amino polyhydroxy cyclo alkanes

Aminoglycosides are characterized by a core structure of amino sugars connected via glycosidic linkages to a dibasic aminocyclitol, which is most commonly 2-deoxystreptamine. Aminoglycosides are broadly classified into four subclasses based on the identity of the aminocyclitol moiety:

(1) no deoxystreptamine (e.g., streptomycin, which has a streptidine ring)

(2) a mono-substituted deoxystreptamine ring (e.g., apramycin)

(3) a 4,5-di-substituted deoxystreptamine ring (e.g., neomycin, ribostamycin)

(4) a 4,6-di-substituted deoxystreptamine ring (e.g., gentamicin,kanamycin)

The core structure is decorated with a variety of amino and hydroxyl substitutions that have a direct influence on the mechanisms of action.

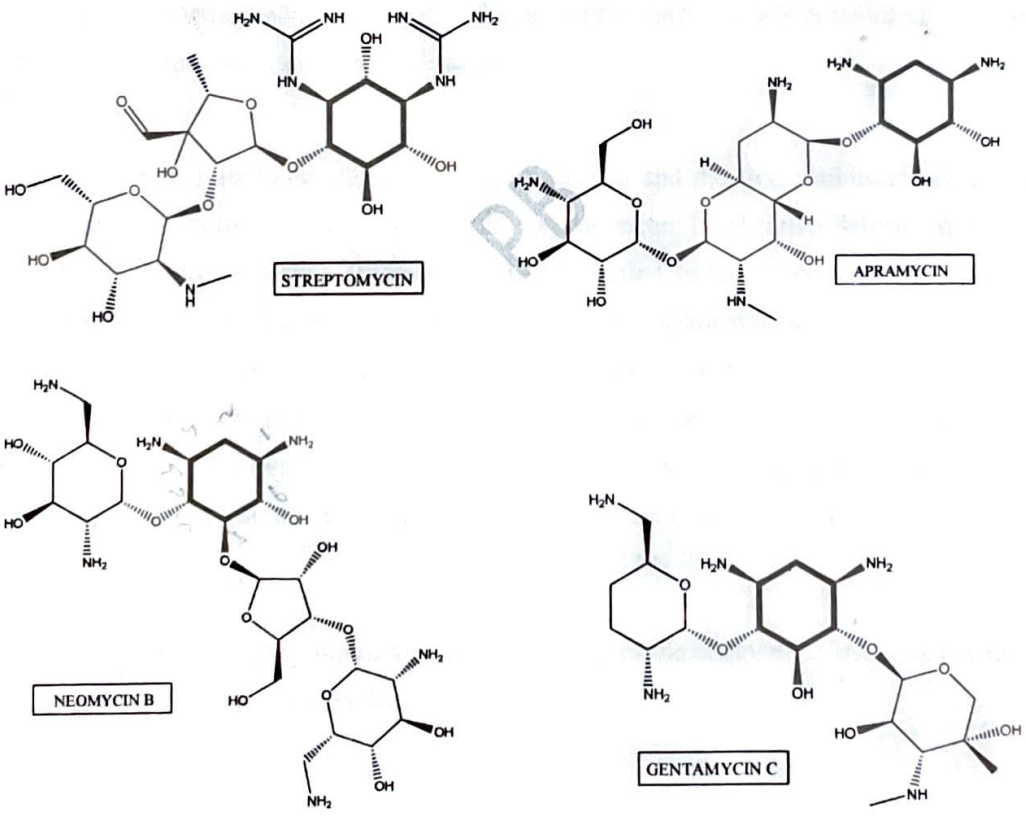


Fig 1: Structures of representative aminoglycosides. The deoxystreptamine and streptidine rings are in bold.

Mode of action:

Aminoglycosides act by inhibiting protein synthesis by high affinity binding to the A-site on the 16S ribosomal RNA of the 30S subunit (The 30S subunit provides the binding site for mRNA and is responsible for monitoring base-pairing between the codon on mRNA and the anticodon on tRNA). As a result of the interaction, the antibiotic promotes mistranslation of mRNA by inducing codon misreading on delivery of the aminoacyl tRNA. This results in erroneous protein synthesis; wherein incorrect amino acids assemble into a polypeptide that is subsequently released to cause damage to the cell membrane and elsewhere. The various aminoglycoside classes have different specificity to different regions of the A-site. Hence, the exact mechanism of binding and its after effects varies by chemical structure (i.e., NH_2 and OH substituents on the core structure), but all aminoglycosides have rapid bactericidal effects. Aminoglycosides first enter the bacterial cell by increasing permeability of the membrane via electrostatic binding with the membrane phospholipids. When they reach the cytoplasm, inhibition of protein synthesis and mistranslation of proteins occur, which builds up over time. This leads to rapid and accelerated cell death.

