Medicinal Chemistry - III

B. Pharm 6th Semester

Unit - 1

÷ Antibiotics ÷

*** Introduction of antibiotics ÷** The term antibiotic is derrived from two word.

- Anti and biotics anti means to kill and biotics means bacteria.
- It means any chemical molecule or Medicine which are used to kill the bacteria is called antibiotics.

Antibiotics
↓ ↓
Anti + Biotics
↓ ↓
To kill Bacteria.

- Antibiotics are prepared from the killed and Attenuated bacteria for killing ~~the~~ those bacteria.
- The first bacteria was isolated and seperched by the scientist Luies pashure in 1877.
- They discovered the Anthrox bacteria into the plant.
- In 1929 the First scientist Alexender flemming was discoverd the first antibiotics Penicilline which is obtained from the penicillium notetum in the plant of Tobacco.

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÷ Characterstics of Antibiotics ÷

→ It is the metabolic product of the bacteria which is obtained from the killed and Attenuated bacteria & Micro-organism.

→ It is synthetic product produced by structural analogue of the naturally occuring antibodies.

→ Antibiotic are the synthetic they are prepared with the help of bacteria in the lab.

→ It is the antagonist to growth of the survival one of the more species of the microorganism.

→ Antibiotic are used to kill or supressed the growth of other bacteria or Microorganism.

→ It is used in very low concentrations or affected in very low concentration.

→ Antibiotic which are used to kill all type of bacteria Gram +ve or -ve they are called broad spectrum.

→ They are used only a specific bacteria.

÷ Classification of antibiotics ÷

1) According to the spectrum activity.

2) According to the Mechanism of action.

3) According to the chemical structure.

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(1) According to the spectrum activity :-

A) **Broad spectrum antibiotics :-**
- Cephalosporin.
- Chloramphenicol
- Tetracycline.

B) **Narrow spectrum Antibiotics :-**
- Penicillin-G
- Streptomycin.
- Erythromycin.
- Bacitracin.
- Nystatin.

(2) According to the mechanism of action :-

(i) **Inhibit cell wall synthesis.**
- Penicillins
- Cephalosporins
- Cycloserine.
- Vancomycin.
- Bacitracin.

(ii) **Inhibit Protein synthesis :-**
- Tetracycline
- Chloramphenicol
- Erythromycin.
- Clindamycin

(iii) **Causes leakage from cell membrane :-**

(a) Polypeptides
- Polymyxins
- Bacitracin
- Colistin

(b) Polyenes
- Amphotericin-B
- Nystatin
- Hamycin.

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(iv) Cause Misreading of M-RNA code and affect permeability
Aminoglycosides :-

Streptomycin
Gentamycin
Neomycin.

(v) Inhibit DNA Gyrase Enzyme

Fluroquinolones - Ciprofloxacin.
- Norfloxacin.

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(vi) Interfere with DNA Function :-

Refampin.
Metronidazole.

(vii) Interfere with DNA Synthesis :-

Acyclovir
Zindovudine.

(viii) Interfere with intermediatary metabolism

Sulfonamides.
Sulfones
Para Amino salicylic Acid.
Ethambutol
Pyrimethamine
Trimethoprim.

(3) According to the chemical structure.

(i) β- Lactam Antibiotics :- Penicillins
Cephalosporin.
β- Lactamase
Monobactams.
Carbapenems.

(ii) Aminoglycosides :- Streptomycin
Gentamycin
Neomycin
Kanamycin

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(iii) Tetracycline :- Oxytetracycline
Doxycycline

(iv) Nitrobenzene derivative → Chloramphenicol

(v) Quinolones and fluroquinolones :-
↓
Nalidixic Acid
Norfloxacin
Ciprofloxacin
Ofloxacin etc.

(vi) Macrotides :- Azithromycin
Roxithromycin
Erythromycin [MARE]

(vii) Sulphonamides related drugs :- Sulfadiazine
Sulfamethoxazole
Sulfones (Dapsone)
Para-aminosalicyclic Acid (PAS)

(viii) Diaminopyrimidine - Pyrimethamine

(ix) Polypeptide Antibiotics :- Polymyxin-B
Colistin
Bacitracin etc.

(x) Glycopeptide :- Vanomycin

(xi) Polyene Antibiotics ÷ Nystatin
Hamycin.

(xii) Oxazolinedinones ÷ Zinezolide.

(xiii) Nitrofuran Derrivative Nitrofurantoin
Furazolidone.

(xiv) Nitroimidazole derrivatives Metronidazole
Tinidazole etc.

(xv) Imidazole/Azole derrivative Fluconazole
Ketoconazole
Clotrimazole
Miconazole etc.

(xvi) Nicotinic Acid derrivatives Isoniazid
Pyrazinamide

(xvii) other antibiotics ÷ Griseofulvin.
Limomycin.
Viomycin.
Vamomycin.

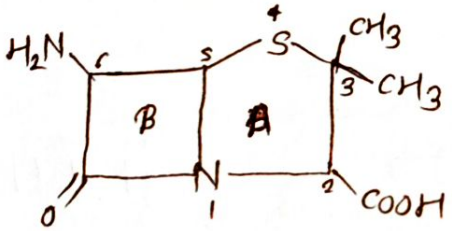
÷ β- Lactam Antibiotics ÷

→ Such Antibiotics in which contain the β- Lactam ring in their structure they are called β- Lactam antibiotics.

→ All β- Lactam antibiotic contain 4 membered β-Lactam ring which is fused through nitrogen and tetrahedral carbon atom to second heterocyclic ring.

→ They contain four membered hetrocyclic ring in which the nitrogen is hetroatom is present and fuse sulfer containing ring is present.

→



→ On the basis of there exampl –

(i) Penicillins
(ii) Cephalosporins
(iii) Thienamycin
(iv) Clavulanic Acid.

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1) Pinicillins ÷ β- Lactam ring is fused with thiazolidine ring.

