

← ANTINEOPLASTIC AGENTS →

* What is neoplasm?

Neoplasm, cancer or tumour is defined as the growth of mass of abnormal tissue formed due to excessive autonomous (excessive independent) and uncoordinated cell proliferation.

In short, neoplasm is described as, uncontrolled division of cells due to loss of mechanism of cells.

This phenomenon occurs as a result of loss of control mechanism of cell and abnormality in chromosomes or mutation in DNA.

Antineoplastic Agents →

Antineoplastic or anticancer drugs are the drugs that prevent or inhibit the maturation and proliferation of neoplasms.

Antineoplastic agents travel the body and destroy cancer cells.

Many of the side effects associated with antineoplastic agents occur because treatment destroys the body's cells (normal) in addition to cancerous cells.

NOTE :- The term "neoplasm" means new growth and the process of cell proliferation is called neoplasia.

Classification of Anti-Cancer Drugs →

1. Alkylating Agents :- Mechlorethamine*, Thiopeta
melphalan, chlorambucil
Cyclophosphamide
Busulfan, Thiopeta.
2. Antimetabolites :- Mercaptopurine*, Thioguanine
Fluorouracil, fluorouridine
Cytarabine, Methotrexate*
Azathioprine
3. Antibiotics :- (mycin/bicin) → Dactinomycin
Daunorubicin, Doxorubicin
Bleomycin
4. Plant product :- Etoposide, Vinblastin Sulphate
Vincristin Sulphate.
5. Miscellaneous :- Cisplatin, Mitotane

General Side effect / toxicity of Anti-Cancer Drugs:-

- GIT :- Diarrhoea, nausea and Vomiting.
Shedding of mucosa, haemorrhages.
- Stomatitis (Condition that causes painful swelling and sores inside the mouth)
- Alopecia (in skin, due to damage of cell in hair follicles)
- Oligozoospermia in males; (decrease sperm count)
- Amenorrhoea in females; (absence of menstrual periods)
- Cytotoxic Agents causes abortion, foetal death, teratogenesis in pregnant women.
- Hyperuricaemia (excess of uric acid in blood)
- Depression in bone marrow
- inhibition of lymphocyte function result in suppression of cell mediated and humoral immunity

• Alkylating Agents :-

It is an oldest and most useful of anti-neoplastic drugs.

It act directly on the cells (Cytotoxic Drugs).

* Mode of Action :-

Alkylating agents

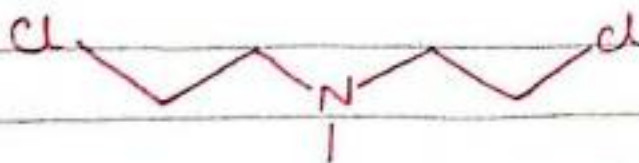
produce Carbonium ions (C^+) highly reactive and commonly binding site is 7-N group of guanine.

Transfer alkyl groups or substituted alkyl groups to cellular macromolecules by forming covalent bonds.

Cross linking / abnormal base pairing / scission of DNA strand.

Inhibition of DNA synthesis.