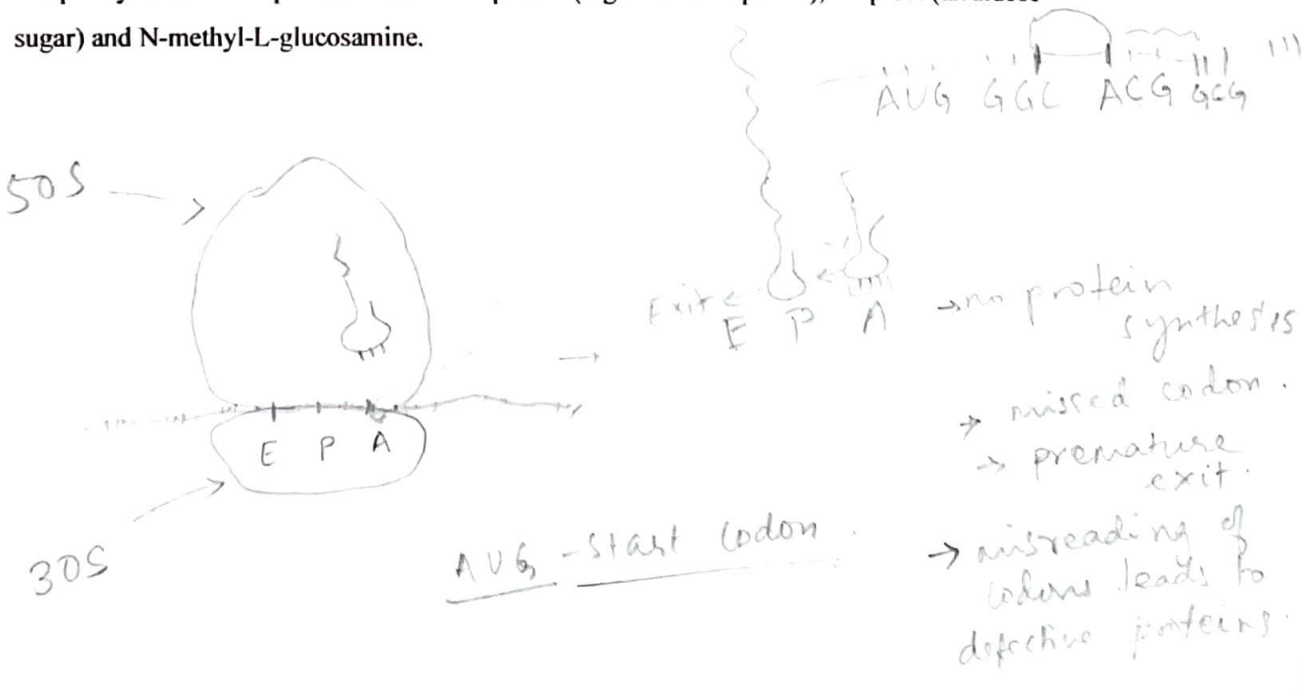
Streptomycin:

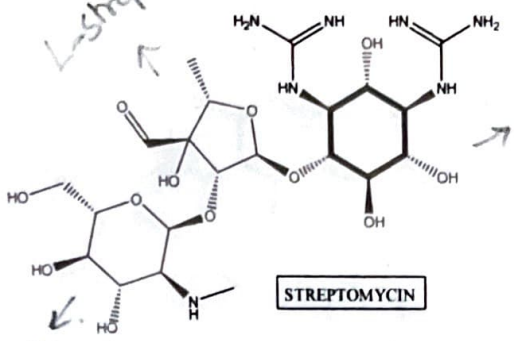
It was the second antibiotic discovered after penicillin and the first antibiotic used against tuberculosis. Streptomycin was discovered by American biochemists Selman Waksman, Albert Schatz, and Elizabeth Bugie in 1943. It was first isolated from the soil organism, *Streptomyces griseus*. It is mainly used in the treatment of tuberculosis in conjunction with other drugs such as isoniazid and rifampicin. It is also used to treat infection caused by *Streptococcus faecalis* in combination with penicillin. It exerts bacteriostatic action in low concentration and bactericidal in high concentration in a vast variety of Gram positive and Gram negative bacteria. It is also used to treat tulaemia and bubonic plague.

tularemia

SAR of streptomycin:

Streptomycin is made up of three units : streptidine (diguanido compound), streptose (an aldose sugar) and N-methyl-L-glucosamine.





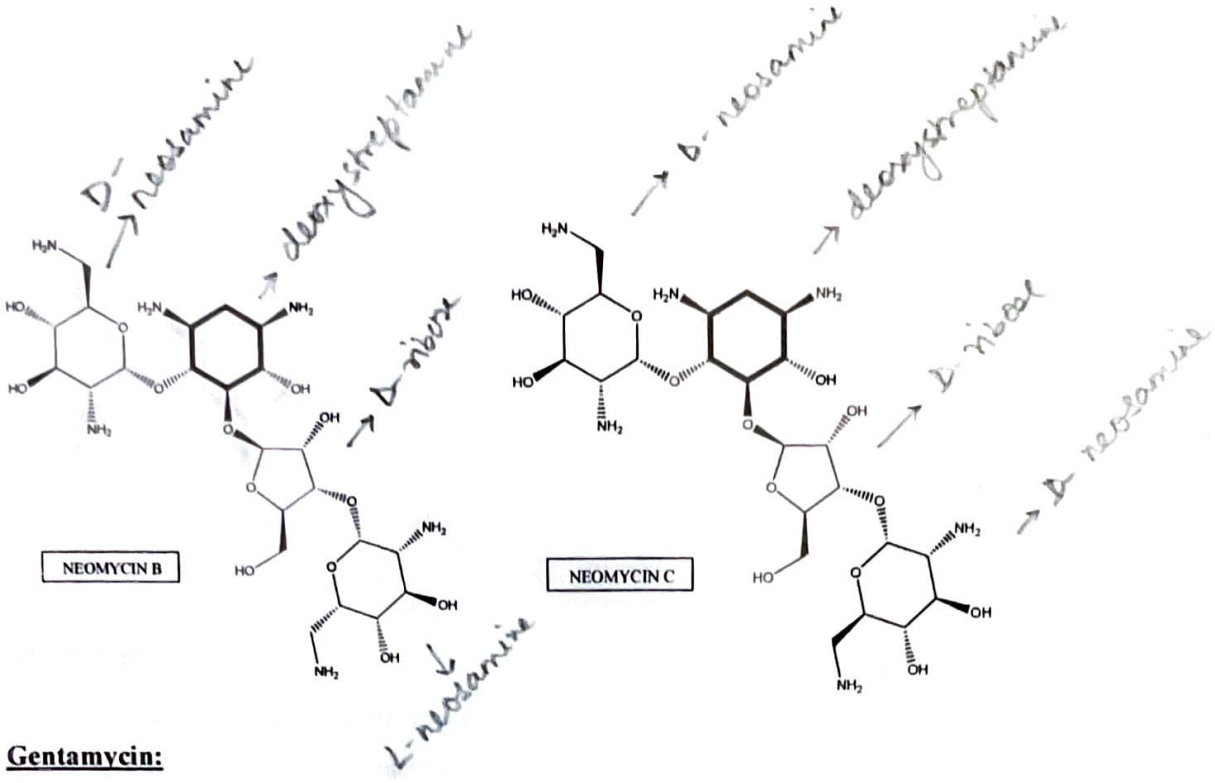
1. Reduction -CHO to CH_2OH gives dihydrostreptomycin, which is similar in activity but causes deafness.
2. Oxidation of -CHO group to Schiff base derivatives leads to inactive compounds.
3. Oxidation of $-CH_3$ in streptose ring to $-CH_2OH$ gives a compound with similar activity.
4. If $-CH_3$ in aminomethyl group in the third ring is replaced by larger alkyl groups, activity reduces. Hence, $-NHCH_3$ is essential for activity. Also, N-atom must be 2°.
5. Replacement of the guanido groups in streptidine ring diminishes antibiotic activity.