(ii) Cephalosporins ÷ β- Lactam ring is fused with dihydrothiazine.

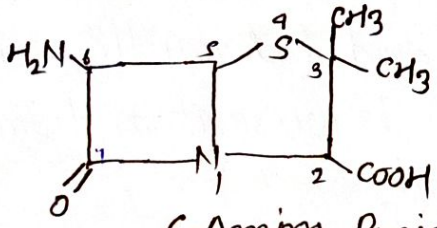
(iii) Thienamycin ÷ β- Lactam ring is fused with Pyrroline ring.

(iv) Clavulanic Acid ÷ β- Lactam ring is fused with oxazolidine ring.

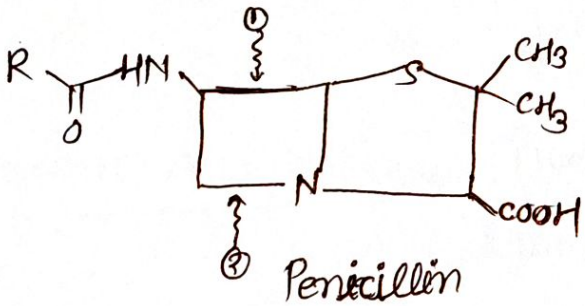
Penicillins

⇒ In 1929 Scientist Alexender flemming was discoverd the first antibiotics Penicillin which is obtained from the penicillium notatum in the plant of Tobacco.

⇒ Penicillins can be considered as amino derivatives of 6-Aminopenicillanic acid (6APA)



6-Amino Penicillanic Acid



Penicillin

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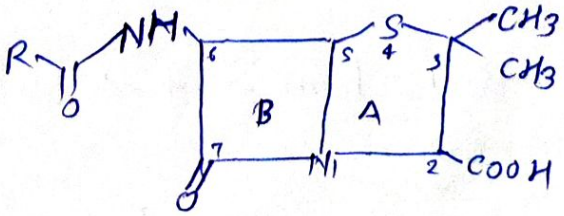
⇒ Two enzymes Penicillinase / β-lactamase and Amidase enzyme metabolise the penicillin so they inhibit the mode of action of penicillin.

⇒ Basically Penicillinase or β-Lactamase is act on the site of action of -I

⇒ And Amidase is act on the site of action of -II.

Chemistry of Penicillin :-



Penicillin

⇒ The penicillin structure is the seven membered compound which contain two fuse ring.

→ One is (A) and one is (B).

→ (A) is Thiazolidine ring and (B) is β-lactam ring.

→ It contains amide group at the position no Six.

→ It contains Ketone ring at the position no seven.

⇒ It contains di Methyl group at the position no 3 (three).

⇒ It contains the carboxylic acid group at the position no two.

∴ Degradation of Penicillin ∴

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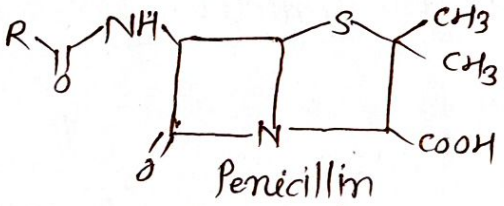
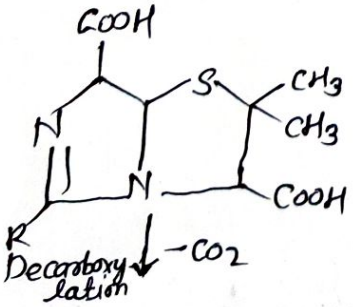


Penicillin

Acid H^+

Penicillenic Acid ⇌

Penillic Acid



Decarboxylation $-CO_2$

Penilloic Acid

Hydrolysis H_2O

Penamaldic Acid

Penicillamine + Penaldic Acid

$-CO_2$

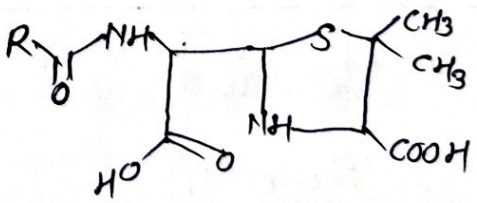
Penicilloaldehyde

Base OH^-

β-Lactamase & Acylase

Penicilloic Acid

[opening of β-lactam ring]

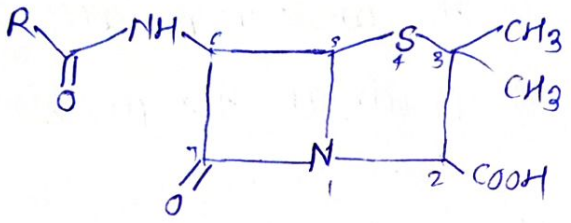


End Products :-

Acid :- Penilloic Acid
Penicillamine
Penicillaldehyde.

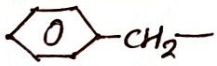
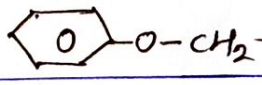
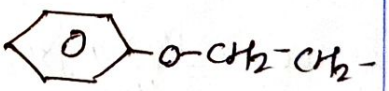
Base + Enzyme :-
Penicilloic Acid.

