Chapter 3. Anti-Neoplastic Drugs

Syllabus

- **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.

3.1 ANTI NEOPLASTIC AGENTS/ ANTICANCER DRUGS

- These are the drugs used in the treatment of cancer also known as antineoplastic agents.
- **Cancer** cell also known as neoplasm (new growth) is an abnormal and uncontrolled growth or cell division.

Characteristic Feature of Cancer

- Uncontrolled proliferation (decreare apoptpsis, increase telomerase (RNA dependent DNA polymerase expression).
- Uncontrolled differenciation and loss of the function
- Invasiveness – Tendency to spread over healthy cell
- Metastasis- Spead to different part of body

Etiology

- Over expression of growth factor receptor on the cells.
- Production of their own extracellular growth factor
- Production of cell cycle transducer e.g. cyclin-dependent kinases (cdks), cdk inhibitors and cyclins
- Inhibit apoptosis and tumor suppression gene
- Activation of oncogenes
- Tumor directed angiogenesis

Classification of Cancer Cells

1. **Carcinoma:** Carcinomas are the most common type of cancer formed by epithelial cells. Most cancers of the breast, colon, and prostate are adenocarcinomas (cancer on glandular cells)**.**
2. **Sarcoma:** Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels, and fibrous tissue. E.g., Osteosarcoma.
3. **Leukemia:** Cancers that begin in the blood-forming tissue of the bone marrow are called leukemias. E.g., Blood cancer (Leukemia; increase no. of WBCs)
4. **Lymphoma:** Lymphoma is cancer that begins in lymphocytes (T cells or B cells). In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body. There are two main types of lymphoma:
   a. **Hodgkin lymphoma** – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.
   b. **Non-Hodgkin lymphoma** – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.
5. **Multiple Myeloma**: Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. Multiple myeloma is also called plasma cell myeloma and Kahler disease.
6. **Melanoma**: Melanoma is cancer that begins in cells that become melanocytes, which are specialized cells that make melanin (the pigment that gives skin its color).
7. **Germ Cell Tumors**: rise to sperm or eggs.
8. **Blastoma:** It is common in children. It is the tumor that resemble an immature or embryonic tissue. E.g., nephroblastoma, medulloblastoma, and retinoblastoma.
9. **Neuroendocrine Tumors**: Neuroendocrine tumors form from cells that release hormones into the blood in response to a signal from the nervous system.
10. **Carcinoid Tumors**: Carcinoid tumors are a type of neuroendocrine tumor. They are slow-growing tumors that are usually found in the gastrointestinal system (most often in the rectum and small intestine).

Classification of Antineoplastic or Anticancer Agents

(1) Alkylating agents

(a) *Nitrogen mustards :* Mechlorethamine, Cyclophosphamide, Chlorambucil, Ifosfamide, Melphalan

(b) *Nitrosoureas :* carmustine, lomustine

(c) *Alkylsulphonates :* Busulfan

(d) *Ethylenimines :* Thiotepa

(e) *Triazenes :* Dacarbazine

(2) Antimetabolites :

(a) *Folate antagonists :* methotrexate (MTX)

(b) *Purine analogues :* 6-mercaptopurine, 6-thioguanine, Azathioprim, flutarabine, pentostatin, cladribine.

(c) *Pyrimidine analogues :* 5-fluorouracil, floxuridine, cytarabine.

(3) Natural products

(a) *Plant products :* Vinca alkaloids (vincristine & vinblastine), Podophyllotoxin, Etoposide & Taxol.

(b) *Antibiotics :* Actinomycin-D, Doxorubicin, Daunorubicin, Bleomycin, Mithramycin, Mitomycin-C.

(c) *Hormones and antihormones :* Prednisone, Diethylstilbesterol, Ethinyl estradiol, Medroxy progesterone,
Megestrol, Tamoxifen.

(d) *Enzymes :* L-asparginase

(e) *Biologic response modifiers :* Interferons (α, β and γ)

(4) Miscellaneous agents : Cisplatin, hydroxyurea, procarbazine

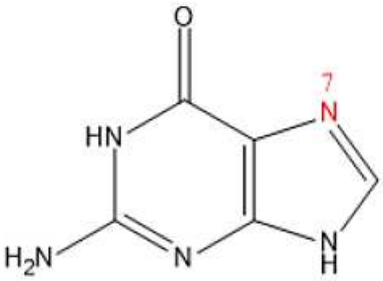
Medicinal Chemistry of Anticancer Agents

1) Alkylating agents

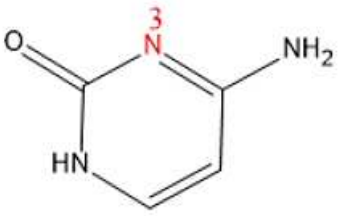
Mechanism of Action:

- ✓ Alkylating the DNA stands
- ✓ Alkylating agents form a highly reactive *carbonium ion* which react instantaneously with an electron donor such as an amine, hydroxyl or sulfhydryl group present at the DNA base pair.
- ✓ Most of the alkylating agents are the Bifunctional alkylating agents (having two alkylating groups) can cause intrastrand cross linking of two nucleophilic site such as N7 of guanine, N1 & N3 of Adenine and N3 of Cytosine in the DNA strand.

