomenclature of Penicillins

Nomenclature of penicillins was done in different systems.

Chemical abstract system(CAS):

•According to this system penicillins are numbered starting from "S" atom. Sulphur atom is assigned the 1st position and "N" atom is assigned number 4.

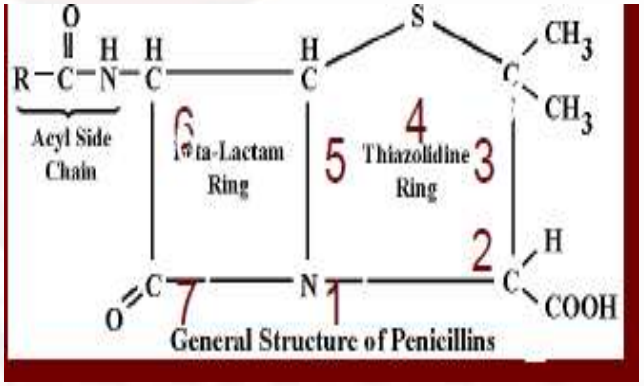


6- Acyl amino-2,2-dimethyl-3- carboxylic acid

United States Pharmacopoeia (USP system):

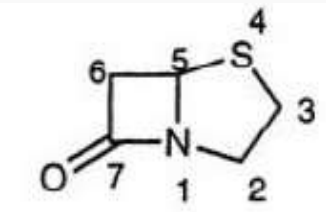
•The USP system of naming penicillins is the reverse of CAS.

•According to this system the nitrogen atom is given the 1st position and "S" atom is assigned the 4th position.



4-thia-1-azabicyclo [3.2.0] heptane

As derivatives of Penam:
Unsubstituted bicyclic system together with amide corbonyl group has been named as penam. According to this method penicillins are named as 4-Thia-1-azabicyclo[3.2.0] heptane-7-one.

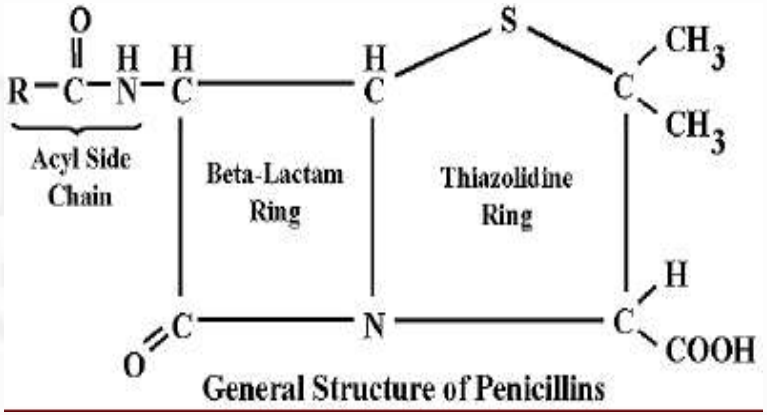


Penam
(4-Thia-1-azabicyclo-[3.2.0]heptane)-7-one

4. **As derivatives of penicillanic acid**:
In this method penicillins are named as derivatives of penicillanic acid ring system with 6- acyl amino -2,2-dimethyl penam -3- carboxylic acid.

5. **As derivatives of penicillins (on the basis of "R" group) … TRIVAL SYSTEM**
In this system 6-corbonyl amino penicillanic acid portion of the molecule is named as penicillin and the different penicillins are distinguished on the basis of "R" group on the acyl amino side chain.

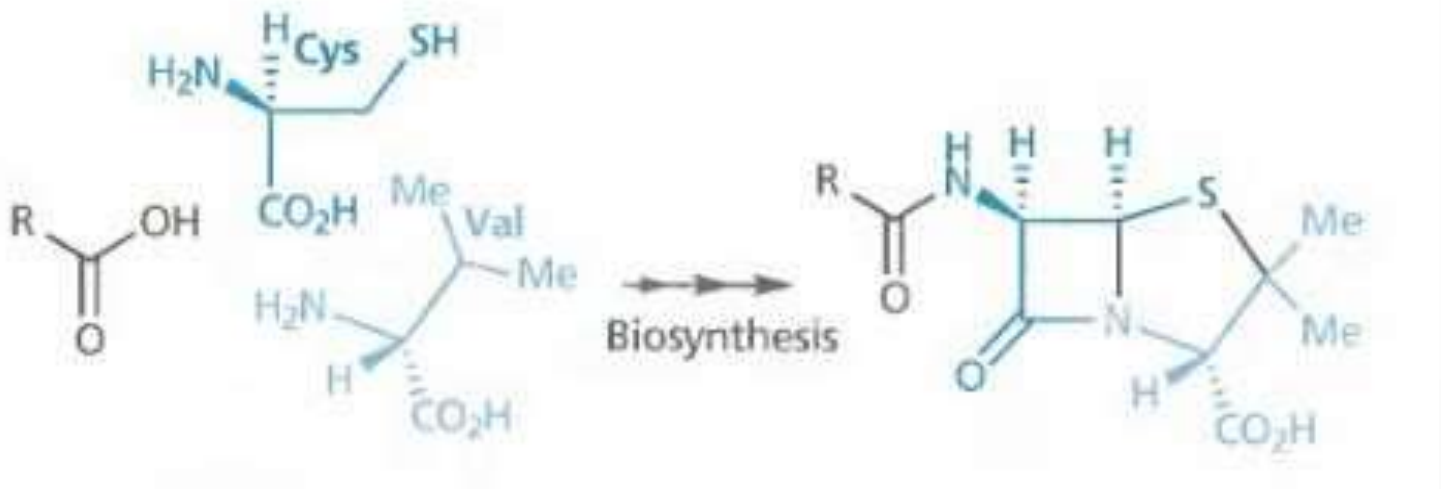
This system of naming of penicillins is simple and serves as a good measure for naming and comparing closely related penicillin structures. However this system is not well suited for compounds having the ring Modified Derivatives.



