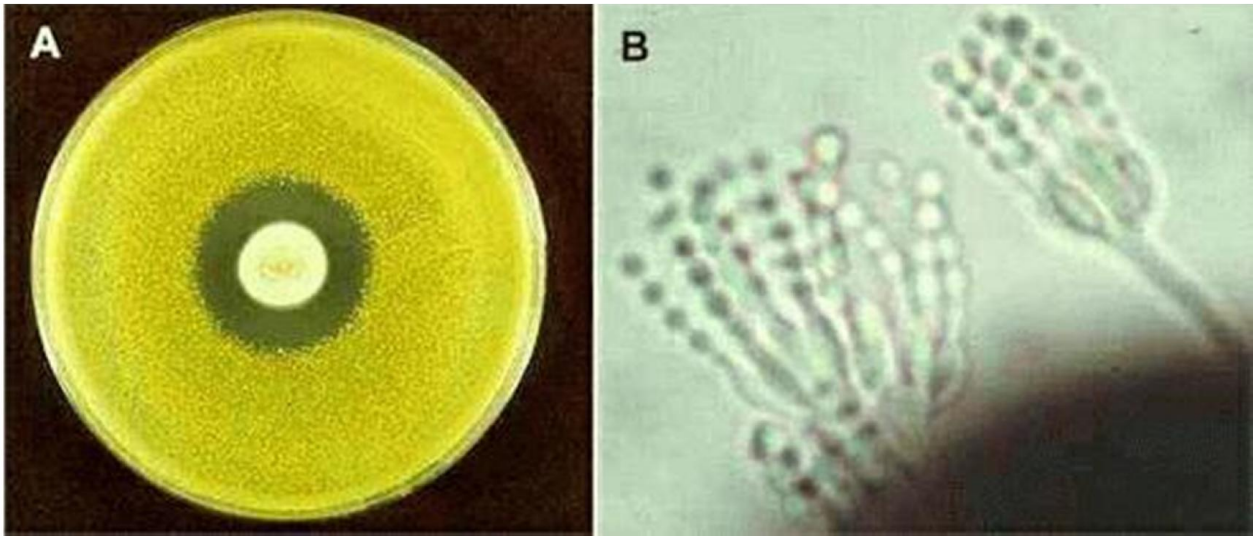
CHEMOTHERAPEUTIC DRUGS

ANTIBIOTICS

HISTORICAL BACKGROUND

1928 Alexander Fleming, Discovered "miracle drug" Penicillin
Inhibition of S. aureus colonies by mold Penicillium notatum;



Definition of Antibiotics

Antibiotic: Substance produced by a microorganism or a similar product produced wholly (synthetic) or partially (semi-synthetic) by chemical synthesis and in low concentrations inhibits the growth or kills of microorganisms

Commercial production

The commercial production of antibiotics for medicinal use follows a general pattern, differing in detail for each antibiotic. The general scheme may be divided into six steps:

1. Preparation of a pure culture of desired organism.
2. Fermentation, during which antibiotics is formed.
3. Isolation of antibiotics from culture medium.
4. Purification
5. Assay for potency, sterility and absence of pyrogens.
6. Formulation into acceptable and stable dosage forms.

Classification of Antibiotics

According their mechanism of Antibiotics actions;

- Inhibition of Cell Wall Synthesis (most common mechanism) →(β –Lactam)
- Inhibition of Protein Synthesis (Translation) (second largest class) →(Aminoglycosides, Tetracyclines, Erythromycins, Chloramphenicol)
- Alteration of Cell Membranes →(Amphotericin B)
- Inhibition of Nucleic Acid Synthesis or action on DNA and/or RNA →(Actinomycin, Rifampin

According their **structures**;

1.β-Lactam antibiotics.

2.Tetracyclines antibiotics.

3. Aminoglycoside antibiotics.

4. Macrolides antibiotics.

5. The lincomycins.

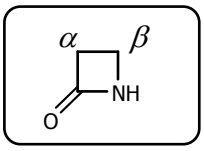
6. The polypeptides

ANTIBIOTICS

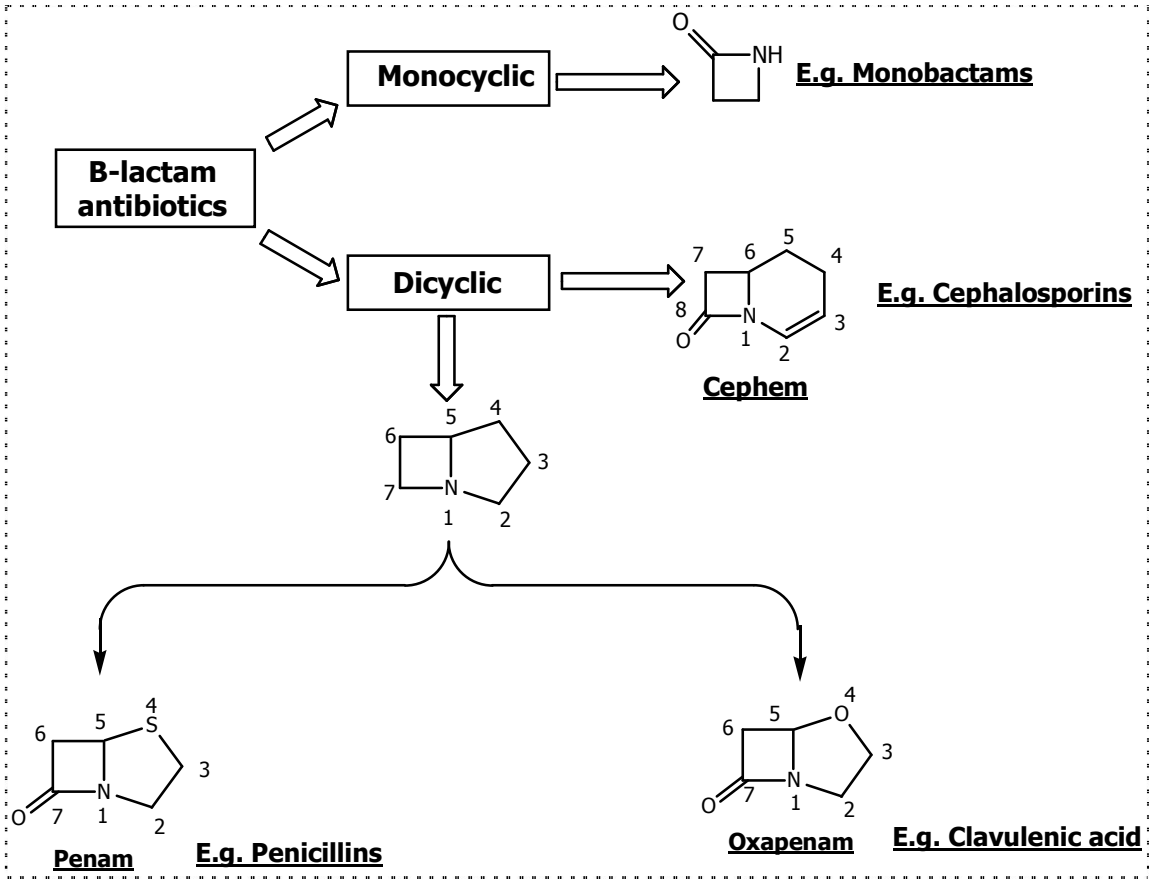
INHIBITORS OF BACTERIAL CELL WALL BIOSYNTHESIS

β-LACTAM ANTIBIOTICS

- **β-lactam ring [cyclic amide]:** is the main part of penicillin and cephalosporin structures.

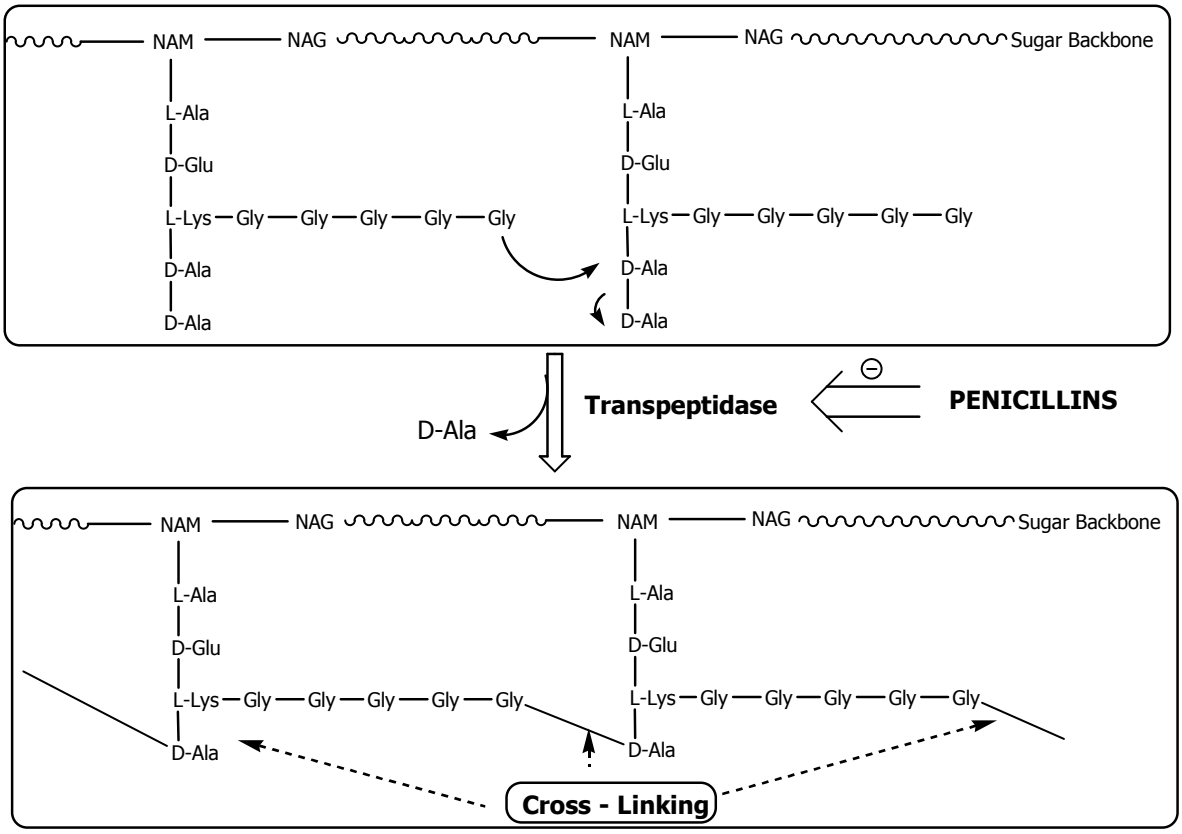


- **β-lactam antibiotics classified into:**



M.O.A. of β-lactam antibiotics [Penicillins & Cephalosporins] [Selective inhibition of bacterial cell wall synthesis]

- Bacterial cell wall is with **Peptidoglycan structure** [peptide + sugar].
- It contains two types of sugar: **NAM** [N-Acetyl Muramic acid] & **NAG** [N-Acetyl Glucosamine].
- The peptide moiety binds to NAM.
- **Cross-linkage** occurs by displacement of D-alanine of one chain by glycine in another → this is done by **Transpeptidase enzyme**.
- β-lactam antibiotics cause **irreversible inhibition of transpeptidase enzyme** → no cross-linkage → leakage of important components and entrance of water → swelling and rupture of cell → **[Bactericidal effect].**

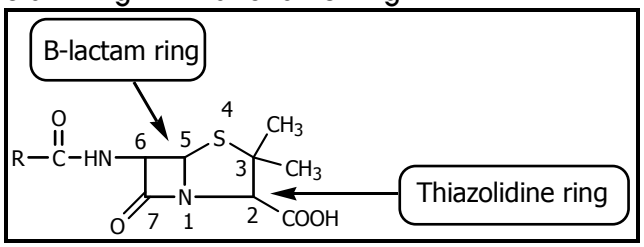


- Transpeptidase enzyme takes penicillin molecule instead of D-ala – D-ala moiety.

