# ANTI-BIOTICS

→ Derived from word 'anti-biosis'

↓

means 'against life'

→ Natural produced substances which inhibit the growth of microorganism and kills them.

## Historical Background

→ first antibiotic used by Ancient Chinese. They discover moldy soybeans to treat pimples.

→ began in 1890, Rudolph emmerich and oscar law discover first Anti-biotic, pyocynase used to treat cholera and typhus.

→ In 1877, french biologist Louis pasteur and Jules francois Joubert. Anthrax bacilli were killed when some bacteria grow in culture.

→ In 1909, Paul ehrlich discover arsenic based drug 'salvarson' which kills treponema pallidum (syphills)

→ In 1932, first commericially available anti-biotic was protosil.

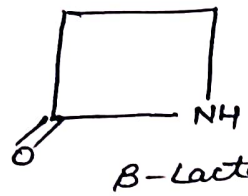
→ In 1928, Alexender flaming discover penicillin

→ In 1945, Alexender flaming get Nobel prize in 'physiology and Medicine'.

→ End of 1940 and early 1950, use of Streptomycin and Tetracycline was discovered for tuberculosis.

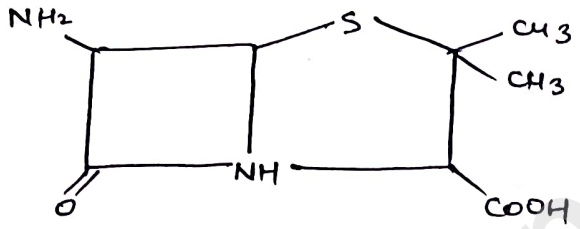
# β - Lactam Anti-biotics

→ β - Lactam ring is present




β-Lactam ring

→ 4 membered ring in which N act as heterogeneous atom and a ketonic group present



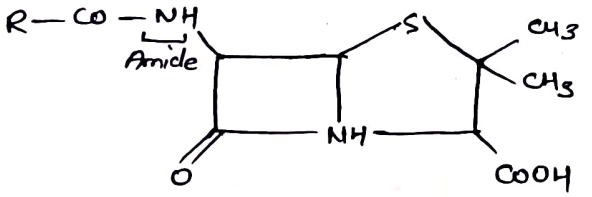

Penicillinoic Acid

→ If S atom containing ring can be additionally fused in β- Lactam ring with 2 Methyl groups and one carboxylic Acid group called penicillinoic Acid.

Beta - Lactams

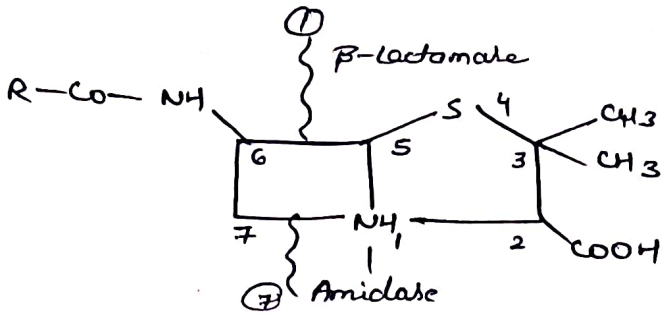
- Penicillin
- Cephalosporins
- β-Lactamase enzyme inhibtors
- Monobactams

## PENICILLIN




[General Penicillin Ring]

- first Anti-biotic
- discover by Alexender flaming in 1929.

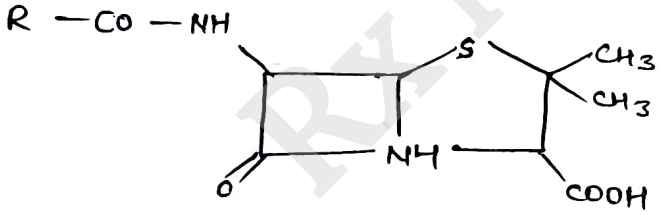



→ β- Lactamase enzyme secreted by bacteria when we take anti-biotic to fight with drug and may breaks bond between 5 and 6 C of ring and may inactivates with Action.

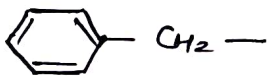
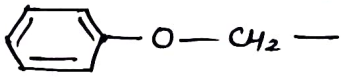
→ When Antibiotic taken, to fight with drug, the bacterias also secrete amidase enzyme that breaks bond between 1 and 7th C of ring and inactivate the action.

→ Bond actions can decrease or ineffect the efficacy of Structure.

## CLASSIFACTION

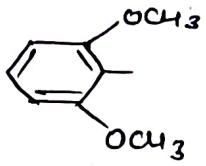



General Structure

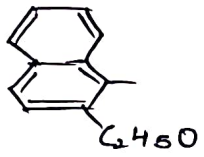
| Name of drugs | R |
|---|---|
| **1. Natural Penicillin** | |
| Aminopenicillanic Acid | H |
| Benzyl penicillin (Penicillin-G) |  |
| Phenoxymethylpenicillin (Penicillin-V) |  |

2. Semi-Synthetic – Parenteral

Methicillin




Nafcillin

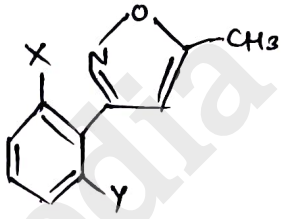



3. Semi Synthetic – Oral

Oxacillin (X, Y = H)

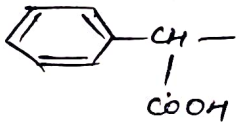
Cloxacillin (X = Cl, Y = H)

Dicloxacillin (X, Y = Cl)

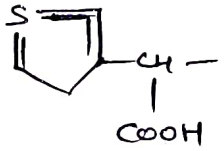



4. Semi Synthetic – Broad spectrum parenteral

Carbenicillin



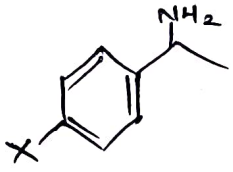

Ticarcillin




5. Semi Synthetic – Broad Spectrum oral

Ampicillin (X = H)

Amoxycillin (X = OH)

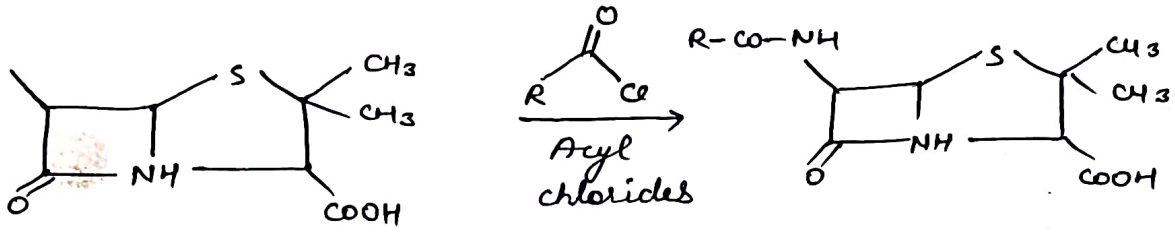



## SYNTHESIS

→ Penicillin is prepared by fermentation process.

→ It can be prepared by isolation of 6-amino penicillonic Acid [6-APA] from fermentation media.