Neomycin:

Neomycin was isolated from the same family of bacteria as streptomycin in the same laboratory. In 1949 it was isolated from *Streptomyces fradiae*. Neomycin is most widely used for local infections like burns, ulcers, wounds, conjunctivitis etc. it displays broad spectrum activity against a plethora of pathogens.

Structure of Neomycin:

Neomycin is available as a pair of epimers, Neomycin B and C. The structure consists of four rings viz., D-neosamine, deoxystreptamine, D-ribose and L-neosamine.

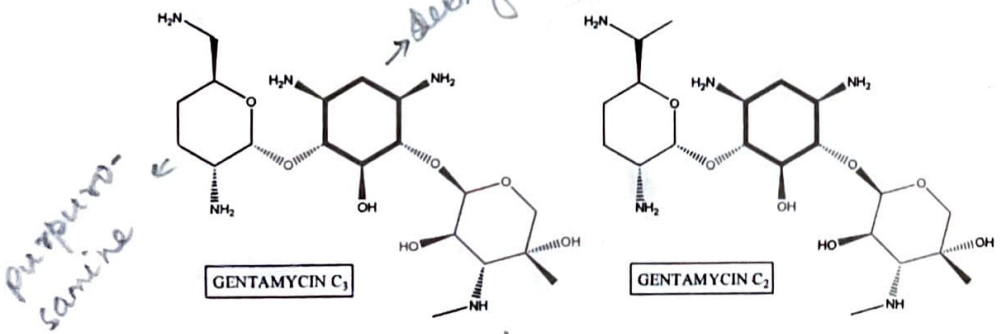


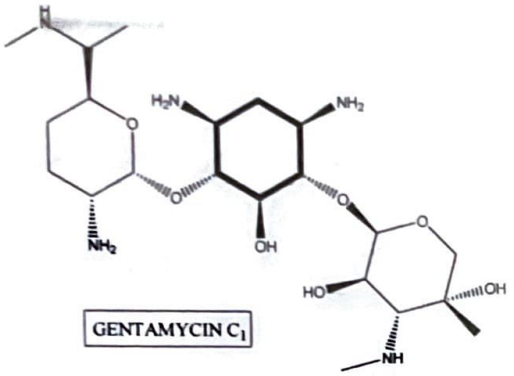
Gentamycin:

Gentamicin is naturally produced by the bacterium *Micromonospora purpurea*. It was patented in 1962, approved for medical use in 1964. Gentamicin is active against a wide variety of bacterial pathogens, mostly Gram-negative bacteria such as *Pseudomonas*, *E. coli*, *Klebsiella pneumoniae* and Gram-positive *Staphylococcus*. It is used in the treatment of respiratory tract infections, urinary tract infections, blood, bone and soft tissue infections caused by these bacteria.

Structure of Gentamicin:

It contains a 2-deoxystreptamine (aminocyclitol) backbone. It is substituted at C-4 by aminosugar purpurosamine and at C-6 by another aminosugar called garosamine. There are three gentamicin C analogues which differ in the substitution at the 6' position of the purpurosamine ring.



