

# MEDICINAL CHEMISTRY-II

## Unit-1 | Part-3



# ANTINEOPLASTIC AGENTS

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## UNIT-1 ANTI-NEOPLASTIC

### ANTI-NEOPLASTIC AGENTS

- Antineoplastic or anticancer drugs are used for treating malignancies or cancerous growths.
- Either these drugs are used alone [chemotherapy] or in combination with surgery or radiation therapy.

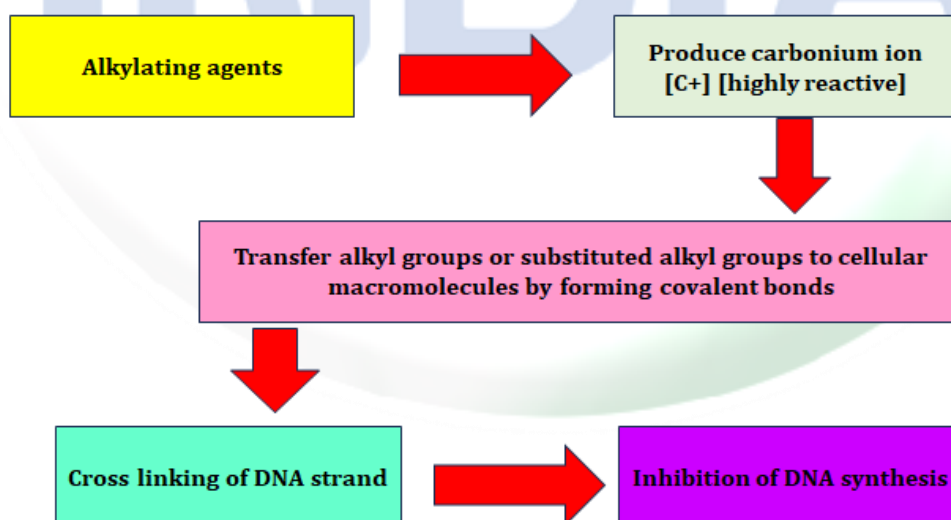
### Cancer is classified into the following categories;

- Carcinoma
- Sarcoma
- Leukaemia
- Lymphoma & myeloma
- Central nervous system cancers

### ALKYLATING AGENTS

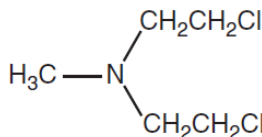
- Alkylating agents** are chemically reactive compounds. It combines most easily with nucleophilic centres, and a fully saturated carbon atom of the alkylating group attaches to the nucleophile.
- The term **alkylating agent** is used for a compound that reacts with a substance by joining with covalent bond and alkylates it.
- Any antineoplastic agent that acts by such a mechanism is an alkylating agent.

### MECHANISMS OF ACTION OF ALKYLATING AGENTS



Drug	Uses	Structure
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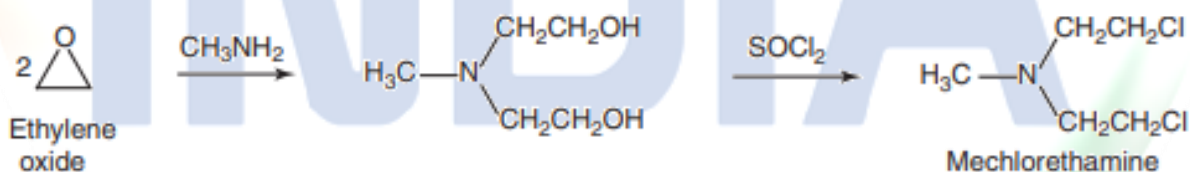
## B. PHARMA 5<sup>TH</sup> SEM | MEDICINAL CHEMISTRY-II

