ANTI-NEOPLASTIC AGENTS

2

OBJECTIVES

- Alkylating Agents
- Mechanism of Action of Alkylating Agents
- Cross linking with second Guanine
- Antimetabolites
- Antibiotics
- Plant Products Miscellaneous Agents

INTRODUCTION

Antineoplastic agents are used to treat the cancer. Cancer is a group of disease involving an abnormal and uncontrolled cell division in most of the normal body cells. This new cell growth invade the surrounding structures. The cancer may be benign and malignant. Benign tumors do not metastaise (spread of cancer to other locations in the body) but malignant do metastaise. Cancer is classified according to the type of cell in which new growth occurs as.

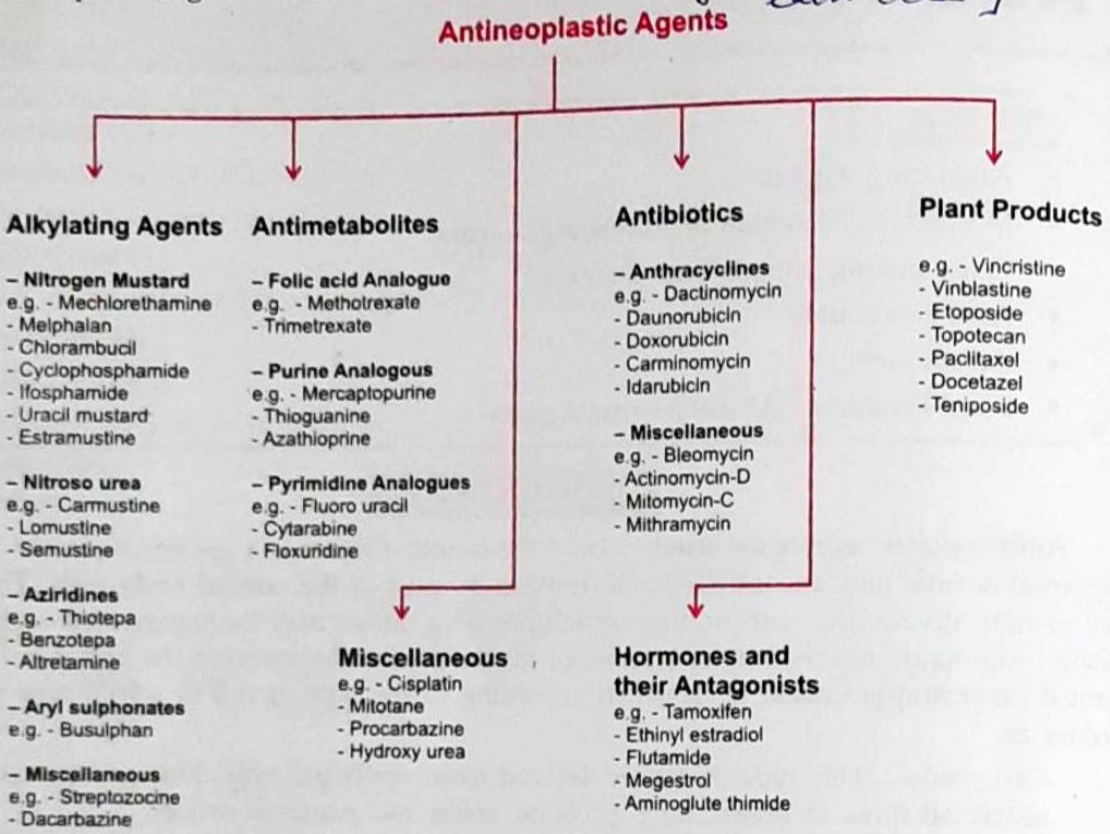
1. **Carcinoma** : This type of cancer derived from epithelial cells. This group represents nearly all those in breast, lung, prostate, colon and pancreas cancer.
2. **Sarcoma** : This type of malignant tumor arises from transformed cells of connective tissue. This tumor is made of cartilage, fat, vascular, cancellous bone and hematopoietic tissues.
3. **Leukemia and Lymphoma** : These two malignant tumors derived from haematopoietic (blood cell forming). This tumor mature in lymph nodes and blood respectively. Lymphomas are Hodgkin Lymphoma and the non-Hodgkin Lymphomas. The enlarged Lymph nodes are usually painless.
4. **Germ cell tumor** : It is derived from germ cells. It may be malignant or benign. Germ cells normally found in the ovary and testis.
5. **Blastoma** : It is common in children. It is a tumor that resembles an immature or embroynic tissue. Examples are nephroblastoma, medulloblastoma and retinoblatoma.

Cancer can be treated by many ways including chemotherapy, surgery, radiation therapy and neoplasting agents. The antineoplastic agents are the specialized drugs used primarily to treat cancer. The first antineoplastic agents were used in 1940s, which were made naturally or synthetically. Antineoplastic agents can be used alone or in combination with other antineoplastic drugs. These drugs destroy the cancer cells but have some side effects like nausea, hair loss, mouth ulcer and lowering of the blood cells.

Antineoplastic agents have different mode of action and their effect depends upon cytotoxic action which is selective for benign cells i.e. rapidlly dividing cells.

Classification :

Antineoplastic agents can be classified as follows : [give one structure from each class]

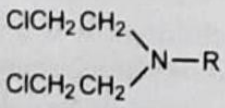


ALKYLATING AGENTS

Alkylating agents chemically bound to nucleic acid and bring about the changes in DNA and RNA of cells. This include cross-linking between strands of DNA which results in breaking of the nucleic acid which will not be replicated. This altered DNA unable the functioning of the cell, resulting in cell death. Normal cells may also be affected.

Alkylating agents are the derivatives of nitrogen mustards, first alkylating agents, tested as anticancer was-

Das having mustard like smell.

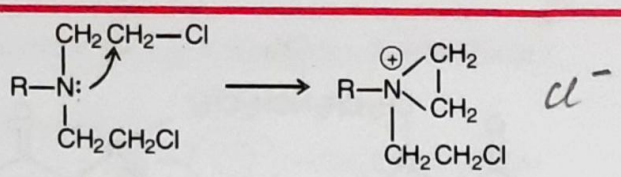


Nitrogen Mustard

Further development in nitrogen mustard gave new alkylating agents, found to have cytotoxic action against cancer.

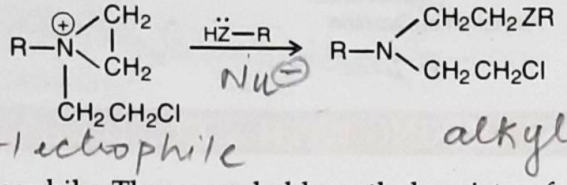
MECHANISM OF ACTION OF ALKYLATING AGENTS

All alkylating agents have common feature that at physiological pH they form aziridinium ion. This aziridinium ion then alkylate the components of DNA in biological system.



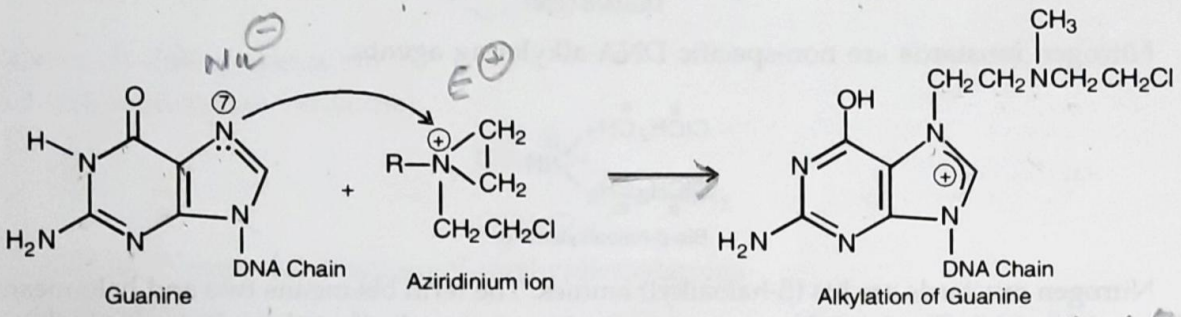
Aziridinium ion

This aziridinium ion acts as a electrophile and alkylate the nucleophilic centres like amino, sulphadryl groups, hydroxyl or carboxyl groups in biological system.

