ANTI-NEOPLASTIC AGENTS

VIPW
MC
B PHARM III/I

Introduction

- **Cancer*** is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems, this process is called metastasis.

✓ **Characteristics of Cancer Cells:**

- Cancer involves the development and reproduction of abnormal cells
- Cancer cells are usually nonfunctional
- Cancer cell growth is not subject to normal body control mechanisms
- Cancer cells eventually metastasize to other organs via the circulatory and lymphatic systems.

Types of Tumors :

·**Benign:** non cancerous and not an immediate threat to life, even though treatment eventually may be required for health.

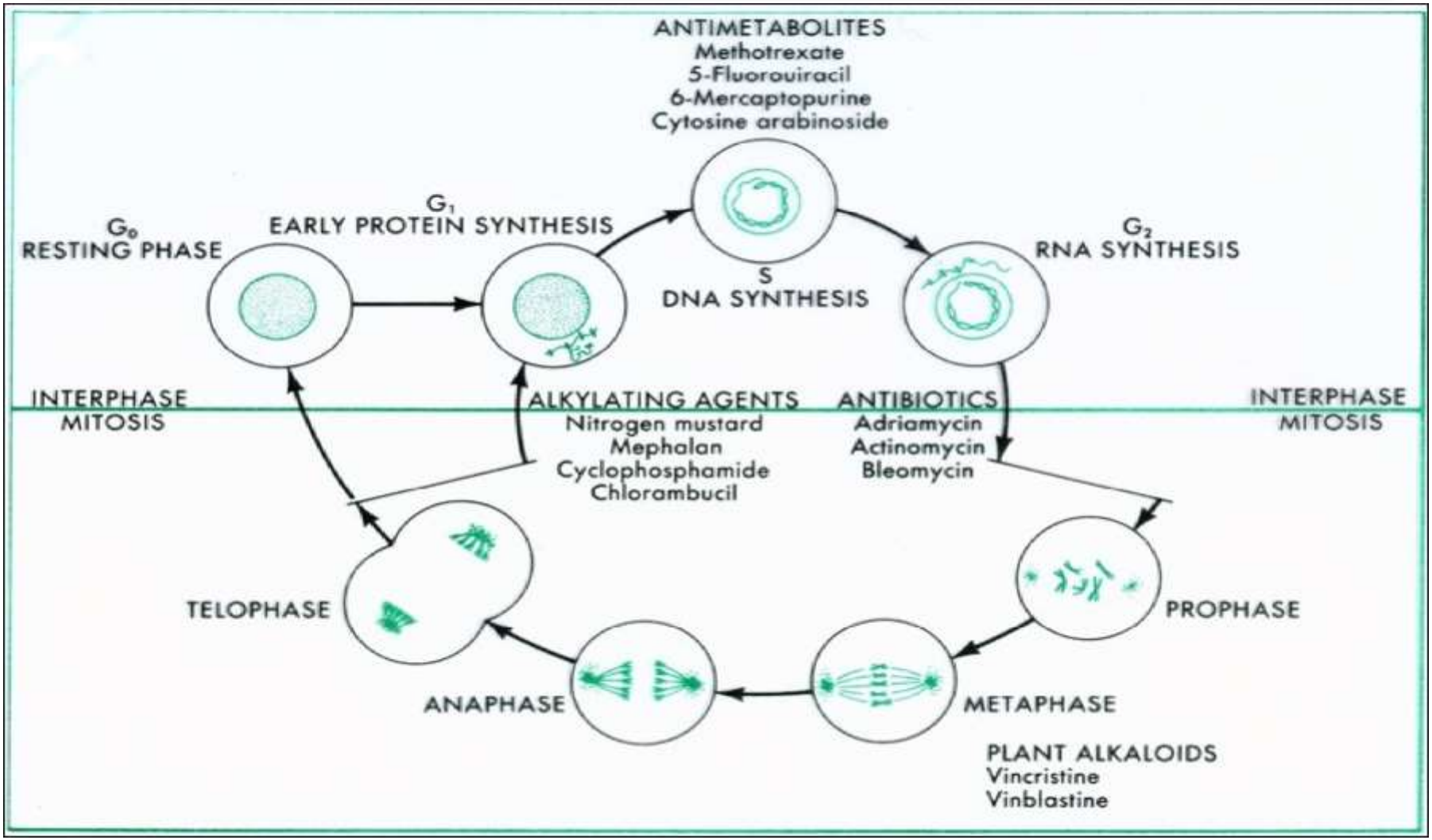
· **Malignant** : tending to worsen and cause death, invasive and metastasis

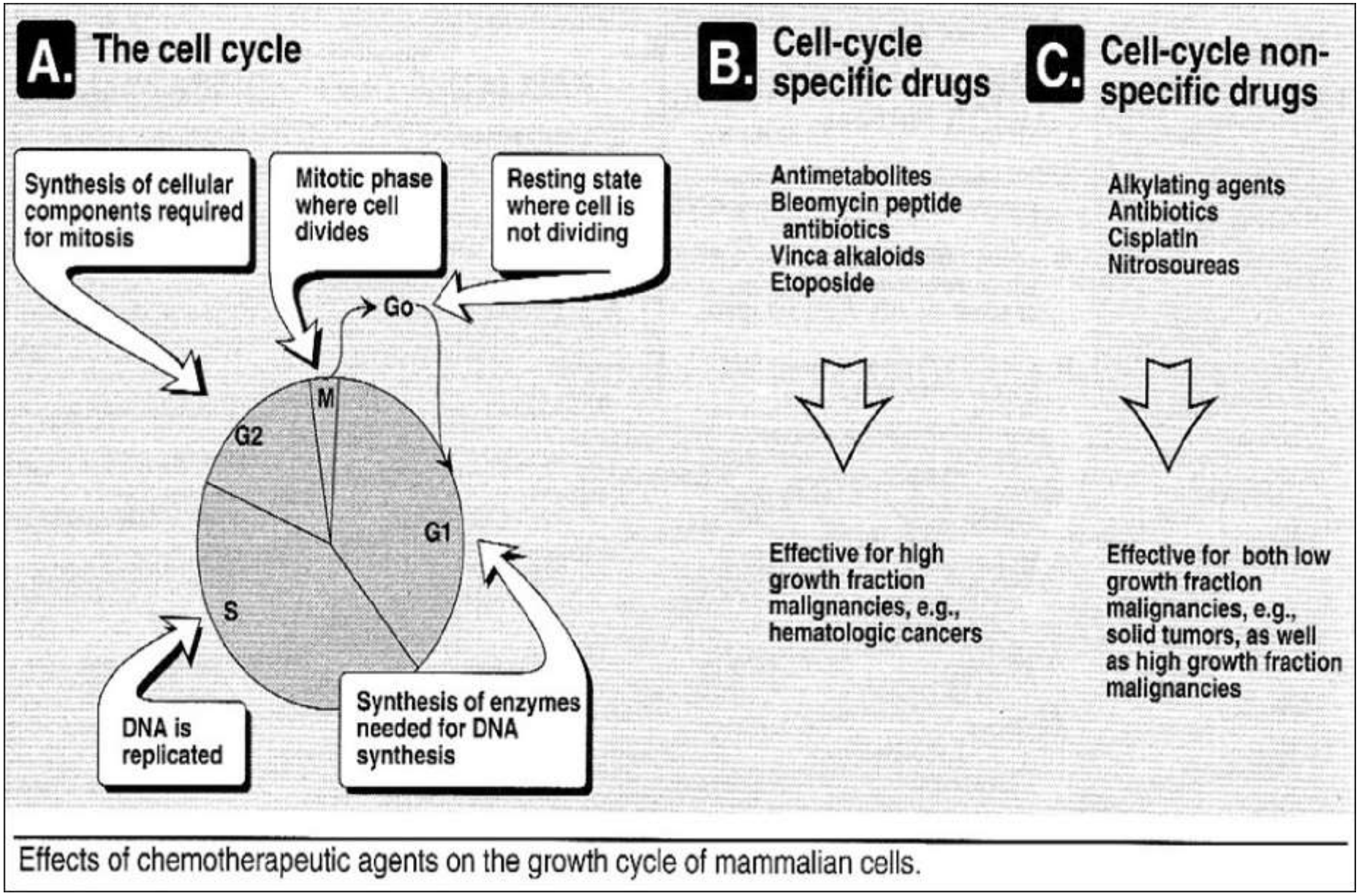
- Categorized based on the functions/locations of the cells from which they originate:

1. **Carcinoma** - skin or in tissues that line or cover internal organs. E.g., Epithelial cells. 80-90% reported cancer cases are carcinomas.
2. **Sarcoma** - bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
3. **Leukemia** - White blood cells and their precursor cells such as the bone marrow cells, causes large numbers of abnormal blood cells to be produced and enter the blood.
4. **Lymphoma** - cells of the immune system that affects lymphatic system.
5. **Myeloma** - B-cells that produce antibodies- spreads through lymphatic system.
6. **Central nervous system cancers** - cancers that begin in the tissues of the brain and spinal cord.

- **Antineoplastic agents are drugs used for the treatment of cancer.**
- The fraction of tumor cells that are in the replicative cycle (“Growth factor”), influence their susceptibility to most cancer chemotherapeutic agent.
- Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas non proliferating cells [those in G0 phase] usually survive the toxic effect of these drugs.
- Normal cells and tumor cells go through growth cycle. However , normal and neoplastic tissue may differ only in the number of cells that are in the various stages in the cycle. Chemotherapeutic agents that are effective only in replicating cells.

The cell cycle and cancer drugs





Effects of chemotherapeutic agents on the growth cycle of mammalian cells.

Classification

1) Based on site of action
2) Chemical classification

1. Based on site of action

I. **Phase specific agents:** These drugs acts at particular phase of cell cycle and more effective in proliferating cells.

a) G1 – Vincristine

b) S–Methotrexate, Cytarabine, 6-TG, 6-MP, 5-FU, Daunorubicin, Doxorubicin

c) G2 – Daunorubicin, Bleomycin

d) M – Vincristine, Vinblastne, Paclitaxel etc.

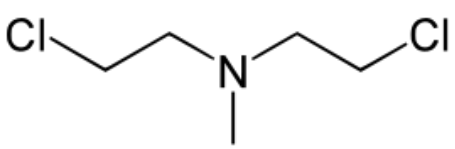
II. **Phase non specific agents:** Nitrogen Mustards, Cyclphosphamide, Chlorambucil, Carmustine, Dacarbazine, Busulfan, L-Asparginase, Cisplatin, Procarbazine and Actinomycin D etc.

III. These drugs are specifically effective against proliferating cells but they are not phase specific: e.g. Fluorouracil, cyclophosphamide, Dactinomycin.

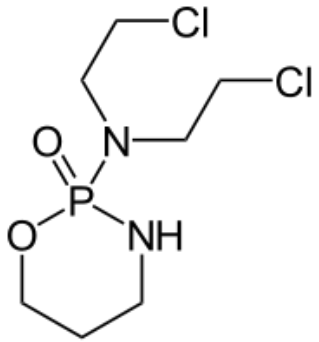
2. Chemical classification

a. Alkylating Agents

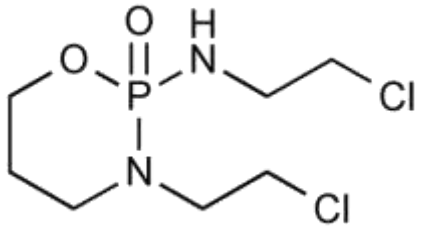
1. Nitrogen mustards – Mechlorethamine (Mustine HCL), Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil



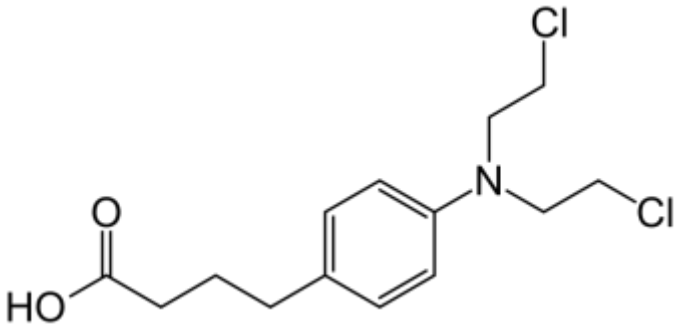
Mechlorethamine



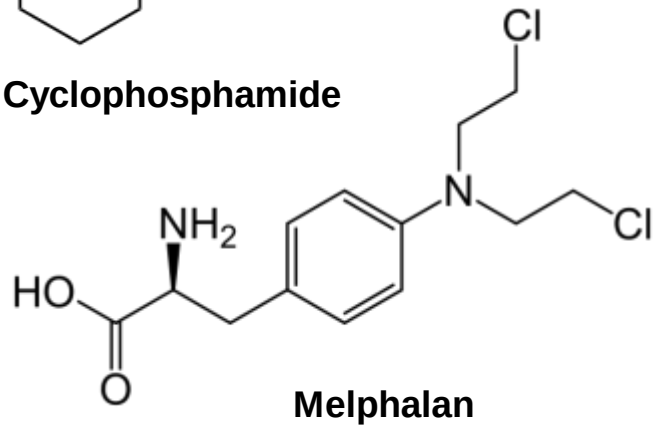
Cyclophosphamide



Ifosfamide



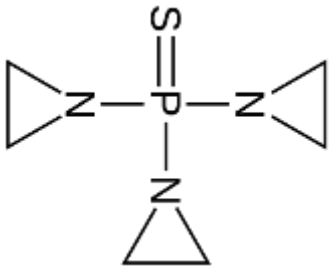
Chroambucil



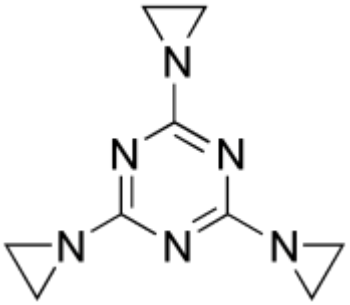
Melphalan

2. Ethylenimine - Thio-TEPA, hexamethylmelamine (Altretamine)

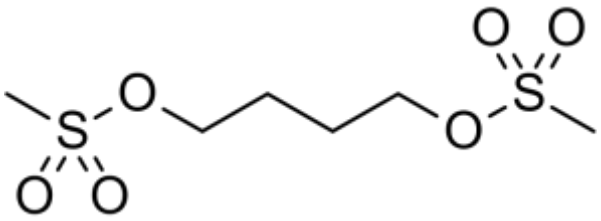
3. Alkyl sulfonate – Busulfan



Thiotepa

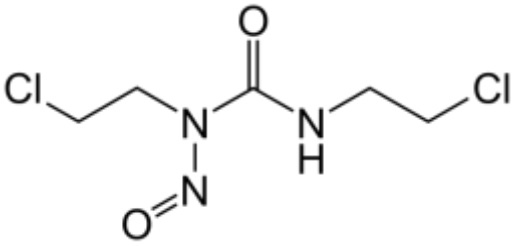


Triethylene melamine

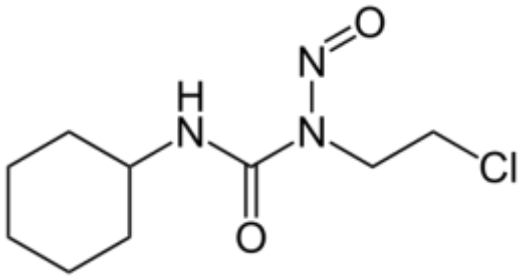


Busulphan

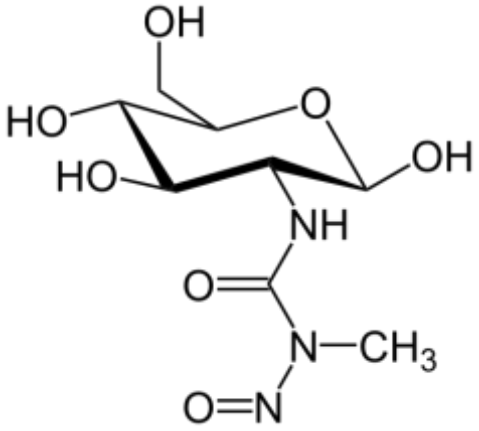
4. Nitrosoureas – Carmustine, Lomustine, Streptozocin



Carmustine

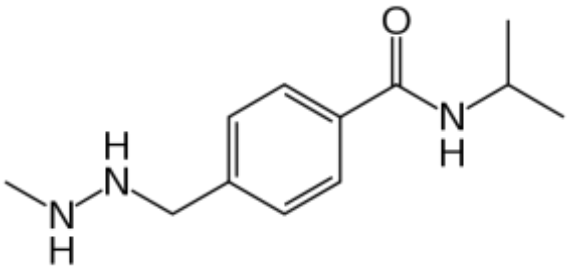


Lomustine

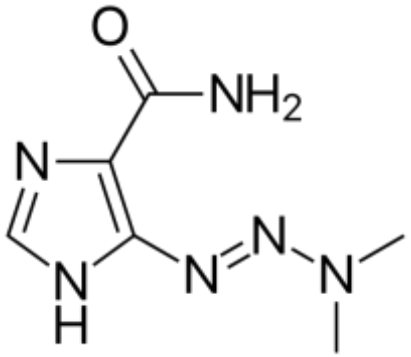


Streptozocin

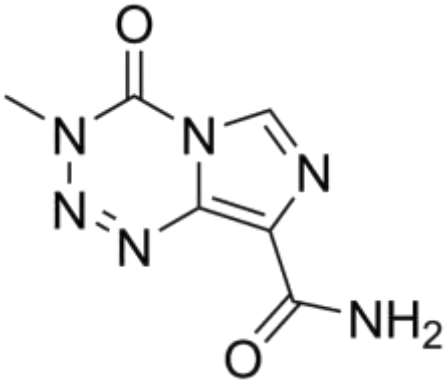
5. Triazines - Procarbazine, Dacarbazine, Temozolomide