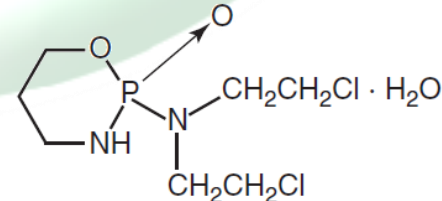
<b>Mechlorethamine</b>	<ul style="list-style-type: none"> <li>It is used for the treatment of stages III and IV of Hodgkin's disease, lymphosarcoma, chronic myelocytic or chronic lymphocytic leukaemia, polycythaemia vera, mycosis fungoides, and bronchogenic carcinoma.</li> <li>It is also used for the treatment of metastatic carcinoma.</li> </ul>	 <p>2,2'-Dichloro-N-methyl diethylamine</p>
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### SAR OF ALKYLATING AGENTS

- 2 chloroethyl group is essential for activity.
  - Other halogens than Cl decreases the activity.
  - Increases or decreases in ethyl chain decreases the activity.
- Due to the substitutions Nucleophilic undergoes cyclization with ethyl chain & carbonium ions forms which attack on DNA
- May be methyl group or phenyl, substituted phenyl, pyridine, phenyl- alanine, which will make stable compounds
- Methyl group is weak e<sup>-</sup> donating.  
Other aromatic group with e<sup>-</sup> withdrawing nature may decrease the nucleophilicity of Nitrogen atom which reduces the cyclization & carbonium ion formation.

### SYNTHESIS



Drug	Uses	Structure
<b>Cyclophosphamide</b>	<ul style="list-style-type: none"> <li>It is used in the treatment of malignant lymphomas, multiple myeloma, leukaemia, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, and carcinoma of breast.</li> </ul>	 <p>2-[Bis(2-chloroethyl)amino] tetrahydro-1, 3, 2-oxazaphosphorin-2-oxide monohydrate</p>

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	<ul style="list-style-type: none"> <li>It is also used in biopsy-proven minimal change nephrotic syndrome in paediatrics.</li> </ul>	
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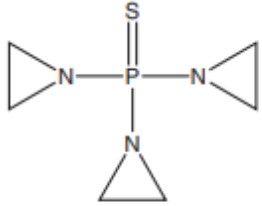
Drug	Uses	Structure
<b>Melphalan</b>	<ul style="list-style-type: none"> <li>It is used alone or as part of many chemotherapeutic regimens as an adjunct to surgery for treating breast cancer.</li> <li>It is used alone or in combination regimens in the treatment of locally recurrent or unrespectable in-transit metastatic melanoma of the extremities.</li> <li>It is used with prednisone in the treatment of amyloidosis.</li> </ul>	<p style="text-align: center;">4-[Bis(2-chloroethyl)amino]-L-phenylalanine</p>

Drug	Uses	Structure
<b>Chlorambucil</b>	<ul style="list-style-type: none"> <li>Chlorambucil is used in the treatment of chronic lymphatic leukaemia, childhood minimal-change nephrotic syndrome, and malignant lymphomas including lymphosarcoma, giant follicular lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas, and Waldenström's Macroglobulinemia.</li> </ul>	<p style="text-align: center;">(ClH<sub>2</sub>CH<sub>2</sub>C)<sub>2</sub>N—(C<sub>6</sub>H<sub>4</sub>)—(CH<sub>2</sub>)<sub>3</sub>COOH</p>

Drug	Uses	Structure
<b>Busulfan</b>	<ul style="list-style-type: none"> <li>It is used in the treatment of chronic granulocytic leukemia.</li> <li>It is also a component of pre-transplant conditioning regimen in bone marrow transplantation for acute myeloid leukaemia and non-malignant diseases.</li> </ul>	<p style="text-align: center;">CH<sub>3</sub>SO<sub>2</sub>O(CH<sub>2</sub>)<sub>4</sub>OSO<sub>2</sub>CH<sub>3</sub> 1,4-Bis(methanesulphonyloxy) butane</p>