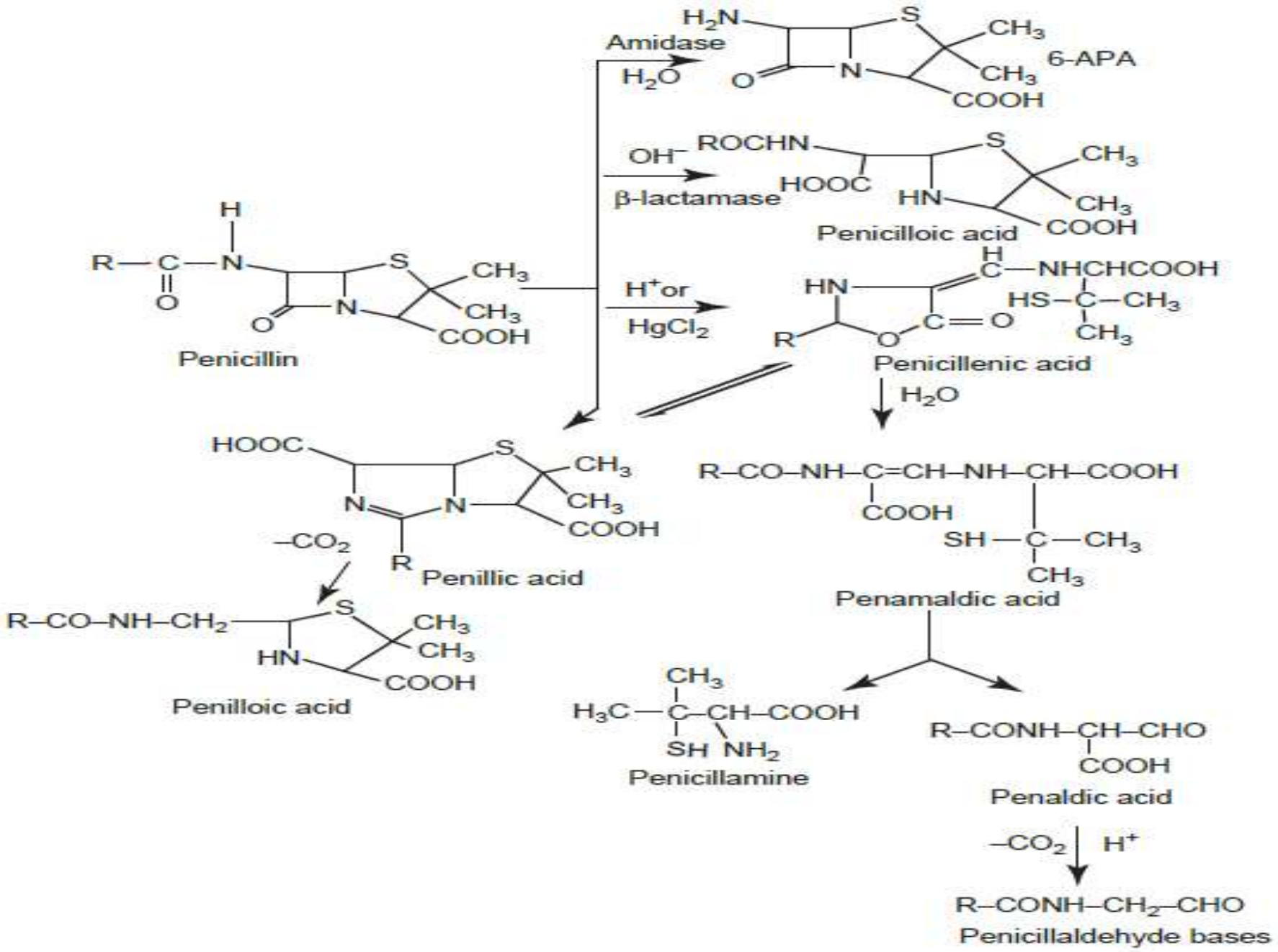
General Structure of Penicillins

Stereo chemistry

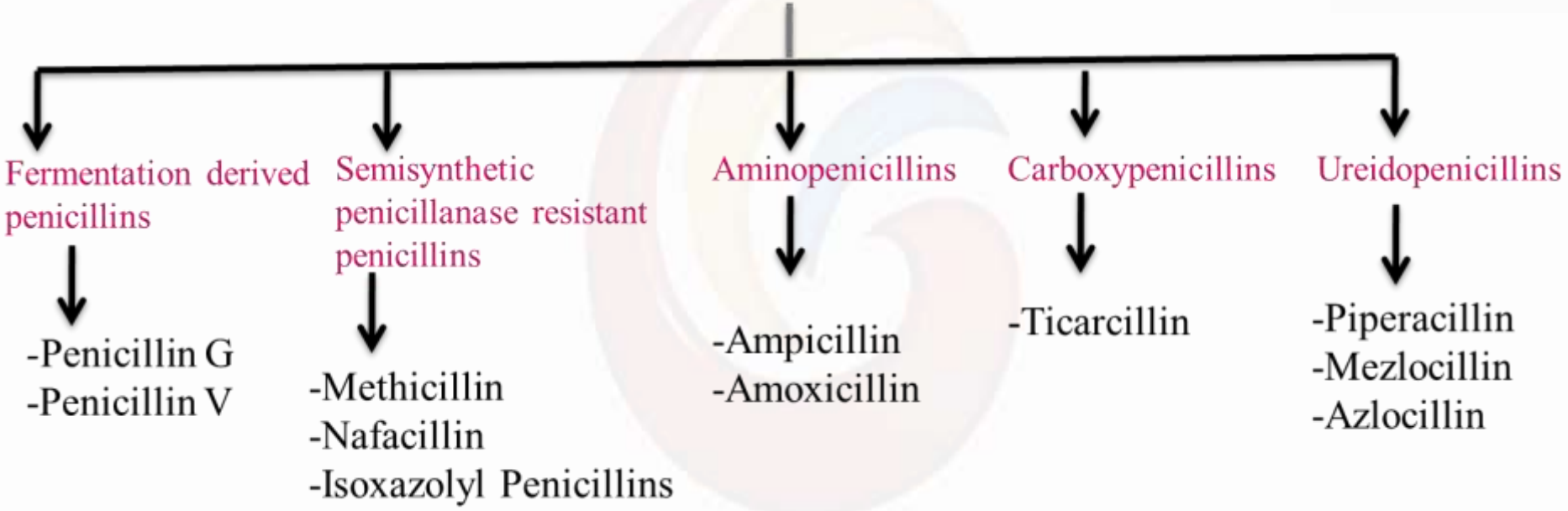
- The penicillin molecule contains three chiral carbon atoms at C-3, C-5 and C-6.
- All natural and synthetic penicillins have the same absolute configuration about these three centers.
- The 6th carbon atom bearing the acyl amino group has the L-configuration, where as the carbon to which the carboxyl group was attached has the D-configuration.
- Thus the acyl amino group and carboxyl group are trans to each other, with the former α and latter in the β orientation relative to penam ring.
- The absolute stereochemistry of the penicillins was designated as 3S:5R:6R.
- The atoms composing the 6-aminopenicillanic acid are biosynthetically derived from two amino acids, L-cysteine and D-valine.

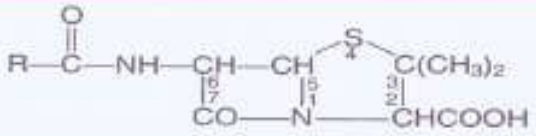


CHEMICAL DEGRADATION



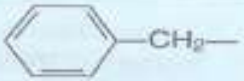
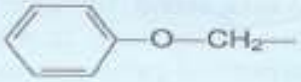
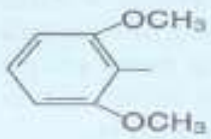
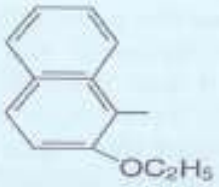
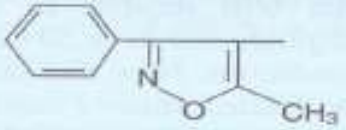
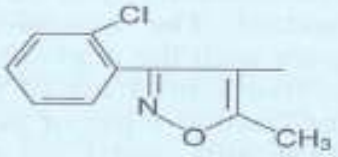