Classification

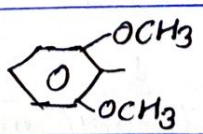
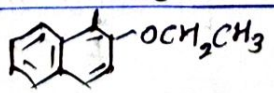


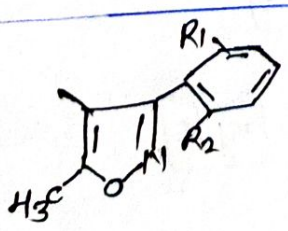
Penicillin (General Structure)

1) Penicillinase Susceptible Penicillins :-

Drug	R
1. Penicillin-G	
2. Penicillin-V	
3. Penethicillin	

2. Penicillinase Resistant Penicillins

4. Methicillin	
5. Naficillin	

R = 

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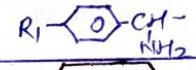
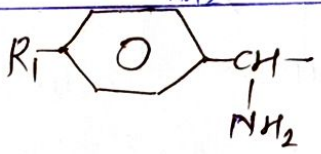
⑥ Oxacillin	$R_1 = R_2 = H$
⑦ Cloxacillin	$R_1 = H$, $R_2 = Cl$
⑧ Dicloxacillin	$R_1 = R_2 = Cl$
⑨ Floxacillin	$R_1 = F$, $R_2 = Cl$

3. Amino Penicillins :-

	R	R_1
10. Ampicillin		-H
11. Amoxycillin		-OH

4) Carboxy Penicillins :-

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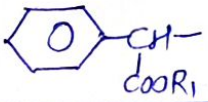
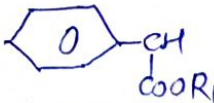
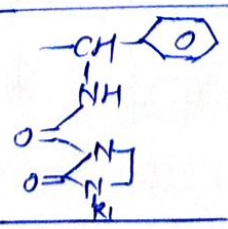
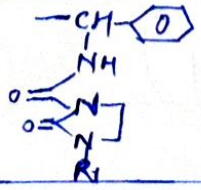
	R	R_1
12 Carbenicillin		-H
13. Indanylcarbenicillin		- 5-Indanol

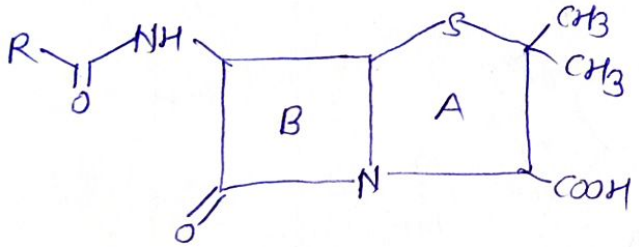
5) Ureido Penicillins :-

	R	R_1
14 Azlocillin		-H
15 Mezlocillin		$-SO_2CH_3$

6) Miscellaneous:-

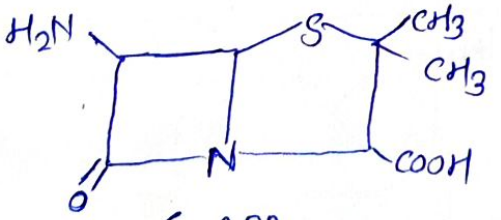
16) Quinacillin
17) Azidocillin
18) Talampicillin
19) Ticarcillin.

SAR of Penicillins (Structure Activity Relationship)



A) - Thiazolidine Ring
B) - β-Lactam Ring
R) - Benzyl, Substituted aryl, or heteroaryl group.

→ 6-APA (6-Aminopenicillanic Acid) is the minimum structure requirement for antibacterial Activity.



6-APA

→ The β-Lactamase or 6-APA Structure are essential for the activity.
→ If we change their structure then their antimicrobial activity will be decrease.

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→ At the α-position of acetyl group, if we use any electron withdrawing group then their anti microbial activity will be increase.

⇒ When any bulky group is attach at the 'R' Position then due to stearic hindrance β-Lactamase enzyme can't dissociate the penicillin so their stability will be increase.

→ When we add any polar group at the acetyl group then their gram negative activity is increase and gram+ve activity is decrease.

→ All natural penicillins are dextro-rotating which are active compound.

:- Mode of Action of Penicillin :-

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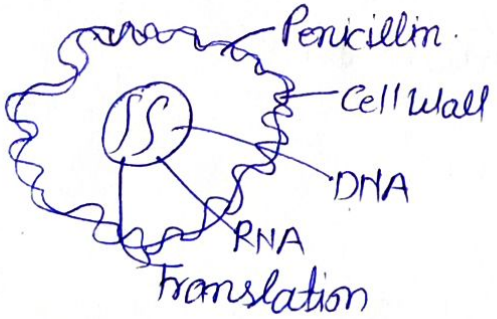


⇒ Penicillin inhibit bactecrial cell wall formation.

→ Cell wall of bacteria is essential for their normal growth and development.

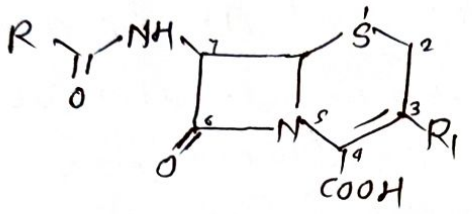
→ Peptidoglycon is a component of cell wall and it provide rigid mechanical stability by virtue of its highly crossed linked lattice work structure.

→ Bactericidal in action.

∴ Cefalosporin ∴

→ Cefalosporin is a β-Lactam antibiotic because it contain β-Lactam ring.

→ β-lactam ring is fused with dihydrothiazine ring.



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∴ Classification ∴

→ Cephalosporins are classified into 4 different groups depending upon its generation system.

1) First Generation Cefalosporins ∴ → Highly active against gram +ve bacteria and lower activity against gram -ve bacteria.

→ Mainly active against Streptococci & Staphylococci

2) Second Generation Cefalosporins ∴ → They are more active against gm -ve bacteria than 1st generation cephalosporins

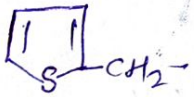
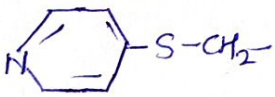
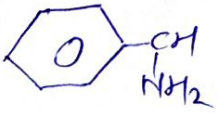
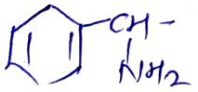
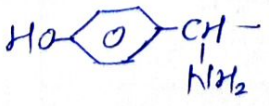
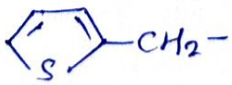
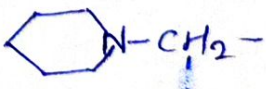
→ Gives higher activity against haemophils influenzae.