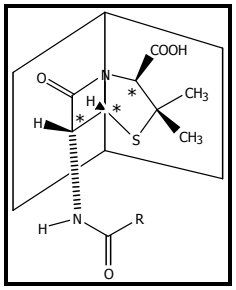
PENICILLINS

Structure & stereochemistry:

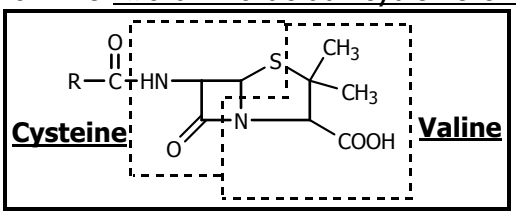
- Bicylic system : β-lactam ring + Thiazolidine ring



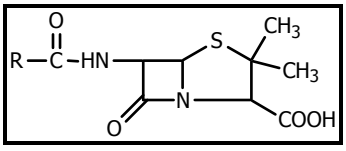
- The two rings are **not plannar** → twisted at N_1 & C_5 axis → half open-book shape.

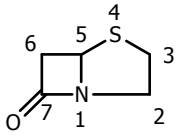
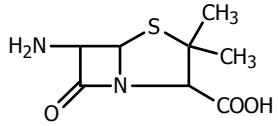
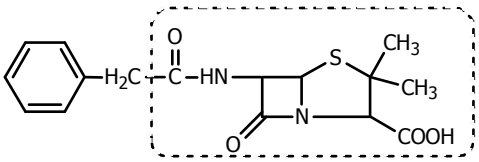


- With three chiral atoms : C_2 [S] , C_5 [R] & C_6 [R].
- Their structure derived from the two amino acids : cysteine & valine.



Nomenclature :

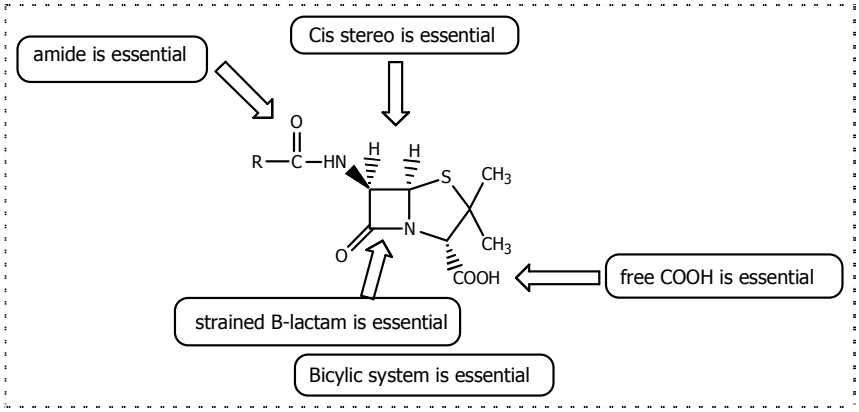


Parent	Chemical name
 Penam	(2S,5R,6R) -6- acyl amino-3,3-dimethyl penam-2-carboxylic acid
 6-Aminopenicillanic acid	Derivatives of 6-APA
 Penicillin G	Using penicillin as suffix & acyl portion as prefix [e.g. benzyl penicillin = Penicillin G]

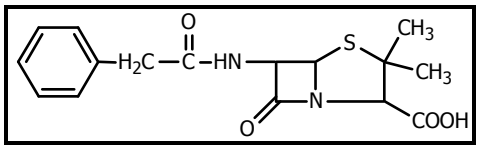
Preparation of Penicillins :

Natural	Biosynthetic	Semisynthetic
Obtained from fermention of *Penicillium chrysogenum*. [e.g Penicillin G]	By addition of different carboxylic acids which incorporated as acyl groups [e.g. Penicillin V by addition of phenoxy acetic acid to medium]	By isolation of 6-APA + synthetic acylation. Acylation is done by: 1. acid chloride. 2. carboxylic acid + DCC [DiCyclohexylCarbodiimde]

SAR :



Penicillin G



- Penicillin G is the **LEAD COMPOUND** of penicillins [as sulphinilamide in sulphonamides].
- The first isolated penicillin → obtained by fermentation of corn steep liquor containing phenyl acetic acid by various strains of *P.notatum & P.chrysogenum*.

Problems [Limitation] of penicillin G:

1. Active ≠ G +ve and some G –ve bacteria. [Narrow spectrum].
2. Inactive orally [acid-labile] → only injection.
3. β-lactamase [penicillinase] sensitive → enzyme produced by resistant bacteria.
4. Short duration of action [rapidly eliminated from kidney → taken every 3-6 hrs].
5. Allergic reactions.

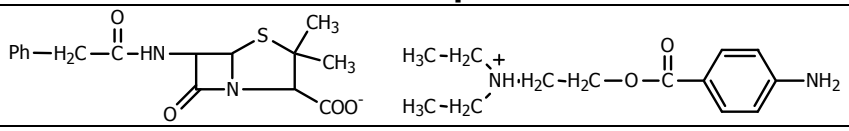
So, we make semisynthetic derivatives to overcome these problems.

- 6-APA is now obtained by enzymatic or chemical hydrolysis of Penicillin G & V NOT by fermentation.

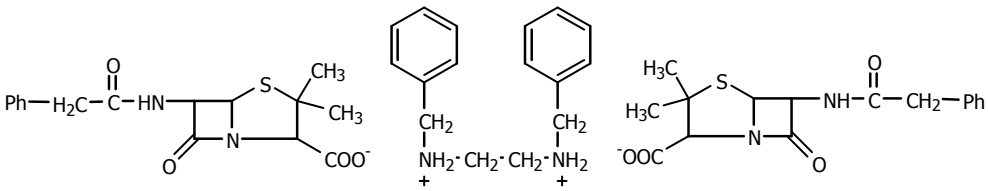
[i] To overcome short duration of action

By making suspension of ↑ M.Wt amino salts.

Penicillin G procaine



Penicillin G benzathine

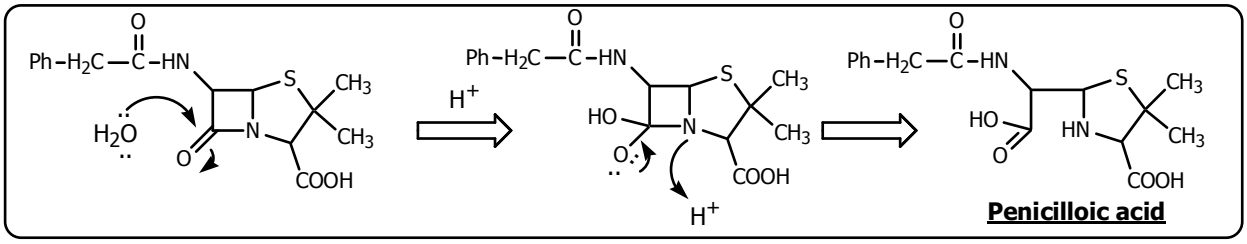


Since benzathine is diamine salt → 2 mole of penicillin G

[ii] To overcome acid sensitivity of penicillin G [oral inactivity]

Acid sensitivity is due to :

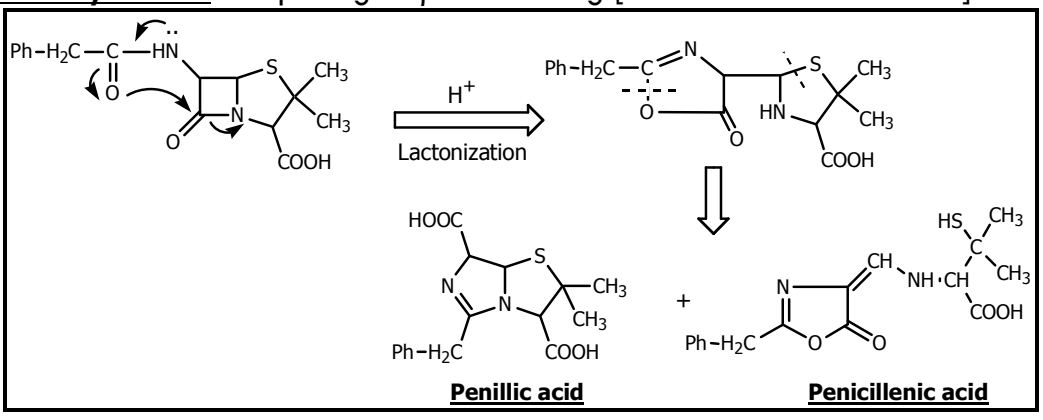
1. **Ring strain:** β-lactam ring is highly strained [4-membered], it's with large angle & trosional strains → acid-catalyzed opening of the β-lactam ring [essential moiety].



2. **Highly reactive β-lactam carbonyl group:** C=O of β-lactam susceptible to nucleophiles. [Not behave as normal tertiary amide which is resistant of nucleophilic attack].

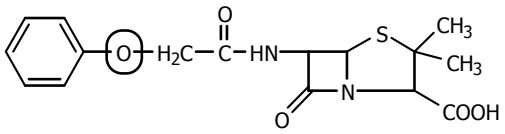
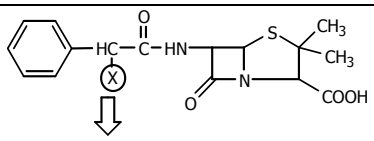
- **Normal amides** are with ↓↓ electrophilicity of carbonyl oxygen due to resonance While that of β-lactam ring is with ↑ electrophilicity that the two ring system isn't in the same plane so, resonance doesn't occur.

3. **Influence of acyl chain:** → opening of β-lactam ring [self destruct mechanism].

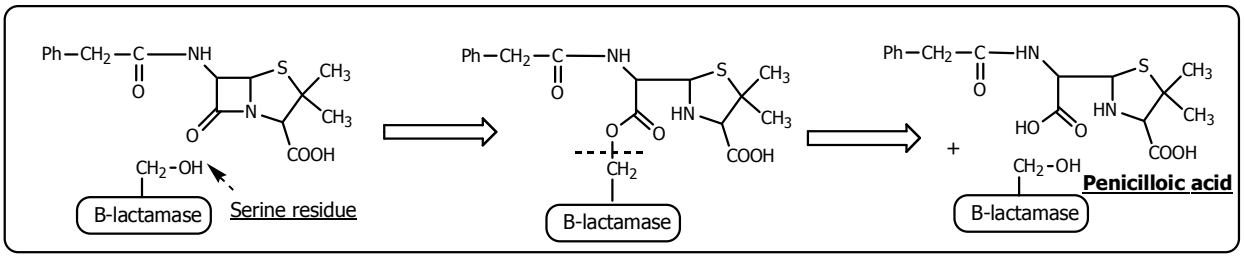


To overcome acid sensitivity:

- The first tow factors can't be treated since β-lactam is the essential moiety which can't be replaced; the only factor we can overcome is the third [acyl chain].
- This is done by ↓ tendency of acyl carbonyl group to act as a nucleophilie **by attachment of e-withdrawing group** to it.

Phenoxymethyl penicillin [Penicillin V]	**Ampicillin & Oxacillin**
	 NH_2 : Ampicillin Heterocycle : Oxacillin
Can be GIVEN ORALLY. Disadvantages : 1. Sensitive to penicillinase. 2. Less active than penicillin G. 3. Allergy.	• Amino is e-donating group BUT can act as e-withdrawing group in two cases : 1. When involved in resonance. 2. When it's protonated [NH_3^+] So, it acts in ampicillin as e-withdrawing group making it orally active.