Drug	Uses	Structure
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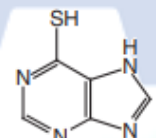
<b>Thiotepa</b>	<ul style="list-style-type: none"><li>It is used for treating breast, ovarian and bladder cancer.</li><li>It is also used as conditioning for bone marrow transplantation</li></ul>	 <p>Tri-(1-aziridinyl) phosphine sulphide</p>
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### ANTIMETABOLITES

- Antimetabolite drugs are the first effective chemotherapeutic agents. These drugs are low molecular weighed analogues of folic acid, pyrimidine or purine.
- Their structures are similar to those of naturally occurring molecules involved in nucleic acid (DNA and RNA) synthesis.
- Antimetabolites are identical to the chemicals required for normal biochemical activity. However, they are sufficiently different to interfere with normal cell functioning

#### MECHANISM OF ACTION

- Antimetabolites are structurally similar to normal metabolic constituents, like folic acid, pyrimidines, or purines.
- They act by inhibiting the enzymes required for folic acid regeneration or pyrimidine or purine activation of DNA or RNA synthesis in neoplastic cells.
- Antimetabolites commonly kill the cells in S phase.

Drug	Uses	Structure
<b>Mercaptopurine</b>	used for remission induction and maintenance therapy of acute lymphatic leukaemia	

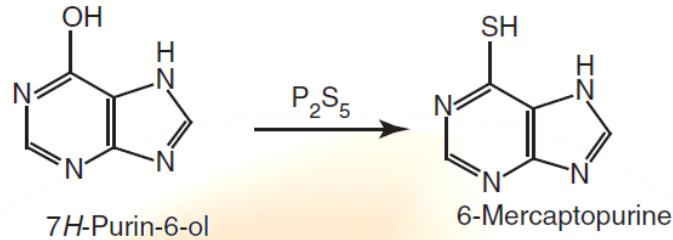
#### SAR OF MERCAPTOPYRINE

- The activity of the drug increases with increase in the carbon chain upto 15-16 carbons, after that, it again decreases.
- Substituent at position 6 which can lead to the increase in the resonance at 6<sup>th</sup> position will lead to increase in the activity of the drug.
- Introduction of the hydrophobic substituent at 6<sup>th</sup> position will increase the activity of the drug.
- Substitutions at 2<sup>nd</sup> position may not change the activity of the drug, or it may decrease the activity of the drug depending upon the type of substituent.

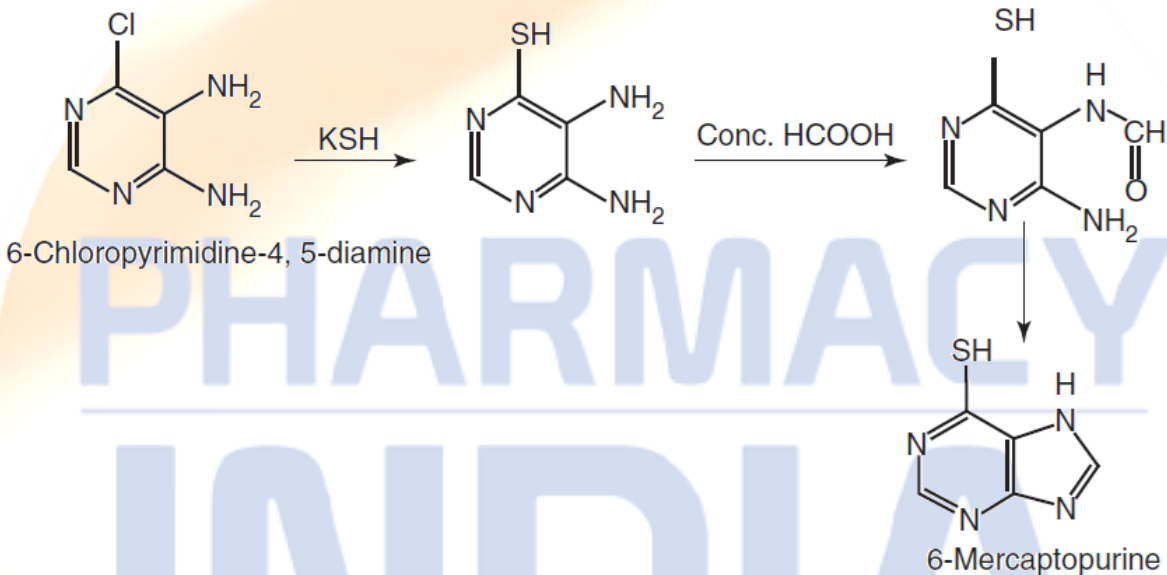
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### SYNTHESIS

