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MEDICINAL CHEMISTRY - III

UNIT 1

TOPIC :

- **Aminoglycosides :** Streptomycin, Neomycin, Kanamycin

Aminoglycosides

→ Aminoglycosides are bactericidal antibiotics composed of amino sugars linked to an aminocyclitol nucleus, which act by inhibiting bacterial protein synthesis through binding to the 30S ribosomal subunit. They are mainly effective against aerobic Gram-negative bacteria.

Classification

A. Based on Source

From Streptomyces (–mycin)

- Streptomycin
- Gentamicin
- Tobramycin
- Neomycin
- Kanamycin

From Micromonospora (–micin)

- Amikacin
- Netilmicin

B. Based on Generation

1st generation: Streptomycin, Neomycin
2nd generation: Gentamicin, Tobramycin
3rd generation: Amikacin, Netilmicin

Mechanism of Action

Aminoglycosides enter bacterial cells by oxygen-dependent active transport.
They bind irreversibly to the 30S ribosomal subunit.
This leads to:
Inhibition of initiation complex
Misreading of mRNA
Formation of defective proteins
Defective proteins damage the bacterial cell membrane.
Result → bacterial cell death

Hence, aminoglycosides are bactericidal.

Spectrum of Activity

Highly Active Against

- Aerobic Gram-negative bacteria:
  - *E. coli*
  - *Klebsiella*
  - *Pseudomonas aeruginosa*
  - *Proteus*

Also Active Against

- *Staphylococcus aureus* (in combination therapy)
- *Mycobacterium tuberculosis* (streptomycin)

Not Effective Against

- Anaerobic bacteria
- Most Gram-positive bacteria alone

Mechanisms of Resistance

- Enzymatic inactivation (acetylation, phosphorylation, adenylation)
- Reduced drug uptake by bacteria
- Alteration of ribosomal binding site
- Efflux pumps
- Amikacin is least affected by resistance enzymes.

Therapeutic Uses

- Severe Gram-negative infections
- Septicemia
- Urinary tract infections
- Respiratory tract infections
- Tuberculosis (streptomycin)
- Endocarditis (with β-lactams)
- Hospital-acquired infections

Adverse Effects

- Nephrotoxicity (kidney damage)
- Ototoxicity (hearing loss, vestibular damage)
- Neuromuscular blockade (rare)

- Hypersensitivity reactions (rare)
- Toxicity increases with high dose and prolonged use.

Streptomycin

- Streptomycin is the first clinically useful aminoglycoside antibiotic, discovered in 1943 from Streptomyces griseus.
- It is bactericidal and mainly effective against Mycobacterium tuberculosis and aerobic Gram-negative bacteria.
- Streptomycin acts by inhibiting bacterial protein synthesis through binding to the 30S ribosomal subunit.

Classification

- Streptomycin belongs to the group of:
  - Aminoglycoside antibiotics
  - First-generation aminoglycosides
  - Obtained from Streptomyces species

Structure

→ Streptomycin is composed of three structural components:
  - Streptidine (aminocyclitol nucleus)
  - Streptose (sugar moiety)
  - N-methyl-L-glucosamine

→ These components are linked by glycosidic bonds.
The molecule contains multiple $-NH_2$ and –OH groups, making it highly polar and basic.

Nomenclature

- The name streptomycin is derived from:
  - *Strepto* → from *Streptomyces*
  - *Mycin* → antibiotic nature
- Chemical name reflects:
  - Presence of amino sugars
  - Aminocyclitol nucleus

Stereochemistry

→ Streptomycin has multiple chiral centers.

→ Correct stereochemical configuration is essential for:

- Binding to 30S ribosomal subunit
- Antibacterial activity

→ Any change in stereochemistry → loss or reduction of activity.

Mechanism of Action

→ Streptomycin enters bacteria via oxygen-dependent transport.

→ It binds irreversibly to the 30S ribosomal subunit.

→ Causes:

- Inhibition of initiation complex
- Misreading of mRNA

→ Produces faulty proteins → cell membrane damage.

→ Results in bacterial cell death.

→ Hence, streptomycin is bactericidal.

Uses

- Tuberculosis (first-line in combination therapy)
- Plague (*Yersinia pestis*)
- Tularemia
- Brucellosis (with other antibiotics)
- Gram-negative infections
- Endocarditis (with penicillins)

Chemical Degradation

1. Hydrolysis
   - Glycosidic bonds break in acidic or alkaline conditions.
   - Leads to loss of activity.
2. Thermal Degradation
   - High temperature reduces stability.
3. Oxidative Degradation
   - Minor oxidation may occur during storage.

Prevention

→ Store in cool, dry place

→ Protect from moisture and heat

→ Avoid extreme pH

Structure–Activity Relationship (SAR)

Aminocyclitol (Streptidine)

- Essential for ribosomal binding
- Loss → inactive drug

Amino Groups ($-NH_2$)

- Provide basic character
- Enhance binding to rRNA

Sugar Moieties

- Influence potency and selectivity

Glycosidic Linkages

- Essential for correct molecular shape
- Hydrolysis → loss of activity

Stereochemistry

→ Correct spatial arrangement is crucial for activity

Neomycin

→ Neomycin is a broad-spectrum aminoglycoside antibiotic obtained from Streptomyces fradiae.

