

ANTIHISTAMINIC

AGENTS

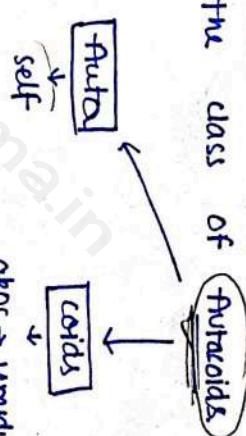
Syllabus →

- Antihistaminic agents : histamine, receptors and their distribution in the human body.
- H₁- Antagonists
- H₂- Antagonists
- Gastric proton pump inhibitors

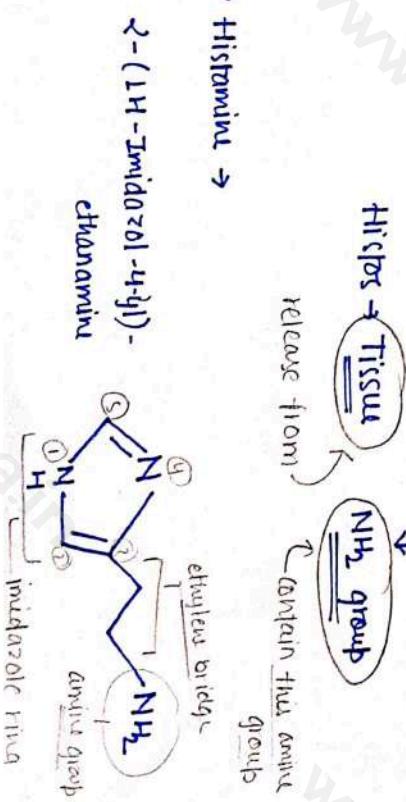
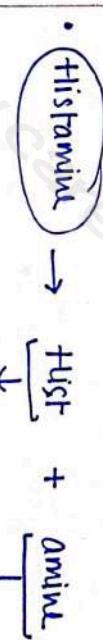
• Antihistaminic agents ⇒

These are those agents or drugs which inhibit the action of histamine in human body.

- Histamine → It is a chemical substance present in our body and it comes under the class of autacoids.



• Autacoids → these are the local hormones, which release from the tissue and act at the site of synthesis and release.



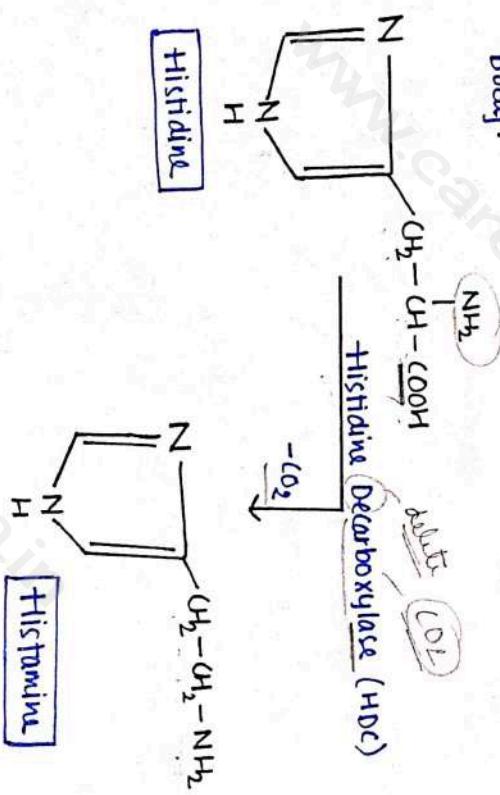
- Histamine is discovered by Sir Henry

Dale in 1910.

Biosynthesis, Storage, Release and Catabolism of Histamine

Synthesis →

Histamine is synthesized by decarboxylation of Histidine which is found in all organs and tissue of the human body.



Storage →

Histamine mostly present inside the

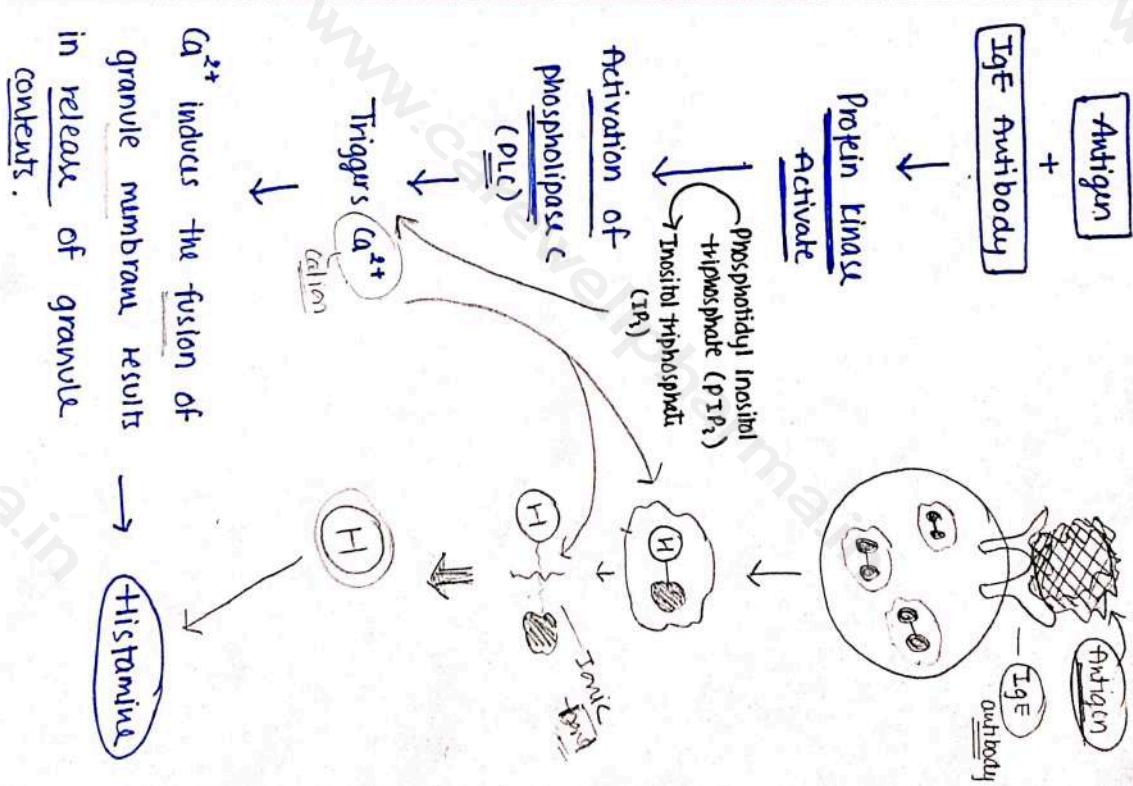
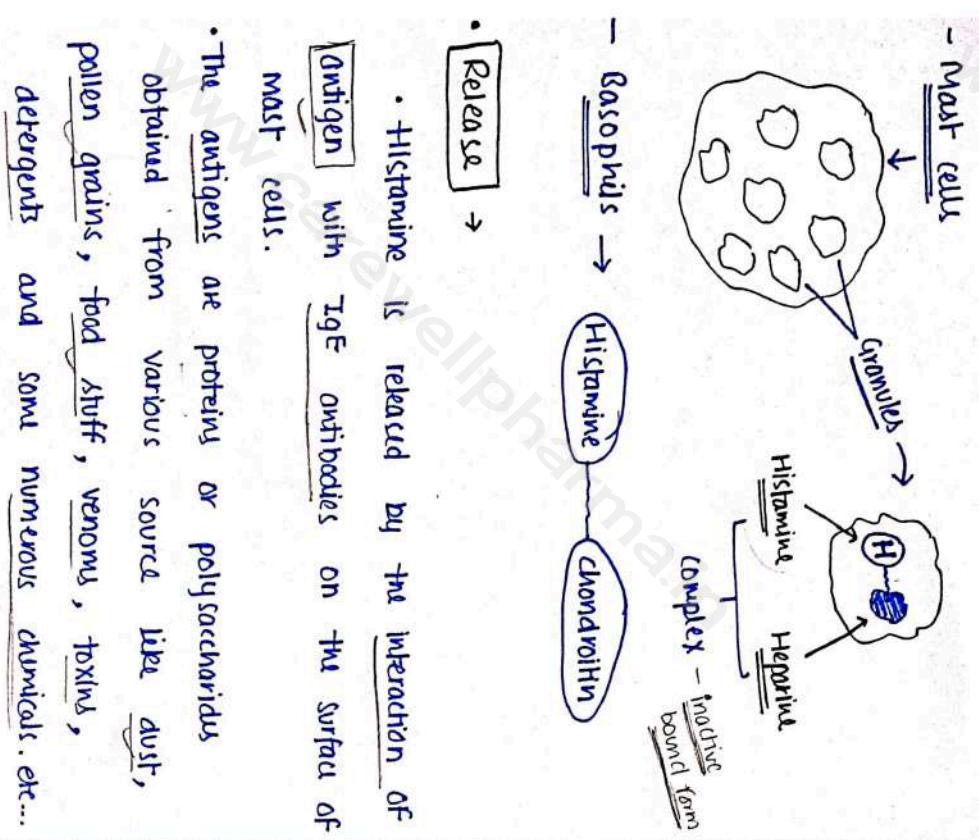
mast cells and basophiles

Both mast cells and basophils are the type of white blood cells and a part of immune system.

It is also stored in enterochromaffin-like (ECG) cell and a variety of neurons.
 ① $\xrightarrow{\text{HDC}}$ ② $\xrightarrow{\text{Histaminergic neurons}}$

Usually histamine (mast cells) found in throughout the body, but in high concentration is present in skin, musosal cell of the lungs, intestine, urinary tract and tissue adjacent to the circulation.

Its concentration is also found high in mammalian cerebro spinal fluid (brain).



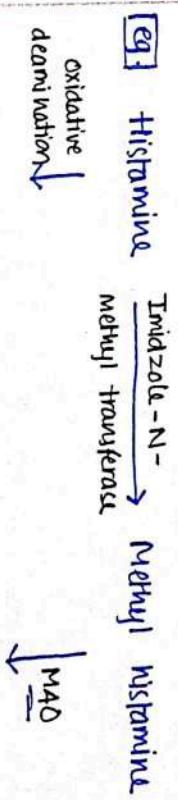
- there are also some other inflammatory mediators release such as prostaglandins, leukotrienes, kinins and platelet activating factor.
- ◎ After release of histamine from mast cells it performs following physiological effects:-
- Hyper sensitivity
- Itching, sneezing, watery eye and running nose.
- Contracts smooth muscles of the lungs.
- Tissue injury
- Inflammation — cause pain
- Allergic reactions
- Some physiological role of histamine →
- Bronchospasm — cause due to irritation, ↓ inflammation, or allergic reaction hard to breathe of the airways.

- Vasodilation → cause hypotension.
 - Gastric secretion → increase HCl secretion e.g. Acidity ↑, Ulcer ↑ etc...
 - produce oedema → fluid and plasma protein may come to extracellular fluid.
- etc....

• Catabolism →

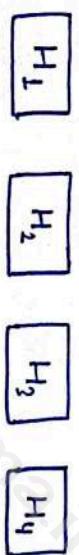
Histamine inactivate by many reactions and enzyme which change the structure of histamine

— After changing structure, histamine does not bind with receptor due to change its structure



HISTAMINE RECEPTORS

There are mainly four receptor, in which histamine bind and give their pharmacological effects :-



All these receptors are G-protein coupled receptor and give their action by the mechanism of GPCR.

Distributions →

① $H_1 \Rightarrow$ stimulate phospholipase C - PLC

• Location :-

- smooth muscle of respiratory and lungs



Intestine GT tract

- CNS neurons

- vascular endothelial cells, in heart

- T-cells, B-cells, neutrophils, eosinophils

• Effects →

- Pain, pruritus (itching), Vasodilation,

hypotension, headache, Bronchoconstriction

- Increased vascular permeability at inflammation sites

- Triple response

- oedema formation

- severe allergic response

- IgE production.

② $H_2 \Rightarrow$ stimulate adenylycyclase and

increase cAMP.

• Location :-

- Gastric parietal cells

- vascular smooth muscles

- CNS, heart and uterus.

• Effects :-

- increase in gastric acid secretion (HCl).

- vascular permeability, vasodilation.

③ $H_3 \Rightarrow$

• Location :-

- mostly found in CNS.

• Effects :-

- inhibition of histamine release
(pre-synaptic auto receptor)

- modulates the release of 5-HT,

dopamine, NAO, Ach and GABA

In CNS by acting as heteroreceptor.

④ $H_4 \Rightarrow$

• Location :-

- Hematopoietic cells

\hookrightarrow the stem cells that give rise to other blood cells.

• Effects :-

- modulate immune function.