→ It can be done with Chemical Reaction with Acyl chlorides.




6-APA

Penicillin

## MECHANISM OF ACTION

PBP – Penicillin Binding Protein

They are responsible for cross linking during synthesis of peptidoglycon which provide strength to the bacterial Cell

Penicillin binds with PBP

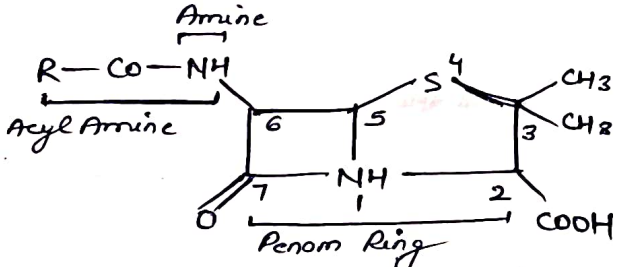
↓

Interfare with synthesis of peptidoglycon

↓

Leakage of Cell wall and Cell death.

## STERIOCHEMISTRY




→ 2S, 5R, 6R Configuration

→ Acylamine group – α to Penam ring ] C2 – L Configuration

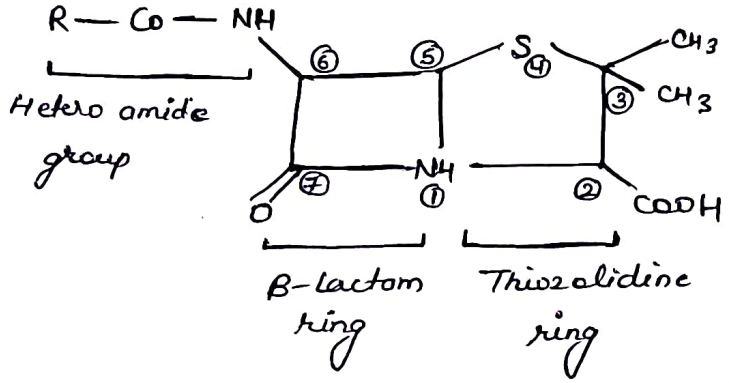
→ Carboxy group – β to Penam ring ] C6 – D Configuration

→ Dexorotatory

→ pka Value – 25–30

→ Penicillins are Amino Acid derivatives — L-cysteine, L-valine

## STRUCTURE ACTIVITY RELATIONSHIP [SAR]




1. The penicillionic Acid ring is essential for Activity.
2. The β- Lactam and Thiozoladine ring is essential for the Activity.
3. At position 2, the carboxy Group (COOH) is essential for activity.
4. At position 4, sulphur also essential for activity.
5. At position 3, 2 methyl group is essential, also can be replaced with more active ring or compounds
6. At position 7, the ketonic group is essential for its Activity.
7. At position 3, if the branching of C can be done, the activity decreases due to more Sterric hyndrense.

8. On N of Heteroamide group, if branched or EWG can be attached, activity increases.

↓

They prevent β- Lactamase enzyme attack from bacteria by clouds formation of branches and increased the stability.

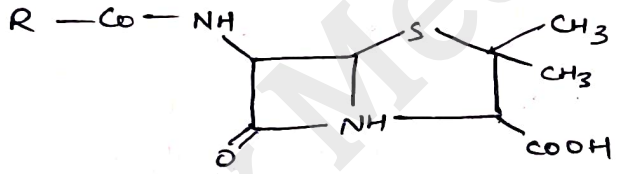
9. In heteroamide group, on R group, the substitution of long chain or bulky group can enhance the activity.

10. On R, Polar group can decrease the Activity

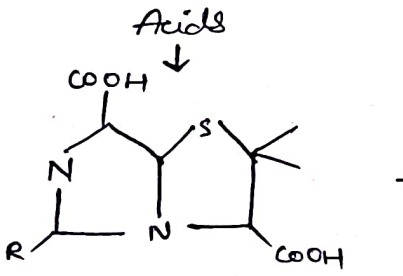
↓

easily degrades

## CHEMICAL DEGRADATION



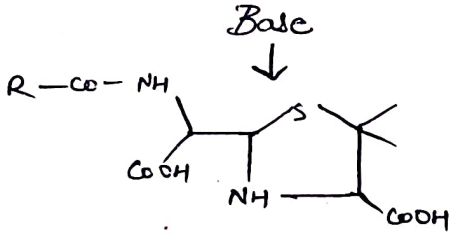

Penicillin




Penicillinic Acid

↓ Decarboxylase

Penillotic Acid




(β-Lactam Ring Open)

↓

Penamaldic Acid

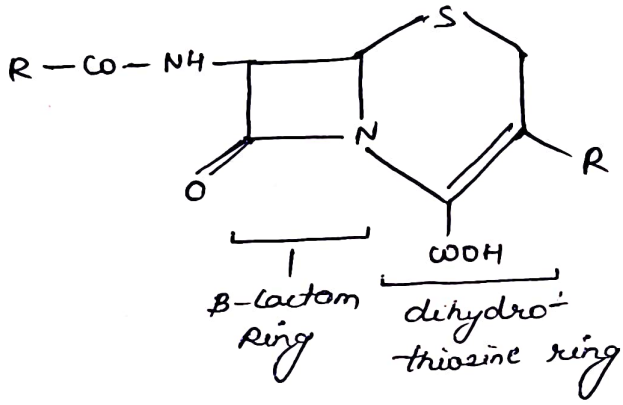
↓ Decarboxylase enzyme

Penicillin Aldehyde

# CEPHALOSPORIN ANTIBIOTICS

After Penicillin,

Cephalosporins formed through chemically modifications of penicillin synthetically.




## MECHANISM OF ACTION

It shows its action by inhibiting cell wall synthesis.

Peptidoglycan linked the cell membrane
(Transpeptidase enzyme help in linkage)

↓

Decrease peptidoglycan linkage [loose]
by inhibit transpeptidase enzyme

↓

Puncture the Cell Membrane

## USES

→ In Meningitis Inflomation

↓

Kill menigococci, Pnemococci, H. Influenza

→ Effect more of gram -ve bacteria

→ Used of Urinary tract Infections (UTI)

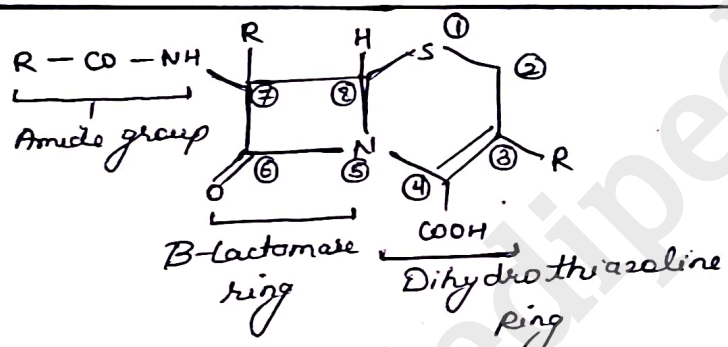
## SIDE - EFFECTS

→ Hypersensitive like anaphylaxis ;
(drug cannot suit the body → Rashes itching etc)