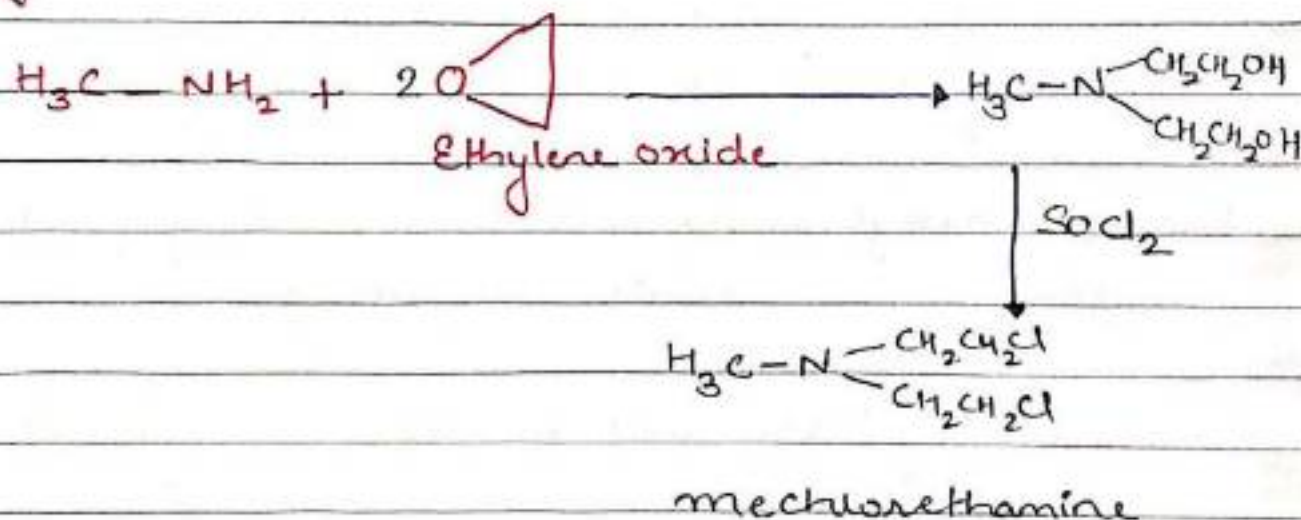
1. Mechlorethamine :-



M.O.A →

The drug binds with the guanine nitrogen base pair this results in the fragmentation of the DNA by the repair enzymes. This leads to the prevention of the DNA synthesis. This also affects the RNA Transcription in the Cells.

Synthesis :-



SAR of Mechlorethamine :-

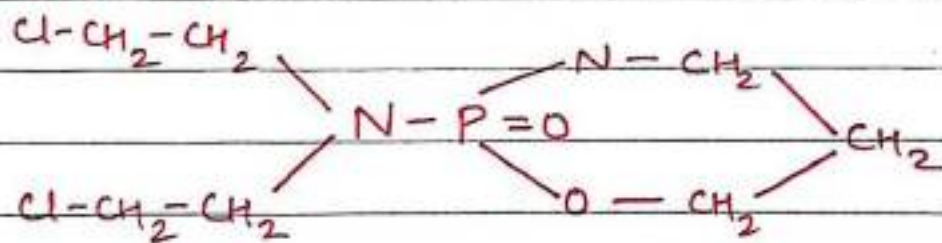
- Replacement of the Sulfur atom by nitrogen will lower the toxicity.
- 2-chlorethyl group is essential for the activity.
- Binding with the amino-group will increase the oral route availability of the drug.
- Introduction of Phenyl group substituted as enhance the availability of the drug for oral administration.
- Is Aromatic ring introduction, resulting the stability.

and distribution of the drug throughout the body.

• Uses!:-

- Treatment of prostatic cancer by modification of the drug into estrogen analogues.
- It was also used for the treatment of Hodgkin's disease, chronic myelocytic leukemia.

2. Cyclophosphamide!:-



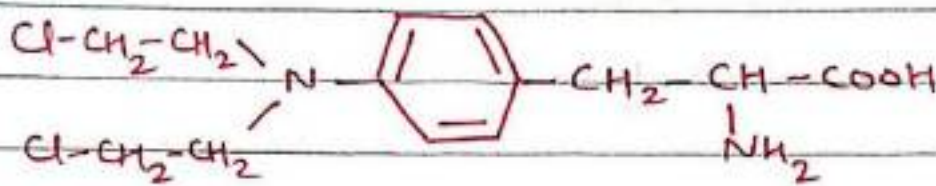
Mechanism of Action:-

- The main effect of cyclophosphamide is due to its metabolite Phosphoramide Mustard.
- Phosphoramide mustard forms DNA crosslinks between (interstrand crosslinkages) and within (intrastrand crosslinkages) DNA strands at guanine N-7 position, this eventually lead to cell deaths.