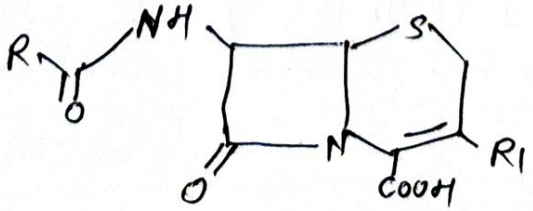
3) Third Generation Cefalosporins → They have broad spectrum of antibacterial activity & being active against microbes ressistant to 1st and 2nd generation cefalosporins

4) Fourth Generation :- → Gives advantages ouver other Cefalosporins.

- Extented spectrum of activity.
- increased stability from Plasmid and Chromosomally modified β-Lactamase enzyme.
- Used in the treatment of infection due to aerobic gm-ve bacilli, resistant to 3rd generation cephalosporins.

(1) First Generation Cefalosporins.

Drug	-R	$-R_1$
1. Cephalothin		$-CH_2OCOCH_3$
2. Cephapirin		$-CH_2OCOCH_3$
3. Cephalexin		$-CH_3$
4. Cephradine		$-CH_3$
5. Cephacetril	$-CH_2-C\equiv N$	$-CH_2OCOCH_3$
6. Cefadroxil		$-CH_3$
7. Cephaloridin		



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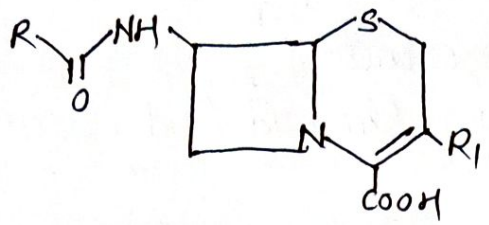
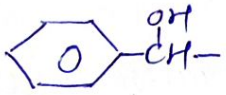
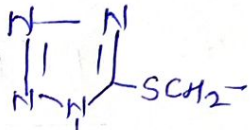
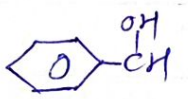
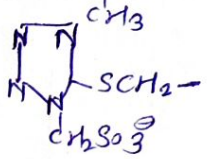
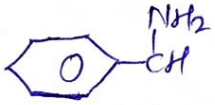
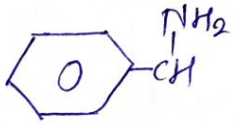
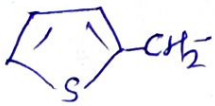
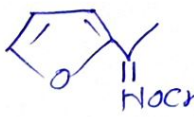
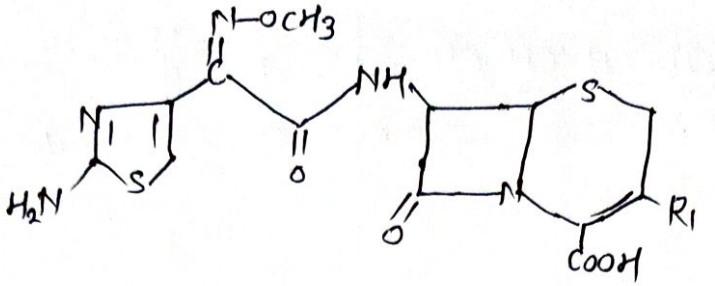
2) Second Generation Cephalosporin :-



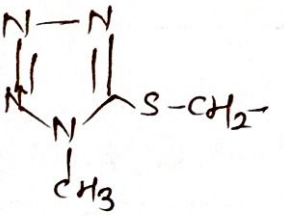
	R	R_1
1. Cefamandole		
2. Cefonicid		
3. Cefaclor		$-Cl$
4. Loracarbef ('S' is replaced by carbon)		$-Cl$
5. Cefoxitin		$-CH_2OCONH_2$
6. Cefuroxime		$-CH_2OCONH_2$
7. Cefprozil		$-CH=CH-CH_3$

KCL Pharmacy

3- Third Generation Cephalosporin

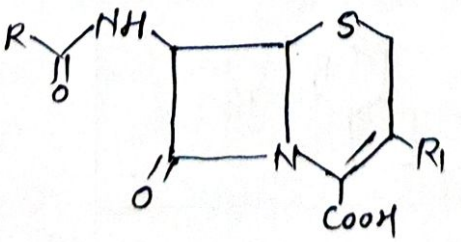


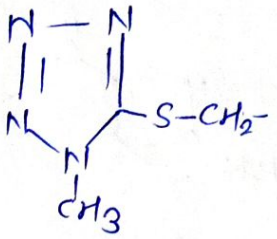
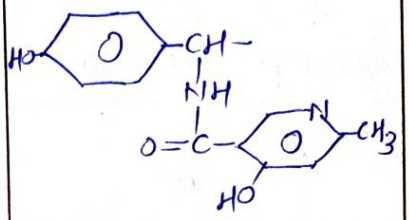
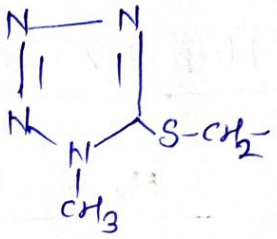
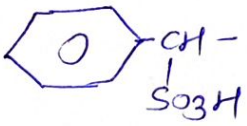
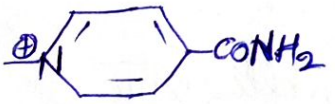
A) With 2-Aminothiazolyl-Oximino Moeity :-

Name	R
1. Cefotaxime	$-CH_2OCOCH_3$
2. Ceftizoxime	$-H$
3) Cefmenoxime	
4) Cefzidime	
5) Cefpodoxime	$-CH_2OCH_3$
6) Cefixime	$-CH=CH_2$

