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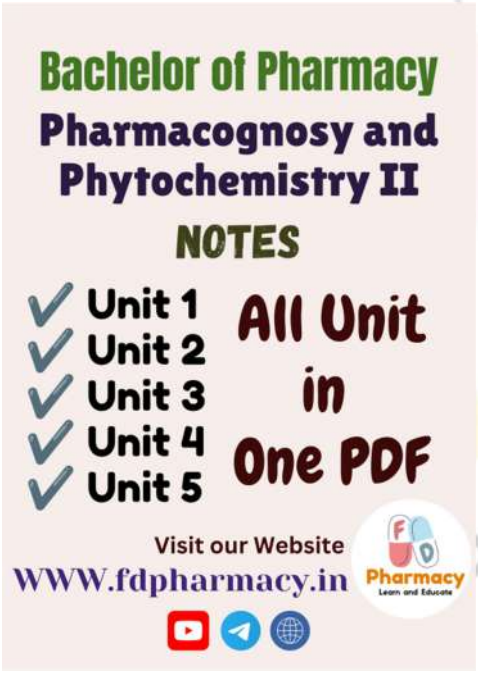
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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Anti-neoplastic agents :**

  Alkylating agents : Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa

Antineoplastic Agents

- Antineoplastic agents, also called anticancer drugs, chemotherapy, or cytotoxic drugs, are used to treat cancer by inhibiting the growth and proliferation of malignant cells. These drugs target rapidly dividing cells and can act through various mechanisms depending on their class.

Cancer

Cancer is a serious disease characterized by uncontrolled growth and spread of abnormal cells in the body. These abnormal cells may form tumors and can spread to other organs via the blood or lymphatic system.
Cancer is usually named after the organ or type of cell where it originates, such as:

- Breast cancer
- Lung cancer

Other related terms:

- Neoplasm: An abnormal mass of tissue.
- Tumor: Can be benign or malignant; used interchangeably with neoplasm in some contexts.

Tumor

- A tumor is an abnormal growth of cells that forms a mass or lump. Tumors are classified into:

Type	Features
Benign Tumor	Non-cancerous; usually grows slowly; does not spread; can often be removed surgically
Malignant Tumor	Cancerous; grows rapidly; can invade nearby tissues; spreads through blood or lymphatic system; harder to remove surgically

Classification of Cancer

Cancer can be classified based on the type of tissue involved:

Type	Description
Carcinomas	Originates from epithelial cells; most common type of cancer
Sarcomas	Originates from connective tissues like bone, cartilage, fat, or muscle
Leukemias	Cancers of blood-forming tissues like bone marrow; abnormal proliferation of white blood cells
Lymphomas	Cancer of the lymphatic system, affecting lymph nodes and lymphoid tissues

Causes of Cancer

Cancer arises due to mutations or changes in the DNA of cells, which lead to uncontrolled cell division and abnormal growth.

Common causes include:

1. Genetic mutations – Inherited or spontaneous changes in DNA that predispose cells to cancer.
2. Environmental exposures – Prolonged contact with carcinogens like chemicals, pesticides, and industrial pollutants.
3. Smoking – Major risk factor for lung, oral, and other cancers.
4. Alcohol consumption – Increases risk of liver, esophageal, and breast cancer.
5. Infections – Certain viruses (e.g., HPV, EBV), bacteria (e.g., H. pylori), and parasites can trigger cancer.
6. Hormonal imbalances – Abnormal hormone levels may promote the growth of hormone-dependent cancers (e.g., breast or prostate cancer).

Signs and Symptoms of Cancer

Cancer can present with general or site-specific symptoms, such as:

- Fatigue – Persistent tiredness not relieved by rest
- Unexplained weight changes – Sudden loss or gain
- Skin changes – Yellowing, darkening, or redness of the skin; sores that do not heal
- Bowel or urinary changes – Persistent constipation, diarrhea, or blood in urine/stool
- Persistent cough or hoarseness – Especially in lung or throat cancer
- Breathing difficulties – Shortness of breath or chest pain
- Fever or night sweats – Common in blood cancers like leukemia or lymphoma

Treatment of Cancer

Treatment depends on cancer type, stage, and patient health, and often involves multimodal therapy:

1. Surgery – Removal of localized tumors; effective for benign and some malignant tumors
2. Chemotherapy – Use of antineoplastic agents to kill rapidly dividing cancer cells
3. Radiation therapy – High-energy radiation to destroy cancer cells and shrink tumors
4. Targeted therapy – Drugs that target specific molecules or pathways in cancer cells
5. Immunotherapy – Stimulates the immune system to attack cancer cells
6. Hormonal therapy – Used for hormone-dependent cancers to block hormone action

Classification of Anti-neoplastic agents

→ **Alkylating agents :** Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa

→ **Antimetabolites :** Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine

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

→ **Plant products :** Etoposide, Vinblastin sulphate ,Vincristin sulphate

→ **Miscellaneous :** Cisplatin, Mitotane.

