ANTI-NEOPLASTIC DRUGS

Introduction

Cancer is an abnormal growth of Cells. which also can spread to other organs.

→ Cancer medically known as malignant neoplasm

→ In cancer cells divide and grow uncontrollably, form malignant tumor.

Normal

Malignant tomor

Tumor
- Benign Tumor
- Malignant Tumor

* Benign Tumor :- donot spread to other parts of body.

* Malignant Tumor :- This tumor have ability to multiply uncontrollably and spread to various parts of body.

#Types of Cancer

Carcinoma

- Derived from Epithelial Cells.
- Most common Cancer develop in Breast, Prostate, Lung, Pancreas and colon. are Carcinomas

Sarcoma

- Derived from Connective Tissue
- develop from outside the Bone marrow. Exam Bone, cartilage, fat, nerve.

Lymphoma/ Leukemia

- these 2 Cancer arise from Cells that make Blood
- Leukemia is most common Cancer in about 30% Childrens.
- far more adults develop Lymphoma and Leukemia

Germ cell Tumor

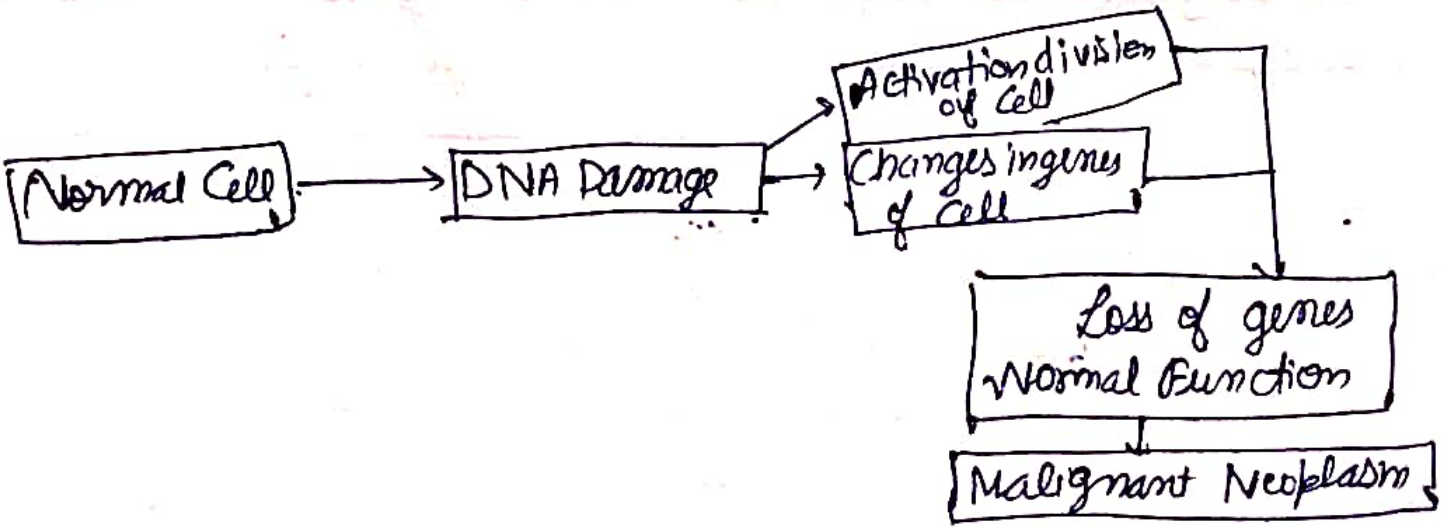
Cancer arise in testicles of males and ovary in Females

Blastoma

Cancer derive from Embryonic tissue.

Most Common in Children than in adults

☆ Malignancy Pathway :-



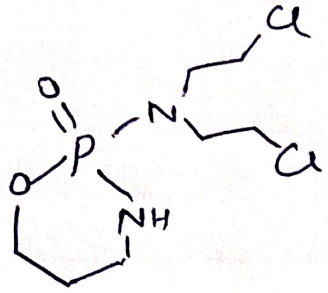
Antineoplastic Agents: The agents used to treat Cancer and prevents further growth or division.