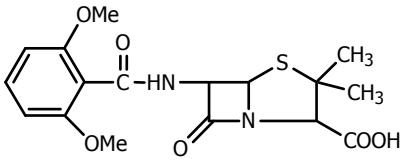
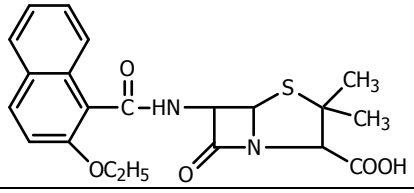
[iii] Sensitivity to β-lactamase

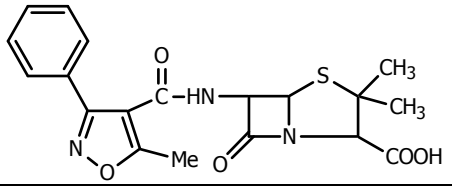
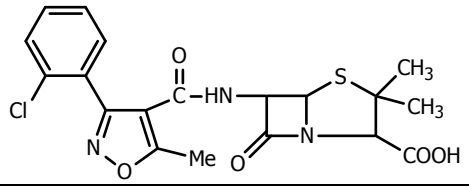
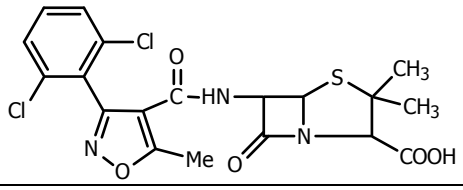
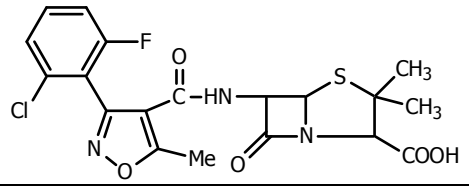


To overcome this problem:

[1] Modify structure of β-lactam antibiotic :

By placing a **bulky group on the side chain** → shielding and steric hindrance.

β-lactamase resistant but acid sensitive	
Methicillin	**Nafcillin**
	

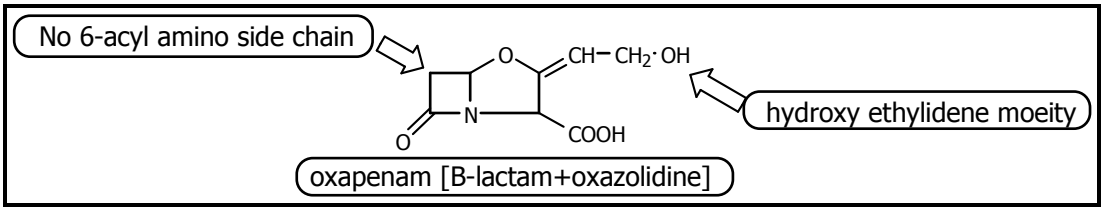
β-lactamase resistant with acid stability	
Oxacillin	**Cloxacillin**
	
Dicloxacillin	**Flucloxacillin**
	

[2] Use β-lactamase inhibitors:

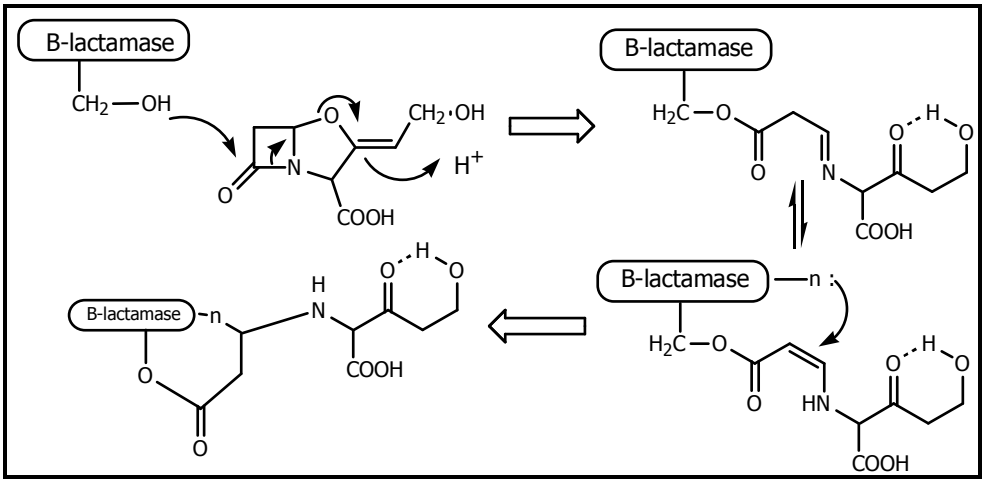
[i] Natural β-lactamase inhibitor

Clavulanic acid

- isolated from *streptomyces clavuligerus*, with weak antibacterial action but potent inhibitor to β-lactamsae.
- Combined with Amoxicillin [Augmentin®] or better combined with Ticarcillin.

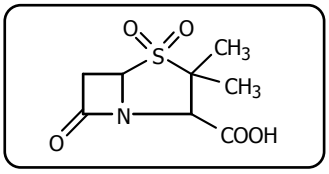


M.O.A: Irreversible inhibitor to β-lactamase [suicide substrate] [mechanism-based inhibitor].

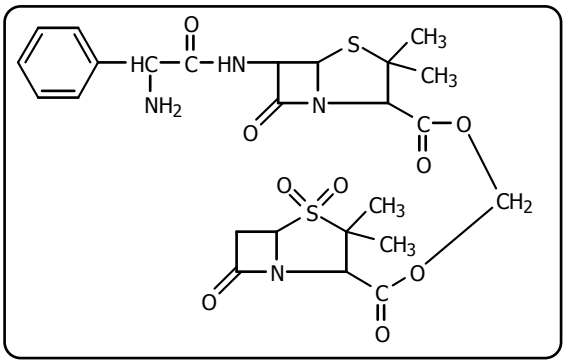


[ii] Semisynthetic β-lactamase inhibitors

Sulbactam



- It's penicillanic acid sulphone with weak antibacterial action.
- Act by the same M.O.A as clavulenic acid.
- Poorly absorbed orally, with ↑ bioavailability parentrally. So, to solve this problem → **Sultamicillin** [mutual prodrug = double ester of formaldehyde hydrate in which one OH esterified with ampicillin & the other with sulbactam] → **Unasyn® tablets.**



Sultamicillin

[iv] Narrow spectrum [with poor activity ≠ G –ve]

Broad spectrum Antibiotics

Notice that :

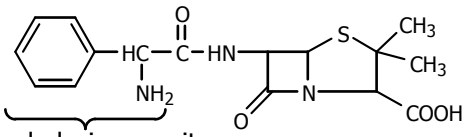
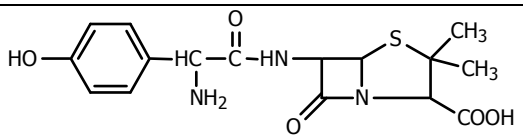
- Hydrophobic gp on side chain [e.g. Penicillin G] : active ≠ G+ve with poor activity ≠ G-ve.
- Hydrophilic gp on side chain : ↑ activity ≠ G-ve & ↓ activity ≠ G+ve bacteria.

G-ve activity ↑ if the hydrophilic gp [NH_2 , OH , COOH] is attached to C α to Carbonyl.

Broad spectrum Antibiotics

[i] Class I:

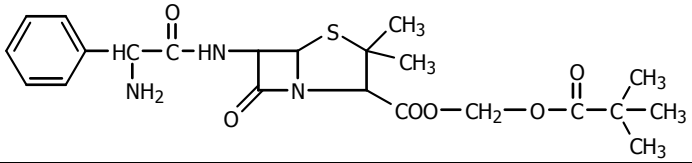
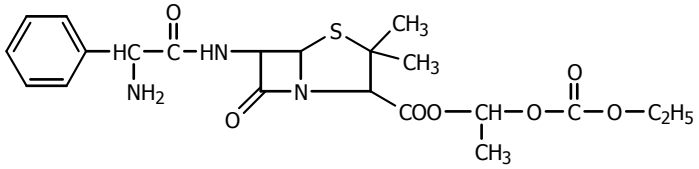
- Taken orally [hydrophilic gp is amino]

Ampicillin	Amoxicillin
 Phenyl glycine moiety	
Poorly absorbed → disruption of gut flora → diarrhea	Similar properties to ampicillin but with better absorption.→ ↓ diarrhea
Properties : • Active ≠ G+ve & G-ve bacteria [not produce β-lactamase] → sensitive to β-lactamase [why?] • Acid resistant [active orally] [why?] • Non-toxic. • Inactive ≠ pseudomonas aeruginosa [resistant species].	
N.B: Ampicillin is poorly absorbed from GIT → disruption of gut flora → diarrhea. This is due to presence of amino & carboxylic group → Zwitter ion which ↓ solubility. So, we make amoxicillin with P-OH group which improve absorption by : 1. Make amoxicillin with 3 polar groups [NH_2, COOH and OH], effect of zwitter ion. 2. Make H-bonding which ↑ solubility & absorption.	

Prodrugs of Ampicillin [to overcome poor absorption] : [by blocking of COOH]

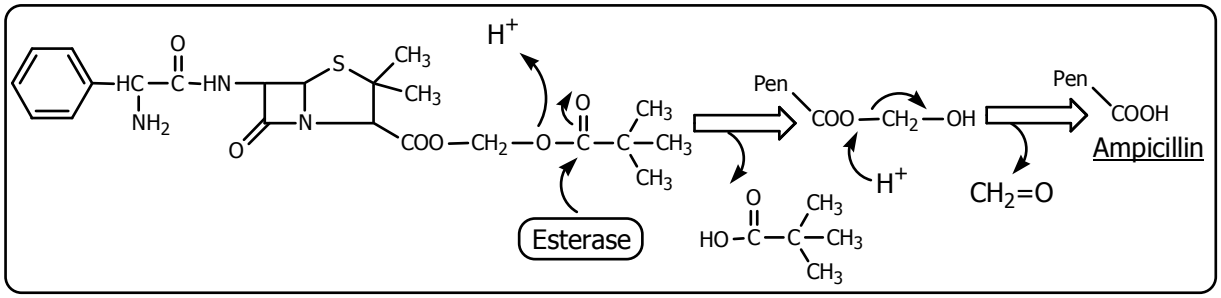
Ampicillin not absorbed due to presence of dipolar nature [COOH & NH_2] → so , we block one of them → esterification of COOH.

- When we make esters of ampicillin to improve its oral bioavailability :
  - It's supposed to be cleaved by esterase enzyme to give free ampicillin BUT pencillin nucleus is very bulky that prevent approach of esterase enzyme.
  - So, we make DOUBLE ESTER which contains a second ester moiety far from pencillin nucleus easy to be attacked by esterase.
  - That's why we CAN'T MAKE SIMPLE METHYL ESTER AS A PRODRUG FOR AMPICILLIN.

Pivampicillin	
Bacampicillin	

By non-specific esterase → Ampicillin

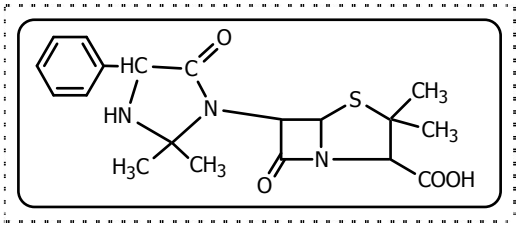
For Pivampicillin :



Hetacillin

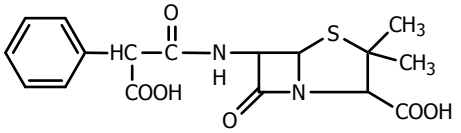
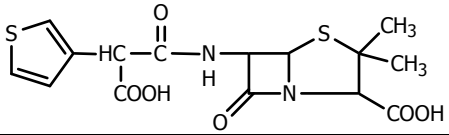
[blocking of amino group]

- Hetacillin is formed by acylation of ampicillin with acetone as follows.
- In aq. solution → Ampicillin. [it's with slower excretion than ampicillin].