→ Local Irritation

→ Renal Toxicity

## STRUCTURE ACTIVITY RELATIONSHIP [SAR]



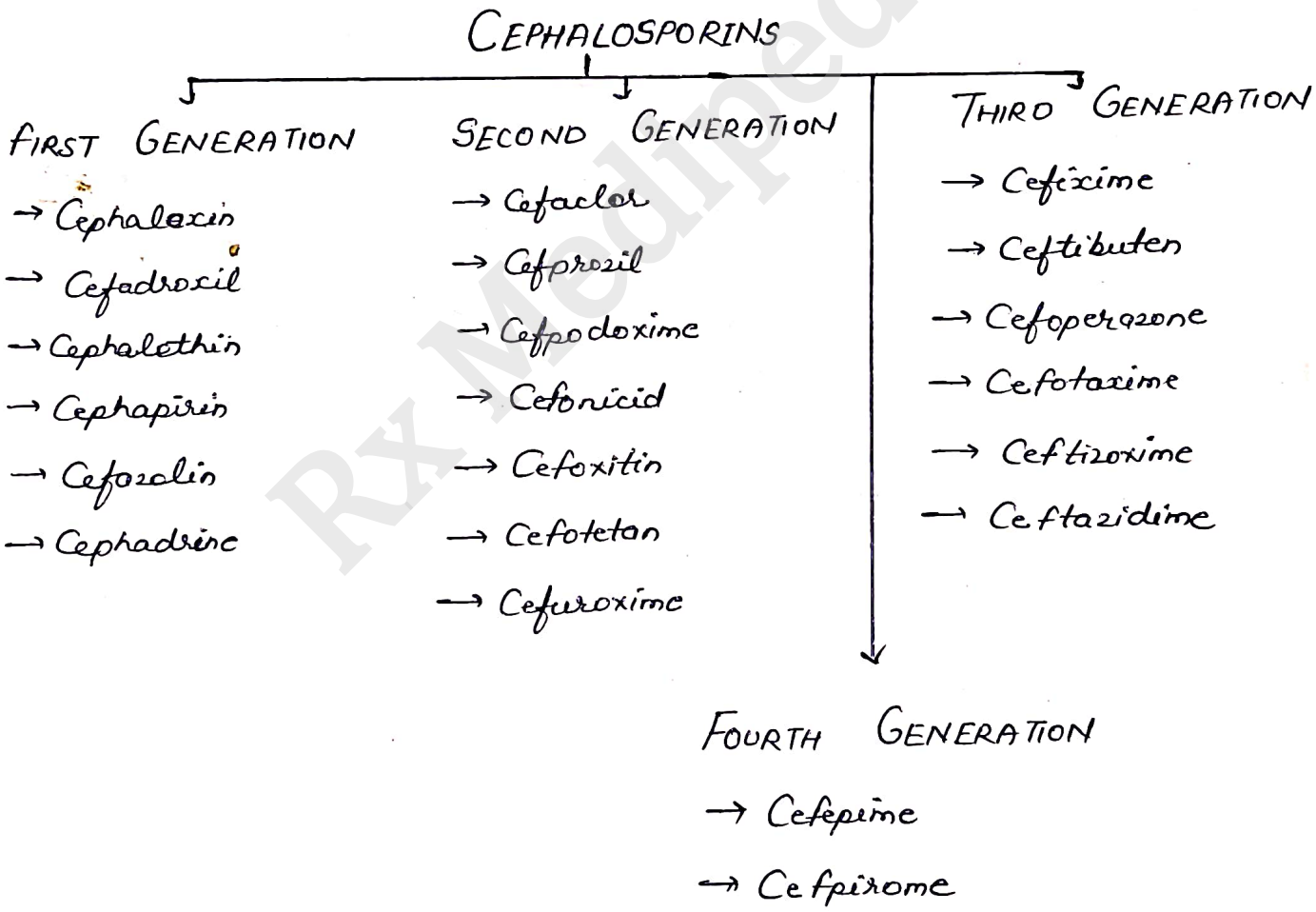

1. β-Lactam Ring is essential for the Activity.
2. Dihydrothiocslidine ring is essential for the Activity.
3. Amide group also essential for the Activity.
4. On 7C and 8C, As form is essential for the Activity. if we convert into trans form, it decrease the activity.
5. On position 1, If we replace S with Oxygen (O) it decrease the Stability than S.
6. On position 1, If we replace S with Methyl Group ($CH_2$), stability decreases more than O [Oxygen]

7. On 3rd position, addition long chain will decrease anti-microbial activity.

8. On 4th Position, COOH replaced with different salts for form pro drugs.

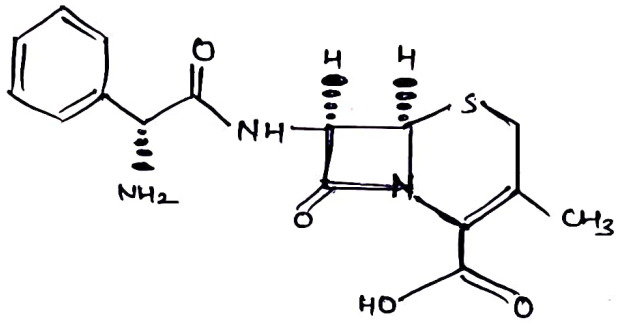
9. On 6th position, ketone group essential, Replacement may decrease Anti-microbial Activity.

## CLASSIFICATION



# FIRST GENERATION

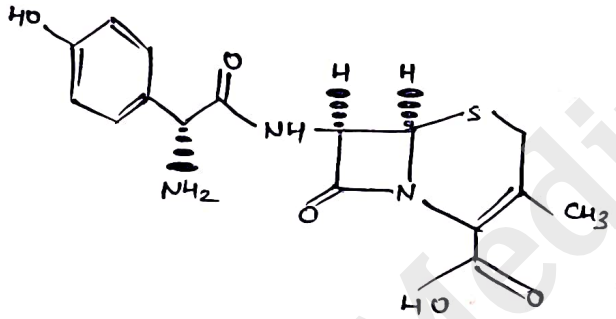
## 1. Cephalexin



→ Used to treat Urinary tract infections

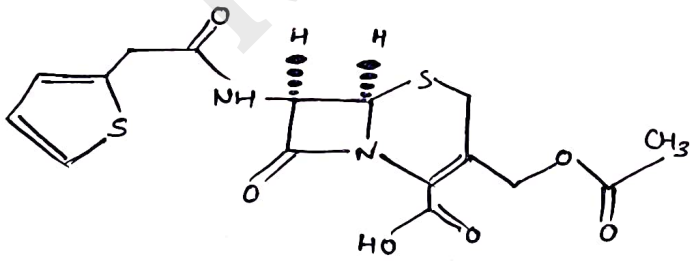
→ Used in soft tissue Infections and minor wounds.

## 2. Cefadroxil



→ Used as Anti-bacterial drug.