Classification of Antineoplastic Agents

- **Alkylating Agents**
  - Nitrogen mustard
    - Mechlorethamine (Mustine HCl)
    - Cyclophosphamide
    - Ifosfamide
    - Chlorambucil
  - Ethylenimine
    - Thio-Tepa
  - Alkyl Sulphonate
    - Busulfan
  - Nitro Sourea
    - Carmustine,
    - Lomustine
  - Triazine
    - Dacarbazine
- **Antimetabolites**
  - Folate Antagonist
    - Methotrixate
  - Purine Antagonist
    - 6-Mercaptopurine
    - 6-thioguanine
    - Azathioprine
  - Pyrimidine Antagonist
    - 5-Fluorouracil,
    - Cytarabine
  - Vinka Alkaloids
    - Vincristine
    - Vinblastine
- **Taxanes**
  - Paclitaxel
- **Antibiotics**
  - Actinomycin
  - Doxorubicin
  - Daunorubicin
  - Mitoxantrone
  - Bleomycins
  - Mithramycin
- **Miscellenous**
  - Hydroxy-urea
  - Procar-Bazine
  - L-Aspara-ginase
  - Cisplatin
  - Carbo-platin

Nitrogen Mustards

★ Cyclophosphamide:



N,N- bis(2-Chloroethyl)-1,3,2- oxazaphosphinan -2- amine 2- oxide

MoA- Cyclophosphamide forms DNA crosslinks between and within DNA Strands (Known as interstrand and Intrastrand crosslinkages). This is irreversible and leads to Cell aposposis.

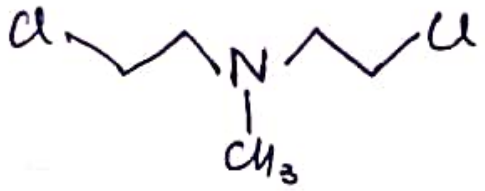
SAR- Bis-2-Chloroethylamino group is essential for antineoplastic activity.
→ Chloro atom provides maximum activity.
→ Triethylene derivatives are remain inactive
→ Nitrogen atoms are Essential for their activity.

Metabolism:- oral cyclophosphamide is rapidly absorbed and oxidise in liver.
→ Excreted in urine unchanged.

Uses:- lymphoma, Multiple myeloma, leukemia, ovarian cancer, Break cancer, lung cancer etc.

Adverse Reaction:- loss of appetite, Vomiting, hair loss, and bleeding from the bladder.

☆ Mechlorethamine:-



2- Chloro-N-(2-Chloroethyl)- N- methylethan-1-amine

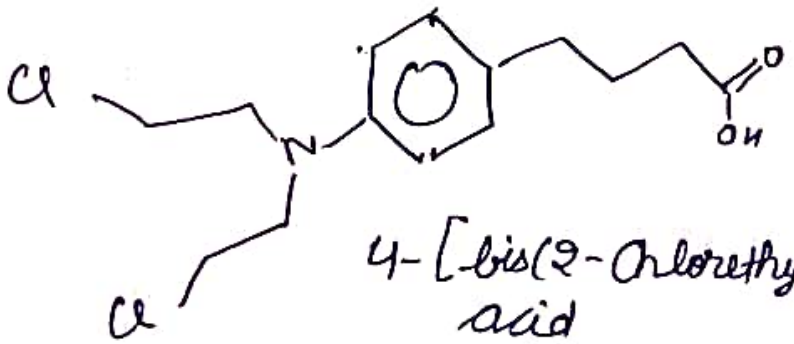
MOA:- It binds to DNA of abnormally growing cell, cross linked with strands and preventing cell duplication.

Metabolism:- Rapid transformation and combines with water compounds of cells. So drug is no longer present in active form a few minutes after administration.

Uses:- lymphosarcoma, chronic myelocytic leukemia, Bronchogenic carcinoma, used to treat skin disease.

Adverse Reaction:- Toxic for women who are Pregnant / Breastfeeding or of childbearing age; damage to mucous membrane of eyes, skin, and respiratory tract.

☆ Chlorambucil:-



4-[bis(2-Chloroethyl) amino] benzenebutanoic acid

MOA:- It Interfere with DNA replication and damage the DNA in cell result in Cellular apoptosis

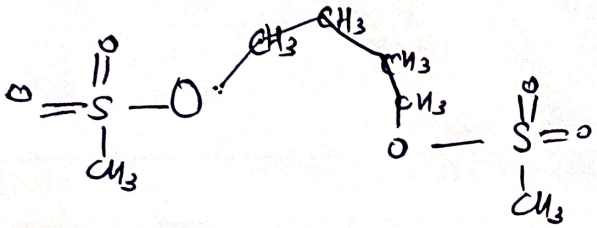
Metabolism:- Metabolized in liver.

Uses - In lymphocytic leukemia, Hodgkin's disease, breast, ovarian and testicular cancer.

Adverse effects: Bone marrow suppression, infertility, allergic reactions.