Adenine

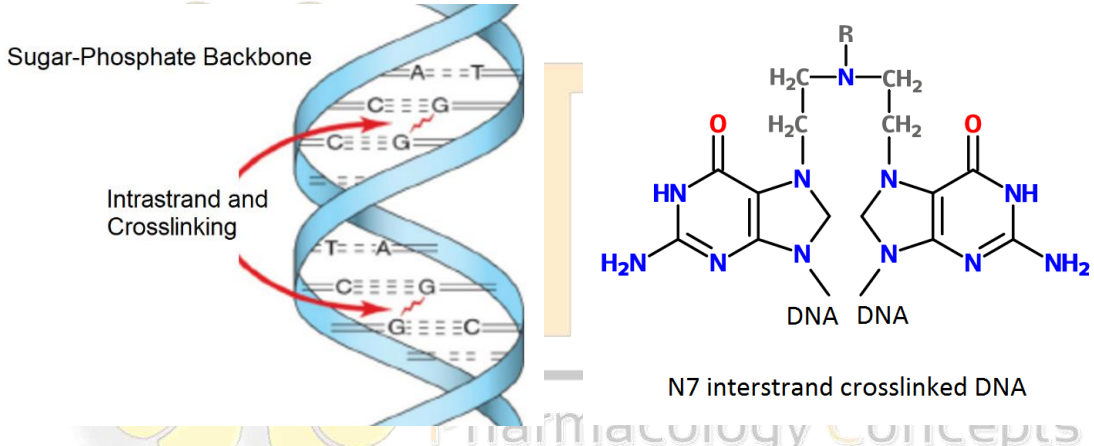


Guanine



Cytosine

***Nucleophilic Groups**

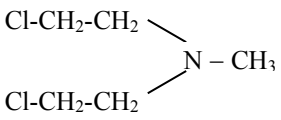


N7 interstrand crosslinked DNA

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

A) *Nitrogen Mustards*

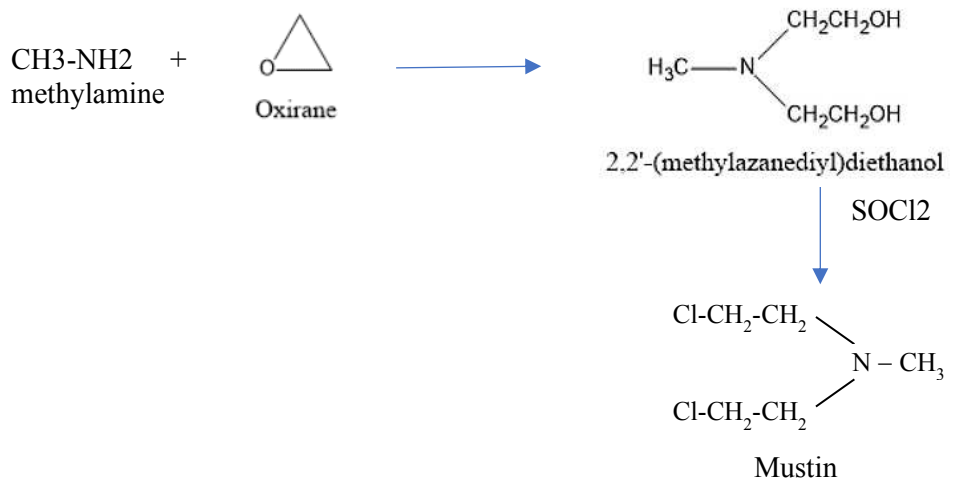
1. Mechlorethamine (Mustine)



2,2-dichloro-N-methyldiethylamine

Mechlorethamine rapidly undergoes intramolecular transformation to the active form in aqueous solution. The solutions lose their activity very rapidly. Hence it is supplied in dry powder form (supplied in rubber stoppered vials containing a mixture of 10 mg mechlorethamine hydrochloride and 90 mg of sodium chloride) and a solution is prepared in 10 ml of sterile water immediately prior to injection.

