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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Antibiotics** : Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin



Antibiotics

Antibiotics, originally obtained from **microorganisms**, have been recognized as an important class of **anticancer agents**.

These drugs inhibit cancer cell growth by **interfering with DNA function** and are widely used in chemotherapy.

Drugs to study (B.Pharm syllabus):

- **Dactinomycin (Actinomycin D)**
- **Daunorubicin**
- **Doxorubicin**
- **Bleomycin**

Mechanism of Action

Antineoplastic antibiotics combat cancer cells through **multiple mechanisms**:

1. Intercalation into DNA

- Drugs like **Doxorubicin** and **Daunorubicin** insert themselves between DNA base pairs.
- This **disrupts DNA replication and transcription**, leading to **cell cycle arrest and apoptosis**.

2. Inhibition of Topoisomerases

- Some antibiotics inhibit **topoisomerase II**, an enzyme essential for DNA replication and repair.
- This inhibition causes **DNA strand breaks**, impairs repair, and results in **cell death**.

3. Formation of Free Radicals

- **Bleomycin** generates **free radicals**, which induce **oxidative DNA damage**.
- Leads to **single- and double-strand DNA breaks**, preventing DNA replication and transcription, ultimately causing **apoptosis**.

4. Cross-Linking of DNA

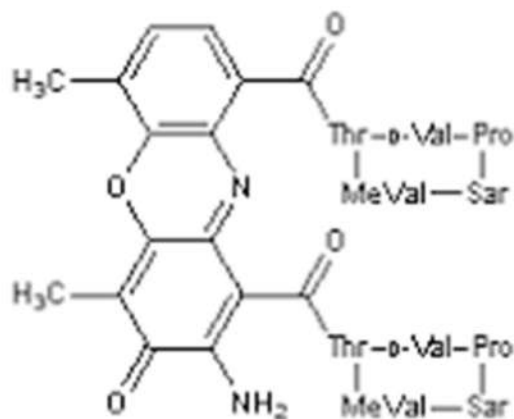
- Some antibiotics can **form covalent bonds between DNA strands**, preventing their proper separation.
- This blocks **DNA replication and transcription**, inhibiting tumor growth and inducing **cell death**.

Dactinomycin (Actinomycin D)

- Dactinomycin is an **antineoplastic antibiotic** derived from **Streptomyces species**.
- It is classified as a **DNA intercalating agent** that **inhibits transcription** by binding to DNA.
- Used in **pediatric tumors (Wilms' tumor, rhabdomyosarcoma), testicular cancer, and gestational trophoblastic tumors**.
- Administered **intravenously** due to poor oral absorption.

Chemical Structure

- **IUPAC Name:** 2-Amino-4,6-dimethyl-3-(β-D-lyxofuranosyl)amino-1,9-dihydroxy-1H-pyrrolo[3,2-e]indole-5,10-dione peptide derivative
- **Molecular Formula:** C₆₂H₈₆N₁₂O₁₆
- **Molecular Weight:** 1255.42 g/mol
- **Chemical Structure**



Mechanism of Action

- **DNA Intercalation:**
 - Dactinomycin inserts itself **between adjacent guanine-cytosine base pairs** in DNA.
 - Stabilizes the DNA helix and **prevents elongation by RNA polymerase**.
- **Inhibition of Transcription:**
 - Prevents **RNA synthesis**, which subsequently **reduces protein synthesis**.
- **Cell Cycle Effect:**
 - **Non-phase specific**; affects both dividing and non-dividing cells.
- **Cytotoxicity:**
 - Leads to **apoptosis due to transcriptional inhibition** and secondary DNA damage.

Synthesis of Dactinomycin

1. Source:

- Naturally produced by fermentation using **Streptomyces aureofaciens** or related species.

2. Fermentation:

- Cultured under optimized conditions to produce **dactinomycin**.

3. Isolation & Purification:

- Extraction with organic solvents followed by **chromatography** to obtain clinical-grade dactinomycin.

Uses

1. Pediatric malignancies:

- Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma.

2. Gestational trophoblastic tumors:

- Choriocarcinoma treatment.

3. Testicular cancer:

- Combined with other chemotherapeutic agents.