Uses:-

- It is used in the treatment of WBC Cancers and Lymphoma.

3. Melphalan :-



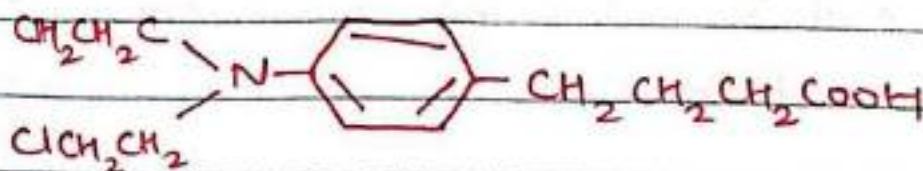
Mechanism of Action :-

- It chemically alter the DNA nucleotide guanine through alkylation and causes linkage between Strands of DNA.
- This chemical alteration inhibit DNA Synthesis, function necessary for Cell to survive.

Uses :-

- In the treatment of Ovarian Cancer and multiple myeloma (a tumor of antibody producing cells).

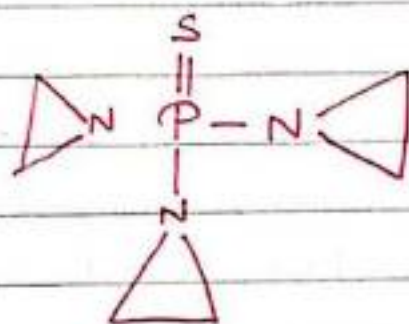
4. Chlorobucil :-



Uses :-

Chlorambucil is used to treat certain types of cancer of the blood and lymph nodes such as chronic lymphocytic leukemia, lymphosarcoma, giant follicular lymphoma and Hodgkin's disease.

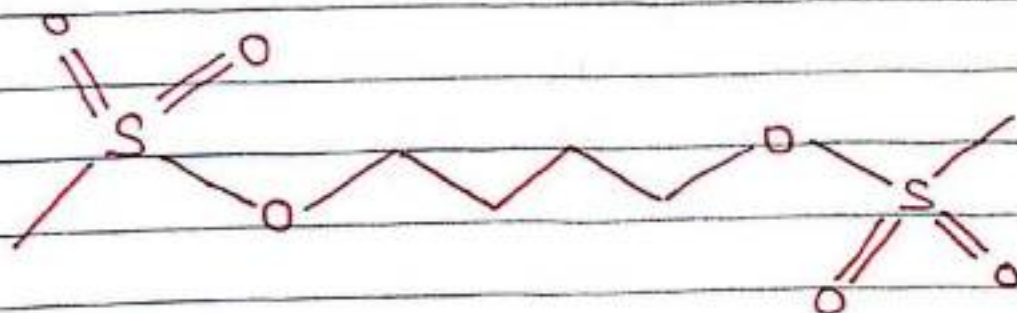
5. Thiopeta Thiotepe



Uses :-

- Thiopeta is used to treat cancer, it works by slowing or stopping the growth of cancer cells.
- Thiopeta is often given into the bladder to treat bladder cancer.

6. Busulfan :-



Uses :-

- It basically used in blood disorders such as polycythemia Vera and myeloid metaplasia.
- In such condition, busulfan used in regimens prior to bone marrow transplant.
- In treatment of chronic myelogenous leukemia.

• Antimetabolites :-

- They are chemically Virtue of Its similarity in structure to a metabolite, blocks its action.
- They act on inhibition / prevent the combination of metabolite with specific enzyme.

Mechanism of Action :-

Antimetabolites generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.

- Inhibit DNA replication or repair by mimicking normal cell compound; S phase specific, therefore cell division and the growth of tumours inhibited.

1. Mercaptopurine →

6-mercaptopurine falls under the category of purine antagonist antimetabolite.

→ Mechanism of Action :-

→ Mercaptopurine competes with hypoxanthine and guanine which are purine derived structure.



6-MP inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides that are building blocks for RNA and DNA.