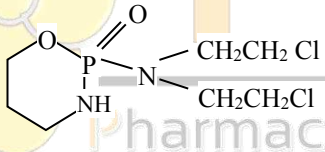
Synthesis:



Uses :

- ✓ Used in Hodgkin's disease, carcinoma of lung and other solid tumors
- ✓ Topically used in mycosis fugoides (T-cell lymphoma)

2. Cyclophosphamide



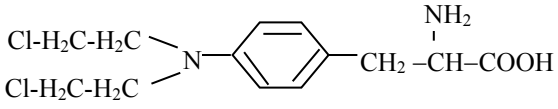
2-bis(2-chloroethyl) amino perhydro 1, 3, 2-oxaza-phosphorinane-2-oxide

Cyclophosphamide, which is activated to give aldophosphamide, then converted to* ***phosphoramide mustard (cytotoxic molecule)* *and* ***acrolein*** *which causes bladder damage that inhibited by* ***Mesna (a cytoprotective agents).***

Uses:

- ✓ Used in Hodgkin's disease, carcinoma of lung and other solid tumors.
- ✓ Used as immunosuppressant in autoimmune diseases like rheumatoid arthritis, multiple sclerosis, and wegener's granulomatosis.

3. Melphalan

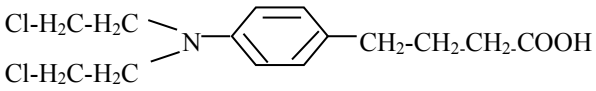


4-bis (2-chloro ethyl) amino L-phenylalanine

User:

- ✓ Used in Hodgkin's disease, carcinoma of lung and other solid tumors.
- ✓ Multiple myeloma and carcinoma of breast and ovary.
- ✓ It can be also used in retinoblastoma (Retinal Cancer).

4. Chlorambucil



4-[4-bis(2-chloroethyl)-aminophenyl] butyric acid

Uses:

- ✓ Used in Hodgkin's disease, carcinoma of lung and other solid tumors.
- ✓ Chronic lymphocytic leukemia.
- ✓ It can be used for non- Hodgkin's lymphoma, polycythemia, ovarian carcinoma.

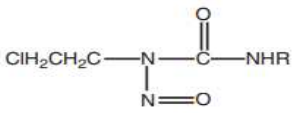
PC Used as immunosuppressantAll alkylating agents have more than one active alkylating group per molecule. Depending upon this number the compounds are termed as di or polyfunctional.

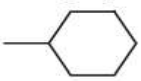
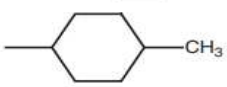
PC The actions of nitrogen mustards resemble to some extent the biological effects produced by ionising radiation. Hence, nitrogen mustards are also called radiomimetic drugs.

B) *Nitrosoureas*

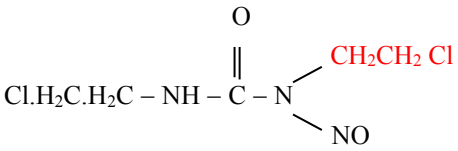
PC These compound having the nitroso (R-NO) and Urea (NH2-CO-NH2) moiety in the ring system

PC They are chloro ethyl nitrosoureas, highly lipid soluble and easily cross the blood brain barrier, therefore they may be used against tumours of the brain and meninges.



Name	R
Carmustine	—CH_2CH_2Cl
Lomustine	
Semustine	
Chlorozotocin	Glucose

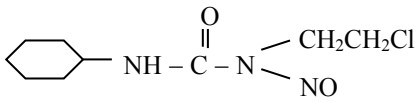
5. Carmustine



1, 3-bis(2-chloroethyl) 1-nitrosousea

Uses : Brain tumours (because of its ability to cross blood-brain-barrier) Hodgkin's disease, multiple myeloma and non-Hodgkin's lymphomas.

6. Lomustine



1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea

Uses : Brain tumors, Hodgkin's disease, malignant melanoma,lung cancer and various solid tumours.

C) *Alkylsulphonates*

7. Busulfan (Busulphan)

It has a selective effect on the **bone marrow**, depressing the formation of granulocytes and platelets.

$H_3C\text{-}SO_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}SO_2\text{-}CH_3$

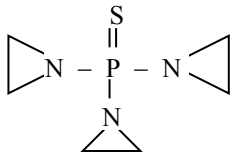
1, 4-butanediol dimethanesulphonate

Uses

- ✓ Used in the treatment of chronic granulocytic leukemia.
- ✓ Immunosupressant

D) *Ethylenimines (Aziridines)*

8. Thiotepa



tris-(1-aziridinyl) phosphine sulphide

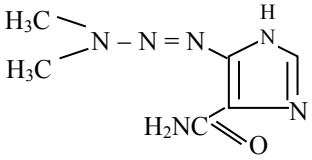
It is supplied in vials containing 15 mg of thiotepa, 80 mg of sodium chloride and 50 mg of sodium bicarbonate. It is stored at 2° to 8 °C.

Dose : 15 - 30 mg by parenteral route.

Uses : Used in the treatment of breast cancer, ovarian cancer and various lymphomas.