Alkylating Agents

- Alkylating agents are a class of antineoplastic drugs used to treat cancer. They are among the oldest and most effective chemotherapy agents, first confirmed by clinical trials in the mid-1940s.
- These drugs are particularly effective against rapidly dividing cancer cells because they directly damage DNA, thereby inhibiting cell replication and leading to cell death.

Mechanism of Action

Alkylating agents work by adding alkyl groups to DNA, leading to interference with DNA replication and transcription.

Stepwise Mechanism :

1. Alkylation
    - Alkylating agents transfer an alkyl group (methyl or ethyl) to DNA, primarily at the N7 position of guanine bases.
    - Nitrogen mustard derivatives first undergo intramolecular cyclization to form an aziridinium ion, a highly reactive intermediate.
2. DNA Cross-Linking
    - The reactive aziridinium ion alkylates two guanine bases, forming covalent bonds between DNA strands (interstrand cross-linking) or within the same strand (intrastrand cross-linking).
    - Cross-linking prevents DNA strand separation, which is essential for replication and transcription.
3. DNA Damage
    - Alkylation induces structural distortions and breaks in DNA.
    - The damage leads to errors during replication and triggers cell cycle arrest.
4. Cell Death
    - If the DNA damage is irreparable, it leads to apoptosis (programmed cell death), particularly in rapidly dividing cancer cells.

Examples

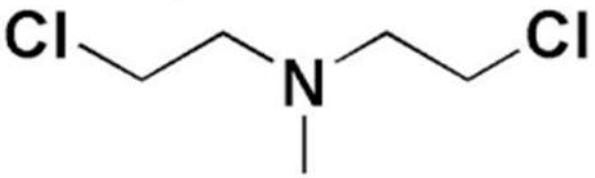
- Meclorethamine*,
- Cyclophosphamide,
- Melphalan,
- Chlorambucil,
- Busulfan,
- Thiotepa

Mechlorethamine

- Mechlorethamine is a nitrogen mustard alkylating agent, one of the earliest chemotherapeutic drugs.
- It is a highly reactive cytotoxic compound that acts by alkylating DNA, leading to cross-linking, strand breakage, and inhibition of DNA replication.
- It is used primarily in cancer chemotherapy, especially for Hodgkin's lymphoma and other lymphoid malignancies.
- Due to its high reactivity, it is unstable in aqueous solution and usually handled as a hydrochloride salt or freshly prepared solutions.

Chemical Structure

- IUPAC Name: 2-Chloro-N-(2-chloroethyl)-N-methylethanamine
- Molecular Formula: $C_4H_9Cl_2N$
- Molecular Weight: 156.03 g/mol
- Chemical Structure



Mechanism of Action

- DNA Alkylation:
  - Mechlorethamine forms highly reactive ethylene immonium ions.
  - These ions covalently bind to nucleophilic sites on DNA, especially guanine N7 positions, causing:
    - Interstrand and intrastrand cross-links
    - DNA strand breakage
    - Inhibition of DNA replication and transcription
- Cell Cycle Effect:
  - Non-phase specific but most active in rapidly dividing cells, including cancer cells.
- Cytotoxicity:
  - Leads to apoptosis or cell death due to irreparable DNA damage.

Synthesis of Mechlorethamine

1. Starting Material:
    - Ethylenediamine or 2-chloroethylamine derivatives.
2. Alkylation Reaction:
    - React methylamine with 2-chloroethyl chloride in anhydrous conditions to introduce chloroethyl side chains.
3. Purification:
    - The crude product is purified under controlled conditions to obtain Mechlorethamine hydrochloride, the clinically used salt form.

Uses

1. Cancer chemotherapy:
    - Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia (historically).
2. Topical treatment:
    - Applied as mechlorethamine ointment for cutaneous T-cell lymphoma (CTCL).
3. Research tool:
    - Used in studies of DNA cross-linking and alkylation.

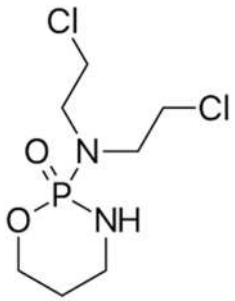
- Note:
    - Highly toxic; careful handling and storage required.
    - Side effects include myelosuppression, nausea, vomiting, alopecia, and local tissue necrosis if extravasation occurs.