Procarbazine

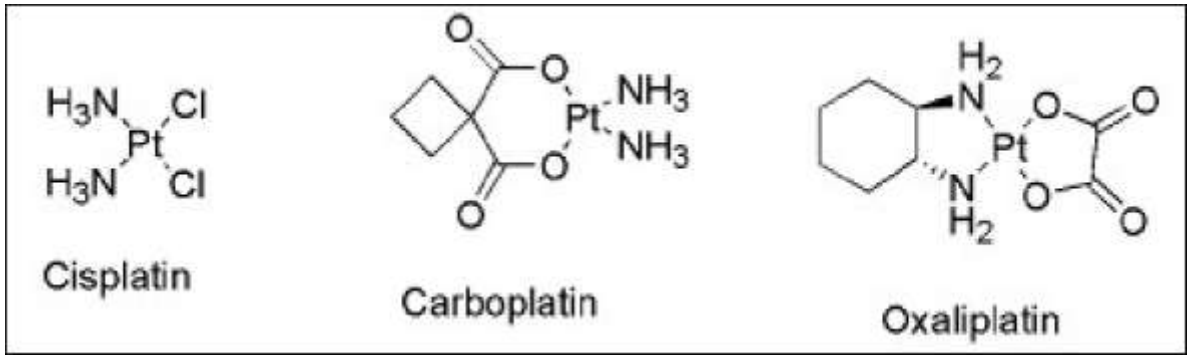


Dacarbazine



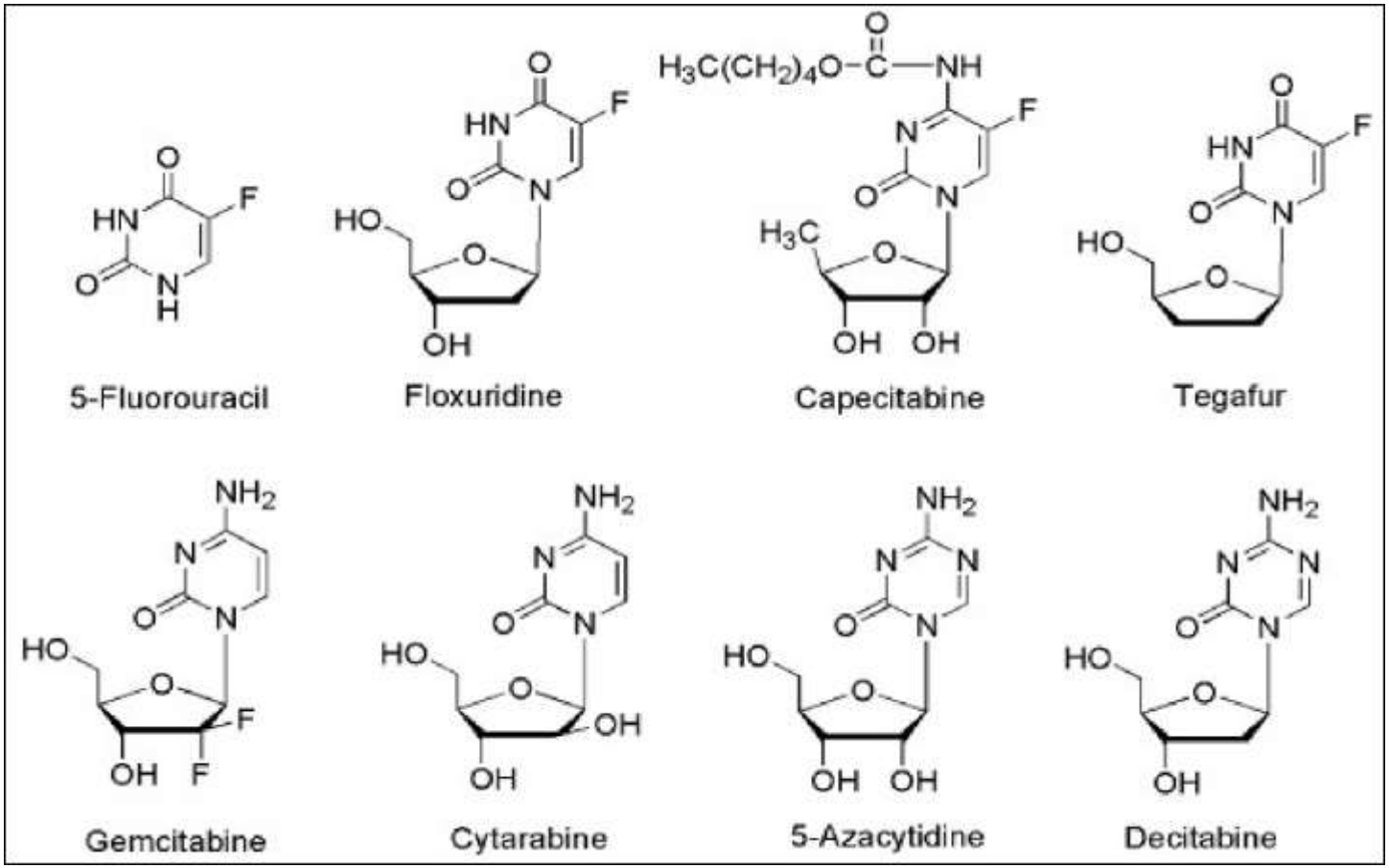
Temozolomide

b. Platinum coordination complexes – Cisplatin, Carboplatin,Oxaliplatin

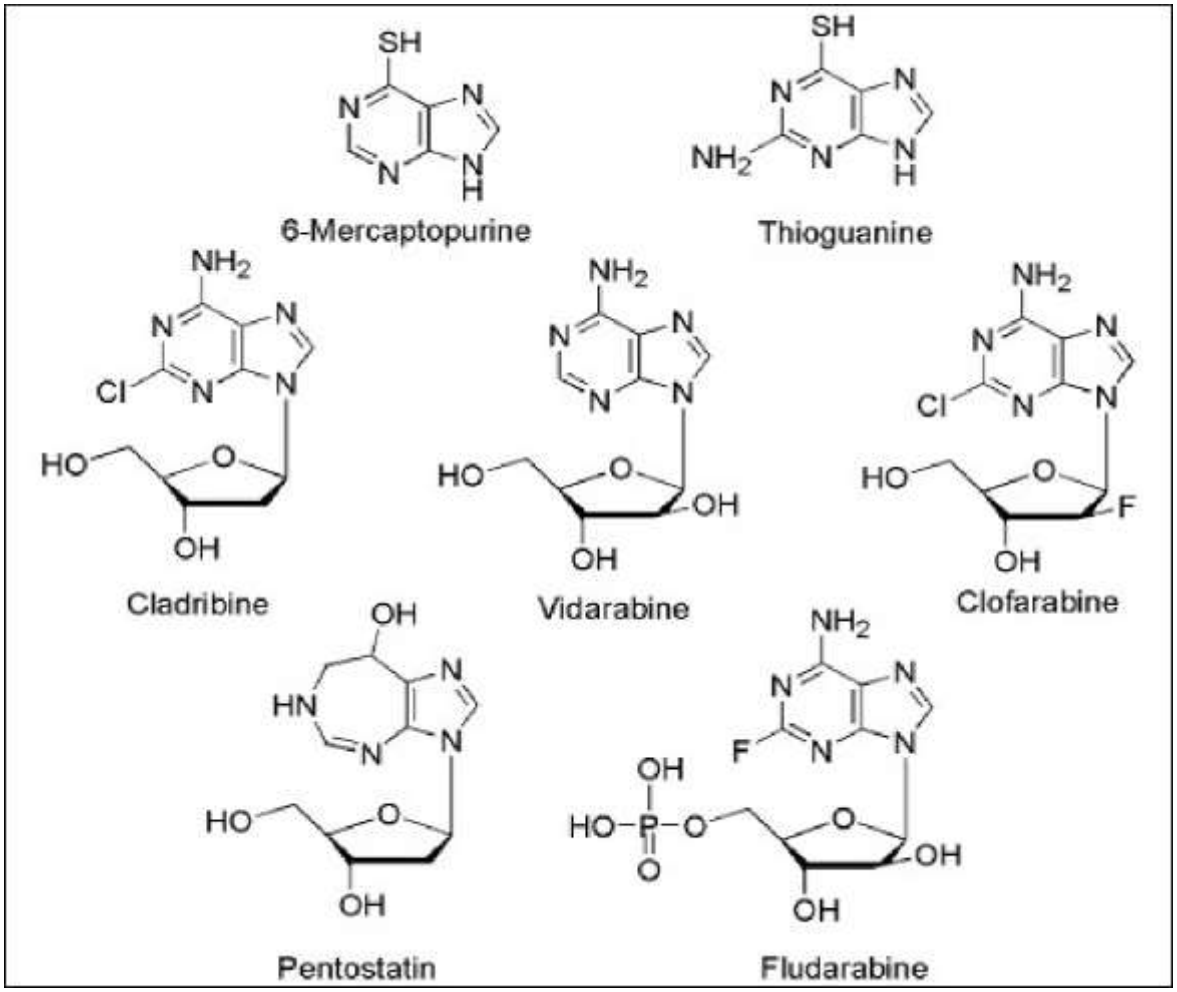


c. Antimetabolites –

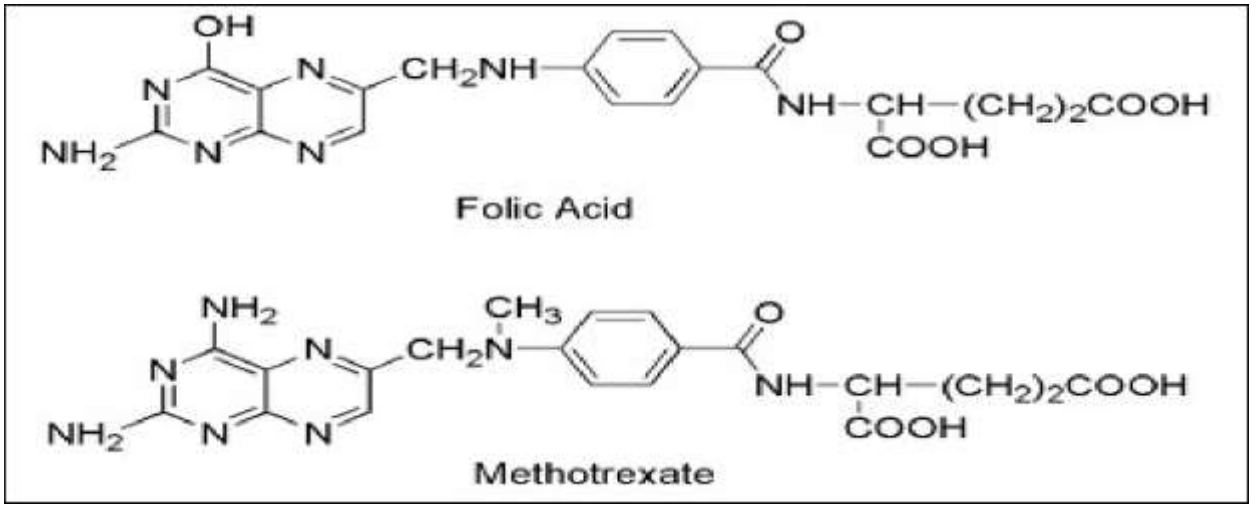
I. Pyrimidine analogs – 5-Fluorouracil , Cytarabine (cytosine arabinoside), Capecitabine, Gemcitabine



II. Purine analogs – 6-Mercaptopurine, 6-Thioguanine, Azathioprine, Fludarabine, Cladribine, Pentostatin

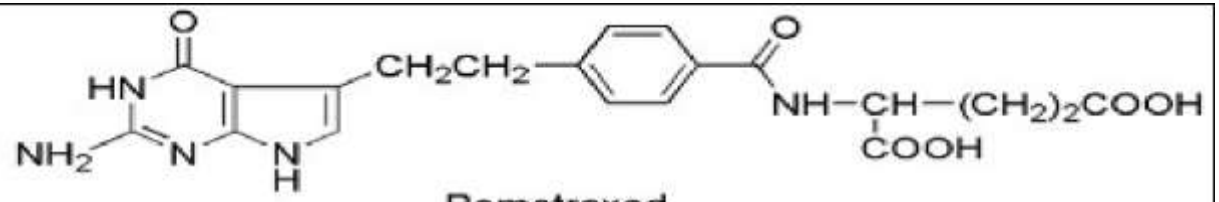


III. **Folic acid analogues** – Methotrexate, Pemetrexed

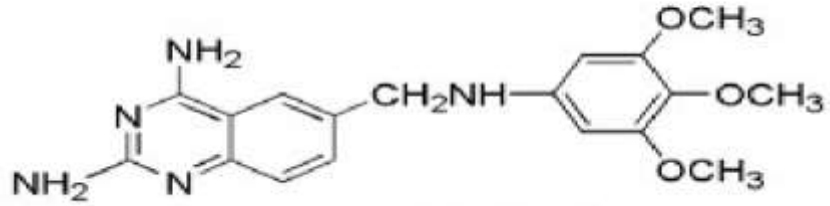


Folic Acid

Methotrexate

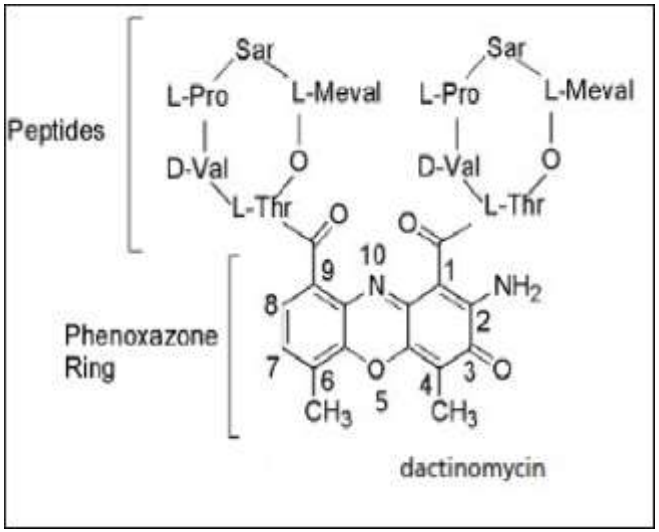


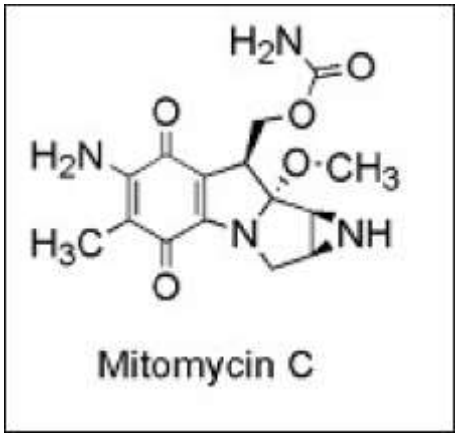
Pemetrexed

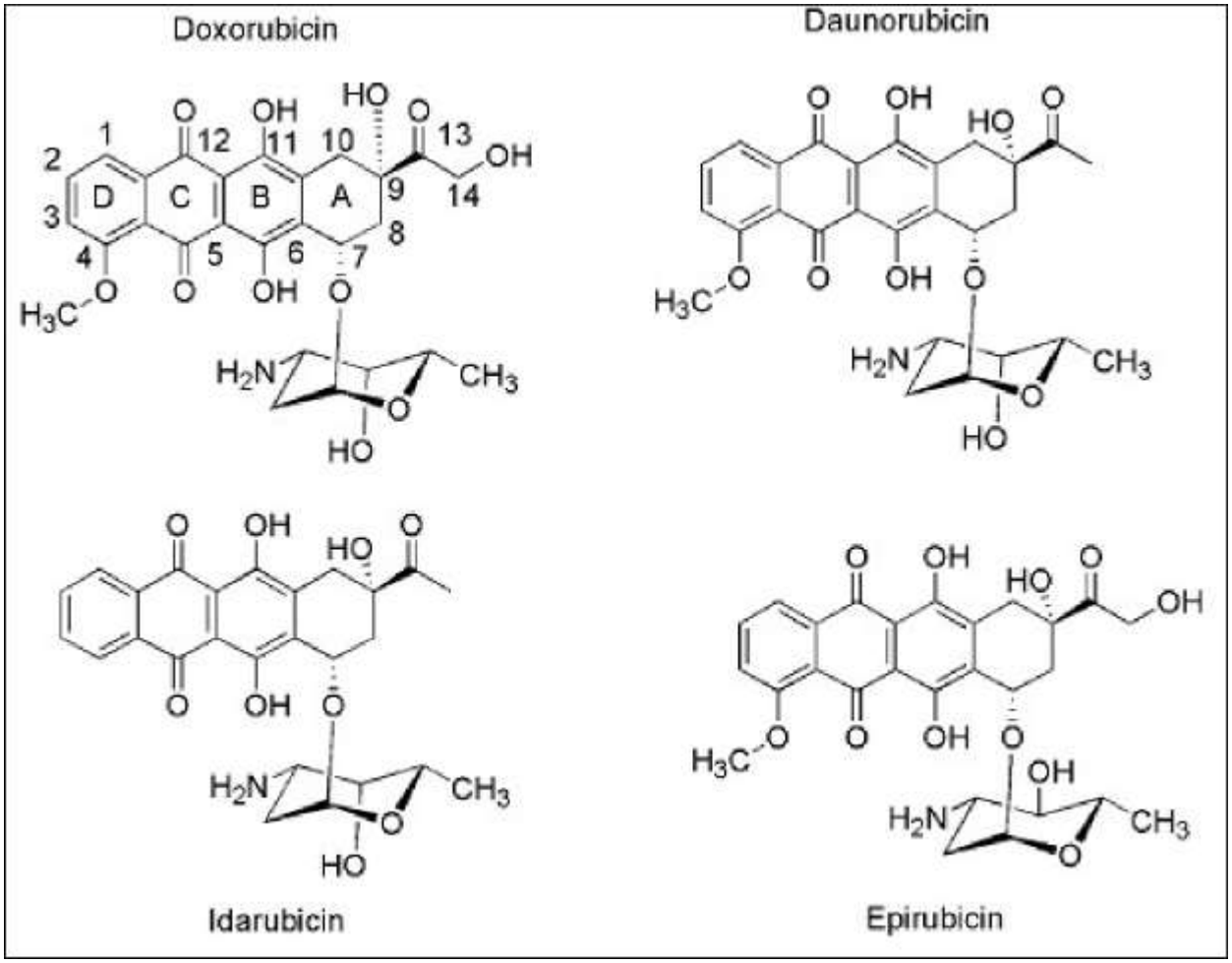


Trimetrexate

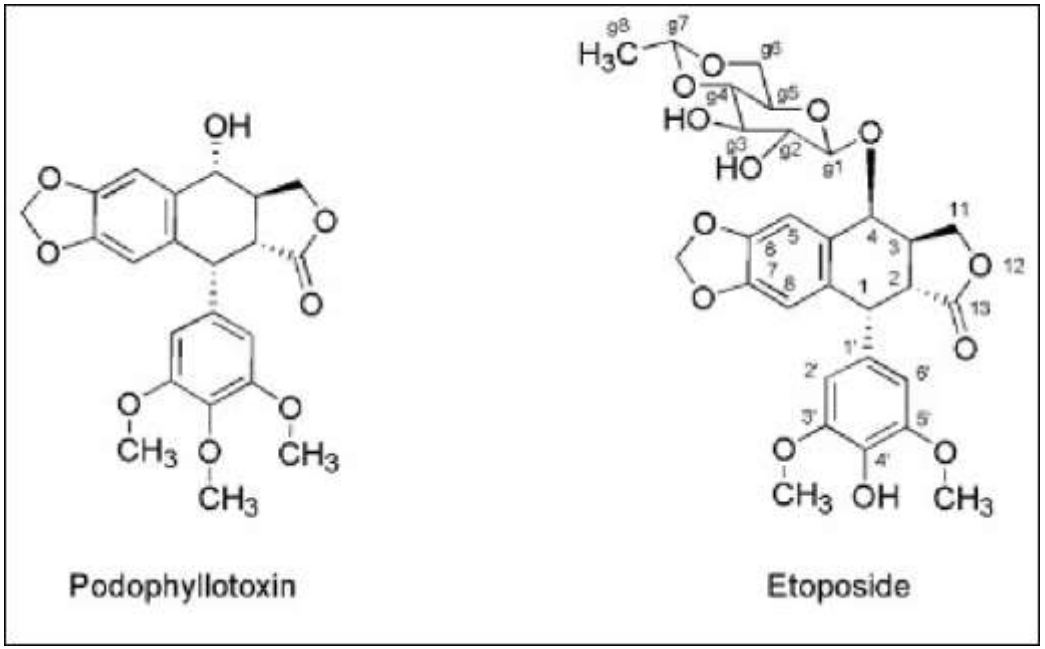
d. Anticancer Antibiotics – Actinomycin-D (Dactinomycin), Bleomycin, mitomycin-C, anthracyclines (e.g. Doxorubicin, Daunorubicin, Idarubicin, epirubicin, Valrubicin), Streptozocin