E) *Triazenes*

9. Dacarbazine



5-(3, 3-dimethyl-1-triazeno)-imidazole-4-carboxamide

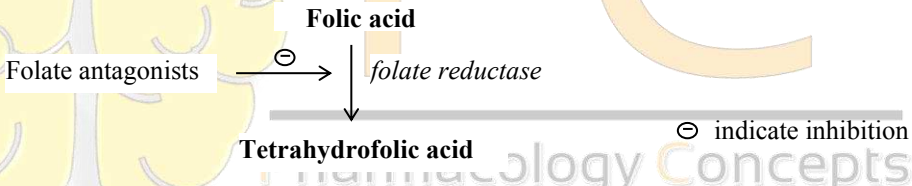
Uses: Used in the treatment of malignant melanoma, Hodgkin's disease and sarcomas.

2) Antimetabolites

General Mechanism of action: Antimetabolites are drugs that block vital cellular metabolic reactions by virtue of its close structural similarity to the metabolite (i.e., antimetabolites prevent the biosynthesis or utilisation of normal cellular metabolites).

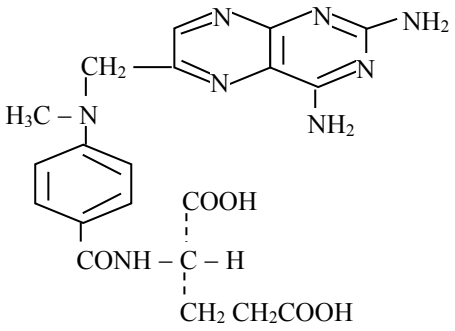
A) *Folate Antagonists:*

Mechanism of action: Folic acid is essential for the production of the co-enzyme *tetrahydrofolic acid*. The conversion of folate to tetrahydrofolic acid is carried out by *folate reductase*. Folate antagonists block *folate reductase* irreversibly and prevent the production of tetrahydrofolic acid.



Lack of tetrahydrofolic acid leads to inhibition of DNA synthesis and cell replication.

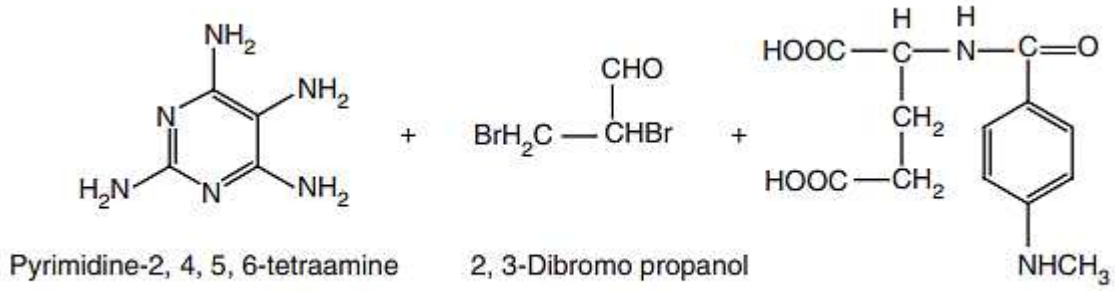
10. Methotrexate



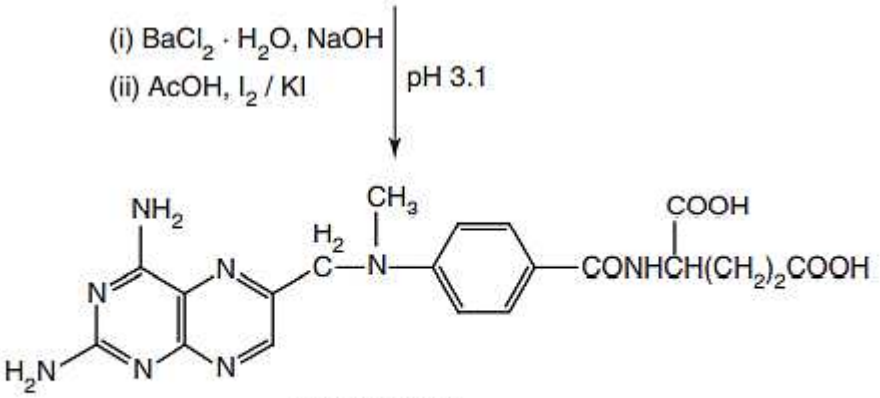
N-{4-[(2,4-diaminopteridin-6 yl methyl) methylamino] benzoyl} L-glutamic acid

It has low lipid solubility and dose not cross blood brain barrier. It has actively taken up into cell by the folate transport system and is metabolized to polyglutamate derivetives.