Inhibition of purine synthesis by 6MP converted to the nucleotide analog 6-MP ribose phosphate (6-thioinosinic acid or TIMP).



Incorporation into nucleic acids; TIMP is converted to thioguanine monophosphate (TGMP), which after phosphorylation to di and triphosphates can be incorporated into RNA.



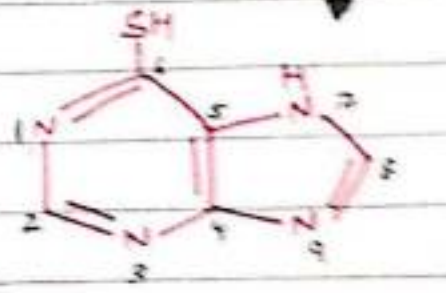
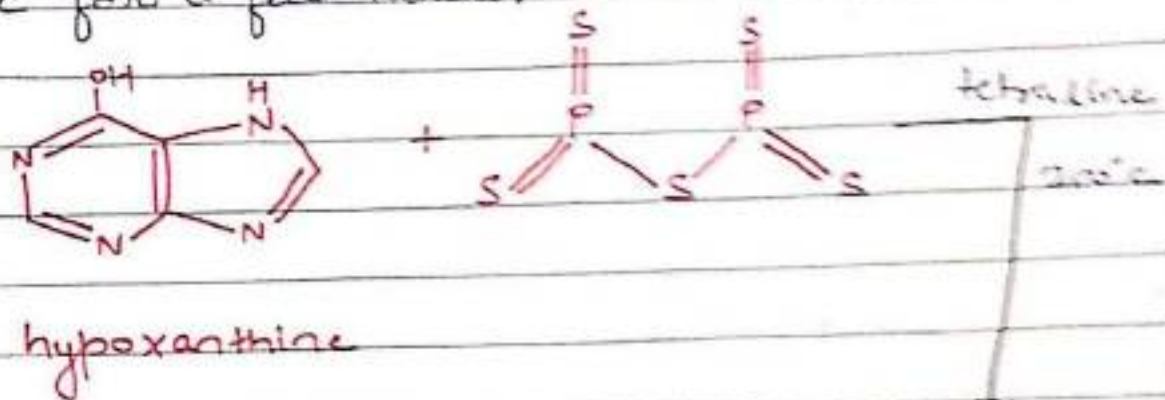
The deoxy-ribonucleotide analogs that are also formed are incorporated into DNA.

This results in non functional RNA and DNA.

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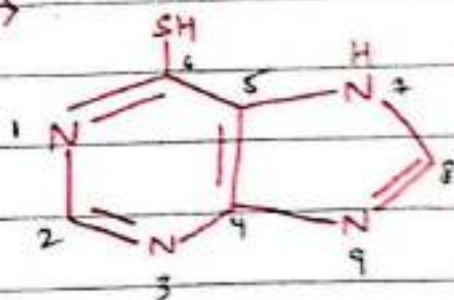
• Synthesis :-

In the presence of tetraline as a solvent hypoxanthine is heated along with excess of phosphorous pentasulfide. These are heated at 200°C for a few hours.



G-mercaptapurine

• SAR →



• The activity of the drug increases with increase in the carbon chain upto 15-16 carbons after that it again decreases in actions.

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- Substituent at 6th position which can lead to the increase in the resonance and resulting increase in the activity of drug.
- At 6th position, substituent of hydrophobic atom, result in increase the activity of the drug.
- Substitution at 2nd position, leads to decrease in activity of drug depending upon the nature of substituent.

Uses :-

G-MP is used to treat acute lymphoblastic or lymphocytic leukemia.

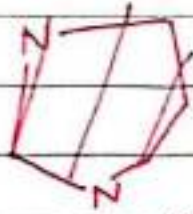
2. Thioguanine :-

Thioguanine interfere with the nucleotides in the DNA as well as in the RNA of cell and false sequencing of these results in the cytotoxicity of the cell.

