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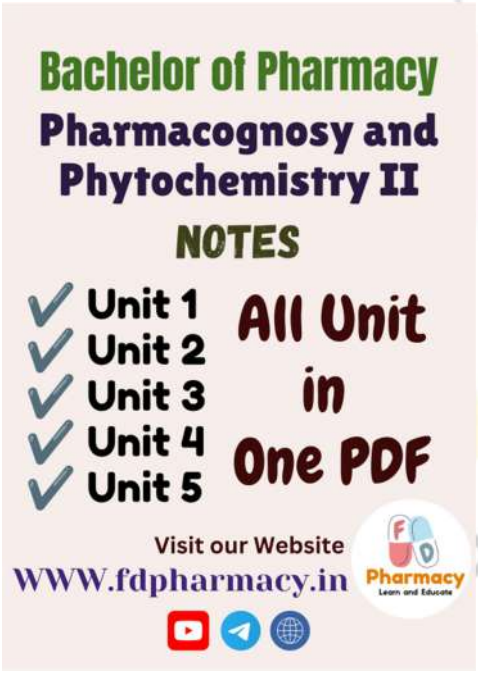
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# MEDICINAL CHEMISTRY - II

## 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:

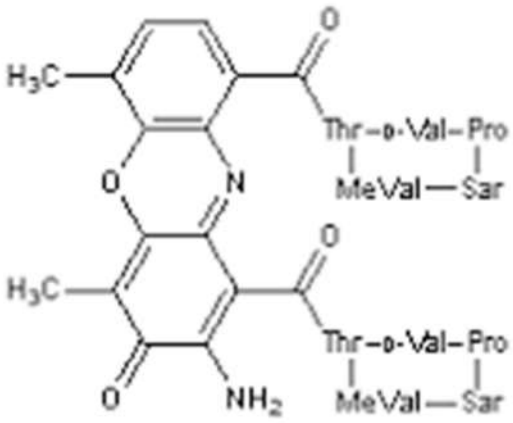
1. Intercalation into DNA
    - Drugs like Doxorubicin and Daunorubicin insert themselves between DNA base pairs.
    - This disrupts DNA replication and transcription, leading to cell cycle arrest and apoptosis.
2. Inhibition of Topoisomerases
    - Some antibiotics inhibit topoisomerase II, an enzyme 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: $C_{62}H_{86}N_{12}O_{16}$
- 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

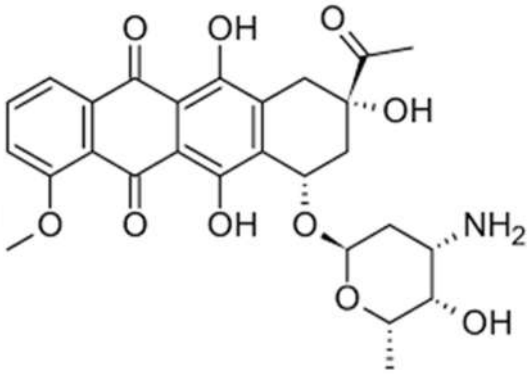
1. Pediatric malignancies:
    - Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma.
2. Gestational trophoblastic tumors:
    - Choriocarcinoma treatment.
3. Testicular cancer:
    - Combined with other chemotherapeutic agents.
4. Side Effects:
    - Myelosuppression, mucositis, nausea, vomiting, hepatotoxicity, 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

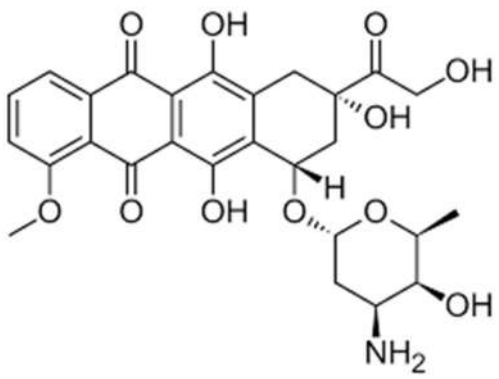
1. Hematologic malignancies:
    - Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL).
2. Other cancers (rarely):
    - Sometimes used in combination chemotherapy for solid tumors.
3. Side Effects:
    - Myelosuppression, cardiotoxicity (dose-dependent), alopecia, nausea, vomiting, mucositis, 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

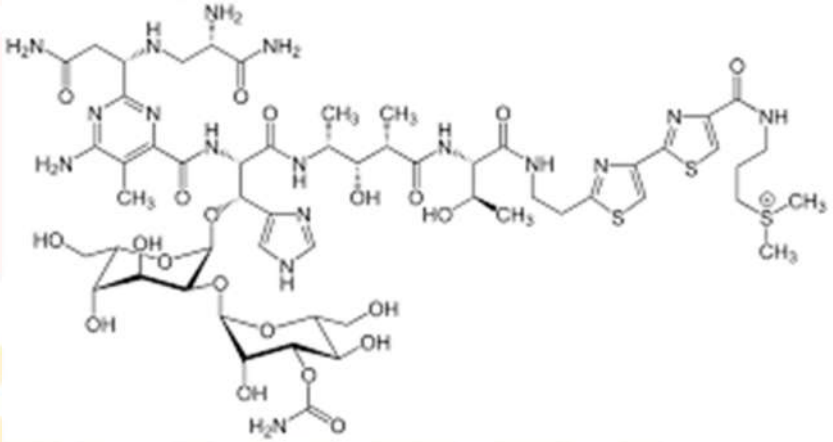
1. Hematologic malignancies:
    - Acute leukemias, lymphomas, and multiple myeloma.
2. Solid tumors:
    - Breast cancer, ovarian cancer, bladder cancer, sarcomas, and gastric cancer.
3. Side Effects:
    - Myelosuppression, cardiotoxicity (dose-dependent), mucositis, alopecia, nausea, vomiting, and 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 $A_2$, 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 $Fe^{2+}$ or $Cu^{2+}$, which reacts with $O_2$ 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 $A_2$ and $B_2$.
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