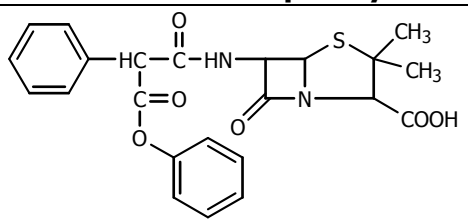
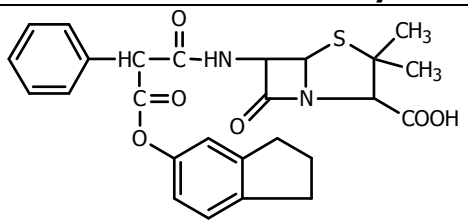


[ii] Class II:[taken parentrally]

[a] Carbenicillin & Ticarcillin

Carbenicillin	Ticarcillin
	
• Introduction of COOH group ↑ G-ve activity. • Clinical use restricted to ↑ dose therapy of *P.aeroginosa* & *Proteus vulgaris*. • ☐-lactamase sensitive & acid labile [given as I.V. as disodium salt → introduction of ↑ amount of Na^+]. • If taken orally → decarboxylate rapidly to benzyl penicillin → loss activity ≠ G-ve]	• Sulfur-based Bioisostere to carbenicillin. • With the same spectrum but show higher pharmacokinetic properties [↑ serum level & longer duration] due to low metabolism.

We make two prodrugs of Carbenicillin to ↑ oral activity :

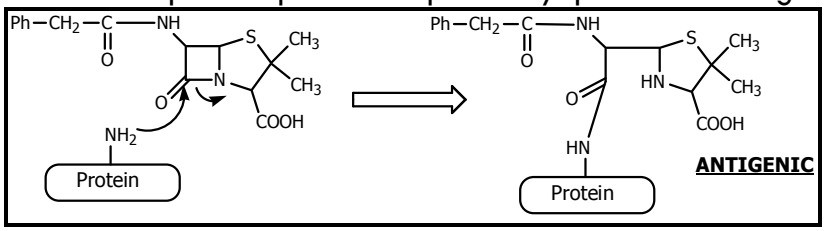
Carbenicillin phenyl	Carbenicillin indanyl
	

[v] Allergic Reactions

- Especially Penicillin G , Ampicillin & Amoxicillin [but all penicillins are reported to cause these reactions].

Causes:

1. Penicillin binds to plasma protein → penicilloyl protein → antigenic.



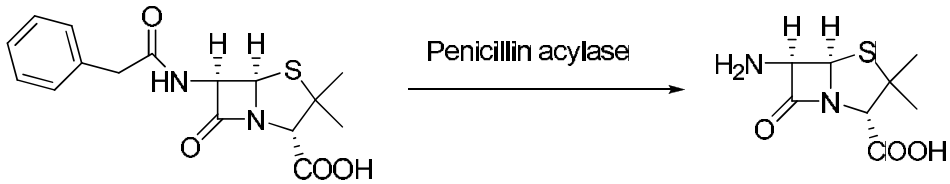
2. Polymeric impurities in ampicillin dosage forms → antigenic

Ampicillin undergo pH-dependent polymerization [especially in conc. solution] → by nucleophilic attack of amino gp in one molecule on β-lactam ring of the other molecule.

Preparations of penicillins:

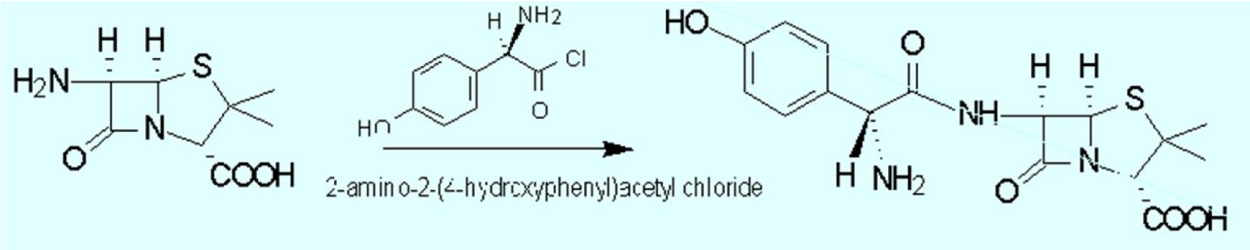
Members of this family of antibiotics differ from each other due to different groups attached to B-lactam ring. These differences include spectrum,stability to gastric acidity and susceptibility to bacterial B-lactamase enzyme.

- The start product for synthesis of semi-synthetic penicillins is 6-Amino-Penicillanic Acid (6-APA) which is produced from penicillin G by acylase enzyme.



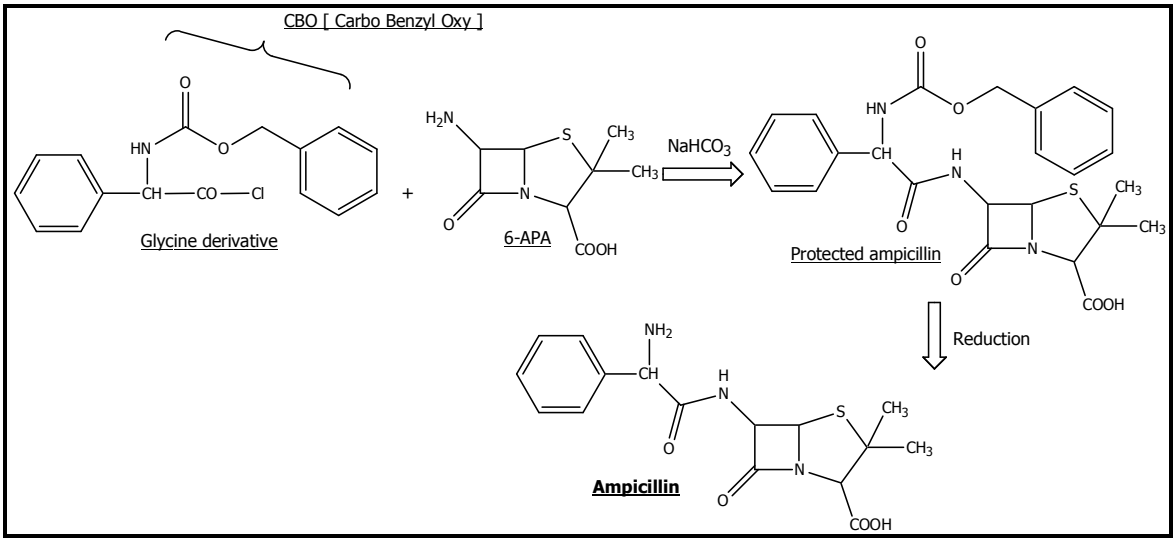
Penicillin G 6-APA

Synthesis of amoxicillin

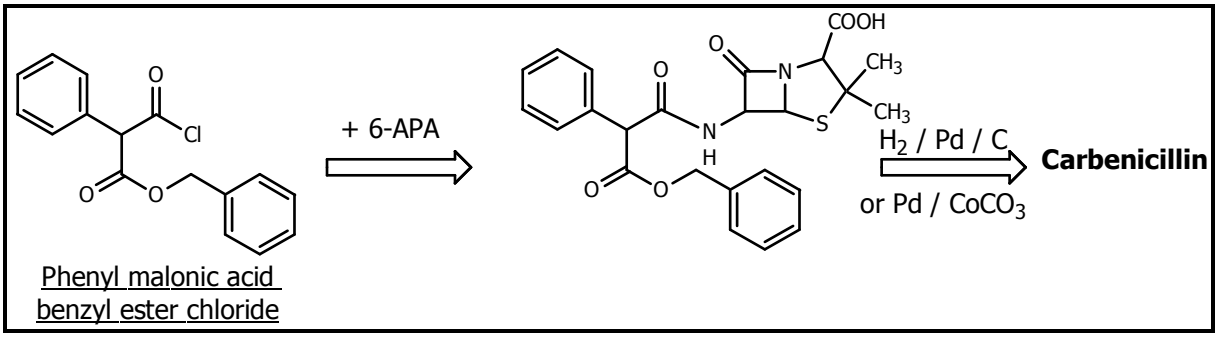


Semi-Synthesis of Ampicillin :

[1]



Synthesis of Carbenicillin :



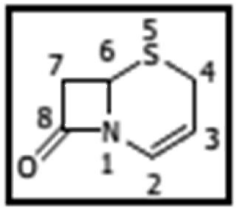
Cephalosporin

Obtained:

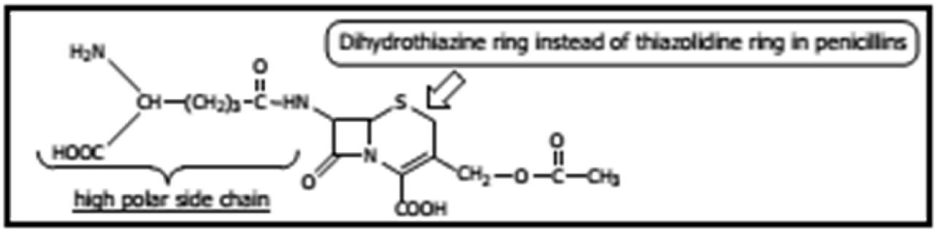
- Naturally from cephalosporium strains
- semi-synthetically through acylation of 7-ACA [7-AminoCephalosporonic Acid .[

.

The basic structural unit is 2-cephem.



The first one discovered is Cephalosporin C.



It's derived from the same biosynthetic precursors as penicillin [from Valine & Cysteine

Advantages

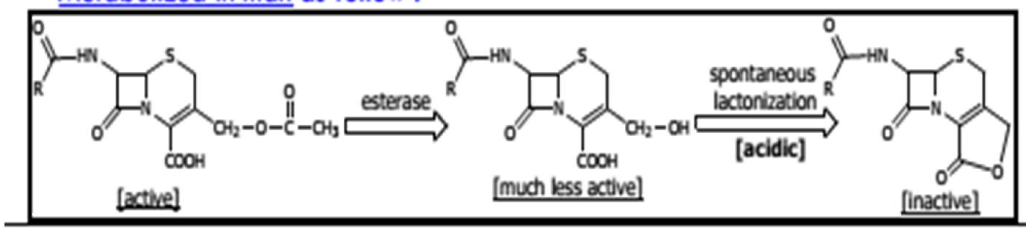
- Low risk of allergic reactions
- More stable to penicillinase than Penicillin G [equivalent to Oxacillins due to bulky side Chain].

1. Active ≠ G+ve& G-ve [Broad spectrum].

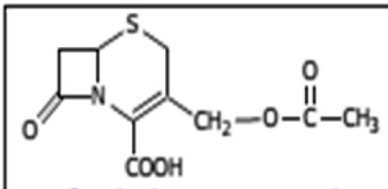
Disadvantages

2. .Not absorbed orally due to:
   - Acetomethoxy group undergo lactonization in acidic medium .
   - High polarity of side chain [low GIT absorption].

- Metabolized in man as follow :



Nomenclature:



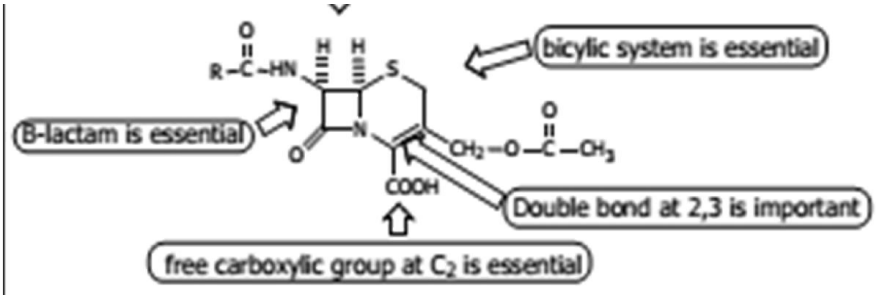
Cephalsporanic acid

- Use Cephalosporanic acid & refer to substituents at C_7.
- E.g. Cephalosporins = 7-acylamino cephalosporanic acid.
- **Applied only** to derivatives that have 3-acetoxymethyl group.