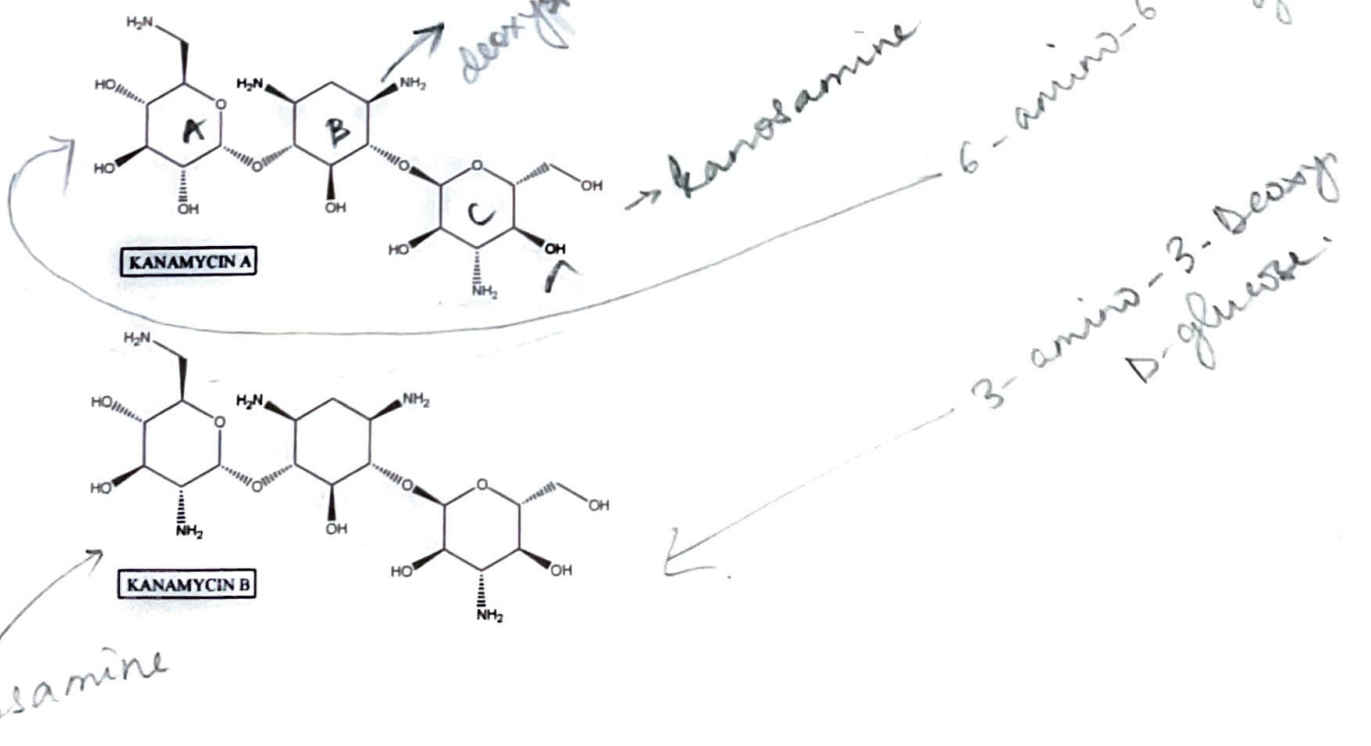


GENTAMYCIN C_1

Kanamycin:

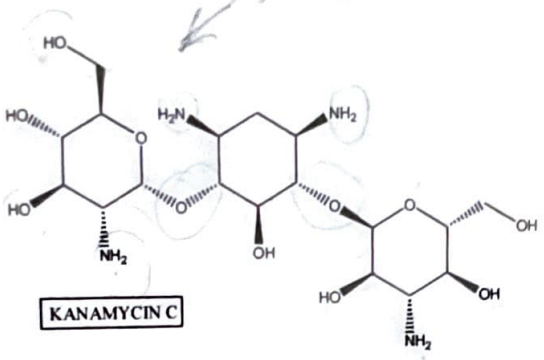
Kanamycin was first isolated in 1957 by Hamao Umezawa from the bacteria *Streptomyces kanamyceticus*. It is used to treat bacterial infections and tuberculosis. It is effective against Gram-positive bacteria like *Staphylococcus pyogenes* and *Staphylococcus epidermidis*. In combination with penicillin, it is found to be effective against *Streptomyces fecalis*. It is also used to treat gastrointestinal infections caused by Gram-negative bacteria such as *Klebsiella, Proteus, Enterobacter and Serratia.*

Structure of Kanamycin:



KANAMYCIN A

KANAMYCIN B



KANAMYCIN C

Kanamycin is isolated as a mixture of three components – Kanamycin A, B and C. The structure consists of three rings connected through glycosidic linkages. They are 2-deoxystreptamine, an aminosugar kanosamine ring at C-6 and another aminosugar at C-4.

SAR of aminoglycosides:

The important structural features in aminoglycosides responsible for interaction with rRNA are:

1. The substituent at C6' position of ring I (ie., ring attached to C-4 of deoxystreptamine)
2. The number of protonated -NH_2 groups of Ring I
3. The linkage between the sugar rings and the central deoxystreptamine ring (Ring II)

Other features:

1. -NH_2 group at 6' and 2' position of ring I are important for activity. Thus, Kanamycin B (6' and 2' -NH_2) is more active than Kanamycin A (6' -NH_2 and 2' OH) or Kanamycin C (6' -OH and 2' -NH_2)
2. Methylation at 6'-C or 6'-NH_2 group does not lower antibacterial activity.
3. 2'-OH and 6'-NH2 group cannot be removed – activity is lowered. But 3'-OH and 4'-OH removal does not affect antibacterial activity.
4. Ring II may be ribose (neomycin), streptose (streptomycin) or streptamine (kanamycin).
5. Ring III changes are less sensitive. 2"-position functional group activity: -NH_2>-OH>-H. 3"-NH_2 group maybe 1° or 2°- both are equally active. 4"-OH maybe axial or equatorial.

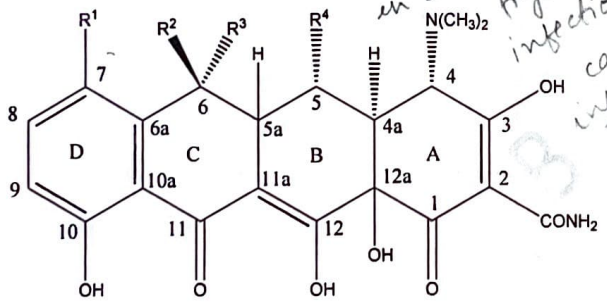
Tetracyclines:

Tetracyclines are a large class of antibiotics discovered by Duggar. In 1945, he discovered the first tetracycline antibiotic called chlortetracycline (Aureomycin) isolated from the soil bacteria *Streptomyces aureofaceans*. By 1948, a number of other analogues were isolated from various *Streptomyces* species and prescribed as antibiotics.