Synthesis:



Pyrimidine-2, 4, 5, 6-tetraamine 2, 3-Dibromo propanol



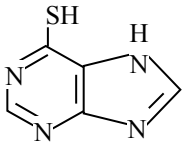
Methotrexate

Uses:

- ✓ Used in the treatment of acute lymphoblastic leukemia & choriocarcinoma.
- ✓ In combination with other anticancer drugs it is used in the treatment of lymphosarcoma, Burkitt's lymphoma, carcinoma of testes, bladder, breast, pharynx and tongue.
- ✓ Also used as immunosupressant

B) *Purine Analogues*

11. 6-Mercaptopurine (6-MP)



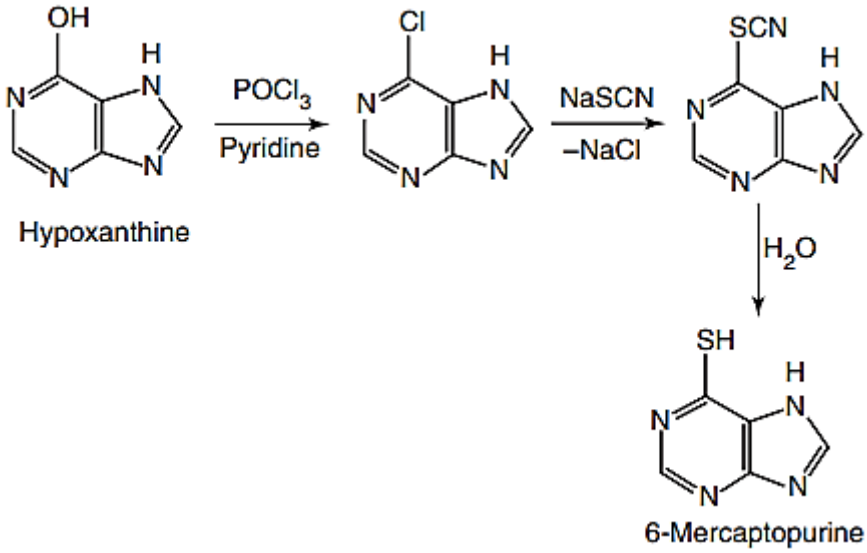
Purine –6-thiol

MOA:

- ✓ 6-Mercaptopurine is converted by *hypoxanthine-guanine phosphoribosyl transferase (HGPRT)* to 6-thioinosinic acid (TIMP) which inhibits some enzymes involved in purine synthesis and hence of DNA.

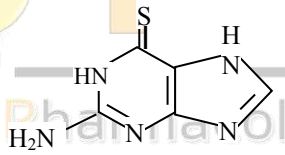
- ✓ 6-mercaptopurine is metabolised to 6-methylmercaptopurine ribotide (MMPR) and thioguanylic acid in human body are responsible for its cytotoxic effects.

Synthesis:



Uses: Used in the treatment of leukemia.

12. 6-Thioguanine (6-TG)



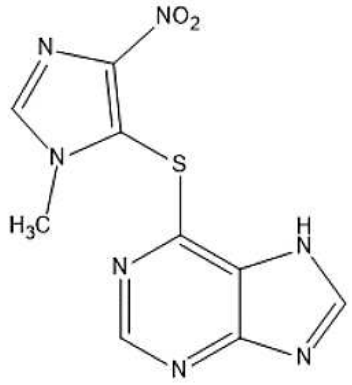
2-aminopurine-6 (1H)-thione

MOA:

- ✓ It inhibits purine nucleotide interconversion.
- ✓ It's incorporation into DNA leads to strand breaks.
- ✓ It decreases intracellular level of guanine nucleotides resulting in inhibition of glycoprotein synthesis.

Uses: Used in the treatment of non-lymphoblastic leukemia.

13. Azathioprine



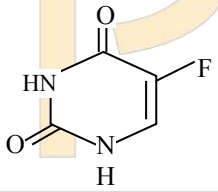
6-(3-methyl-5-nitroimidazol-4-yl)sulfanyl-7*H*-purine

MOA: Purine synthesis inhibitors

Use: Mainly used as immunosuppressant for facilitating the survival of organ and tissue transplantation.

C) *Pyrimidine Analogues*

14. 5-fluorouracil (5-FU)



5-fluoropyrimidine-2, 4(1H, 3H) dione

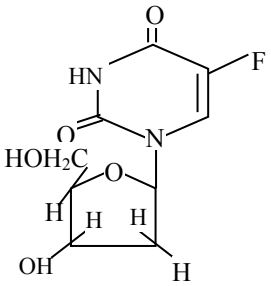
MOA:

- ✓ This a fluorinated analogue of pyrimidine.
- ✓ 5-fluorouracil is metabolised to 5-fluoro 2' deoxyuridine 5' phosphate (FdUMP) which competitively inhbits *thymidylate synthetase* (an enzyme that converts 2'-deoxyuridylic acid to thymidylic acid for DNA synthesis).
- ✓ Inhibition of DNA synthesis results in "***thymineless death***" of cells.

Uses :

- ✓ Used in the carcinoma of stomach, colon, rectum, breast and ovaries.
- ✓ Also given topically for skin cencer, actinic keratoses, and Bowen's disease.
- ✓ It is also used as eye drop for treatment of ocular surface squamous neoplasia.