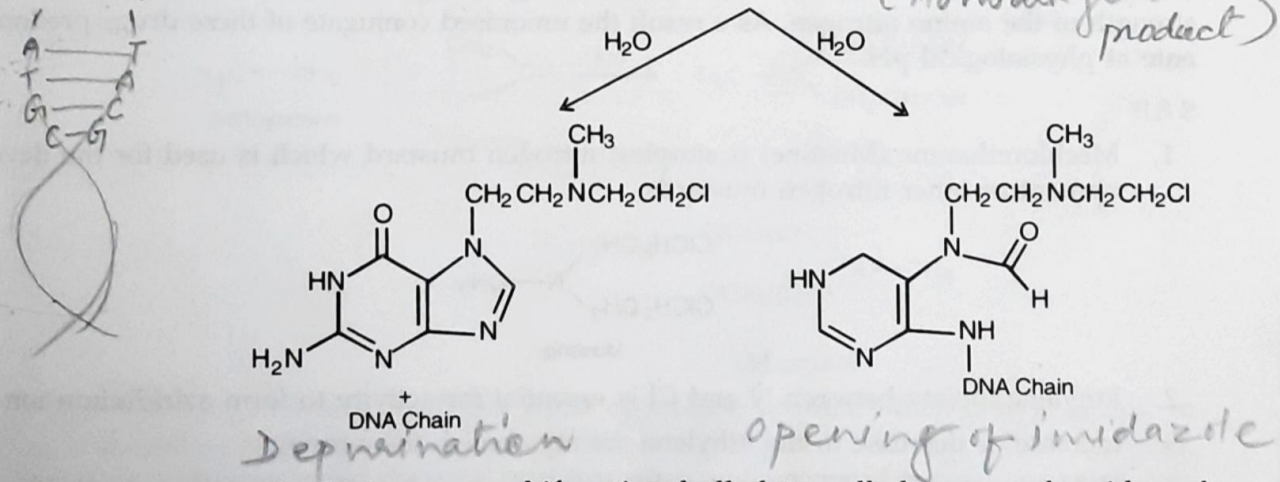


Here Z may be nucleophile. The second chloroethyl moiety of aziridinium ion can react by repetition of intramolecular cyclization sequence.

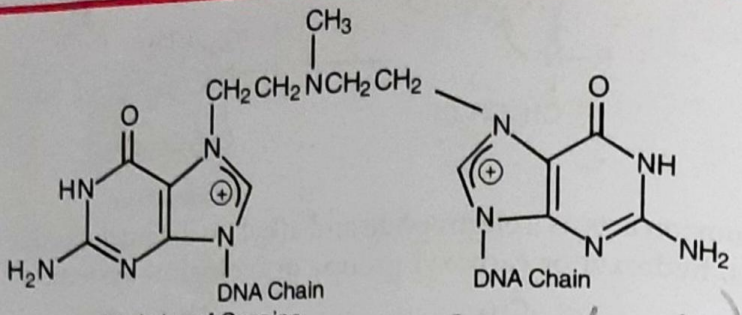
The alkylating agents alkylate the DNA at 7th position of guanine residue (oxo tactomer favoured). After alkylation guanine residue become more acidic and enol tautomer preferred. In this enol form, Guanine can make abnormal base pair with thymine. There may be possibility to opening of imidazole ring or depurination by excision of Guanine residue.



(Monoalkylated product)



Nitrogen mustard which acts as a bifunctional alkylator, alkylate second residue of guanine, results in the cross-linking of two nucleic acid chains. In this way nucleic acid function gets impaired and leads to cytotoxic effect of alkylating agents.



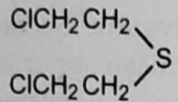
Alkylation of Guanine

(Dialkylated product)

CROSS LINKING WITH SECOND GUANINE

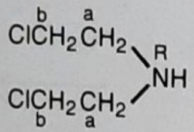
A) NITROGEN MUSTARD

These are cytotoxic chemotherapeutic agents similar to sulfur mustard or mustard ga



Mustard Gas

Nitrogen mustards are non-specific DNA-alkylating agents.

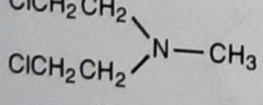


Bis-β-haloalkylamine

Nitrogen mustards are bis (β-haloalkyl) amines. The term bis means two and halo mean halogen (chloride). The two chlorine atoms having strong –I effect thus decrease the bas strength of the amino nitrogen. As a result the unionised conjugate of these drugs predom nate at physiological pH.

SAR

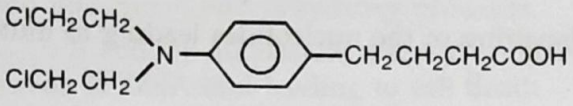
1. Mechlorethanine (Mustine) is simplest nitrogen mustard which is used for the deve opment of other nitrogen mustards.



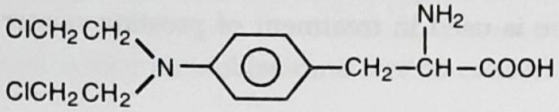
Mustine

2. Ethylene moiety between N and Cl is essential for activity to form aziridinium ion.
3. Increase or decrease in the ethylene moiety abolish the activity.
4. Halogen other than Cl decreases the activity.
5. Methyl group which is having weak electron donating property can be replaced b electron withdrawing groups in order to slow down the formation of aziridinium io

hence increases the activity for e.g. Chlormabucil, Melphalam

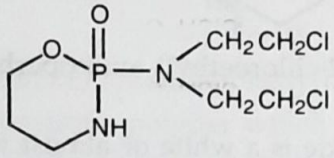


Chlorambucil



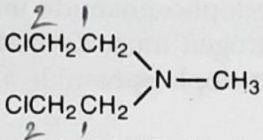
Melphalan

6. Methyl group can be replaced by highly electron withdrawing groups for e.g. cyclophosphamide.



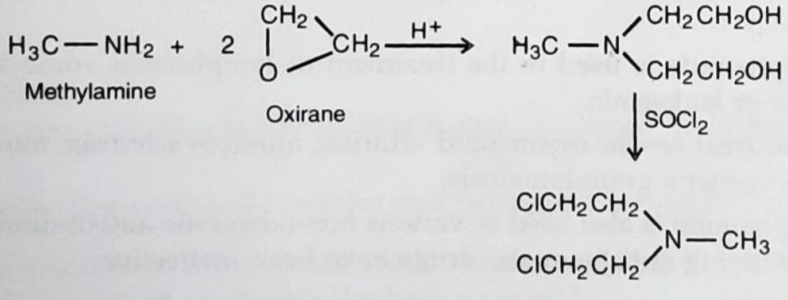
Various alkylating agents are :

1) Mechlorethamine (Mustine)



IUPAC Name : 2,2-Dichloro-N-methyldiethylamine

Synthesis



(Mustine)

Properties : It is a white or almost white crystalline powder which is hygroscopic in nature. It should be kept in well-closed container, in a cool place. It is very soluble in water. In the body it undergoes rapid chemical transformation and converted to reactive aziridinium ion. It is excreted unchanged in urine.

