Chapter 3: Aminoglycoside Antibiotics

Syllabus: Streptomycin, Neomycin, Kanamycin

3.1. HISTORY & DEVELOPEMENT

- In October 1943: Streptomycin was one of the first aminoglycoside drugs to be discovered and isolated by A. I. Schatz a PhD students in laboratory of S. A. Waksman at Rutgers University in a research project funded by Merck and Co, isolated it from the soil actinobacterium ***Streptomyces griseus***.
- Its main claims to fame are its ability to control tuberculosis (*Mycobacterium tuberculosis*) and plague (*Yersinia pestis*).
- There's an unfortunate side to the Schatz–Waksman story. Waksman convinced Schatz to sign over his royalty rights to streptomycin to what was supposed to be a nonprofit foundation But Schatz later learned that the foundation was paying royalties to Waksman.
- Waksman get so much recognition for discovery of streptomycin.
- Waksman (but not Schatz) was awarded the 1952 Nobel Prize in physiology or medicine for his work that led to the discovery of streptomycin.
- Waksman and his laboratory staff discovered several antibiotics, including actinomycin, streptothricin,streptomycin, , neomycin, fradicin, candicidin, and candidin.
- Streptomycin and neomycin found extensive application in the treatment of numerous infectious diseases

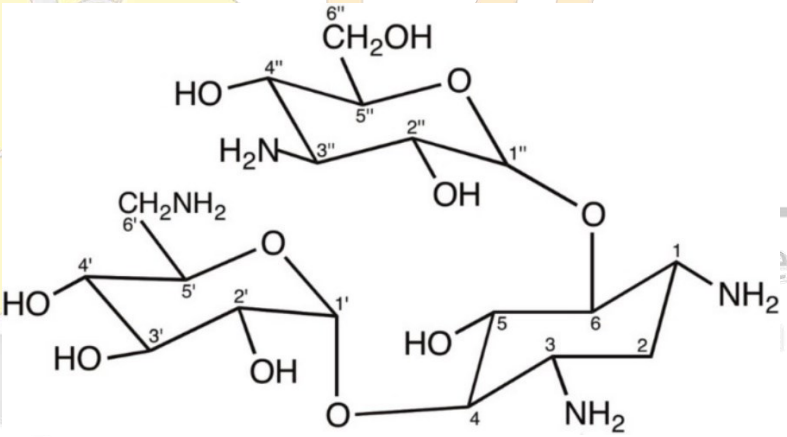
3.2. AMINOGLYCOSIDE

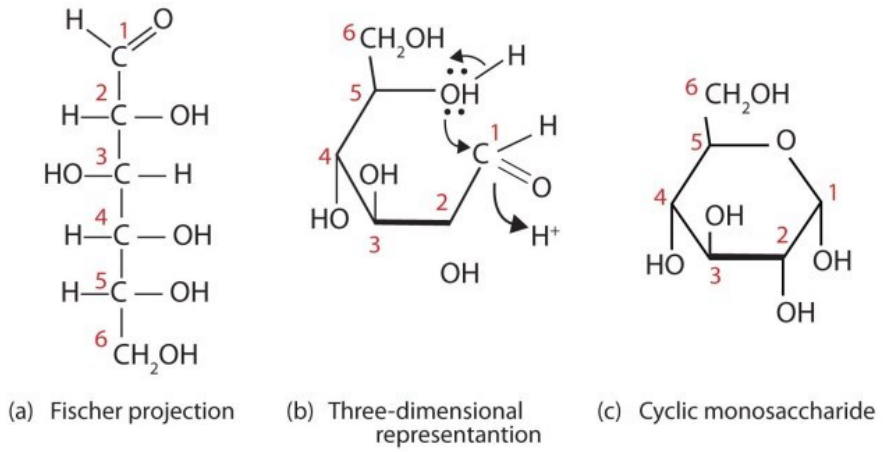
- These are the antibiotics produced by *streptomyces* and *micromonospora* species,
- Compounds derived from *Streptomyces* have "**mycin**" suffixes whereas those from *micromonospora* have "**micin**" suffixes.
- **Classification:**
    - Mycins: Streptomycin, Kanamycin, Neomycin, Tobramycin, Framycetin
    - Micins: Gentamicin, Sisomicin

Table 4.1 Examples of aminoglycoside antibiotics.