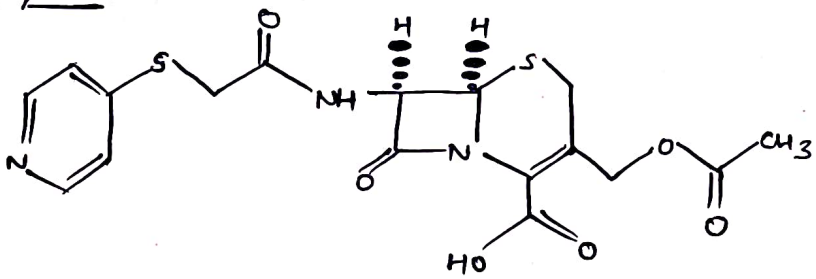
## 3. Cephalothin



→ Used as Anti-Microbial Agent

→ Used as Anti-bacterial Agent

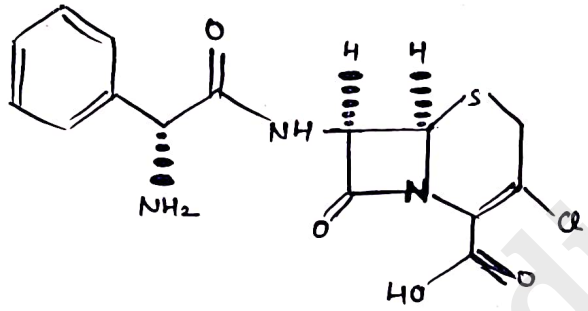
4. Cephapirin



→ Effective against Gram +ve and Gram -ve bacteria

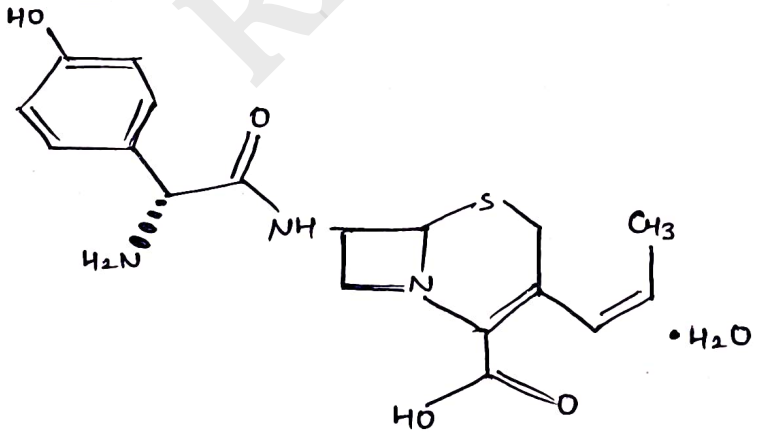
## SECOND GENERATION

1. Cefaclor



→ Used for treatment of Non-life threatening infections caused by H. influenza.

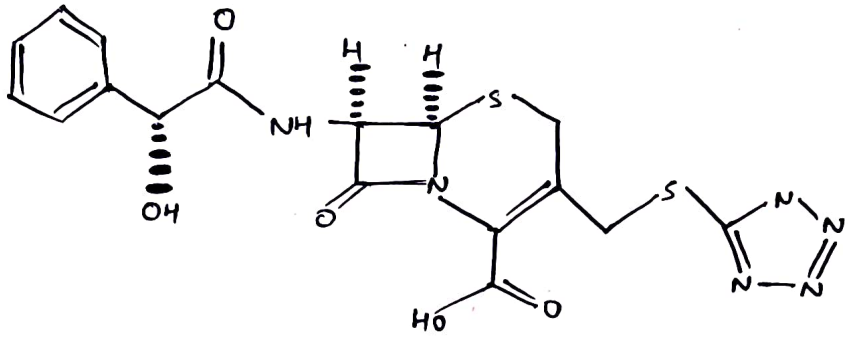
2. Cefprozil



→ Used to treat bronchitis

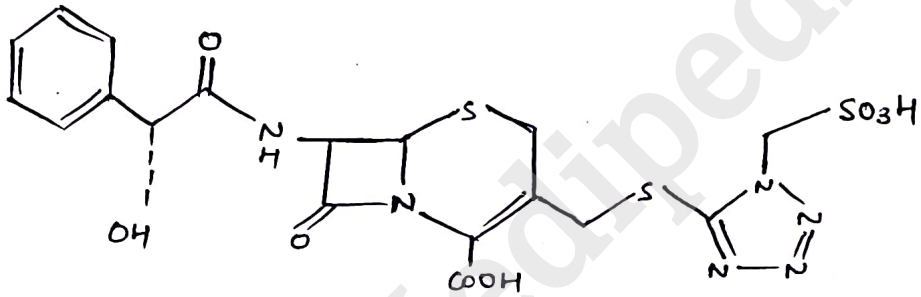
→ Used in ear, skin and other bacterial infections.

3. Cefamandole



→ Used to treat lower Respiratory tract, skin, bone and joint infections.

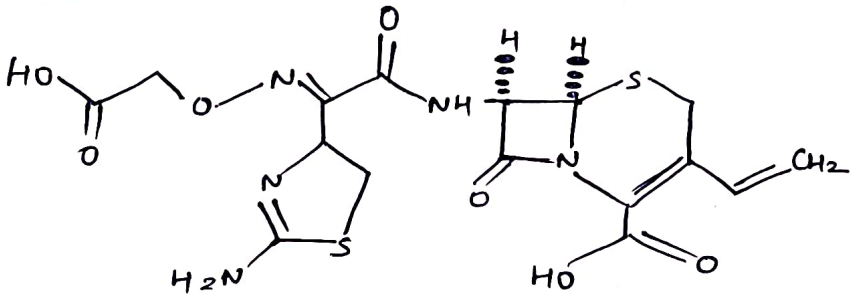
4. Cefonicid



→ Used for UTI, lower Respiratory infections and bone infections.

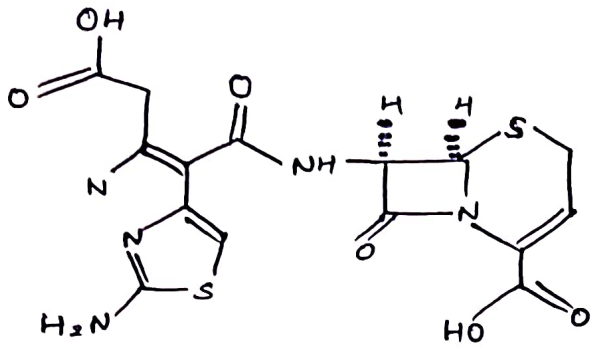
## THIRD GENERATION

1. Cefixime



→ Used to treat Gonorrhoea, bronchitis and urinary tract infections.

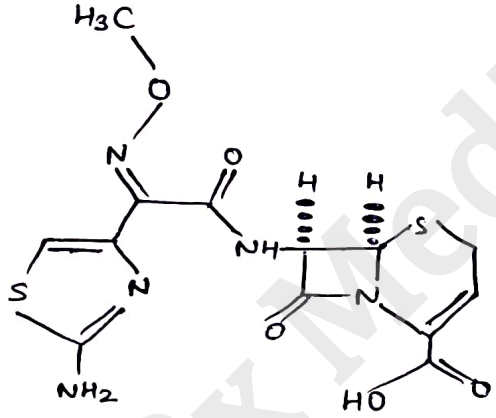
2. Ceftibuten



→ Used to treat UTI, Respiratory tract infections.

→ Used in pharyngitis and tonsilitis.