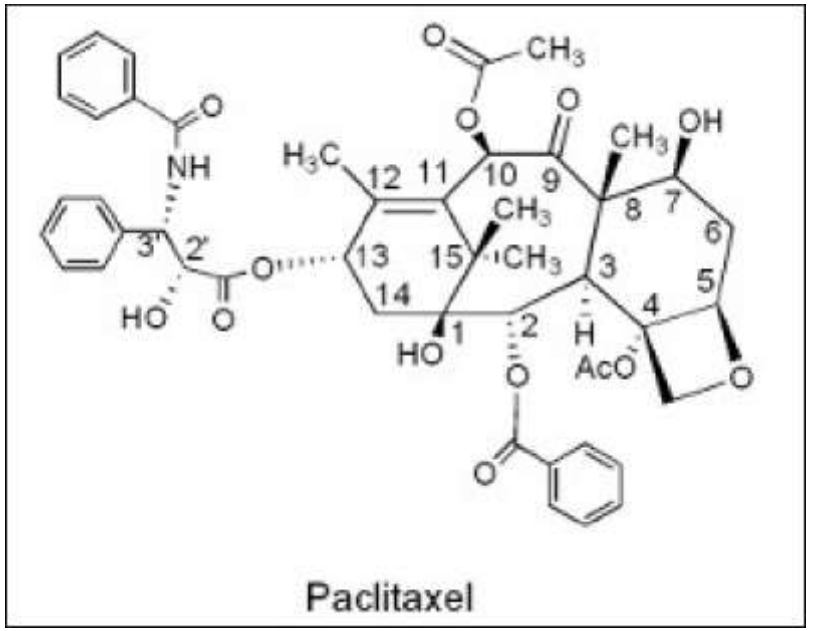


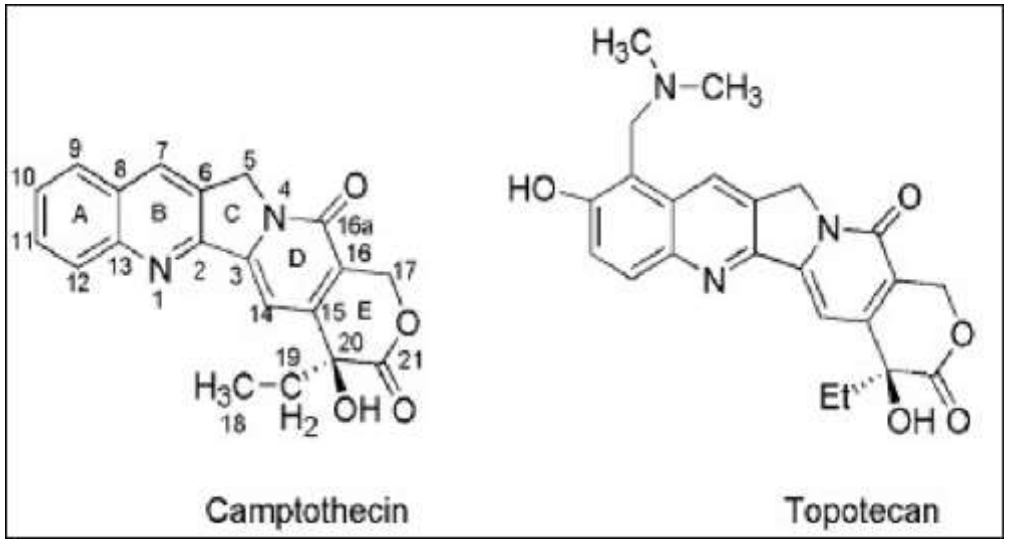


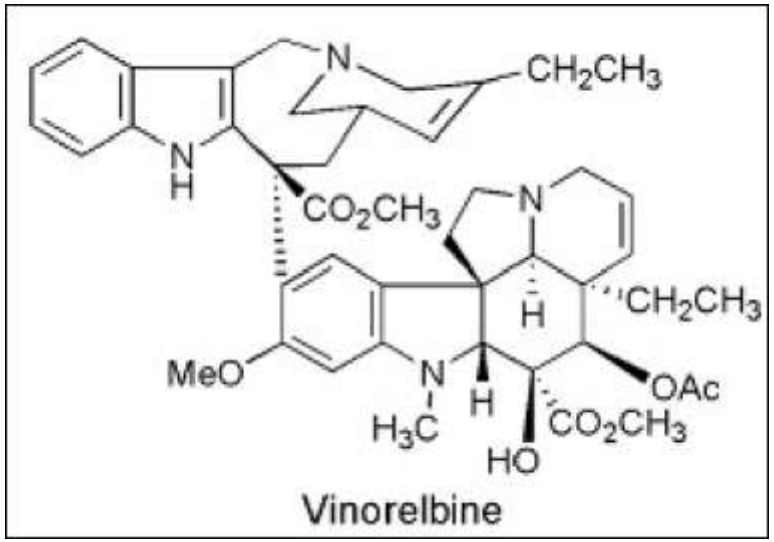


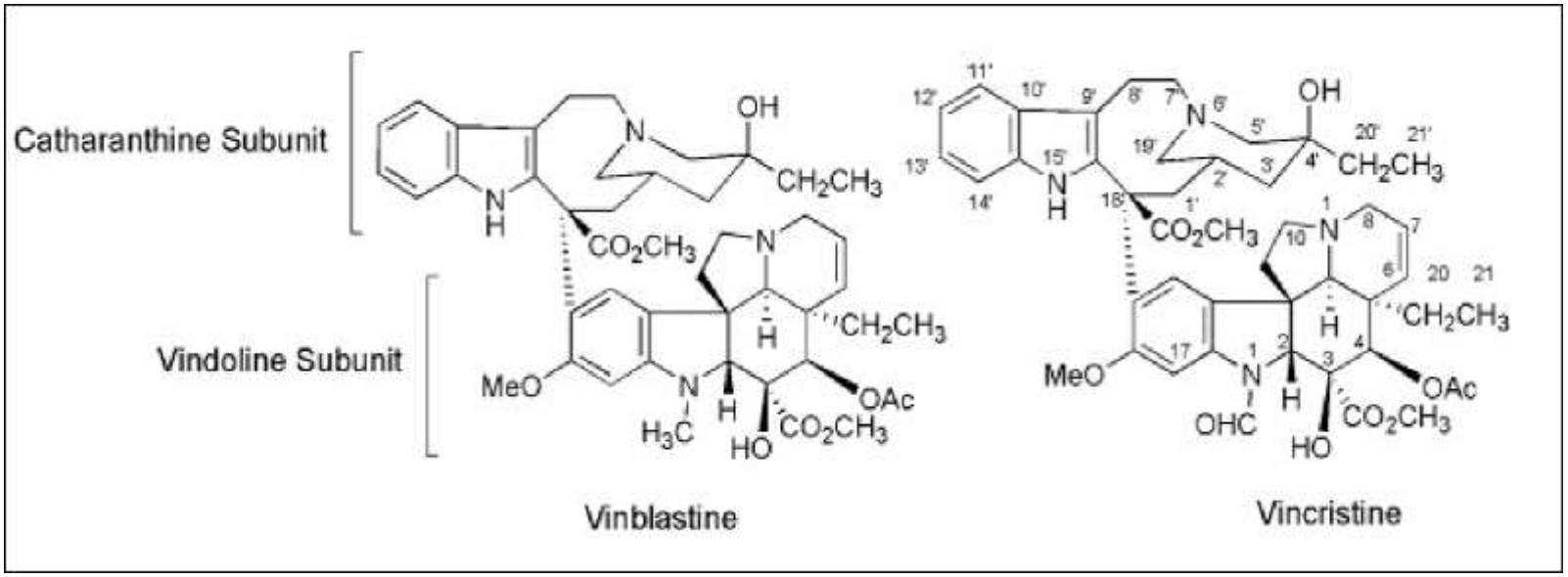
e. Plant products- vincristine, vinblastine, podophyllotoxin, etoposide, camptothecin, paclitaxal





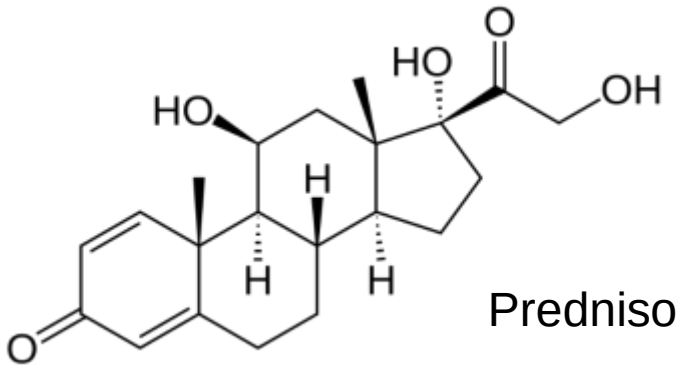

Camptothecin
Topotecan


Vinorelbine


Catharanthine Subunit
Vindoline Subunit
Vinblastine
Vincristine

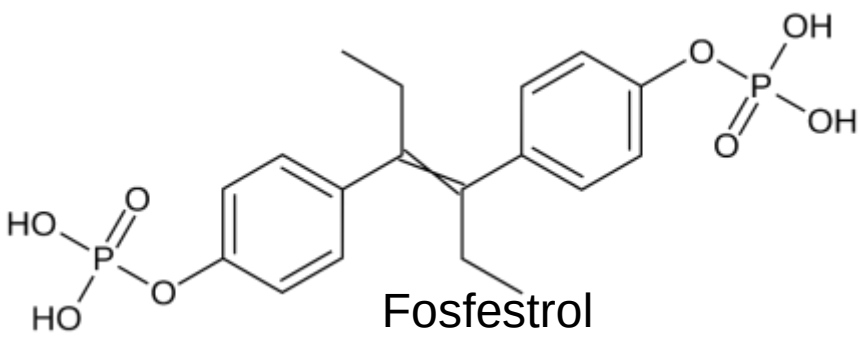
h. Hormonal drugs –

1. Glucocorticoids – Prednisolone and others

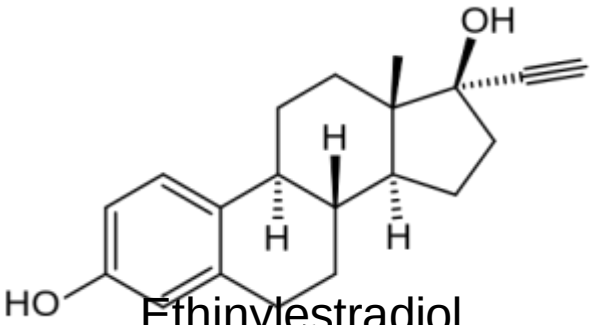


Prednisolone

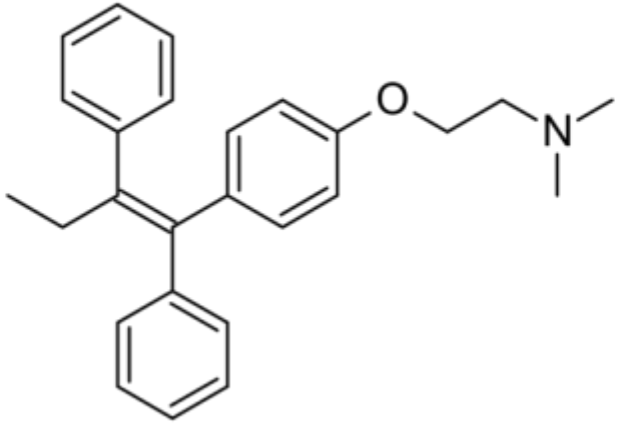
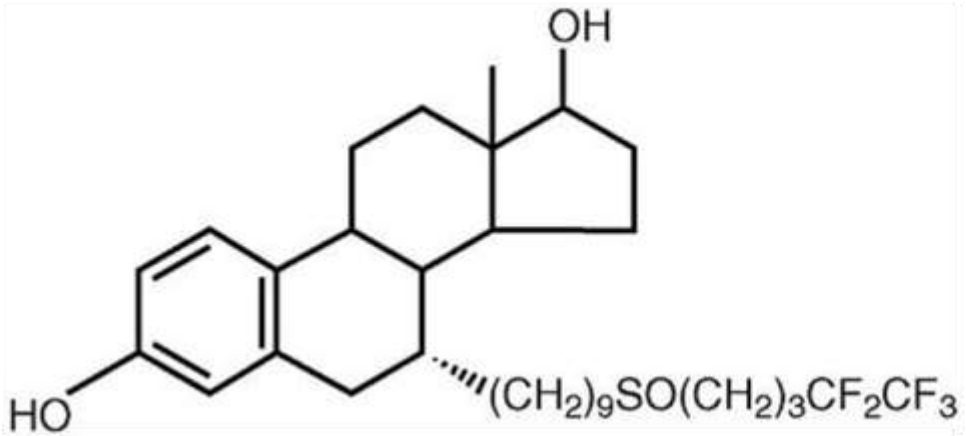
2. Estrogens – Fosfestrol, Ethinylestradiol

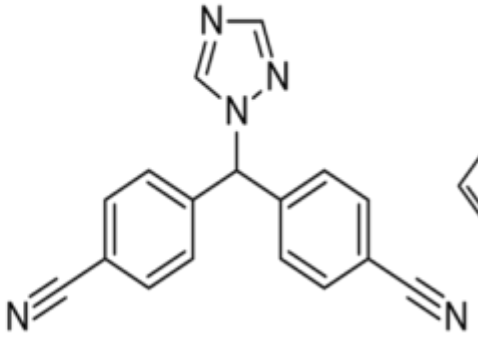
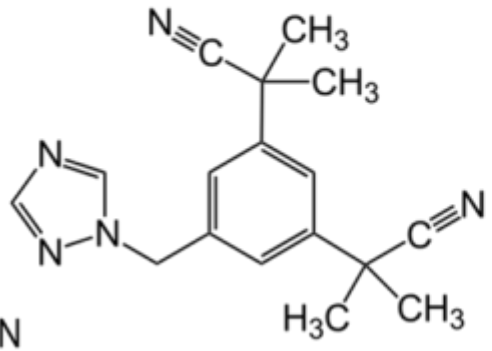
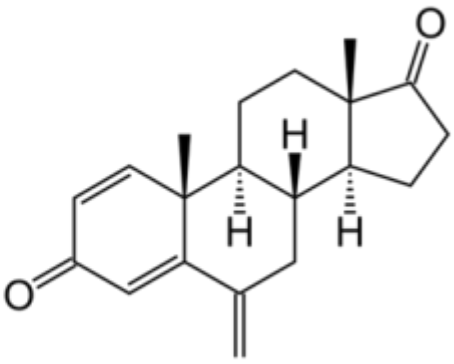
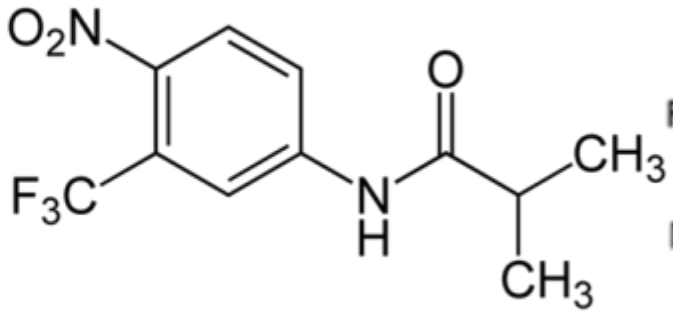
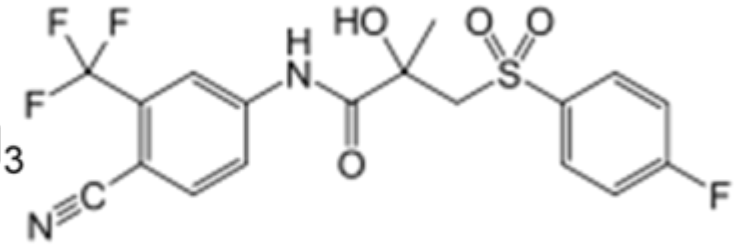


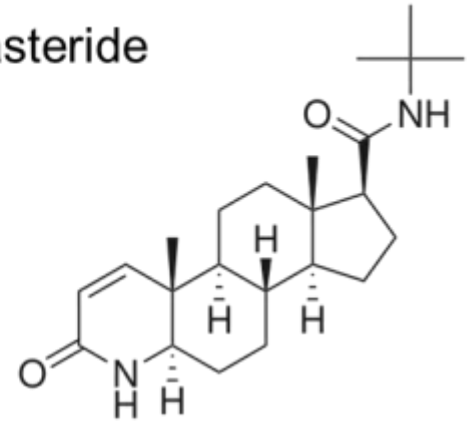
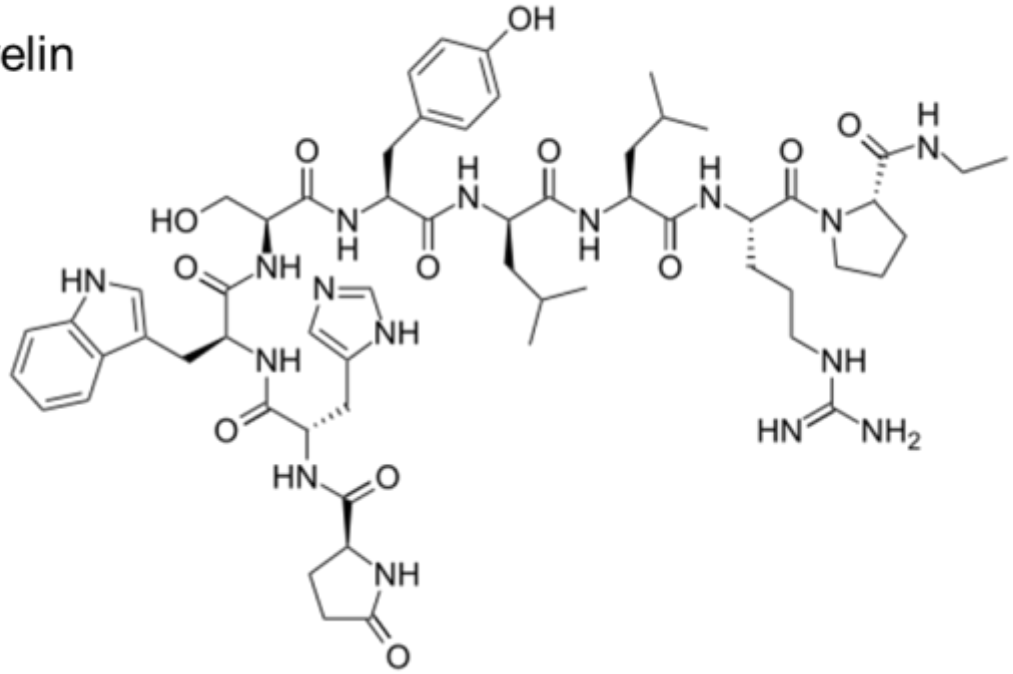
Fosfestrol



Ethinylestradiol

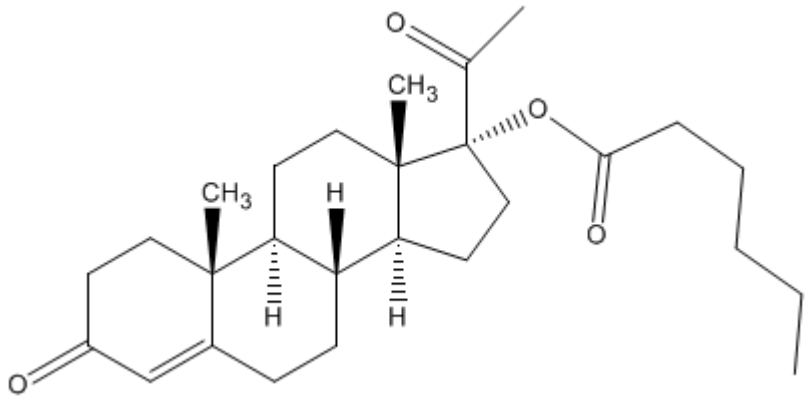
3. Selective estrogen receptor modulators- Tamoxifen, Toremifene	Tamoxifen 
4. Selective estrogen receptor down regulators – Fulvestrant	

5. Aromatase Inhibitors – Letrozole, Anastrozole, Exemestane	Letrozole  Anastrozole   Exemestane
6. Antiandrogens – Flutamide, Bicalutamide	Flutamide   Bicalutamide

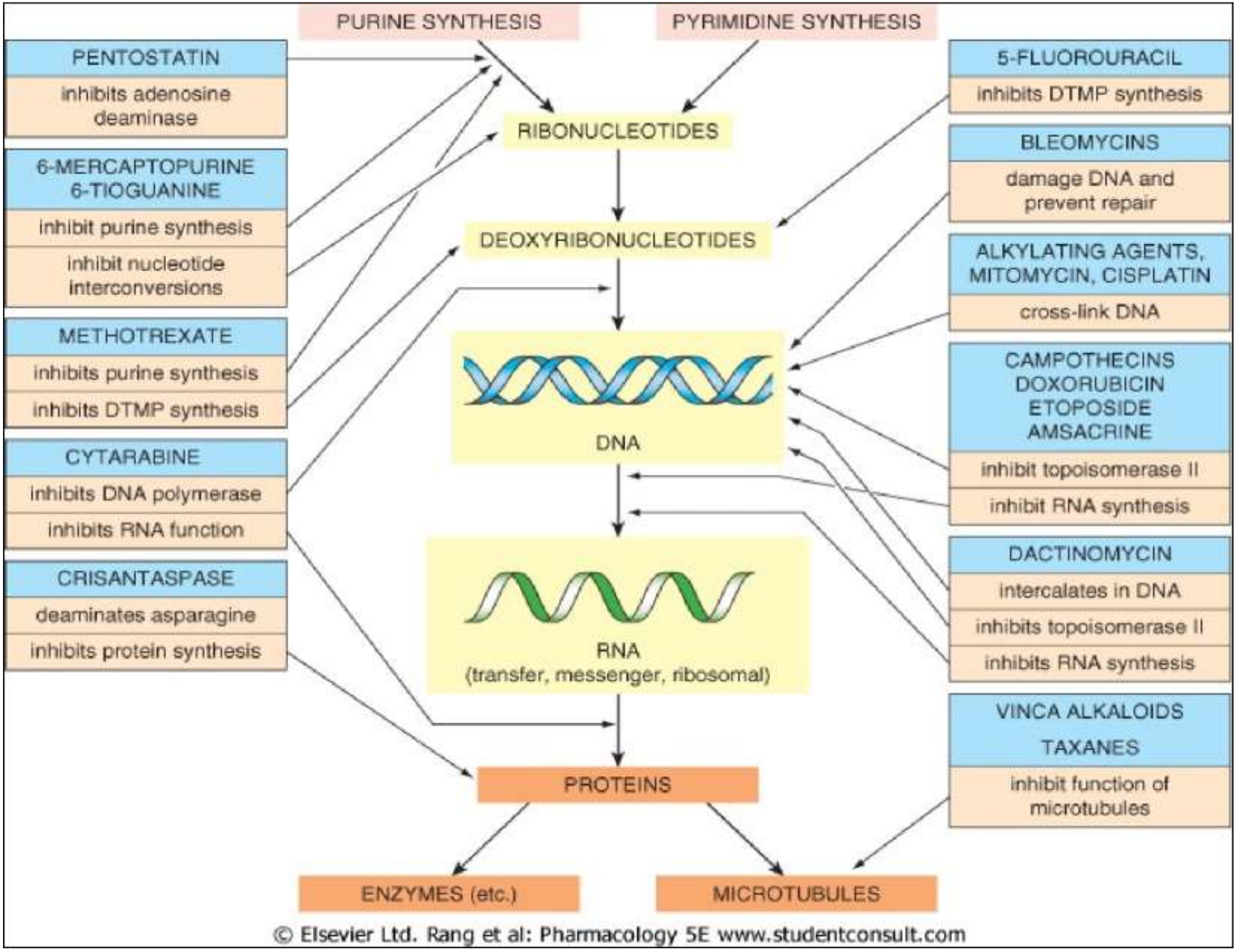
7. 5-α reductase Inhibitors – Finasteride, Dutasteride	Finasteride 
8. GnRH analogues – Nafarelin, Leuprorelin, triptorelin	Leuprorelin 