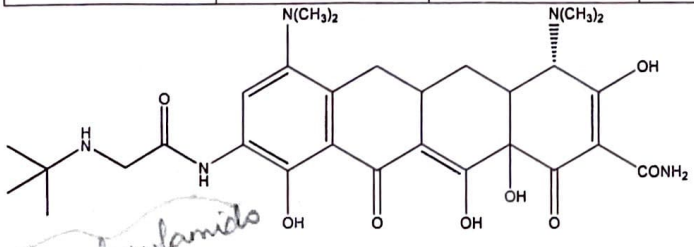
They are octahydronaphthacene derivatives which contain four linearly fused 6-membered carbocyclic rings with multiple substituents. There are multiple stereocenters in the molecule; hence activity is sensitive to the stereochemistry of these centres. Their hydrochloride salts are available as capsules. They form chelates with various metal ions which reduces water-solubility of the drug. Hence, these are not taken with milk or vitamins.

Tetracyclines are low-cost, broad-spectrum antibiotics effective against both Gram-positive and Gram-negative bacteria. Eg. *Streptococci, Staphylococci, Bacillus, Klebsiella, Vibrio cholerae* etc. It is used in the treatment of respiratory tract and gastrointestinal tract infections and also life-threatening diseases like meningitis, septicemia and endocarditis.

Structure of Tetracyclines:



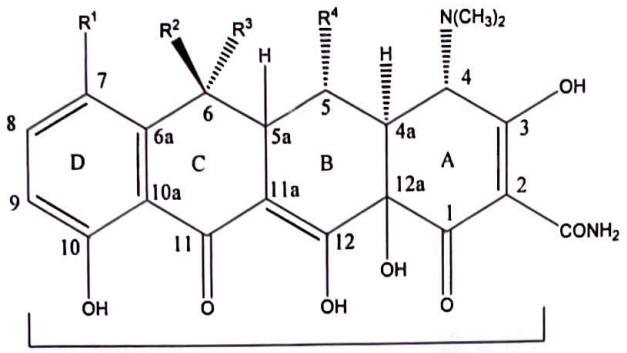
Name	R^1	R^2	R^3	R^4
Tetracycline	H	OH	CH_3	H
Chlortetracycline	Cl	OH	CH_3	H
Oxytetracycline	H	OH	CH_3	OH
Demeclocycline	Cl	OH	H	H
Metacycline	H	$=CH_2$	-	OH
Doxycycline	H	CH_3	H	OH
Minocycline	$N(CH_3)_2$	H	H	H
Meclocycline	Cl	$=CH_2$	-	OH

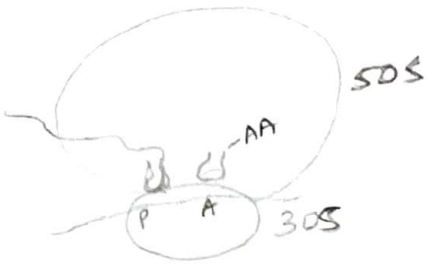


TIGECYCLINE

Tigecycline and its analogues were introduced in 2005 as a subgroup of tetracyclines.

SAR of tetracyclines:





Inviolate zone: Changes in this zone are not possible without significant loss of activity.

1. The linearly fused tetracyclic nucleus is important for activity.
2. Conversion of -$CONH_2$ group to nitrile leads to 20-fold decrease in activity.
3. Keto-enol tautomerism between C2 and C3 is very important for biological activity.
4. Any modification at C3 leads to loss in activity.
5. Epimerisation at C4 leads to loss in activity.
6. Removal of -$N(CH_3)_2$ group at C4 leads to loss in activity.
7. $=CH_2$ group at C6 increases activity.
8. Electron-donating or -withdrawing groups at C7 increases antibacterial activity. -$N(CH_3)_2$ group at C7 increases activity manifolds. -NO_2 group at C7 gives more potent but carcinogenic drug.
9. D-ring should always be aromatic otherwise complete loss in activity results.

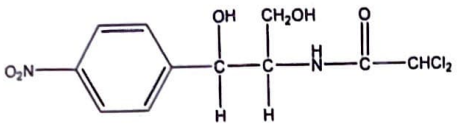
Mode of action:

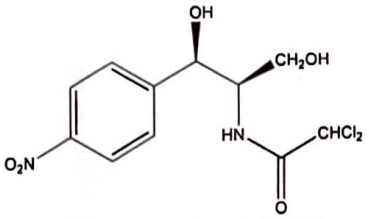
Tetracyclines inhibit protein synthesis by binding to the bacterial ribosome involved in translation process. There are two main binding sites for the tRNA molecule – the P-site that binds the tRNA bearing the peptide chain and the acceptor aminoacyl A-site. Tetracyclines reversibly bind to the 30S subunit at the a-site to prevent attachment of the aminoacyl tRNA, terminating the translation process. As a result, protein synthesis is inhibited and bacterial growth slows down (bacteriostatic). This allows the body's immune system to destroy them.

Chloramphenicol:

Chloramphenicol was first isolated 1947 by Ehrlich from a soil bacteria *Streptomyces Venezuela* and used clinically in 1949 under the trade name Chloromycetin. They have also been isolated from other bacteria like *S.omiyamensis* and *S.phacochromogenes.* It is important as it is capable of exerting its effect against viral diseases as well as those due to bacterial invasion and opens up the whole field of the chemotherapy of virus and *rickettsia* infections in man including typhus, undulant fever, *Salmonella septicaemia*, whooping cough, gastroenteritis, *lymphogranuloma inguinale*, typhoid and paratyphoid.

Structurally, it has a p-substituted nitrobenzene ring. The substituent contains a dichloroacetyl moiety as well as two chiral centres which gives rise to 4 possible stereoisomers. Out of these, only D (-) threo isomer is biologically active as antibiotic.