Cyclophosphamide

- Cyclophosphamide is a nitrogen mustard derivative and a bifunctional alkylating agent used in chemotherapy and immunosuppression.
- It is a prodrug that requires hepatic activation by cytochrome P450 enzymes to form active alkylating metabolites.
- Used in cancer therapy, including leukemias, lymphomas, breast cancer, ovarian cancer, and also in autoimmune diseases.
- Administered orally or intravenously.

Chemical Structure

- IUPAC Name: 2-[Bis(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorine
- Molecular Formula: $C_7H_{15}Cl_2N_2O_2P$
- Molecular Weight: 261.09 g/mol
- Chemical Structure



Mechanism of Action

- Prodrug Activation:
  - Cyclophosphamide is metabolized in the liver by CYP450 enzymes to form 4-hydroxycyclophosphamide and aldophosphamide.
  - Aldophosphamide spontaneously forms phosphoramide mustard, the active alkylating agent, and acrolein, a toxic byproduct.
- DNA Alkylation:
  - Phosphoramide mustard alkylates DNA, particularly guanine N7, causing:
    - Interstrand and intrastrand DNA cross-links
    - DNA strand breakage
    - Inhibition of DNA replication and transcription
- Cell Cycle Effect:
  - Non-phase-specific, affecting both dividing and resting cells but more toxic to rapidly dividing cells.
- Cytotoxicity:
  - Leads to apoptosis due to irreparable DNA damage.

Synthesis of Cyclophosphamide

1. Formation of Phosphoramide Intermediate:
    - React bis(2-chloroethyl)amine with phosphoryl chloride ($POCl_3$) under controlled conditions to form phosphoramide mustard derivative.
2. Cyclization:
    - Intramolecular cyclization forms the oxazaphosphorine ring, generating cyclophosphamide.
3. Purification:
    - The final product is purified as a stable crystalline powder for oral or IV formulation.

Uses

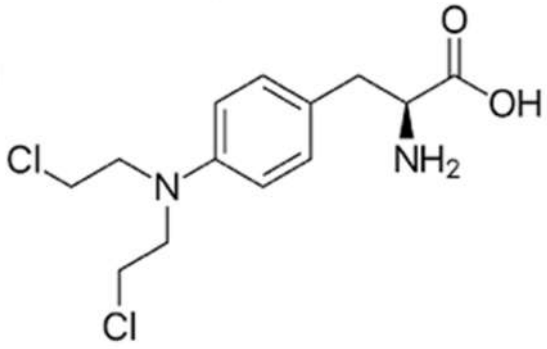
1. Cancer chemotherapy:
    - Leukemias, lymphomas, breast cancer, ovarian cancer, and multiple myeloma.
2. Immunosuppressive therapy:
    - Autoimmune diseases such as systemic lupus erythematosus (SLE), vasculitis, and nephrotic syndrome.
3. Bone marrow transplantation:
    - Used as conditioning regimen to suppress immune response.
4. Other notes:
    - Requires hydration and mesna co-administration to prevent acrolein-induced hemorrhagic cystitis.
    - Side effects include myelosuppression, nausea, vomiting, alopecia, and gonadal toxicity.

Melphalan

- Melphalan is a nitrogen mustard alkylating agent used primarily in cancer chemotherapy.
- It is a derivative of phenylalanine, making it an amino acid-linked alkylating agent.
- Melphalan is particularly effective in multiple myeloma, ovarian cancer, breast cancer, and lymphomas.
- Administered orally or intravenously, depending on the clinical requirement.

Chemical Structure

- IUPAC Name: L-Phenylalanine mustard; 2-amino-4-(bis(2-chloroethyl)amino)butanoic acid
- Molecular Formula: $C_{13}H_{18}Cl_2N_2O_2$
- Molecular Weight: 305.19 g/mol
- Chemical Structure



Mechanism of Action

- DNA Alkylation:
  - Melphalan forms highly reactive ethylene immonium ions, which alkylate DNA, primarily at the N7 position of guanine.
  - Causes:
    - DNA cross-linking (interstrand and intrastrand)
    - DNA strand breakage
    - Inhibition of DNA replication and RNA transcription
- Cell Cycle Effect:
  - Non-phase-specific, but more toxic to rapidly dividing cells like cancer cells.
- Cytotoxicity:
  - Leads to apoptosis or cell death due to irreparable DNA damage.