9. Progestins –

Hydroxyprogesterone acetate, etc



10. GnRH antagonists – Cetorelix, Ganirelix, Abarelix


PURINE SYNTHESIS
PYRIMIDINE SYNTHESIS
PENTOSTATIN
inhibits adenosine deaminase
6-MERCAPTOPURINE
6-TIOGUANINE
inhibit purine synthesis
inhibit nucleotide interconversions
METHOTREXATE
inhibits purine synthesis
inhibits DTMP synthesis
CYTARABINE
inhibits DNA polymerase
inhibits RNA function
CRISANTASPASE
deaminates asparagine
inhibits protein synthesis
RIBONUCLEOTIDES
DEOXYRIBONUCLEOTIDES
DNA
RNA
(transfer, messenger, ribosomal)
PROTEINS
ENZYMES (etc.)
MICROTUBULES
5-FLUOROURACIL
inhibits DTMP synthesis
BLEOMYCINS
damage DNA and prevent repair
ALKYLATING AGENTS, MITOMYCIN, CISPLATIN
cross-link DNA
CAMPOTHECINS
DOXORUBICIN
ETOPOSIDE
AMSACRINE
inhibit topoisomerase II
inhibit RNA synthesis
DACTINOMYCIN
intercalates in DNA
inhibits topoisomerase II
inhibits RNA synthesis
VINCA ALKALOIDS
TAXANES
inhibit function of microtubules
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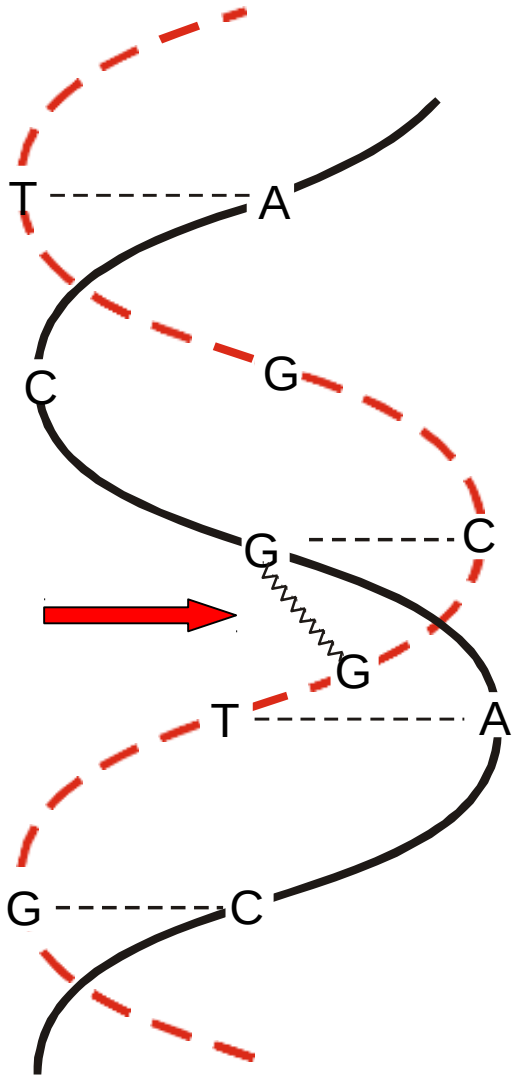
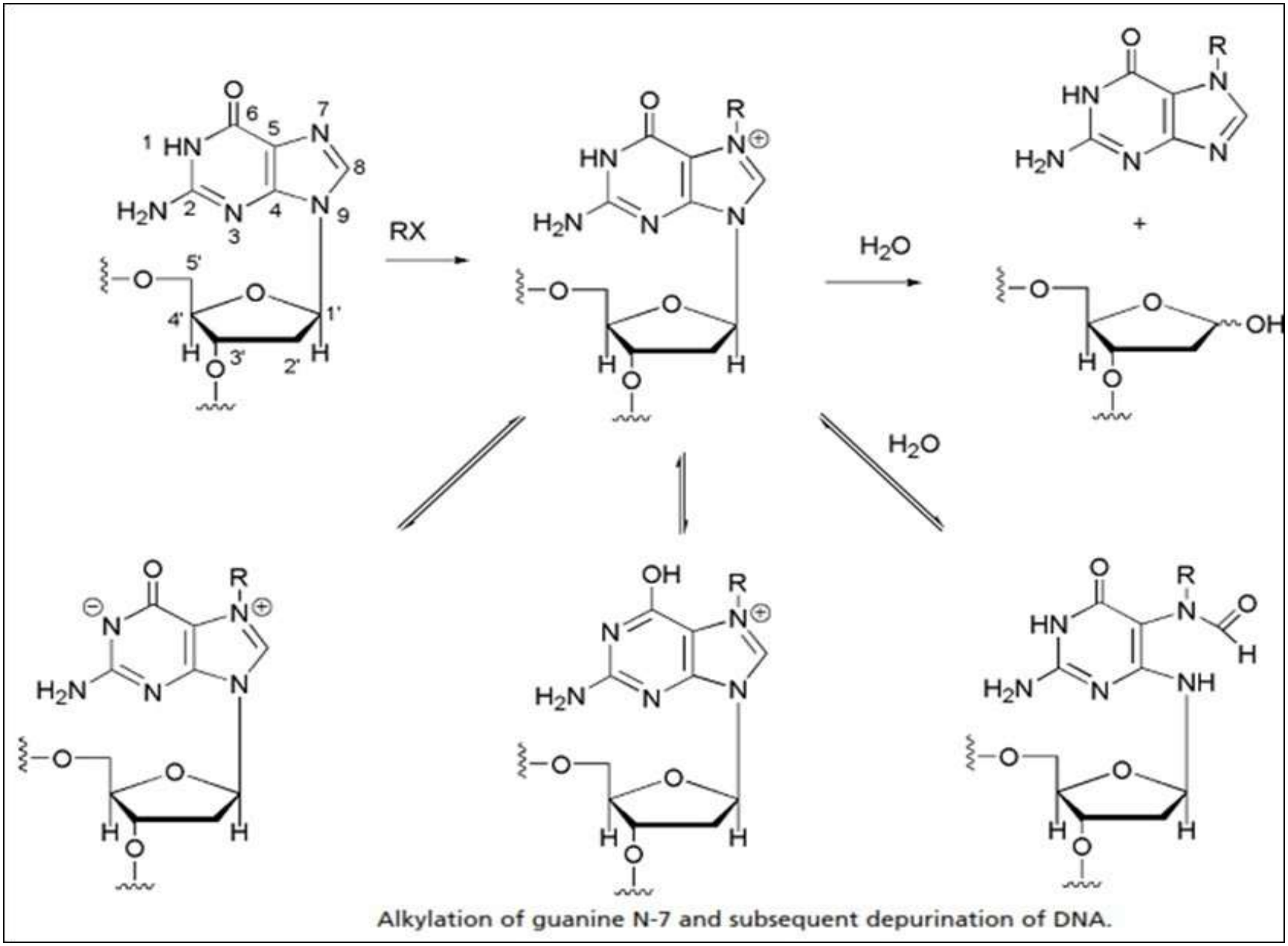
A. Alkylating agents

- The alkylating agents are a class of drugs that are capable of forming covalent bonds with important biomolecules.
- The major targets of drug action are nucleophilic groups present on DNA (especially the 7-position of guanine); however, proteins and RNA among others may also be alkylated.
- There are several potential nucleophilic sites on DNA, which are susceptible to electrophilic attack by an alkylating agent (N-2, N-3, and N-7 of guanine, N-1, N-3, and N-7 of adenine, 0–6 of thymine, N-3 of cytosine).
- Potential mechanisms of cell death include activation of apoptosis caused by p53 activation and disruption of the template function of DNA.
- The most important of these for many alkylating agents is the N-7 position of guanine whose nucleophilicity may be enhanced by adjacent guanine residues.



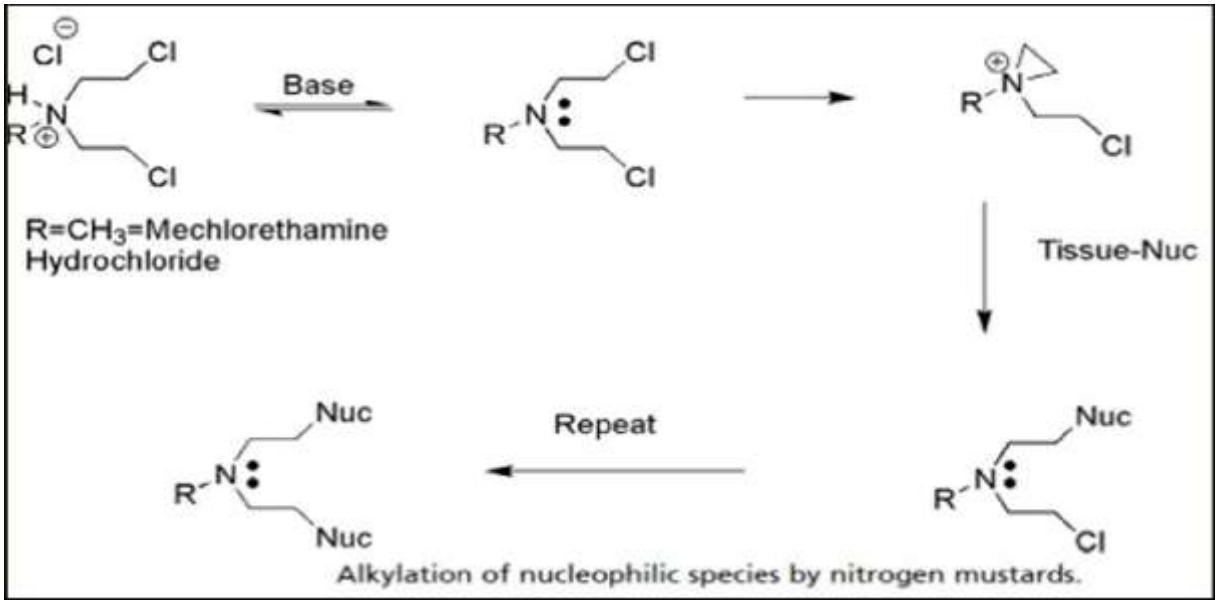
- Additionally, alkylation has been proposed to result in altered base pairing away from the normal G-C: A-T hydrogen bonds because of alterations in tautomerization.
- The alkylation also leads to increased acidity of the N-1 nitrogen reducing the pK from 9 to 7 to 8 giving rise to a zwitter ionic form that may also mispair.
- For those agents that possess two reactive functionalities, both inter strand and intra strand cross-linking becomes possible. When inter strand links occur, separation of the two strands during replication is prevented and therefore replication is blocked.



Alkylation of guanine N-7 and subsequent depurination of DNA.

1. Nitrogen mustard

- Developed from mustard war gases of Word War I which were highly reactive vesicants.
- First chemicals used for cancer Rx.
- Not cell cycle specific, but still more active in dividing tissues.
- "Radiomimetic" -- action on DNA resembles radiation.

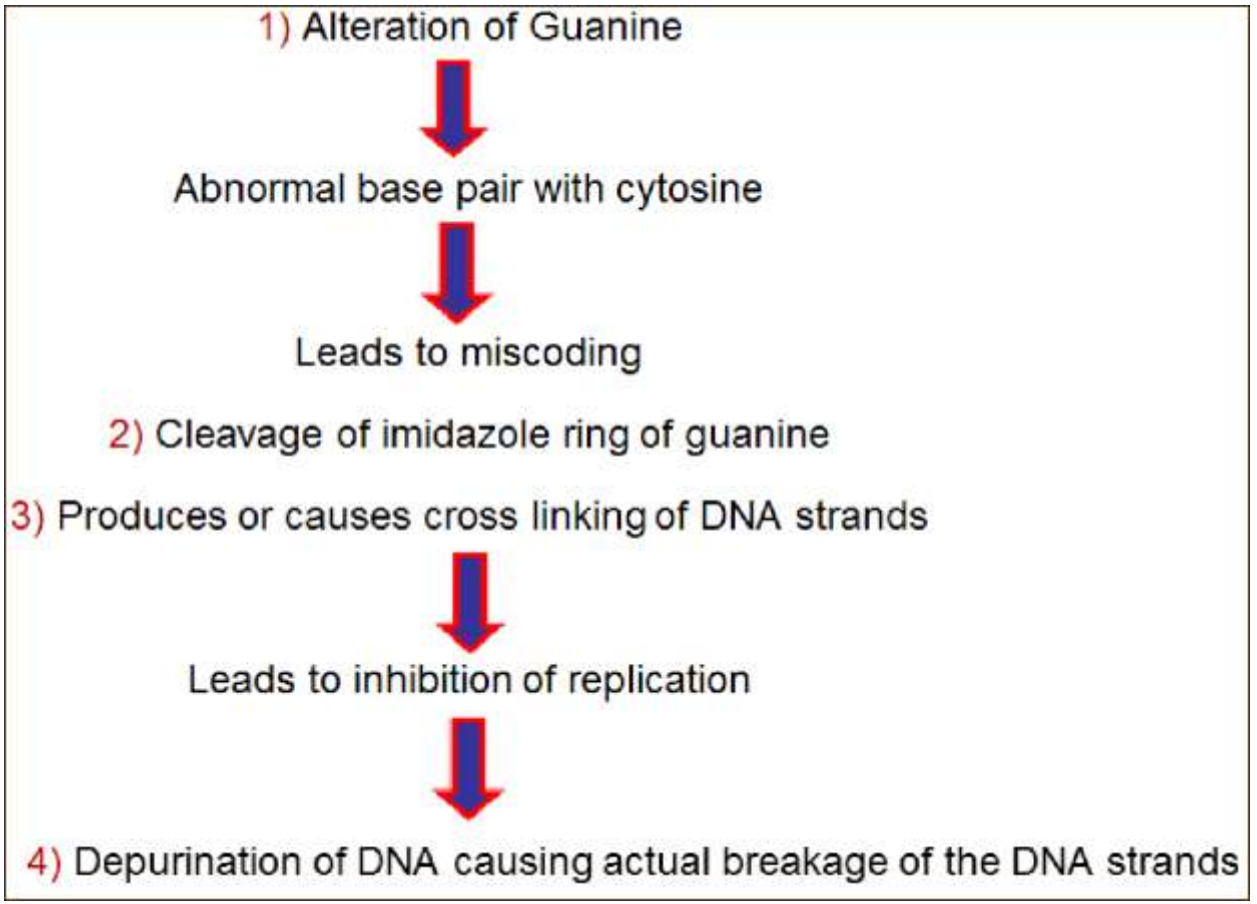


Alkylation of nucleophilic species by nitrogen mustards.

The nucleophile may be-

- SH of protein
- -N of protein, DNA base
- =O of DNA base

- At physiological PH, aliphatic mustard hydrochlorie converted into aziridium ion that reacts with nucleophile.
- These agents acts by alkylating the N7 of guanine in DNA which leads to



a) **Mechlorethamine:** 2,2 dichloro-N-methyl diethylamine hydrochloride

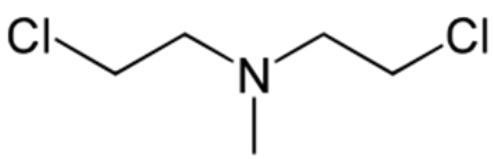
- Given by i.v administration of freshly prepared solution because gradual degradation of the aziridium ion by interaction with water.
- **Uses:**

· Hodkin's disease

· Lymphomas

· Thrombocytopenia

· Leucopenia



Mechlorethamine

- Important candidate of well known MOPP regimen.

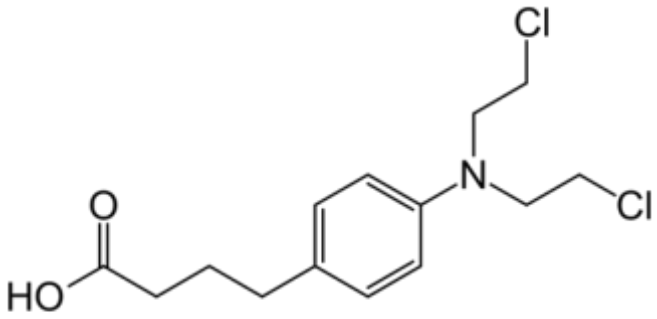
M- Mechlorethamine, O- Oncovin, P-Procarbazine, P- Prednisone

b) Chlorambucil: p- (di (2-chloroethyl) amino) phenyl butyric acid

•Quite stable compound to aziridium ion so it can be given orally.

•**Uses:** Especially in

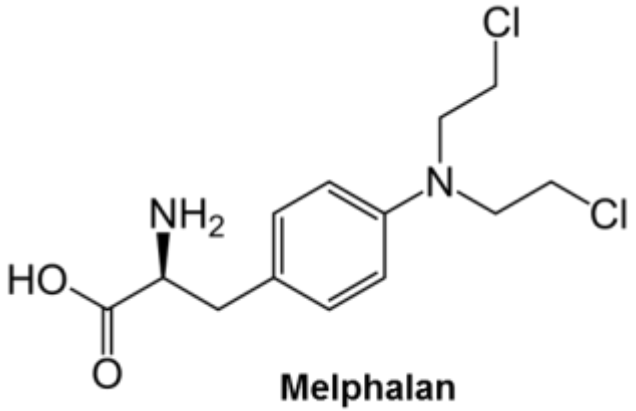
- Chronic lumphocytic leukemia
- Primary macroglobulinemia
- Lymphosarcoma
- Hodkin's disease



Chroambucil

c) Melphalan: 4-[Bis(2-chloroethyl)amino]-L-phenylalanine

- **Uses:**
- Multiple myeloma
- Breast cáncer
- Ovarian cancer



Melphalan

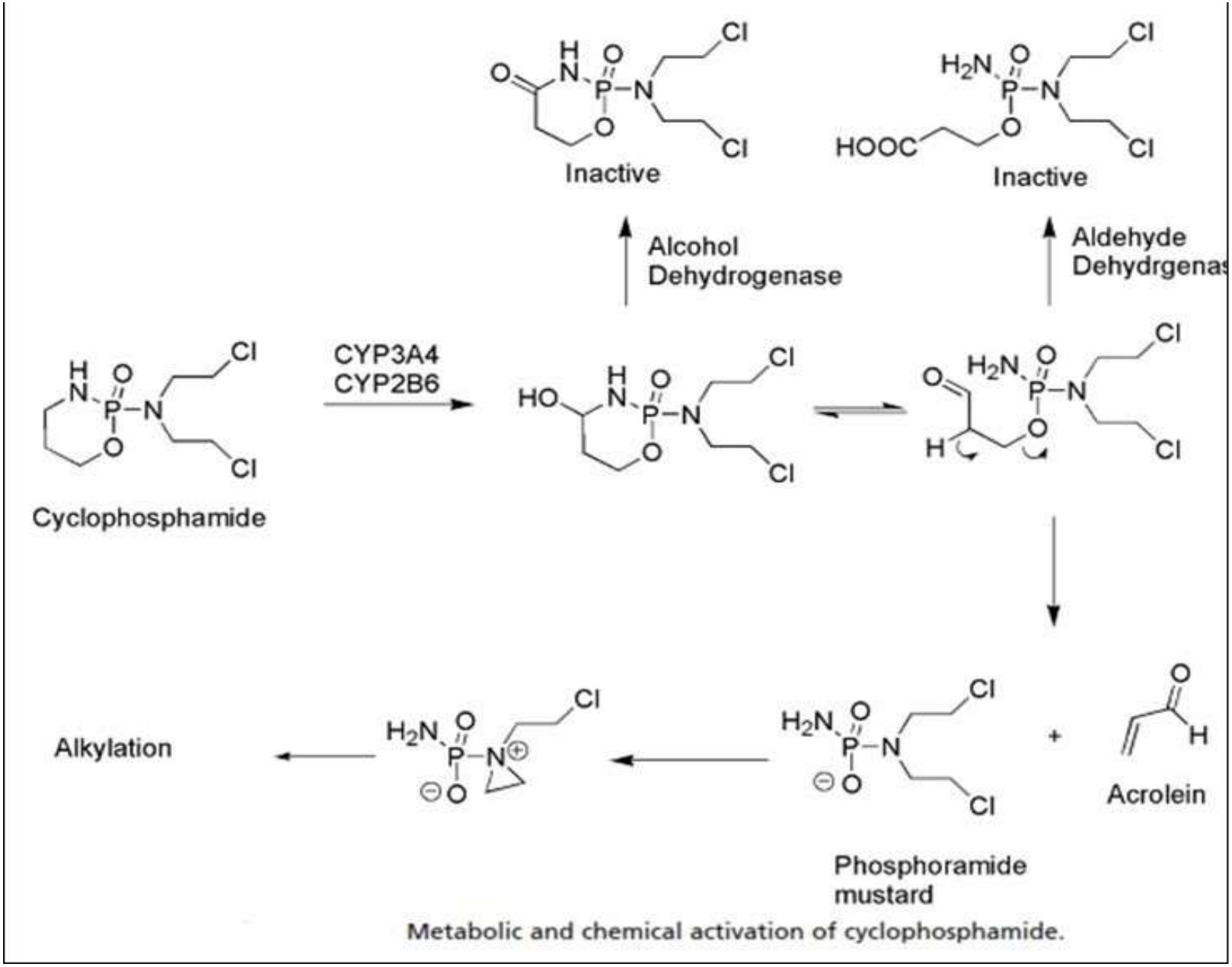
d) Cyclophosphamide- (*RS*)-*N*,*N*-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine-2-oxide

•In these case, aziridinium cation formation is not possible until the electron-withdrawing function has been altered. In the case of cyclophosphamide, it was initially believed that the drug could be selectively activated in cancer cells because they were believed to contain high levels of phosphoramidase enzymes.

•Drug was activated by cytochrome P450 (CYP) isozymes CYP2B6 and CYP3A4/5 to give a carbinolamine that could undergo ring opening to give the aldehyde.

•The ionized phosphoramide is now electron-releasing via induction and allows aziridinium cation formation to proceed. Acrolein is also formed as a result of this process, which may itself act as an electrophile that has been associated with bladder toxicity.

- To decrease the incidence of kidney and bladder toxicity, the sulfhydryl (-SH) containing agent mesna may be administered and functions to react with the electrophilic species that may be present in the kidney.
- The sulfonic acid functionality serves to help concentrate the material in the urine, and the nucleophilic sulfhydryl group may react with the carbinolamine, aziridinium cation, the chloro substituents of cyclophosphamide, or via conjugate addition with acrolein.
- This inactivation and detoxification may also be accomplished by other thiol-containing proteins such as glutathione. Increased levels of these proteins may occur as cancer cells become resistant to these alkylating agents.
- **Uses** - Multiple myeloma
  - Chronic lymhatic leukemia
  - Acute leukemia
  - Acute lymphoblastic leukemia



Metabolic and chemical activation of cyclophosphamide.

e) Mitomycin-C

•Antibiotic obtained from the cultures of s. cespitosus.