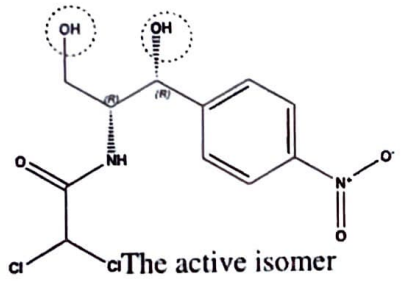


threo isomer of chloramphenicol

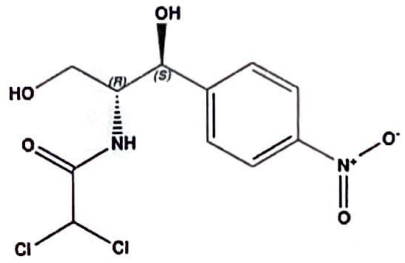
Chloramphenicol is effective against a wide variety of both Gram-positive and Gram-negative bacteria. It is used in the treatment of typhoid fever caused by *Salmonella typhi*. It is also very effective in the treatment of diseases caused by *Haemophilus influenzae* including meningitis. It produces excellent result against *Neisseria meningitidis*.

SAR of Chloramphenicol:

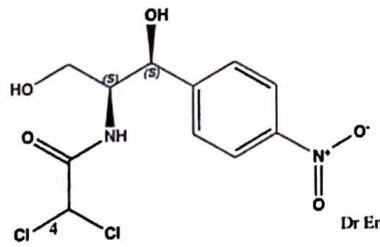
Stereochemistry of chloramphenicol

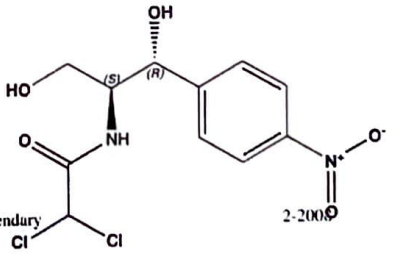


The active isomer



D(−) threo



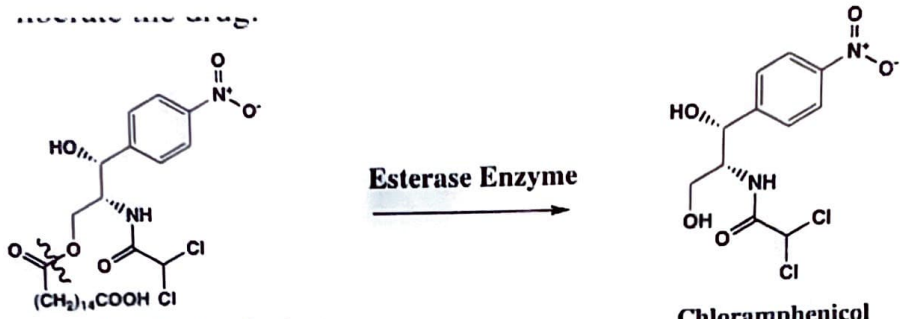


D(+) threo

Dr Eman R. El-Bendary 2-2008

1. Only the 1R,2R isomer is antibiotically active.
2. Replacement of phenyl ring by other aromatic or alicyclic rings (eg. Naphthyl, furyl, cyclohexyl etc.) results in loss of activity.
3. Replacement of NO_2 by NH_2, OH, NHR, CN results in loss of activity. However, replacement by $COCH_3$ and SO_2CH_3 gives active compounds.
4. Shifting of NO_2 from p- to o- or m- leads to loss in activity.
5. Replacement of OH and increasing or decreasing chain length of CH_2OH leads to complete loss of activity.
6. Other dihalo derivatives of acetamido side chain are less active relative to chloramphenicol. However, among the trihalo derivatives, $COCF_3$ has 1.7 times activity than parent compound.
7. Both the OH groups are essential for activity.

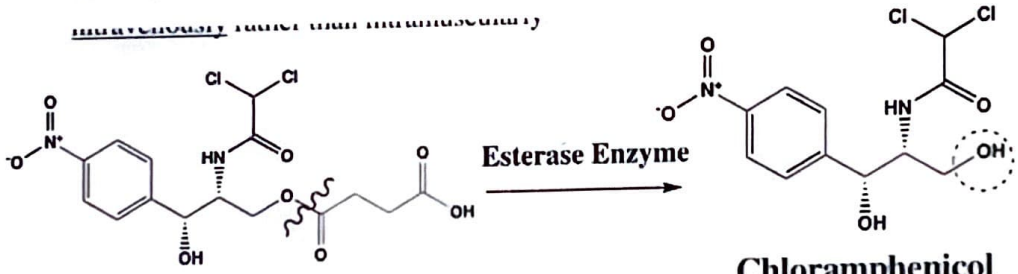
Chloramphenicol is bitter in taste. This can be masked by forming palmitate esters with C3 - OH group. The ester is hydrolysed in the duodenum to release the active drug.



Chloramphenicol palmitate

Chloramphenicol

Chloramphenicol has poor water solubility. It is converted to 3-hemisuccinyl ester which forms a water-soluble sodium salt suitable for intravenous administration. This is also hydrolysed in the body to release the active drug.



Chloramphenicol succinate ester

Chloramphenicol

Mode of action:

Chloramphenicol works by inhibiting protein synthesis in bacteria and to a lesser extent in human cells. The drug readily penetrates the bacterial cell wall. It specifically attaches to the 50S ribosomal unit reversibly. It then hinders the access of aminoacyl tRNA to the A-site for amino acid incorporation, thus interfering with transfer of the elongating peptide chain to the newly attached aminoacyl tRNA at the ribosome-mRNA complex. The interaction between *peptidyltransferase* and its amino acid substrate cannot occur and peptide bond formation is inhibited.