CLASSIFICATION OF ANTIHISTAMINES

H_1 -Antagonists

↓

first Generation

- Diphenhydramine HCl*
- Dimenhydrinate.
- Doxylamine succinate

- Clemastine fumarate

- Diphenyl pyramine HCl

- Tripelennamine HCl

- Chlorcyclizine HCl

- Medizina HCl

- Reldizine HCl

- Chlorpheniramine maleate

- Triprolidine HCl*

- Trimuprazine Tartrate

- Phenidamine Tartrate

- Promethazine HCl*

- Cyproheptadine HCl

- Azatadine maleate

H_2 -Antagonists

↓

Gastric Acid Inhibitors

- Cimetidine*
- Famotidine
- Ranitidine ↗

Gastric Proton Pump Inhibitors (PPI)

- Omeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole

- **Second Generation**

- Astemizole
- Loratadine
- Cetirizine
- Levocetirizine

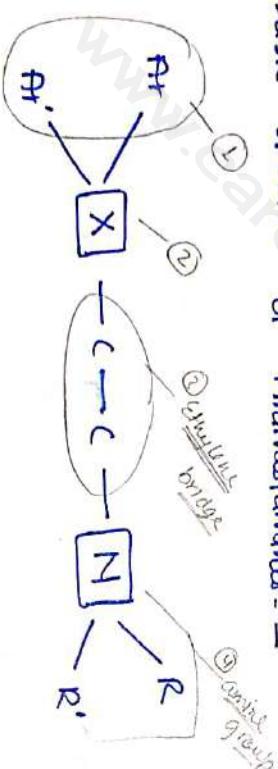
- **Mast cell stabilizer**

- Cromolyn sodium

SAR OF ANTI-HISTAMINES

→ for H₁-Antagonists

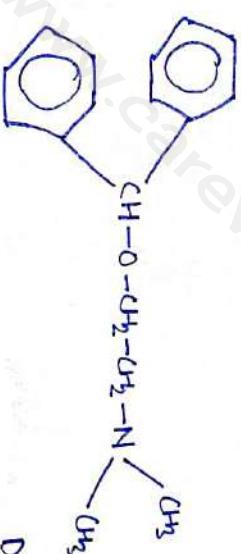
- Basic structure of Antihistamines -



- Both alkyl group can be phenyl or any one heterocyclic ring which also increase activity.
- Ar' may be methyl aryl group which show activity.

Methyl aryl group

Doxylamine
↓ activity ↑



- Structurally, substitution (modification) is possible on:—

- Aryl group

e.g. Bromo diphenylhydramine or

The chemical structure of bromodiphenylhydramine is shown. It consists of a central nitrogen atom bonded to two methyl groups (CH₃) and two phenyl groups (Ar). One phenyl group is substituted with a bromine atom (Br).

- Substitution of Ar, R', O-CH₃ group on aryl ring increase the activity.

- Ethylen bridge

- Amino group

- Substitution on Aryl group →

- Diaryl substitution is essential for activity.

— Nature of \boxed{X}

- It can be substituted by three major elements.
- $\boxed{X} = \text{Nitrogen (N)}, \text{Oxygen (O)}, \text{Carbon (C)}$.
- If X , substituted with any other element than activity of drug is less / lost.
- Now, they form three types of drugs.

i) When $X = N$ (Nitrogen)

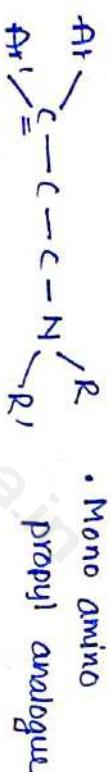


ii) When $X = O$ (oxygen)



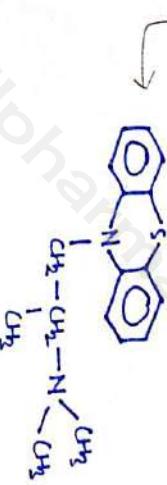
• Amino alkyl ether analogue

iii) When $X = C$ (carbon)



— Substitution on ethylene chain

- Most of the antihistamines have ethylene chain and which is essential for activity.
- Branching of the ethylene chain can decrease the activity.
- But Promethazine is an exceptional case.



— Amino group

- 3° amino group is essential for activity.
- The tertiary amino may be a part of heterocyclic ring which increase the activity multifold.

e.g.: Chlorcyclizine



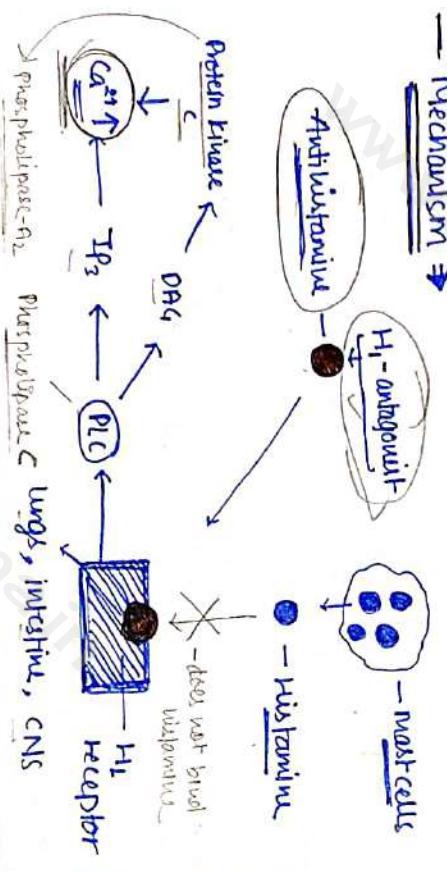
H₁-Antagonists

- Those agents which blocks the H₁ receptor and inhibit the action of histamine.
- These are of two types:-

- I) first generation (sedative)
- II) second generation

I) H₁ antagonists (first generation)

- These are competitive inhibitors of histamine at H₁-receptor.



- The histaminergic receptors are G-protein coupled type.
- H₁ receptor are coupled to phospholipase-C and their activation leads to the formation of Insitol phosphate (IP₃) and diacylglycerol (DAG).
- IP₃ → rapid release of Ca²⁺ from endoplasmic reticulum
- DAG → activates Protein kinase C.
- Also activates phospholipase A₂.

- Now, H₁-antagonist bind to the H₁ receptor and block this receptor. So, histamine does not bind with receptor and not give any action.

- # H₁-antagonists (first generation) cause sedation due to more selectivity for CNS neurons.

- Also due to their lipophilicity.

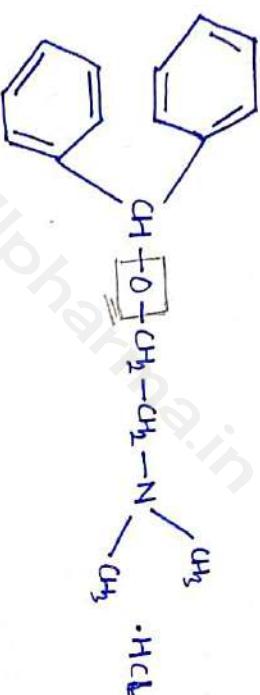
- functions →
- BBB easily cross
- Relaxation of smooth muscles - Bronchodilation.
 - Decrease vascular permeability

- Pain, pruritus, headache, hypotension → decrease ↓

- Various Drugs of first generation H₁-Antagonists

Synthesis →

1) Diphenhydramine Hydrochloride

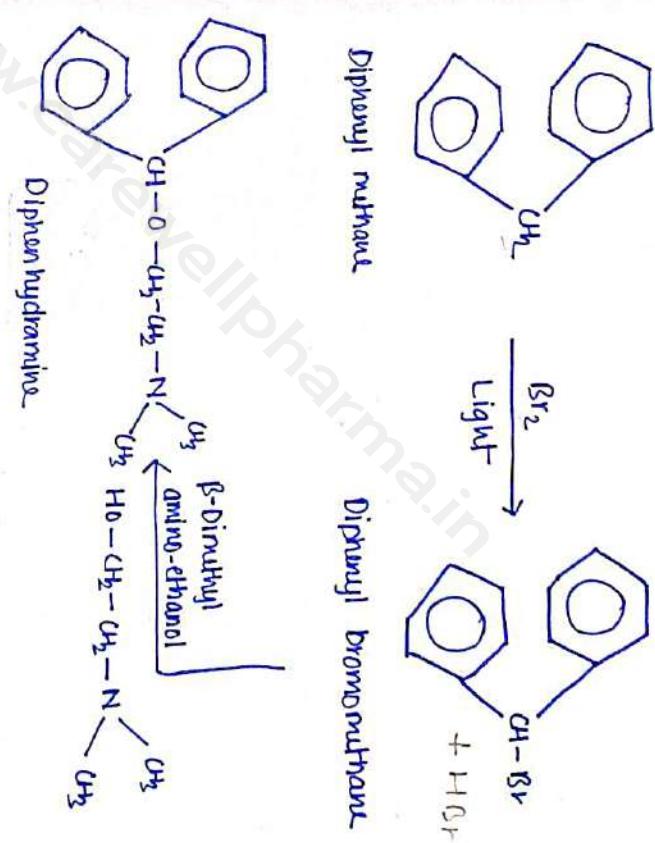


It is a first generation antihistamine which is mainly used for treating allergies.

M.O.A →

It is a competitive antagonist of H₁ receptor.

- It also act on CNS (centrally) and cause sedation, drowsiness.
- It also have some antimuscarinic activity.

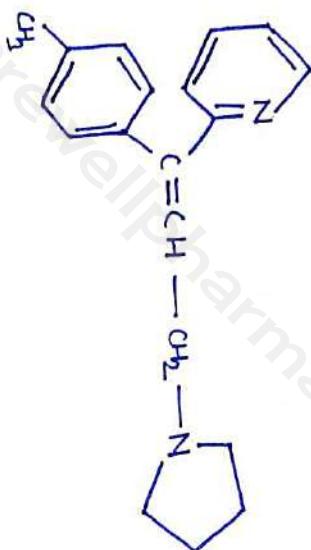


- Uses →
 - Used to treat allergic condition like pain, pruritis, rhinitis, hay fever, common cold, rashes, watery eye, cough, runny nose & sneezing etc.
 - Easily cross BBB so cause sedation and used to relax and fall asleep (treat insomnia).

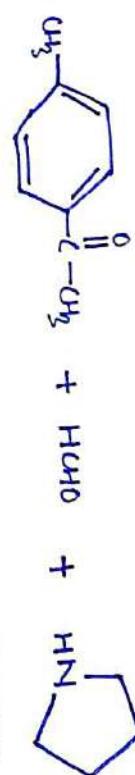
- used in prevention & treatment of motion sickness.

- also used in treatment of parkinson due to antimuscarinic activity.

ii) Triprolidine Hydrochloride



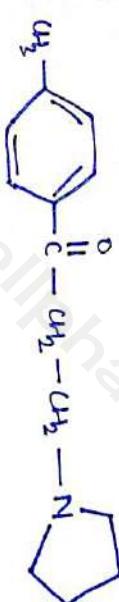
- synthesis ⇒



4-methylacetophenone

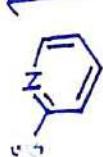
pyrrolidine

→ Mannich reaction



4'-methyl-3-pyrrolidinopropiophenone

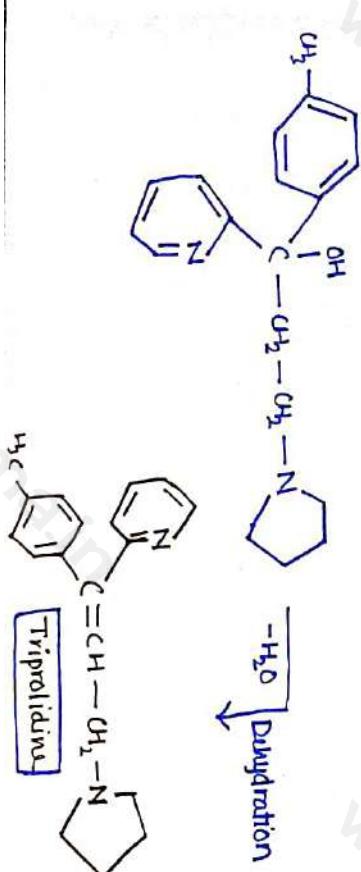
2-bromopyridine



→

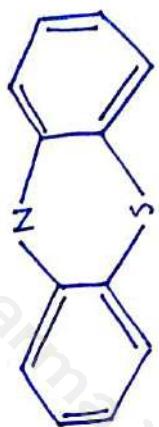
It is also a first generation H1-antagonist.

- MOA ⇒
- Bind with H1-receptor and block the receptor and also the action of histamine.
- Uses ⇒
- Used to control the symptoms of histamine.
- Combined with other cold drugs to provide relief in common cold.



iii) Promethazine Hydrochloride

It is the hydrochloride salt form of promethazine. It having antihistaminic, sedative and antiemetic properties.