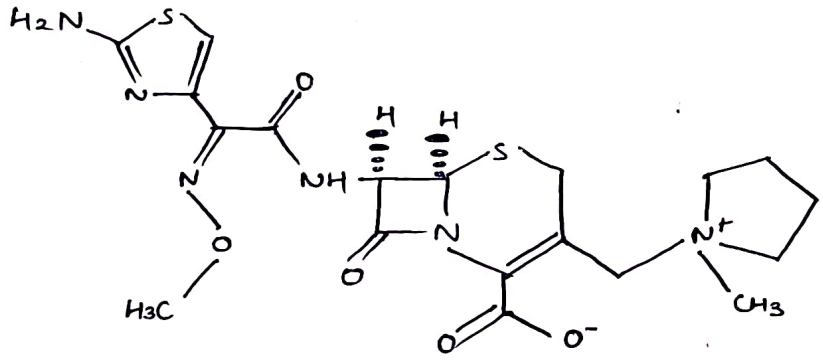
3. Ceftizoxime



→ Used to treat Gram +ve and Gram -ve bacterial Meningitis.

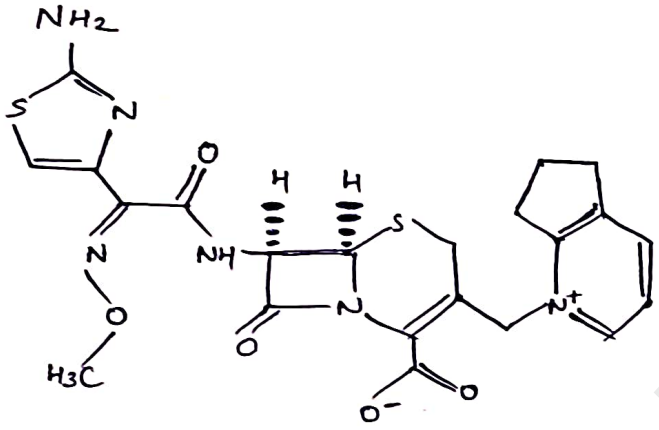
## FOURTH GENERATION

1. Cefepime



→ Used to treat UTI, lower respiratory tract infections and skin infections

2. Cefpirome



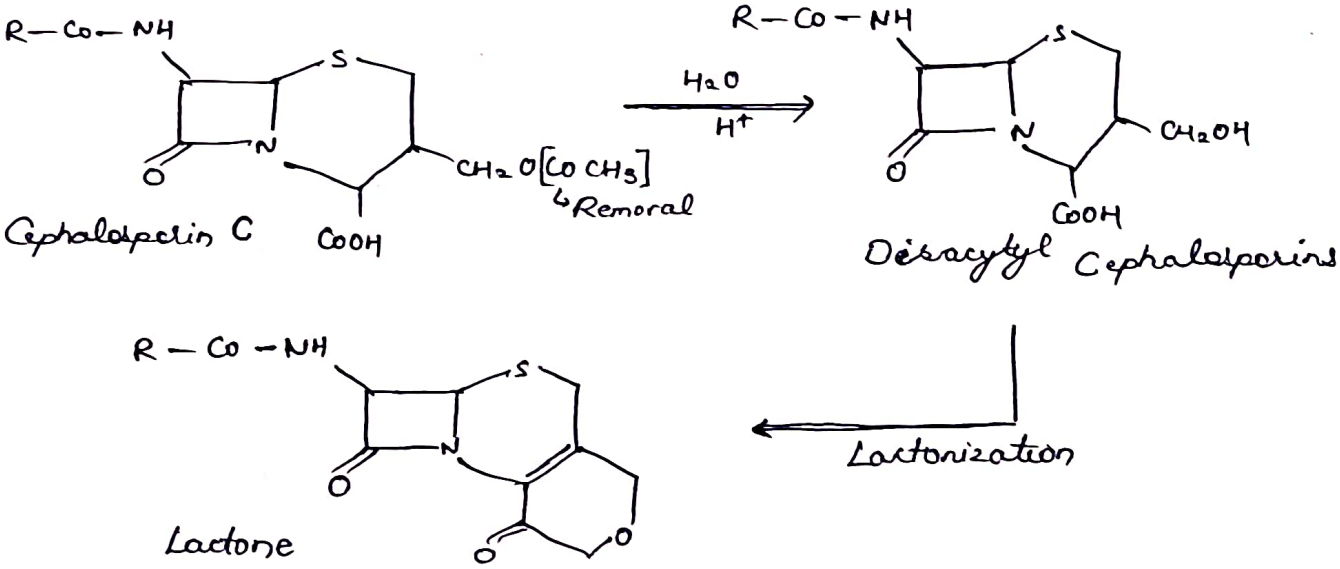
→ Effective against staphylococci and β-Lactamase-producing strain

## CHEMICAL DEGRADATION

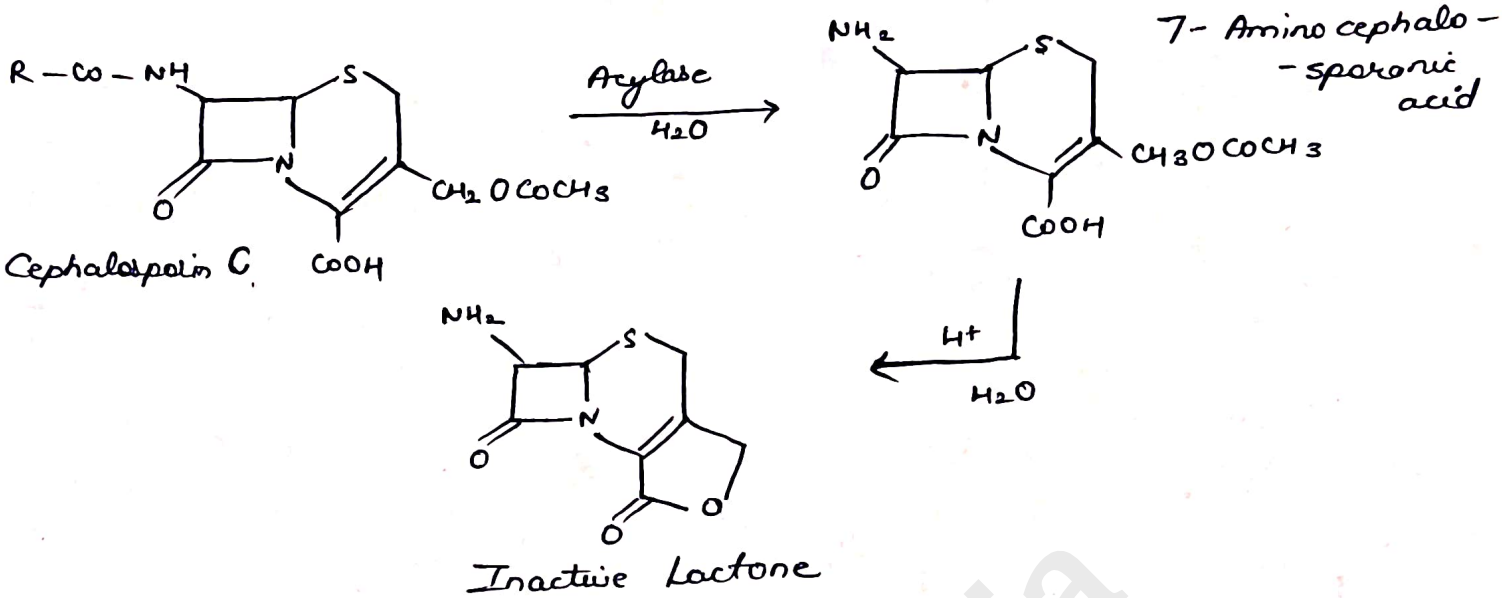
Cephalosporins degrades in strong acidic solution, An acylase and β-Lactamase enzymes.