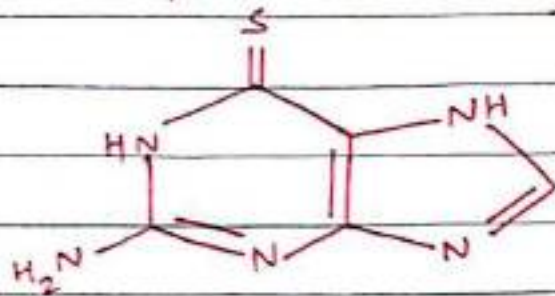
This drug also inhibited the purine synthesis and induction of cytotoxicity in the cell.

* M.O.A is similar as mercaptopurine.*

Structure :-



Structure :-

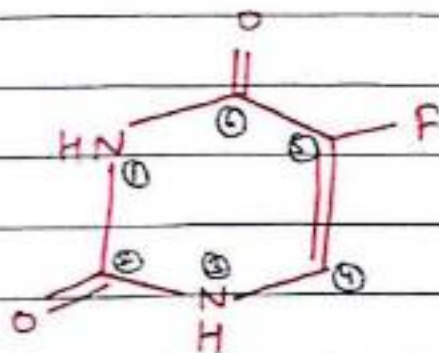


6-Thioguanine

Uses :-

- It is used in treatment of acute myelogenous leukemia.
- It can be also used for the treatment of chronic myelogenous leukemia.

3. Fluorouracil :-



5-Fluorouracil

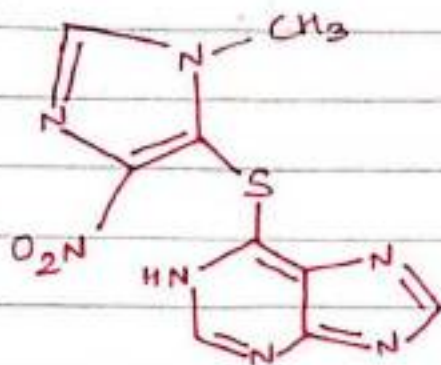
• M.O.A :- Fluorouracil binds to thymidylate synthase and inhibits it, result 2'-deoxyuridylic acid is not converted and cell dies.

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• Uses :-

- It used in treatment of Colon anal and rectal Cancer
- Breast Cancer & GIT Cancers treatment!
- It used clinically for Cervical and thymic cancer.

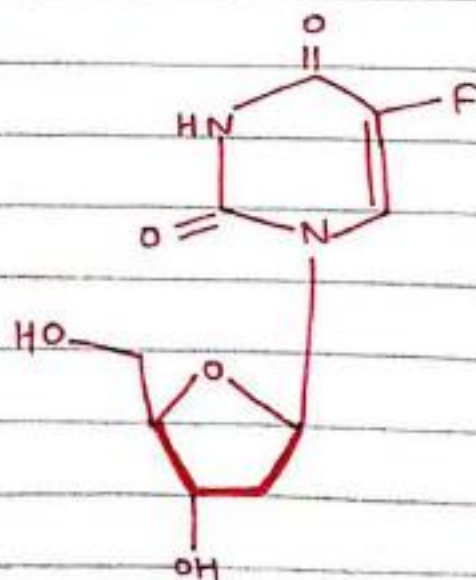
4. Azathioprine :-



• Uses :-

- It used as an immunosuppressive agent for prevention of rejection of the transplanted organs.
- It is given for the treatment of Autoimmune hepatitis, pemphigus and Rheumatoid arthritis.

5. floxuridine :-

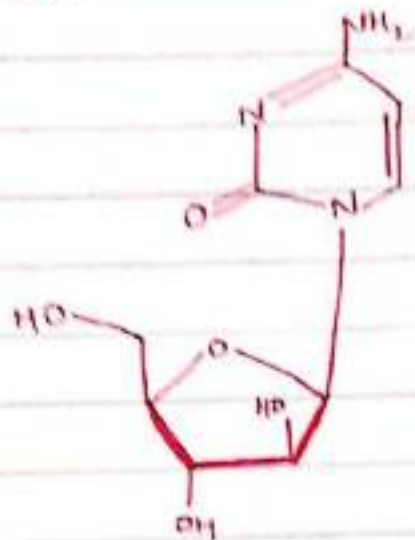


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Uses :-

Flouxindine is used to treat cancer of gastrointestinal (GI tract (cancer of the stomach or intestines)).