$\cdot \text{HCl}$



Phenothiazine

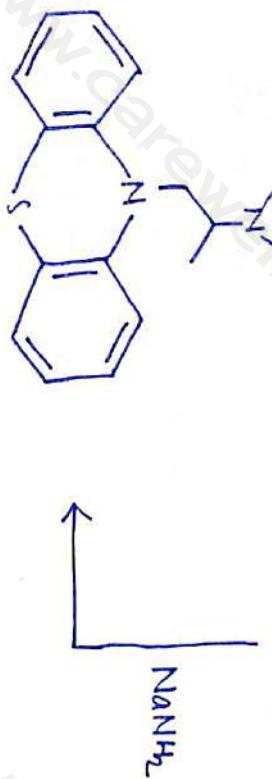
1-dimethylamino-
2-propylchloride

- mechanism of action →

- It act as a H_1 receptor antagonist.
- It also inhibit the central histaminergic receptors (dopamine, serotonin).
- It also act as anticholinergic (moderate affinity)

[OR]

Promethazine →

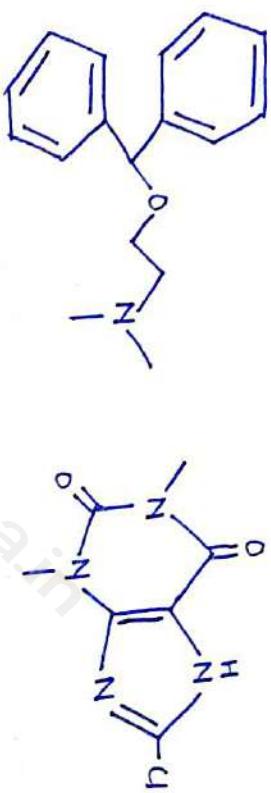


- Used as sedative for treatment of insomnia.
- used for medication of allergy like rhinitis and other allergic reactions.

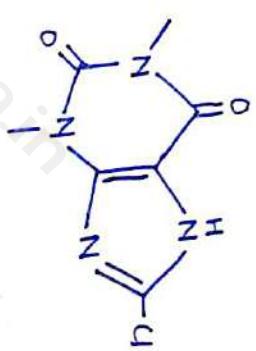
Synthesis of promethazine

Alkylation of phenothiazine with 1-dimethylamino-2-propylchloride give promethazine.

4) Dimenhydrinate \Rightarrow



Diphenhydramine



β -chlorophylline



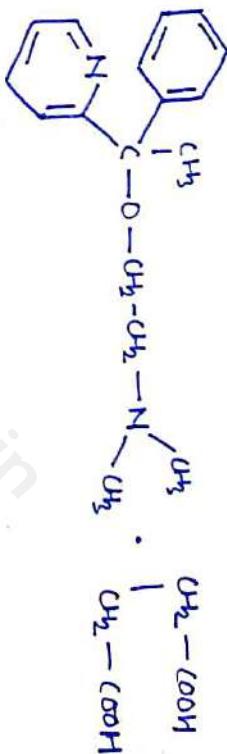
• MOA \rightarrow

- The antihistaminic property is due to H_1 antagonism in the vestibular system, in the brain.

• Uses \rightarrow

- used to treat allergic symptoms, allergy, hay fever & common cold
- used to treat insomnia.
- prevent morning sickness in pregnant woman in combination with Vitamin B₆ (pyridoxine).

5) Doxylamine succinate \Rightarrow



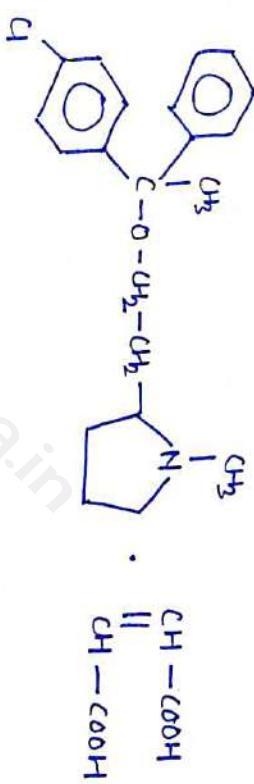
• MOA \rightarrow

- H_1 antagonists (same).

• Uses \rightarrow

- used to treat nausea, vomiting & prevent motion sickness.
- helps in treatment of ear congestion
- relieve vestibular disorder

• Uses \rightarrow



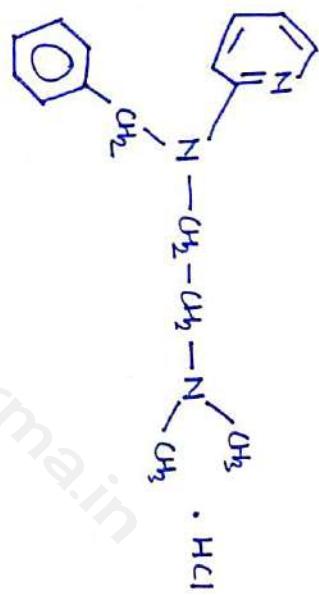
6) Clemastine fumarate \Rightarrow

- MOA →
 - H_1 Antagonists (same as other).

- Uses →

- treat allergic symptoms (same as others).
- it also have some anticholinergic activity.

g) Diphenylpyramine hydrochloride ⇒



- MOA →

- H_1 Antagonists (same as other)

- also have little anticholinergic activity.

- Uses →

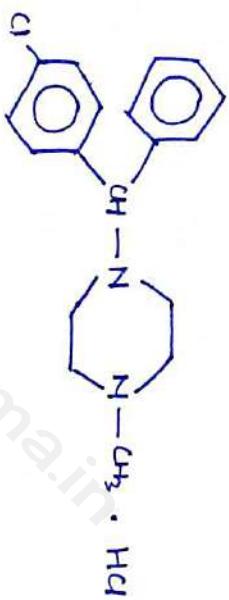
- used in treatment of upper respiratory tract allergic condition like asthma, hay fever, rhinitis.

- MOA →

- competitive antagonists for H_1 receptor, after binding on H_1 receptor it suppress the activity of histamine (cause temporary relief).

- Uses →

- same as other.



g) Chlorcyclizine hydrochloride ⇒

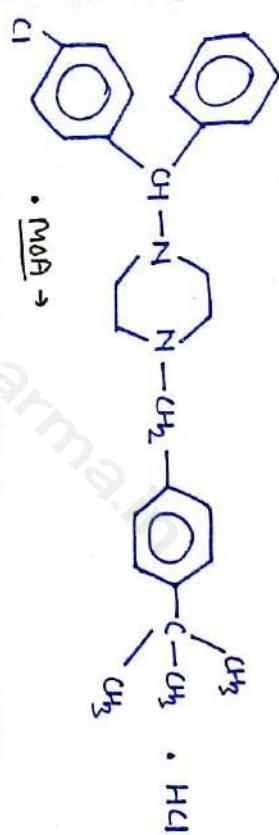
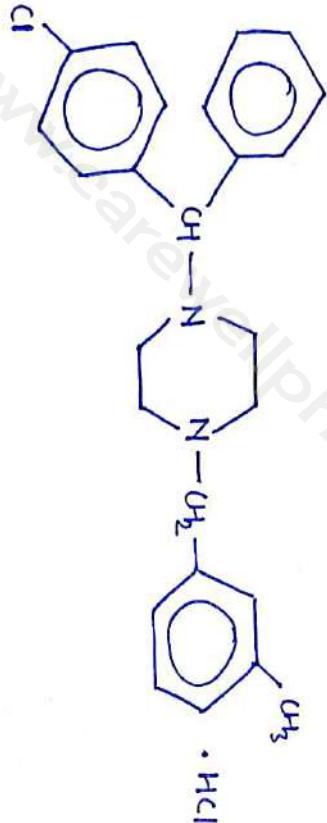
• MOA →

- H_1 Antagonists (same as other).

• Uses →

- treat allergic symptoms like rhinitis, urticaria and pruritus.
- used for treating hepatitis C.

10) Meclozine hydrochloride ⇒



pregnancy.

11) Buclozine hydrochloride ⇒



- Blocks H_1 receptor in vomiting centre

- also block muscarinic receptors.

- used as an anti-nausea or antiemetic agent
- also act as CNS depressant.

12) Chlorpromazine maleate ⇒

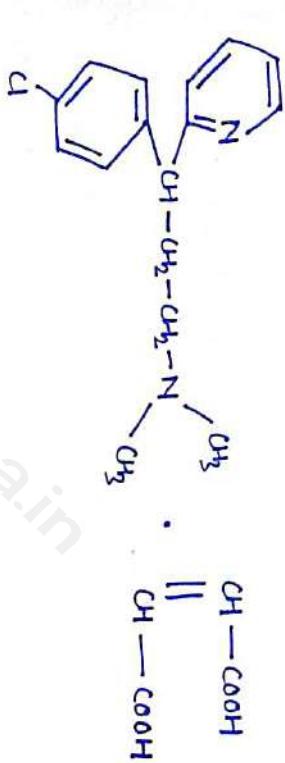
• MOA →

- H_1 Antagonists (same as other)

- also act as dopamine antagonists & anticholinergic.

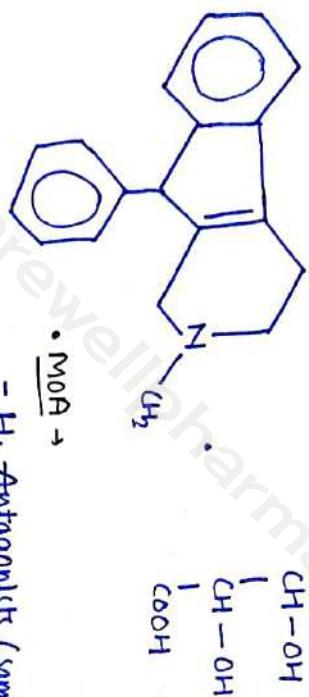
• Uses →

- used for treating of nausea, motion sickness or vertigo.
- safely used in the treatment of nausea in



- MOA →
 - H_1 antagonists (same as other)
- USS →
 - relieving allergic symptoms (same as others).

13) Phenidamine tartarate →

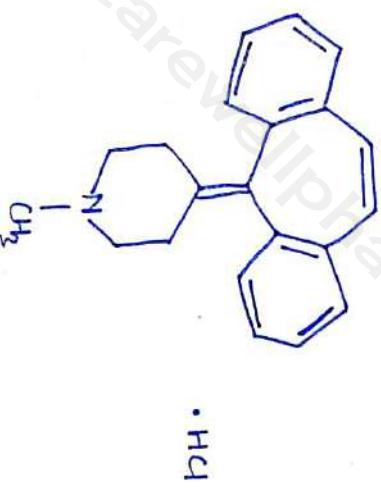


• MOA →

- H_1 Antagonists (same as others).

- MOA →
 - same (H_1 antagonist)
- USS →
 - treat allergic symptoms (same as others)
 - act as sedative, hypnotic & antiemetic

15) Cyproheptadine hydrochloride →

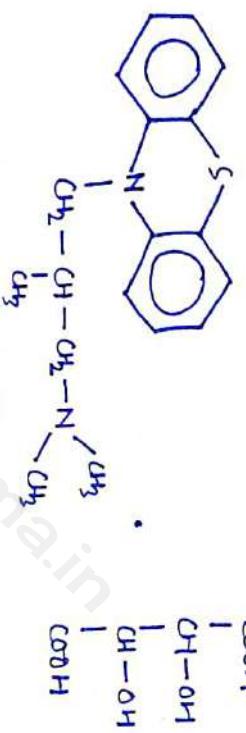


• HCl

• MOA →

- H_1 Antagonists (same as others).

14) Trimiprazine tartrate → Alimemazine



• MOA →

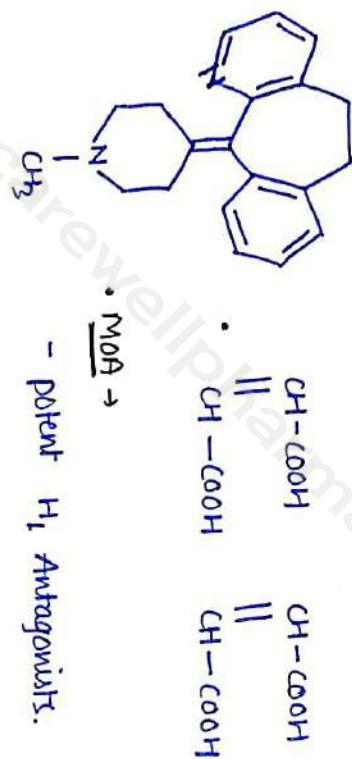
- potent H_1 antagonists
- also have anticholinergic, antidopaminergic and anti serotonergic activity.

• USS →

- treat allergic reactions
- treatment of akathisia (movement disorder).

- used as an antiemetic in cyclic vomiting syndrome

16) Fexofenadine Maleate ⇒



• MOA →

- potent H₁ Antagonists.

- Uses →

- treating the symptoms of upper respiratory mucosal congestion in perennial and allergic rhinitis.
- relief of nasal congestion and eustachian tube congestion.

11) H₁ Antagonists [Second Generation]

• Major side effect of first generation antagonist is sedation, drowsiness because they easily cross the BBB.

• But these second generation H₁-antihistamines does not cross BBB, so it does not cause sedation.

- They are more selective for peripheral H₁ receptors.
- They are hydrophilic in nature.

— mechanism & uses are same as first

generation but does not give their action on CNS.