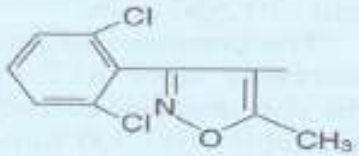
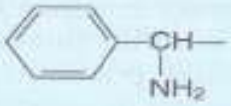
Classification of Penicillins

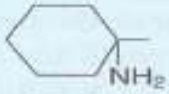
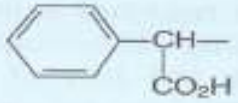
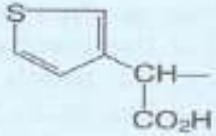
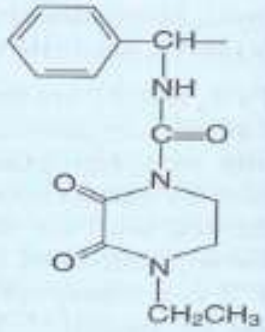
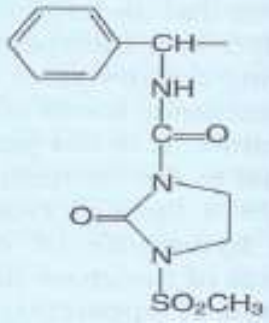




STRUCTURE

OF PENICILLINS

Generic Name	Chemical Name	R Group
Penicillin G	Benzylpenicillin	
Penicillin V	Phenoxymethylpenicillin	
Methicillin	2,6-Dimethoxyphenyl-penicillin	
Nafcillin	2-Ethoxy-1-naphthyl-penicillin	
Oxacillin	5-Methyl-3-phenyl-4-isoxazolylpenicillin	
Cloxacillin	5-Methyl-3-(2-chlorophenyl)-4-isoxazolylpenicillin	
Dicloxacillin	5-Methyl-3-(2,6-dichlorophenyl)-4-isoxazolylpenicillin	
Ampicillin	D-α-Aminobenzyl-penicillin	

Generic Name	Chemical Name	R Group
Amoxicillin	D-α-Amino-*p*-hydroxybenzylpenicillin	
Cyclacillin	1-Aminocyclohexyl-penicillin	
Carbenicillin	α-Carboxybenzyl-penicillin	
Ticarcillin	α-Carboxy-3-thienyl-penicillin	
Piperacillin	α-(4-Ethyl-2,3-dioxo-1-piperazinylcarbonyl-amino)benzylpenicillin	
Mezlocillin	α-(1-Methanesulfonyl-2-oxoimidazolidino-carbonylamino)benzyl-penicillin	