Alkyl Sulphonate:

★ Busulphan



Butane-1,4-diyl dimethanesulfonate

MOA:- It leads to break in DNA molecule and the cross linking strands. result in interfere in DNA formation and apoptosis

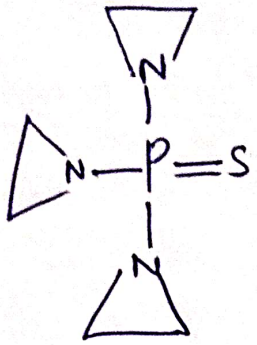
Metabolism:- 1° metabolized in liver by glutathione-S-transferases

Therapeutic Uses:- → In chronic Myelogenous leukemia (CML)

ADR - hyperpigmentation, seizures, hepatic, Emesis.

Ethylenediamine

☆ Thiotepa :



1,1',1''- Phosphorothioyltriaziridine

MOA - It stops tumor by crosslinking guanine nucleobases in DNA double helix strands, directly attacking DNA.

Metabolism :- Metabolized by oxidative desulfurization mediated by CYP2B1 and CYP2C11.

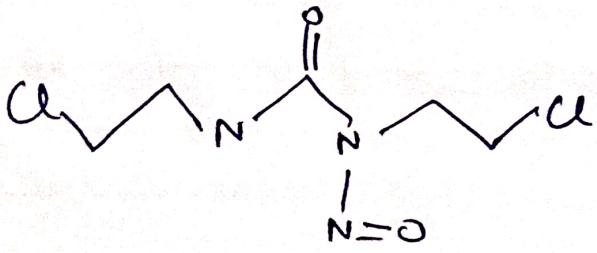
Uses :- Breast Cancer, adenocarcinoma of ovary cancer, papillary thyroid cancer, bladder cancer.

ADR :- Bone ~~mor~~ marrow suppression, leukopenia, thrombocytopenia and anemia.

→ liver and lung toxicity.

Nitrosoureas

☆ Carmustine :-



1,3- Bis (2- Chloroethyl)- 1- nitrosourea

MOA :- Act as Alkylating agent, can form interstrand Crosslinks in DNA, prevents DNA replication and DNA transcription-

Metabolism :- Rapid metabolism in liver

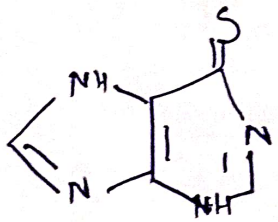
Uses :- In multiple myeloma, lymphoma.

ADR :- → Bone marrow depression
→ Pulmonary fibrosis
→ Effects on liver, kidneys and eyes.

(2) ANTI METABOLITE

Purine Antimetabolite

* Mercaptopurine :-



3,7- dihydropurine - 6- thione

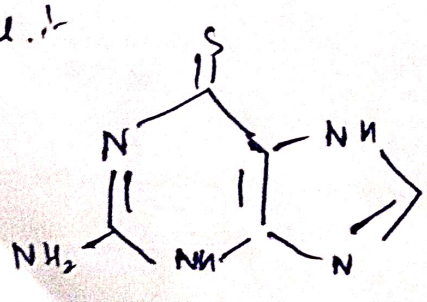
MoA :- Inhibition of purine synthesis.
→ Non-functional DNA and RNA

Metabolism :- Metabolise in liver

Uses :- Cancer, autoimmune diseases, leukemia, myloid leukemia and ulcerative colitis.

ADR :- → Include diarrhea, nausea, vomiting, loss of appetite, fatigue, stomach pain, skin rash etc.

* Thioguanine :-



2- amino - 1H - purine - 6(7H) - thione

MOA:- Thioguanine is purine antagonist. It is pro-drug that is converted directly to thioguanine monophosphate. by enzyme. hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

↓

Immunosuppressive activity also. but incorporation of these nucleotides into DNA

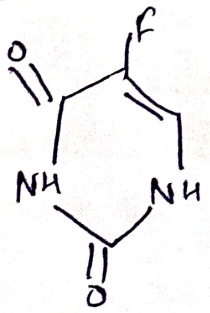
Metabolism:- Metabolise in Liver.

Uses:- → Acute leukemias,
→ & chronic myelogenous leukemia,
→ Inflammatory Bowel disease etc

ADR:- Nausea, Vomiting, loss of appetite and mouth sores may occur.

Pyrimidine Antimetabolite

★ 5-Fluorouracil:



5-Fluoro-1H,3H-pyrimidine-2,4-dione

MOA:- 5-Fluorouracil

↓

Reduce thymidine

↓

Lack thymidine

↓

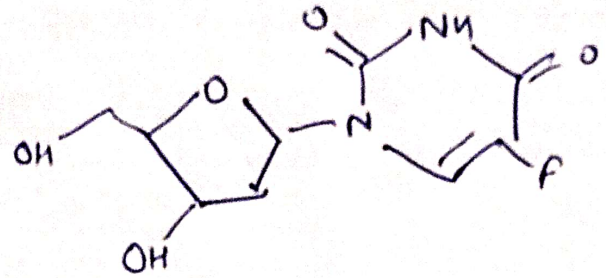
Imbalanced cell growth → DNA synthesis Decreases

Uses:- Stomach, colon, breast, ovaries, liver, Skin cancers

Metabolism: In liver.