→ 3-Acetoxymethyl group is most Reactive Site.

1. Degradation of Strong Acid



## 2. Degradation in Presence of Acylase :

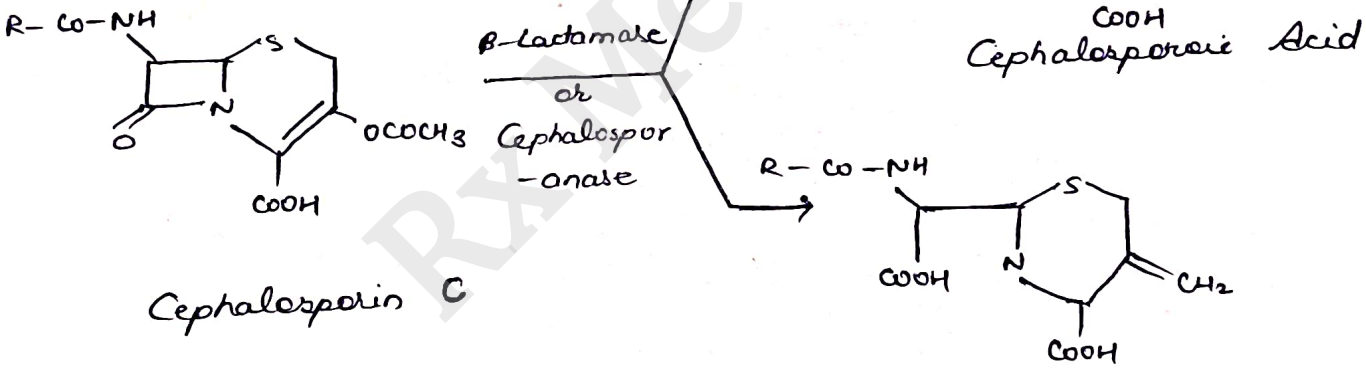






Inactive Lactone

## 3. In presence of β-Lactamase



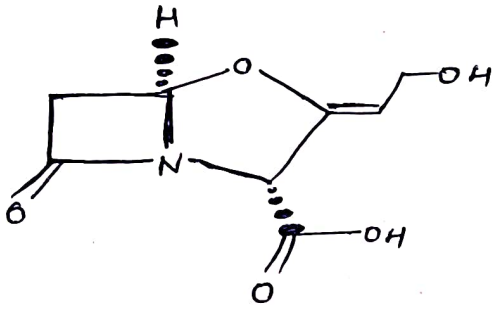

Cephalosporin C

Anhydro-deacetyl Cephalosporoic Acid

# β - LACTAMASE INHIBITORS

β- Lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β- Lactam antibiotics by opening the β-Lactam ring.

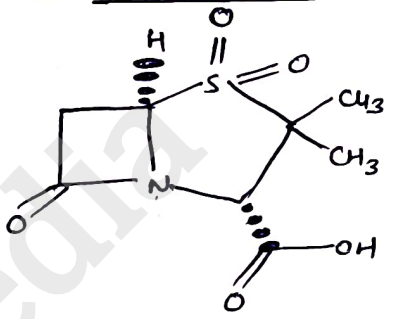
## 1. Clavulanic Acid



→ Combination of amoxicillin and the pottasium salt of clavulanic Acid are used for treatment of skin, respiratory and ear infections

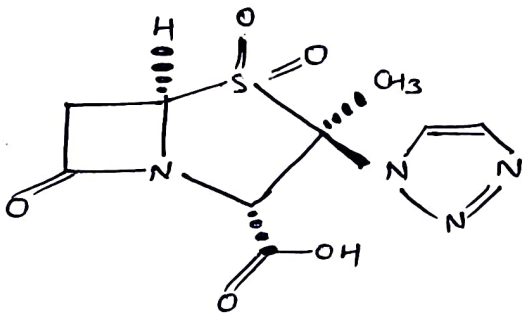
→ Combination of pottasium clavulonate and penicillin used to treat lower respiratory tract infections.

## 2. Salbactam



→ Combination of salbactam with ampicillin used for the treatment of skin, tissue, Intra-abdominal infections.

## 3. Tazobactam



→ Combination with broad-spectrum penicillin used to treat appendicitis and pelvic inflamatory disease.

→ Combination with Ceftolozone sulfate used for treatment of intra-abdominal infections.

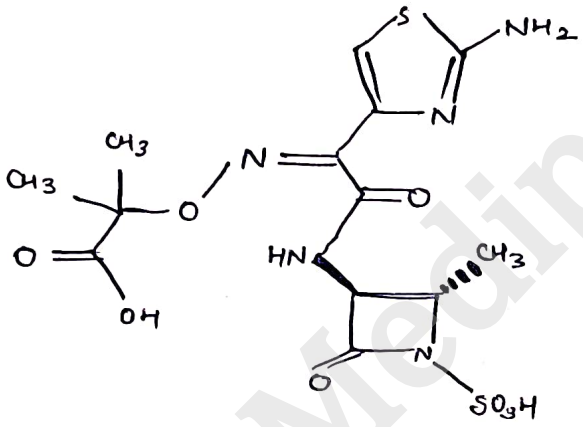
# MONOBACTAMS

→ Monobactams are β-Lactam compounds wherein the β-Lactam ring is alone and not fused to another ring.

→ They are obtained from the "bacterium Chromobacterium violaceum"

→ They are not effective against Gram positive bacteria.

## Aztreonam




→ It is active only against aerobic Gram Negative bacteria such as Neisseria and Pseudomonas.

→ Used for treating Pneumonia, Septicemia and Urinary tract infections.

# AMINOGLYCOSIDES

→ The name Amino-glycoside derived from two words Amino + glycoside because in this antibiotic two amino group is present and they are connected with glycoside linkage so their name is aminoglycoside.

→ Obtained from different types of Streptomyces bacteria.

Examples: Streptomycin, Tobramycin, Neomycin, Sisomycin, Kanamycin, Nitilmycin, Amikacin, Gentamycin

→ Most widely used against gram Negative bacteria in combination with Vancomycin / Penicillin.

→ Streptomycin is oldest Antibiotic.

→ Drugs are water soluble, stable in solution and more active at alkaline pH than acidic pH.

→ In 1940, the Scientist wakesman first of all discovered this bacteria from actinomyces species.

→ He ~~Recover~~ get a Nobel prize for his work on Streptomycin

## CHEMISTRY

Aminoglycosides are so named because their structure consist of amino sugars linked glycosidically.