Macrolide antibiotics

In 1952, erythromycin and carbomycin were reported as new antibiotics which were isolated from *Streptomyces* species. Erythromycin was important as it could be used as penicillin substitute in people allergic to the latter. Semi-synthetic derivatives of erythromycin have superior pharmacokinetic properties due to their enhanced acid stability and improved distribution properties.

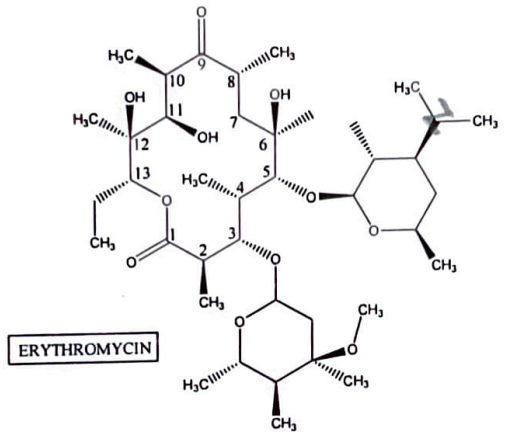
The spectrum of activity of macrolides resembles that of penicillin. In addition, they are also effective against bacterial strains that are resistant to penicillin. These are generally effective against most G+ bacteria and limited number of G- bacteria. *Streptococci*, *pneumococci*, *staphylococci*, and *enterococci* are usually susceptible to macrolides. Macrolides are used to treat respiratory tract infections, soft tissue infections, *Mycoplasma pneumoniae*, Chlamydia infections, gonorrhea and syphilis.

Macrolides attach to the 50S subunit of bacterial ribosomes and inhibit protein synthesis. They block the enzymes (*peptidyltransferase*) that catalyze the transfer of new amino acid residues to the growing peptide chain. Macrolide antibiotics do so by binding reversibly to the P site on the 50S subunit of the bacterial ribosome. They display bacteriostatic activity.

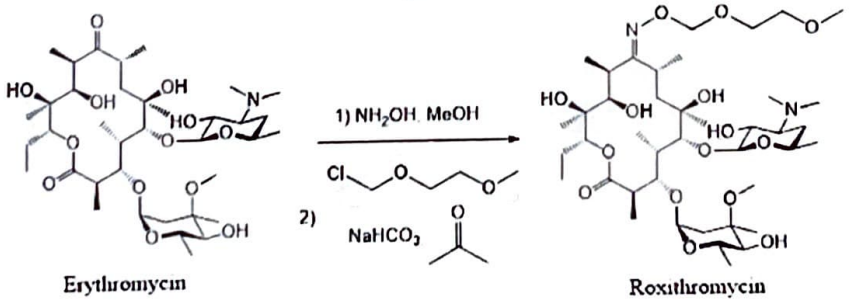
The general structure of macrolides contains three characteristic parts:

1. A highly substituted macrocyclic lactone – known as aglycone.
2. A ketone group.
3. A deoxyamino sugar – called glycon and a neutral deoxy sugar; both glycosidically attached to the aglycon unit.

Erythromycin:

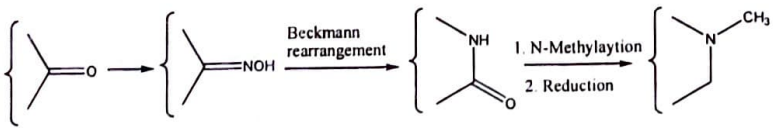


McGuire et al reported the isolation of erythromycin from *Streptomyces erythraeus* in 1952. The aminosugar attached through a glycosidic link to C5 is desosamine. The 3° amine of desosamine confers a basic character to erythromycin. The other sugar unit attached to C3 is called cladinosè and is unique to the erythromycin molecule.

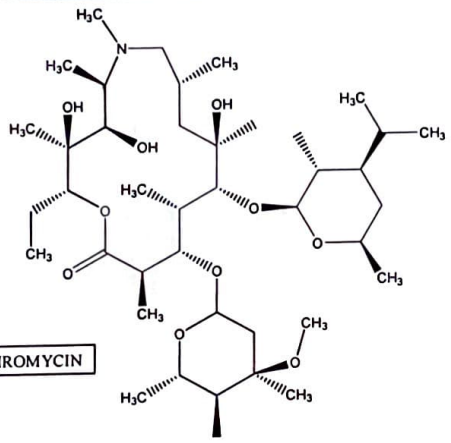


Erythromycin Roxithromycin

The C9 keto group may be modified chemically to give erythromycin analogues that are more effective. Roxithromycin is prepared from an oxime derivative of erythromycin. It is 6-fols stronger than the parent compound. Beckmann rearrangement of the C9 oxime followed by N-methylation and reduction of the resulting ring-expanded lactam gives another more effective analogue – Azithromycin.



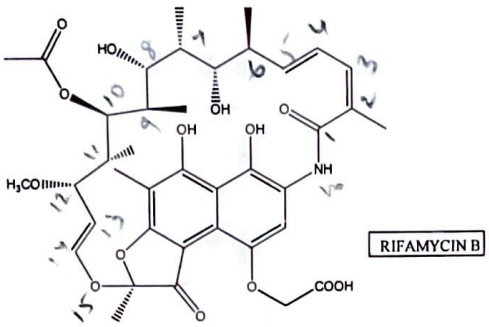
It is a prototype of a series of nitrogen-containing, 15-membered ring macrolides known as azalides. Removal of the 9-keto group coupled with incorporation of a weakly basic tertiary amine nitrogen function into the macrolide ring increases the stability of azithromycin to acid-catalyzed degradation. These changes also increase the lipid solubility of the molecule, thereby conferring unique pharmacokinetic and microbiological properties.