Name	Source
Streptomycin	*Streptomyces griseus*
Neomycin	*S. fradiae*
Kanamycin	*S. kanamyeleticus*
Gentamycin	*Micromonospora purpura*
Netilmicin	*Micromonospora species*
Tobramycin (Nebramycin)	*S. tenebrarius*
Framycetin (Soframycin)	*S. decaris*
Paromomycin	*S. rimosus and S. paramomycinus*
Amikacin	It is 1-L-(-) 4-amino-2-hydroxy butyryl kanamycin

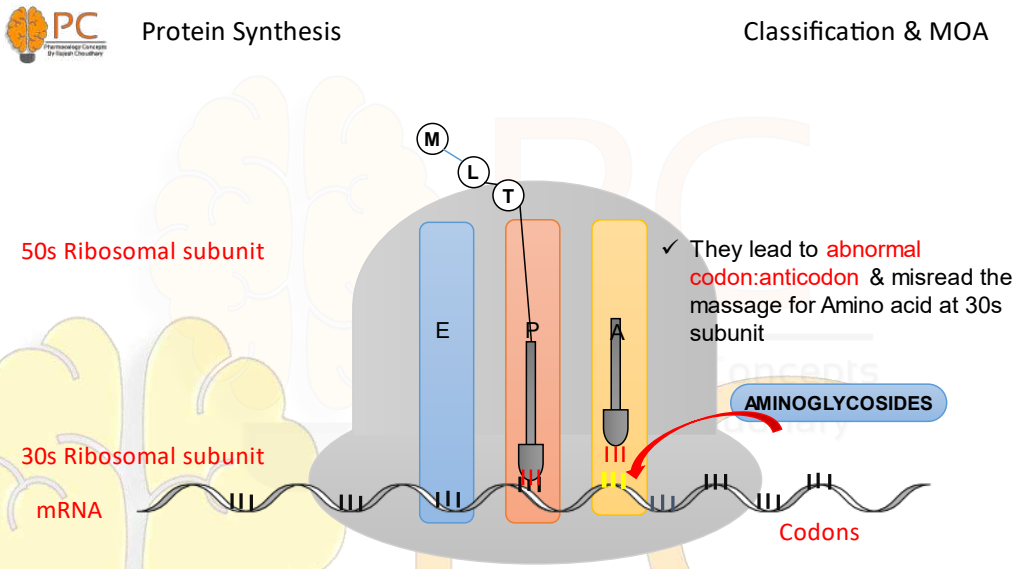
Chemistry: They contain one or more aminosugars (glucosamine or neosamine) joined in glycosidic linkage to a basic 6-membered carbon ring (Aminocyclitol).





(a) Fischer projection (b) Three-dimensional representantion (c) Cyclic monosaccharide

Mechanism of Action : All aminoglycoside antibiotics are ***bactericidal***. They inhibit bacterial protein synthesis by combining with 30s ribosomal subunit of bacterial ribosome and induce miscoding (misreading) of m-RNA codons resulting in incorporation of 'wrong' aminoacids in bacterial peptide chains (some antibiotics of this category in addition bind to 50s ribosomal subunit). They also interfere with the binding of aminoacetyl t-RNA, which prevents chain elongation.



The penetration of aminoglycosides trough the cell membrane of bacteria depends on **oxygen-dependent active transport** by a polyamine carrier system, hence they have minimal activity against anaerobic bacteria.

Antibacterial spectrum : Aminoglycosides are "narrow spectrum" antibiotics and are effective against gram negative aerobic bacilli. Gram positive bacteria are resistant to aminoglycoside antibiotics (except *S. aureus* and *S. epidermidis*).

Bacterial Resistance: Resistance to aminoglycosides is occurs in many ways like: **inactivation through microbial enzymes** which **phosphorylate/adenylate or acetylate** the aminoglycosides, **failure of penetration** through their transport system and decreased affinity to ribosomal unit.

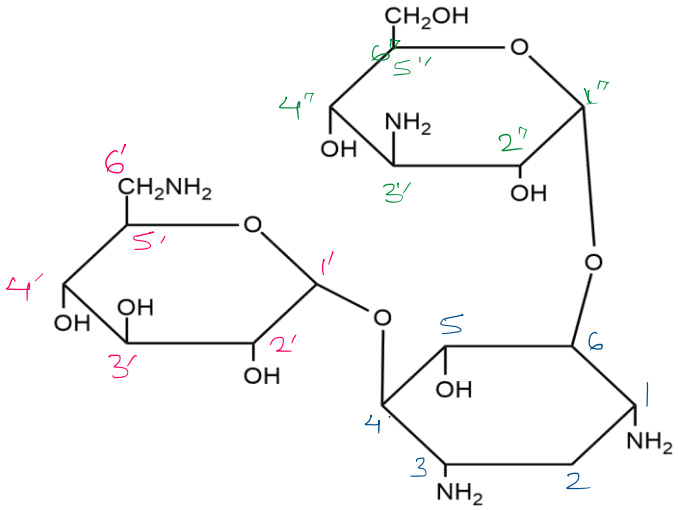
Pharmacokinetic: Aminoglycosides are generally used as sulfated salts and easly ionize in solution, hence not or poorly absorbed orally from the intact gastrointestinal tract. They are highly polar compounds that do not enter cells readily. They do not cross BBB. The kidney clears aminoglycosides, and excretion is directly proportionate to creatinine clearance through glomerular filtration.