All have atleast one aminohexose and some have a amino group.

eg. Streptomycin

Neomycin

## MECHANISM OF ACTION

Bacteriocidal Action

↓

They bind with Ribosomal DNA [30S]

↓

Cause mis-reading of Codes

↓

Stops the translation process

↓

Another new form of protein which is

Not Necessary

↓

Damage of Cell Membrane Semi-permeability

↓

Cell wall Leaked

↓

Bacteria Dead

## CHARACTERISTICS

→ Poorly Absorbed from GIT

→ Poorly Penetrated in CNS

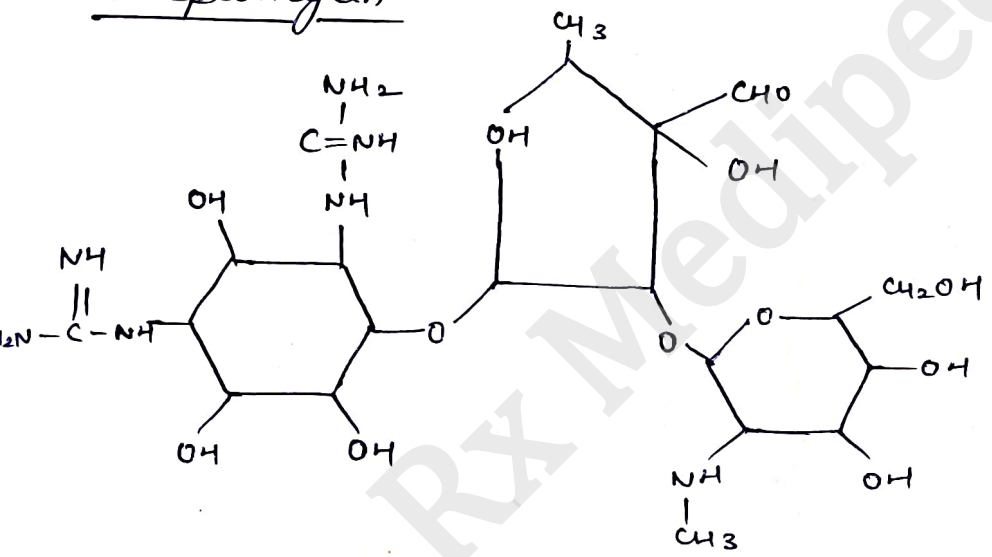
→ Excreted through kidney

→ fast Resistance

## SIDE EFFECTS

→ Nephrotoxicity

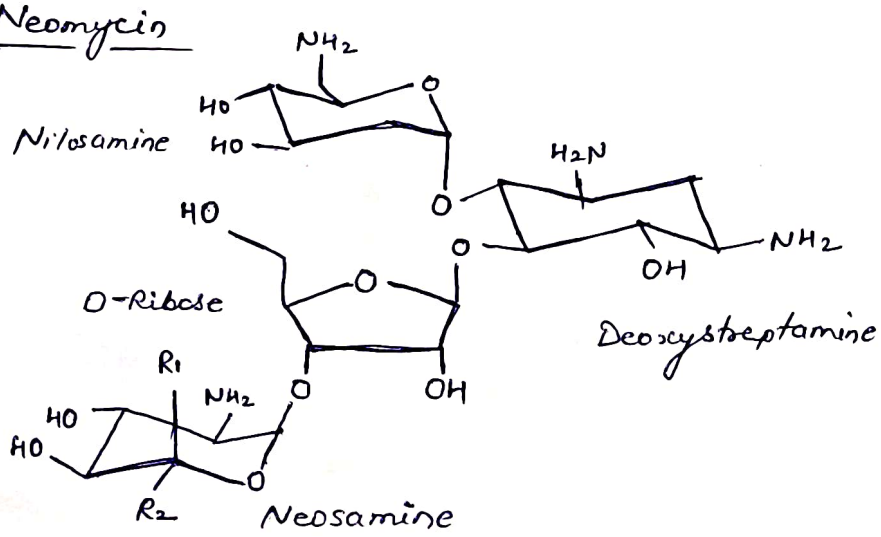
### 1. Streptomycin




→ Most Commonly used in tuberculosis.

→ Also used in Gonorrhoea.

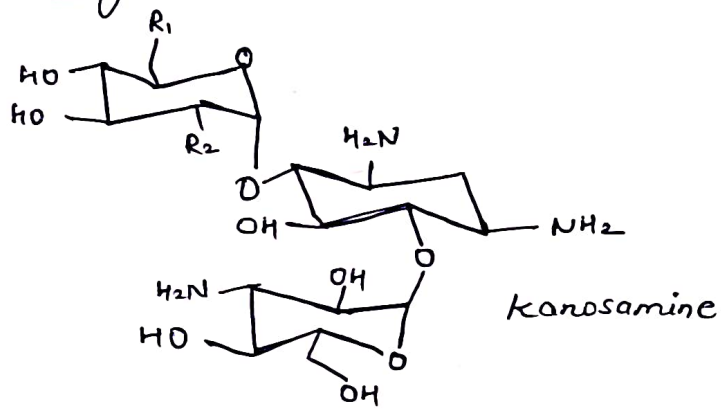
### 2. Neomycin



→ Used in treatment of GIT infections, dermatological infections.

→ Used in abdominal surgery to reduce infections from bacterial flora of the bowel.

3. Kanamycin



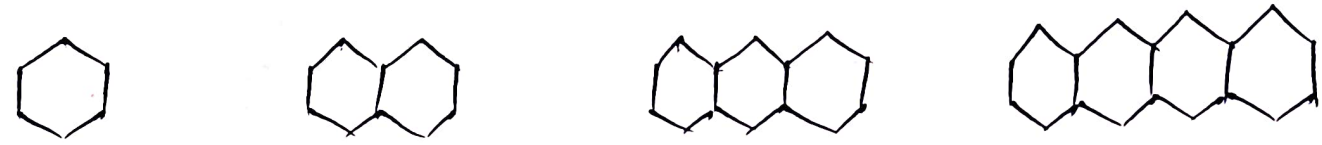

Kanosamine

→ Used in infections of the intestinal Tract

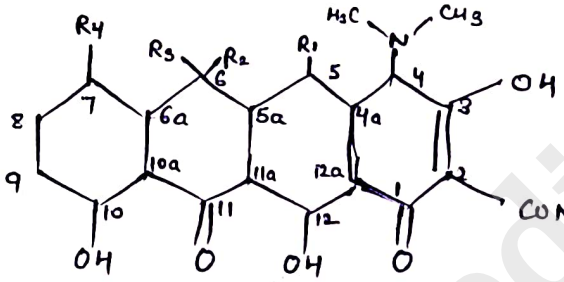
→ Used in systemic infections from gram Negative bacilli.

# TETRACYCLINE

→ Antibiotic contain 4 fused cycline Rings, called octahydronapthacene rings [ Tetracycline ]



Benzene Napthalene Anthracene Napthacene




Tetracycline

→ Tetracycline is obtained ~~thr~~ from Streptomycin bacteria through fermentation process.

Streptomycene bacteria
↓ fermentation
Tetracycline
↓ Acid / Base
Salts

→ Tetracycline
- ↓ Acid / Base → Salts
- ↓ Al, mg, Ca, Fe → Chelate [form cyclic Structure with Metal]

→ Milk is not consumed after Tetracycline Antibiotic

↓

Milk contain calcium Metal

↓

form chelate.