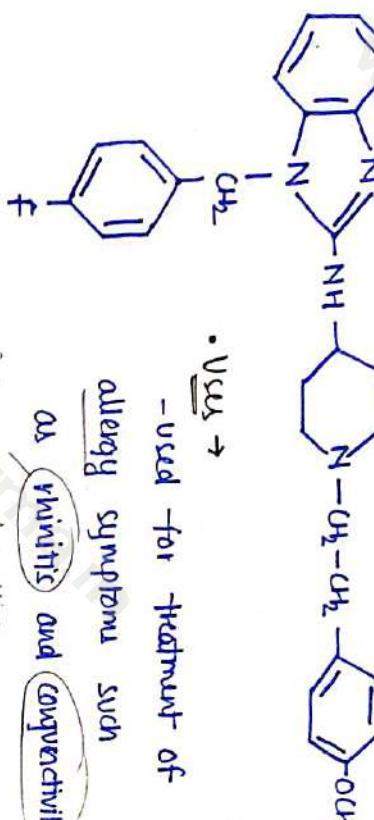
- Various drugs →

1) Astemizole

- MOA →
- Reversible blockade of H₁ receptor in GIT, uterus, large blood vessels & bronchial muscle.



3) Cetirizine →

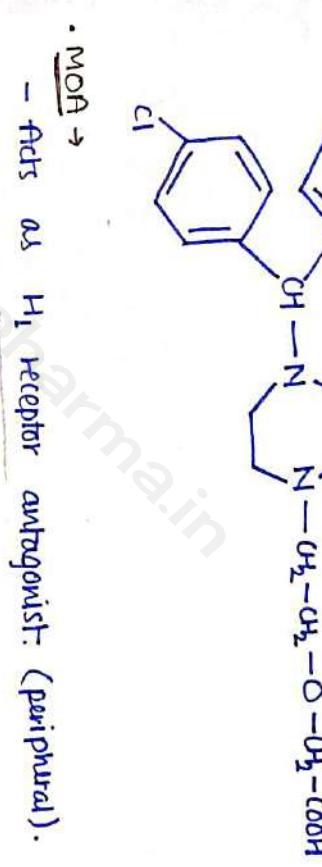


- Uses →
 - used for treatment of allergy symptoms such as rhinitis and conjunctivitis. Inflammation & swelling of mucous membrane of nose.
- MOA →
 - acts as H₁ receptor antagonist (peripheral).

2) Loratadine →

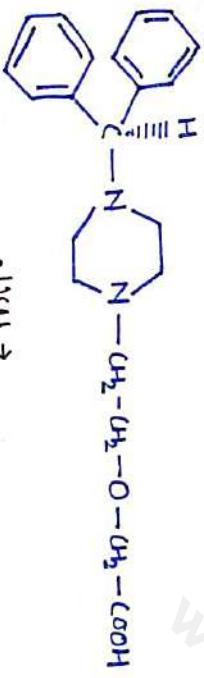


- MOA →
 - competitively antagonist of H₁ receptor (peripheral).



4) Levocetirizine → Levostatory enantiomer of Cetirizine

- Uses →
 - used to relieve allergy symptoms like runny nose, itchy eye, sneezing, itchy etc..



- Uses →
 - used alone or in combination with pseudoephedrine sulphate for relief of seasonal allergic such as rhinitis, pruritus and erythema.

- MOA →
 - active enantiomer of cetirizine which blocks H₁ receptor.
- Uses →
 - similar as Cetirizine but more potent.

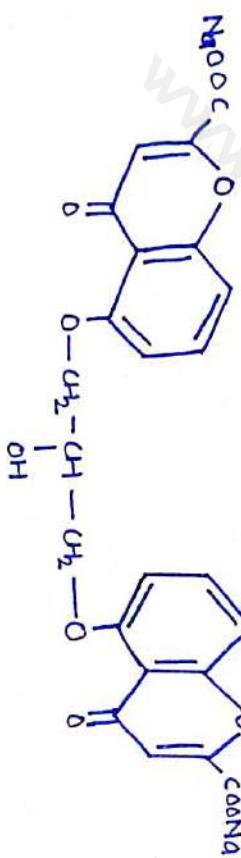
III) Mast cell stabilizers

- It inhibits the release of histamine, leukotrienes and other substances that cause hypersensitivity reactions from the mast cells.
- It is a mast cell stabilizer and it have anti-inflammatory activity.

↳ inhibit the release of prostaglandins

and leukotriene and inhibit activation of eosinophils, neutrophils, monocytes & platelets.

1) **Cromolyn sodium** →



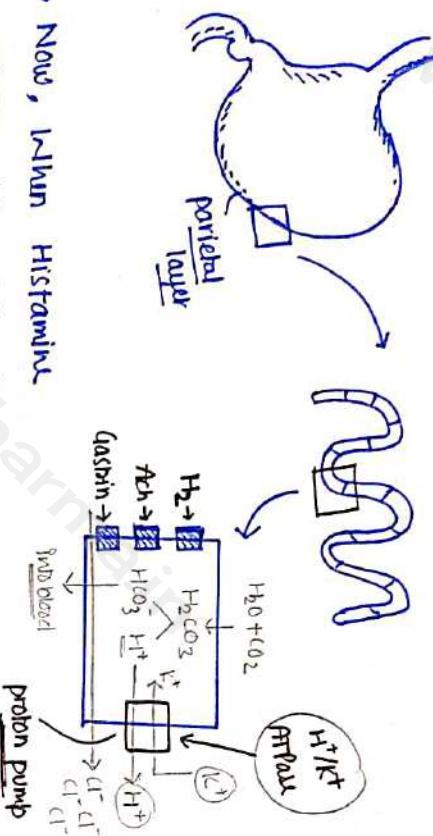
H₂-Antagonists

- These are those agents or drugs which block the H₂-receptor which present in the stomach.
- These drugs mostly decrease the production of acid in stomach.
- These drugs are used in the treatment of gastric and duodenal ulcer.
- Mechanism ⇒
 - H₂ receptor are present in the parietal cells in the parietal layer of stomach.

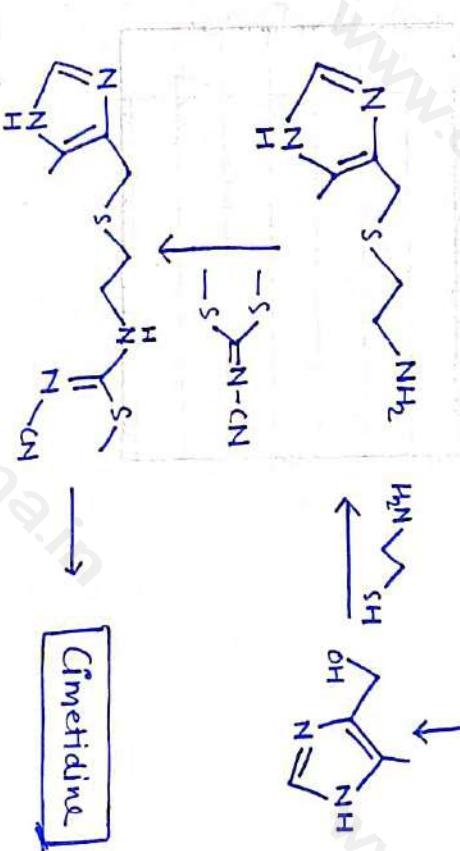
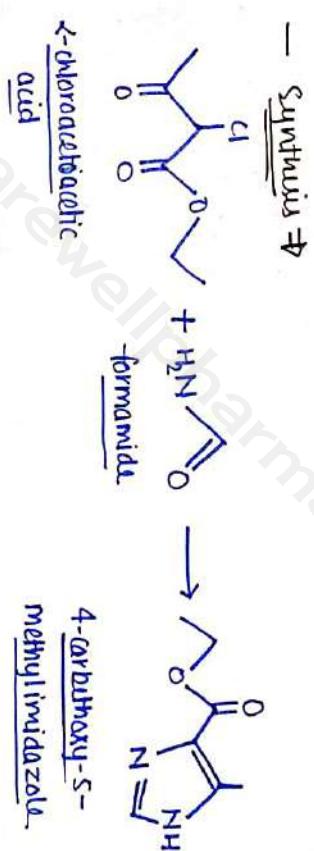
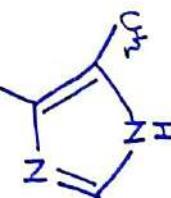
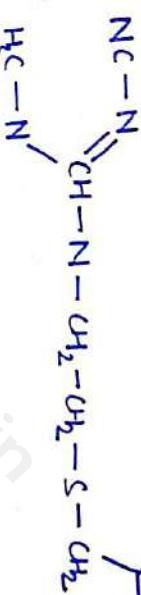
- MOA →
 - It inhibit degranulation of mast cells thus preventing the release of histamine and leukotrienes.

- Uses →
 - Used for the management of bronchial asthma.
 - Its nasal solution is used for allergic rhinitis.
 - Its eye drop are used to treat allergic conjunctivitis - inflammation at outer margins of eyeball and inner eyelid.

- Now, when Histamine release, it bind with H_2 receptor
- Now, H_2 receptor are also GPCR, so it activates the cAMP
- Now thus cAMP increase $[Ca^{2+}]$ which further increase or activate proton pump and increase the secretion of H^+ \rightarrow exocytosis
- Which further increase the production of HCl .
- Now, H_2 Antihistamine block the H_2 receptor so all the mechanism inhibit. and all the action of Histamine reduced.
- HCl decrease \downarrow .



• Various Drugs \rightarrow



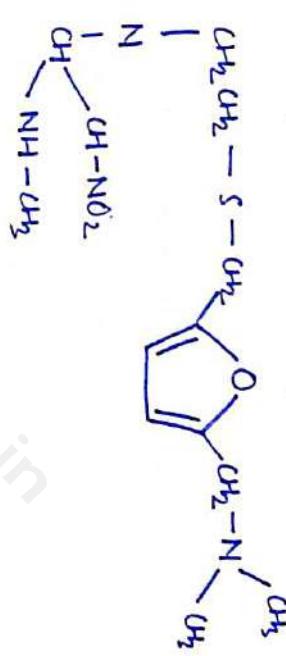
- MOA →

- Antagonist of H_2 -receptor and decrease the activity of histamine.

- Uses →

- Used in treatment of gastric and duodenal ulcers.

2) famotidine →



• MOA →

- more potent competitive inhibitors of Histamine H_2 receptor than Cimetidine.

- Uses →

- used in treatment of gastric and duodenal ulcers.

- Mechanism →

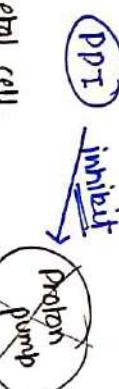
- There are one enzyme H^+/K^+ ATPase which present in parietal cell of stomach and it is responsible for HCl secretion.

3) Ranitidine →

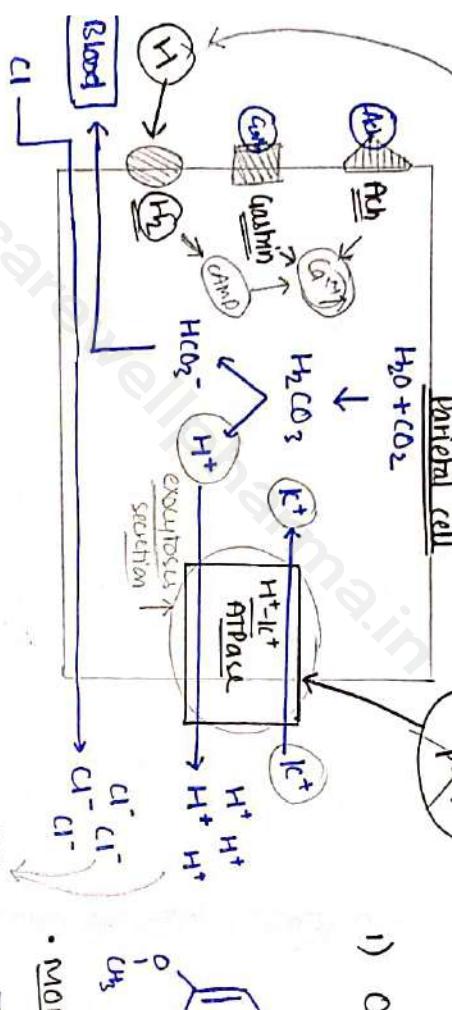
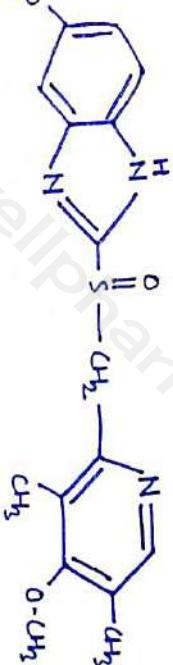
- MOA →
- same as other.

- Now these drugs contain a Sulphonyl group In a bridge between substituted benzimidazoles and purine rings.

- H⁺ blocks gastric acid secretion even if Histamine bind with their receptor.
- Now, H⁺ ion does not secrete out so production of HCl decreases.



1) Omeprazole →

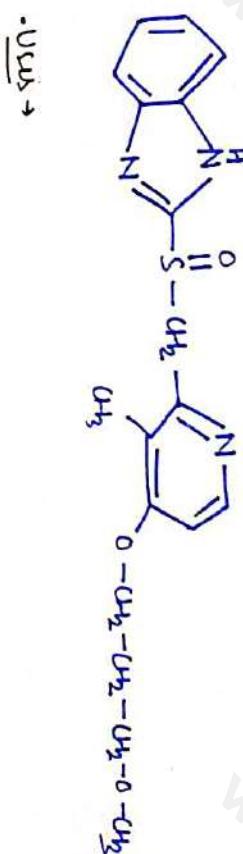
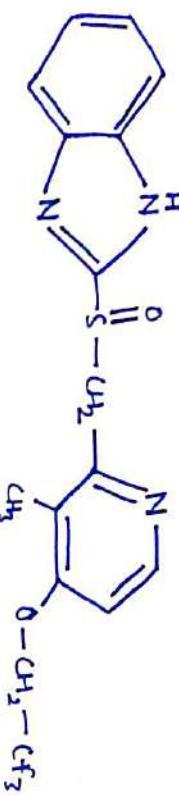


• MOA →

- Selective and irreversible proton pump inhibitors.
- H⁺ suppresses gastric acid secretion by inhibiting the H⁺-K⁺-ATPase in gastric parietal cells.