We make semisynthetic products of Cephalosporin C to

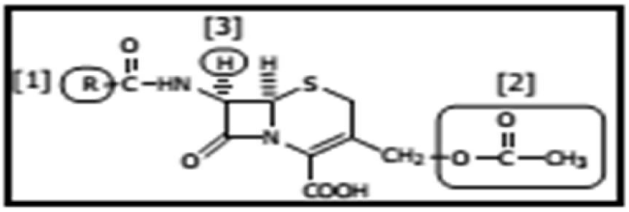
1) Increase spectrum of activity .
2) Increase stability ≠ b-lactamase .
3) Improve oral bioavailability& pharmacokinetics .

SAR of Cephalosporin C:



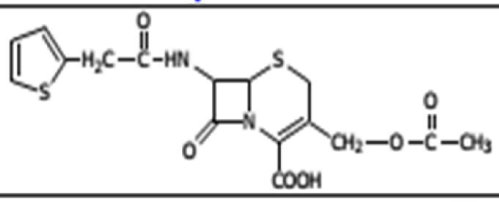
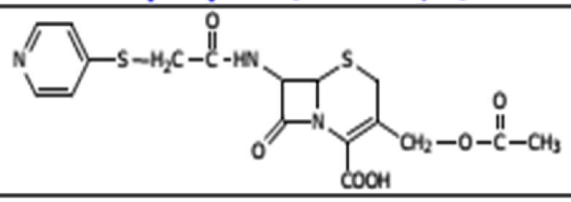
Modification of semisynthetic cephalosporins:

1) Substitution at acyl amino by different acids.
2) 3- acetyl-methoxy side chain : nucleophile substitution of 3-acetoxy gp by N or S nucleophiles or reduction of 3-acetoxy to3-methyl .
3) Substitution atC7 : e.g.7 methoxyl group [Cephamycins].



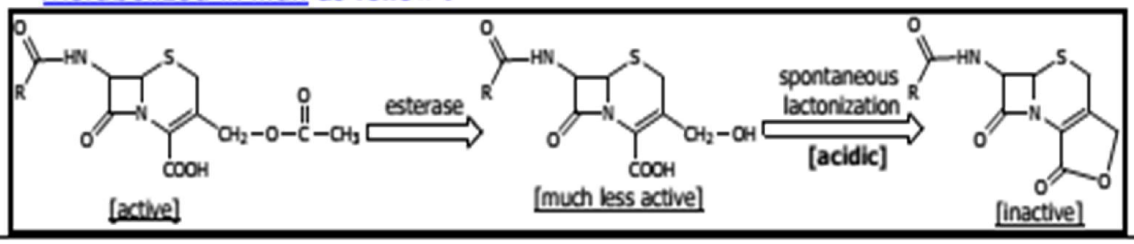
Frist Generation Cephalosporins

1) Analogues by modification of 7-acylamino example: Cephalothin Cephapirin

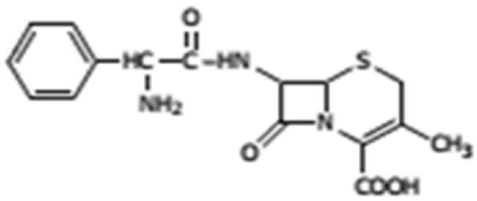
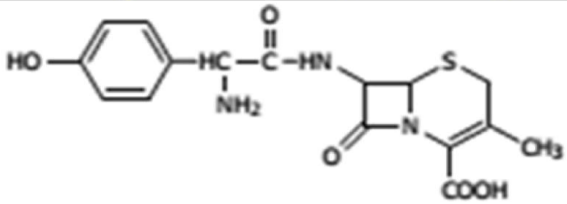
Cephalothin	Cephapirin [Cefatrexyl®]
	

Used Parentrally

- Spectrum is broader > penicillin G [similar to Ampicillin].
- Poorly absorbed from GIT → used parentrally as aqueous solution of Na salts.
- ↓ chance of allergy → can be used for patients allergic to penicillins.
- Metabolized in man as follow :



2) Analogues by variation of 3-acetoxy methyl

Cephalexin [Ceporex®]	Cephadroxil [Duricef®]
	

All with 3-Methyl group → Can be used orally

It maintains its activity through:

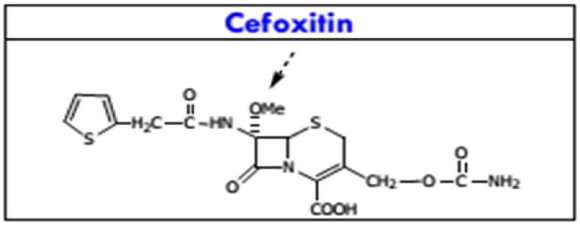
a) No lactonization occurs due to absence of 3-acetoxy methyl .
b) Methyl gp atC3 make balance between hydrophilicity & lipophilicity lead to increase absorption .
Analogues by sub

3) Analogues by substitution at C7 by methoxyl group [Cephamycins]

Example: Cefoxitin.

Properties of Cefoxitin: [2 generation

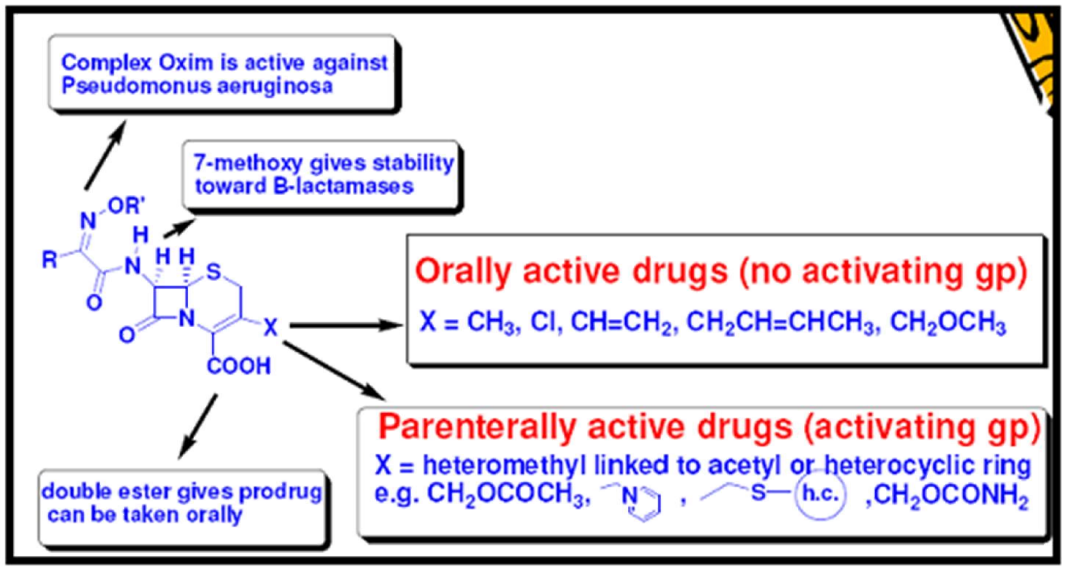
a) Stable to b-lactamase due to presence of 7a-methoxy [make steric hinderance [
b) Stable to mammalian hydrolytic enzymes [esterases]due to presence of amide not ester .
c) Broader spectrum of activity than other cephalosporins [due to b-lactamase resistance .[
d) Poor GIT absorption and taken by injection due to highly polar side chain. It taken with local anesthetic [painful .[



Amides are less hydrolyzed than esters due to:

a. Esterase present in all tissues while amidases present in some tissues only .
b. Due to resonance of amides make carbonyl gp less electrophilic hydrolysis .

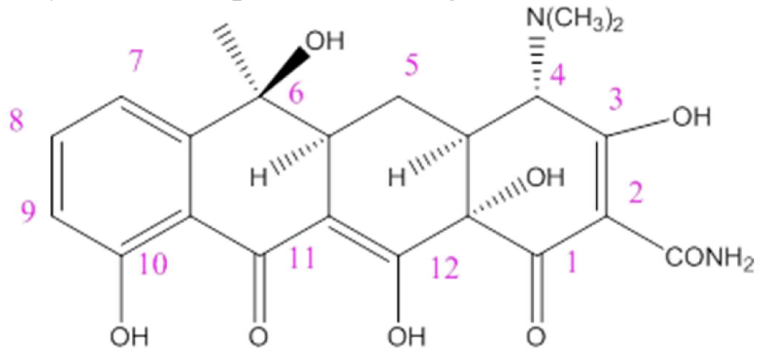
Summary



- Other generation: Cefotaxime, Ceftriaxone and Cefepime
  - Active against gram-negative bacteria
  - Active against Pseudomonas aeruginosa
  - Penetrates the CNS => used for meningitis.

Tetracycline Antibiotics

Tetracyclines are produced by *actinomyces* which have broad antibacterial spectrum. The basic skeleton of tetracyclines is naphthacene ring.

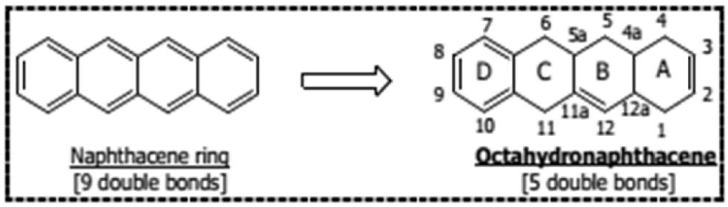


Mechanism of Action:

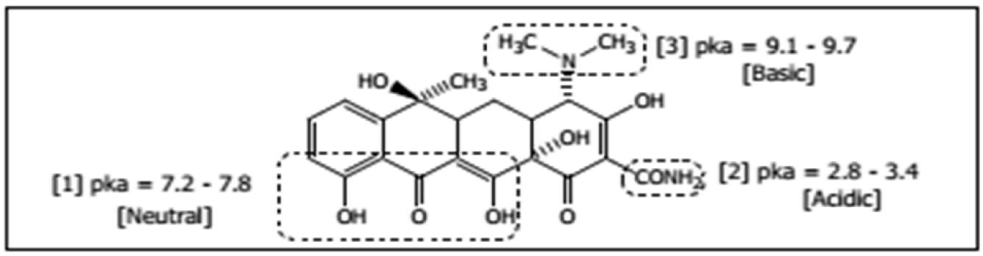
Tetracyclines inhibit bacterial protein synthesis by blocking the attachment of the t-RNA-amino acid to the ribosome.

Physical & Chemical Properties :

1. Contain highly functionalized, partially reduced Naphthacene ring system



2. They are amphoteric substances : They are with 3 pka values :



3. Tetracyclines show incompatibility when co-administered with milk , antacids or hematinic. This is due to chelation. So, to avoid that, take ion preparation 1 hr before or 2 hrs after administration of

4. They are painful upon I.M injection: due to chelation with Ca+2 present in muscles led to insoluble complex precipitation and cause pain & irritation.

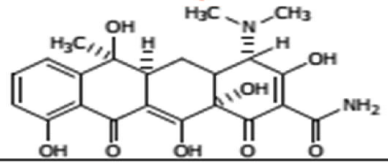
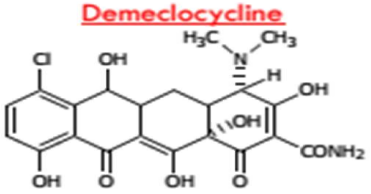
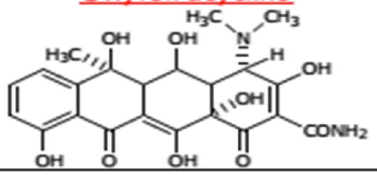
   So, to solve this problem: Add EDTA to injectable product [to form water soluble complex with Ca+2.