Reduced enzymatically to its semiquinone radical

↓

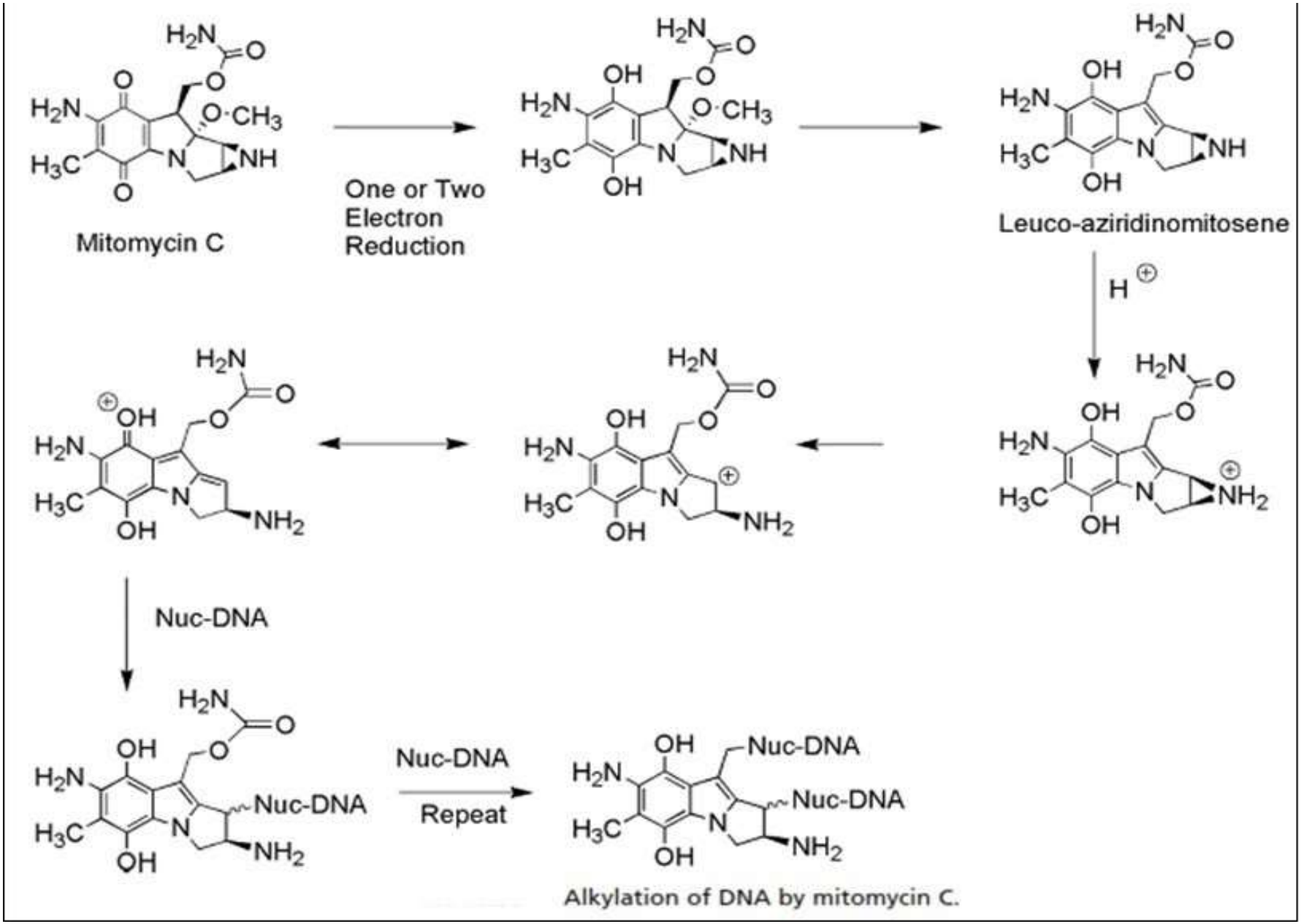
Vinylogous carbinolamine system is obtained

↓

Stable carbonium ion

↓

Alkylates DNA

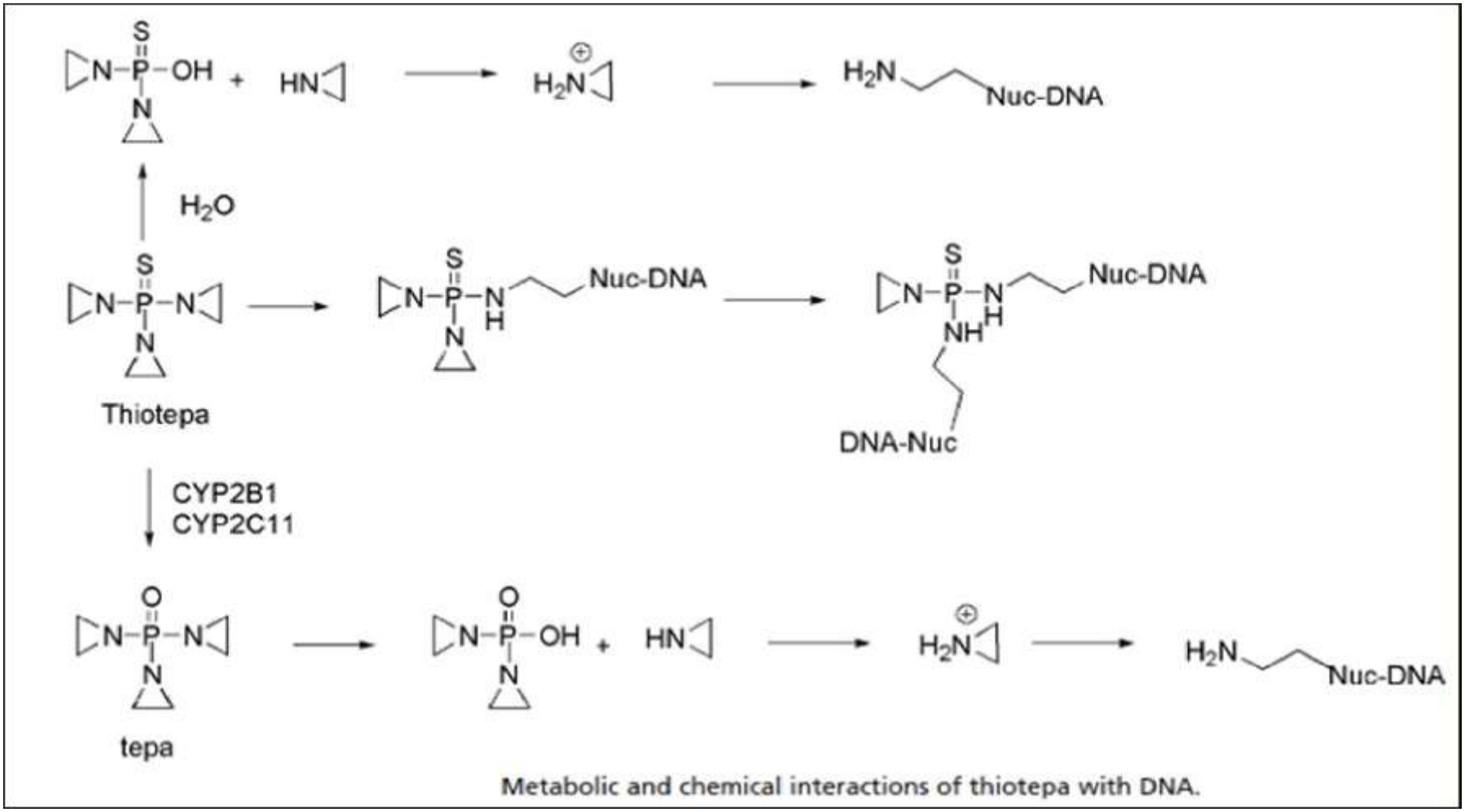


Alkylation of DNA by mitomycin C.

- Alkylation step results from opening of the aziridium ring and also vinylogous carbinolamine
- Causes cross linking in double helical DNA.
- The 2-amino group of guanine residues are alkylated.
- **Uses:**
  - Breast cancer
  - Gastric cancer
  - Pancreatic cancer

2. Ethylenimine - Thio-TEPA, hexamethylmelamine (Altretamine)

Thiotepa- 1,1',1''-phosphorothioyltriaziridine

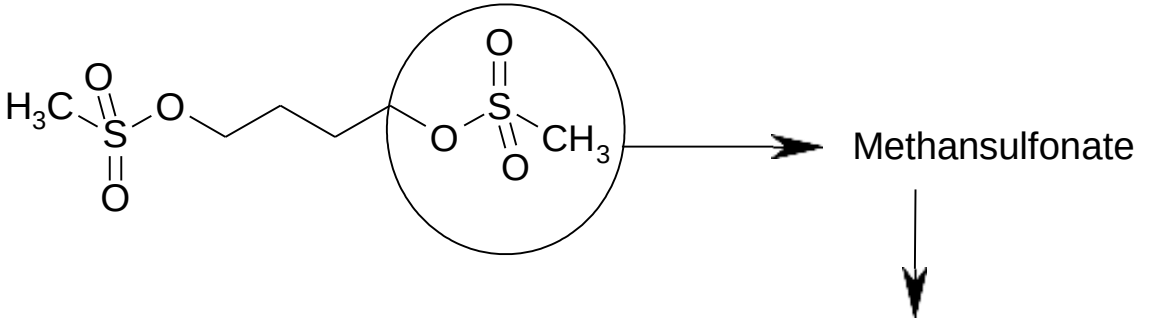


Metabolic and chemical interactions of thiotepa with DNA.

- **Uses:**
  - Breast cancer
  - Ovarian cancer
  - Bronchogenic cancer

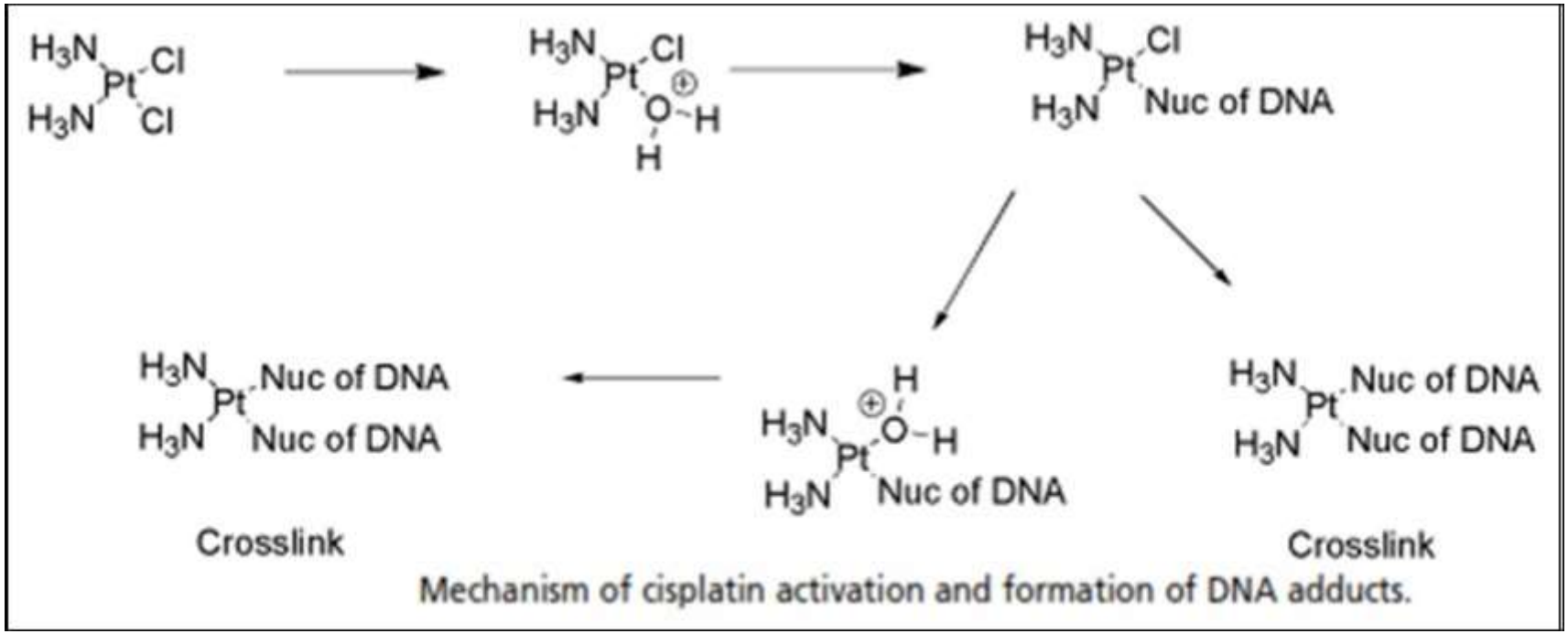
3. Alkyl sulfonates

- **Busulfan-** butane-1,4-diyl dimethanesulfonate
- Busulfan utilizes two sulfonate functionalities as leaving groups separated by a
- four-carbon chain that reacts with DNA to primarily form in- trastrand cross-link at 5’-GA-3’sequences.



- **Uses:**
  - Chronic granulocytic leukemia
  - Bone marrow transplant

- **Carmustine -** 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU)
- **Uses:**
  - Higher lipophilicity, so higher penetration in BBB. It can be used in cerebral tumors.
  - Hodkin's disease
  - Lymphoma
  - **Lomustine -** *N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea (CCNU)
  - **Uses:**
  - Primary and metastatic brain tumors.
  - Secondary therapy in Hodkin's disease.



Mechanism of cisplatin activation and formation of DNA adducts.

C. Antimetabolites

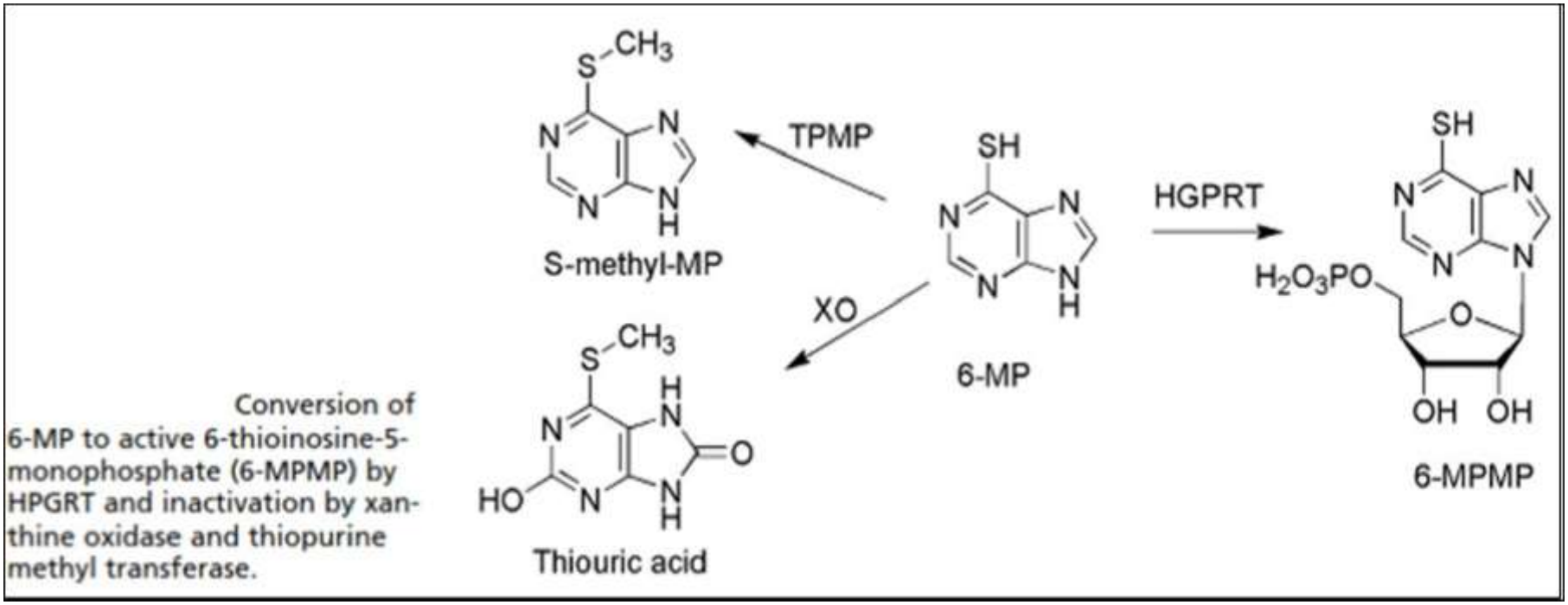
- Antimetabolites are compounds closely related in structure to a cellular precursor molecule, yet these imposter substances are capable of preventing the proper use or formation of the normal cellular product.
- These antimetabolites are similar enough in structure in many cases to interact with the normal cellular process but differ in a manner sufficient to alter the outcome of that pathway.
- Most antimetabolites are effective cancer chemotherapeutic agents via interaction with the biosynthesis of nucleic acids. Therefore, several of the useful drugs used in antimetabolite therapy are purines, pyrimidines, folates, and related compounds.
- The antimetabolite drugs may exert their effects by several individual mechanisms involving enzyme inhibition at active, allosteric, or related sites.

- Most of these targeted enzymes and processes are involved in the regulatory steps of cell division and cell/tissue growth. Often the administered drug is actually a prodrug form of an antimetabolite and requires activation in vivo to yield the active inhibitor.
- The administration of many purine and pyrimidine antimetabolites requires the formation of the nucleoside and finally the corresponding nucleotide for antimetabolite activity.
- An antimetabolite and its transformation products may inhibit several different enzymes involved in tissue growth.
- These substances are generally cell cycle specific with activity in the S phase.
- The purine and pyrimidine antimetabolites are often compounds incorporated into nucleic acids and the nucleic acid polymers (DNA, RNA, etc.).

- The antifolates are compounds designed to interact at cofactor sites for enzymes involved in the biosynthesis of nucleic acid bases. The biosynthesis of these nucleic acid bases depend heavily on the availability of folate cofactors, hence antimetabolites of the folates find utility as antineoplastic agents.

1. Purine analogues:

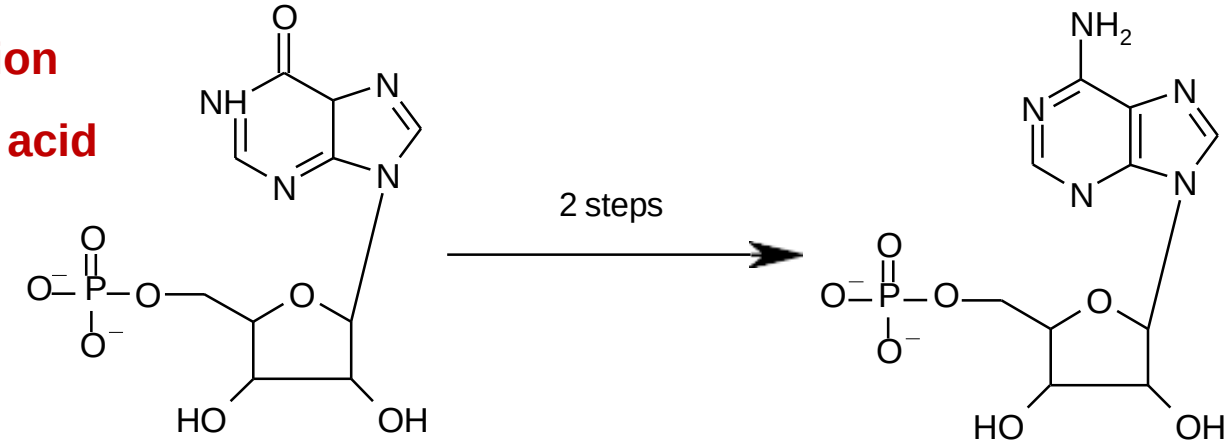
- The design of antimetabolites based on purine structure began with isosteric thiol/sulfhydryl group to replace the 6-hydroxyl group of hypoxanthine and guanine.
- One of the early drug was 6-mercaptopurine (6-MP), the thiol analog of hypoxanthine. This purine requires bio activation to its ribonucleotide, 6-thioinosinate (6-MPMP), by the enzyme HGPRT.
- The resulting nucleotide is a potent inhibitor of an early step in basic purine biosynthesis, the conversion of 5-phosphoribosylpyrophosphate into 5-phosphoribosylamine.
- The ribose diphosphate and triphosphates of 6-mercaptopurine are active enzyme inhibitors, and the triphosphate can be incorporated into DNA and RNA to inhibit chain elongation. However, the major antineoplastic action of 6-MP appears to be related to the inhibition of purine biosynthesis.

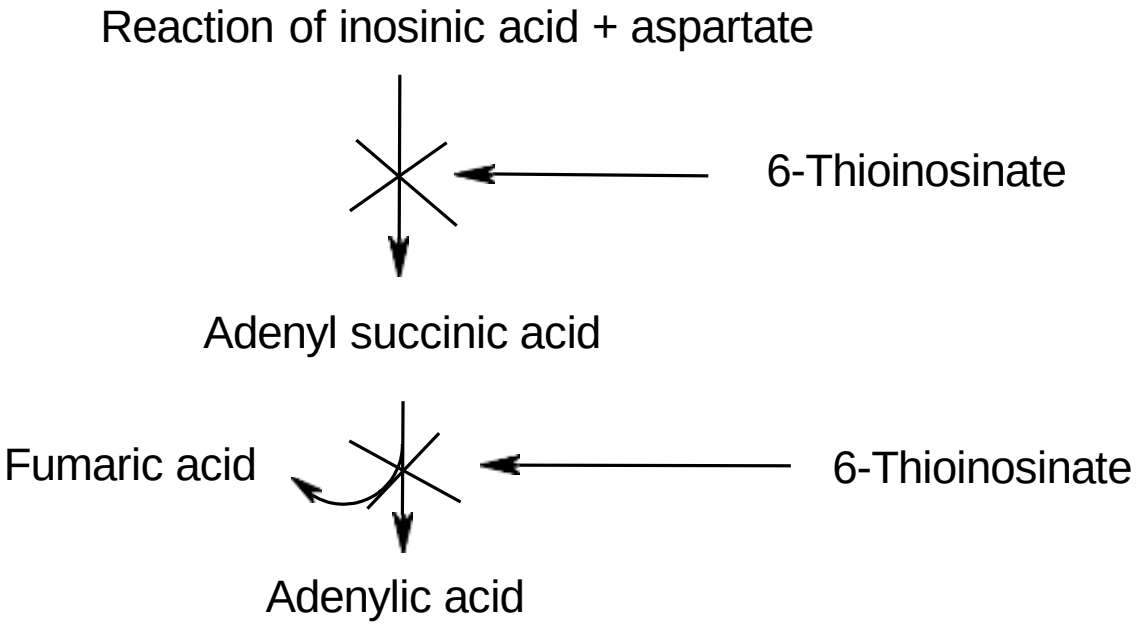


Conversion of 6-MP to active 6-thioinosine-5-monophosphate (6-MPMP) by HPGRT and inactivation by xanthine oxidase and thiopurine methyl transferase.