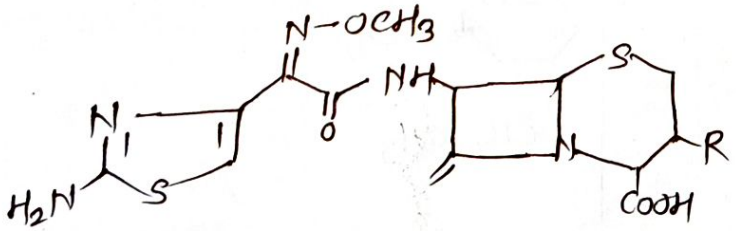
KCL Pharmacy

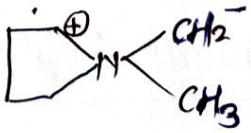
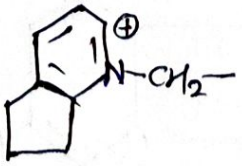
B) With different Acyl Residues -



	R	R_1
1) Cifivitril	$-CH_2SCH=CH-CN$	
2) Ceffpiramide		
3) Cefsuladin		

4) Fourth Generation Cephalosporins :-



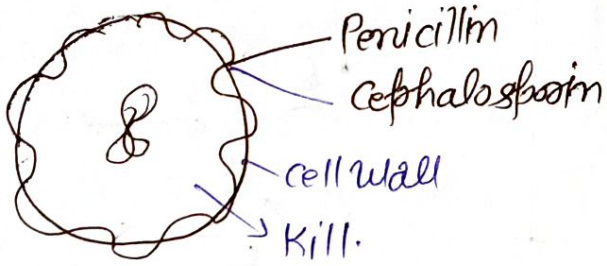
	R
1) Cefepime	
2) Cefpirome	

KCL-Pharmacy

:- Mechanism of Action :-

KCL - Pharmacy

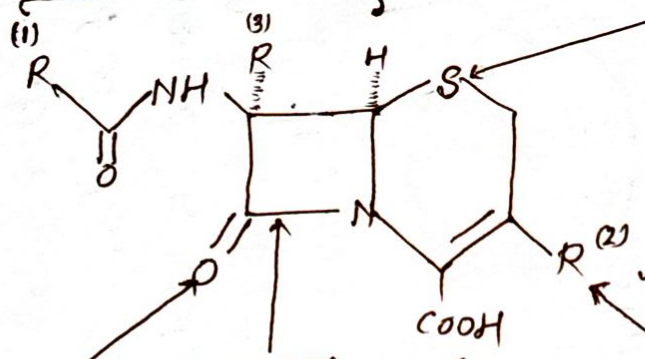
→ It is similar to penicillins.
→ Cephalosporins inhibit bacterial cell wall formation
→ Cell wall of bacteria is essential for their normal growth and development.
→ Peptidoglycon is a components of cell wall and it provide rigid mechanical stability by virtue of its highly cross linked lattice work structure.
⇒ Bactericidal in action.
→ Inhibits enzyme → transpeptidase that brings about cross linking between 5th glycine of already existing peptidoglycon in cell wall & 4th Amino ā of newly formed peptidoglycon.



Side effect :- 1) Hypersensitivity like anaphylaxis, skin rashes, Organulocytopenia, haemolytic anaemia.
2) Local irritation.
3) Renal Toxicity.
4) Disulfiram like effect.

Uses :- → Useful for meningitis by acting against meningococci pneumococci, H. Influenza & Enteric gm-ve bacilli.
→ Cephalexin – Used for UTI
→ Cefaclor – Infection caused by H-Influenzae.
→ Cephalothin Sodium - Resistant to penicillinase produced by S. Aureus.
→ Cefotaxime → used for meningitis given in cerebrospinal fluid.
→ Ceftizoxime Sodium - used for meningitis.

SAR of cephalosporin



7-Position Substituent
- Semi synthetic incorporation
- Influence the Antibacterial Activity
- Affects binding of β-Lactamase

Cis-Stereochemistry Essential.

Exchange S with
O = oxacepham
C = carbacepham

6 Membered dihydrothiazine ring.

β-Lactam Rmg

Carbonyl Group.
→ Lone pair electron Located on nitrogen atom not fed to carbonyl group to form a stabilized resonance structure thus more electrophilic for nucleophilic Attach.

Carboxylic Acid useful during formulation & drug development

3-Position Substituent
Chemical / Metabolic instability
< effect on Antibacterial Activity

KL Pharmacy

:- Tetracyclines :-

KCL - Pharmacy

* Because this antibiotic contains four cyclic rings so on the basis of their structure their name is tetracycline ring
* The all four cycles are octahydronaphtacene Nucleus.
* This antibiotics is derrived from the streptomycese bacteria species (by fermentation).
* The tetracycline antibiotic can form the salt with the reaction with acid and base.
* They can also react with the some metals, Al, Mg, Ca & Fe & they form the chelate complex.
* This class of antibiotics have three different types of antibiotics. Tetracycline, Chlortetracycline, Oxytetracycline which are derrived from the actinomycetes bacteria.
* Initially only two antibiotics are available Penicillin & streptomycin, then all the disease is controlled by these two antibiotics.
* but after the discovery of tetracyclin they are widely used as a antibiotic:
* They are very stable antibiotic.
* And it was discovered by the scientist B.M. Duggar in 1948.
* And the next tetracycline antibiotics Oxytetracycline is discovered by the scientist (A. C Finlay) in 1950. This antibiotic is derrived from Streptomyces rimosus.

Chemical Nature of Tetracyclines:-

⇒ Very slightly soluble in water.

- Are amphoteric.
- Are soluble in solutions of alkali hydroxides and carbonates and dilute salts.

Therapeutic Uses :- - Very popular for low dose oral and topical therapy of acne.

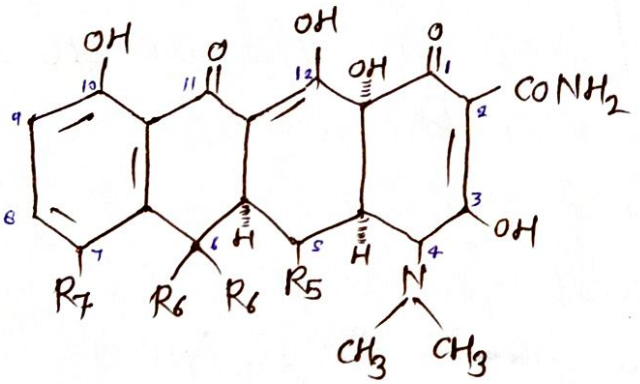
→ Community acquired urinary tract infections.