4. Side Effects:

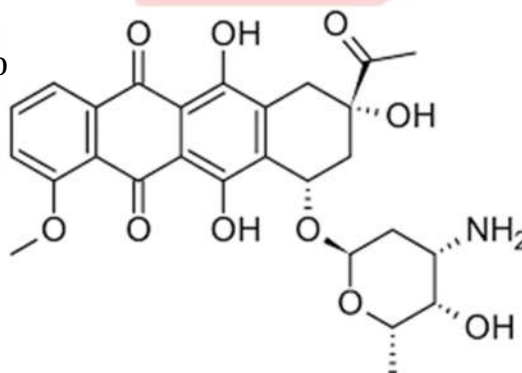
- Myelosuppression, mucositis, nausea, vomiting, hepatotoxicity, alopecia, and risk of secondary malignancy with long-term use.

Daunorubicin

- Daunorubicin is an **anthracycline antibiotic** used as a **cytotoxic chemotherapeutic agent**.
- It is produced by ***Streptomyces peucetius* var. *caesius***.
- Used primarily in **acute myeloid leukemia (AML)**, **acute lymphoblastic leukemia (ALL)**, and other hematologic malignancies.
- Administered **intravenously**, as it has poor oral bioavailability.

Chemical Structure

- **IUPAC Name:** (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione
- **Molecular Formula:** $C_{27}H_{29}NO_{10}$
- **Molecular Weight:** 527.53 g/mol
- **Chemical Structure**



Mechanism of Action

- **DNA Intercalation:**
 - Inserts between DNA base pairs → disrupts DNA replication and transcription.
- **Topoisomerase II Inhibition:**
 - Stabilizes the DNA-topoisomerase II complex → prevents **DNA religation** → causes DNA strand breaks.
- **Generation of Free Radicals:**
 - Metabolized to **semiquinone radicals** → induces oxidative stress → damages cellular membranes, DNA, and proteins.
- **Cell Cycle Effect:**
 - **Non-phase specific**, affecting both dividing and non-dividing cells.
- **Cytotoxicity:**
 - Leads to **apoptosis** due to DNA damage and oxidative stress.

Synthesis of Daunorubicin

1. Source:

- Produced naturally by ***Streptomyces peucetius var. caesius***.

2. Fermentation:

- Cultivation under optimized conditions to produce daunorubicin.

3. Isolation & Purification:

- Extraction with organic solvents and chromatographic techniques
→ clinical-grade daunorubicin.

Uses

1. Hematologic malignancies:

- Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL).

2. Other cancers (rarely):

- Sometimes used in combination chemotherapy for solid tumors.

3. Side Effects:

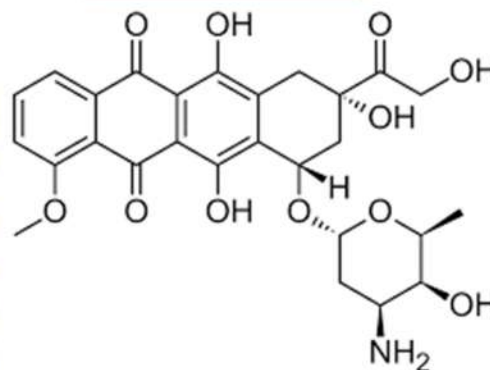
- Myelosuppression, cardiotoxicity (dose-dependent), alopecia, nausea, vomiting, mucositis, and potential for secondary malignancy.

Doxorubicin (Adriamycin)

- Doxorubicin is an **anthracycline antibiotic** and a **cytotoxic chemotherapeutic agent**.
- Produced by ***Streptomyces peucetius* var. *caesius***.
- Used in **hematologic malignancies** (e.g., leukemia, lymphoma) and **solid tumors** such as **breast cancer, ovarian cancer, and sarcomas**.
- Administered **intravenously** due to poor oral absorption.

Chemical Structure

- **IUPAC Name:** (8S,10S)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione
- **Molecular Formula:** $C_{27}H_{29}NO_{11}$
- **Molecular Weight:** 543.52 g/mol
- **Chemical Structure**



Mechanism of Action

- **DNA Intercalation:**
 - Doxorubicin inserts between **DNA base pairs**, disrupting replication and transcription.
- **Topoisomerase II Inhibition:**
 - Stabilizes the DNA-topoisomerase II complex → prevents DNA religation → causes **DNA strand breaks**.
- **Generation of Free Radicals:**
 - Metabolized to **semiquinone radicals** → oxidative stress → damages DNA, lipids, and proteins.
- **Cell Cycle Effect:**
 - **Non-phase specific**, affecting both dividing and non-dividing cells.
- **Cytotoxicity:**
 - Leads to **apoptosis** due to DNA damage and oxidative injury.