- Now, when PPI introduce into parietal cells from blood its Sulphonyl group bind with H⁺ K⁺ ATPase-SH enzyme thus they form Drug enzyme complex.
- which further metabolize easily & irreversibly inactivate the proton pump.

↓
Dyspepsia, gastritis & oesophagitis due to hypersecretion of acid.

2) Lansoprazole \Rightarrow 

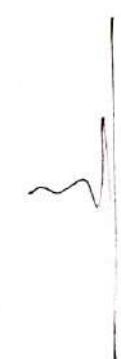
- MOA \rightarrow
- same as other.

4) Pantoprazole \Rightarrow

• Uses \rightarrow
 - used in treatment of duodenal and gastric ulcer.
~~→ Zollinger-Ellison syndrome (ZES syndrome).~~
 (in which tumors cause the stomach to produce too much acid, resulting in peptic ulcers).
 - treatment of gastroesophageal reflux.
 Stomach content rise up into esophagus. — same as other.
 which cause heart burn, chest pain,
 vomiting etc..

• MOA & uses \rightarrow

- MOA \rightarrow
- same as other.



COMPLETE

3) Rabeprazole \Rightarrow

- MOA \rightarrow
- same as other.

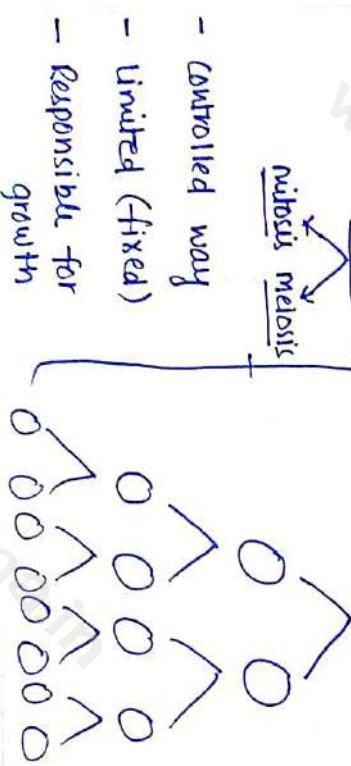
ANTI-NEOPLASTIC AGENTS

- These are those agents or drugs which are used in the treatment of cancer.

Anti-neoplastic agents
oppose neoplasm drugs
CANCER

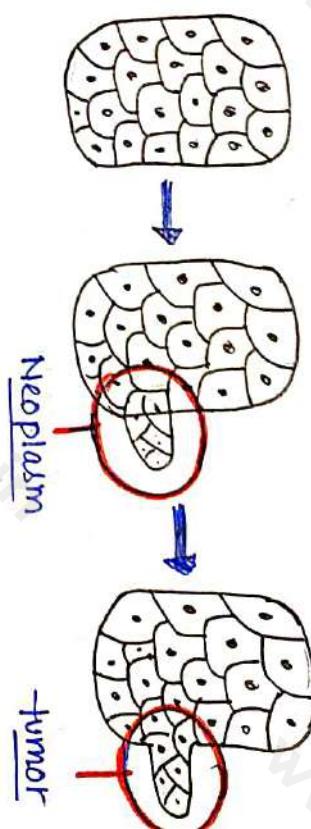
It is a group of disease which involve an abnormal and uncontrolled cell division in body cells.

— through cell division

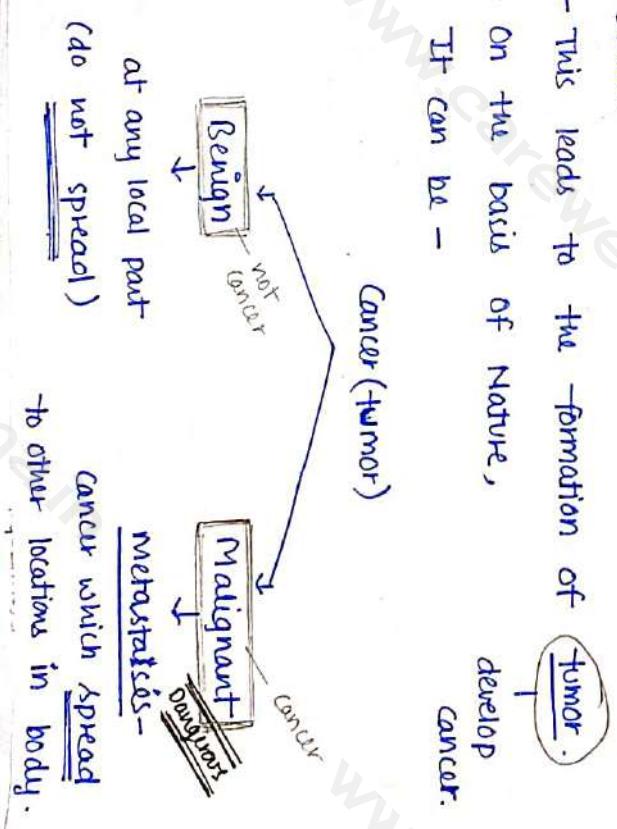


— parent cells

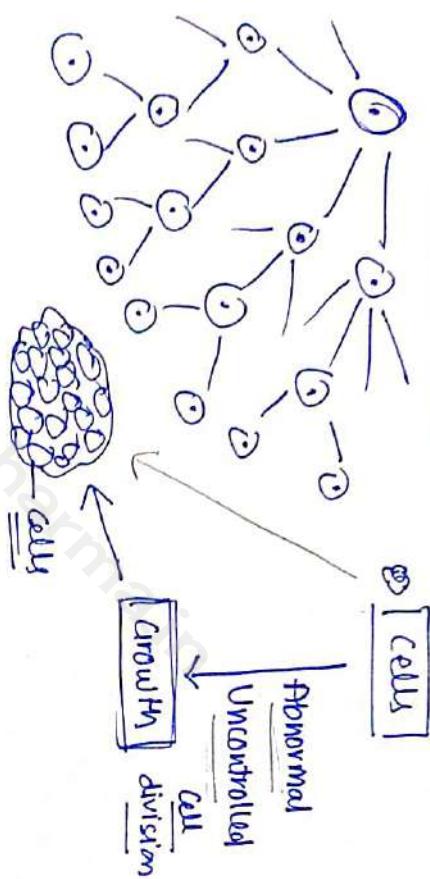
- Neoplasm — An abnormal mass of tissue that forms when cells grow and divide more than they should or do not die when they should.
- This leads to the formation of tumor.
- On the basis of nature, it can be —



Cancer (tumor)



In condition of cancer



- Growth do not follow proper way
- Uncontrolled cell division
- Invade tissue - metastasis (spread)
- No apoptosis (stop cell death)

Reason →

- Chemicals - plastic etc
- Radiations - UV rays
- Heredity - genetic - ^{Onco genes} _{Onco suppressor genes} → Onco stimulated gene
- Diet (tobacco, etc.) -
etc...
etc, Jatro, Uva, etc, Chel etc...

Types of cancer →

It can be classified as many ways . it is mainly based on where it begins -

- i) Carcinomas - It begins in the skin or the tissue that covers the surface of internal organs and glands.
- [eg.] Breast cancer, prostate cancer, lung cancer and colorectal cancer etc..

ii) Sarcomas - A sarcoma begins in the tissue that supports and connect the body.

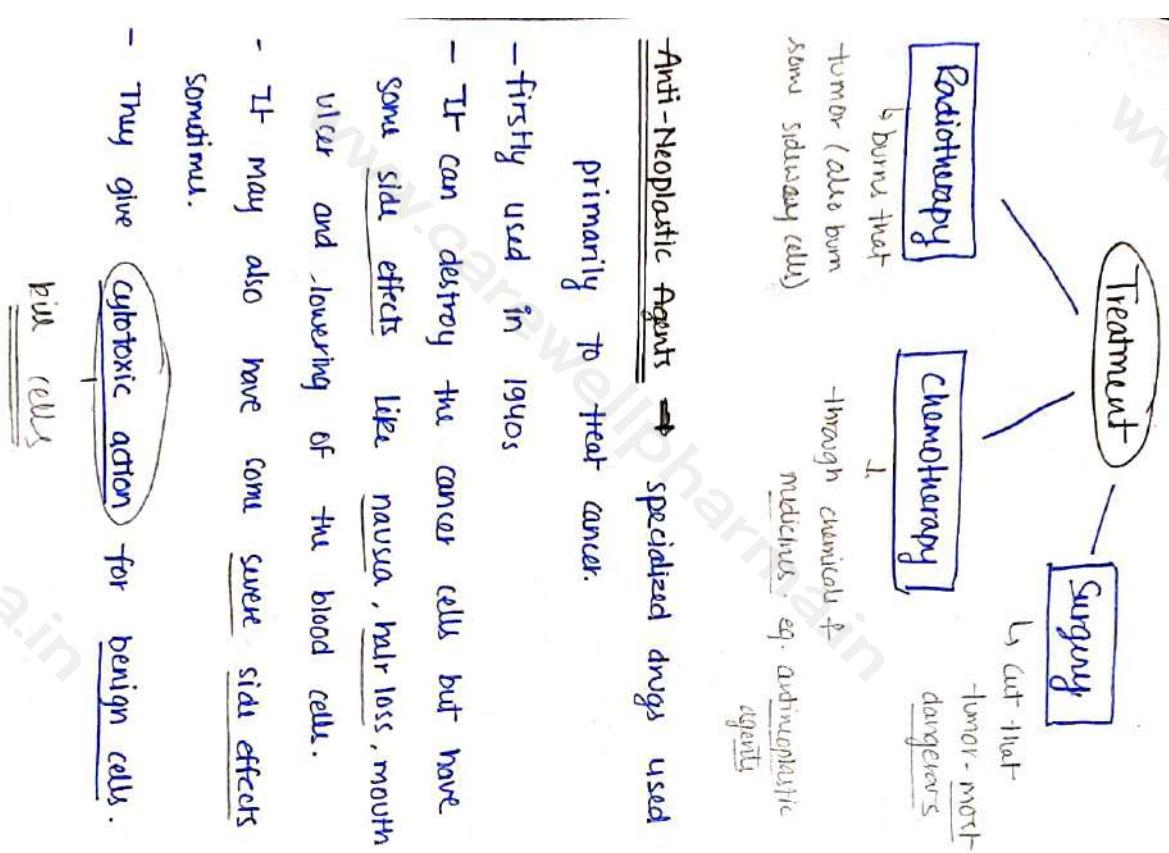
A sarcoma can develop in fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage or bone.

iii) Leukemias - Blood cancer.

It begins when healthy blood cells

change and grow uncontrollably .

- iv) Lymphomas - It begins in the lymphatic system. helps to fight against infections -