Mechanism of Action : Mustine can act by three different ways-

a) It damages DNA via the formation of cross link.

b) It prevents the DNA synthesis and RNA transcription by attachment of alkyl group DNA bases.

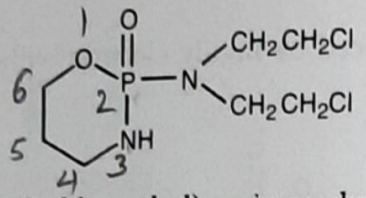
c) By induction of mispairing of the nucleotides leading to mutations.

Uses :

1. It is used in the treatment of Hodgkin's disease.
2. It is used topically in the treatment of mycosis fugoides (T-cell lymphoma).
3. Its estrogen analogue is used in treatment of prodrug.

2) Cyclophosphamide

(prodrug)



IUPAC Name : (RS)-2-Bis-(2-chloroethyl) aminoperhydro-1,3,2- oxazaphosphorinan 2-oxide monohydrate.

Propeties : Cyclophosphamide is a white or almost white crystalline powder which hygroscopic in nature and soluble in water. It should be stored in well closed container in cool place. It is well absorbed orally and activated in liver where cytochrome-450 mixe function oxidase system converts cyclophosphamide into 4-hydroxy cyclophosphamide, cy totoxic phosphoramide and non nitrogen mustard metabolites. Further cyclophosphamid by enzymatic oxidatoin gives 4-oxocyclophosphamide and carboxy phosphamide as inactiv metabolites.

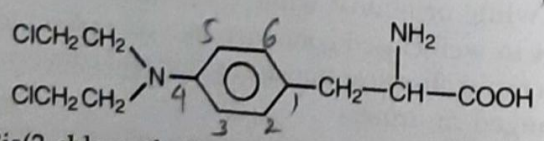
Mechanism of Action : The active metabolite of cyclo phosphamide i.e. phosphoramid mustard forms DNA cross links between and within DNA strands at guanine N-7 positions This is irreversible and leads to cell death.

Uses :

1. Cyclophosphamide is used in the treatment of lymphomas, some solid tumors and some forms of leukaemia.
2. It is used to treat severe rheumatoid arthritis, multiple sclerosis, minimal change disease and wegener's granulomatosis.
3. Cyclophosphamide is also used in various non-neoplastic autoimmune diseases where disease-modifying antirheumatic drugs have been ineffective.

3) Melphalan

phenyl alanine



IUPAC Name : 4-Bis(2-chloroethyl)amino-L-phenylalanine.

Properties : Melphalan is white or almost white crystalline powder which is practically

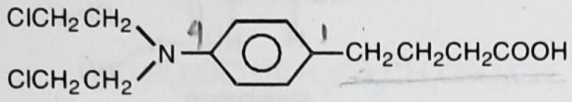
insoluble in water but soluble in dilute mineral acids. It should be kept in well closed container and protected from light. Melphalan is incompletely absorbed. It is not actively metabolised and converted into mono and dihydroxy products.

Mechanism of Action : It acts by alkylation, alters the nucleotide guanine by causes cross linking between strands of DNA and leading to cell death.

Uses :

1. Melphalan is used mainly in the treatment of multiple myeloma and carcinoma of breast and ovary.
2. It is also used to treat ocular retinoblastoma (retina cancer).

4) Chlorambucil



IUPAC Name : 4-[4-Bis (2-chloroethyl)aminophenyl]butyric acid.

Properties : It is a white crystalline powder which is practically insoluble in water, soluble in dilute solutions of alkali hydroxides. It is stored in air tight container and protected from light. It is rapidly absorbed from the G.I.T. and metabolised in liver into its phenylacetic acid mustard (active metabolite).

Mechanism of Action : Chlorambucil alkylates and cross-links DNA during DNA replication and damage the DNA in a cell.

Uses :

1. Chlorambucil is mainly used in chronic lymphocytic leukemia.
2. It can be used for non-Hodgkin lymphoma, polycythemia, ovarian carcinoma.
3. It is also used as an immunosuppressive agent for various autoimmunee disorders.

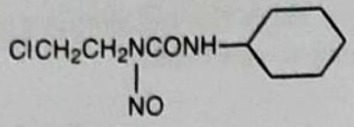
B) NITROSOUREAS

Nitrosoureas are class of compounds that include a nitroso (R–NO) group and a urea ($O{=}C(NH_2)_2$) group. Carmustine, Lomustine and Samustine are synthetic drugs of this category whereas Streptozotacin is the natural antibiotic obtained from *Streptomyces achromogenes* and Chlorozotocin a related compound has been prepared.

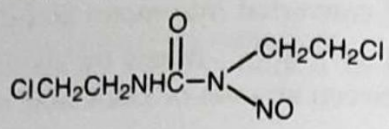
Mechanism of Action :

Nitrosoureas undergo nonenzymatic breakdown to form carbocations which are strong electrophiles and can alkylate purine and pyrimidine bases of DNA. Further, nitroso ureas also liberates organic isocyanates which carbomylate lysine residues of proteins and inactives DNA repair enzymes. For e.g. Lomustine generate 2-chloroethyl carocation which alkylate guanine base of DNA and cyclohexyl isocyanate which carbomylate E-NH_2-lysine of proteins.

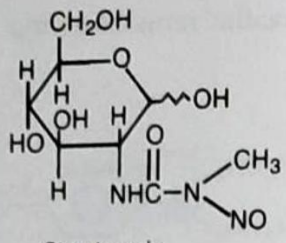
Uses : The nitroso ureas are useful in the treatment of brain tumors, Hodgkin's disea lung cancer, malignant melanoma and some solid tumors.



Lomustine



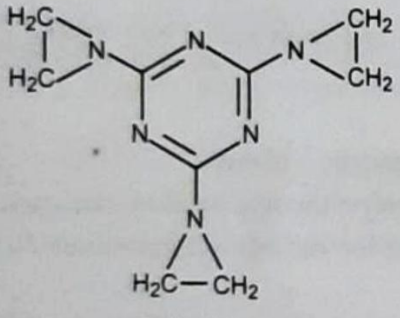
Carmustine



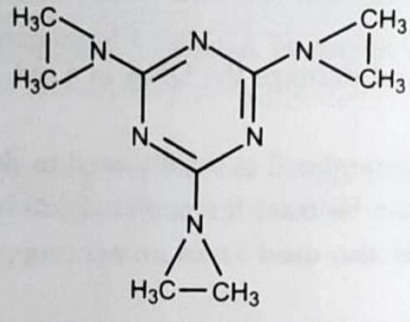
Streptozocin

C) AZIRIDINES

Aziridines reactivity is due to ring strain, they do not act as readily as aziridinium io with nucleophiles. These include Thiotepa, Tretamine and Altretamine.

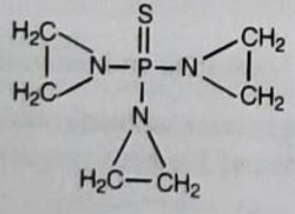


Tretamine



Altretamine

1) Thiotepa (Thiophosphoramide)



IUPAC Name : Tris(aziridin-1-yl) phosphine sulphide

Properties : Thiotepa is white, fine crystalline flakes which is freely soluble in water. It is stored at low temperature (2° to 8°) as it gets polymerize and inactivated at higher temperature. Thiotepa is metabolised into triethylene phosporamide (TEPA). The adjacent thiophosphoryl group is electron withdrawing therefore, reduces the activity of aziridine ring system. Thiotepa is also metabolized by oxidative desulfurization mediated by CYP2B1

and CYP2C11.

Mechanism of Action : It acts on 7th position of guanine base of DNA and stop tumor growth by cross linking with DNA double helix strands so that the cells can no longer divide.