ADR: → Include Nausea, Vomiting, Diarrhea, headache, hair loss (Alopecia)

☆ Floxuridine:



5-Fluoro-1-[4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl]-1H-pyrimidine-2,4-dione.

MOA - Interfers with DNA Synthesis, Inhibition of RNA formation.

↓

Primarily works by stopping the growth of newly born cells.

↓

Selectively kills rapidly dividing cells

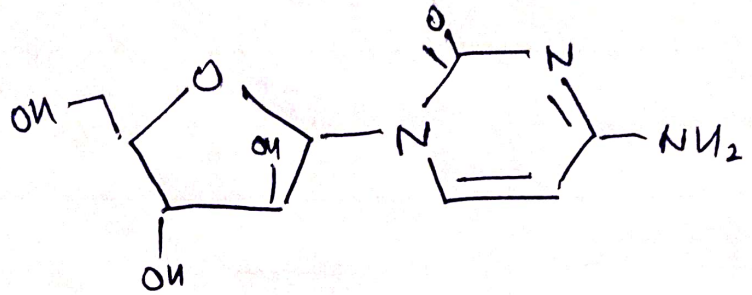
Metabolism:- In liver by thymidine phosphorylase and Cyt P450 2A6 Enzymes.

Uses:- treatment of Colorectal cancer.

→ In Kidney and Stomach cancers

☆ Cytarabine;

2- ~~Azm~~



4- Amino- 1- [(2R, 3S, 4S, 5R)- 3, 4- dihydroxy- 5- (hydroxymethyl) oxolan- 2- yl] pyrimidin -2- one.

MOA - Act direct DNA Damage and incorporation into DNA.

↓

Cytarabine is toxic to wide variety of proliferating cells.

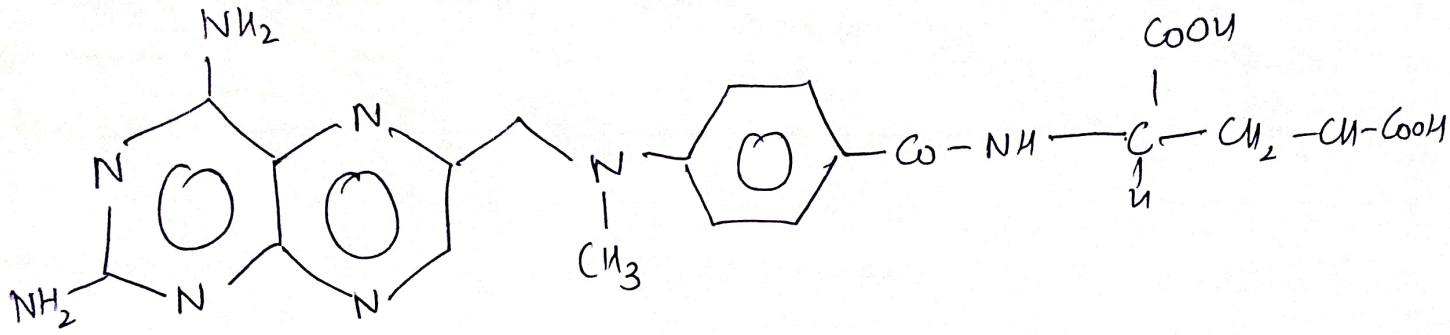
Metabolism :- Metabolize intracellularly into triphosphate form.

Uses - In acute Myeloid Leukemia, acute lymphocytic leukemia (ALL), Bone marrow suppression

ADR - Impaired Body defenses, hemorrhage, may leads to Infection, Kidney damage

3. FOLIC ACID ANTAGONIST

☆ Methotrexate



2-[(4-{[2,4-Diaminopteridin-6-yl)methyl](methyl)amino}benzoyl)amino]pentanedionic acid

MoA: De-Nove Synthesis (Pathway) Required for DNA Synthesis. and folate is essential for Base (Purin & Pyrimidin) Biosynthesis. So, Synthesis will be inhibited.

→ Methotrexate inhibits the Synthesis of DNA, RNA, and Proteins.