→ Opthalmic infections.

→ Upper respiratory tract infections etc.

∴ Classification ∴

→ All of the tetracyclines have the basic structure shown below.



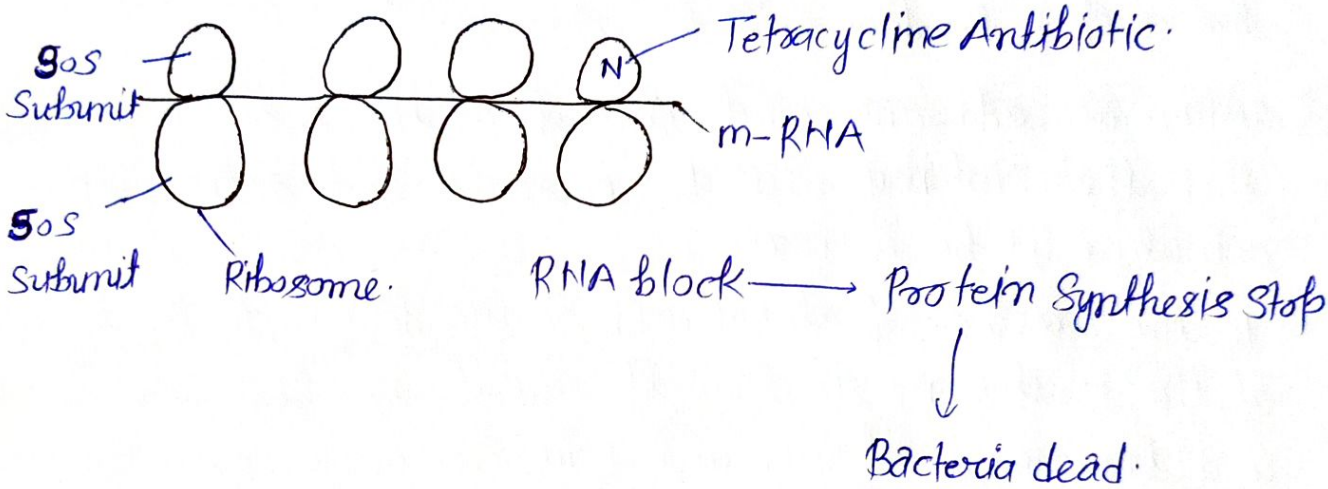
KCL-Pharmacy

Name	R_7	R_6	R_6	R_5
1. Tetracycline	$-H$	$-CH_3$	$-OH$	$-H$
2. Chlortetracycline	$-Cl$	$-CH_3$	$-OH$	$-H$
3. Oxytetracycline	$-H$	$-CH_3$	$-OH$	$-OH$
4) Demeclocycline	$-Cl$	$-H$	$-OH$	$-H$
5) Methacycline	$-H$		$=CH_2$	$-OH$
6) Doxycycline	$-H$	$-H$	$-CH_3$	$-OH$
7) Minocycline	$-N(CH_3)_2$	$-H$	$-H$	$-H$

÷ Mechanism of Action ÷

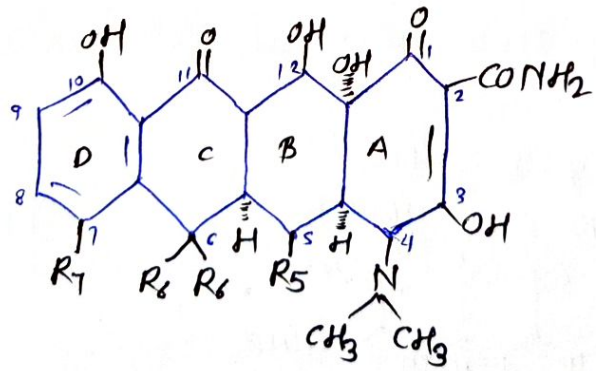
→ The main mechanism of action of tetracyclin is bind with the 30S Submit of the Ribosome.

→ And they stop the tRNA at the site of m-RNA. so the protein synthesis is stop inside the bacteria and bacteria becomes dead.



÷ Structure Activity Relationship ÷ (SAR)

KCL Pharmacy



→ The four cyclic structure is essential for the activity if we change their structure like increase are decrease cycle then their activity will be decrease.

→ The basic nucleus is polycyclic, Octahydro, Nathacene, Carboxamide which contaimes ring A, B, C, D. and essential for the activity

→ The keto enol isomerism at the carbon no 1 and the carbon no 3 is good for the antibacterial activity.

→ When we add any chemical group at the position no six then their activity will be decrease.

→ When we use methylation at the carbon no six then the carbon bonding will be increase.

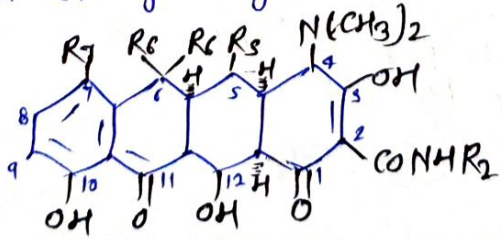
→ When we add any (carbon) group at the position no Seven then their potency will be increase and antibacterial activity will be increase.

→ In the presence of strong acid if we dehydrate the tetracycline at the position no six then it convert into the oxytetracycline and the new compound and which is more powerful.

→ A cis type of fusion b/w ring A & B with α-OH group is necessary for the retention of activity.

→ Tetracyclines are low water soluble derivatives which can be overcome by aminoalkylation at Carboxamide group using mannich reaction.

Ex- Roliteracycline, Lymecycline.