Uses :

1. Thiotepa is used in the treatment of various solid tumors including breast, ovary and bladder carcinoma.
2. Thiotepa is also used in the treatment of various lymphomas.

D) ARYLSULPHONATES

The most important member of this group is Busulfan

Bulsulfan

$$CH_3SO_2OCH_2CH_2CH_2CH_2OSO_2CH_3$$

IUPAC Name : 1,4- Butanediol dimethane sulphonate

Properties : It is a white or almost white crystalline powder which is very slightly soluble in water. It is stored in light resistant container.

Busulfan contains two labile methanesulfonate groups (OSO_2CH_3) attached to opposite ends of a four carbon alkyl chain. Busulfan hydrolysed to give methane sulfonate groups and carbonium ions.

Busulfan is metabolised in liver by glutathione S-transferase (GST) enzyme and give tetrahydrothiophene, tetrahydrothiophene-12-oxide, sulfolane and 3-hydroxysulfolane as inactive metabolites.

Mechanism of Action : Its mechanism involves the cross linking between guanine and adenine interstand by an SN^2 reaction in which nucleophile guanine N^7 attacks the carbon adjacent to mesylate leaving group. This type of damage cannot be repaired by cellular mechanism.

Use : Busulfan has a selective immunosuppressive effect on bone marrow. It is used to treat chronic granulocytic leukaemia.

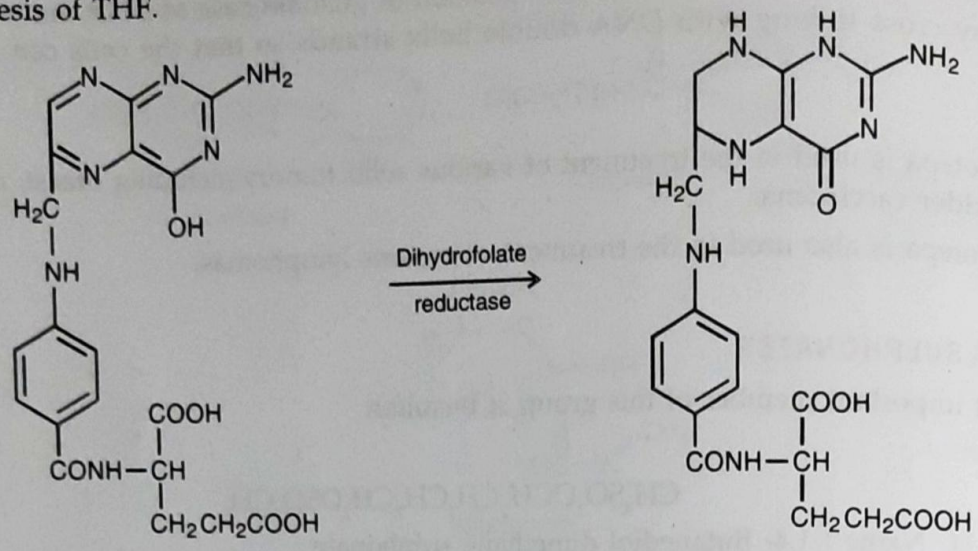
ANTIMETABOLITES

Antimetabolite is a substance that replaces or inhibits a specific metabolite (Intermediate and product of metabolism) of a cell thus interferes with the normal cellular metabolic function. In other words, antimetabolites prevent the biosynthesis and utilisation of normal cellular metabolites. An antimetabolite is similar in structure to a metabolite. So, due to its structure similarity, antimetabolites readily incorporated into DNA or RNA and interfere with cellular function. For e.g. antifolate competitively inhibit the folic acid and produce toxic effects on cells i.e. they stop cell growth and cell division.

A) FOLIC ACID ANALOGUES

Folic acid gets reduced into tetrahydrofolic (THF) acid by the enzyme dihydrofolate reductase. THF is necessary for the synthesis of purines, thymidine and some amino acids.

Folic acid analogues competitively inhibits the enzyme dihydrofolate reductase and prevent the synthesis of THF.

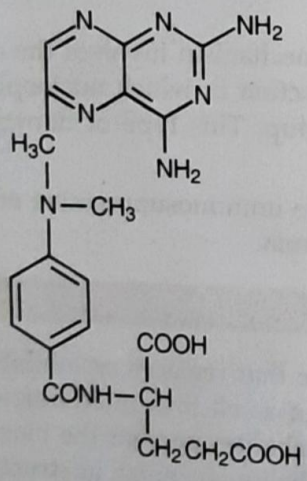


Folic acid

Tetrahydrofolic acid (THF)

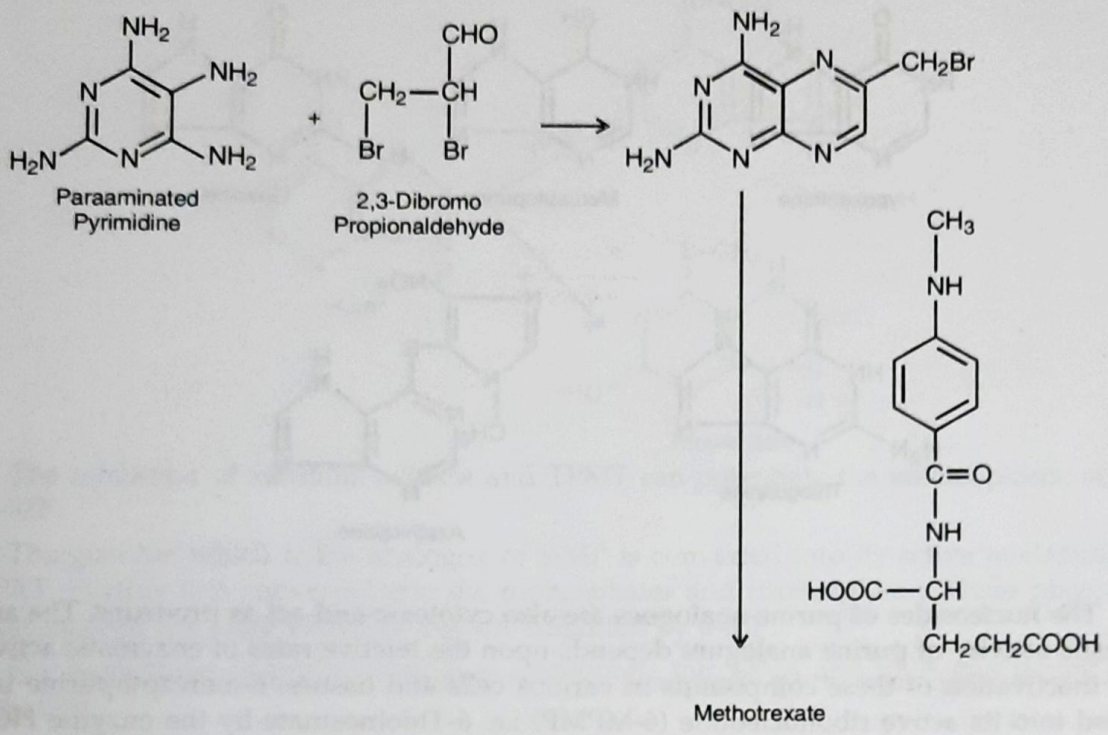
Methotrexate is the classical antimetabolite of folic acid and structurally derived by N-methylation of para amino benzoic acid (PABA) and bioisosteric replacement of pteridine hydroxyl by the amino group. The presence of amino group increases the basicity and gives higher enzyme affinity.

1) Methotrexate



IUPAC Name : 4-Amino-10-methyl folic acid.