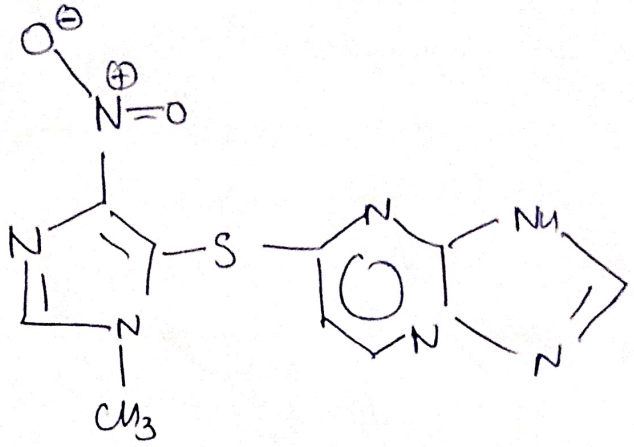
Metabolism: It undergoes hepatic and intracellular metabolism

Uses: In Breast Cancer,

- → Head and neck Neoplasm
- → leukemia
- → lymphoma
- → lung cancer
- → Bladder Neoplasms

ADR:- Hepatotoxicity (Liver Damage),
Nausea, fatigue,
fever, kidney failure.

☆ Azathioprine: (Purine Analogue)



6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)sulfanyl]-7H-purine

MOA: Purines are needed to produce DNA and RNA. By inhibiting purine synthesis, less DNA and RNA are producing for synthesis of WBC and cause immunosuppression.

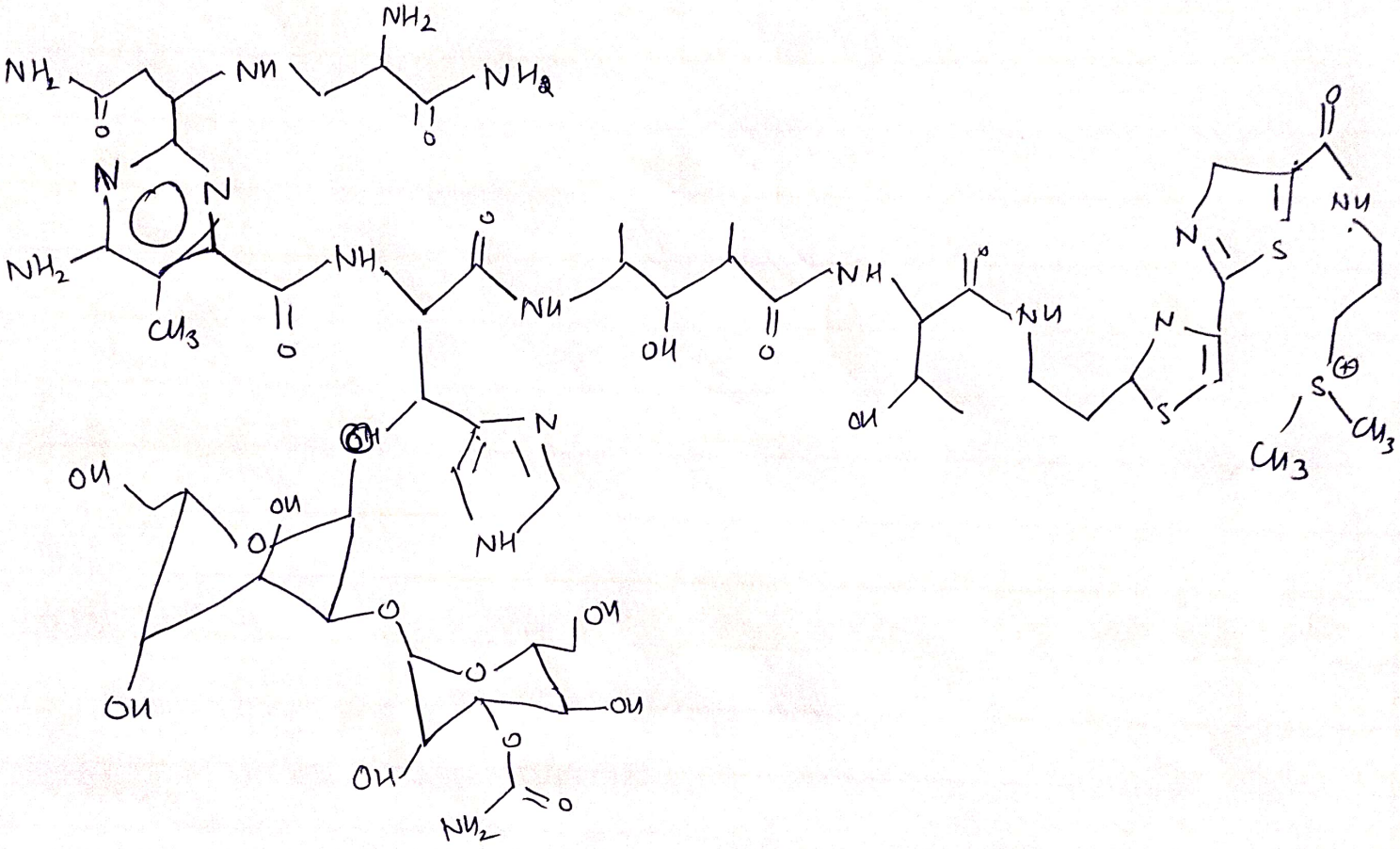
Uses- In immunosuppressant disease.
→ Rheumatoid Arthritis
→ Vasculitis.