→ It is bactericidal in nature and acts by inhibiting bacterial protein synthesis.

→ Because of its high toxicity on systemic use, neomycin is mainly used topically and orally (not absorbed).

Classification

Neomycin belongs to:

- Aminoglycoside antibiotics
- First-generation aminoglycosides
- Derived from Streptomyces species

Structure

Neomycin consists of:

- Aminocyclitol nucleus (2-deoxystreptamine)
- Four amino sugar units (neamine, neobiosamine, etc.)
- Linked by glycosidic bonds

Key Features

- Contains many $-NH_2$ and –OH groups
- Highly polar, basic, and water soluble
- Exists mainly as neomycin B (active form)

Nomenclature

- Name derived from:
  - Neo → new
  - Mycin → antibiotic from *Streptomyces*
- Usually supplied as:
  - Neomycin sulfate

Stereochemistry

- Neomycin has multiple chiral centers
- Proper stereochemical orientation is essential for:
  - Binding to bacterial ribosomes
  - Antibacterial activity
- Any stereochemical change → loss of activity

Mechanism of Action

- Neomycin enters bacteria by oxygen-dependent active transport.
- Binds irreversibly to the 30S ribosomal subunit.
- Causes:
  - Misreading of mRNA
  - Inhibition of protein synthesis
- Produces defective proteins → cell membrane damage
- Results in bacterial cell death
- Hence, neomycin is bactericidal.

Uses

- Topical treatment of skin, eye, and ear infections
- Intestinal antiseptic (oral, pre-surgical bowel preparation)
- Hepatic encephalopathy (reduces ammonia-producing bacteria)
- In combination creams & ointments

Chemical Degradation

1. Hydrolysis
   - Glycosidic bonds may hydrolyze in extreme pH
   - Leads to inactivation
2. Thermal Degradation
   - Heat reduces stability
3. Oxidative Degradation
   - Minor oxidation during storage

Prevention

→ Store in cool, dry place

→ Protect from heat & moisture

→ Avoid extreme pH conditions

Structure–Activity Relationship (SAR)

Aminocyclitol Ring (2-Deoxystreptamine)

- Essential for ribosomal binding
- Removal → inactive drug

Amino Groups ($-NH_2$)

- Provide basic nature
- Enhance binding to bacterial rRNA

Sugar Moieties

- Affect antibacterial potency
- Essential for correct molecular shape

Glycosidic Linkages

- Maintain structural integrity
- Hydrolysis → loss of activity

Stereochemistry

- Correct 3D configuration essential for activity

Kanamycin

→ Kanamycin is a broad-spectrum aminoglycoside antibiotic obtained from Streptomyces kanamyceticus.

→ It is bactericidal in nature and is mainly effective against aerobic Gram-negative bacteria.

→ Kanamycin acts by inhibiting bacterial protein synthesis through binding to the 30S ribosomal subunit.

Classification

→ Kanamycin belongs to:

- Aminoglycoside antibiotics
- First-generation aminoglycosides
- Derived from Streptomyces species

Structure

Kanamycin consists of:

- Aminocyclitol nucleus: 2-deoxystreptamine
- Three amino sugar units linked by glycosidic bonds
- Multiple $-NH_2$ and $-OH$ groups

Key Features

- Highly polar and basic
- Water soluble
- Common forms: Kanamycin A (most active)

Nomenclature

→ Name derived from:

- Kana → Kanamycin-producing organism
- Mycin → antibiotic from *Streptomyces*

→ Marketed mainly as:

- Kanamycin sulfate

Stereochemistry

- Kanamycin contains several chiral centers
- Correct stereochemical configuration is essential for:
  - Ribosomal binding

- Antibacterial activity
- Any change in stereochemistry → reduced or lost activity

Mechanism of Action

- Kanamycin enters bacterial cells via oxygen-dependent active transport.
- Binds irreversibly to the 30S ribosomal subunit.
- Causes:
  - Misreading of mRNA
  - Inhibition of protein synthesis
- Leads to production of non-functional proteins.
- Results in bacterial cell death.
- Hence, kanamycin is bactericidal.

Uses

→ Severe Gram-negative bacterial infections
→ Tuberculosis (second-line drug)
→ Urinary tract infections
→ Septicemia
→ Hospital-acquired infections
→ Limited use due to toxicity

Chemical Degradation

1. Hydrolysis
   - Glycosidic bonds are unstable in extreme pH
   - Results in inactivation
2. Thermal Degradation
   - High temperature accelerates degradation
3. Oxidative Degradation
   - Minor oxidation may occur during storage

Prevention

- Store in cool, dry place
- Protect from moisture and heat
- Maintain neutral pH

Structure–Activity Relationship (SAR)

Aminocyclitol Ring (2-Deoxystreptamine)

- Essential for binding to 30S ribosomal subunit

Amino Groups ($-NH_2$)

- Provide basic nature
- Enhance electrostatic binding to rRNA

Sugar Moieties

- Influence potency and spectrum of activity

Glycosidic Linkages

- Maintain correct molecular conformation
- Hydrolysis → loss of activity

Stereochemistry

- Correct spatial orientation is critical for antibacterial action