6. Cytarabine :-



USES :-

It is used alone or with other chemotherapy, drug to treat certain types of leukemia (cancer of the WBCs).

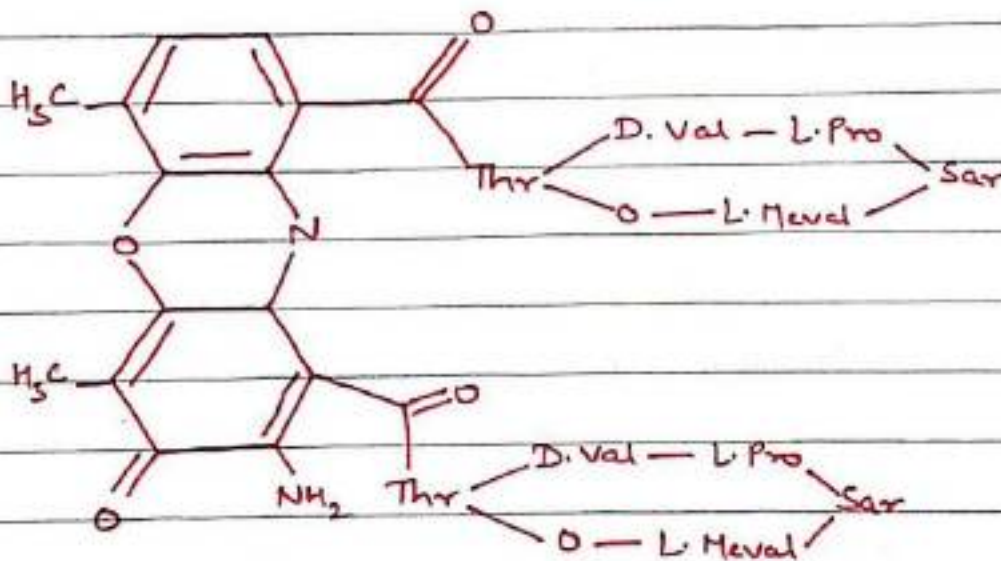
- In acute myeloid leukemia, acute lymphocytic leukemia (ALL).

- ANTIBIOTICS →

1. Dactinomycin :-

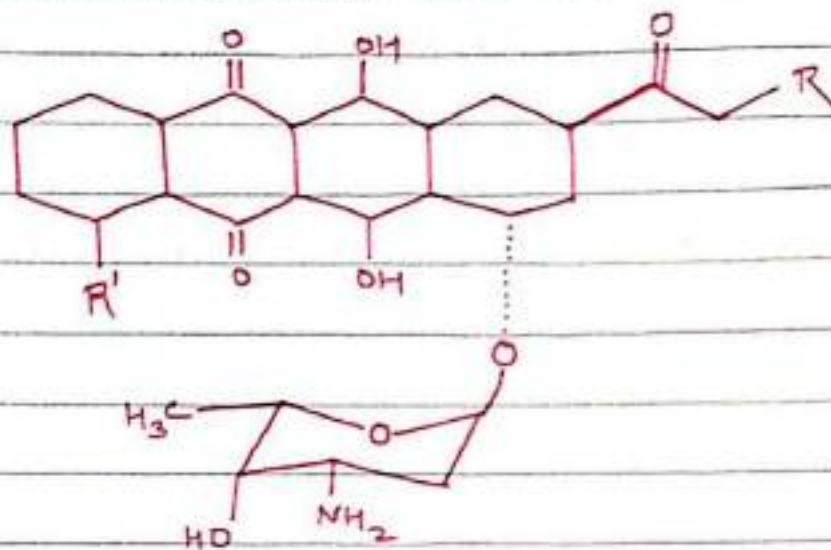
It is obtained from fermentation tanks of *Streptomyces parvulus* belongs to actinomycetes group.