ADR:- → Hair loss
→ Diarrhea
→ fatigue
→ Skin Rashes

(4) Antineoplastic Antibiotics :-

→ They also known as anticancer or antitumor antibiotic and quite similar as Quinolones.

★ **Bleomycin** (Isolated from Streptomyces Verticillus)



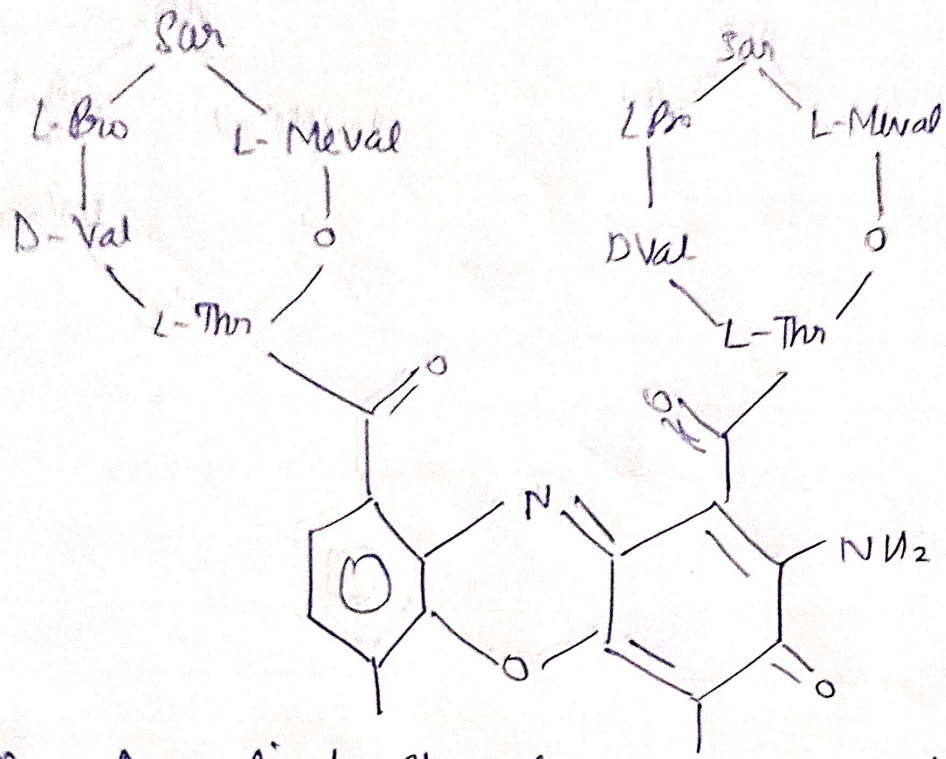
MOA – It Starts Breaking of DNA Strands and inhibit incorporation of thymidine into DNA Strands.

Metabolism :- Primarily metabolise in Kidney

Use :- In testicular cancer, Ovarian Cancer, Hodgkin's disease, neck cancer (Squamous cells).

ADR :- Pulmonary fibrosis
Kidney Failure

✡ Dactinomycin or Actinomycin D :



MoA - Drug binds strongly to DNA, interfere with DNA Synthesis

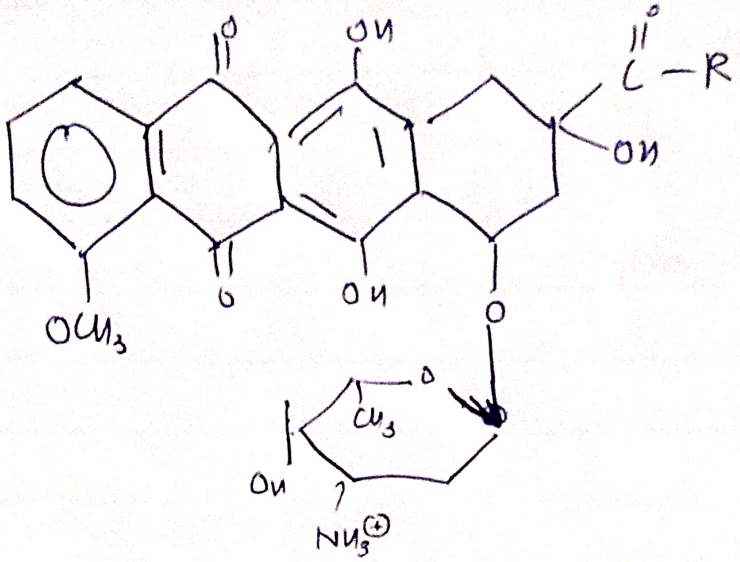
Metabolism:- 36-hour half life, large distribution volume, minimal metabolic Breakdown