ADR:

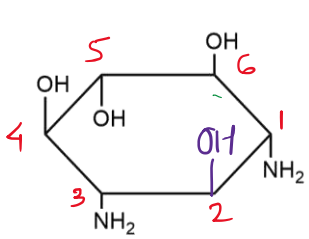
- **Ototoxicity:** damage VIII cranial nerve (cochlear and vestibular damage).
- **Nephrotoxicity:** tubular damagr resulting low urine concentration, low GFR, albuminuria and nitrogen retention.
- **Neuromuscular blockade:** reduce the acetylcholine (Ach) release from motor nerve endings.

3.3. STRUCTURAL ACTIVITY RELATIONSHIP OF AMINOGLYCOSIDE

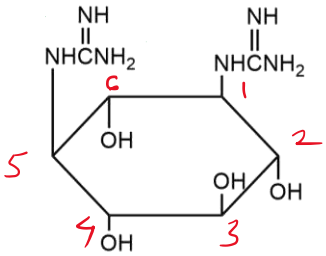
The aminoglycosides consist of two or more amino sugars joined in glycoside linkage to a highly substituted 1,3-diaminocyclo hexane (aminocyclitol), which is a centrally placed hexose ring.



The hexose ring is a 2-deoxy streptamine in all aminoglycosides except streptomycin and dihydrostreptomycin, where it is streptidine

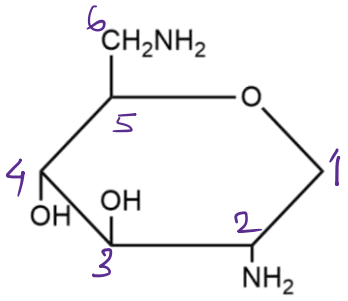


Streptamine



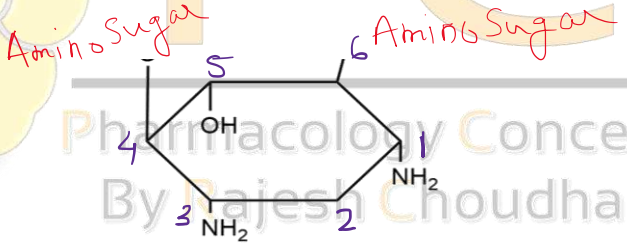
Streptidine

- In kanamycin and gentamycin families, two amino sugars are attached to 2-deoxy streptamine.
- In streptomycin, two amino sugars are attached to strepidine.



Amino Sugar

- Bacterial enzymes target the aminosuger moiety at C-6 and C-2 position for inactivation.
- At C-6, substitution with methyl group increase the bacterial resistance properties.
- Cleavage of 3-OH and/or 4-OH group dose not affect the activity
- At C-6 and C-2, both amino groups increase the activity (Kanamycin-B) as compared to C-2 hydroxyl group (Kanamycin A)

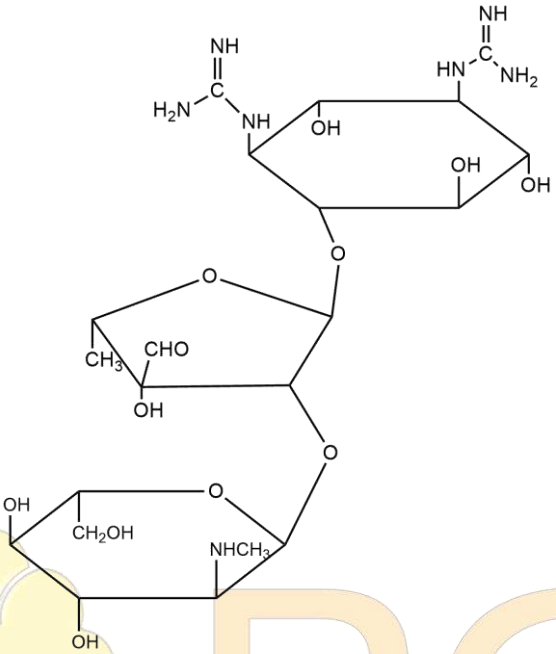


Hexose Ring

- At C-1 amino group, acylation (amikacin), and ethylation (1-N ethyl sisomycin) helps to retain the antibacterial potency.
- 2-hydroxylation and 5-deoxygenation increase the bacterial resistance property (inhibits the bacterial enzyme inactivation).