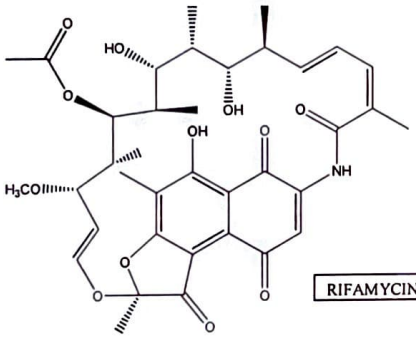
AZITHROMYCIN

Ansamycins:

Ansamycins or ansa macrolides are antibiotics that contain an aromatic nucleus and an ansa bridge. Ansa (Latin for 'handle') bridge is a long chain that connects two non-adjacent position of an aromatic system. The main difference between various derivatives of ansamycins is the aromatic moiety, which can be a naphthalene ring or a naphthoquinone ring as in rifamycin and the naphthomycins. Another variation consists of benzene or a benzoquinone ring system as in geldanamycin or ansamitocin. Ansamycins show anti-microbial activities against many G+ bacteria and few G- bacteria. Rifamycins are a subclass of ansamycins with high potency against mycobacteria. This resulted in their widespread use in the treatment of tuberculosis, leprosy, and AIDS-related mycobacterial infections. In general, the rifamycins (A, B, C, D, E), are produced by the *Streptomyces mediterranei* species. Although the natural rifamycins are not used in therapy, some semisynthetic rifamycins have therapeutical roles. It has been observed that its oxidation, when followed by hydrolysis, generated a quinone molecule, rifamycin S, a compound with potent antimicrobial activity. Subsequent reduction to the hydroquinone form produced rifamycin SV (30.6.5) with high potency against mycobacteria.



RIFAMYCIN B



RIFAMYCIN S

The potent antibacterial activity of the rifamycins, streptovaricins and tolypomycins is a consequence of the specific inhibition of DNA-dependent RNA polymerase, the enzyme responsible for most of the transcription of DNA to RNA. Clear evidence exists to prove that ansamycins such as rifampicin have no effect on eukaryotic RNA polymerases, hence less toxicity.

Peptide antibiotics:

They are a diverse class of natural products; some containing only amino acids joined by amide bonds, whereas others contain non-amino acid constituents. Amino acids range from commonly found ones to uncommon ones. The peptide array maybe linear or cyclic or combination of both.

Mode of action:

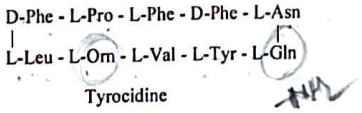
The membrane permeability is mostly recognized as the well-accepted mechanism to describe the action of cationic Anti-Microbial Peptides (AMPs). These cationic AMPs generally have membrane-binding activity. They destroy membrane structures of bacteria or cancer cells, resulting in the massive exudation of cell contents and ultimately leading to the death of

bacteria or cancer cells. The cationic AMPs can bind to the outer structures of the cell membranes by the interaction among positive charges and negative charges. The extracellular membrane of Gram-negative bacteria contains a negatively charged lipopolysaccharide (LPS). The cationic AMPs can replace the divalent cations such as Mg^{2+} and Ca^{2+} bound to LPS, cause a breakage or a cavity on the outer membranes of bacteria and eventually go through extracellular membranes. The cationic AMPs pass through the outer membranes and bind to the negatively charged phospholipids on the inner membranes of the cells combined by electrostatic attraction, causing the formation of a cavity or a temporary passage on the cell membranes, thereby resulting in the disintegration or permeability of cell membranes, and eventually causing the contents of the bacteria to overflow, microbial body lysis and death.

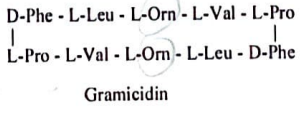
In another proposed mechanism, AMPs enter cells without membrane disruption and inhibit essential intracellular functions by binding to nucleic acids or intracellular proteins. The fundamental differences between microbial and mammalian membranes protect mammalian cells against AMPs and enable selective action of these peptides

Peptide antibiotics exert nephrotoxicity and neurotoxicity in general. However, local administration, which is the most common delivery route for AMPs, reduces the risk for any systemic toxicology concerns. The presence of unnatural D-amino acids in these drugs also presents toxicity concerns.

1. Tyrothricin – antibiotic mixture isolated from *Bacillus brevis*. It is a mixture of two different antibiotics: gramicidin and tyrocidine. Both gramicidin and tyrocidine are short polypeptides which disrupt the cell membranes of some, primarily Gram-positive, bacteria. Tyrothricin and its component antibiotics are too toxic to be taken internally but are sometimes used as topical antibiotics.

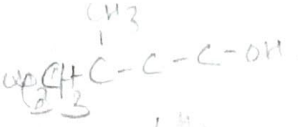


Tyrocidine



Gramicidin

2. Bacitracin – isolated from a strain of *Bacillus subtilis* in 1945. It is now produced from the *Bacillus licheniformis*. It is bactericidal antibiotic active against a wide variety of G+ organisms and very few G- organisms. It is used in topical preparations for local infections. It is nephrotoxic.
3. Polymyxin – they were simultaneously discovered and isolated from two species, *Bacillus polymyxa* and *Bacillus aerosporus* in 1947. It is an amphiphilic molecule



containing cyclic heptapeptide ring, tripeptide side chain connected to terminal hydrophobic fatty acid chain. Polymyxins are highly active against many Gram-negative bacteria.

Mechanism of action and resistance

Polymyxins are cationic, surface-active agents that disrupt the structure of cell membrane phospholipids and increase cell permeability by a detergent-like action. Gram-negative bacteria are much more sensitive than Gram-positive bacteria because they contain more phospholipid in their cytoplasm and outer membranes.

High renal and neuro toxicity is observed with these drugs. Hence, topical use is done on burns and sores.