15. Floxuridine



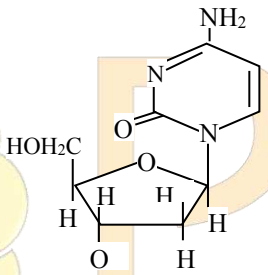
1-(2-deoxy-β-D-ribofuranosyl)-5-fluorouracil

MOA: Similar to 5-fluorouracil (thymidylate synthetase inhibitor)

Uses:

- ✓ Used in the treatment of malignant neoplasms of the liver and GIT.
- ✓ Mainly in colon cencer.

16. Cytarabine (Cytosine arabinoside, Ara C)



4-amino-1 β-D-arabinofuranosyl pyrimidin-2(1H)-one

1-β-D-arabino-furanosyl cytosine

MOA: Cytarabine is converted in the body to Ara-cytosine triphosphate which competitively **inhibits DNA polymerase** resulting in blockade of DNA synthesis.

Uses :

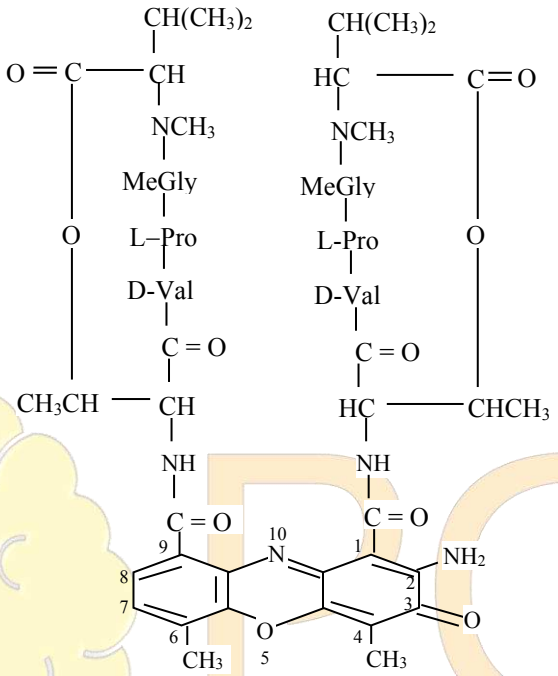
- ✓ Used in the treatment of acute non-lymphoblastic leukemia.
- ✓ Cytarabine is used as an antiviral agent in the treatment of Herpes infection and encephalitis.

Raltitrexed *inhibit thymidylate synthetase.* ***Pemetrexed*** *inhibit thymidylate transferase.* ***Gemcitabine,*** *a new analouge of cytarabine.*

Antibiotics: Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin

3) Antibiotics

17. Actinomycin-D (Dactinomycin)

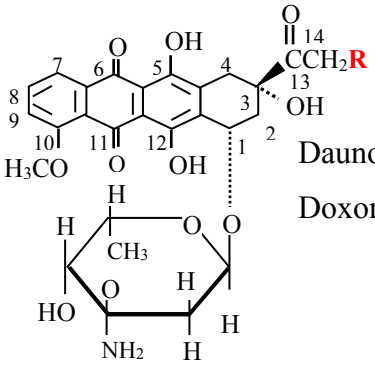


Actinomycin-D is produced by ***Streptomyces chrysomallus*** and other species of *Streptomyces*. It is made up of amino acids.

MOA: It binds to double helical DNA, intercalates in the minor groove of DNA between adjacent guanosine-cytosine pairs, **block DNA dependent RNA polymerase** and hence transcription of DNA molecule is blocked.

Uses : Used in the treatment of carcinoma of uterus, testis, Kaposi's sarcoma, osteogenic sarcoma, Wilm's tumour and Ewing's sarcoma.