Synthesis of Melphalan

1. Starting Material:
    - L-Phenylalanine or its derivatives.
2. Alkylation:
    - React L-phenylalanine with 2-chloroethylamine or 2-chloroethyl chloride derivatives to introduce bis(2-chloroethyl)amino groups.
3. Purification:
    - The final product, Melphalan, is purified as a hydrochloride salt for stability and clinical use

Uses

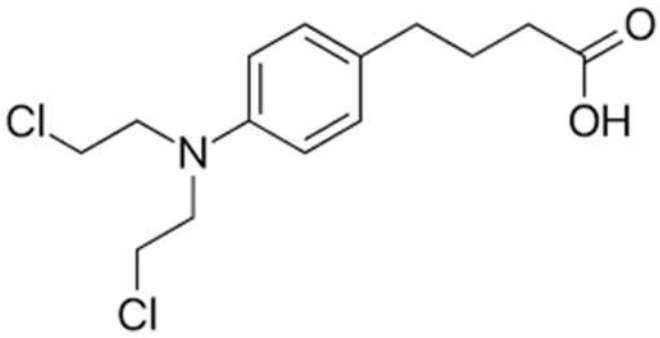
1. Cancer chemotherapy:
    - Multiple myeloma (most common use), ovarian cancer, breast cancer, lymphomas.
2. Bone marrow transplantation:
    - High-dose melphalan is used as a conditioning regimen before transplantation.
3. Mechanism-based selectivity:
    - Selectively uptaken by cells via amino acid transporters, enhancing efficacy against tumor cells.
4. Other notes:
    - Side effects include myelosuppression, nausea, vomiting, alopecia, and risk of secondary malignancies

Chlorambucil

- Chlorambucil is a nitrogen mustard alkylating agent used primarily in cancer chemotherapy.
- It belongs to the aryl nitrogen mustard group, making it less reactive and more selective compared to classical nitrogen mustards like mechlorethamine.
- Used mainly in chronic lymphocytic leukemia (CLL), Hodgkin's and non-Hodgkin's lymphomas, and certain solid tumors.
- Administered orally, which is advantageous for long-term therapy.

Chemical Structure

- IUPAC Name: 4-[Bis(2-chloroethyl)amino]benzenebutanoic acid
- Molecular Formula: $C_{14}H_{19}Cl_2NO_2$
- Molecular Weight: 304.22 g/mol
- Chemical Structure



Mechanism of Action

- DNA Alkylation:
  - Chlorambucil forms highly reactive ethylene immonium ions after entering the cell.
  - These ions alkylate DNA, primarily at guanine N7 positions, causing:
    - DNA interstrand and intrastrand cross-links
    - DNA strand breakage
    - Inhibition of DNA replication and RNA transcription
- Cell Cycle Effect:
  - Non-phase-specific; effective against rapidly dividing cells, particularly lymphoid cells.
- Cytotoxicity:
  - Leads to apoptosis due to irreparable DNA damage.

Synthesis of Chlorambucil

1. Starting Material:
    - 4-aminophenylbutyric acid.
2. Alkylation Reaction:
    - React the amino group with 2-chloroethyl chloride to introduce bis(2-chloroethyl)amine groups.
3. Purification:
    - The final product is purified as chlorambucil for oral administration.

Uses

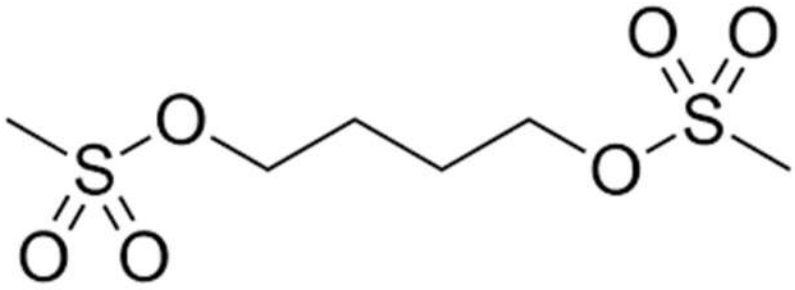
1. Chronic lymphocytic leukemia (CLL):
    - Mainstay therapy for indolent forms of leukemia.
2. Hodgkin's and non-Hodgkin's lymphoma:
    - Used as part of combination chemotherapy regimens.
3. Other malignancies:
    - Occasionally used in ovarian cancer and other solid tumors.
4. Advantages:
    - Oral administration allows long-term outpatient therapy.
    - Less toxic and slower-acting than mechlorethamine, reducing acute adverse effects.
5. Side Effects:
    - Myelosuppression, nausea, vomiting, risk of secondary malignancies, and infertility.