Synthesis



Properties : It is yellow to orange brown crystalline hygroscopic powder which is practically insoluble in water but soluble in dilute solutions of mineral acids, alkali hydroxides and carbonates. It is readily absorbed in low doses. It poorly crosses blood brain barrier. It is converted into its 7-hydroxmetabolites in high dose.

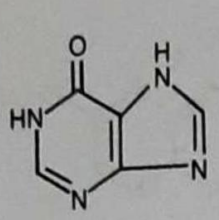
Mechanism of Action : Methotrexate inhibits the enzyme dihydrofolate reductase thus prevents the formation of THF.

Uses :

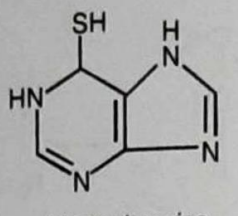
1. Methotrexate is used to treat psoriasis, acute lymphoblastic leukaemia and choriocarcinoma.
2. It has also been used as an immunosuppressant.
3. It is also used to treat rheumatoid arthritis, inflammatory myositis, lupus, breast, neck and lung cancer.

B) PURINE ANALOGUES

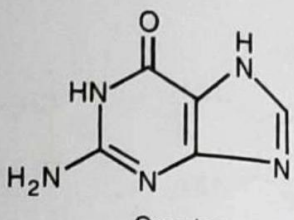
Purine structure containing analogues are mercaptopurine, thioguanine and azathioprine. The structure of these analogues are similar to hypoxanthine and guanine. These analogues have sulfhydryl/thiol group at position 6 of the purine ring instead of oxygen respectively.



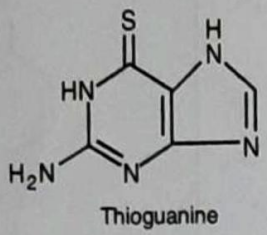
Hypoxanthine



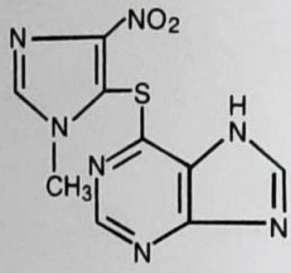
Mercaptopurine



Guanine

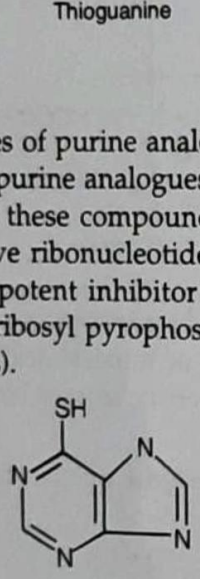


Thioguanine



Azathioprine

The nucleosides of purine analogues are also cytotoxic and act as prodrugs. The oplastic activity of purine analogues depends upon the relative rates of enzymatic ac and inactivation of these compounds in various cells and tissues. 6-mercaptopurine verted into its active ribonucleotide (6-MPMP) i.e. 6-Thioinosinate by the enzyme H This nucleotide is potent inhibitor of Glutamine amidophospho ribosyl transferase convert 5-phosphoribosyl pyrophosphate into 5-phosphoribosylmine (initial step for sis of basic purines).



6-Mercaptopurine (6-MP)

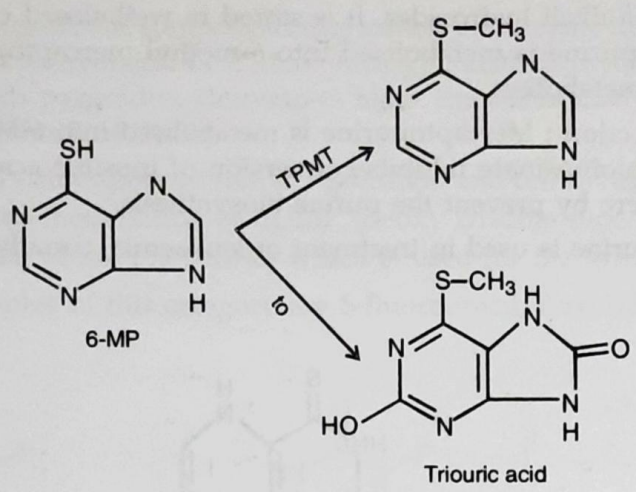
6-MPMP

5-Phosphoribosyl pyrophosphate → (Glutamine; Amido phospho ribosyl transferase) → 5-Phosphoribosylamine

↓

Purine Bisynthesis

Further xanthine oxidase and thiopurine 5-methyl transferase (TPMT) convert into inactive S-methyl-MP and Thiouric acid.



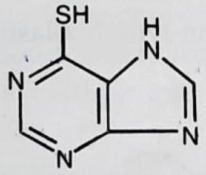
Triouric acid

The inhibition of xanthine oxidase and TPMT can potentiate the antineoplastic activity of 6-MP.

Thioguanine which is the analogue of 6-MP is converted into its active nucleotides by HGPRT. Further it is converted into the diphosphates and triphosphates. These phosphates inhibit most of the same enzymes that are inhibited by 6-MP.

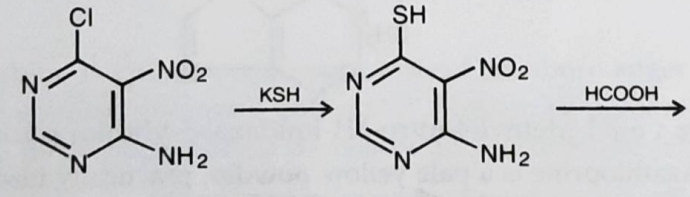
The nucleotides of purine analogues incorporate into DNA and RNA and inhibit chain elongation.

1) Mercaptopurine

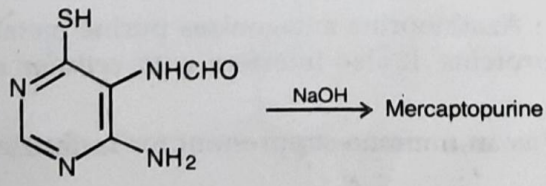


IUPAC Name : 3,7-dihydropurine-6-thione,purine-6-thiol

Synthesis :



4-Amino-6-Chloro-5-Nitro Pyrimidine

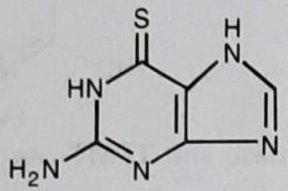


Properties : It is a yellow crystalline powder which is practically insoluble in water but soluble in solutions of alkali hydroxides. It is stored in well closed container and protected from light. Mercaptopurine is metabolised into 6-methyl mercaptopurine, 6-thiouric acid, sulphates and other metabolites.

Mechanism of Action : Mercaptopurine is metabolised into 6-MPMP (6-Thioinosinate) by HGPRT. This 6-Thioinosinate inhibits conversion of inosinic acid to adenylic acid and xanthylic acid and there by prevent the purine biosynthesis.

Use : Mercaptopurine is used in treatment of leukaemia, usually with other agents.

2) Thioguanine



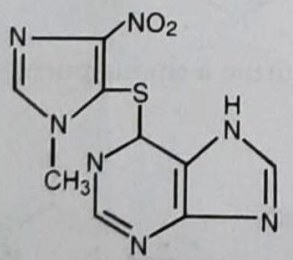
IUPAC Name : 2-Aminopurin-6-Thiol

Properties : Thioguanine is a pale yellow crystalline powder, insoluble in water, soluble in solutions of alkali hydroxides. Thioguanine is converted into its active metabolites i.e. thioguanylic acid and thioguanosine phosphate derivative and inactive metabolites i.e. 2-amino-6-methylthiopurine and thioxanthine in the body.