Route-I. From: 7H-Purin-6-ol



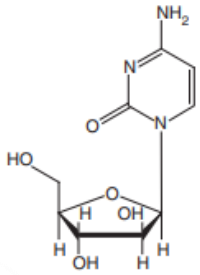
Route-II. From: 6-Chloropyrimidine-4,5-diamine

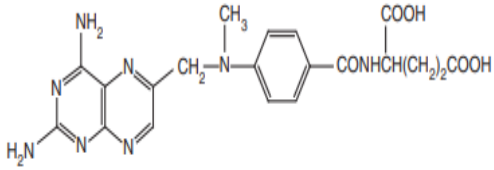


Drug	Uses	Structure
Thioguanine	<ul style="list-style-type: none"> <li>It is used for remission induction and remission consolidation treatment of acute non-lymphocytic leukaemia.</li> </ul>	 <chem>Nc1ncnc2n(cnc12)S</chem> 2-Amino purine-6-thiol

Drug	Uses	Structure
Floxuridine	<ul style="list-style-type: none"> <li>It is given by continuous regional intra-arterial infusion (in patients that cannot be cured by surgery or other methods) for the management of gastrointestinal adenocarcinoma metastatic to the liver.</li> <li>It is given through hepatic intra-arterial infusion for the management of liver cancer.</li> </ul>	 <chem>Fc1cnc(=O)n1[C@@H]2O[C@H](CO)[C@@H](O)[C@H]2O</chem> Floxuridine

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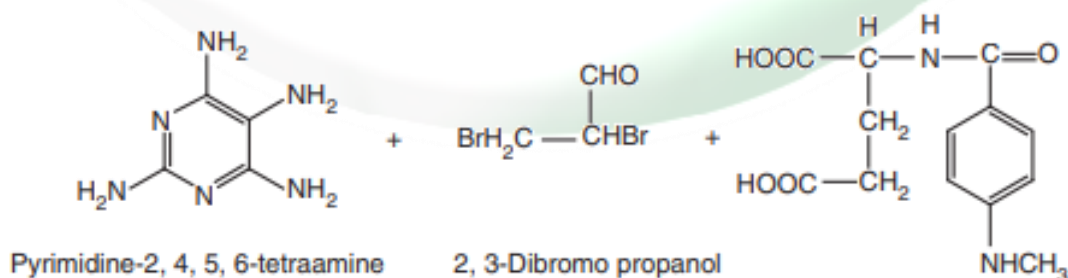
Drug	Uses	Structure
Cytarabine	<ul style="list-style-type: none"> <li>It is used for treating acute non-lymphocytic leukaemia, acute lymphocytic leukaemia, and the last phase of chronic myelocytic leukaemia.</li> </ul>	

Drug	Uses	Structure
Methotrexate	<ul style="list-style-type: none"> <li>It is used for treating acute non-lymphocytic leukaemia, acute lymphocytic leukaemia, and the last phase of chronic myelocytic leukaemia.</li> </ul>	