Busulfan

- Busulfan is an alkylating agent belonging to the alkylsulfonate class.
- It is a bifunctional alkylating agent that primarily affects rapidly dividing cells.
- Used mainly in chronic myeloid leukemia (CML) and as part of preparative regimens for bone marrow transplantation.
- Administered orally or intravenously.
- Less reactive than nitrogen mustards, leading to a slower onset of cytotoxicity but better safety profile for long-term therapy.

Chemical Structure

- IUPAC Name: 1,4-Butanediol dimethanesulfonate
- Molecular Formula: $C_6H_{14}O_6S_2$
- Molecular Weight: 246.3 g/mol
- Chemical Structure



Mechanism of Action

- DNA Alkylation:
  - Busulfan forms reactive carbonium ions that alkylate DNA, primarily at guanine N7 positions, leading to:
    - Interstrand and intrastrand cross-links
    - DNA strand breakage
    - Inhibition of DNA replication and transcription
- Cell Cycle Effect:
  - Non-phase-specific, but more toxic to rapidly dividing cells like hematopoietic cells.
- Cytotoxicity:
  - Causes apoptosis due to irreparable DNA damage.
  - Slower onset than nitrogen mustards, allowing less acute toxicity.

Synthesis of Busulfan

1. Starting Material:
    - 1,4-butanediol
2. Methanesulfonation Reaction:
    - React 1,4-butanediol with methanesulfonyl chloride (CH_3SO_2Cl) in the presence of base (like triethylamine or pyridine) to form busulfan.
3. Purification:
    - The crude product is purified to obtain crystalline busulfan suitable for oral or IV use.

Uses

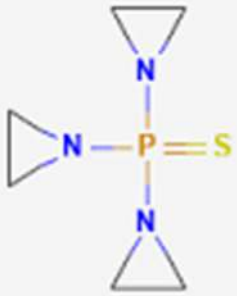
1. Chronic Myeloid Leukemia (CML):
    - Historically a mainstay therapy before tyrosine kinase inhibitors.
2. Bone Marrow Transplant Conditioning:
    - Used in myeloablative regimens to suppress bone marrow prior to transplant.
3. Other Uses:
    - Occasionally used in other hematologic malignancies as part of combination therapy.
4. Side Effects:
    - Myelosuppression, pulmonary fibrosis (long-term use), hepatic veno-occlusive disease, nausea, vomiting, and alopecia.

Thiotepa

- Thiotepa is a polyfunctional alkylating agent belonging to the aziridine class.
- It is a highly reactive cytotoxic agent used in cancer chemotherapy and bone marrow transplantation conditioning.
- Thiotepa acts by alkylating DNA, leading to cross-linking, strand breakage, and inhibition of DNA replication.
- Administered intravenously; also used as a topical therapy in certain cancers like bladder cancer.

Chemical Structure

- IUPAC Name: Triethylenethiophosphoramide
- Molecular Formula: $C_6H_{12}N_3PS$
- Molecular Weight: 189.21 g/mol
- Chemical Structure



Mechanism of Action

- DNA Alkylation:
  - Thiotepa's aziridine rings form ethylene immonium ions that covalently bind to nucleophilic sites on DNA, particularly guanine N7.
  - Causes:
    - DNA cross-linking (interstrand and intrastrand)
    - DNA strand breakage
    - Inhibition of DNA replication and transcription
- Cell Cycle Effect:
  - Non-phase-specific; toxic to both dividing and resting cells, with preference for rapidly dividing tumor cells.
- Cytotoxicity:
  - Leads to apoptosis due to irreparable DNA damage.

Synthesis of Thiotepa

1. Starting Material:
    - Triethanolamine or derivatives.
2. Reaction with Thionyl Chloride:
    - Convert triethanolamine to the corresponding phosphoramide intermediate using thionyl chloride ($SOCl_2$).
3. Aziridine Formation:
    - Cyclization forms three aziridine rings, generating thiotepa.
4. Purification:
    - The final product is purified as a stable crystalline powder for IV or topical use.

Uses

1. Cancer chemotherapy:
    - Breast cancer, ovarian cancer, and other solid tumors.
2. Bone marrow transplant conditioning:
    - High-dose thiotepa is used to suppress bone marrow before transplantation.
3. Topical therapy:
    - Bladder cancer (instillation therapy).
4. Side Effects:
    - Myelosuppression, nausea, vomiting, alopecia, immunosuppression, and hepatotoxicity.