Mechanism of Action : Thioguanine is converted into its active metabolite i.e. 6-thioguanilyic acid (TGMP) by HGPRT. This TGMP inhibit the synthesis of guanine nucleotides as well as inhibit the conversion of iosinic acid to xantylic acid.

Use : It is used in the treatment of non-lymphoblastic leukaemia.

3) Azathioprine



IUPAC Name : 6-[(1-Methyl-4-nitro-1H-imidazol-5-yl)thio] purine.

Properties : Azathioprine is a pale yellow powder, practically insoluble in water, soluble in dilute alkali hydroxides solutions. It is well absorbed after oral administration and converted to active metabolites i.e. 6-mercaptopurine and 6-thioinosinic acid.

Mechanism of Action : Azathioprine antagonizes purine metabolism and inhibit synthesis of DNA, RNA and proteins. It also interfere with cellular metabolism and inhibit mitosis.

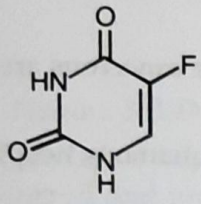
Use : It is mainly used as an immuno-suppressant for facilitating the survival of organ and tissue transplants.

C) PYRIMIDINE ANALOGUES

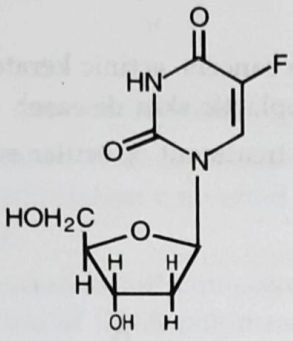
Pyrimidine analogues are the compounds that inhibit the enzyme thymidylate synthetase, enzyme responsible for conversion of 2′-deoxyuridylic acid to thymidylic acid for DNA synthesis. In other words pyrimidine derivatives block the action of thymidylate synthetase (TS) and inhibit the synthesis of DNA.

The TS system plays an important role in replication and cell division. The TS enzyme is responsible for reductive methylation of dUMP (deoxy Uridine mono Phosphate) to yield dTMP (deoxy Thymidine Mono Phosphate) which is used for the synthesis of DNA.

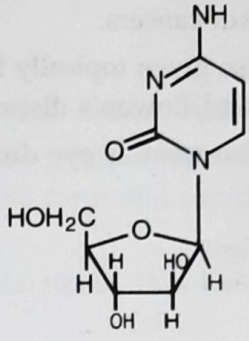
The classical examples of this category are 5-fluorouracil, floxuridine and cytarabine.



5-Fluoro uracil



Floxuridine



Cyfarabine

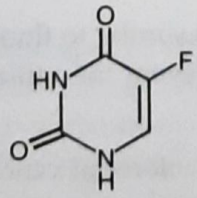
5-fluoro uracil is designed to block the conversion of uridine to thymidine. The 5-Fluoro uracil is differ from uracil at position-5 where fluorine atom replace the hydrogen atom of uracil. The carbon-fluorine bond is stronger and less susceptible to enzymatic cleavage as compare to carbon-hydrogen bond.

On parentral administration of floxuridine, it converts into its active monophosphate derivative which is potent competitive inhibitor of TS enzyme.

Modification on normal ribose or deoxyribose moiety has produced useful drugs such as cytarabine.

Structurally cytarabine is cytosine arabinose instead of ribose suger. The only difference in structure is the epimeric hydroxyl group at 2′ position of pentose sugar. Cyarabine must be converted into its monophosphate derivative and incorporate into DNA synthesis.

1) Fluorouracil



IUPAC Name : 5-Fluorouracil, 5-Fluoropyrimidine-2, H (1H, 3H)-dione.

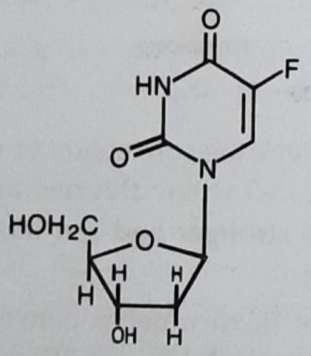
Properties : It is a white or almost white, crystalline powder, sparingly soluble in water, and stored in tightly closed light resistant container. Fluorouracil is incompletely absorbed from G.I.T. Fluorouracil is catabolised in liver results to give CO_2, urea and α-fluoro-β-alanine as a metabolic products.

Mechanism of Action : Deoxyribosemonophosphate metabolite of fluoro uracil inhibt the enzyme TS which results inhibition of formation of thymidylate from uracil, which leads to the inhibition of DNA and RNA synthesis and cell death.

Uses :

1. Fluoro uracil is used systemicaly for anal, oesophageal, stomach, pancreatic, breast and skin cancers.
2. It is also given topically for skin cancers, actinic keratoses (pre cancerous area of crusty skin) and Bowen's disease (neoplastic skin disease).
3. It is also used as eye drops for treatment of ocular surface squamous neoplasia.

2) Floxuridine



IUPAC Name : 5-fluoro-1-[(2R, 4S, 5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,2,3,4-tetrahydropyrimidine-2,4-dione.

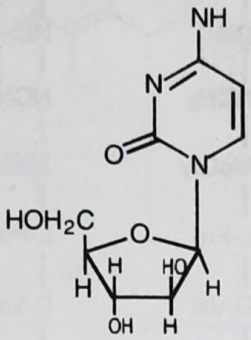
Properties : It is a white crystalline powder, soluble in water, ethanol and DMSO. It is poorly absorbed from G.I.T. and metabolised to 5-fluoro uracil by the enzyme dihydropyrimidine dehydrogenase. This drug is excreted as urea, fluoro uracil, α-fluoro-β-ureidopropionic acid, dihydrofluoro uracil, α-fluoro-β-guani-dopropionic acid and α-fluoro-β-alanine in urine.

Mechanism of Action : Its action is similar to fluoro uracil, apart from that it also inhibit uracil riboside phosphorylase which prevent the utilization of uracil in RNA synthesis.

Uses :

1. It is mainly used in treatment of colorectal cancer (colon cancer).
2. It can also be used for treatment of kidney and stomach cancer.

3) Cytarabine



IUPAC Name : 1-β-D-arabino furanosylcytosine, cytosine arabinoside, Ara-C.

Properties : It is a white or almost white crystalline powder, freely soluble in water. It is poorly absorbed and after phosphrylation converted to active form and rapidly deaminated to inactive uracil arabinoside.

Mechanism of Action : Its action is not completely understood. It is believed that cytarabine acts through the inhibition of DNA polymerase.

Use : Cytarabine is given with thioguanine and doxorubicin or daunorubicin in the treatment of leukaemia especially non-lymphoblastic leukaemia.