Uses: → In Solid tumors
→ Muscle Related Cancers
→ Testicular cancer.

ADR: → Bone marrow Suppression
→ Vomiting
→ Mouth ulcers
→ liver problems
→ hair loss

✱ Anthracyclin Antibiotics :

Very closely related to Tetracyclins



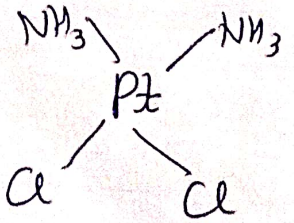
MOA - Inhibit DNA and RNA Synthesis by interfering between Base pairs of DNA/RNA Strands, thus preventing replication of rapidly growing cancer cells

Uses - Breast cancer, Childhood Solid tumors, Soft tissue Sarcomas, Multiple myeloma and Break Cancer

ADR - → Suppression of Bone marrow
→ Suppression of GIT regeneration
→ Myocardial (♡) Toxicity.

Miscelleneous

✱ Cisplatin



diammine dichloroplatinum

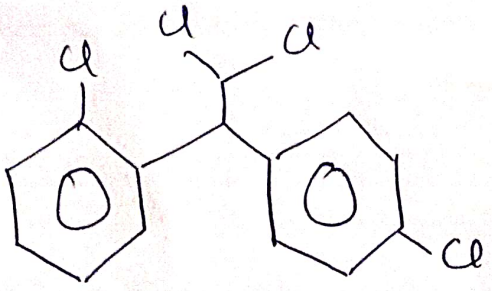
MOA - Interfere with DNA replication, Kill fastest proliferating cells.

Metabolism: This activation begins with formation of glutathione conjugate that metabolized to a cysteinyl -glycine-conjugate. and to reactive thiol.

Uses:- → treatment of solid malignancies.
→ Small cell lung cancer,
→ Squamous cell carcinoma of head.

ADR:- → loss of appetite,
→ diarrhea
→ loss of taste may occur,
→ Nausea and vomiting.
→ Nerve damage

★ Mitotane :-



1-Chloro-2-[2,2-dichloro-1-(4-Chlorophenyl)-ethyl]-benzene

MOA: Oral Chemotherapeutic agent indicated in treatment of adrenal cortex carcinoma

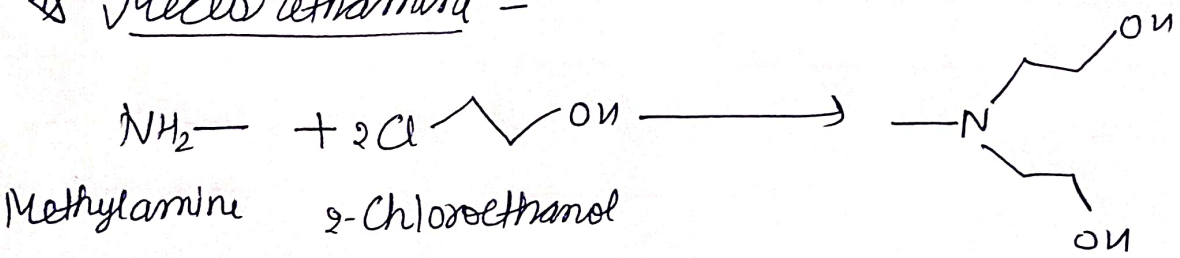
Metabolism : Abt. 65% ingested drugs were found to pass in Stool.

Uses:- → Metastatic therapy
→ adrenocortical carcinoma.