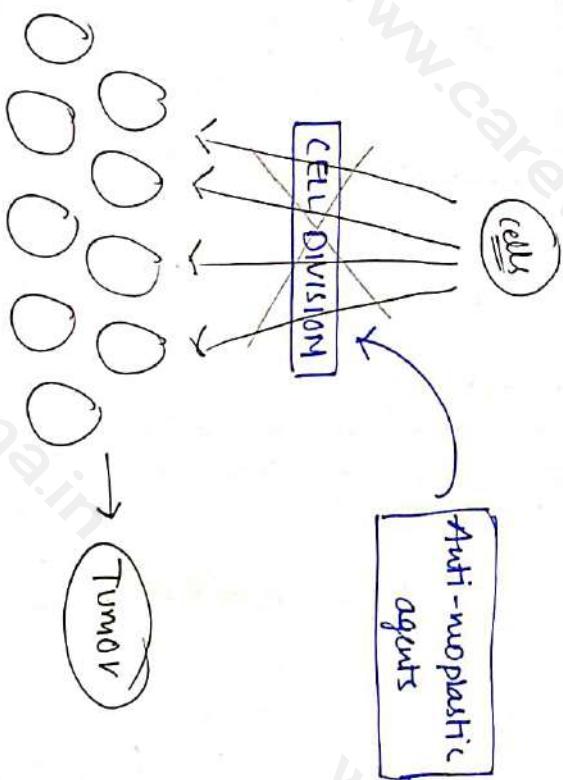


Mechanism →

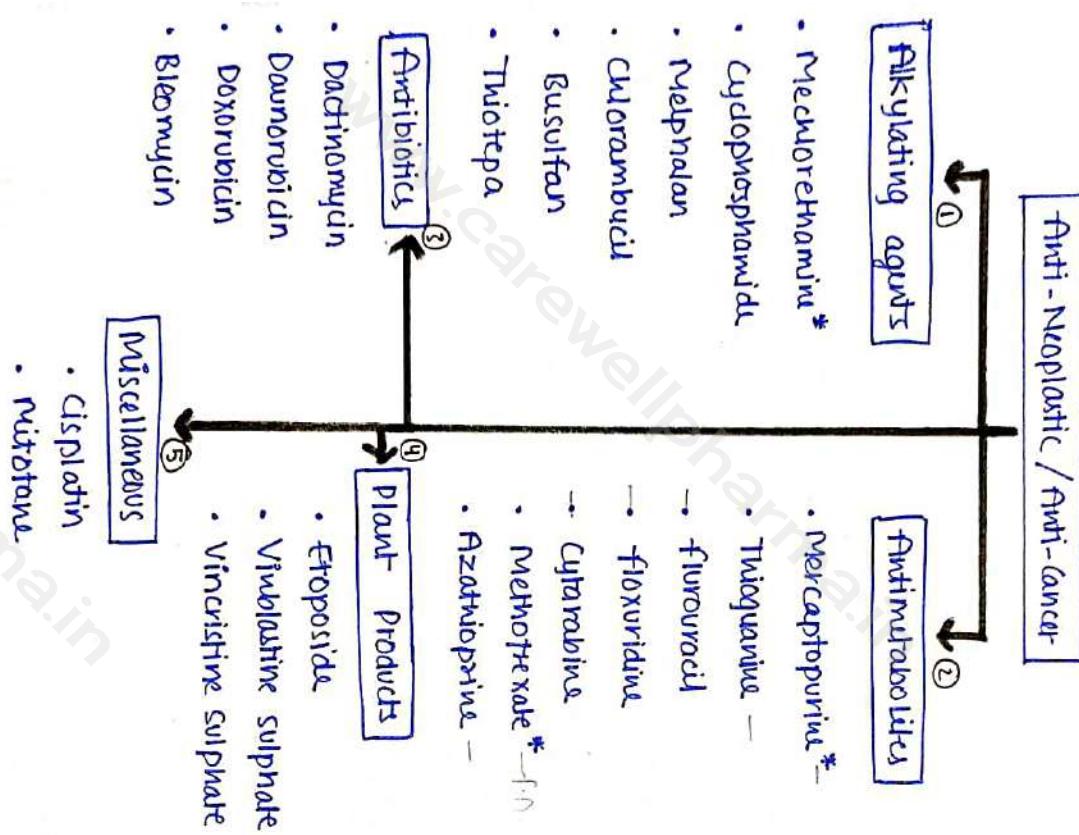
The main reason of cancer is abnormal + uncontrolled cell division (proliferation of cells).

So,

- If we control or stop this cell division, then we can control the development of cancer.
- The main mechanism of this agents are to stop or control the cell division.
- Now their also vary with their types :—



Classification →



① **Alkylating Agents** ⇒

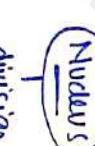
Those agents which comes under the class of anti-neoplastic or anticancer drugs.

- These drugs binds covalently with the structure of DNA which inhibit the replication of DNA resulting in the decrease-
ment of cell division.

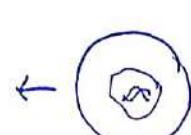
— Mechanism ⇒

Normally cell division

Karyokinesis — division of Nucleus



division of genetic material



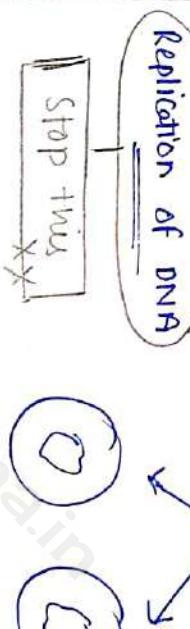
Karyokinesis



↓



Cytokinesis



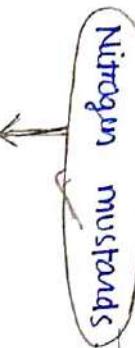
Replication of DNA

—> Karyokinesis

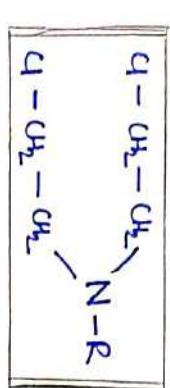
—> Cytokinesis

- Alkylating agents blocks the replication of DNA.

- Alkylating agents are the derivatives of

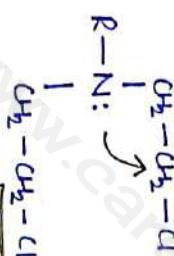
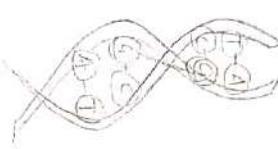
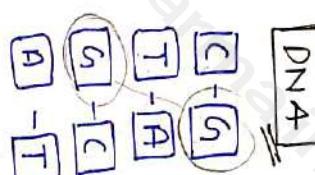


These are cytotoxic drugs - therapeutic agents similar to mustard gas.



- Alkylating agents form

Aziridinium ion.



Nitrogen mustard

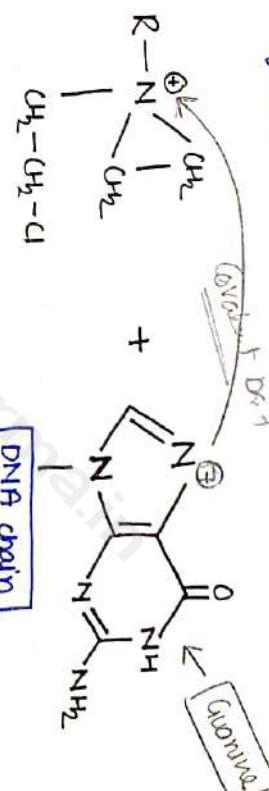
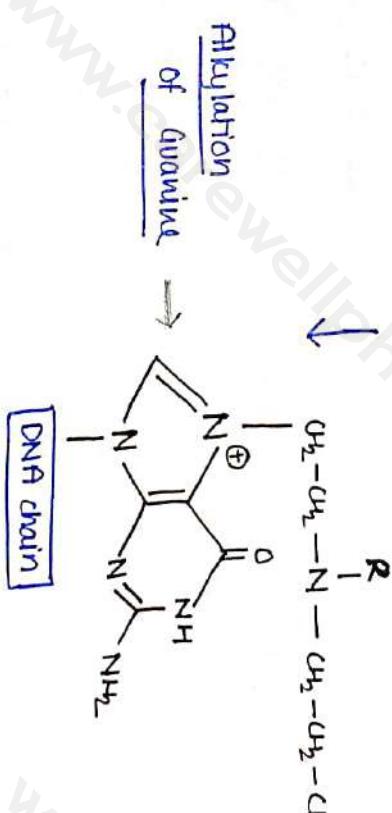
C - Cytosine
T - Thymine
A - Adenine

G - Guanine



Aziridinium ion

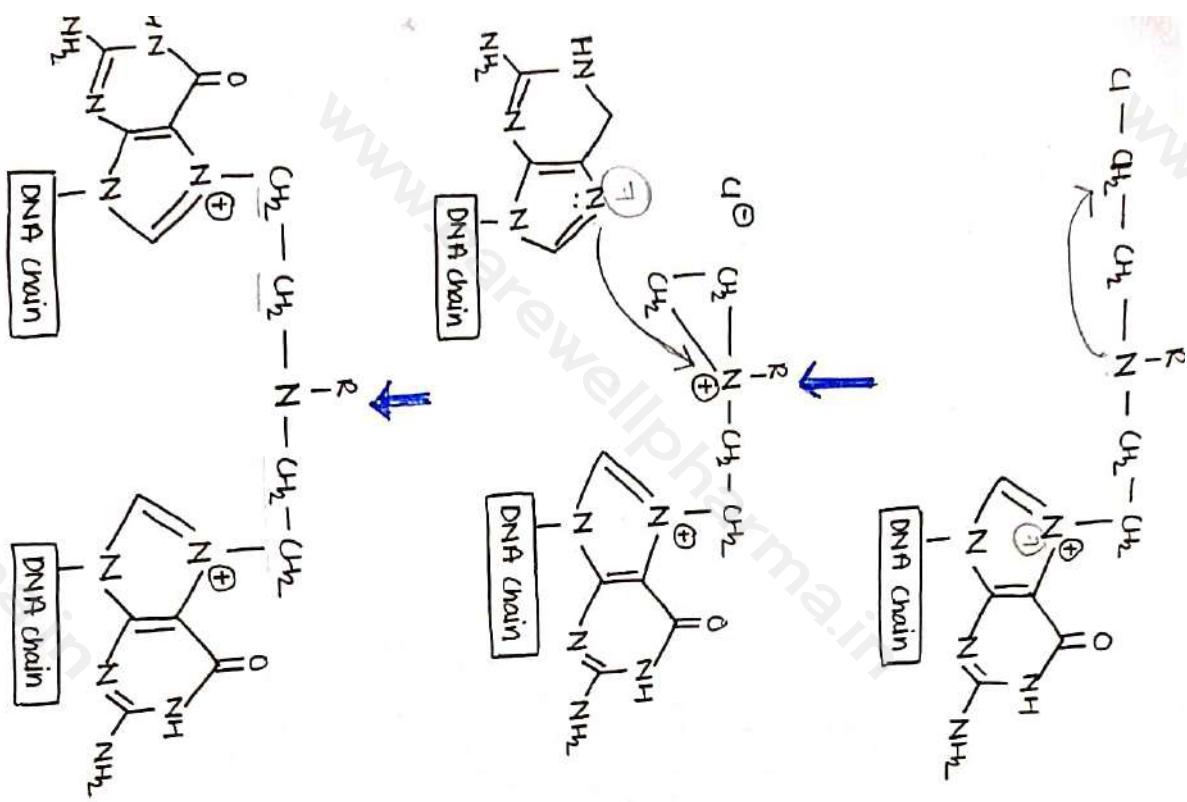
- Now this alkylating agent binds (bind covalently) the DNA at 7th position of guanine.



- Now this alkylating agent again binds with 7th position of guanine (DNA), on their second side.

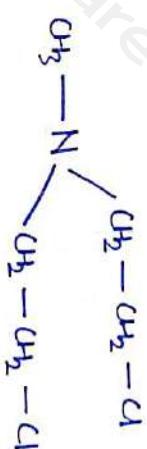
Aziridinium ion

Carbenium ion



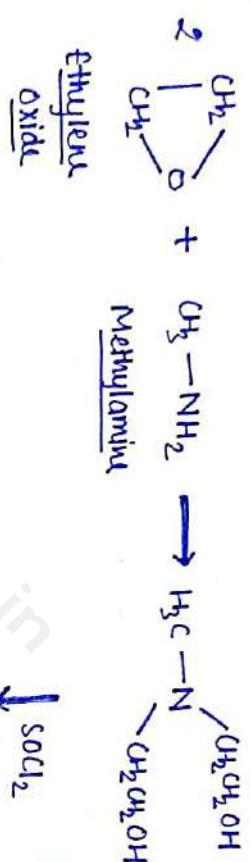
- Thus results in the cross-linking of two nucleic acid chains, Abnormal base pairing & scission of DNA strand. Nitrogenous base
- mismatch the pair of Nitrogenous base pair in DNA. → Inhibition of DNA synthesis.
↓
Decrease cell division / cell death

• Various Drug ⇒
 ① Mechlorethamine (Mustin) ⇒

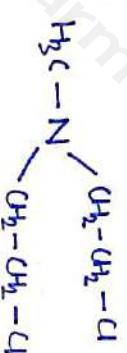


- Mechanism →
- It comes under the class of Nitrogen mustards.
 - It damages DNA via the formation of cross link (prevent DNA synthesis).
 - induction of mispairing of the nucleotides leading to mutations.

Synthesis \Rightarrow



Mechlorethamine
(Mustin)

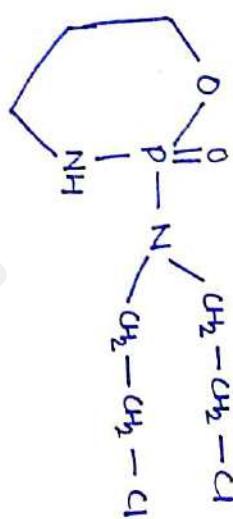


In this synthesis, ethylene oxide reacts with methylamine to give α,ω -(methylimino) diethanol which further on chlorinated with SOCl_2 gives mustin [OR] mechlorethamine.

Uses \Rightarrow

- Used in the treatment of Hodgkin's disease (Cancer of part of immune system lymphatic system).
- also used for the treatment of metastatic carcinoma.
- used topically in the treatment of mycosis fungoides (T-cell lymphoma). Most common type of blood cancer.

② Cyclophosphamide \rightarrow



MOA \rightarrow

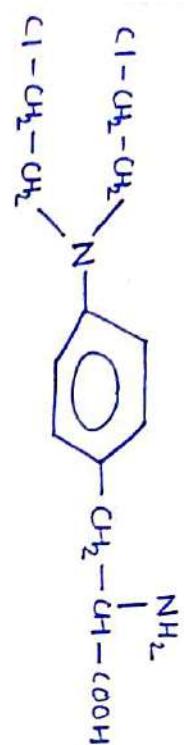
- The active metabolite of cyclophosphamide i.e. phosphoramid mustard forms DNA cross links between and within DNA strands at guanine N-7 position.