ANTIBIOTICS

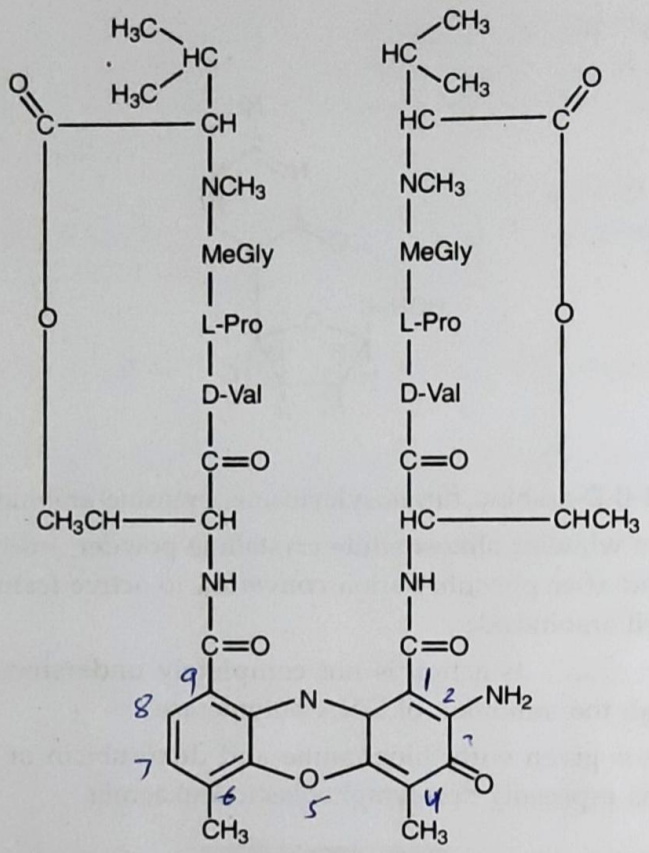
The anticancer antibiotics are the drugs that affect DNA synthesis and replication by incorporate into DNA or by donating electrons which results in the production of highly reactive suproxide (oxygen compounds) that cause breakage of DNA strands. Many of the antineoplastic antibiotics are obtained from fungus streptomyces include bleomycin, mitomycin, dactinomycin and doxorubicin. These compounds also having antibacterial activity but due to their high toxicity these are not used as antibiotics.

Antineoplastic antibiotics acts by several mechanism include intercalation, alkylation and strand breakage. Intercalation is a process by which a planar molecule of the appropriate size inserts itself between adjacent base pairs of DNA which cause local unwinding and disrupt template function of DNA. Apart from that intercalation may also result in inhibition of topoisomerase enzymes (responsible for transcription process).

a) Actinomycin

Actinomycin are obtained from some species of streptomyces. They all are contains same phenoxazone chromophose (3-phenoxazone-1,9-dicarboxylic acid or actinocin) which is responsible for the yellow-red colour of the compound but they differ in the attached peptide portion. The most acceptable compound of this category is actinomycin D (Dactinomycin)

1) Dactinomycin



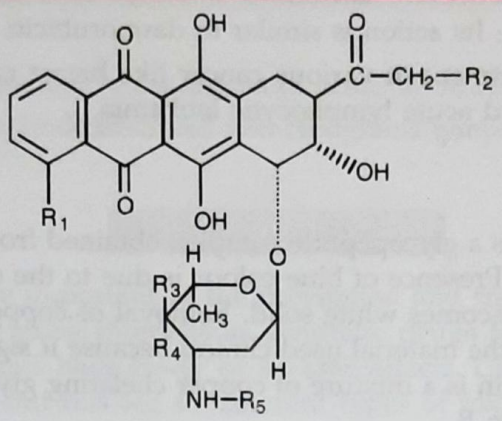
Dactinomycin having L-threonine, D-valine, L-proline, N-Methyl glycine and L-N-methylvaline amino acids. The hydroxyl group of L-threonine forms lactone ring with L-methylvaline.

Dactinomycin binds non covalently to double strand. DNA by intercalation process and inhibit the DNA function. Phenoxazone ring, peptide loops are responsible for the interaction with DNA base pairs. This makes a stable dactinomycin-DNA complexation and inhibit transcription.

Dactinomycin is bright red, hygroscopic crystalline powder used in treatment of tumours of testis and uterus, kaposi's sarcoma, osteogenic sarcoma and other solid tumors.

A) ANTHRACYCLINES

Anthracyclines antibiotics refers to a planar oxidized anthracene nucleus fused to a cyclo hexane ring which is connected by a glycosidic linkage to an amino sugar. Early anthracyclines were obtained from streptomyces peucetius. The anthracyclines acts by inhibiting topoisomerase II and causes DNA strand breakage and also intercalates with DNA. Hundreds of compounds have been discovered out of which five are used clinically (doxorubicin, daunorubicin, epirubicin, idarubicin and valrubicin).



Drug Name	R_1	R_2	R_3	R_4	R_5
Doxorubicin	CH_3O	OH	H	OH	H
Daunorubicin	CH_3O	H	H	OH	H
Epirubicin	CH_3O	OH	OH	H	H
Idarubicin	H	H	H	OH	H
Valrubicin	CH_3O	$O-C(=O)-C_4H_9$	H	OH	$-C(=O)-CF_3$

Doxorubicin and daunorubicin differ only by a single hydroxyl group at position R_2 but they have different clinical activity. Danurubicin has been used in the treatment of acute leukaemias whereas doxorubicin have cytotoxic activity against a wide range of solid tumours.

1) Daunorubicin

This antibiotic is obtained from streptomyces peucetius or S.coeruleorubidus.

Properties : It is an orange red hygroscopic crystalline powder which is freely soluble in water, stored in airtight container and protected from light. It is rapidly metabolised in liver and converted into its hydroxy analogue daunorubicinol which further break to the aglycone. It is excreted in urine as unchanged drug.

Mechnism of Action : Daunorubicin interacts with DNA by intercalation and inhibit the macromolecular biosynthesis and inhibits the topoisomerase II which relaxs supercoils in DNA transcription.

Use : Daunorubicin is used for acute myeloid leukemia, chronic myelogenous leukemia, acute lmyphocytic leukemia and kaposi's sarcoma.

2) Doxorubicin

Doxorubicin is obtained from S.peucetius or S.coeruleorubidus.

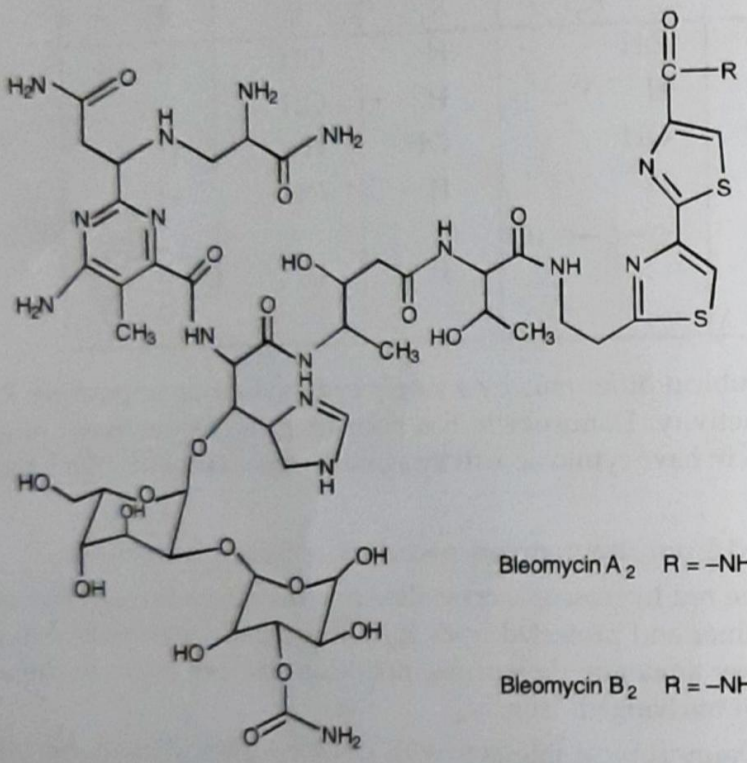
Properties : It is an orange red hygroscopic crystalline powder, soluble in water and stored in air tight container. It is given intravneously and metabolised in liver into its active metabolite doxorubicinol. It is mainly excreted in bile.

Mechanism of Action : Its action is similar to daunorubicin.

Use : It is used in treatment of various cancer like breast cancer, lymphoma, bladd cancer, kaposi's sarcoma and acute lymphocytic leukemia.