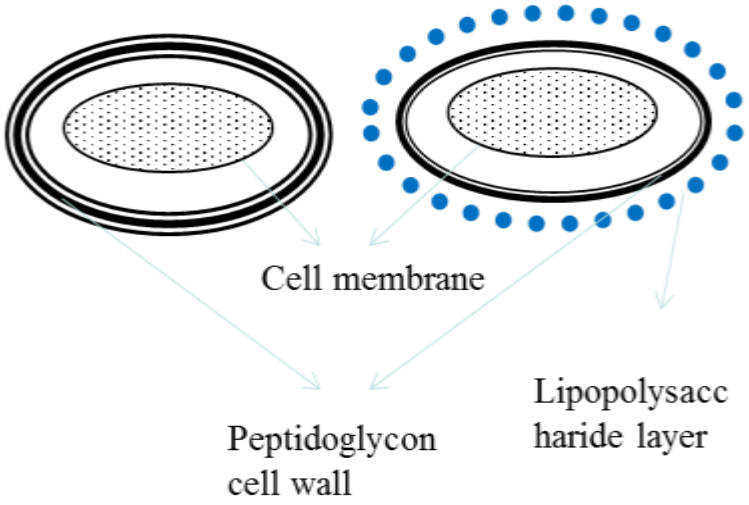
Mechanism of action

Antibiotics

Bacteristatic

Bactericidal

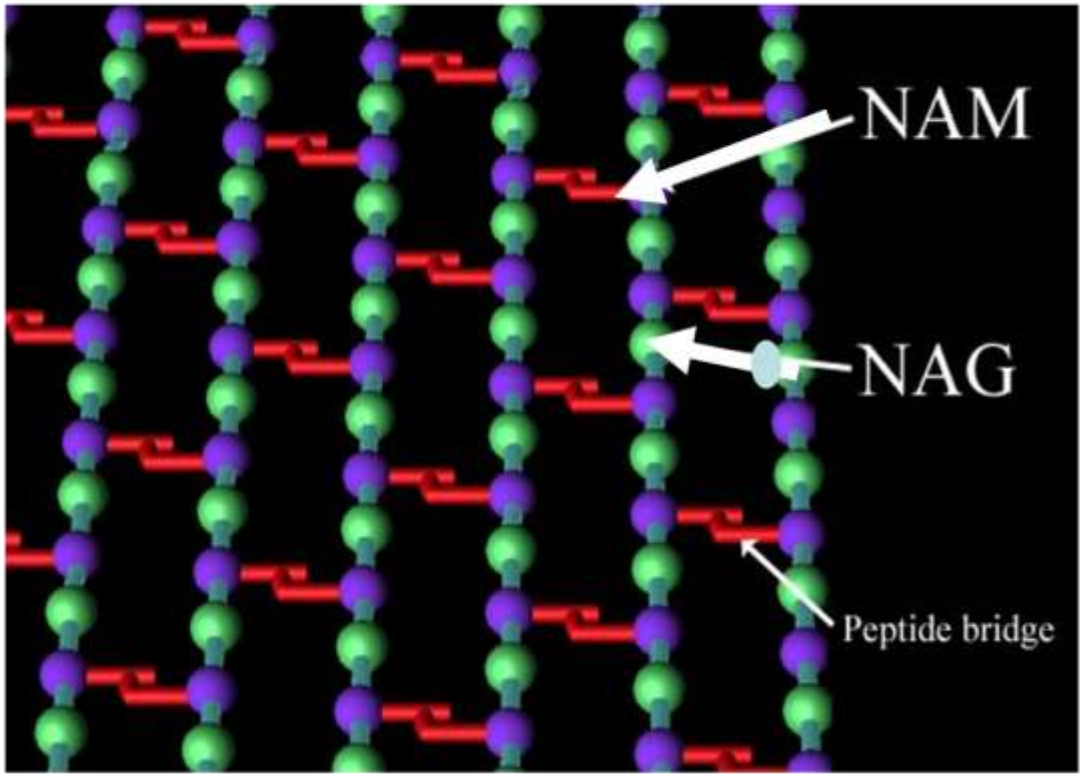
Penicillins



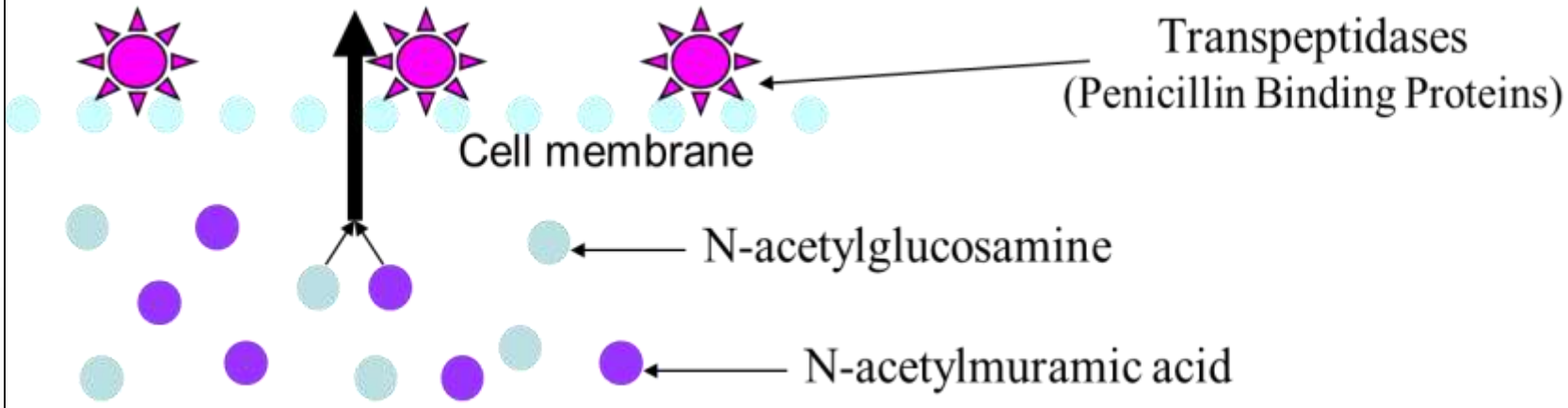
Inhibit the synthesis of peptidoglycon layer containing NAM &NAG connected by penicillin binding proteins(PBP)

Acts on PBP and inhibits the synthesis of Peptidoglycon.