KCL Pharmacy

Name	R_7	R_6	R_6	R_5	R_2
Roliteracycline	-H	$-CH_3$	-OH	-H	$-CH_2$
Lymecycline	-H	$-CH_3$	-OH	-H	$-CH_2NHCH(CH_2)$ COOH

∴ Aminoglycosides ∴

→ The name Aminoglycosides is derived from two words Amino And Glycosids because in this antibiotics two amino group is present and they are connected with the glycosidic linkage so their name is aminoglycoside Antibiotic.

→ Aminoglycoside is obtained from the different type of streptomyces bacteria.

→ The ring is 2-deoxy streptamine → in all aminoglycoside except streptomycine and dehydrostreptomycin.
where the ring is → streptidine.

→ Example of Aminoglycosides ∴

(i) Streptomycin
(ii) Neomycin.
(iii) Kanomycin
(iv) Amikacin
(v) Tobramycin
(vi) Gentamycin
(vii) Sisomycin.
(viii) Nitilmycin
(ix) Spectinomycin etc.

KCL Pharmacy

→ Most widely used against gram -ve enteric bacteria in combination with vancomycin / Penicillin.

→ Streptomycin is the oldest aminoglycosides antibiotic.

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

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

→ He received a noble prize for his work on streptomycin.

← Chemistry / Constitution :-

→ The base → streptomycin itself has an empirical formula $C_{21}H_{39}N_7O_{12}$.

→ Molecule forms a trihydrochloride which indicates the 3-Nitrogen atoms must be basic.

$$C_{21}H_{39}N_7O_{12} + 3HCl \longrightarrow C_{21}H_{39}N_7O_{12} \cdot 3HCl$$

(Streptomycin triacidic base) (Crystalline)

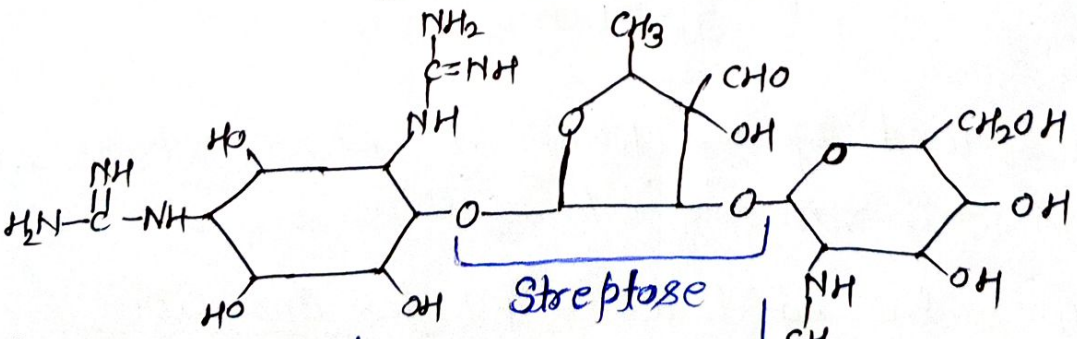
→ Mild acidic hydrolysis cleaves streptomycin into 2-products namely - Streptidine ($C_8H_{18}N_6O_4$) and Streptobiosamine ($C_{13}H_{23}NO_9$).

$$C_{21}H_{39}N_7O_{12} + H_2O \longrightarrow C_8H_{18}N_6O_4 + C_{13}H_{23}NO_9$$

(Streptomycin) (Streptidine) (Streptobiosamine)

∴ Structure of Streptomycin :-

KCL Pharmacy



1,3 diamino cyclohexane

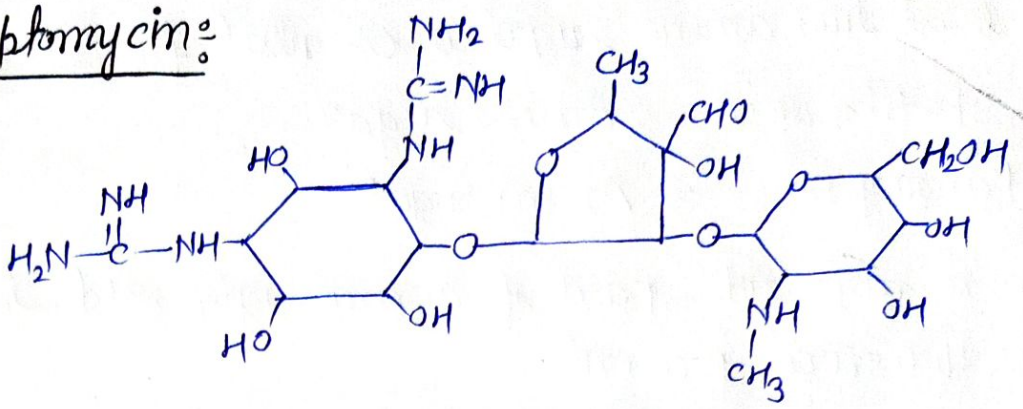
Streptidine.

N-Methyl-L-Glucosamine

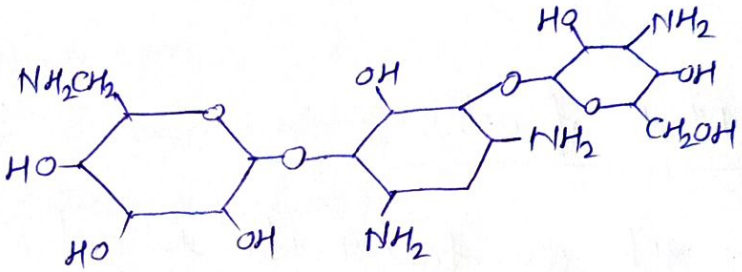
Streptobiosamine.