3) Bleomycins

Antibiotics bleomycin is a glycopeptide complex obtained from streptomyces verticill It is a blue colour chelates. Presence of blue colour is due to the copper present in it. Wh the copper is removed, it becomes white solid. Removal of copper from naturally occuri bleomycin is important for the material used clinical because it significnatly reduces activi The clinically used bleomycin is a mixture of copper chelating glycopeptides that consists bleomycin A_2 and bleomycin B_2.



Bleomycin A_2 R = $-NHCH_2CH_2CH_2-S^{+}(CH_3)_2$

Bleomycin B_2 R = $-NHCH_2CH_2CH_2CH_2NHC(=NH)NH_2$

In the above basic structure of bleomycin a pyrimidine moiety joined to propionam a-β-amino alanine amine side chain, sugar L-glucose, 3-o-carbamoyl D-mannose. It also h a side chain with amino acids L-histidine and L-threonine, a bithiazole carboxylic acid a methyl valerate residue. Cupric ions form chelates with the pyrimidine ring, the imida ring of L-histidine, β-aminoalanine amide and carbamoyl group of mannose.

Bleomycin Sulphate

Bleomycin sulphate is a white or yellowish white powder, hygroscopic in nature, sol in water and stored in air tight container at a temperature 2° to 8°. Bleomycin hydrolase amino peptidase are responsible for inactivation of Bleomycin.

Mechanism of Action : It binds to DNA by interaction and causes scission of DN interacting with molecular oxygen and ferrous or cupric ions.

Uses :

1. It is used in the treatment of carcinoma of head, neck, cervix, vulva and penis.
2. It is also effective in Hodgkin's and non-Hodgkin's lymphoma and germ cell tumours of testis and ovary.

PLANT PRODUCTS

Herbal medicines are important in the prevention and treatment of cancer. Drugs derived from plants are of great interests as synthetic drugs has various undesirable side effects. Plant derived drugs have fewer or no side effects. Cancer cells are susceptible to chemotherapeutic drugs but this led to different types of toxicities in the body. To avoid these problems, nowadays various therapies for the treatment of cancer uses plant derived products. There are four types of plant products used as anti cancer. These are :

a) Vinca alkaloids (Vincristine and Vinblastiine)

b) Epipodophyllotoxins (Etoposide and Teniposide)

c) Taxanes (Paclitaxel)

d) Camptotecin derivatives (Camptotecin and irinotecan)

Vinca Alkaloids : These alkaloids are isolated from the periwinkle plant (Catharanthus roseus) Vinca rosea.

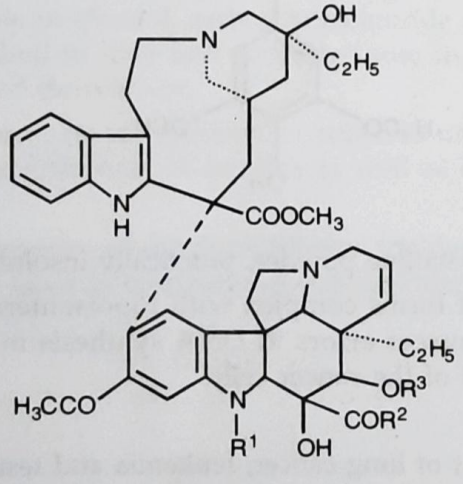
These alkaloids have two basic moieties :

1) Catharanthine (Indole containing moiety)

2) Vindoline (Indoline containing moiety)

Vincristine and Vinblastine are most commonly used alkaloids in this category.

The basic structure of vinca alkaloids is :



Vincristine	$R^1 = -CHO,$	$R^2 = -OCH_3, R^3 = -COCH_3$
Vinblastine	$R^1 = -CH_3,$	$R^2 = -OCH_3, R^3 = -COCH_3$

Properties :

These occurs as a white or slightly yellowish amorphous or crystalline powder. are hygroscopic in nature, Freely soluble in water. These alkaloids gets metabolised liver.

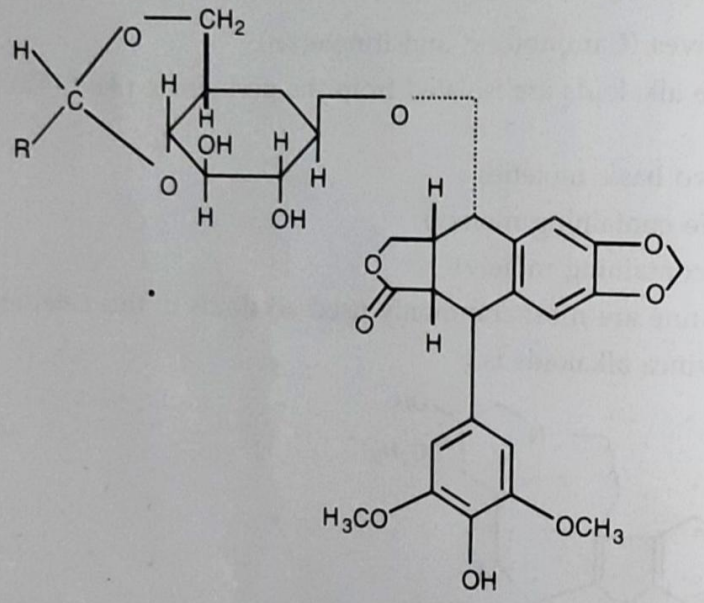
Mechanism of Action : Vinca alkaloids binds specifically with the tubulin protein p in the microtubules of cells and blocks mitosis at metaphase stage.

Uses :

1. Vincristine and Vinblastine are used in the treatment of carcinoma of the b Hodgkin's disease.
2. Used in the treatment of lymphocytic leukaemia.
3. Used in the therapy of metastatic testicular tumours.

Etoposide

It is a semisynthetic glycoside and is related to epipodophyllotoxin.



R = CH_3 (Etoposide)

Properties : It is white crystalline powder, practically insoluble in water.

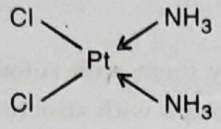
Mechanism of Action : It forms complex with topoisomerase II enzyme and caus breakage of DNA strand. It causees errors in DNA synthesis in cancer cells and helps programmed death (apoptosis) of the cancer cells.

Uses :

1. It is used in the treatment of lung cancer, leukemia and testicular cancer.
2. It is used in combination with bleomycin to treat various types of sarcomas and ly phoma.

MISCELLANEOUS AGENTS

1) Cisplatin



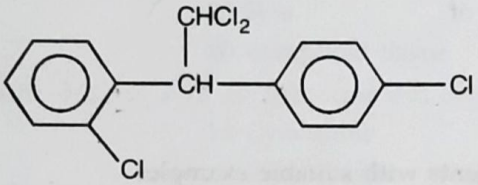
IUPAC Name : Cis-Diamminedichloroplatinum (II)

Properties : It is a yellowish or orange yellow crystalline powder which is slightly soluble in water, kept in air tight container and protected from light. It is effective by intravenous administration and excreted in urine.

Mechanism of Action : Cisplatin damage DNA by the cross links or its action is similar to alkylating agents.

Use : It is used in treatments of various cancers include testicular cancer, esophageal cancer, brain tumors, ovarian cancer, head and neck cancer, breast cancer.

2) Mitotane



IUPAC Name : 1,1-(Dichlorophenyl)-2,2-dichloro-ethane

Properties : It is a white colorless powder having melting point 171 to 172°F. It is less solble in water but soluble in ethanol, carbon tetrachloride and isoctane on oral administration mitotane is metabolised in liver and converted into its dichlorophenylacetic acid or its mono and dihydroxylated derivatives.

Mechanism of Action : Its mechaniism of action is unknown but it is believed that it modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex.

Use : Mitotane is derivative of dichlorodiphenyl trichloroethane (DDT) with anti adreno corticoid properties. It is used in treatment of adrenocortical carcinoma and cushing's syndrome.