5. They are not recommended for pediatrics or children : this is due to chelation with Ca+2

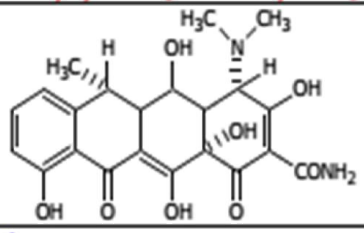
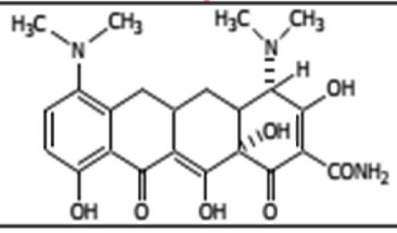
   making insoluble complex that precipitate in teeth making dark colored teeth& deprive bones & teeth

Commercially available tetracyclines

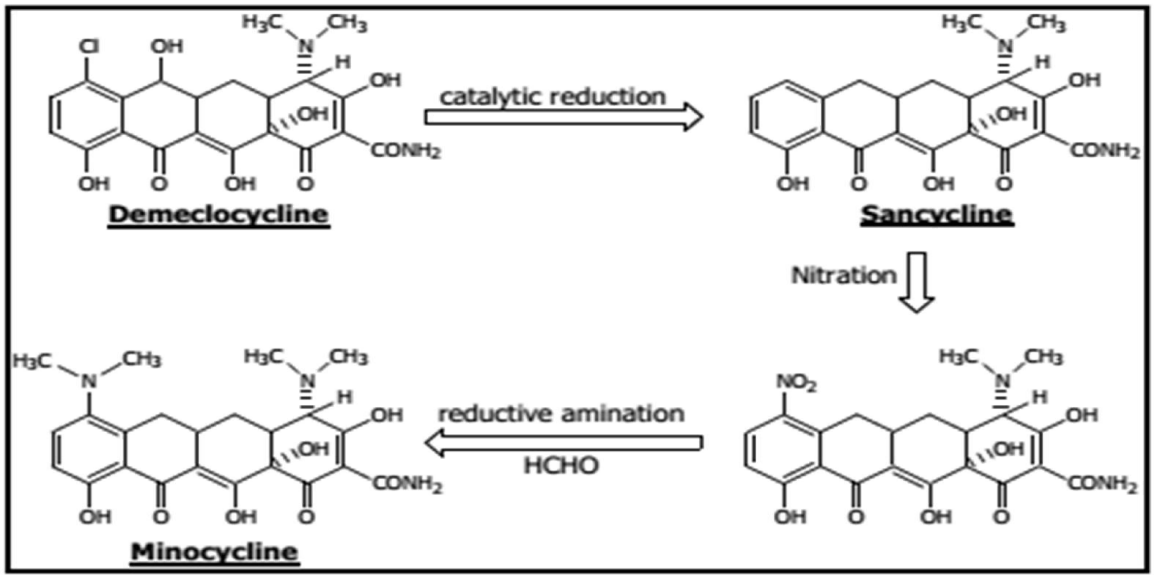
[I] Natural Tetracyclines

Tetracycline 	➢ Produced by fermentation of *Streptomyces aureofaciens*. ➢ Classical & cheap antibiotic.
Demeclocycline 	➢ Produced by fermentation of genetically altered strain of *Streptomyces aureofaciens*. ➢ It lacks 6-methyl of tetracycline → present as 2ry alcohol → more stable > tetracycline & chlorotetracycline to both acids & bases.
Oxytetracycline 	➢ Produced by fermentation of genetically altered strain of *Streptomyces rimosis* . ➢ The most hydrophilic tetracycline on the market.

[II] Semi-synthetic Tetracyclines

Doxycycline [Vibramycin®]	Minocycline
	
➢ Cause ↓ GIT disturbance & with no degradation [due to absence of 6-OH & so, no dehydration occurs]. ➢ The tetracycline of choice for many physicians.	➢ Lipophilic drug → excellent blood level on oral administration [once daily]. ➢ Stable ≠ acids & bases.

Semi-synthesis of Minocycline :

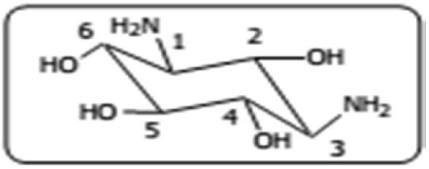


Aminoglycoside Antibiotics

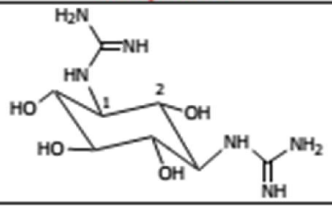
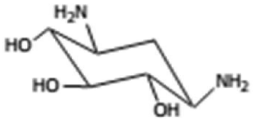
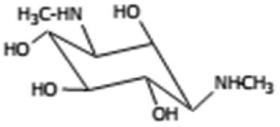
- Obtained from Streptomyces species .
- First one used is Streptomycin. [Lead compound[

General Properties

- They all contain the PHARMACOPHORIC GROUP à1,3-diamino inositol.



- From this moiety ;we have 3pharmacophoric groups :

Streptidine	2-deoxy streptamine	Spectinamine
		 Spectinamine

- OH of these pharmacophores react with several amino sugars by glycoside bonds à pseudo oligosaccharides [Aminoglycosides.[
- Various aminoglycosides are freely water soluble at all pHs .
- React with Basic compounds ; forming acid addition salts .
- Not absorbed in significant amounts from GIT [when given orally local GIT action .

- They are given I.M. or by perfusion and excreted in the active form in high concentration in urine . [so, when there's kidney problem reduce injection dose[

Toxicity:

- Ototoxicity: is due to affinity of theses agents to the sensory cells of the inner ear .
- Kidney tubular necrosis : glomerular functions [due to special affinity of these agents to kidney cells].

Resistance by:

Bacterial elaboration of R-factor mediated enzymes which includes :

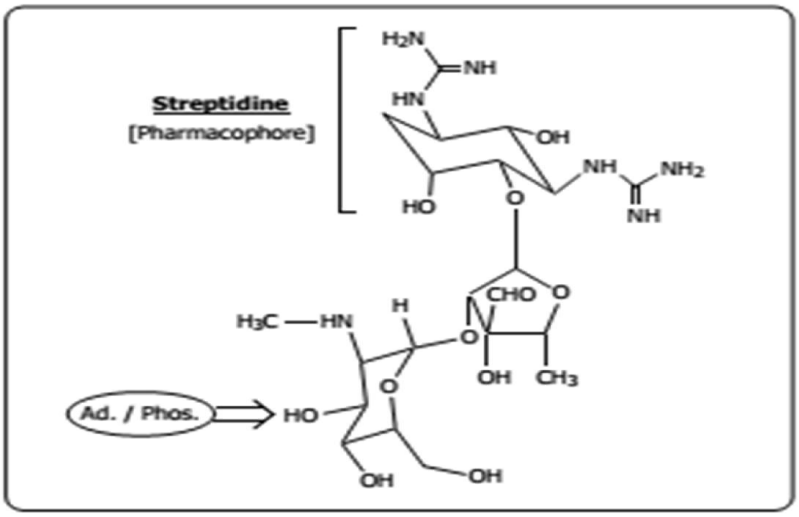
- Aminoglycoside Acetylase [AAC] make N-acetylation of NH- group. /O acetylation .
- Aminoglycoside Phosphorylase [APH] make O-Phosphorylation .
- Aminoglycoside Nucleotide Transferees [ANT] make O-Adenylation [transfer of nucleotides .[

Therapeutic application

- With broad spectrum : Act against G +ve, G –ve [but used only when severe G –ve infection due to their toxicity.
- Streptomycin is used in ttt of T.B .while Spectinomycin is used in ttt of Gonorrhea.

I] Aminoglycosides containing Streptidine]

Example; Streptomycin



]

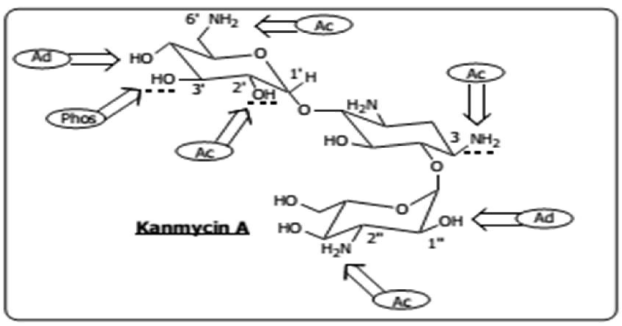
II] Aminoglycosides containing 2-Deoxy streptamine

[i] Kanamycin

It's a mixture of 3 components A,B,C [A predominated

[Unstable to R-factor mediated enzymes: [inactivation

Example:



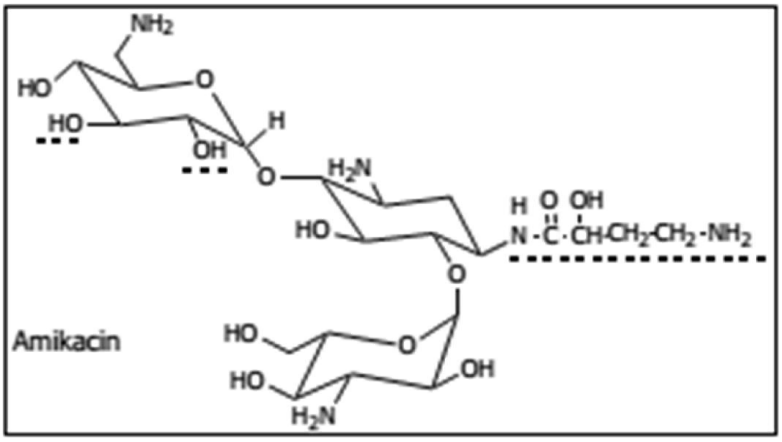
Inactivation by O- phosphorylation

[ii]Amikacin

Semi-synthetic compound obtained by acylation of 3-aminogroup of deoxystreptamine ring of Kanamycin A with g-amino-a-hydroxy butyric acid [L-AHBA] L-isomer > D-isomer in activity.

[ii] Amikacin

[3-N-γ amino-α-hydroxy butyryl kanamycin]



Advantages of Amikacin:

- Less toxic than Kanamycin .
- Resist attack by most bacterial in activating enzymes ; this is due to bulky group [L-hydroxy amino buteryl amide ; L-HABA] which inhibit acetylation , adenylation & phosphorylation in the distant amino sugar ring atC2' ,C3'&C4 . '

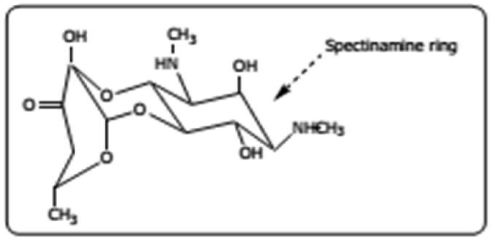
Uses:

Used competitively with Gentamicin for treatment of sensitive strains of T.B.& severe Pseudomonas Aeruginosa infections resistant to other agents .

iii] Aminoglycosides with Spectinamine
Spectinamycin

iii] Aminoglycosides with Spectinamine

Spectinamycin



Uses :

- Used in single bolus injection I.M. ≠ Neisseria gonorrhea & specially Penicillinase-Producing strains of N.gonorrhea [PPNG] → in ttt of gonorrhea ; it doesn't cause oto- or nephro- toxicity.

Macrolide Antibiotics

Properties :

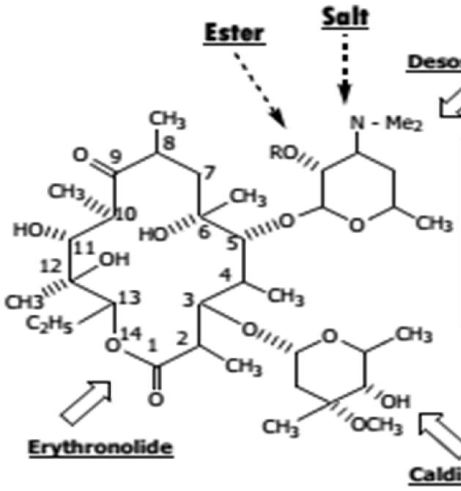
- It's termed MACROLIDES ; that it contains large lactone [cyclic ester] ring.
- They have tow or more sugars attached to 14-membered ring. One of this sugar carries a substituted amino group [so, weakly basic molecule with pka=8].
- They are not very water soluble as free bases but form salts with certain acids :
  - Glucohepatonoic acid → ↑ water solubility.
  - Layryl sulphate & stearic → ↓ water solubility.