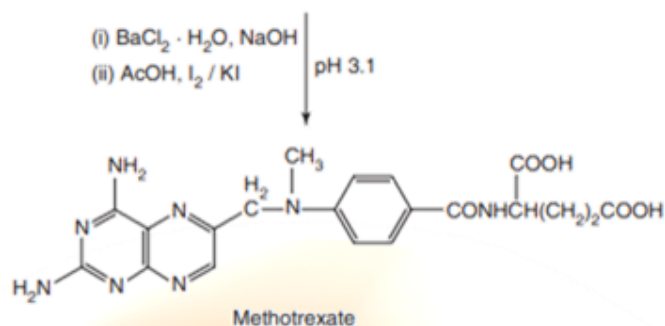
### SAR OF METHOTREXATE

- Replacement of glutamate tail with lipophilic agents can increase the transportation of the drug through folate carrier system.
- Thiourea entity can increase the activity of the drug
- Replacement of Thiazole with imidazole will increase the activity of the drug.
- Tetrahydro quinazolines derivatives will affect the ligand-enzyme interaction in a positive manner, where the dibenzodiazepine ring will show the pharmacophoric features which are essential for the activity of the drug.
- Substitution at 2<sup>nd</sup>, 3<sup>rd</sup> and 6<sup>th</sup> positions in the quinazolinone nucleus will inhibit the action of the drug.
- Substitution at ortho and para positions in phenyl ring will decrease the tendency of the drug to bind with DHFR, thus decreasing the activity of the drug.
- Combining the drug with copper metal can also increase the activity of the drug.

### SYNTHESIS



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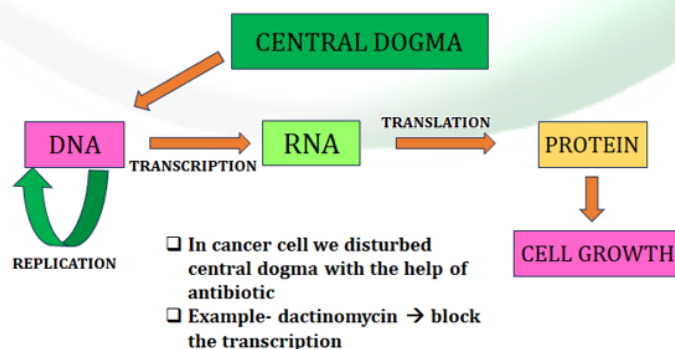


Drug	Uses	Structure
Azathioprine	<ul style="list-style-type: none"> <li>It is used for treating acute non-lymphocytic leukaemia, acute lymphocytic leukaemia, and the last phase of chronic myelocytic leukaemia</li> </ul>	

### ANTIBIOTICS

- Antibiotics act by binding to DNA or fitting into the helical lattice between specific bases, thus blocking the transcription of new RNA and DNA and cell replication.
- For certain types of cancer, therapeutic antibiotics have become an accepted treatment.
- They bind to primary and metastatic cancer cells to inhibit the growth of cancer cells, and limiting the effects on surrounding healthy cells.
- They are also known as the **antitumour** or **anticancer antibiotics**, and can also be used to treat or prevent infections caused due to cancer treatments

### MOA OF ANTIBIOTICS





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Drug	Uses	Structure
<b>Dactinomycin</b>	<ul style="list-style-type: none"> <li>It is used as a part of combination chemotherapy and/or multi-modality treatment regimen for treating Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, non-seminomatous testicular cancer.</li> </ul>	

Drug	Uses	Structure
<b>Daunorubicin</b>	<ul style="list-style-type: none"> <li>It is used for remission induction in acute non-lymphocytic leukaemia (myelogenous, monocytic, and erythroid) in adults.</li> <li>It is also used for remission induction in acute lymphocytic leukaemia in children and adults.</li> </ul>	

Drug	Uses	Structure
<b>Doxorubicin</b>	<ul style="list-style-type: none"> <li>as acute lymphoblastic leukaemia, acute myeloblastic leukaemia, Wilms' tumour, neuroblastoma breast carcinoma, ovarian carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma.</li> </ul>	