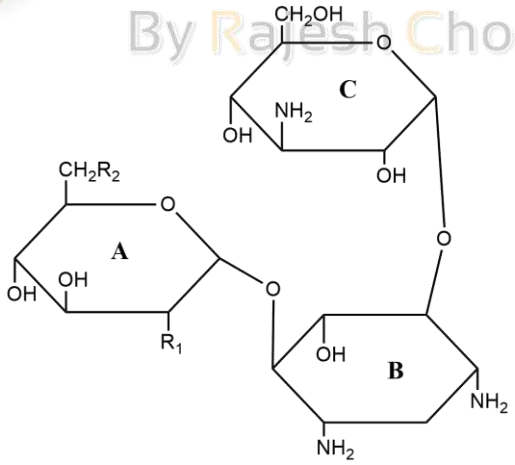
3.4. MEDICINAL CHEMISRTY OF SELECTED DRUGS

A) Streptomycin



- ✓ It is produced by *Streptomyces griseus*
- ✓ **Use :** Used in tuberculosis, brucellosis, plague, tularemia, mycetoma and *Strep. viridans* endocarditis.
- ✓ ***Streptomycin is more effective in alkaline pH (7-8) than acidic pH.***

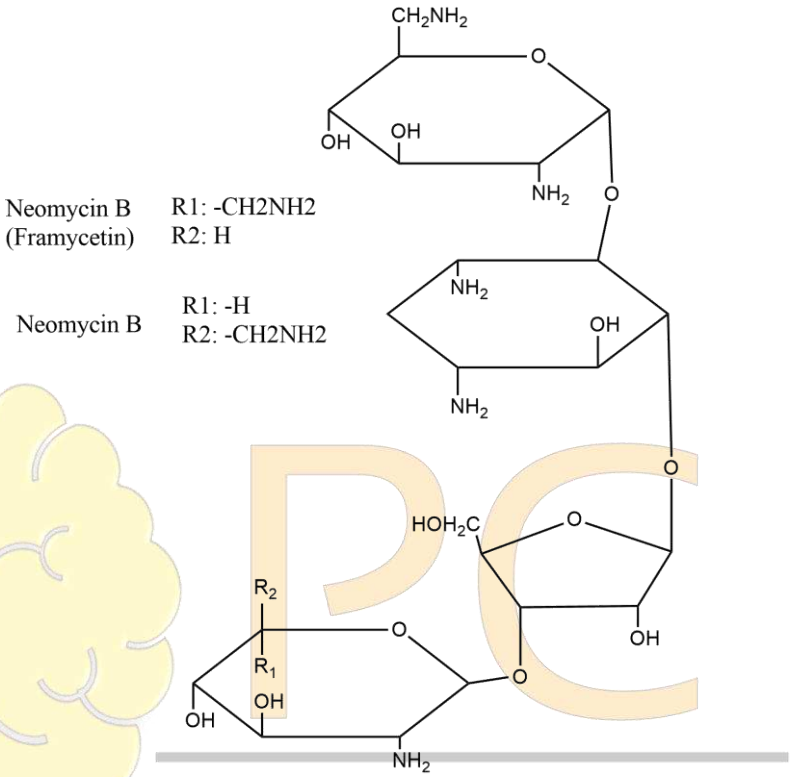
B) Kanamycin



Kanamycin A, R_1 = OH R_2 = NH_2
Kanamycin B, R_1 = NH_2 R_2 = NH_2
Kanamycin C, R_1 = NH_2 R = OH

- ✓ It is produced by *Streptomyces kanamyceticus.* Commercially available Kanamycin is Kanamycin A.
- ✓ **Use :** Used in the treatment of tuberculosis and infections which are reristant to commonly used agents. It is also used in treatment of RTI, UTI, soft tissue infection,

C) Neomycin



- ✓ Neomycin is a mixture of neomycin A, B and C and is produced from *Streptomyces fradiae.*
- ✓ Neomycin A (Neamine) is an incative component and is a common degradation product of Neomycin B & C.
- ✓ **Framycetin (Neomycin B) *:*** It is produced by *Streptomyces lavendulae.* It consists mainly of neomycin B.
- ✓ **Uses :** Used in bacterial diarrhoea and to reduce postoperative infections. Topically used to treat infections of skin and eye.

- ✓ **Ototoxicity is the main side effect of aminoglycosides.**
- ✓ **Streptomycin and gentamicin are more toxic to the vestibular branch of the eighth cranial nerve.**
- ✓ **Neomycin, amikacin and Kanamycin are more toxic to the auditory branch.**
- ✓ **Toxicity is human results from blockade of N-type calcium channel and inhibition of lysosomal phospholipase and sphingomyelinase.**

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