It also inhibits the conversion

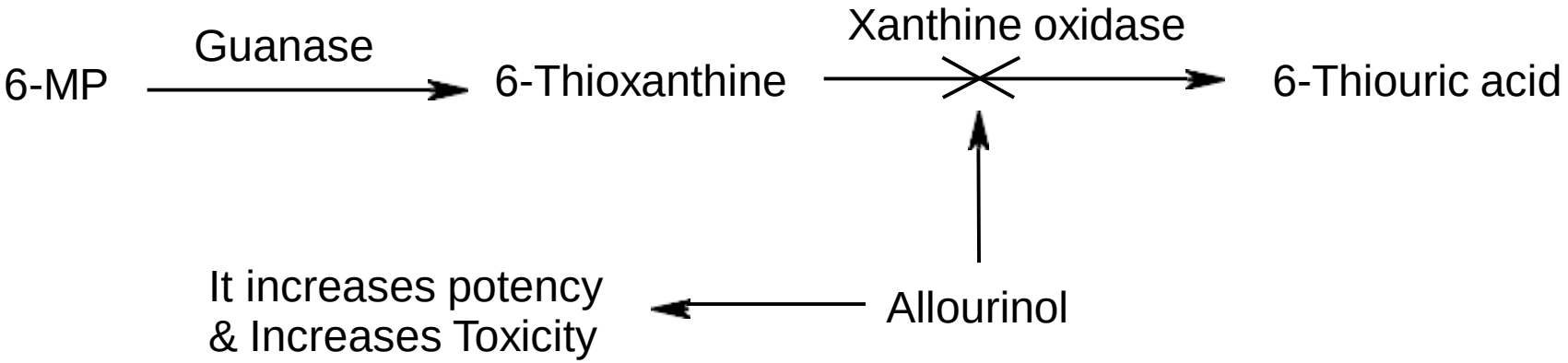
of Inosinic acid to adenylic acid



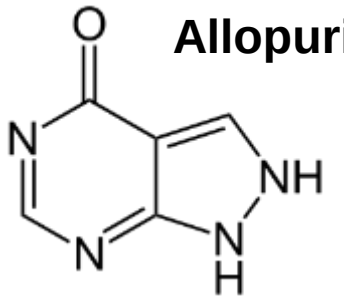


Uses: Acute leukemia

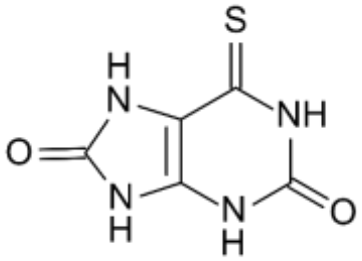
Metabolic degradation of 6-MP by guanase gives 6-thioxanthine.



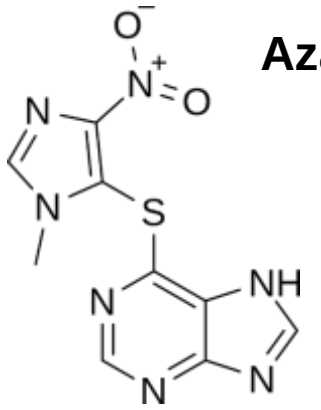
Allopurinol



Thiouric acid



Azathioprine



Allopurinol:

•It is an adjuvant to chemotherapy because it prevents uric acid formation.

•Kidney toxicity caused be the release of purines from destroyed cancer cells.

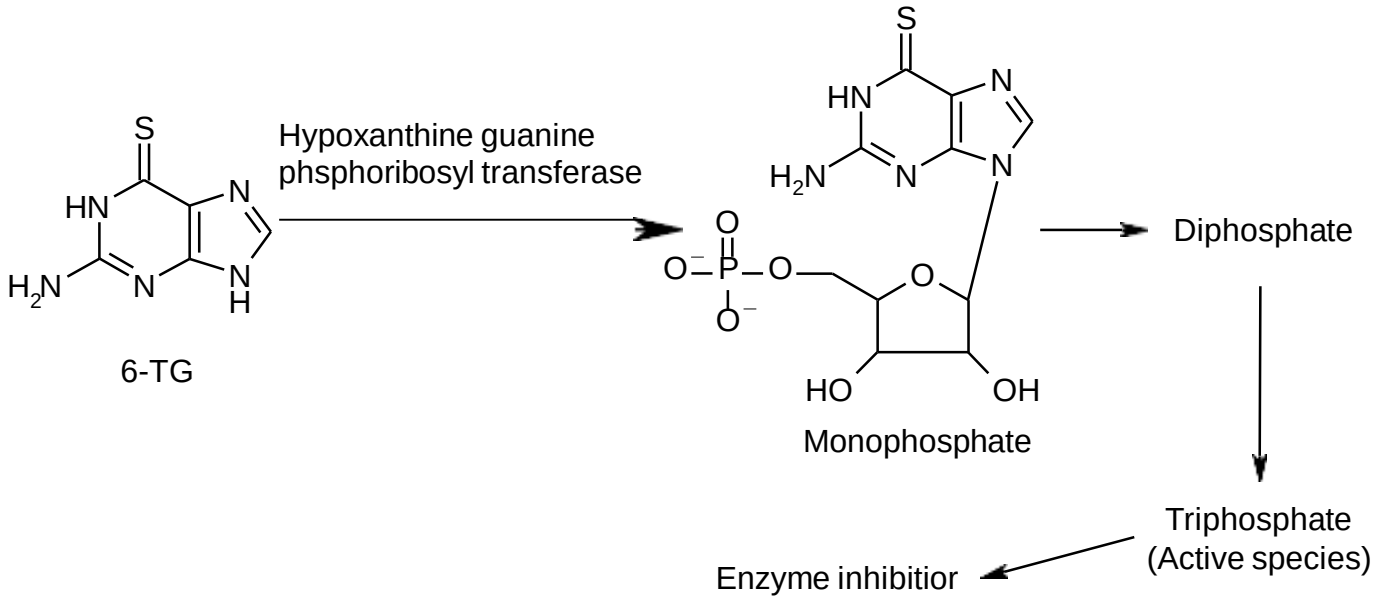
Azathioprine:

• Heterocyclic derivative of 6-MP, azathioprine designed to protect it from catabolic degradation.

•Not significant better antitumor activity than 6-MP.

•Used as an immunosuppressanant.

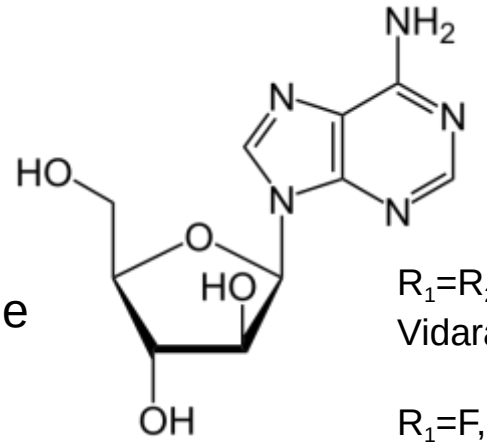
6-Thioguanine (6-TG):



- Thioguanine is also incorporated into RNA & its α-deoxy metabolite is incorporated in to DNA.
- **Uses:** Acute leukemia
- **ADR:** Delayed bone marrow depression, Thrombocytopenia

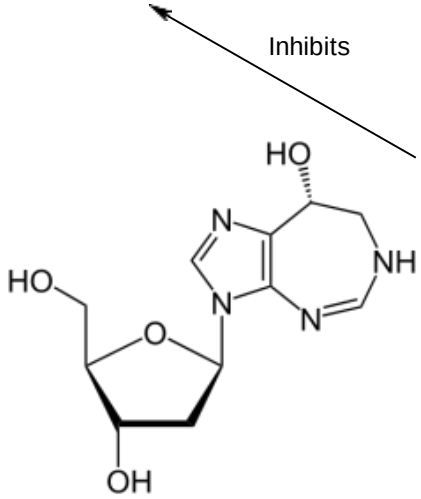
Vidarabine:

- Adenine arabinoside.
- Obtained from the cultures of s. antibioticus.
- Epimeric with D-ribose at 2' position.
- Competitive inhibitor of DNA polymerase enzyme
- Also having antiviral acticity.
- Limited use due to susceptibility to enzyme adenosine deaminase (responsible for resistance)



$R_1=R_2=H$
Vidarabine

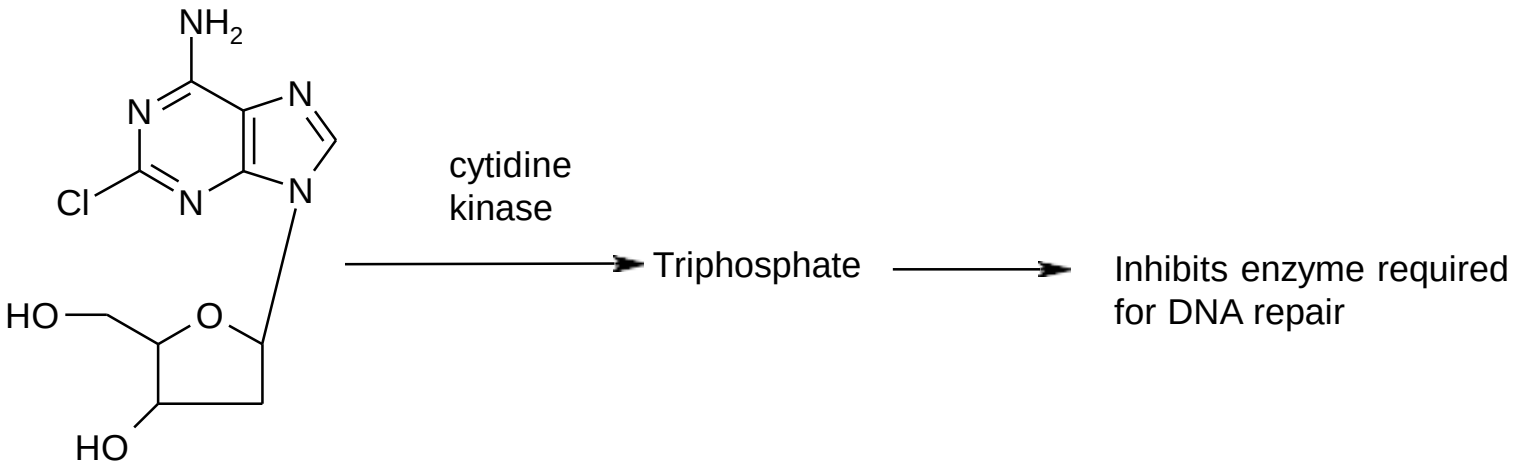
$R_1=F$, $R_2=HOPO_2$
Fludarabine



Pentostatin

Inhibition of the enzyme adenosine deaminase yielding increased cellular levels of deoxyadenosine and deoxyadenosine triphosphate (dATP)

- **2-Chloro-2’-deoxyadenosine (cladarabine):** Resistant to deaminase.



Cladarabine

- Used to treat hairy cell leukemia.

2. Pyrimidine analogues:

•5-fluorouracil (5-FU)

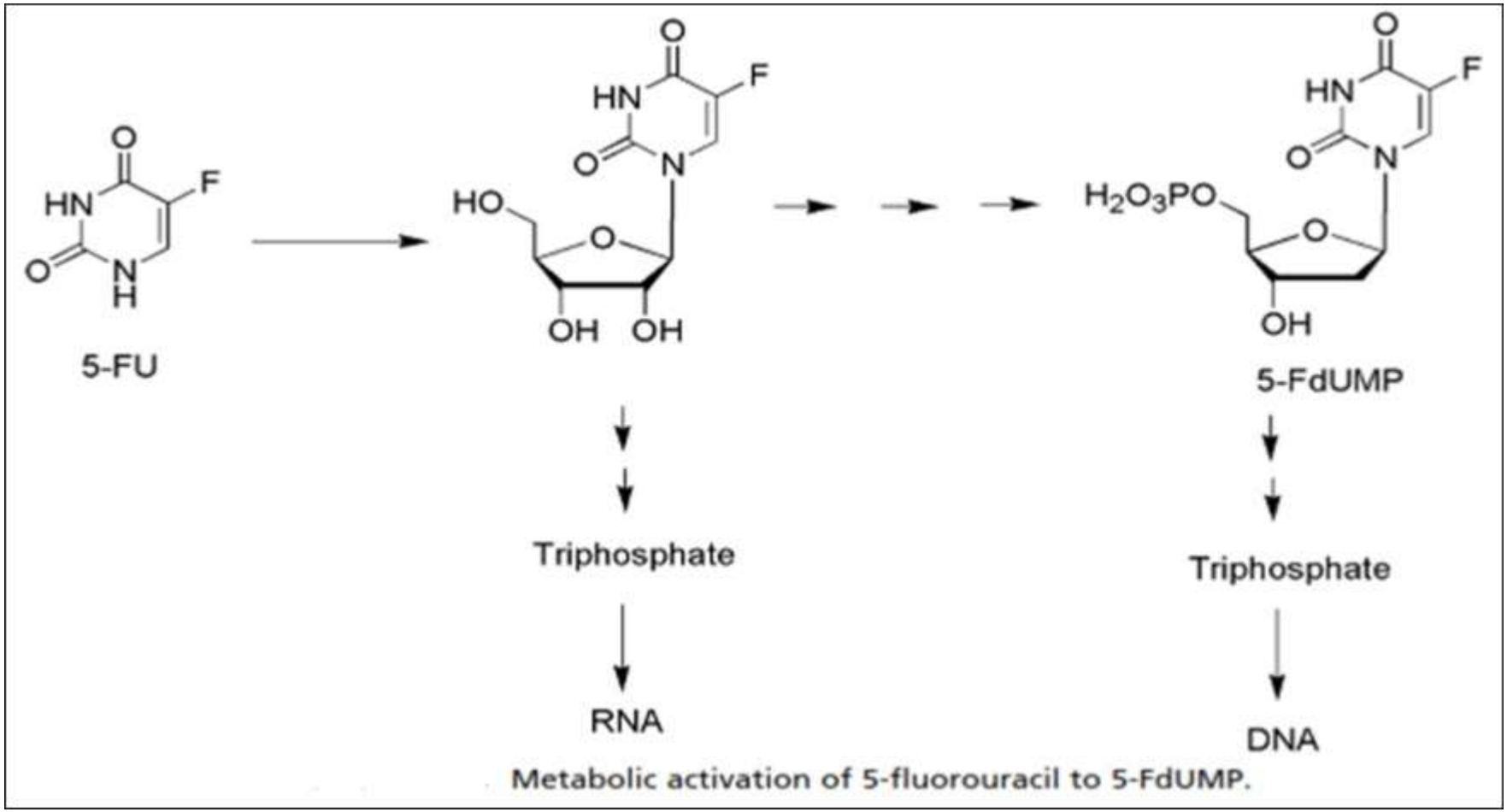
•The pyrimidine derivative 5-fluorouracil (5-FU) was designed to block the conversion of uridine to thymidine.

•The normal biosynthesis of thymidine involves methylation of the 5-position of the pyrimidine ring of uridine.

•The replacement of the hydrogen at the 5-position of uracil with a fluorine results in an antimetabolite drug, leading to the formation of a stable covalent ternary complex composed of 5-FU, thymidylate synthase (TS), and cofactor (a tetrahydrofolate species).

•Anticancer drugs targeting this enzyme should selectively inhibit the formation of DNA because thymidine is not a normal component of RNA..

- TS is responsible for the reductive methylation of de- oxyuridine monophosphate (dUMP) by 5,10-methylenetetrahydrofolate to yield dTMP and dihydrofolate



Metabolic activation of 5-fluorouracil to 5-FdUMP.

- **Uses:** Management of carcinoma of

  - breast

  - Colon

  - Pancreas

  - Rectum

  - Keratoses

- **Adverse effects:**

  - GIT-Hemorrhage

  - Stomatitis

  - Esophagopharyngitis

  - Leukopenia

  - Diarrhoea

Tetrahydrofluoro derivative of 5-FU (Tegafur):

•Slowly get metabolised to 5-FU.

•Active in clinical cancer.

•Less myelosupressive than 5-FU.

Gemcitabine:

•Gemcitabine is the result of fluorination of the 2'-position of the sugar moiety.

•Gemcitabine is the 2',2'-difluoro deoxycytidine species and after its anabolism to diphosphate and triphosphate metabolites, it inhibits ribonucleotide reductase and competes with 2'-deoxycytidine triphosphate for incorporation into DNA.

•**Uses:**

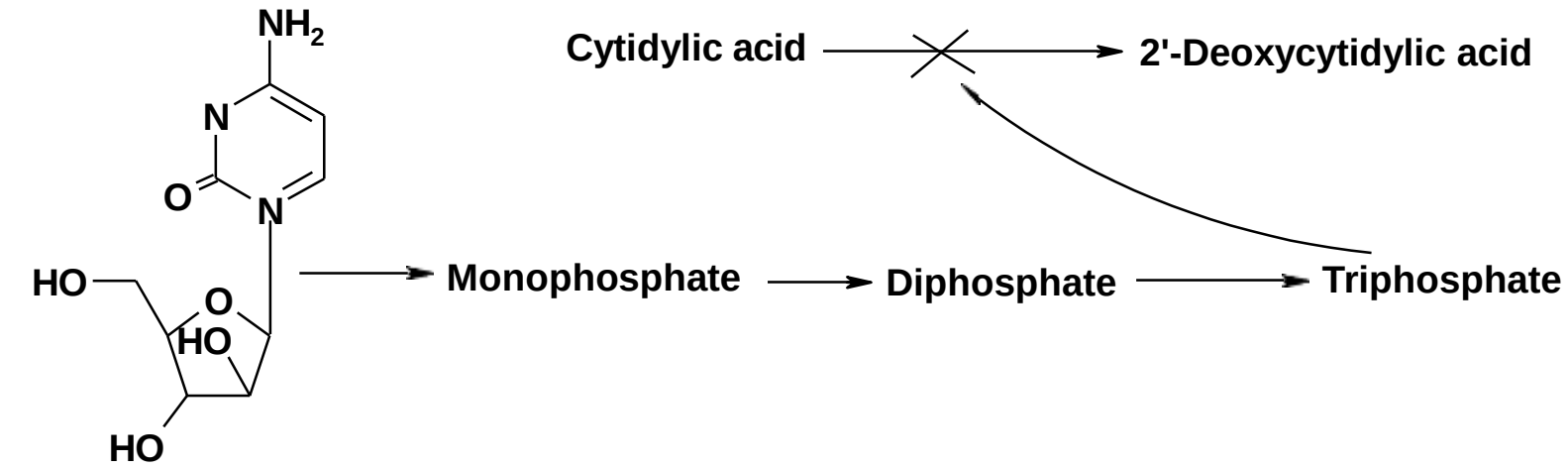
•Used with cisplatin for locally advanced metastatic adeno carcinoma of the pancreas.

•**ADR:** Myelosupression, Teratogenicity, renal toxicity.

Cytarabine:

•Cytosine arabinoside (ara-C or cytarabine) is simply the arabinose sugar instead of ribose, and the only difference in structure is the epimeric hydroxyl group at the 2-position of the pentose sugar.

•This epimeric sugar is similar enough to the natural ribose to allow Ara-C to be incorporated into DNA, and its mechanism of action may include a slowing of the DNA chain elongation reaction via DNA polymerase or cellular inefficiencies in DNA processing or repair after incorporation.