- This is irreversible and leads to cell death.

Uses \rightarrow

- used in the treatment of lymphomas, some solid tumors and some forms of leukaemia (Blood cancer).
- It is also active against Hodgkin's disease, breast, ovarian cancer and lung cancer.
- also used in some various non-neoplastic disease etc...

③ Melphalan →



- MOA →
 - same as other

- Uses →

- used to treat retinoblastoma (retina cancer).

- used with prednisone in the treatment of amyloidosis.

Related to a type of bone marrow cancer called myeloma/multiplex myeloma.

- used mainly in the treatment of multiple plasma cell myeloma and carcinoma of breast and ovary.

④ Chlorambucil →



- MOA →
 - same as other

⑤ Bisulfan →



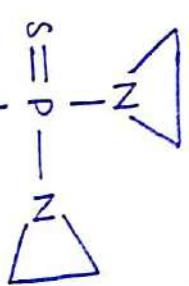
- MOA →

- It is a bifunctional alkylating agent.
- It interacts with the thiol groups of proteins and nucleic acids and forms DNA-protein and DNA-DNA cross links.
- these cross-linkages prevents the synthesis and function of DNA.

- Uses →

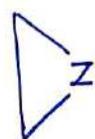
- Used to treat chronic granulocytic leukaemia.
- also used as immunosuppressive effect on bone marrow.

⑥ Thiotepa →



- Moa →

It acts on



7^{th} position of
guanine base of DNA which cause cross-

linking with DNA double helix strands
which further decrease/stop cell division.

- Uss →
 - used for treating breast, ovarian and bladder cancer.
 - also used in the treatment of various lymphomas.

⑦ Antimetabolites →

Metabolites are those important constituents which are responsible for the synthesis of DNA.

[eg]. purine, pyrimidine, folic acid which are used in the synthesis of DNA.

- Antimetabolite is a substance that replaces or inhibit a specific metabolite of a cell which interfere with normal cellular metabolic functions.

• Antimetabolite has similar structure as metabolite which prevent the biosynthesis of DNA.

purine analogues

Antimetabolites

- purine analogues
- pyrimidine analogues
- folic acid analogues

1) purine analogues →

mercaptopurine, thioguanine, azathioprine

These analogue have thiol group at position 6 of the purine ring.

- Normally,

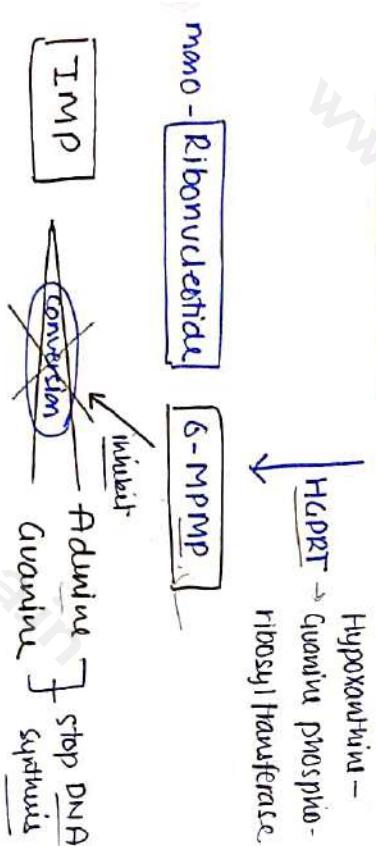
- Purine analogue

- they contain purine ring

- Cytotoxic & prodrug.

- Now these drugs converted into its active.

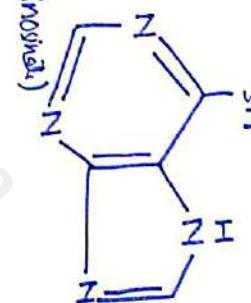
eg - 6-mercaptopurine 6-MP



Ionisine Monophosphate

- MoA →
- It metabolised into 6-MMP (6-thioguanine)

by Hprt

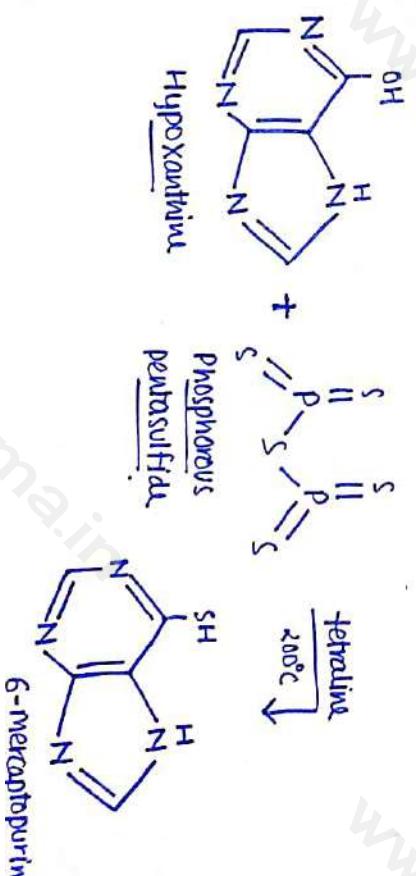


- Inhibits conversion of ionisine acid to adenyllic acid and xanthulic acid
- prevent the purine biosynthesis.

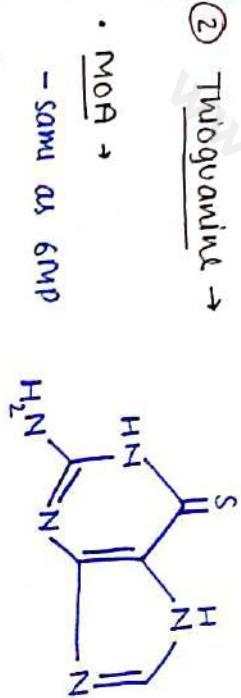
• Uses →

- used in the treatment of acute monocytic leukaemia.

• Synthesis →

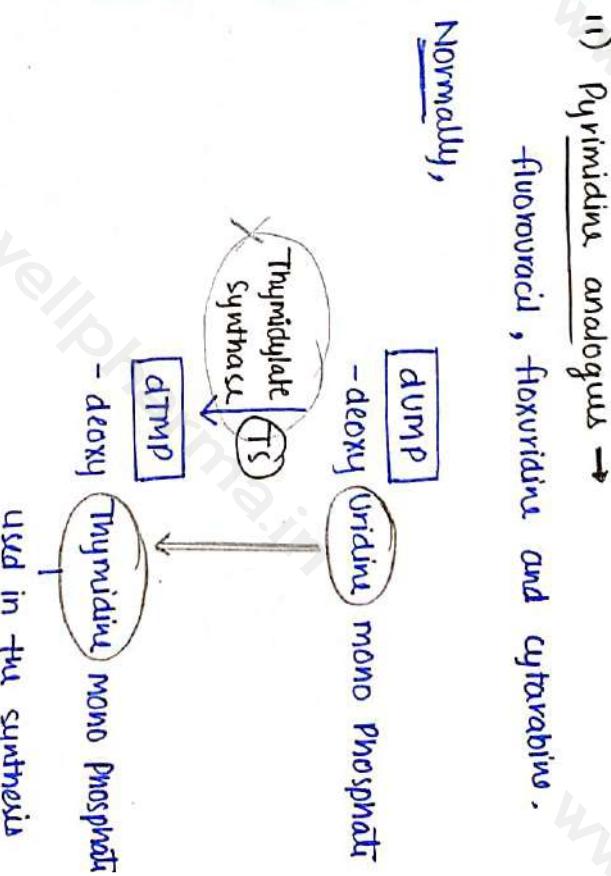
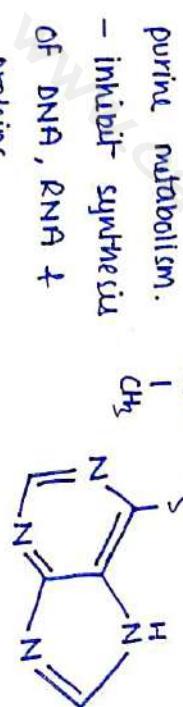


② Thioguanine →



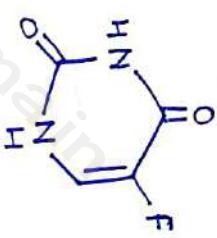
- Uses →
 - used in the treatment of acute non-lymphocytic leukaemia.
 - + type of cancer of blood and bone marrow with excessive immature white blood cells.

③ Azathioprine →



- Now, these pyrimidine analogues inhibit this enzyme (TS) Thymidylate synthase which further inhibit the synthesis of thymidine - which further inhibit DNA + cell division.
- Uses →
 - used as an immuno-suppressant.
 - used for preventing renal transplant rejection.

① fluorouracil →

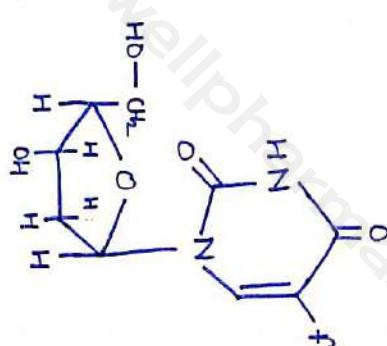


- MoA →
 - inhibit enzyme Thymidylate synthase (same as above).

- Uses →
 - used for treatment of oesophageal, anal, stomach, pancreatic, breast and skin cancers.

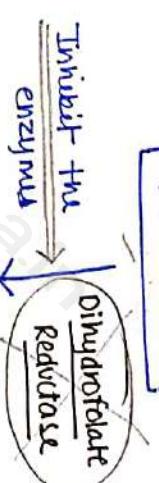
(2) Floxuridine →

- MoA →
 - similar as fluorouracil
- Uses →
 - used for treatment of kidney and stomach cancer.
 - used in treatment of colorectal cancer.



Normally,

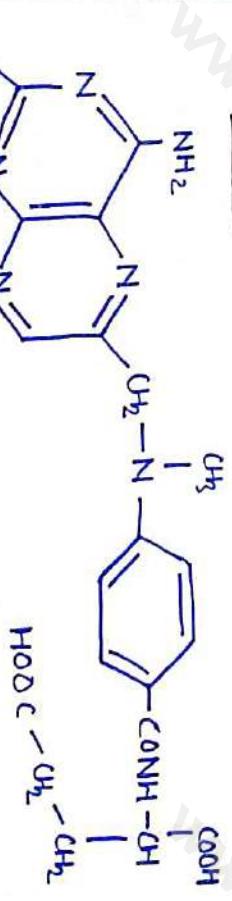
folic acid analogues →
(methotrexate)