18. Doxorubicin and Daunorubicin



Daunorubicin R = H

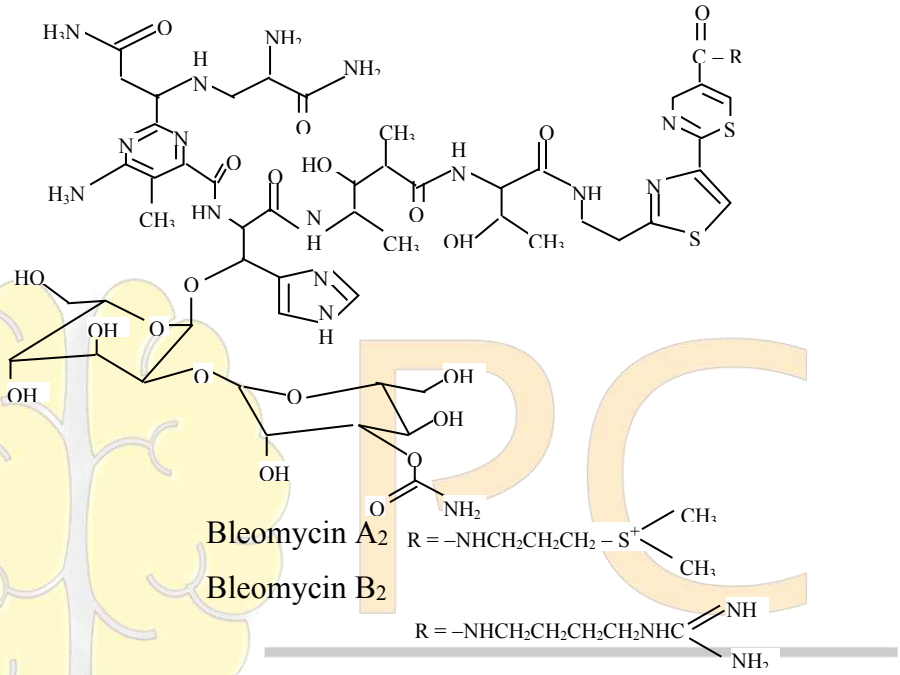
Doxorubicin R = OH

Doxorubicin and Daunorubicin are **anthracycline antibiotic** obtained from *Streptomyces coeruleorubidus and S. peucetius.*

MOA: It intercalate DNA and produce DNA strand breakage. They also interfere on *topoisomerase II (DNA gyrase) enzyme.*

Uses: Used in acute lymphoblastic & myeloblastic leukemias, Hodgkin's & non-Hodgkin's lymphomas breast & ovarian cancers and Wilm's tumour.

19. Bleomycin:



It is a glycopeptide antibiotic. Commercially it is obtained from ***Streptomyces verticillus*** and it is a mixture of bleomycin A_2 (main component) and bleomycin B_2. Bleomycin is inactivated by *bleomycin hydrolase*.

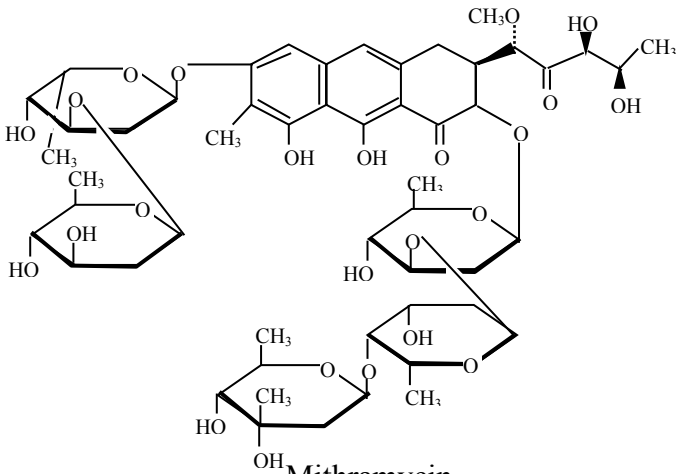
MOA: It produce DNA strand breakage [breakage is due to DNA-bloemycin-Fe(II) complex]. Inhibition of DNA biosynthesis is also reported.

Uses : It is used in Hodgkin's disease, testicular cancer, malignant neoplasm and other malignancies.

20. Mithramycin (Chromomycin, Plicamycin)

It is isolated from *Streptomyces plicatus, S. argillaceus and S. tanashiensis*.

MOA: It inhibits DNA-dependent RNA synthesis by binding to DNA through Plicamycin Mg^{++} complex.



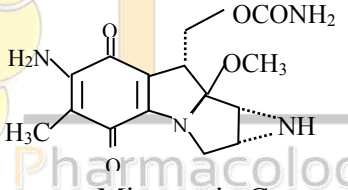
Mithramycin

Uses : Used in chronic myelocytic leukemia and malignant hypercalcemia.

21. Mitomycin-C

Mitomycin C is obtained from *Streptomyces caespitosus*.

MOA: It inhibit DNA synthesis by crosslinking double stranded DNA through guanine and cytosine.

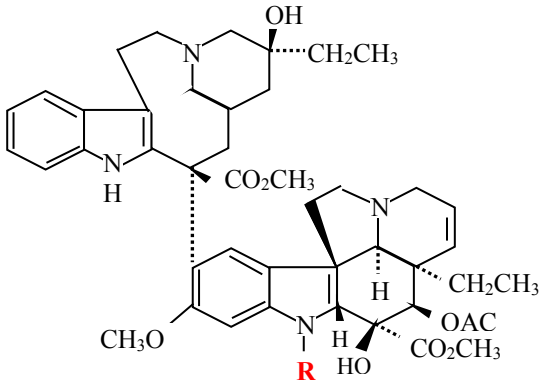


Mitomycin C

Uses: It is used for the treatment of gastric adenocarcinoma, carcinoma of cervix, colon, rectum, pancreas breast and lung.

4) *Plant Products :*

22. Vinca alkaloids



Vincristine: R = CHO

Vinblastine: R = CH_3

Vinca alkaloids are derived from plant *Vinca rosea*, these are vincristine and vinblastine.