∴ classification ∴

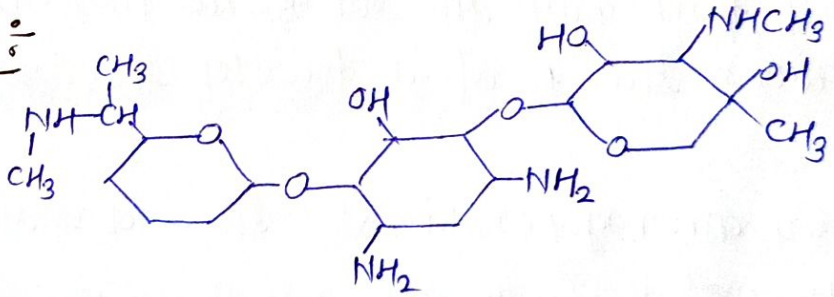
i) Streptomycin ∴



2) Kanamycin ∴ (Kantrex)

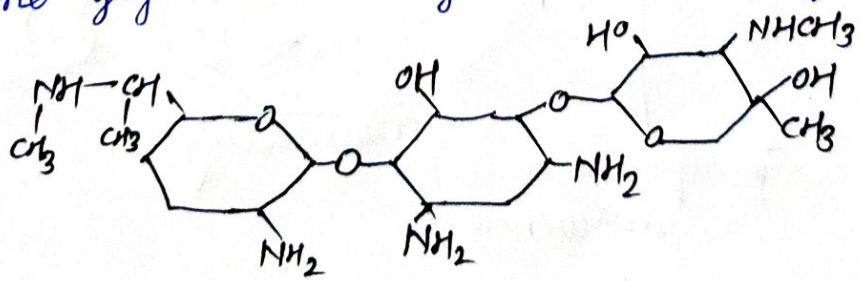


3) Gentamycin ∴



← SAR of Aminoglycosides ∴

i) → In the aminoglycoside at least two amine group and one glycosidic linkage is essential for the activity.



→ The central ring is 2-deoxy streptamine in all aminoglycoside exept streptomycin which contain streptidine mukus.

→ At least two amine sugal is essential for activity.

Ex- Streptomycin — 2 amino sugar.

→ Kanomycin - 3-Amino Sugar.

→ In a glycoside part of a aminoglycoside two imp. structures are present.

A) Amino sugar portion.

B) Hexose ring.

KCL. Pharmacy

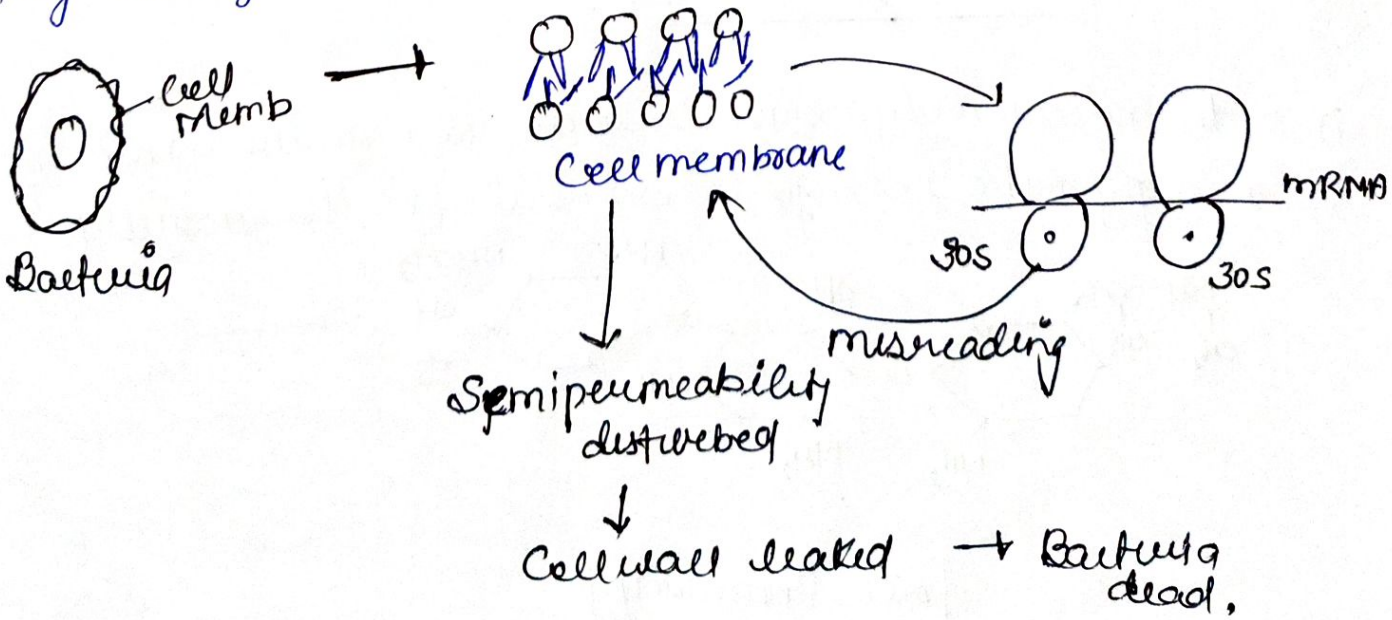
Mode of action

→ Aminoglycoside are bactericidal in action.

→ They bind with the ribosomal DNA portion of 30S Ribosome and causes the ~~inab~~ impairing the proof reading function RNA.

→ Basically aminoglycoside stop the translation process and stop the protein synthesim and by making wrong protein.

they damage the cell membrane semipermeability.



Therapeutic Use

→ Broad antibiotic spectra against aerobic gram +ve and gram -ve bacteria.

→ Streptomycin :- Most commonly used for treatment of tuberculosis.

→ Spectinomycin - For treatment of gonorrhoea.

Characteristic of Aminoglycosides Antibiotics

→ Poorly absorbed from GIT.

→ Poor penetration in CNS

→ Excreted through kidney.

→ Fast resistance developed.

Side effect :-

→ Produce Nephrotoxicity.

Mode of Action :-

→ Effective against gm -ve bacteria.

→ Inhibits protein synthesis.

→ Interferes with ribonucleic acid metabolism.

→ Misreading of code in m-RNA template

Uses :-

→ TB

→ Plague.

→ UTI

→ Meningitis

→ Bacteremia.