M.O.A :- It intercalates the double helical structure of DNA leading to unwinding of the helical structure result in inhibition of nucleic acid synthesis.



Uses :- It is used in treatment of Osteosarcoma
 Locoregional Solid tumours, Ovarian Cancer.
 In Metastatic testicular tumours.

2. Daunorubicin and Doxorubicin.



Daunorubicin $R = H, R' = OCH_3$

Doxorubicin $R = OH, R' = OCH_3$

* M.O.A \rightarrow Mode of action is similar to Dactinomycin.

Uses:- They are used widely in treatment of acute myelogenous leukemia, acute lymphoblastic leukemia and acute promyelocytic leukemia.

3. Bleomycins:-

M.O.A \rightarrow These are relatively high molecular weight peptide antibiotics. They inhibit DNA synthesis produce scissions of single stranded DNA and also inhibit cell DNA repair by a marked inhibition of DNA ligase.

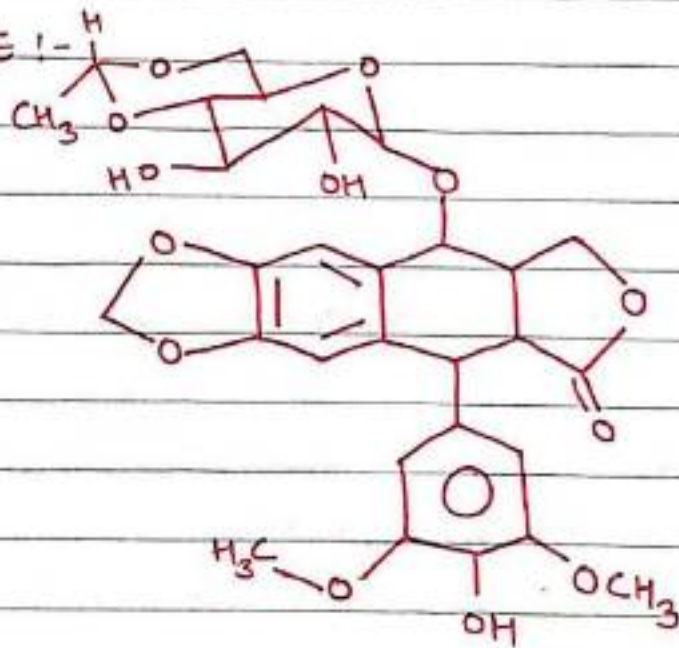
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Uses :-

- It is clinically used in treatment of human epidermal cancer, squamous cell carcinoma of the head and neck.
- It also used in carcinoma of the thyroid and brain tumors.