Synthesis of Doxorubicin

1. Source:

- Naturally produced by ***Streptomyces peucetius var. caesius***.

2. Fermentation:

- Optimized microbial fermentation yields doxorubicin.

3. Isolation & Purification:

- Extraction using organic solvents and chromatographic methods
→ clinical-grade doxorubicin.

Uses

1. Hematologic malignancies:

- Acute leukemias, lymphomas, and multiple myeloma.

2. Solid tumors:

- Breast cancer, ovarian cancer, bladder cancer, sarcomas, and gastric cancer.

3. Side Effects:

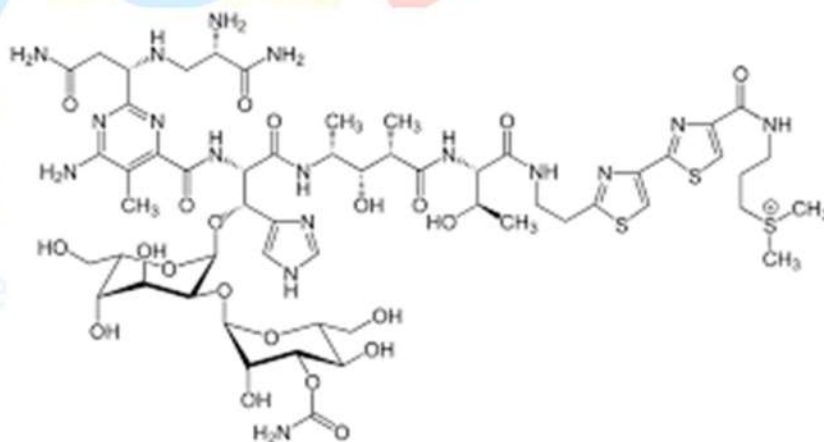
- Myelosuppression, cardiotoxicity (dose-dependent), mucositis, alopecia, nausea, vomiting, and risk of secondary malignancies.

Bleomycin

- Bleomycin is an **antineoplastic antibiotic** produced by ***Streptomyces verticillus***.
- It is classified as a **glycopeptide antibiotic** with **anticancer activity**.
- Used primarily in **Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, ovarian cancer, and squamous cell carcinoma**.
- Administered **intravenously, intramuscularly, or subcutaneously**, and sometimes **intralesionally** for local tumors.

Chemical Structure

- **Molecular Formula:** $C_{78}H_{118}N_{18}O_{23}S_3$ (Bleomycin A₂, most common)
- **Molecular Weight:** ~1415.56 g/mol
- **Structure**



Mechanism of Action

- **DNA Binding:**
 - Bleomycin binds to **DNA**, specifically at **G-C rich sequences**, in the **minor groove**.
- **Metal Complex Formation:**
 - Forms a complex with **Fe²⁺ or Cu²⁺**, which reacts with **O₂** to produce **free radicals**.
- **DNA Strand Breaks:**
 - Free radicals induce **single- and double-strand DNA breaks**, inhibiting DNA synthesis.
- **Cell Cycle Effect:**
 - **G₂-phase specific**, affecting cells before mitosis.

- **Cytotoxicity:**
 - Leads to **apoptosis** due to DNA damage and cell cycle arrest.

Synthesis of Bleomycin

1. **Source:**
 - Naturally produced by **fermentation using Streptomyces verticillus**.
2. **Fermentation:**
 - Cultured under optimized conditions to produce bleomycin A₂ and B₂.
3. **Isolation & Purification:**
 - Extraction from fermentation broth followed by **chromatography** yields clinical-grade bleomycin.

Uses

- Used in the treatment of Hodgkin's lymphoma
- Used in Non-Hodgkin's lymphoma
- Used in testicular cancer (BEP regimen)
- Used in squamous cell carcinoma of head and neck
- Used in cervical cancer
- Used in esophageal cancer
- Used in skin cancers