Drug	Uses	Structure
<b>Bleomycin</b>	<ul style="list-style-type: none"> <li>It is used for the treatment of malignant neoplasm (trachea, bronchus, and lungs), squamous cell carcinoma, and lymphomas.</li> </ul>	

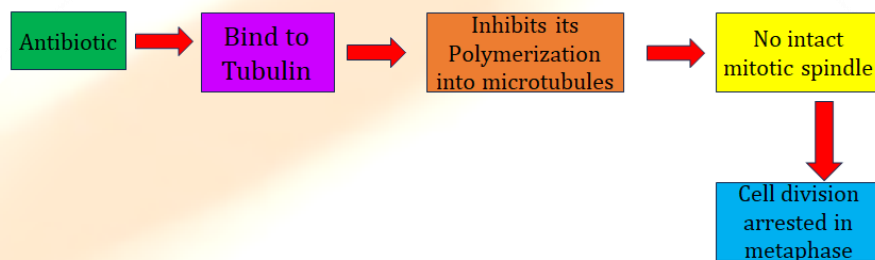
### PLANT PRODUCTS

- For centuries herbal medicines have been used for treating various problems in India.
- Herbal medicines comprise of plants or mixture of plant extracts used for treating illness and promoting health.

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- People suffering from cancer used herbal medicines as the most commonly used complementary and alternative methods.
- Medicinal plants relieve and treat cancer with the help of compounds having antioxidant and anticancer activities so that the carcinogenic cells can be destroyed.
- Some plants have a natural property to inhibit the spreading or risk of developing various forms of cancer.

### MOA OF PLANT PRODUCT



Drug	Uses	Structure
Etoposide	<ul style="list-style-type: none"> <li>• first line treatment in small cell lung cancer.</li> <li>• It is also used for treating other malignancies like lymphoma, non-lymphocytic leukaemia, and glioblastoma multiforme.</li> </ul>	

Drug	Uses	Structure
Vinblastin sulphate	<ul style="list-style-type: none"> <li>• It is used in the treatment of breast cancer, testicular cancer, lymphomas, neuroblastoma, Hodgkin's and non-Hodgkin's lymphomas, mycosis fungoides, histiocytosis, and Kaposi's sarcoma.</li> </ul>	

Drug	Uses	Structure
Vincristin sulphate	<ul style="list-style-type: none"> <li>• Acute Lymphocytic Leukaemia</li> <li>• Hodgkin's lymphomas</li> <li>• Wilms' tumour</li> </ul>	

MISCELLANEOUS

Drug	Uses	Structure
<b>Cisplatin</b>	<ul style="list-style-type: none"> <li>It is used for treating metastatic testicular tumours, metastatic ovarian tumours, and advanced bladder cancer.</li> </ul>	

**MECHANISM OF ACTION**

- Cisplatin destroys the cancerous cells by binding to DNA and interfering with its repair mechanism, thus ultimately causing cell death.
- When cisplatin molecule penetrates the cell membrane intact, one of its chloride ions is replaced by a water molecule.
- The structure obtained then binds to the single nitrogen on a DNA nucleotide.
- Another water molecule replaces the second chloride ion and the platinum binds to a second nucleotide. The complex of cisplatin and DNA attracts HMG (High Mobility Group)-1 and other DNA repair proteins that get irreversibly bound.
- It causes distortion to the DNA shape, thus inhibits effective repair, i.e., the *trans* isomer of cisplatin cannot form 1,2 intrastrand links and also do not exhibit antineoplastic activity.

Drug	Uses	Structure
<b>Mitotane</b>	<ul style="list-style-type: none"> <li>It is used for treating inoperable adrenocortical tumours and Cushing's syndrome</li> </ul>	

**MECHANISM OF ACTION**

- The biochemical mechanism of action of mitotane is still not known.
- But, according to the present data, it changes the peripheral metabolism of steroids and directly suppresses the adrenal cortex.



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