- PLANT PRODUCT :-

1. ETOPOSIDE :-



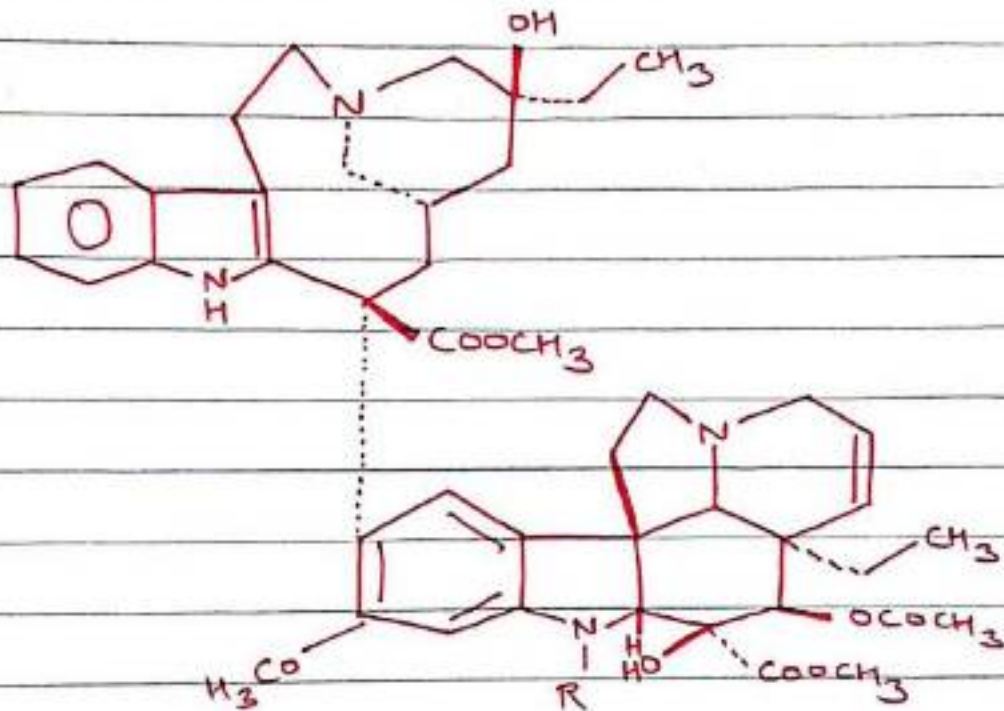
Uses :- Etoposide is used to treat certain forms of lung cancer.

M.O.A → It inhibits DNA synthesis by forming a complex with topoisomerase II and DNA.

This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding.

Accumulated breaks in DNA prevent entry into the mitotic phase of cell division and lead to cell death.

2. Vincristine and Vinblastine :-



Vincristine $R = \text{CHO}$

Vinblastine $R = \text{CH}_3$

M.O.A \rightarrow Both are broad anti-tumor activity, there is an evidence of cross resistance in cell culture. These cause mitotic arrest, by promoting dissolution of microtubule in cells.

These drugs interfere with the synthesis of transfer RNA possibly by acting as acylating agent.

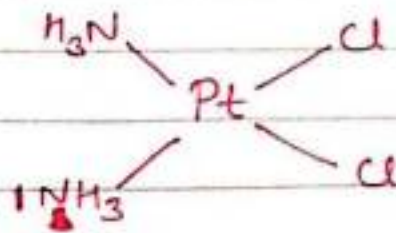
• Uses :-

- Vinblastine used in treatment of Hodgkin's disease, testicular cancer, advanced breast cancer, bladder cancer, brain cancer etc.

- Vincristine mainly used to treat acute leukemia and other lymphomas.

- MISCELLANEOUS :-

1. Cisplatin :-



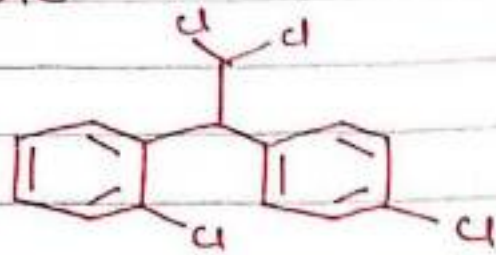
• M.O.A → It is believed that used to kill cancer cells by binding to DNA and interfering with its repair mechanism, leading cell death.

• Uses →

In treatment of advanced bladder cancer, metastatic ovarian cancer and testicular cancer, breast cervical, stomach and prostate cancers.

So

2. Mitotane



M.O.A → Mitotane modifies the peripheral metabolism of steroids and directly suppresses the adrenal cortex.

Uses :- It is used in treatment for adrenal cortex carcinoma.

REFERENCES :-

1. Razdan Balsishen, "Medicinal chemistry" 2nd edition published by CBS publishers and Distributor Pvt. Ltd. pg no - 885

2. M Patel Hariun and Jain Anurekha, "Textbook of medicinal chemistry", published by CBS publishers and distributors Pvt. Ltd. pg no - 810.

3. <https://www.rxlist.com>.