MOA: Vinca alkaloids are "*spindle poisons*". They bind to the microtubule protein "*tubulin*" and causes depolymerisation of microtubules, which are essential for formation of *mitotic spindle**.

**** The mitotic spindle is essential for cell division in which DNA divides into genetically identical daughter cells.***

Dose : Vincristine- 0.5 – 2 mg/m^2/weekly by i.v. route.

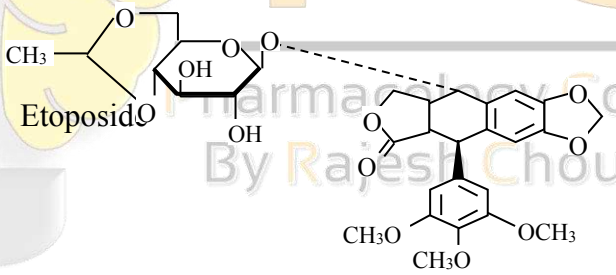
Vinblastine- 0.1 – 0.2 mg/kg weekly by i.v. route.

Uses:

- ✓ ***Vincristine****:* Used in the treatment of acute lymphoblastic leukemia in children, Hodgkin's & non-Hodgkin's lymphomas, Ewing's soft-tissue sarcoma and Wilm's tumour.
- ✓ ***Vinblastine****:* Used along with bleomycin and cisplatin for the treatment of metastatic testicular carcinoma, Also used in the treatment of systemic Hodgkin's and non-Hodgkin's lymphomas.

****Vindesine and Vinorelbin is a semisynthetic vinka alkaloid with similar properties and that mainly used to breast cancer.***

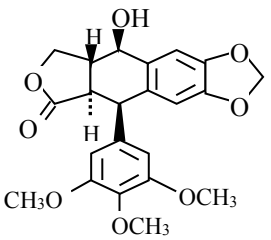
23. Etoposide: Etoposide is a semisynthetic derivative of podophyllotoxin.



MOA: Etoposide induce strand breaks in DNA via *topoisomerare II* cleavage, inhibition of nucleoside transport and inhibition of mitochondrial transport.

Uses: Used in refractory testicular tumours, Kaposi's sarcoma, non-Hodgkin lymphoma, small cell lung cancer, Wilm's tumour & hepatocellular carcinoma.

24. Podophyllotoxin: Podophyllotoxin is obtained from root of the May apple (*Podophyllum peltatum*).

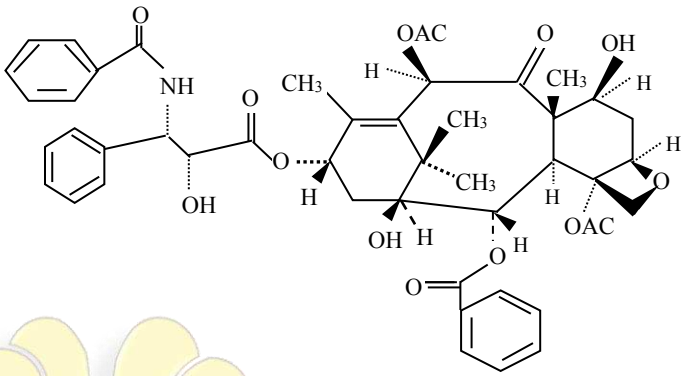


25. Campothecins: Irinotecan and Topotecan.

They are isolated from the stem of the tree *Camptotheca acuminata,* bind to and inhibit *topoisomerase I*, high levels of which occur throughout the cell cycle.

26. Taxol: Paclitaxel and Docetaxel.

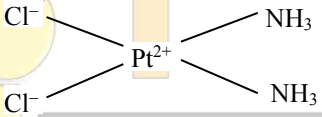
Taxol was isolated from Pacific Yew tree bark. It is an antimitotic agent (act on microtubules & stabilises them in polymerised state).



Taxol

4) Miscellaneous agents

27. Cisplatin

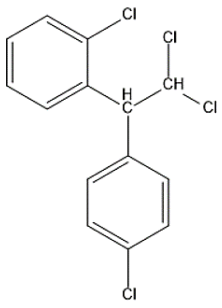


cis-diamine dichloro platinum

MOA: When it enters the cells, chloride ions dissociate leaving a reactive diamineplatinum complex which reacts with water and then interacts with DNA and cause denaturation of DNA chain. It is not absorbed orally, therefore must be given intravenously.

Uses: It is used in the treatment of metastatic testicular and ovarian tumours and bladder cancer.

28. Mitotane



1-chloro-2-[2,2-dichloro-1-(4-chloro phenyl) ethyl] benzene

MOA: Modulate the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. Derivative of DDT with anti-adrenal cortex property

Uses: Used in the treatment of adrenocortical carcinoma and cushing's syndrome.

****