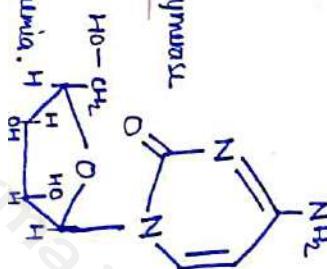
Tetrahydro-folic acid

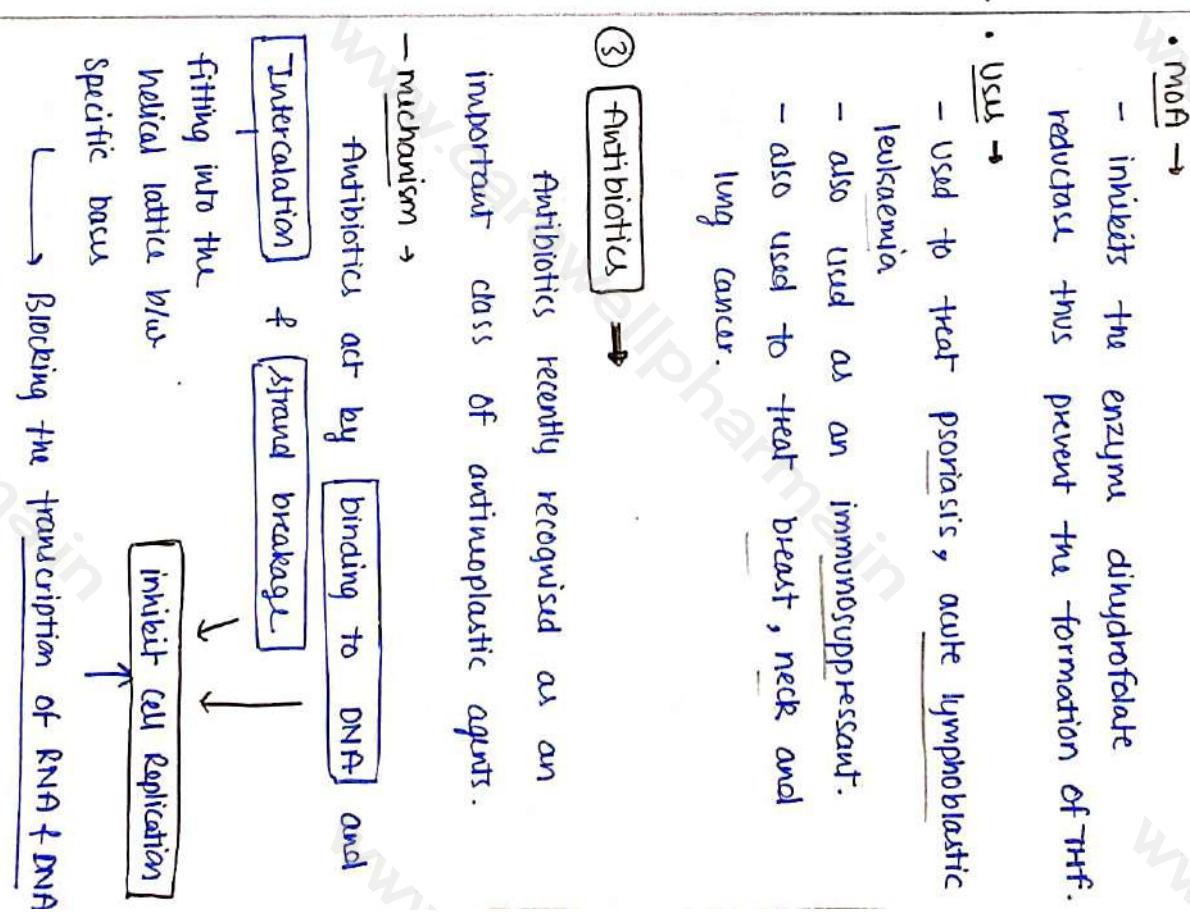
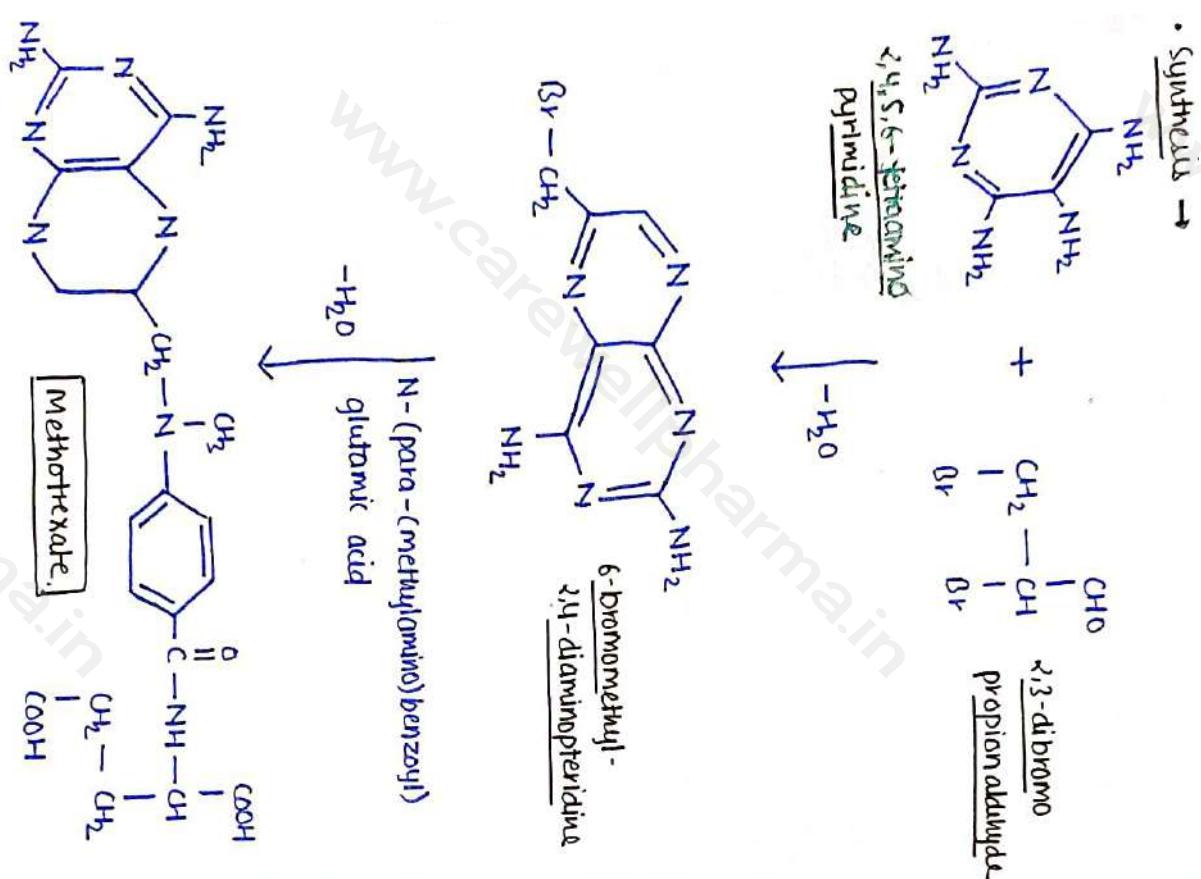
THF
necessary for the synthesis
of purines, thymidine & some
amino acids.

(1) Methotrexate →



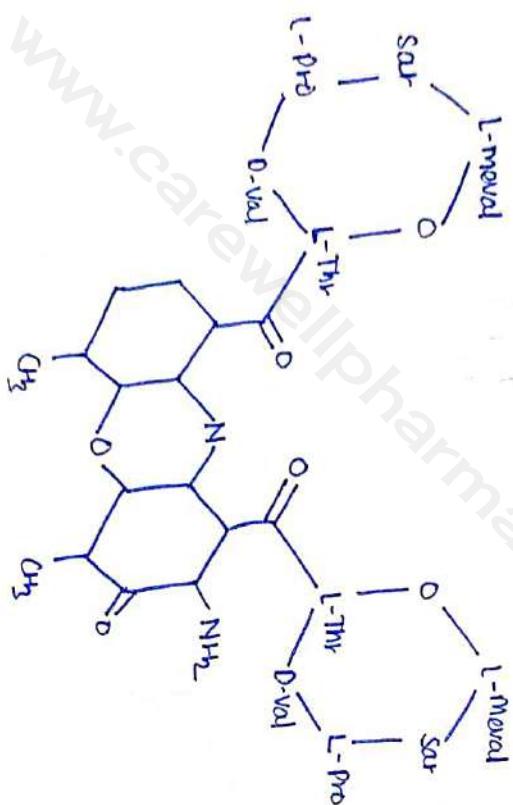
- (3) Cytarabine →
- MoA →
 - inhibit DNA polymerase
 - Uses →
 - used in acute non-lymphocytic leukaemia.





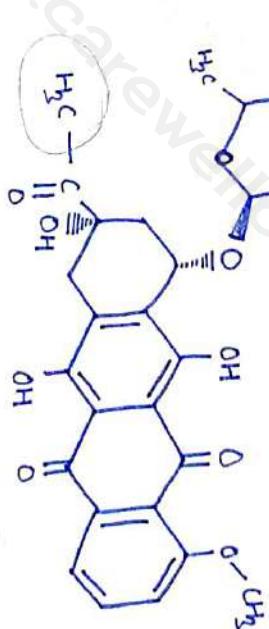
- Many antineoplasti antibiotics are obtained from fungus streptomyces include bleomycin etc..
- Various drugs -

① Dactinomycin →



② Daunorubicin → (daunomycin)

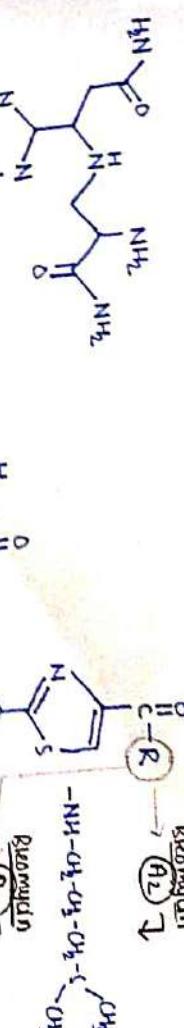
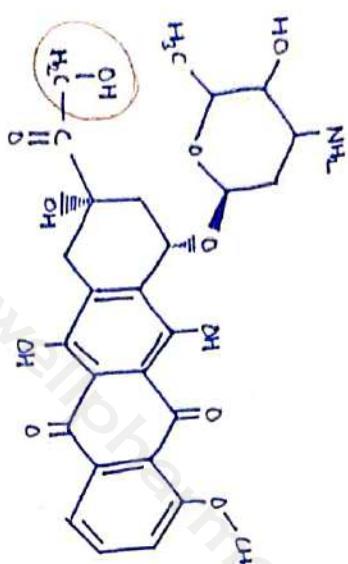
- It comes under the class of anthracyclines
- obtained from streptomyces peucetius



- MOA →
 - It interact with DNA by intercalation and inhibit the macromolecular biosynthesis and inhibit the topoisomerase II which relax super coils in DNA transcription.
- uses →
 - used in treatment of leukemia, kaposi's sarcoma etc.
 - Decline protein synthesis.

③ Doxorubicin →

- It is a cytotoxic anthracycline antibiotic.
- Obtained from *Streptomyces peucetius*.



• MMA →

- same as daunorubicin

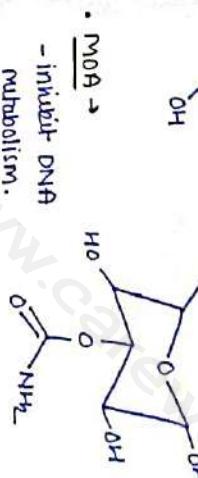
• VCR →

- used in treatment of leukaemia, Kaposi's sarcoma, breast cancer, lymphoma, bladder cancer.

• MMA →

- inhibit DNA metabolism.

- same as other.



• VCR →

- used in the treatment of carcinoma of head, neck, cervix, vulva and penis.

- also used in treatment of trachea, bronchus and lungs..

④ Bleomycin →

- It is obtained from *streptomyces verticillus*.

- It consist of bleomycin A₂ and bleomycin B₂.

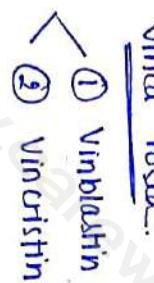
(4) Plant Product →

Plants medicines are important in the prevention and treatment of cancer. Because these are derived from plants so they have less undesirable side effects.

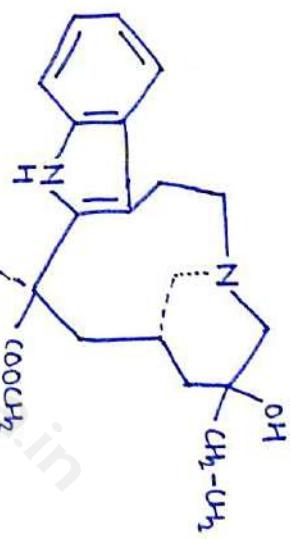
— Various drugs →

1) Vinca alkaloids

— isolated from the periwinkle plants

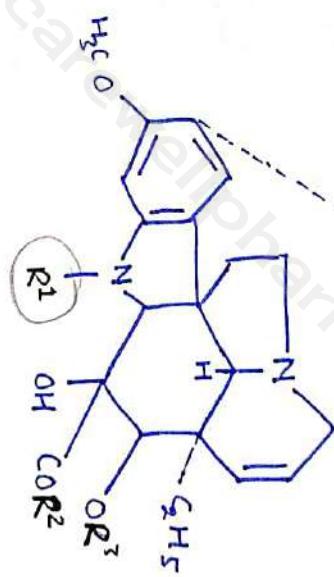


1) Vinblastine Sulphate →



Mechanism → binds → Tubulin

Vinca alkaloids



polymerizes into long chains (filaments) that form microtubules

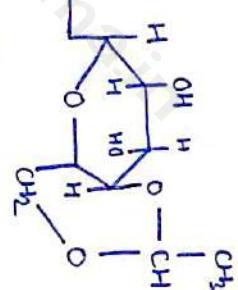
cell division
↓
enable cells to undergo mitosis

2) Vincristine sulphate →



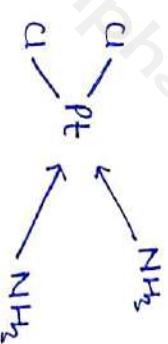
- Uses →
 - used in the treatment of breast cancer, testicular cancer, Hodgkin's lymphomas.
 - used in treatment of Lymphocytic leukaemia.

3) Etoposide →

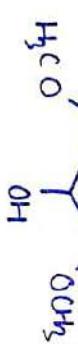


⑤ Miscellaneous

1) Cisplatin →



- MOA →
 - same as alkylating agents.



- MOA →
 - inhibit forms complex

- Topoisomerase II enzyme

- Topoisomerase II enzyme

- breakage of DNA strands

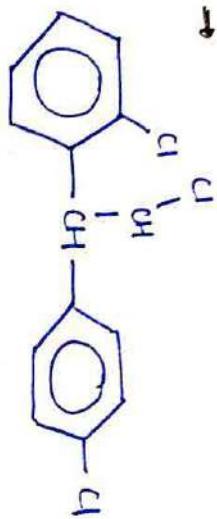
- leads to apoptosis & cell death

*Breaking/repairs
depends on DNA duplexes*

- Uses →
 - it is obtained as extracts of may apple plants.
 - effective in the treatment of lung cancer

- also used to treat leukemia, testicular cancer and Hodgkin's disease.

2) Mitotane →



- MoA →
 - still unknown
 - But acc to present data, it changes the peripheral metabolism of steroids and directly suppress the adrenal cortex.

• Uses →

- used for treating inoperable adrenocortical tumors and Cushing's syndrome