M.O.A :

Bind to 50 S ribosomal subunit → prevent translocation of aminoacyl t-RNA → inhibition of protein synthesis → Bacteriostatic action.

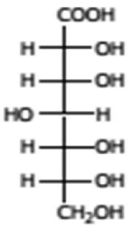
Clinically important macrolides

Erythromycin



	R	Salt
Erythromycin	H	----------
Erythromycin Glucepate	H	Structure A
Erythromycin Stearate	H	CH_3-$(CH_2)_{16}$-COOH
Erythromycin Ethyl succinate	$CO(CH_2)_2$-COO-Et	----------
Erythromycin Estolate	$COCH_2CH_3$	CH_3-$(CH_2)_{11}$-OSO_3H

A =



- Obtained by fermentation of *Sterptomyces erythereus.*
- Consist of :
  1. Erythronolide [large lactone ring , 14-membered, aglycone part].
  2. Desosamine [amino sugar]
  3. Caldinose [neutral sugar].

- Used usually as mixture of 90% Erythromycin A + 10% Erythromycin B + traces of Erythromycin C.

To overcome its bitter taste & its irregular absorption :

1. **Erythromycin salts :**

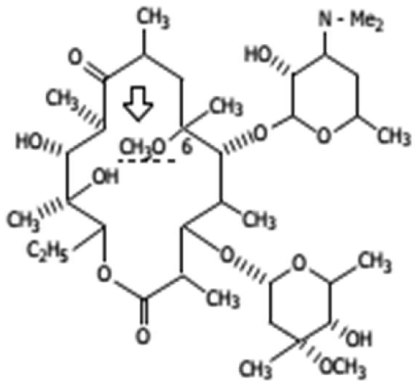
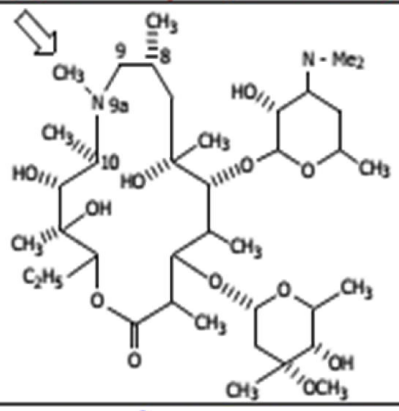
   - Formation of acid salts with dimethyl amino gp of desosamine.
   - E.g. Erythromycin Glucepate & Stearate.
     - Glucepate → freely soluble in water → taken parentrally [I.V].
     - Stearate → ↓ water solublility but is tasteless → taken orally & then release Erythromycin base in intestine; which then absorbed.

2. Erythromycin Prodrugs :

- Erythromycin ethyl succinate : mixed double ester [one carboxylic of succinic acid react with $C_{2''}$ of erythromycin & other carboxylic react with ethanol]. It's insoluble in water [used as oral suspension for pediatrics as it masks bad taste of erythromycin]
- Erythromycin Estolate [$C_{2''}$-propionyl ester] & N-lauryl sulfate salt. It's insoluble in water with super oral absorption compared to erythromycin ethyl succinate.

Semi-synthetic analogues

[To overcome inactivity of Erythromycin in acid medium]

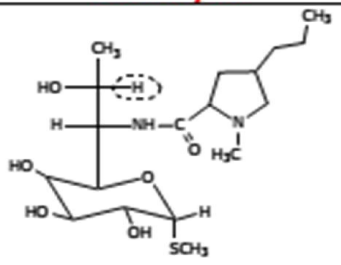
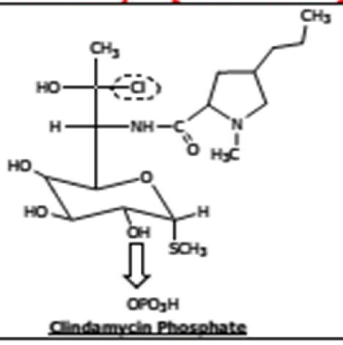
[i] Clarithromycin [Klacid®]	[ii] Azithromycin [Zithromax®]
	
Semi-synthetic drug from erythromycin by METHYLATION OF 6-OH. Advantages : 1. 6-OH involved in cyclic ketal formation which form inactive drug + GIT cramps. [↑activity+↓ cramps] 2. Methylation of 6-OH → the more lipophilic methyl ether → ↓ & less frequent dosage.	➢ Semi-synthetic → RING-EXPANDED ANALOGUE [15-MEMBERED] by insertion of N-methyl between C_9-C_{10} + REMOVAL OF C=O. ➢ Should be taken on empty stomach [otherwise; metallic taste]. Advantages : 1. More acid stable.[Not form cyclic internal ketal] 2. ↑ tissues penetration; so with longer duration [once daily] 3. Greater G-ve activity > Erytho- & Clarithromycin.

Lincosamides

- Chemically distinct but pharmacologically similar to Macrolides.
- Composed of : unusual 8C-sugar (thiomethyl amino-octoside)→ linked by n-propyl substituted N-methyl pyrrolidyl carboxylic acid.
- Weakly basic comounds → form HCl salts.

Metabolism :
Both undergo extensive liver metabolism by N-demethylation → N-DESMETHYL ANALOGUE IS ACTIVE.

Side effects :
↑↑ GIT complains [nausea, vomiting , cramps & drug-related diarrhea].

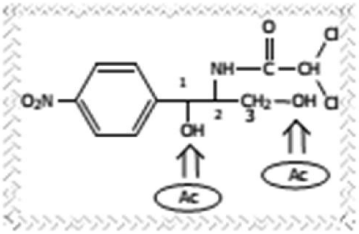
Lincomycin	Clindamcyin [Dalacin-C ®]
	
Natural prduct from fermentation of *Streptomyces lincolnensis.*	➢ Semisynthetic from Lincomycin; by SN_2 reaction which invert 7-R-OH → 7-R-Cl [by $SOCl_2$]

Clindamycin :

- More lipophilic & more bioactive > Lincomycin → better absorbed orally.
- When injected as phosphate prodrug [Clindamycin phosphate] → less painful than erythromycin.
- With clinical spectrum as macrolides but with better distribution into bones.
- Active ≠ G+ve coccal infection especially in patients allergic to β-lactams , with better activity ≠ anaerobes.
- With excellent activity ≠ *Propionabacterium acnes* when applied topically.

Miscellaneous Antibiotics

Chloramphenicol



D(-) threo-2-dicloro acetamido-1-(4-nitro phenyl) propane-1,3-diol

- Natural ; produced by fermentation of *Streptomcyes venezuelae*.
- With simple chemical structure → several methods of total chemical syntheses.

M.O.A :
Binds to 50 S ribosomal subunits in regions near where macrolides bind → inhibit protein synthesis.

Metabolism : [inactive metabolites]
- Orally → rapidly & completely absorbed [with very short $t_{1/2}$].
- Major metabolite is C3-glucuronide ; minor is by deamination , dehalogenation or reduction of aromatic nitro gp. [all are inactive].

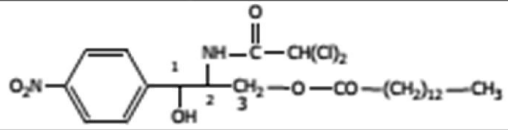
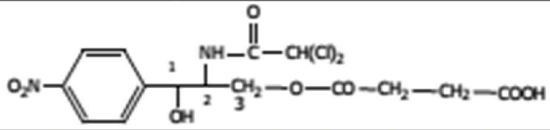
Resistance :
1. R-factor enzymes → acetylation of 1ry & 2ry OH → inactivation [product can't bind to ribosomes]
2. Inability of chloramphenicol to penetrate m.o.

Uses :
- Meningitis : it penetrates CSF.
- Typhoid & Paratyphoid fever : it penetrates well into lymph & mesenteric ganglia.

Side effects : [Not widely used due to its ↑ side effects]

1. Bone marrow depression : → APLASTIC ANEMIA; this is caused by one of the reduction products of aromatic nitro group.
2. Gray syndrome : form of CVS collapse;
   Occur when given in first 48 hrs of life [liver glucuronidation is undeveloped] → rapid accumulation
3. Inhibition of hepatic mixed function oxidases ;
   block metabolism of some drugs → ↑ their concentration [toxicity].

Prodrugs : [C_3-esters]

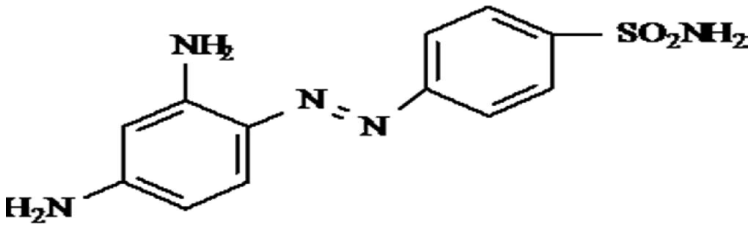
Chloramphenicol Palmitate	Chloramphenicol Hemisuccinate
	
To OVERCOME BITTER TASTE [for pediatric oral suspensions] → cleaved in duodenum to give active drug.	Forms a water soluble sodium salt [used for injection to overcome poor water solubility] [used I.V. not I.M. as it's cleaved in muscles too slowly]

Therapeutic applications : [Of limited use due to its highly side effects].

1. Typhoid & paratyphoid fever , Haemophilus infections [especially epiglottitis & meningitis ; when given with ampicillin]
2. Penumococcal & meningococcal meningitis in β-lactam allergic patients.
3. Anaerobic infections [by bacteroides].
4. Backup for tetracycline in rickettsial infections.
5. As eye drops for ophthalmic infections.