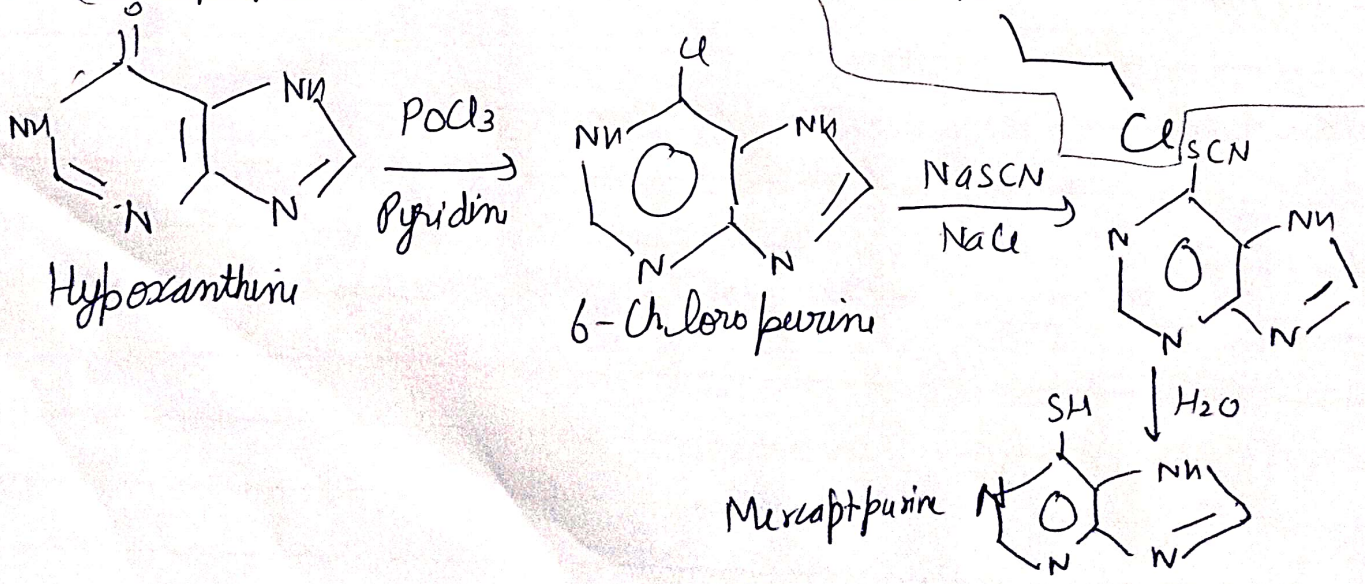
ADR - → Nausea and Vomiting
→ diarrhea
→ leukopenia.

Synthesis

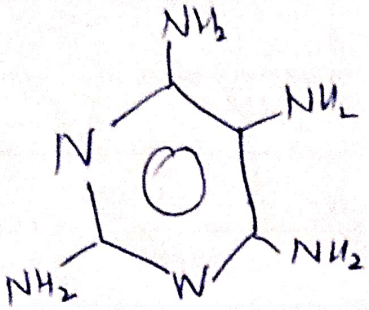
☆ **Mechlorethamine** -



☆ **Mercaptopurine**:



✡ Methotrexate :



2,4,5,6 - Tetraamino Pyrimidin

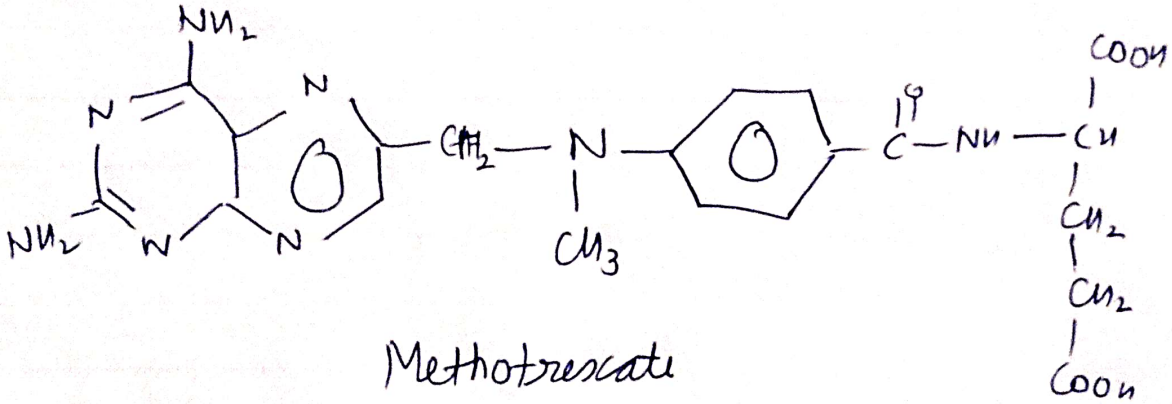
+ $BrCH_2CH(Br)CHO$

2,3-dibromo propionaldehyd

+ Methyl amino Benzoyl glutamate

Cyclization dehydration

Lime Water
NaOH
CH_3COOH



Methotrexate