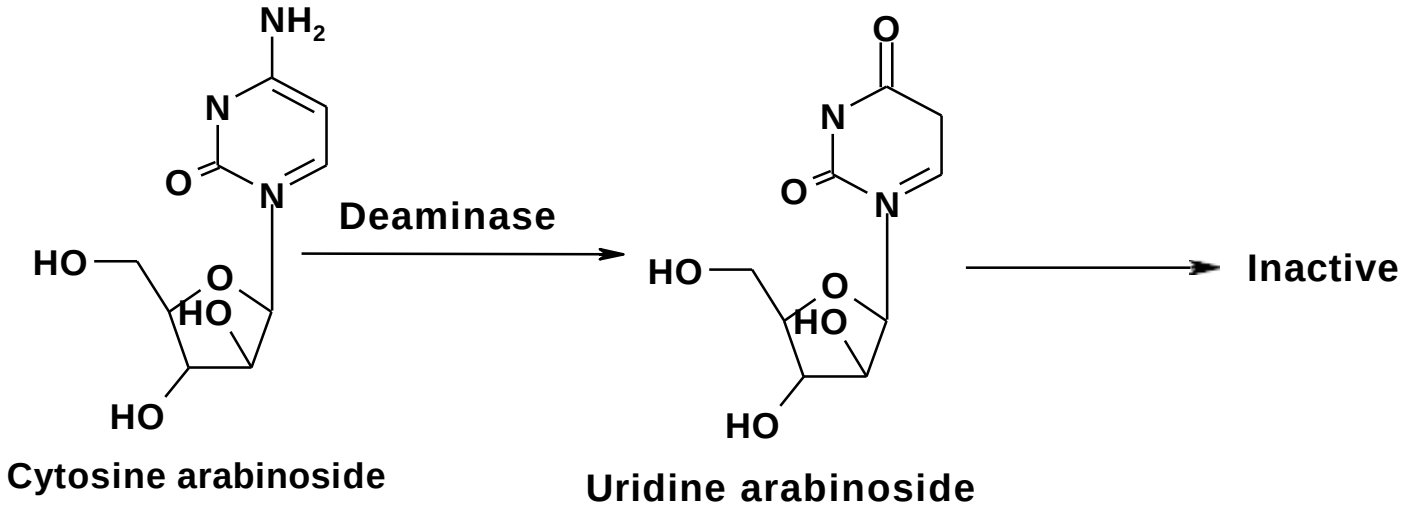


Cytosine arabinoside

- Deaminases causes resistance.

✓ **New analogues of cytarabine is cyclocytidine (ancitabine)**

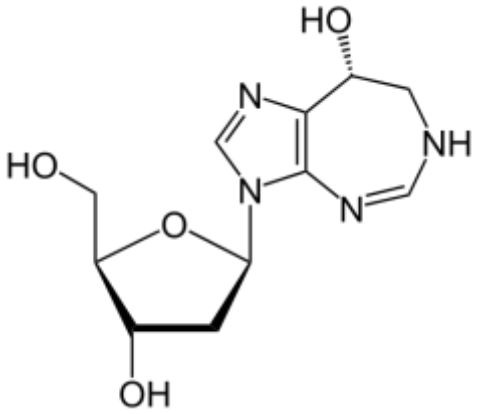
- Resistant to deamination by deaminases laeds to better therapeutic index.
- Uses: Acute granulocytic leukemia



Cytosine arabinoside **Uridine arabinoside**

- **Deaminase inhibitors:**

1) **Pentostatin: Purine analogue**



- 7 membered ring structure

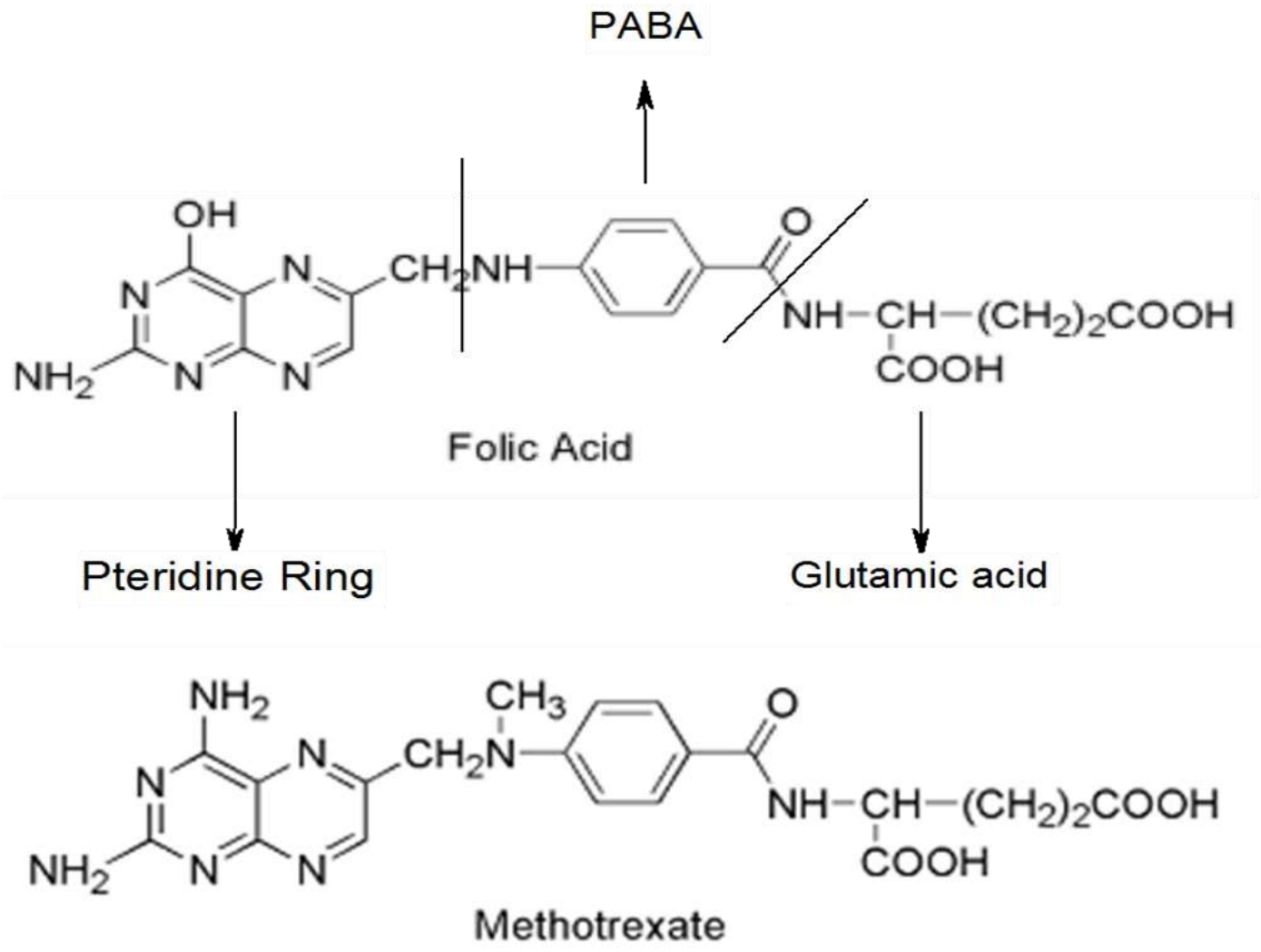
-2’ deoxyformycin

2) EHNA:

- Adenine moiety is modified in the ribose moiety.

- Rationally designed inhibitors

3. Folate antagonists



- Methotrexate is the classic antimetabolite of folic acid structurally derived by *N-methylation* of the para-aminobenzoic acid residue (PABA) and replacement of a pteridine hydroxyl by the bioisosteric amino group.
- The conversion of -OH to $–NH_2$ increases the basicity of N-3 and yields greater enzyme affinity.
- This drug competitively inhibits the binding of the substrate folic acid to the enzyme DHFR, resulting in reductions in the synthesis of nucleic acid bases, perhaps most importantly, the conversion of uridylate to thymidylate as catalyzed by thymidylate synthetase.
- In addition, purine synthesis is inhibited because the *N-10-formyl* tetrahydrofolic acid is a formyl donor involved in purine synthesis.
- THFs are cofactors in at least two key steps in the normal biosynthesis of purines.

- It binds with enzyme so tightly, hence called pseudo-irreversible binding.
- The basis of this binding strength is in the diamino pyrimidine ring, which is protonated at physiological pH.

Uses:

- Acute lymphocytic keukemia
- Prophylexis in meningeal leukemia
- Choriocarcinoma
- Combination therapy for palliative management of breast cancer and osteocarcinoma

ADR: Ulcerative stomatitis, Leukopenia, Abdominal distress

- **Leucoverin** is used in *“Rescue therapy”* with methotrexate.
- It prevents the lethal effects of methotrexate on normal cells by overcoming the blockade of tetrahydrofolinic acid production.
- In addition it inhibits the active transport of methotrexate in to cell and stimulates its efflux.
- Vincristine Increases the cellular uptake of methotrexate.

d. Anticancer Antibiotics

1) Dactinomycin (Actinomycin-D)

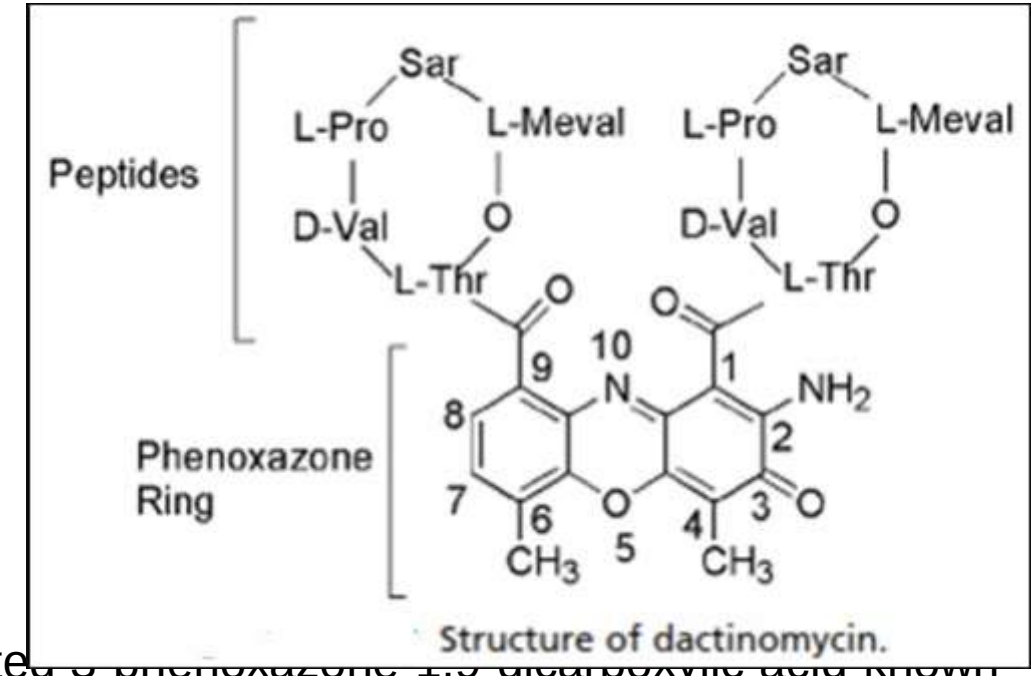
- Obtained from the cultures of

  - Streptomyces parvulus

  - S. Chrysamallus

  - S. Antibioticus

– They are chromopeptide



Structure of dactinomycin.

– Chromophoric part is substituted 3-phenoxazone-1,9-dicarboxylic acid known as “actinosin”.

- **Mechanism of action:**
- Dactinomycin binds noncovalently to double-stranded DNA by partial intercalation between adjacent guanine-cytosine bases resulting in inhibition of DNA function.
- The structural feature of dactinomycin important for its mechanism of cytotoxicity is the planar phenoxazone ring, which facilitates intercalation between DNA base pairs.
- The peptide loops are located within the minor groove and provide for additional interactions.
- The preference for GpC base pairs is thought to be partly related to the formation of a hydrogen bond between the 2-amino groups of guanine and the carbonyls of the L-threonine residues.
- Additional hydrophobic interactions and hydrogen bonds are proposed to form between the peptide loops and the sugars and base pairs within the minor groove.

- The primary effect of this interaction is the inhibition of DNA-directed RNA synthesis and specifically RNA polymerase. DNA synthesis may also be inhibited, and the agent is considered cell cycle specific for the G and S phases.
- **Uses:**

  - Rhabdomyosarcoma

  - Wilm's tumor

  - Life saving for women with chromosarcoma resistant to methotrexate

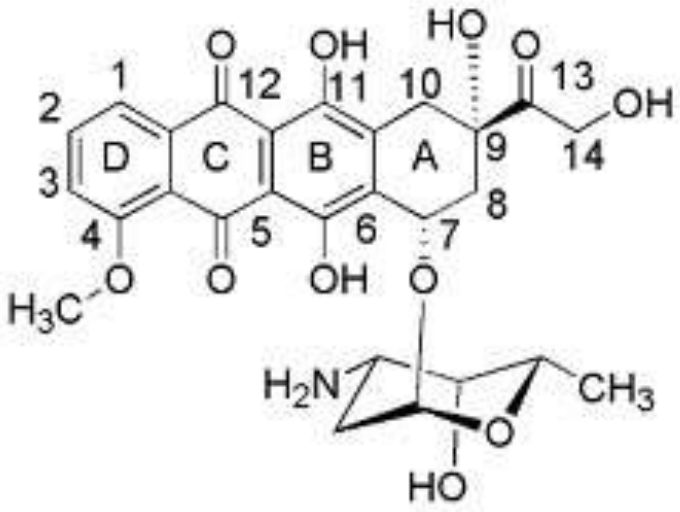
  -In combination with vincristine and cyclophosphamide in solid tumors in children
- **ADR:** Bone marrow depression, Alopecia, erythema

2) Anthracyclines:

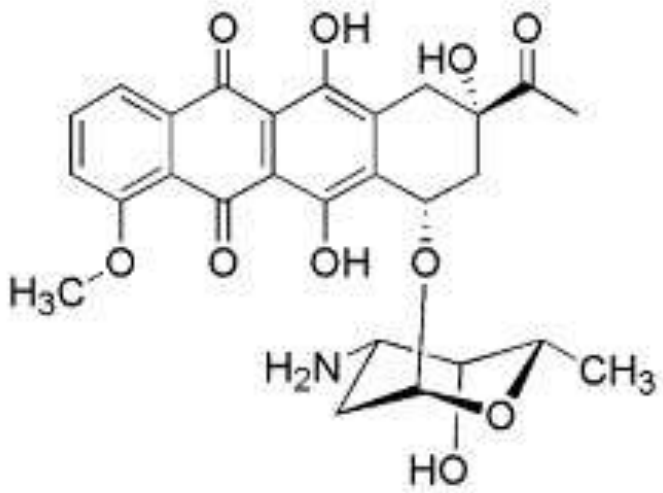
•Obtained from

- S. Coerulorubidus
- S. Peuceticus
- They have tetracycline ring structures with unusual sugar daunosamine attached by glycosidic linkage.

Doxorubicin



Daunorubicin

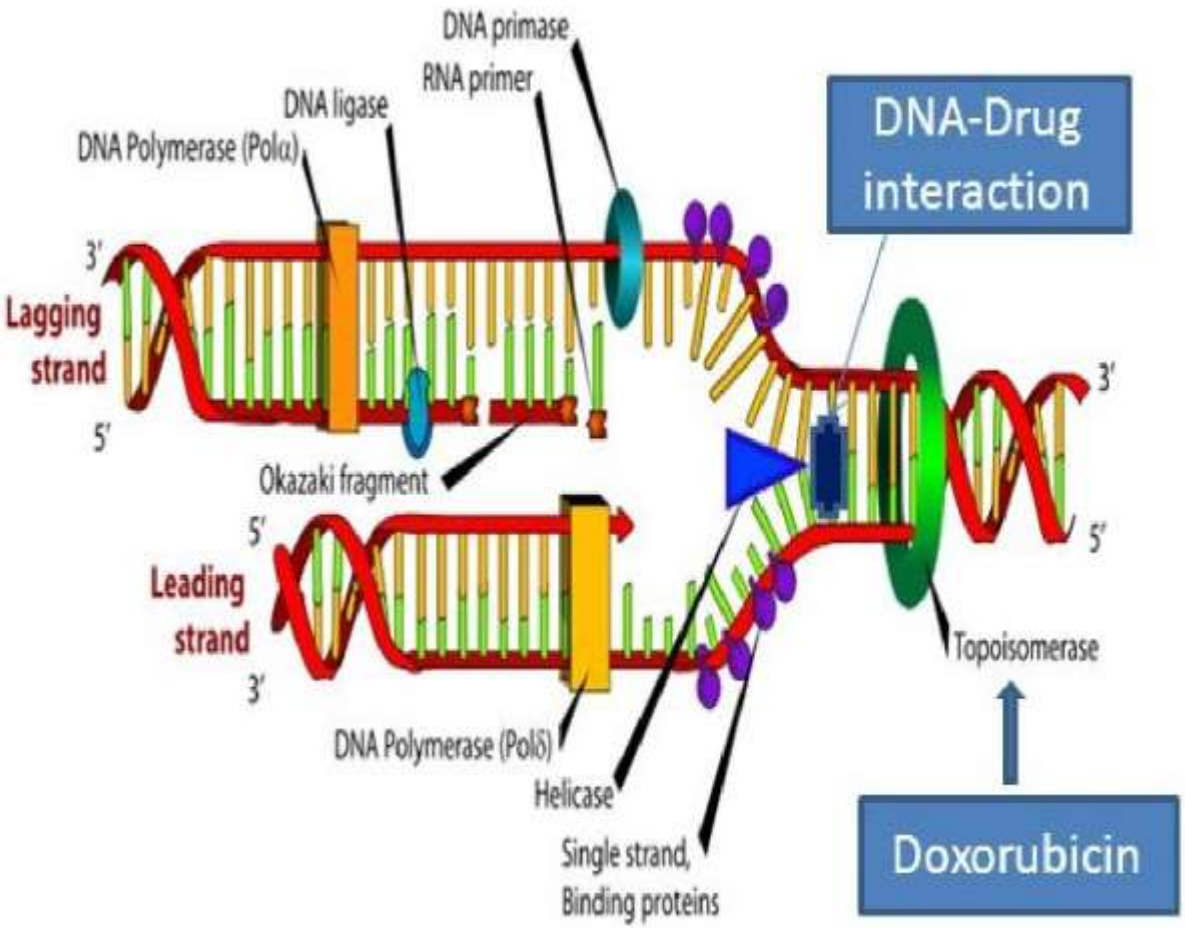


- **Mechanism of action**

1) Intercalation: Doxorubicin intercalates between adjacent nucleotides along the DNA forming a **tight DNA-drug interaction.** This interaction disrupts DNA synthesis and transcription.

2) Enzyme inhibition: Doxorubicin binds and **inhibits topoisomerase II**,a key enzyme involved in DNA synthesis.

3) **Oxygen free radicals** are also produced which damage DNA and prevent DNA synthesis.

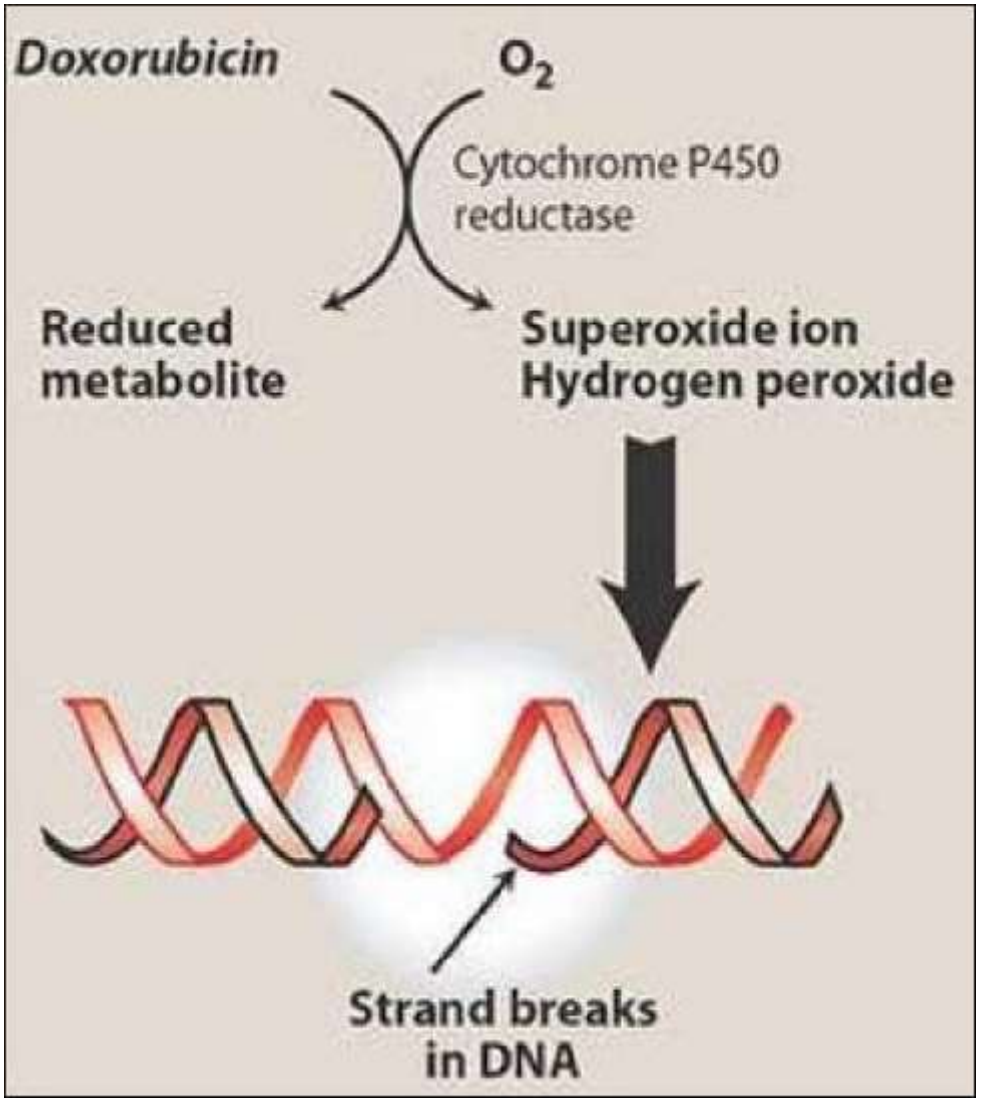


Note:

•Tissue with ample of superoxide Dismutase and glutathione peroxidase activity are protected.