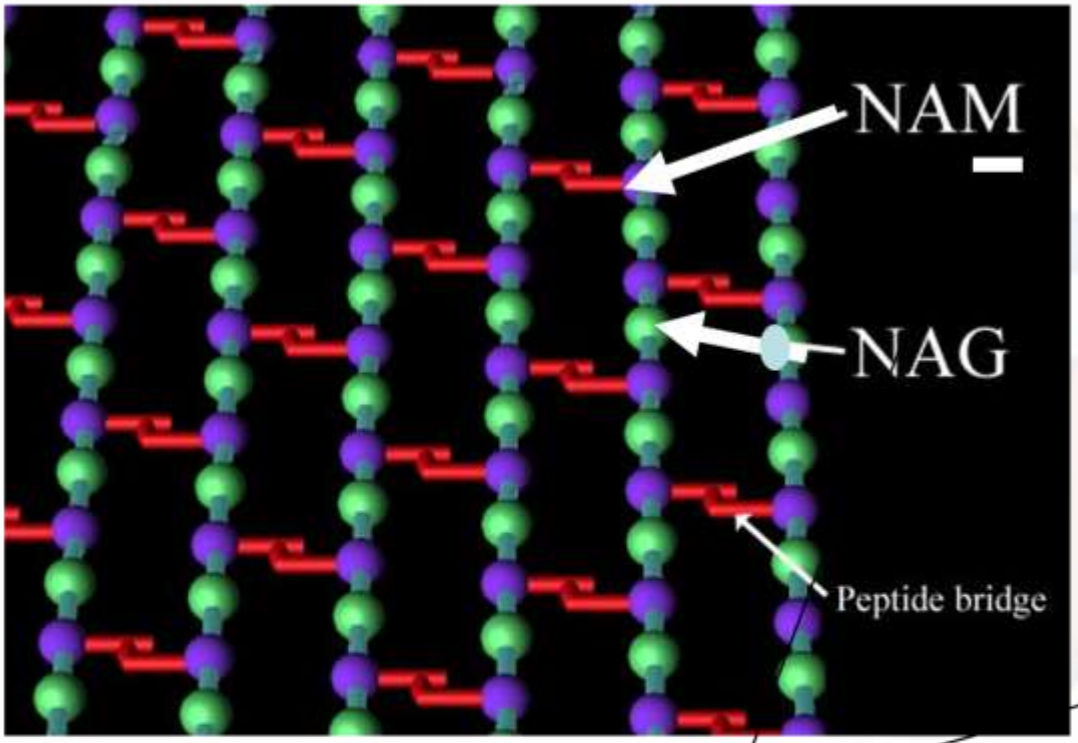
(Peptidoglycan cell wall)



- Transpeptidases located with in the cell membrane are responsible for cross linking the Peptidoglycan chains
- In order to make the rigid grid, There is an enzyme called Transpeptidase,which connects the Little peptide strings perpendicular to the NAM and NAG chains.



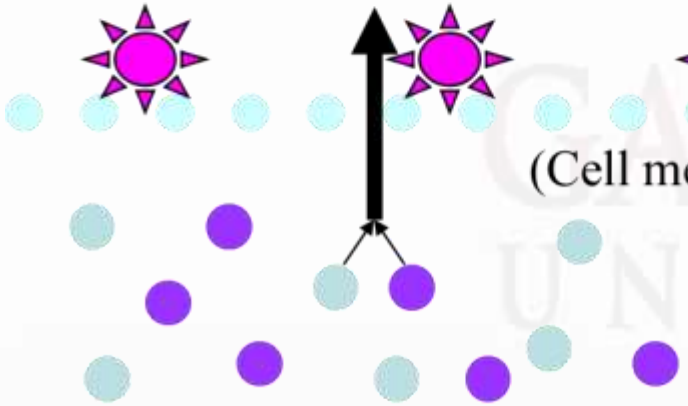
(Peptidoglycan cell wall)

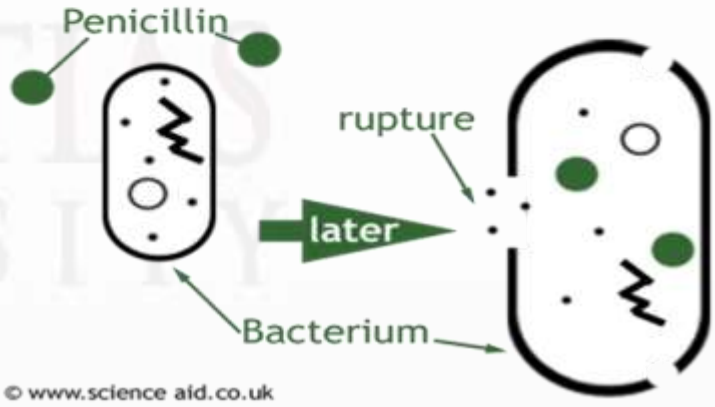


Penicillin's inactivate the transpeptidase enzyme by covalently bonding to the serine residues within the active site.

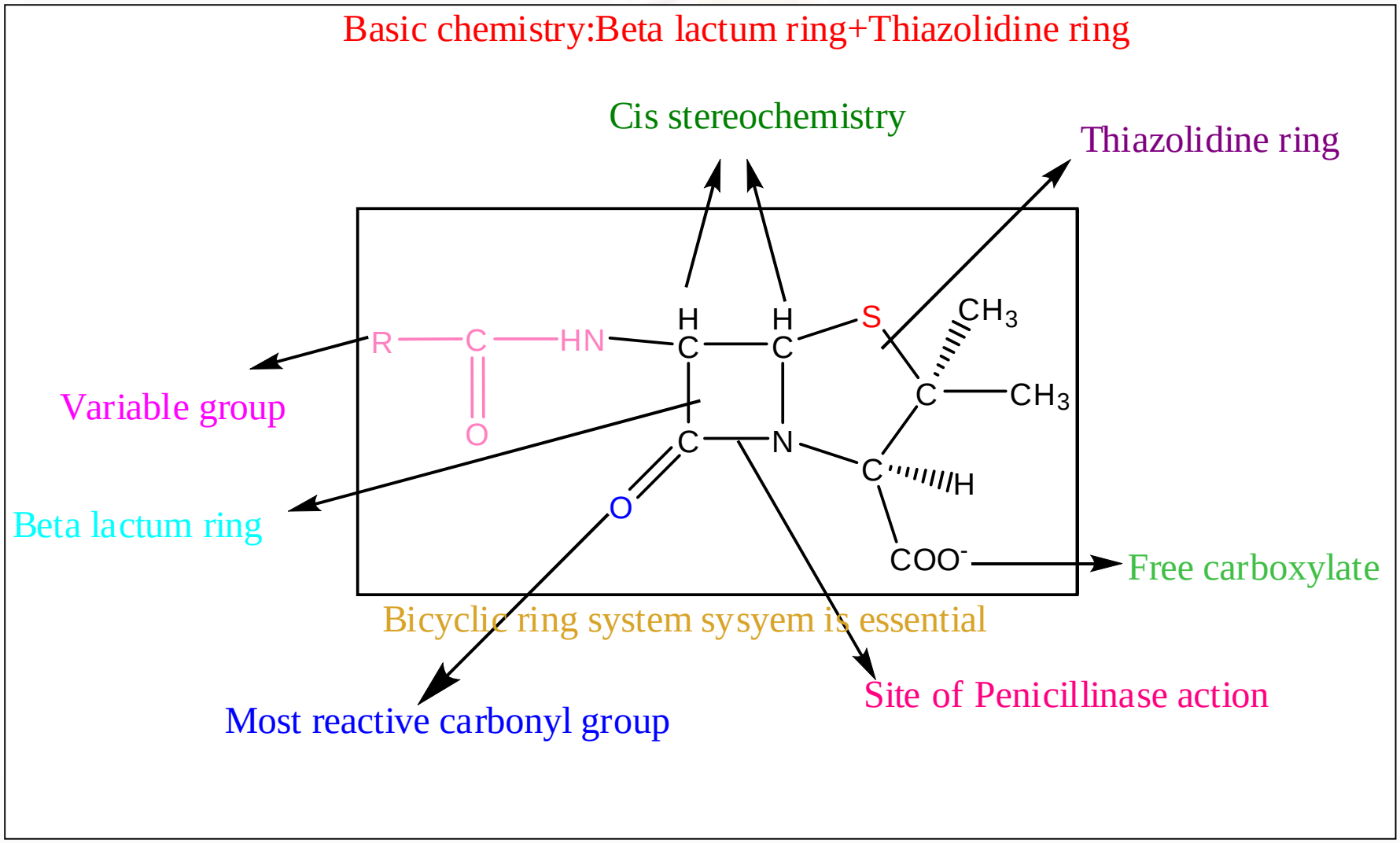
Bonding is by acetylation

Transpeptidases
(Penicillin Binding Proteins)





BASIC STRUCTURE OF PENICILLIN



Penicillins are….

a group of antibiotics that contain 6-amino penicillanic acid side chain attached to the 6-amino group.

•The penicillin nucleus is the chief structural requirement for biological activity.

•The side chain structure determines the many of the antibacterial and pharmacological characterstics.

•The strained β-lactum ring is essential.

•Penicillin contains β-lactum ring is fused with thiazolidine ring.

•The free carboxylic acid is essential. The carbolated ion is binds to the charged ammonium ion of lysine residue in the binding site.

•The bicyclic system is important. The greater the strain, the greater the activity.

•The acyl amino side chain is essential.

•Sulfur is usual but not essential.

•The cis- stereo chemistry of bicyclic ring with respect to the acyl amino side chain is important.

•Oxidation of sulphur to a sulfone or sulfoxide will decrease the activity.

•The methyl groups at position 2 are essential.

•β- lactum corbonyl group at position “7” is must.

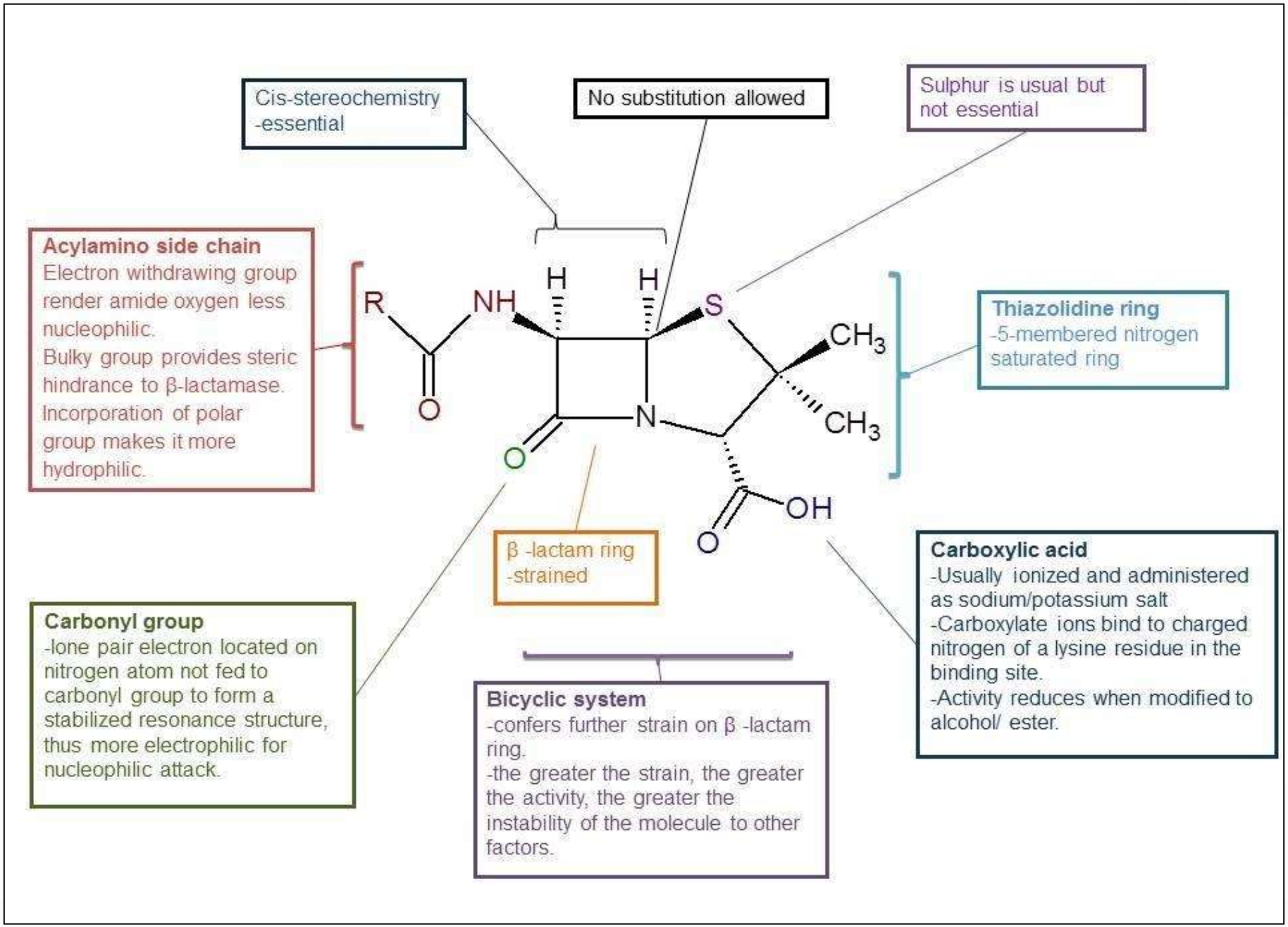
•The carboxylic acid is changed to an alcohol or ester activity is decreased.

•“N” at position 4 is must for antibacterial activity.

•Penicillin molecule contains a ‘3’ chiral carbon atome c-3,c-5,c-6. Disruption of

•These spacial arrangements results in loss of activity.

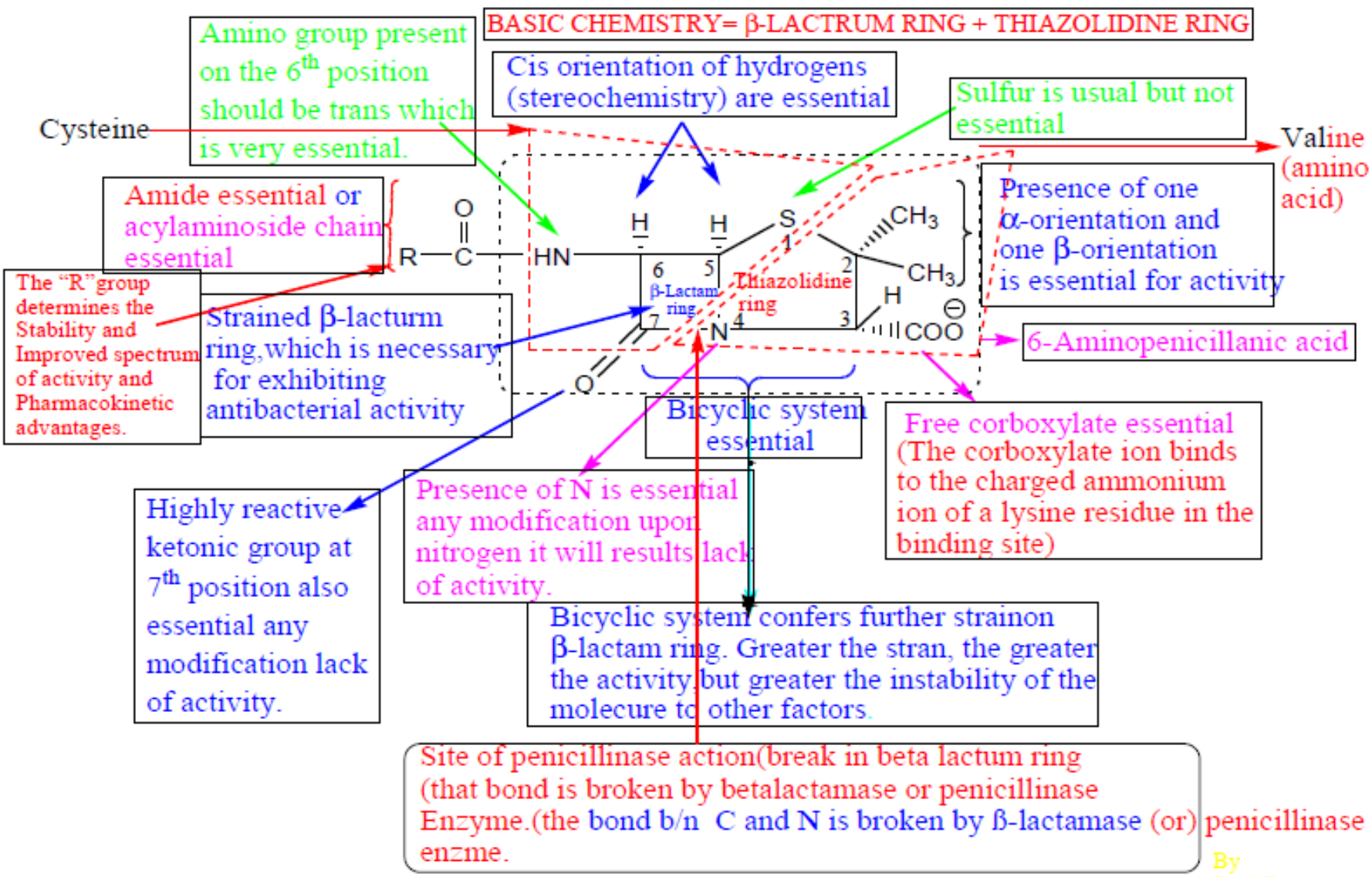
STRUCTURAL ACTIVITY RELATIONSHIP



STRUCTURE - ACTIVITY RELATION SHIP (SAR) OF PENICILLINS

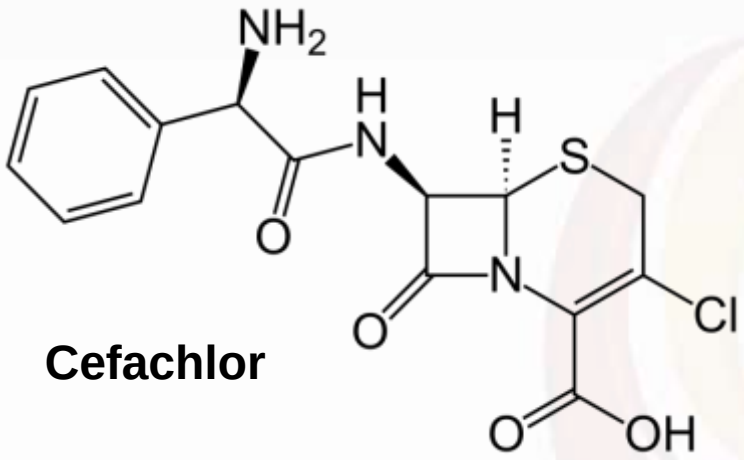
GENERAL STUCTURE OF PENICILLIN OR PENICILLIN CORE STRUCTURE
PENICILLIN NUCLEUS OR BASIC STRUCTUREOF PENICILLIN

BASIC CHEMISTRY= β-LACTRUM RING + THIAZOLIDINE RING

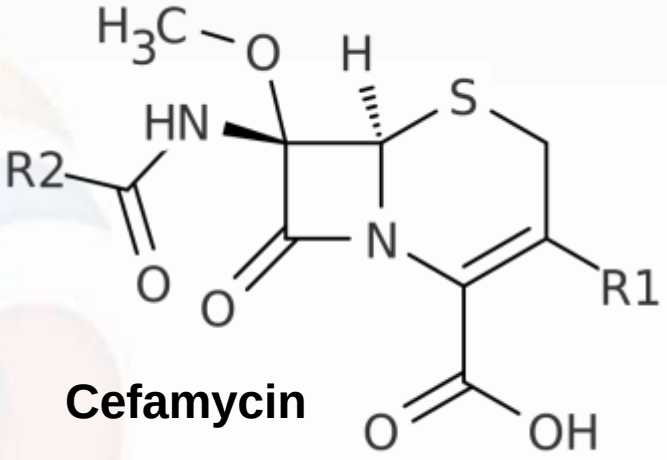


By
Prof. Ravisankar

2nd Generation Cephalosporins

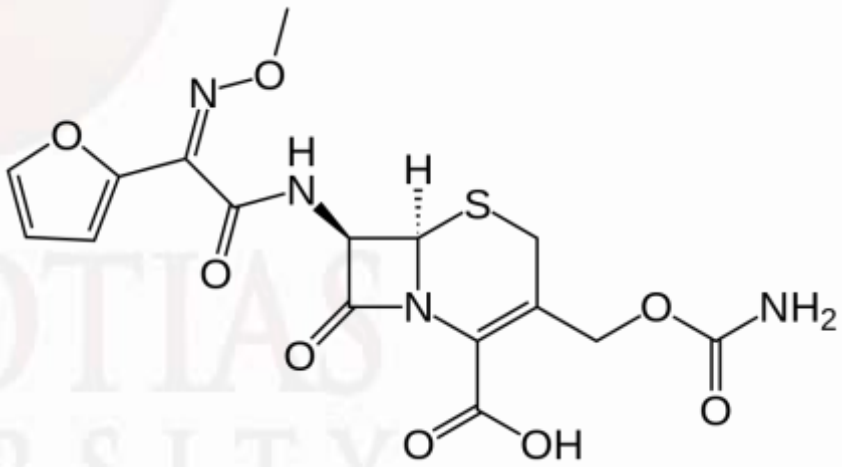


Cefachlor



Cefamycin

- They have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria.
- They are also more resistant to *β-lactamase.*
- **No BBB Penetration.**



Cefuroxime

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