→ firstly obtained from Streptomycin in 1948 by BM Digger

→ AC finley, in 1950 discover chlortetracycline & oxytetracycline.

→ Highly Stable than penicillin & Cephalosporin

→ freely Soluble in carbonates, Alkali hydroxides etc.

## MECHANISM OF ACTION

Tetracycline

↓

Binds with 30's Ribosome

↓

[Responsible for protein Synthesis]

↓

Block 30s Ribosomal

↓

Stop Translation Process

↓

Death Bacterial Organisation

## THERAPEUTIC USES

→ Acne

→ Urinary Tract Infections

→ Opthalmic

→ Respiratory Tract Infections

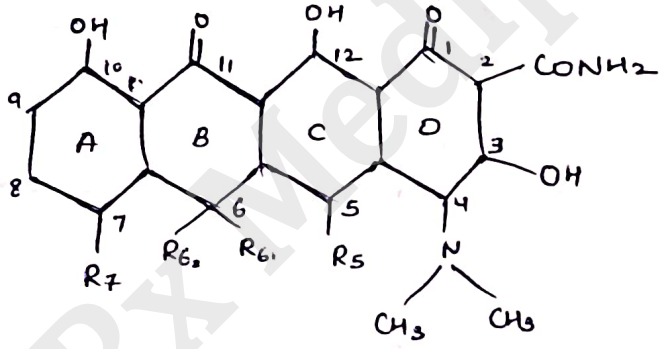
## SIDE EFFECTS

→ Hypersensitivity

→ Local Irritation

→ Renal Toxicity [After long use]

## STRUCTURE ACTIVITY RELATIONSHIP [SAR]




→ 4 Rings A, B, C, D fused with each other are essential for Activity.

→ 2 Ketone at 1C & 11C are essential for Activity.

→ 4 Hydroxyl groups at 10C, 12C, B/w C & D & 3C are essential for Activity

→ At position 1 & 8, Ketoisomerism can be seen that enhance the Activity.

→ At $R_{6_1}$ and $R_{6_2}$, addition of H increase activity but addition of bulky group decreases the Activity.

→ At $R_6$, $=CH_2$ attatchment can increases activity many time.

→ At $R_7$, C group attatchment decrease the potency of drug but increases anti-microbial Activity.

→ Reaction with Strong Acid cause dehydration, that form oxytetracycline product, which is more effective than Tetracycline.

→ Due to presence of 4 ring fused together, Lipophilicity increases and decrease water Solubility.

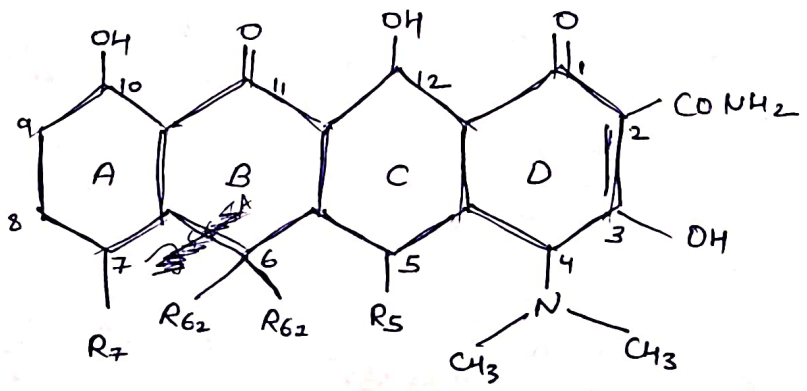
↓

To increase $H_2O$ Solubility, use of mannich Reaction takes place

↓

At $[CONH_2]$ 2C, Aminoalkylation occurs solubility increases

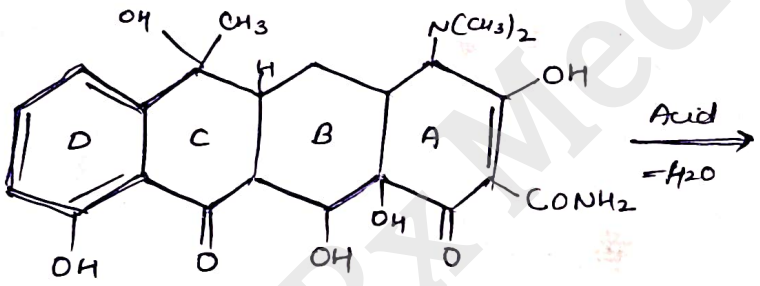
## CLASSIFACATION



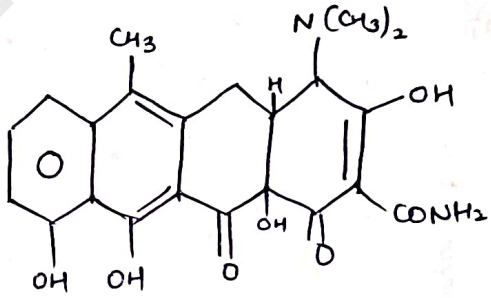
| Name of Compound | $R_5$ | $R_{6_1}$ | $R_{6_2}$ | $R_7$ |
|---|---|---|---|---|
| Tetracycline | H | OH | $CH_3$ | H |
| Oxytetracycline | OH | OH | $CH_3$ | H |
| Chlortetracycline | H | OH | $CH_3$ | Cl |
| Minocycline | H | H | ~~$N(CH_3)_2$~~ H | $N(CH_3)_2$ |
| Doxycyclin | OH | H | $CH_3$ | H |

## CHEMICAL DEGRADATION

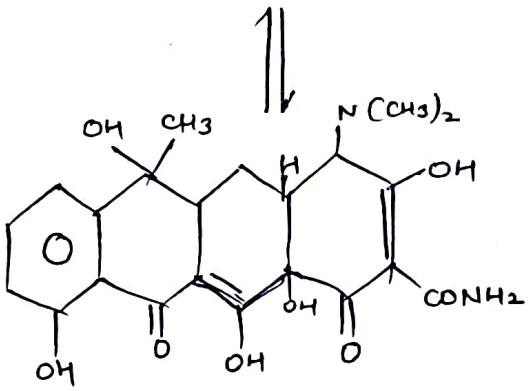
Most of Natural Tetracyclines have tertiary benzylic hydroxyl group at Carbon-6

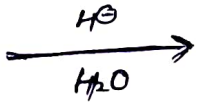


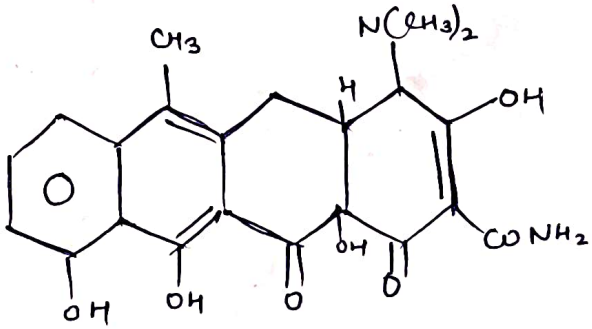

Tetracycline
Active




Anhydrotetracycline
(Inactive)




4-epianhydro tetracycline
(Inactive)