Sulfonamides

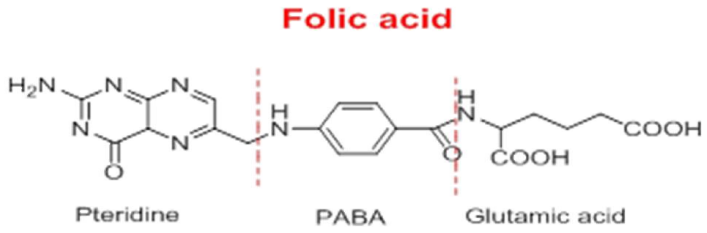
- Originally, sulfonamides were synthesized in Germany as azodyes. In an attempt to expand on earlier ideas of using dyes as antimicrobial agents, a man by the name of Domagk.
- German bacteriologist and pathologist who was awarded the 1939 Nobel Prize for Physiology or Medicine for his discovery (announced in 1932) of the antibacterial effects of Prontosil, the first of the sulfonamide drugs

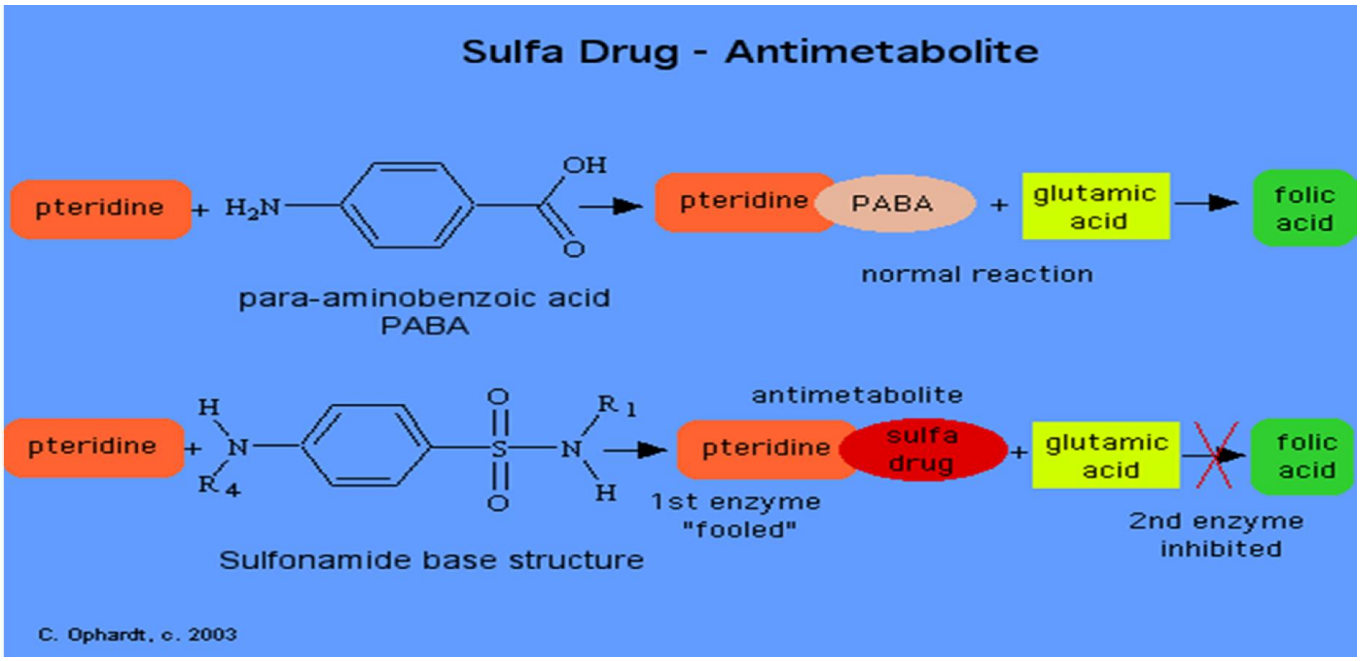


Prontosil

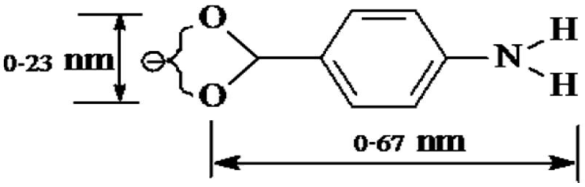
Mechanism of Action

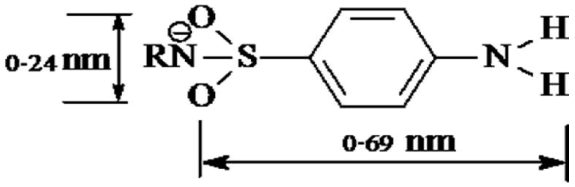
- sulfonamides are structural analogues of PABA.They compete with it for the enzyme dihydropteroate syntheses leading to inhibition of folic acid synthesis with consequent inhibition of DNA & RNA synthesis .



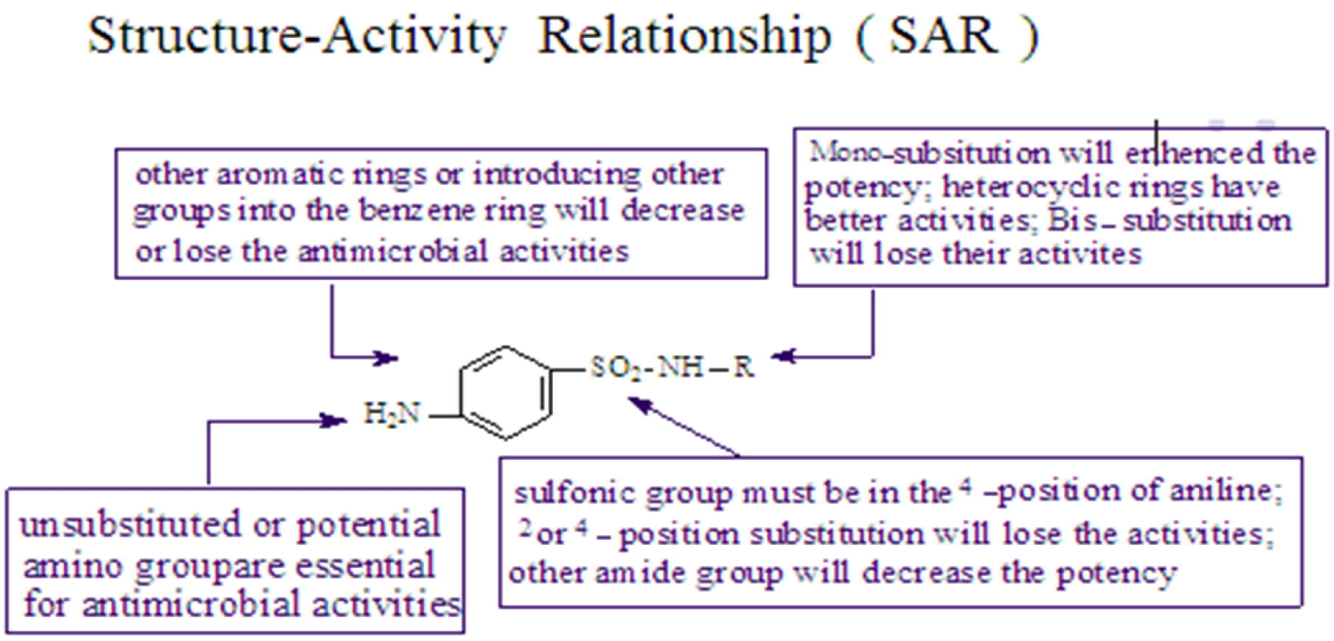


Both the size and distribution of charge of the sulfonamides and PABA molecule are very similar, so sulfa drug play a role of metabolism antagonist.



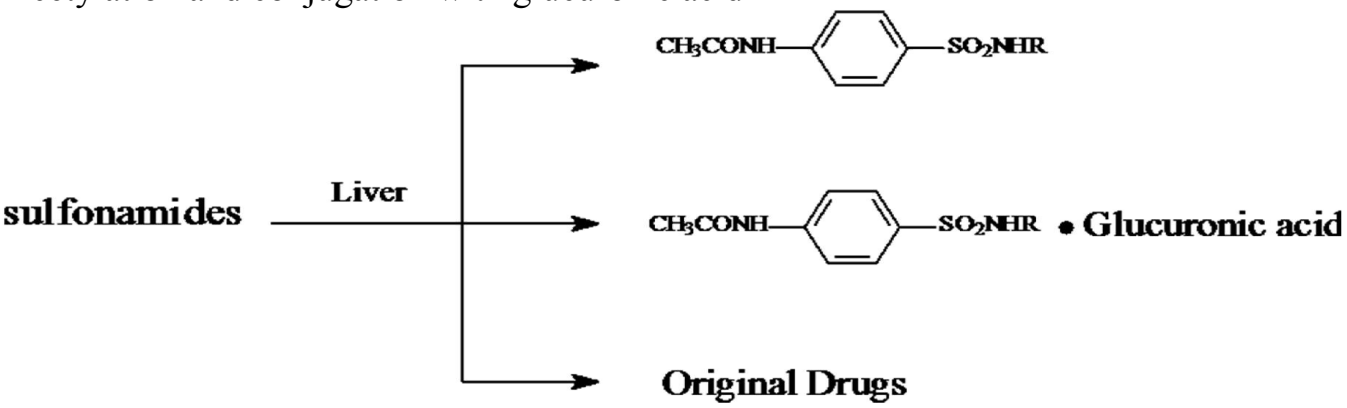


Structure-Activity Relationship (SAR)



Metabolism of sulfonamides

Acetylation and conjugation with glucuronic acid



Therapeutic uses:

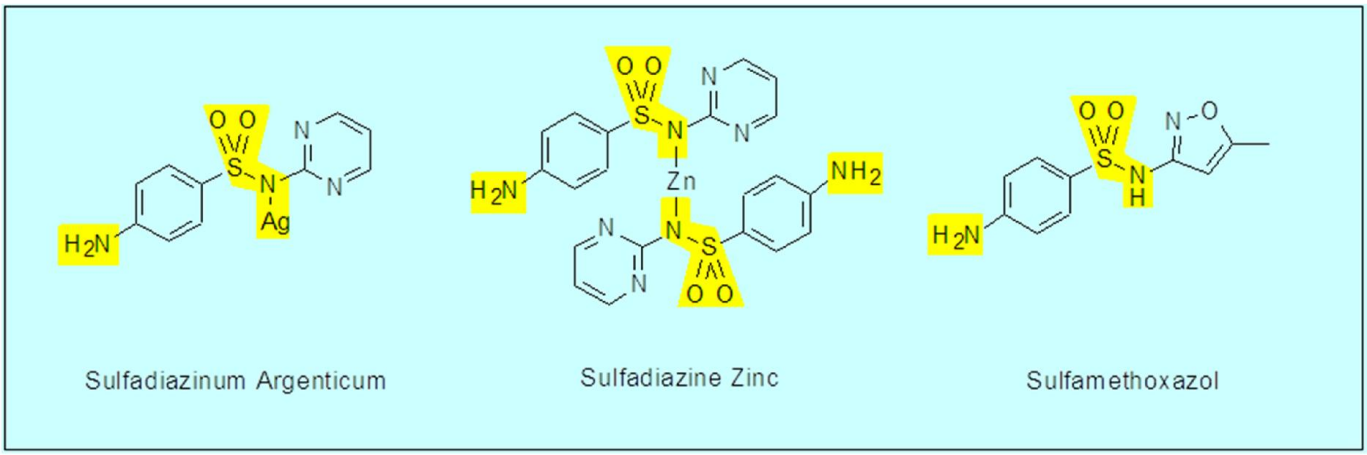
1.Urinary tract infections ,gonococcal urethritis and prostatitis.

2.Salmonella & shigella infections. 3.Respiratory tract infections due to H .influenza & pneumococci.

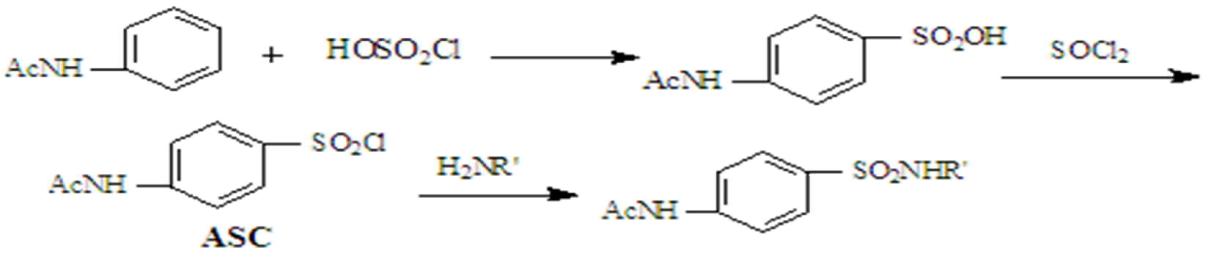
Examples of Sulfonamides drugs : sulfadiazine,sulfadoxine, sulfacetamide,sulfasalazine and sulfamethoxazole.

Sulfadiazine

- 4-Amino-*N*-2-pyrimidinyl benzenesulfonamide
- A white powder, slightly soluble in EtOH or CH_3COCH_3, insoluble in ether and $CHCl_3$.
- Soluble in diluted HCl and Strong base. mp: 255-256°C
- The drug is one of a few sulfonamides that still used in clinic.
- The silver and zinc salts of Sulfadiazine is a very potent antimicrobial in the treatment of burns and wound infections



General synthetic methods of sulfonamide



Synthetic methods of sulfdiazine