•Cardiac tissue lacks superoxide dismutase and catalase enzynes.

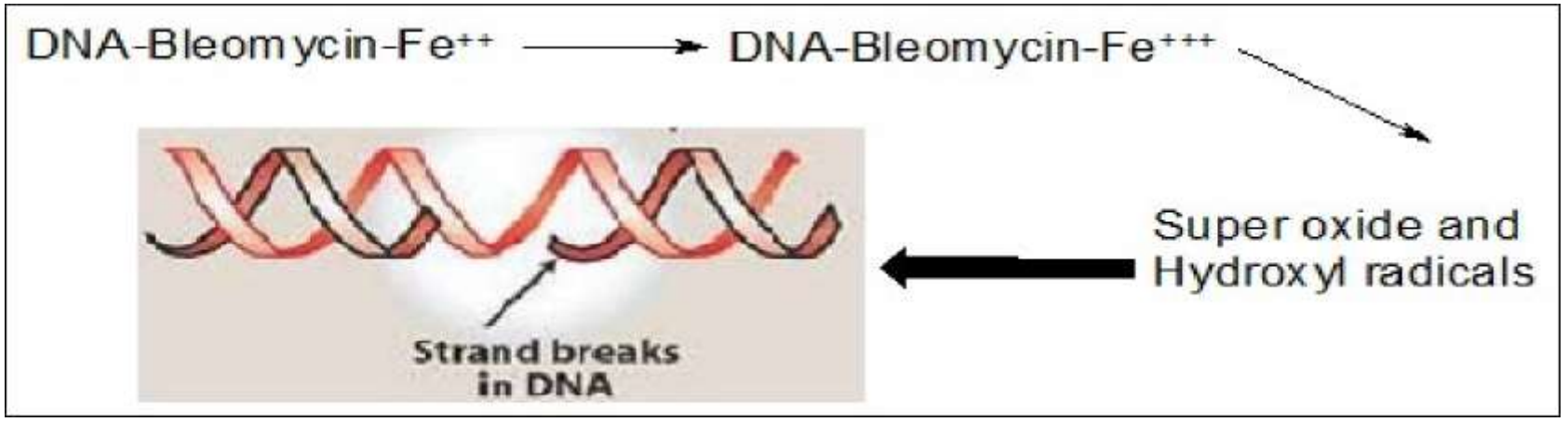
•This may be the reason for the cardiotoxicity of anthra cyclines.



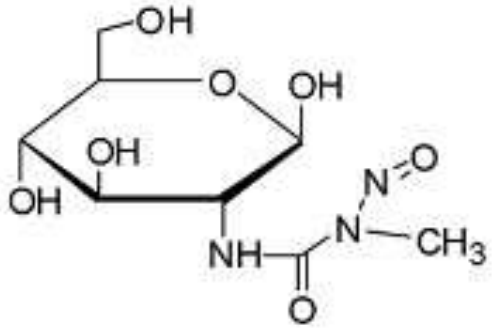
- **Uses:**
- Acute lymphocytic and granulocytic leukemia
- **ADR:**
  - Bone marrow depression
  - Stomatitis
  - Alopecia
  - Cardiac toxicity

3) Bleomycin:

- Glycopeptide isolated from Streptomyces verticillus.
- Mixture of closely related compounds with bleomycin A_2 and B_2 which are available in nature as blue copper chelates.
- **M/A:** The cytotoxic property of bleomycin are due to fragmentation of DNA.
- It appears to cause scission of DNA by interacting with O_2 and Fe^{+2}
- It binds with DNA through its amino terminal peptide and the activated complex generates free radicals that causes DNA breaking.



4) Streptozocin:



Streptozocin

•Isolated from S. achromogens

•It is nitrosoureas derivative of α-Deoxyglucose.

•It is alkylation agent similar in reactivity to other nitrosoureas.

Uses:

•Indicated only for malignant metastatic islet cell carcinoma of pancreas.

ADR: Renal toxicity, mutagenicity.

e) Plant products

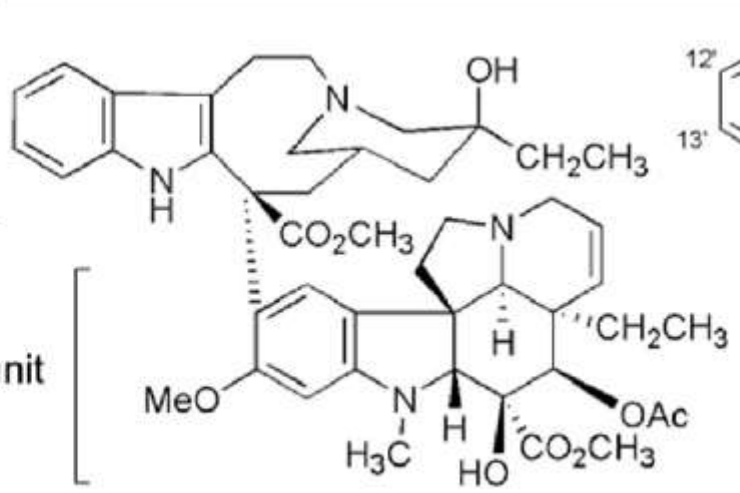
1) Vinca alkaloids

- Binds to the microtubular protein tubulin in a dimeric form
- The drug-tubulin complex adds to the forming end of the
- microtubules to terminate assembly
- Depolymerization of the microtubules occurs
- Resulting in mitotic arrest at metaphase, dissolution of the mitotic spindle, and interference with chromosome segregation
- CCS agents- M phase
- **Uses:** Vinblastine- Systemic Hodgkin's disease, Lymphomas

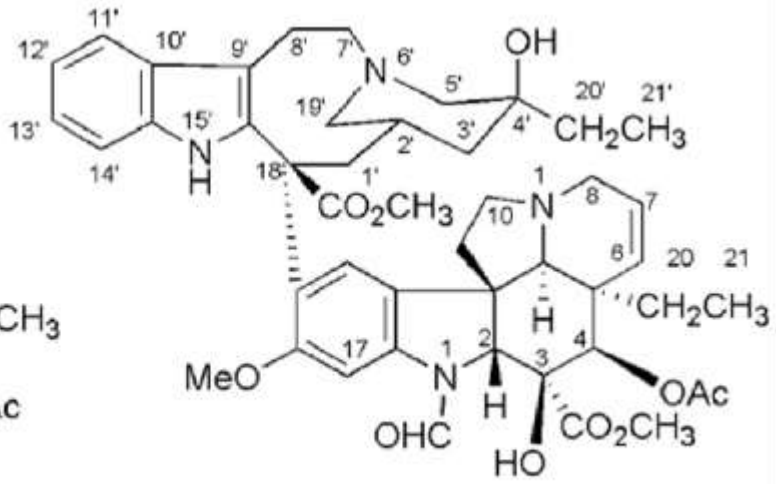
  Vincristine- With prednisone for remission of Acute Leukemia

Catharanthine Subunit

Vindoline Subunit

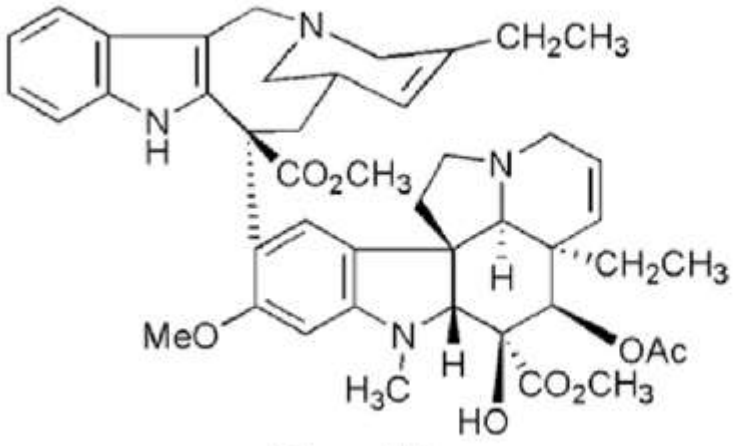


Vinblastine



Vincristine

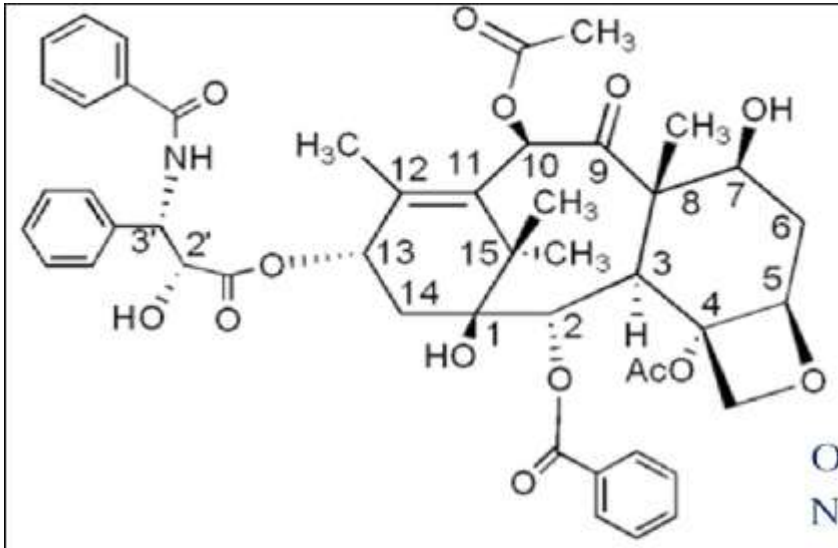
Hodgkin's disease,
Acute lymphocytic leukemia,
Lung cancer



Vinorelbine

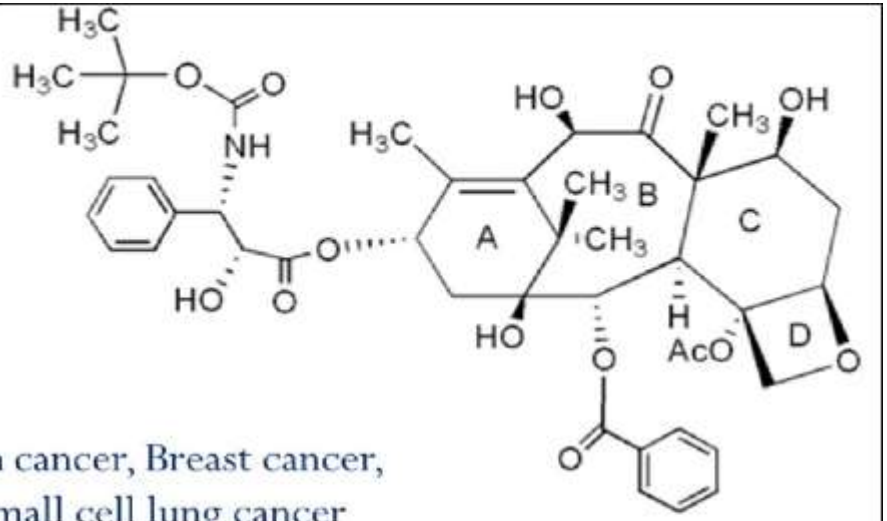
2) Taxanes

- First isolated from bark of Western / Pacific yew (*Taxus brevifolia*)
- It is used for treatment of lung, ovarian and breast cancer.
- Taxanes hyper-stabilizes microtubule structure (freez them). Taxanes binds to the β subunit of tubulin ,the resulting microtubule/ Taxanes complex does not have the ability to disassemble. This adversely affects cell function because the shortening and lengthening of microtubules is necessary for their function.



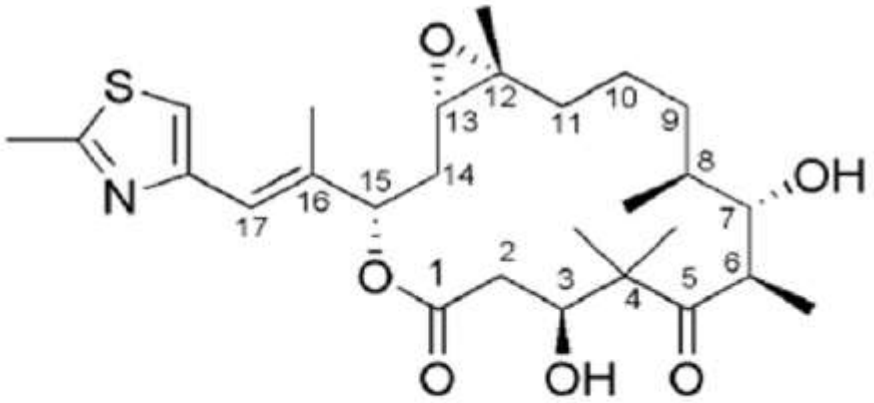
Paclitaxel

Ovarian cancer, Breast cancer,
Non –small cell lung cancer

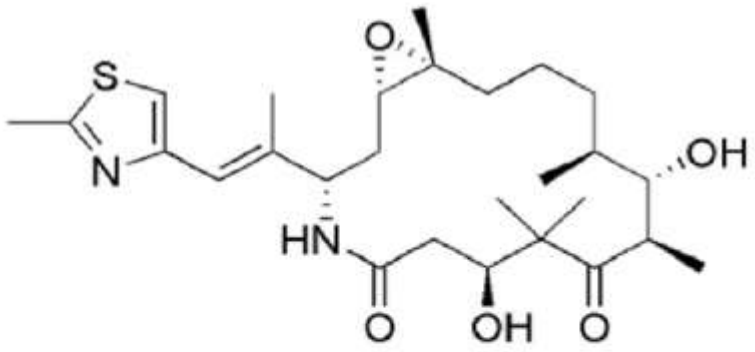


Docetaxel

Semi-synthetic derivatives



Epothilone B



Ixabepilone

3) Epipodophyllotoxin:

•From *Podophyllum peltatum (*May apple)

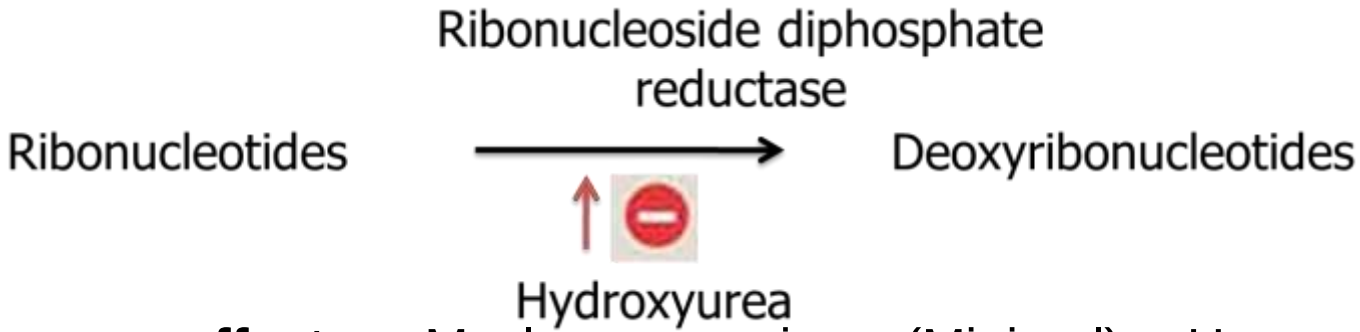
•Resulting in DNA damage through strand breakage induced by the formation of a ternary complex of drug, DNA, and enzyme

•**Uses:** Testicular cancer, small-cell lung carcinoma, Hodgkin lymphoma, carcinoma of breast, Kaposi's sarcoma associated with AIDS

g. Miscellaneous – L-Asparaginase, Asparaginase, Hydroxurea, Mitoxantrone

- **L-Asparaginase:**
- An enzyme isolated from E.Coli.
- Causes catabolic depletion of serum asparagine to aspartic acid and ammonia resulting in reduced blood glutamine levels and inhibition of protein synthesis.
- Neoplastic cells require external source of asparagine.
- Treats childhood acute leukemia
- Can cause anaphylactic shock

- **Hydroxyurea-**
  - An analog of urea
  - Inhibits the enzyme ribonucleotide reductase.
  - Resulting in the depletion of deoxynucleoside triphosphate pools
  - Thereby inhibiting DNA synthesis
  - S-phase specific agent
  - Treats melanoma and chronic myelogenous leukemia



Adverse effects: Myelosuppression (Minimal), Hypersensitivity, Hyperglycemia, Hypoalbuminemia

- **Mitoxantrone**
- Structure resembles the anthracyclines
- Binds to DNA to produce strand breakage
- Inhibits DNA and RNA synthesis
- Treats pediatric and adult acute myelogenous leukemia, non-Hodgkin's lymphomas, and breast cancer
- Causes cardiac toxicity

h. Hormonal drugs

- It involves the manipulation of the endocrine system through exogenous administration of specific hormones, particularly steroid hormones, or drugs which inhibit the production or activity of such hormones.

- Because steroid hormones are powerful drivers of gene expression in certain cancer cells, changing the levels or activity of certain hormones can cause certain cancers to cease growing, or even undergo cell death.

1. **Glucocorticoids** – Prednisolone and others

- Glucocorticoids such as prednisolone and dexamethasone have marked inhibitory effects on lymphocyte proliferation.
- Used in the treatment of leukaemias and lymphomas.
- Their ability to lower raised intracranial pressure, and to mitigate some of the side effects of anticancer drugs, makes them useful as supportive therapy .

Examples

Generic Name	Brand Name
dexamethasone	Dexamethasone Intensol
hydrocortisone	Cortef
methylprednisolone	Medrol
prednisolone	Orapred, Pediapred, Prelone
prednisone	Prednisone Intensol

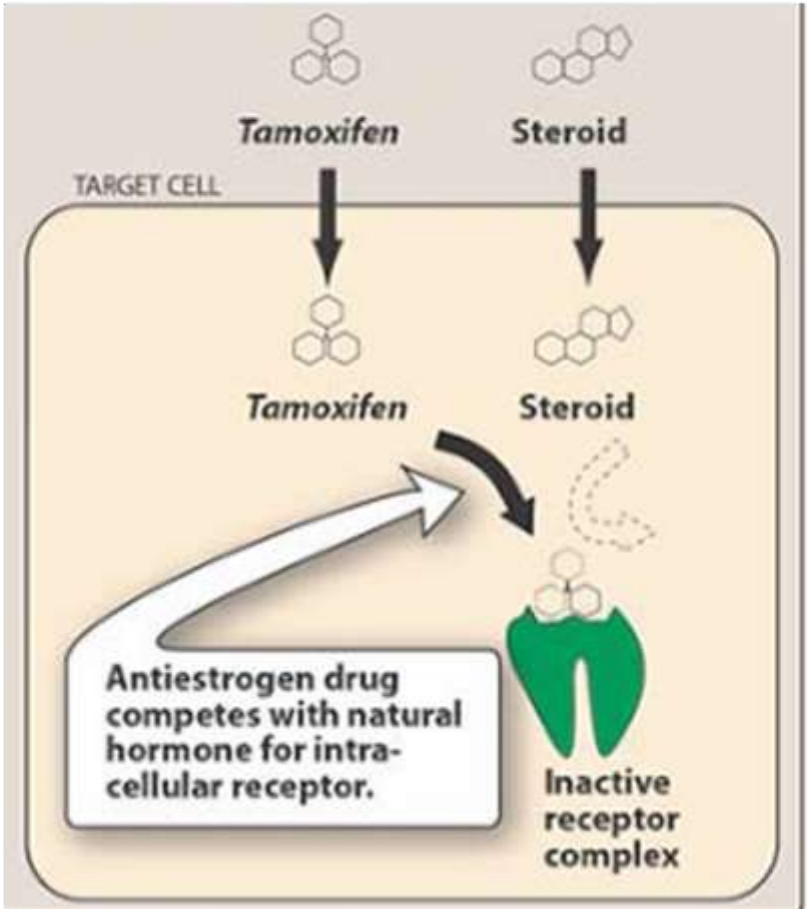
2. Estrogens

- Physiological antagonists of androgens.
- Thus used to antagonize the effects of androgens in androgen dependent prostatic cancer.
- The agonist is occasionally used to treat prostate cancer through suppression of testosterone production.
- Diethylstilbestrol and ethinyloestradiol are two oestrogens used clinically in the palliative treatment of androgen-dependent prostatic tumours.
- The latter compound has fewer side effects. These tumours are also treated with gonadotrophin-releasing hormone analogues
- Oestrogens can be used to recruit resting mammary cancer cells into the proliferating pool of cells, thus facilitating killing by other cytotoxic drugs

3. Selective estrogen receptor modulators- Tamoxifen, Toremifene

- Tamoxifen : Non steroidal antiestrogen

Antagonistic:
Breast and blood vessels



Agonistic:
Uterus, bone, liver, pitutary

- Selective estrogen receptor modulator (SERM), have both estrogenic and anti-estrogenic effects on various tissues
- Binds to estrogen receptors (ER) and induces conformational changes in the receptor
- Has anti-estrogenic effects on breast tissue.
- The ability to produce both estrogenic and anti-estrogenic affects is most likely due to the interaction with other coactivators or corepressors in the tissue and the binding with different estrogen receptors, ER□ and ER□
- Subsequent to tamoxifen ER binding, the expression of estrogen dependent genes is blocked or altered
- Resulting in decreased estrogen response.
- Most of tamoxifen's affects occur in the G1 phase of the cell cycle

Therapeutic Uses

- Tamoxifen can be used as primary therapy for metastatic breast cancer in both men and postmenopausal women
- Patients with estrogen-receptor (ER) positive tumors are more likely to respond to tamoxifen therapy, while the use of tamoxifen in women with ER negative tumors is still investigational
- When used prophylactically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease