Unit-1
Medicinal Chemistry- II

B.Pharma 5th Sem Notes

Unit: 1

Antihistaminic agents: Histamine, receptors and their distribution in the human body

- **H1-antagonists:** Diphenhydramine hydrochloride*, Dimenhydrinate, Doxylamines cuccinate, Clemastine fumarate, Diphenylphyraline hydrochloride, Tripelenamine hydrochloride, Chlorcyclizine hydrochloride, Meclizine hydrochloride, Buclizine hydrochloride, Chlorpheniramine maleate, Triprolidine hydrochloride*, Phenidamine tartarate, Promethazine hydrochloride*, Trimeprazine tartrate, Cyproheptadine hydrochloride, Azatidine maleate, Astemizole, Loratadine, Cetirizine, Levocetrazine Cromolyn sodium
- **H2-antagonists:** Cimetidine*, Famotidine, Ranitidin.
- **Gastric Proton pump inhibitors:** Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

Anti-neoplastic agents

- **Alkylating agents:** Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa
- **Antimetabolites:** Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine
- **Antibiotics:** Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin
- **Plant products:** Etoposide, Vinblastin sulphate, Vincristin sulphate
- **Miscellaneous:** Cisplatin, Mitotane.

Antihistamine:

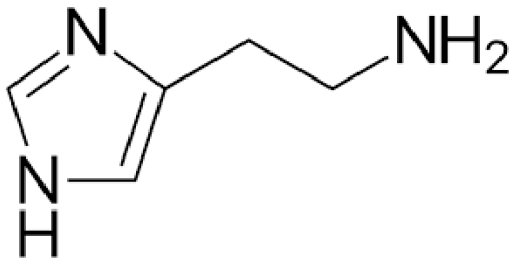
- It also regulates the physiological functions in the gut, and behaves as neurotransmitter.
- Antihistaminic agents (or histamine antagonists) are the drugs that antagonize the action of histamine.

On the basisof the type of H receptor targeted, antihistamines are divided into:

1) **H_1-Antihistamines:** They are used for treating allergicreactions and disorders mediated by mast cells. H_1-antihistamines are sub- divided into two generations. The first generation H_1-antihistamines have acentral effect so are used as sedatives. The second generation H1-antihistamines have low central effects so are used as anti-allergenic grugs.
2) **H2-Antihistamines:** They can reduce the production of stomach acid by reversibly blocking the H_2-histamine receptors found in the parietal cells of gastric mucosa; thus, they are used in gastric reflux diseases.

Histamine:

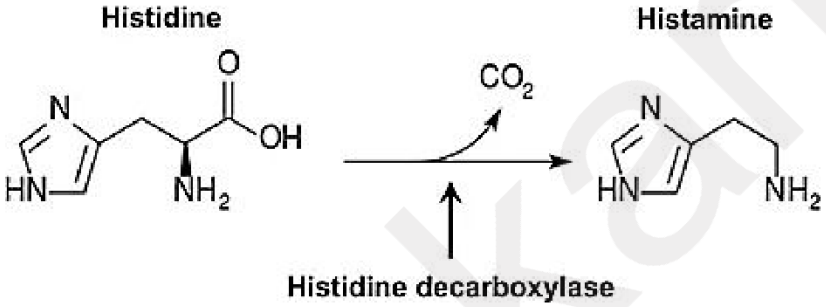
- Histamine is a natural chemical in the body that helps fight off allergies and infections.
- When you have an allergic reaction, histamine is released and can cause symptoms like itching, swelling, and redness. It also helps control your sleep, appetite, and mood.
- It come under the class of Autacoids.
- Autacoids are natural chemicals in your body that act like local hormones. Autacoids mean self-heling.
- Histamines are nitrogen containing organic compounds belonging to the group of amines.
- Histamines are nitrogen containing organic compounds belonging to the group of amines.



- 2-(1H-imidazol-5-yl)ethanamine1H-Imidazole-4-ethanamine
- **Molecular Formula:** $C_5H_9N_3$
- Histamine is discovered by Sir Henry Dale in 1910.

Synthesis:

- Histamine is a monoamine synthesized from the amino acid histidine through a reaction catalyzed by the enzyme histidine decarboxylase (HDC), which removes carboxyl group from histidine.



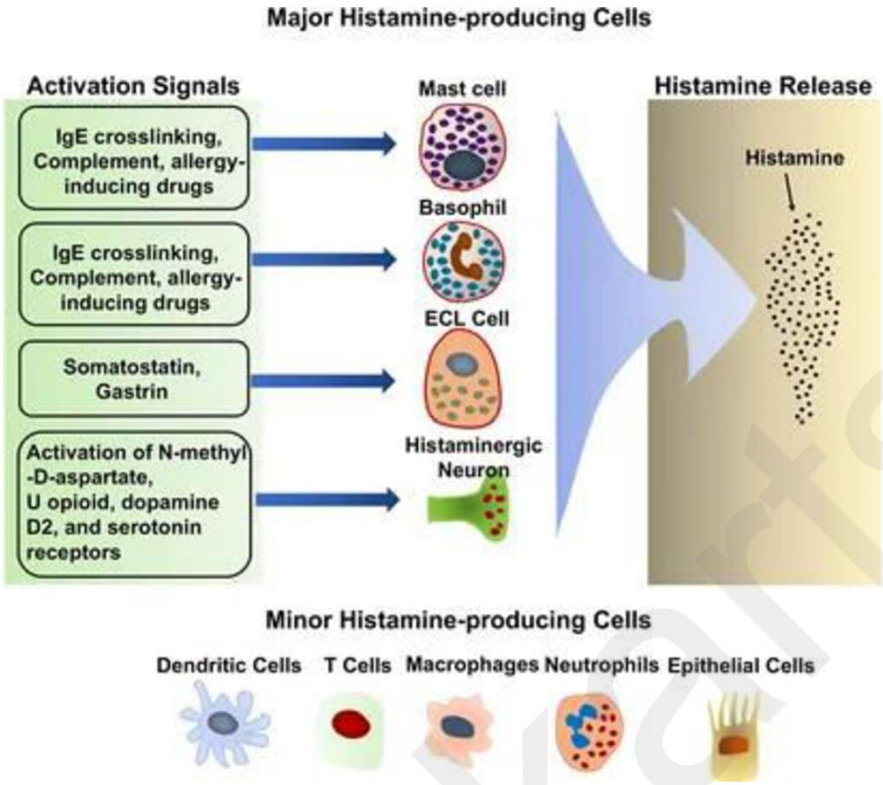
Histamine Release:

Histamine is mainly made by mast cells, basophils, certain brain cells, and cells in the stomach lining.

Histamine is released from cells in response to an antibody called immunoglobulin E (IgE). This antibody may be secreted in response to an invading pathogen such as a virus, bacteria, or an allergenic substance such as pollen. Histamine can also be released in response to injury caused by toxins.

Regardless of the trigger of IgE, the response is a flood of histamine that has various different effects depending on the histamine receptor it comes into contact with. Some examples of these effects include:

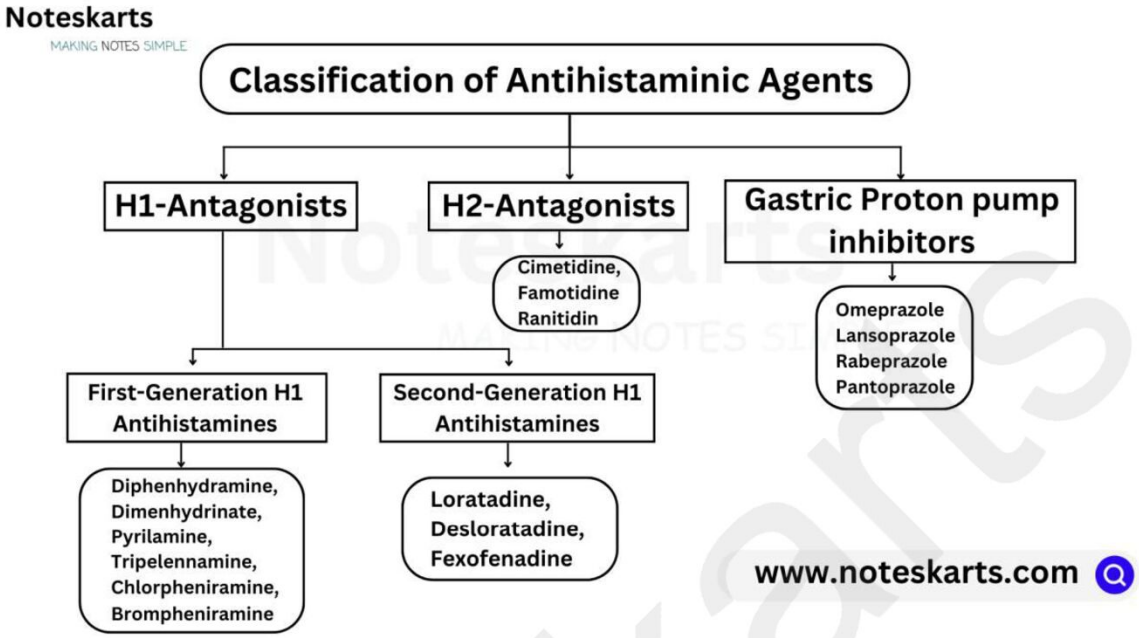
- Contraction of smooth muscle in the lungs, stomach, or womb
- Dilation and increased permeability of blood vessels
- Reduced blood pressure
- Accelerated heart rate
- Increased gastric acid secretion



Histamine Receptors:

Receptor Type	Location	Mechanism of Action	Effects
H1	Smooth muscles, endothelium, central nervous system (CNS)	Activates Gq protein, leading to increased IP3 and DAG, and subsequent release of intracellular Ca^{2+}	Causes vasodilation, increased vascular permeability, bronchoconstriction, contraction of smooth muscles, and stimulation of sensory nerve endings leading to itching and pain
H2	Gastric parietal cells, heart, uterus, CNS	Activates Gs protein, leading to increased cyclic AMP (cAMP)	Stimulates gastric acid secretion, increases heart rate and cardiac output, smooth muscle relaxation
H3	CNS and to a lesser extent peripheral nervous system	Activates Gi protein, leading to decreased cAMP	Modulates neurotransmitter release, particularly histamine, acetylcholine, norepinephrine, and serotonin, plays a role in wakefulness and appetite regulation
H4	Bone marrow, white blood cells, spleen, thymus, lung, colon	Activates Gi protein, leading to decreased cAMP	Involved in chemotaxis of immune cells, modulates immune responses, plays a role in inflammation and allergy responses

Classification of Antihistamine:



H1-antagonists: Diphenhydramine hydrochloride*, Dimenhydrinate, Doxylamines cuccinate, Clemastine fumarate, Diphenylphyraline hydrochloride, Tripelenamine hydrochloride, Chlorcyclizine hydrochloride, Meclizine hydrochloride, Buclizine hydrochloride, Chlorpheniramine maleate, Triprolidine hydrochloride*, Phenidamine tartarate, Promethazine hydrochloride*, Trimeprazine tartrate, Cyproheptadine hydrochloride, Azatidine maleate, Astemizole, Loratadine, Cetirizine, Levocetrazine Cromolyn sodium

H_1-antagonists:

H_1-antagonists, also known as H_1 blockers or antihistamines, are a class of drugs that block the action of histamine at the H_1 receptor, helping to alleviate allergic reactions.

They are of two types:

1. First Generation H_1 Antihistamines
2. Second Generation H_1 Antihistamines

First Generation H_1 Antihistamines

The older, first-generation H_1 antagonists (eg, diphenhydramine, hydroxyzine) are effective in reducing the lesions and pruritus but can produce adverse effects, such as drowsiness and anticholinergic effects.

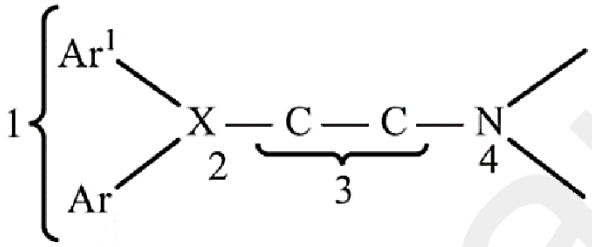
Mechanism of Action:

- The histaminergic receptors are G-Protein coupled type.
- The H1 receptors are coupled to phospholipase C and on activation they form inositol phosphate (IP3) and diacylglycerol from the cell membrane phospholipids.
- Ca^{2+} ions are rapidly released from endoplasmic reticulum under the influence of IP3.
- Protein kinase C is activated by DAG. Thus the turnover of Ca^{2+} ions and the protein kinase C stimulates the Ca^{2+} / calmodulin dependent protein kinase and phospholipase A2.

- The Anti-histaminergic (H_1-antagonist) binds to the H_1 – receptors and decrease the production of phospholipase-c and their activation to form IP3 and DAG. Therefore it inhibits the characteristic response of histamine.

Structure-Activity Relationship:

H_1-Receptor Antagonists



1) Aryl Groups:

- Diaryl substitution is required for H_1 affinity, and is found in first-generation and second-generation antihistamines.
- The co-planarity of two aryl substitutions influences the optimal antihistaminic activity. Active aryl substitutions are as follows:
  - i) Ar is phenyl and hetero aryl group (like 2-pyridyl).
  - ii) Ar^1 is aryl or aryl methyl group.

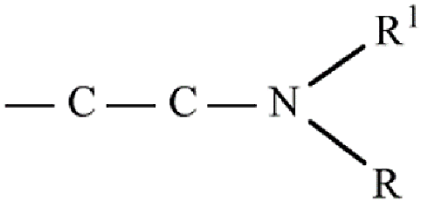
2) Nature of X:

Antihistamines with X = carbon (pheniramine series) signifies the stereo selective receptor binding to the receptors because of its chirality. The active substitutions of X are as follows:

iii) X = Oxygen (amino alkyl ether analogue)
iv) X = Nitrogen (ethylene-diamine derivative)
v) X = Carbon (mono amino propyl analogue)

3) Alkyl Chain:

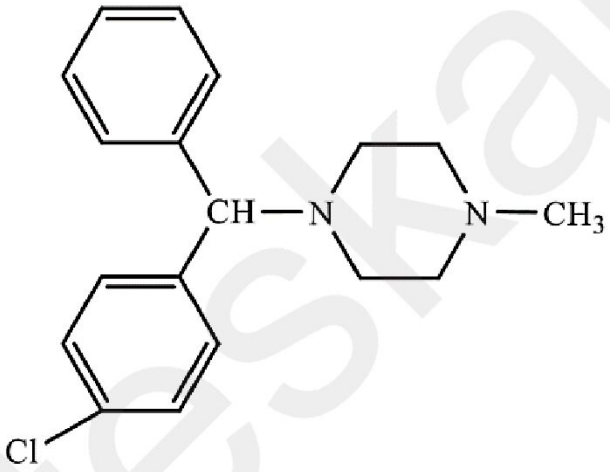
Mostly antihistamines have ethylene chain, the branching of which forms a less active compound.



This general chain is present in all the antihistamines.

4) Terminal Nitrogen Atom:

- The nitrogen atom at the terminal should be a tertiary amine for maximum activity.
- The terminal nitrogen can be the part of heterocyclic ring, for example, antazoline and chlorcyclizine have a high antihistaminic activity.
- The amino moiety on interaction with H_1-receptor shows protonation due to basicity with pka 8.5-10.

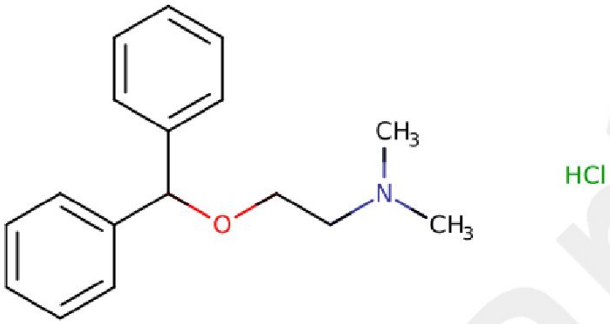


Chlorcyclizine

Diphenhydramine hydrochloride:

- Diphenhydramine is a first-generation antihistamine which is mainly used for treating seasonal allergies. But it also exhibits antiemetic, anti-Parkinson,antitussive, and hypnotic properties.

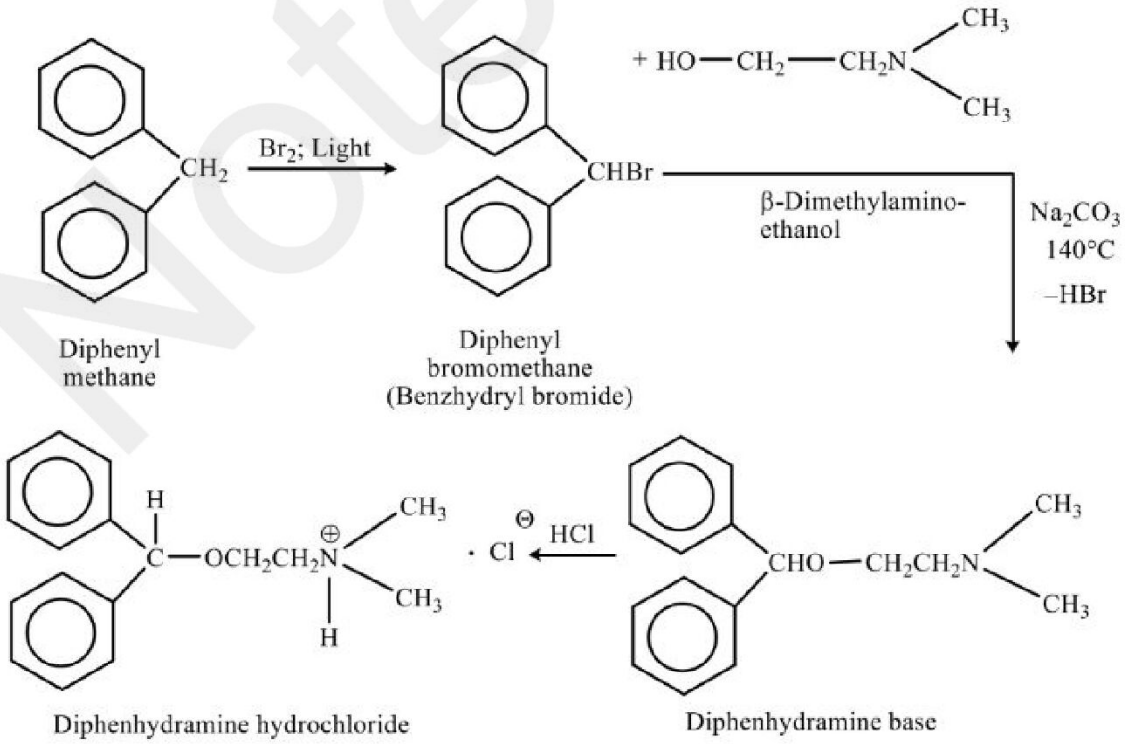
Structure:



Mechanism of Action:

Diphenhydramine functions as an inverse agonist at H1,-receptors, and then it reversing the effect of the histamine on capillaries , reducing allergic reaction symptoms.

Synthesis:

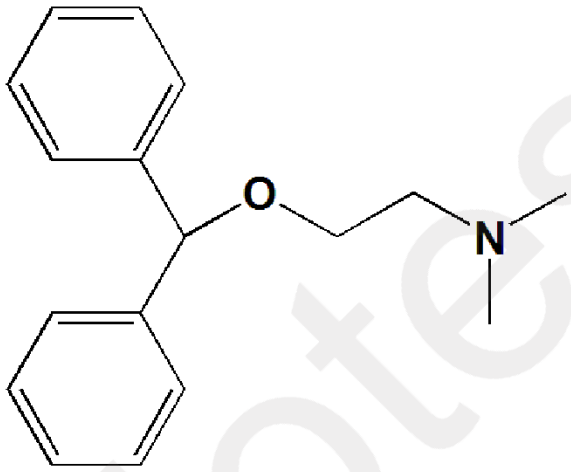


Uses:

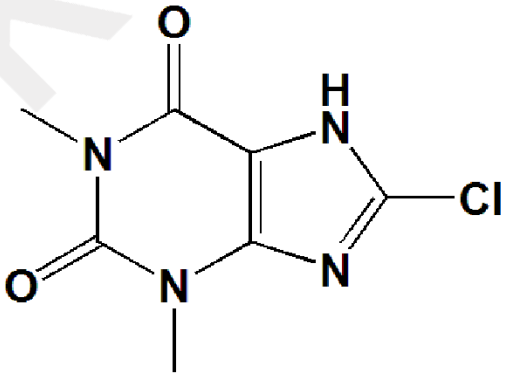
- It is used for preventing and curing nausea, vomiting and dizziness caused by motion sickness.
- It is used for relax and fall asleep.
- It is also used for relieving the symptoms of allergy, fever, common cold, rashes, itching, watery eyes and sneezing.
- It also used in treatment of Parkinson due to anti-muscarinic activity.

Dimenhydrinate:

- Dimenhydrinate is a combination drug as it comprises of diphenhydramine (53-55.5%) and 8-chlorotheophylline (not less than 44-47%) in a salt form, calculatedon the dried basis.



diphenhydramine



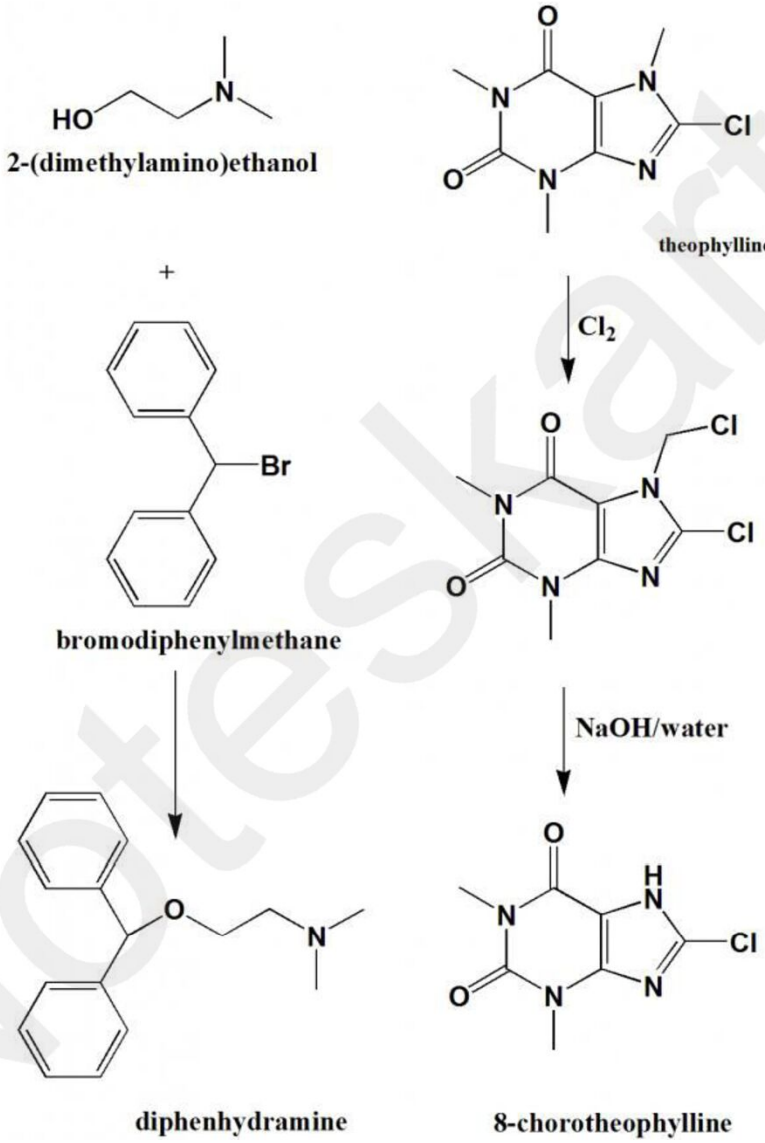
8-chorotheophylline

Mechanism of Action

- The antiemetic property is due to H1 antagonism in the vestibular system.
- Excitatory effects of drug is due to adenosine receptor blockade by 8-chlorotheophylline.

Synthesis:

- Reaction of benzhydrylbromide and 2-dimethylaminoethanol produces diphenhydramine.
- Theophylline anhydrous is warmed up to 50-60°C and dissolved in water, drip N-chlorosuccimide to get a crude product. The product is then dissolved in 5% NaOH aqueous solution to get Chlorotheophyline.



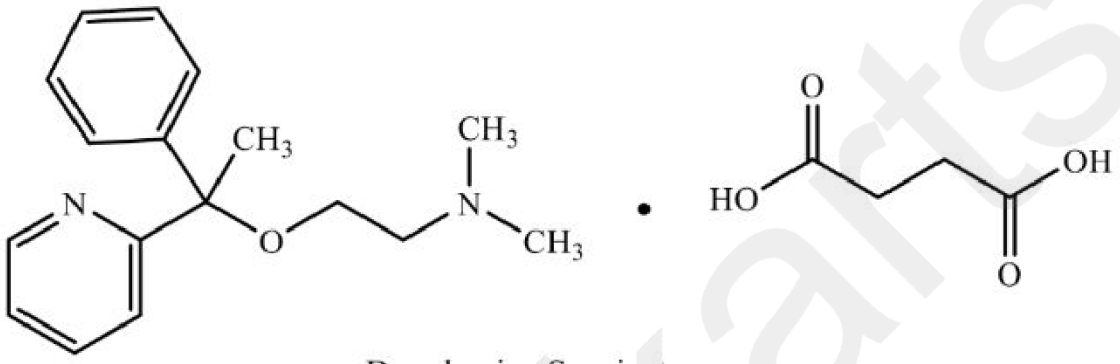
Uses:

- Dimenhydrinate is used to prevent and treat nausea, vomiting, and dizziness caused by motion sickness.
- It works by preventing problems with body balance.
- These symptoms include rash, itching, watery eyes, itchy eyes/nose/throat, cough, runny nose, and sneezing.

Doxylamine Succinate:

- This medication works by blocking certain natural substances (histamine, acetylcholine) that your body makes.
- This effect helps to relieve allergy/cold symptoms such as watery eyes, runny nose, and sneezing.

Structure:



Doxylamine Succinate

Mechanism of Action:

- Doxylamine shows antihistaminic and sedative effects because it acts as an antagonist of the H_1-receptors.
- It also slightly antagonises the muscarinic acetylcholine receptors.

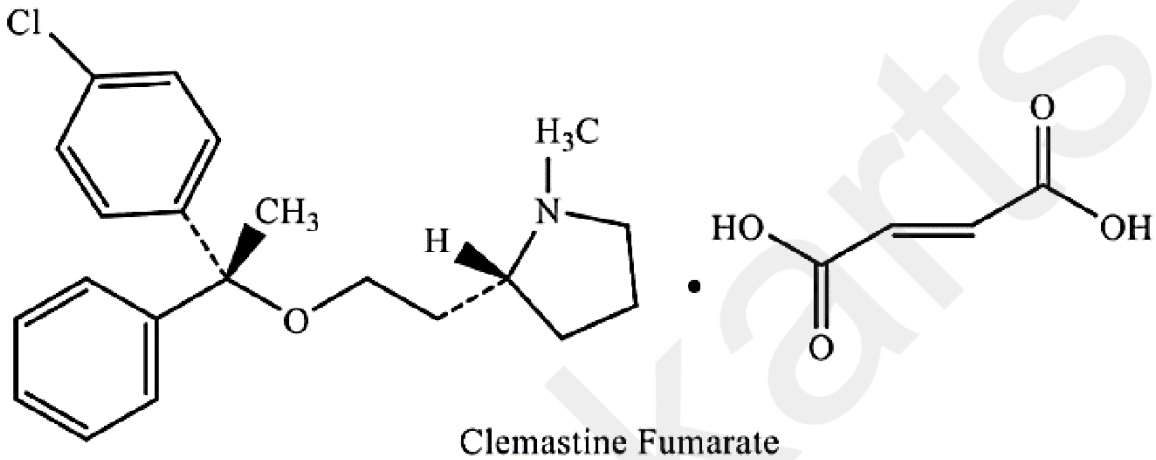
Uses:

- Doxylamine is used in the short-term treatment of insomnia (difficulty falling asleep or staying asleep).
- Doxylamine is also used in combination with decongestants and other medications to relieve sneezing, runny nose, and nasal congestion caused by the common cold.

Clemastine Fumarate:

- Clemastine fumarate is the fumaric acid salt of clemastine.
- An antihistamine with antimuscarinic and moderate sedative properties.
- It is used for the symptomatic relief of allergic conditions such as rhinitis, urticaria, conjunctivitis and in pruritic (severe itching) skin conditions.

Structure:



Clemastine Fumarate

Mechanism of Action:

Clemastine is a selective H1 antagonist. It binds to the H1 receptors and blocks the action of histamine thus temporary relieving the negative symptoms caused due to histamine.

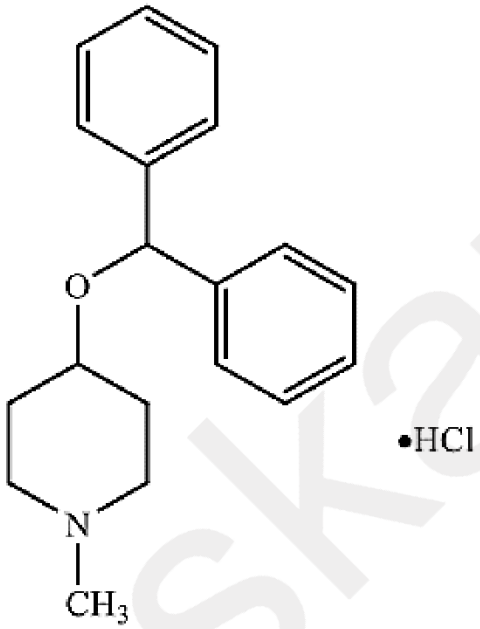
Uses:

- Clemastine is used to relieve hay fever and allergy symptoms, including sneezing; runny nose; and red, itchy, tearing eyes.
- Prescription strength clemastine is also used to relieve the itching and swelling of hives.

Diphenylpyraline Hydrochloride:

- Diphenylpyraline is an antihistamine used for treating allergy by competing with histamine to bind to the H1-receptor sites found on the effector cells.

Structure:



Mechanism of Action:

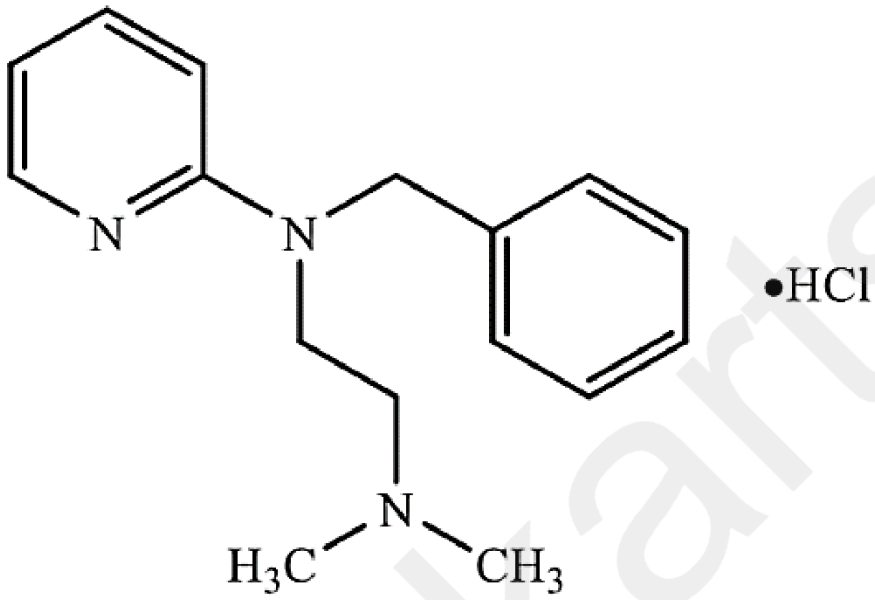
- Diphenylpyraline is used for treating allergy as it competes with histamine for binding on the H1-receptors on effector cells.
- After binding it suppresses the histamine effects, thus causing temporary relief of the allergic symptoms.

Uses:

- Diphenylpyraline is an antihistamine used for the treatment of allergic rhinitis, hay fever, and allergic skin disorders.
- Diphenylpyraline is an antihistamine. Antihistamines used in the treatment of allergy act by competing with histamine for H 1-receptor sites on effector cells.

Tripelennamine Hydrochloride

Structure:



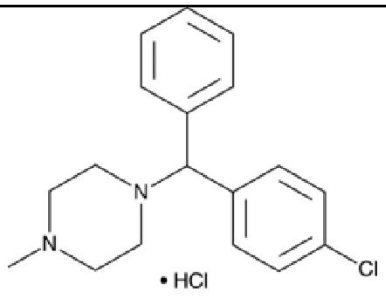
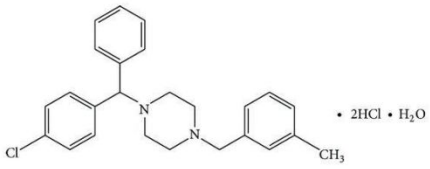
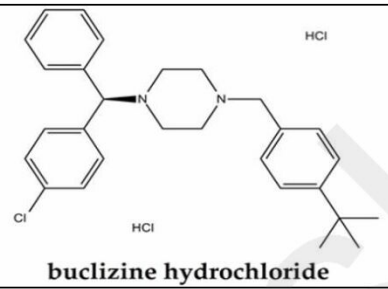
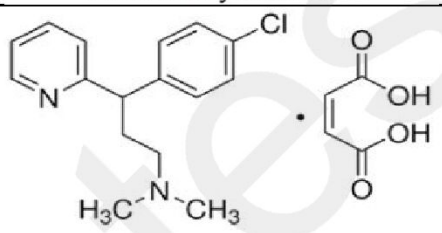
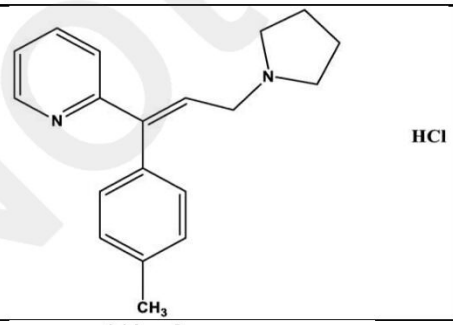
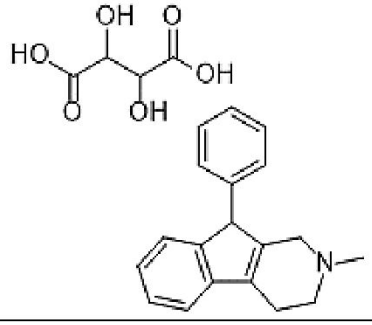
Tripelennamine Hydrochloride

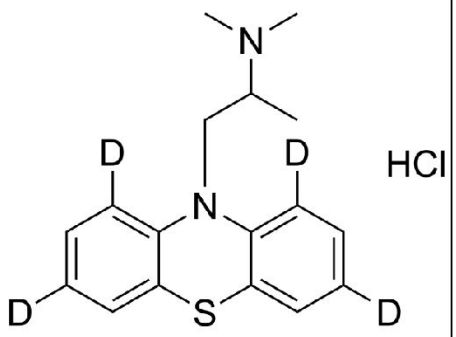
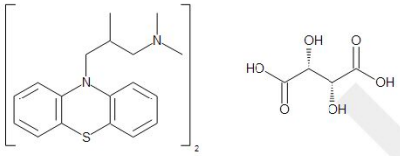
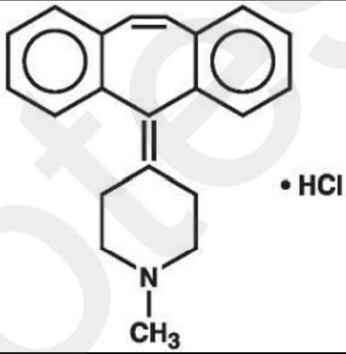
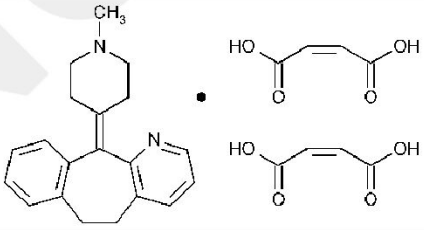
Mechanism of Action:

- Tripelennamine binds to the H1-receptor and blocks the action of endogenous histamine, thus temporarily relieving the negative symptoms caused by histamine.

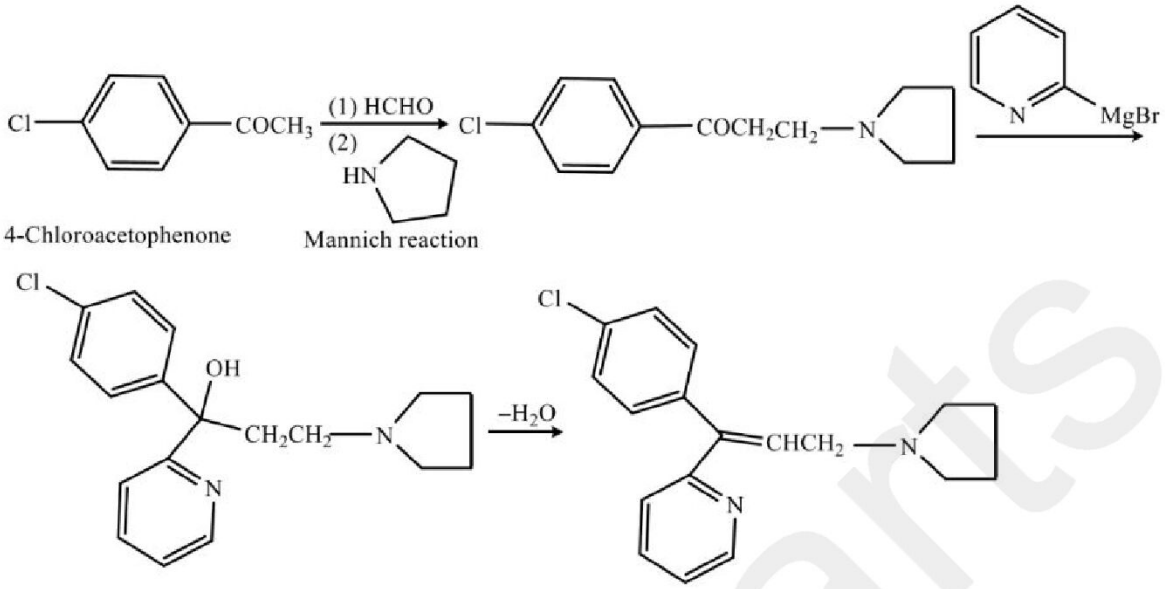
Uses:

- It used in the treatment of upper respiratory track allergic condition like Asthma, hay fever.
- It relieves sneezing, runny nose, itching, watery eyes, hives, rashes, and other
  symptoms of allergies and common cold.

Drug	Structure	Mechanism of Action	Uses
Chlorcyclizine Hydrochloride		Blocks H1 receptors to prevent histamine action.	Allergy symptoms (runny nose, sneezing, itching, watery eyes), motion sickness.
Meclizine Hydrochloride		Blocks H1 receptors, has anticholinergic and antiemetic properties.	Nausea, vomiting, dizziness caused by motion sickness, vertigo.
Buclizine Hydrochloride	 buclizine hydrochloride	Blocks H1 receptors, anticholinergic and antiemetic effects.	Nausea, vomiting, dizziness associated with motion sickness and vertigo.
Chlorpheniramine Maleate		Blocks H1 receptors to reduce allergic symptoms.	Allergic conditions (rhinitis, urticaria, other allergic dermatoses).
Triprolidine Hydrochloride		Blocks H1 receptors to reduce histamine effects.	Allergy symptoms (sneezing, itching, watery eyes, runny nose), hay fever, common cold.
Phenindamine Tartrate		Blocks H1 receptors to prevent histamine action.	Allergic reactions (rhinitis, urticaria).

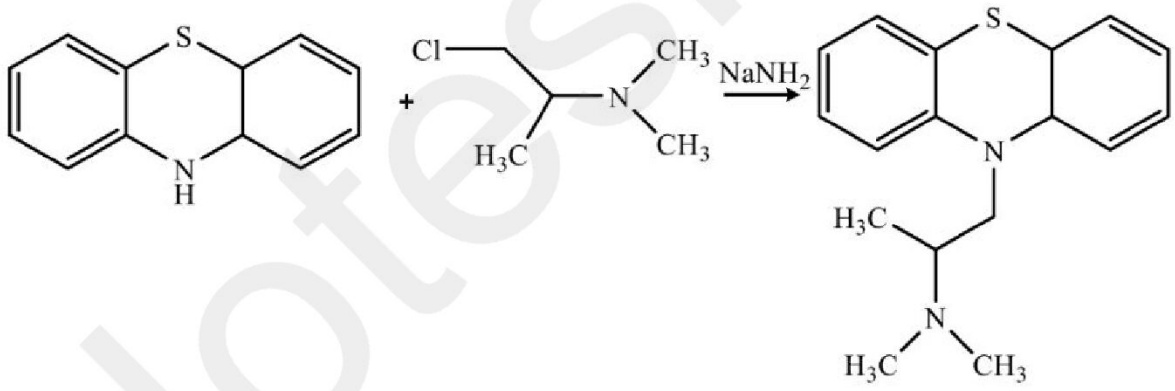
Promethazine Hydrochloride		Blocks H1 receptors, has strong sedative and antiemetic effects.	Allergy symptoms, nausea, vomiting, sedative or sleep aid.
Trimeprazine Tartrate		Blocks H1 receptors, has antipruritic properties.	Symptomatic relief of allergic conditions (rhinitis, urticaria), sedative properties.
Cyproheptadine Hydrochloride		Blocks H1 and serotonin receptors.	Allergy symptoms, appetite stimulant, management of serotonin syndrome.
Azatadine Maleate		Blocks H1 receptors to reduce the effects of histamine.	Allergic rhinitis, other allergic conditions.

Triprolidine hydrochloride Synthesis:



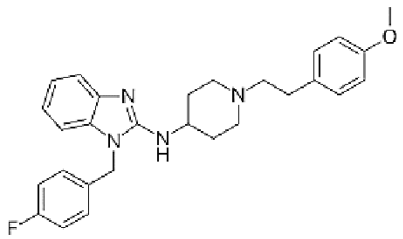
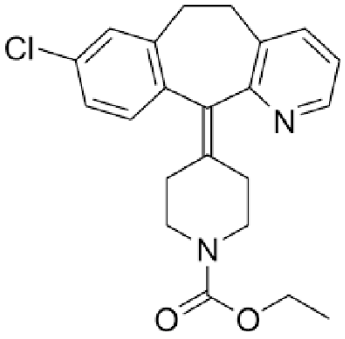
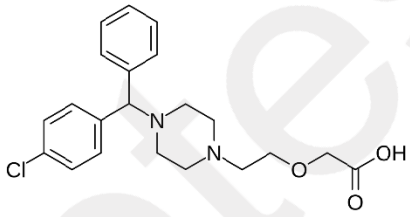
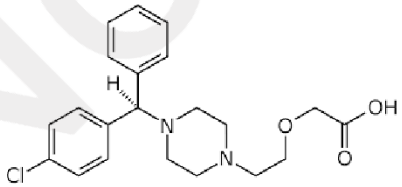
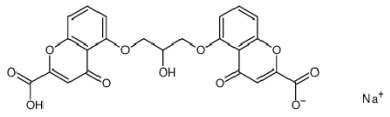
Promethazine hydrochloride Synthesis:

- Promethazine is formed by the alkylation of phenothiazine with 1-dimethylamino-2-chloropropanein the presence of sodium amide



Second Generation H_1 Antihistamines:

Astemizole, Loratadine, Cetirizine, Levocetirizine, Cromolyn sodium

Drug	Structure	Mechanism of Action	Uses
Astemizole		Long-acting antihistamine that selectively inhibits H1 receptors, preventing the effects of histamine.	Used to treat allergic rhinitis and chronic urticaria.
Loratadine		Selective peripheral H1 receptor antagonist, providing relief from allergic symptoms without sedative effects.	Used to treat allergic rhinitis and chronic urticaria.
Cetirizine		Selective inhibition of peripheral H1 receptors, reducing histamine-mediated symptoms.	Used to treat allergic rhinitis and chronic urticaria.
Levocetirizine		Active enantiomer of cetirizine, providing selective inhibition of peripheral H1 receptors.	Used to treat allergic rhinitis and chronic urticaria.
Cromolyn sodium		Mast cell stabilizer that prevents the release of histamine and other inflammatory mediators from mast cells.	Used for prophylactic treatment of bronchial asthma, allergic rhinitis, and allergic conjunctivitis.

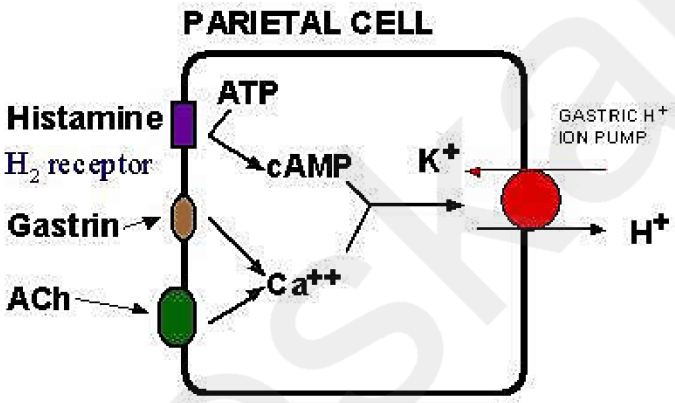
H2-antagonists: Cimetidine*, Famotidine, Ranitidin.

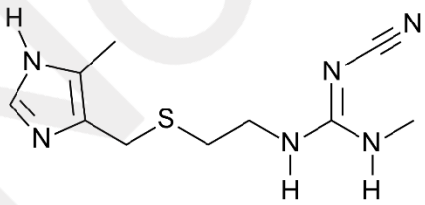
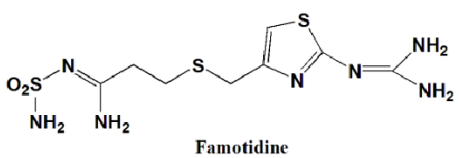
H2-antagonists:

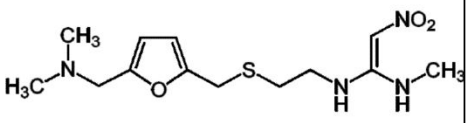
- Histamine H2-receptor antagonists, also known as H2-blockers, are used to treat duodenal ulcers and prevent their return.
- These drugs mostly decrease the production of acid in stomach.

Mechanism of Action:

- Blocks the H2 (histamine) receptor of parietal cells to prevent transport of H+ ions out of the cell into the stomach (acid formation)

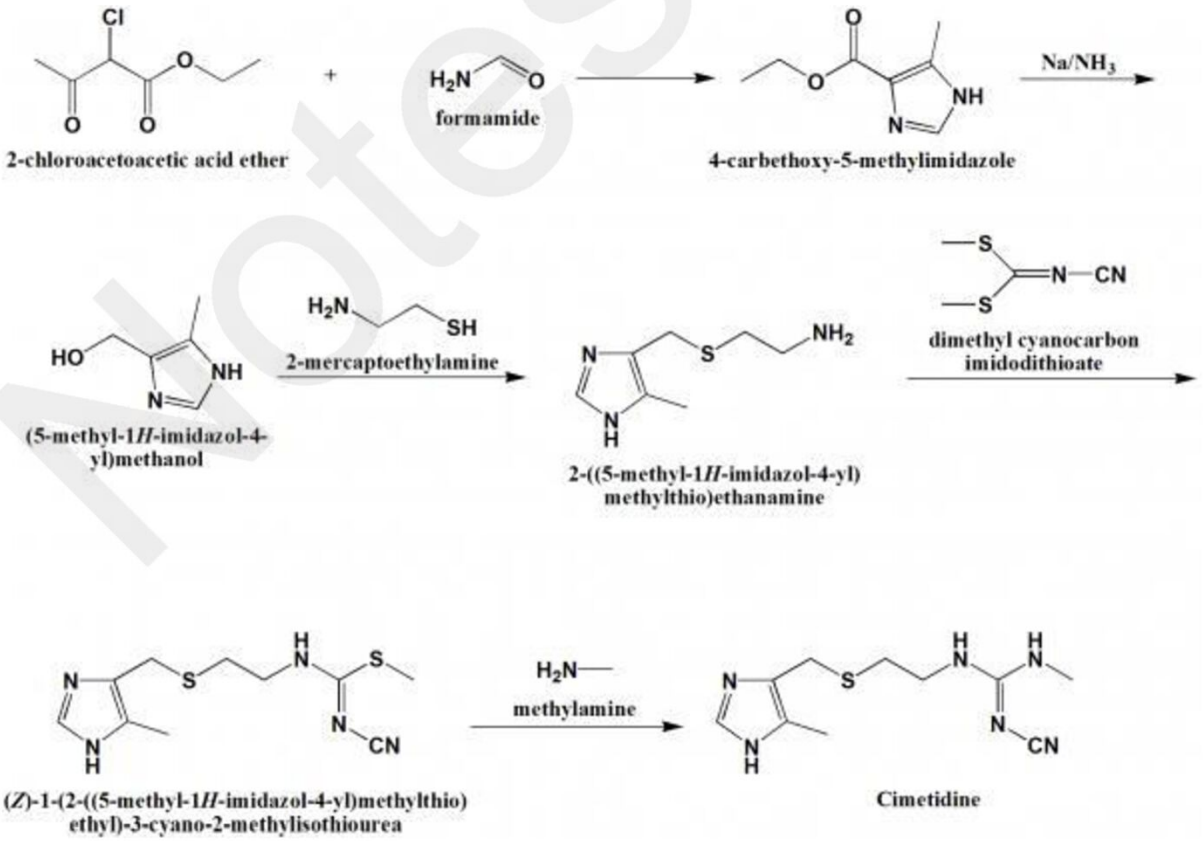


Drug	Structure	Mechanism of Action	Uses
Cimetidine		H2 receptor antagonist that inhibits stomach acid production by blocking histamine action on the parietal cells.	Used to treat peptic ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome.
Famotidine	 Famotidine	H2 receptor antagonist that reduces stomach acid production by inhibiting histamine action on the stomach lining.	Used to treat peptic ulcers, GERD, and conditions that cause excessive stomach acid production.

Ranitidine		H2 receptor antagonist that blocks histamine receptors in the stomach, thereby reducing acid production.	Used to treat and prevent ulcers in the stomach and intestines, GERD, and Zollinger-Ellison syndrome.

Synthesis Of Cimetidine:

i. Reaction of 2-chloroacetoacetic ether with 2 mole of formamide to get 4-carbethoxy-5-methylimidazole.
ii. Reducing the carbethoxy group by sodium in liquid ammonia produces 4-hydroxymethyl-5-methylimidazole.
iii. Hydrochloride of the resulting alcohol is reacted with 2-mercaptoethylamine hydrochloride to give 4-(2-aminomethyl)-thiomethyl-5-methylimidazole dihydrochloride.
iv. On reacting the above formed compound with –cyanimido-S,S-methylamine produces cimetidine.



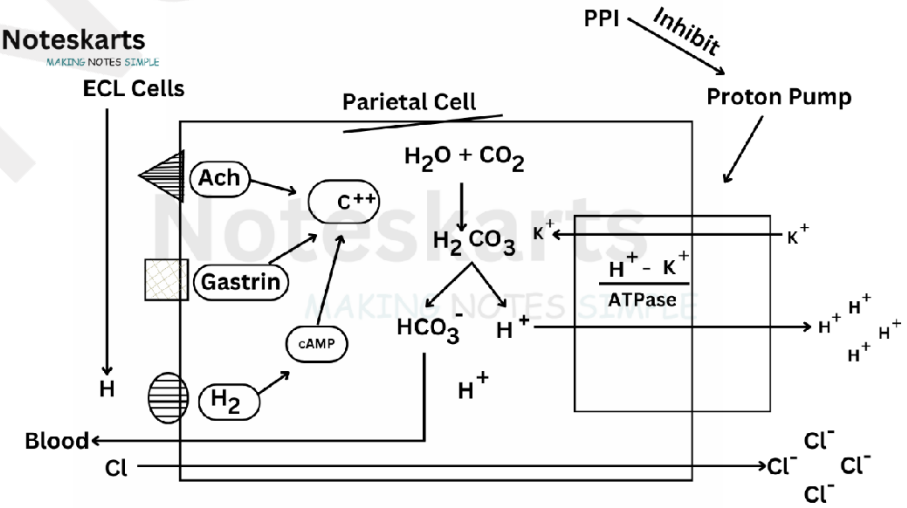
Gastric Proton pump inhibitors: Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

Gastric Proton pump inhibitors:

- Proton pump inhibitors (PPIs) are a class of drugs that reduce the amount of stomach acid produced by glands in the stomach lining.
- They work by binding to and inhibiting the hydrogen-potassium ATPase pump, or "proton pump", which produces stomach acid.
- PPIs are commonly prescribed to treat conditions that occur when stomach acid damages or irritates parts of the digestive system, such as: Chronic acid reflux (GERD), Stomach ulcers.

Mechanism of Action:

- There are one enzyme H^+/K^+ ATPase which present in parietal cell of Stomach and it is responsible for HCL secretion.
- Now these drugs contain a sulphonyl group in a bridge between substituted benzimidazoles and pyridine rings.
- Gastrine hormone produced by G-Cell located in Pyloric gland which act on gastric receptor.
- Now When PPI introduce into parietal cells its sulphonyl group bind with H^+ K^+ ATPase enzyme then they from Drug enzyme complex which further metabolize easily and irreversibly inactivate the proton pump.
- Now H+ ion does not secrete out so production of HCL decrease.
- It blocks gastric acid secretion even it Histamine bind with their receptor.

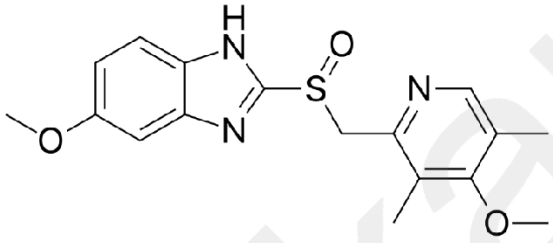


Drugs: Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole

Omeprazole

- **Omeprazole**, a medication used to treat various stomach-related conditions.
- It belongs to the class of drugs known as **proton pump inhibitors (PPIs)**.

Structure:



- Omeprazole's chemical formula is **$C_{17}H_{19}N_3O_3S$**.

Mechanism of Action:

- Omeprazole selectively and irreversibly inhibits the **H^+/K^+-ATPase system** found on the secretory surface of gastric parietal cells.
- By doing so, it suppresses the production of stomach acid, which is important for treating conditions like **GERD**, **peptic ulcers**.

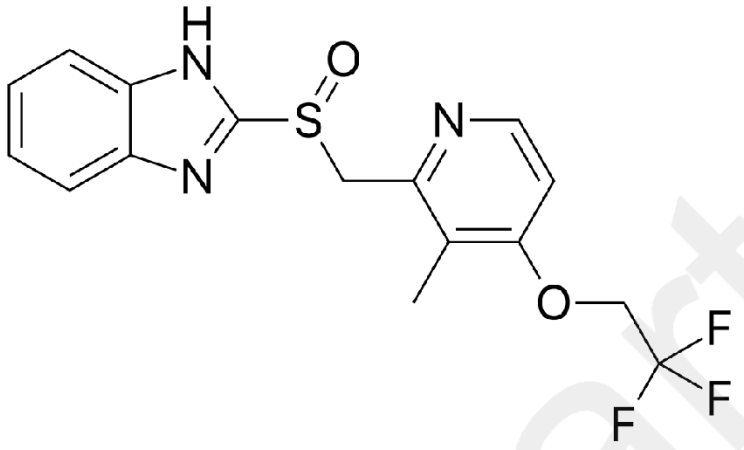
Uses:

- **GERD (Gastroesophageal Reflux Disease)**: Omeprazole treats symptomatic GERD in patients aged 1 year and older.
- **Erosive Esophagitis (EE)**: It helps heal tissue damage caused by acid-mediated GERD in patients aged 1 month and older.
- **Duodenal Ulcers**: Omeprazole treats active duodenal ulcers and reduces the risk of recurrence.
- **Gastric Ulcers**: It's effective in treating active benign gastric ulcers.
- **Upper GI Bleeding Prevention**: In critically ill adult patients, it reduces the risk of upper gastrointestinal bleeding.
- **Pathologic Hypersecretory Conditions**: Used for conditions characterized by excessive gastric acid secretion.

Lansoprazole

It is a proton pump inhibitor used for various gastrointestinal conditions.

Structure:



Mechanism of Action:

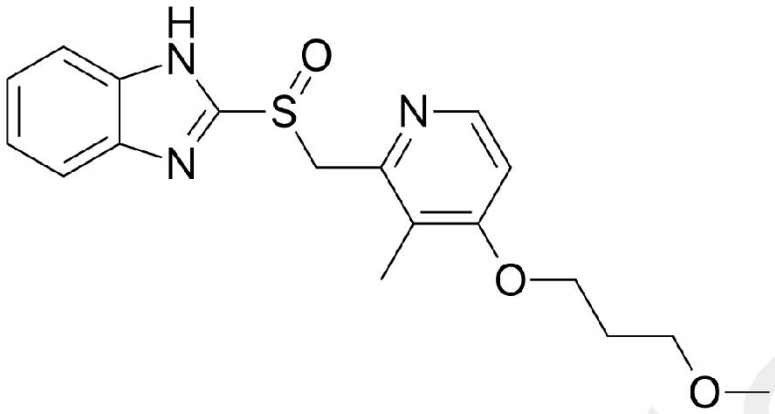
- Omeprazole selectively and irreversibly inhibits the **H^+/K^+-ATPase system** found on the secretory surface of gastric parietal cells.

Uses:

- **Gastric Ulcers:** Lansoprazole treats active gastric ulcers and helps prevent their recurrence.
- **Duodenal Ulcers:** It's also used for active duodenal ulcers and NSAID-induced ulcers.
- **GERD:** Lansoprazole alleviates symptoms of gastroesophageal reflux disease (GERD) and heals erosive esophagitis.
- **Hypersecretory Conditions:** Useful for conditions like Zollinger-Ellison syndrome, where excessive acid secretion occurs.
- **H. pylori Eradication:** In combination with antibiotics, it eradicates Helicobacter pylori infections

Rabeprazole:

- **Structure**: Rabeprazole is a **proton pump inhibitor (PPI)** with the chemical formula **$C_{18}H_{21}N_3O_3S$**



Mechanism of Action:

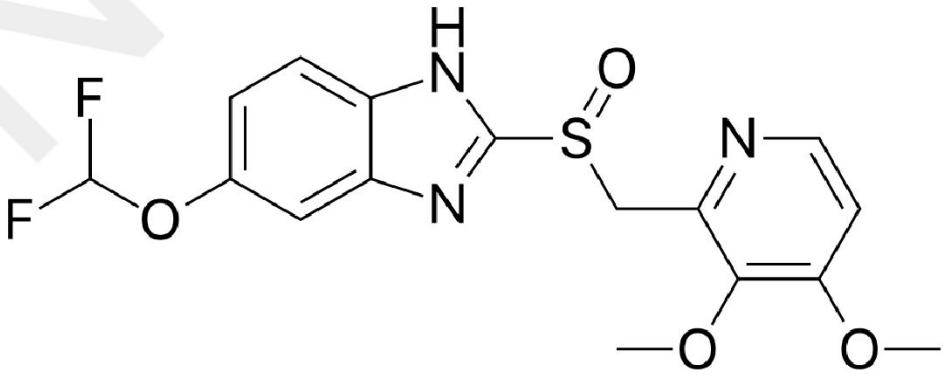
- It irreversibly inhibits the **(H+, K+)-ATPase enzyme** in gastric parietal cells, reducing both basal and stimulated gastric acid secretion.

Uses:

- **GERD**: Treats symptoms of **gastroesophageal reflux disease (GERD)**.
- **Ulcers**: Helps heal **gastric and duodenal ulcers**.
- **H. pylori Eradication**: Used in combination with antibiotics for **H. pylori** infections.
- **Hypersecretory Conditions**: Effective for conditions like **Zollinger-Ellison syndrome**

Pantoprazole:

- **Structure**: Pantoprazole is also a **PPI**, with the generic name **$C_{16}H_{14}F_2N_3NaO_2S$**



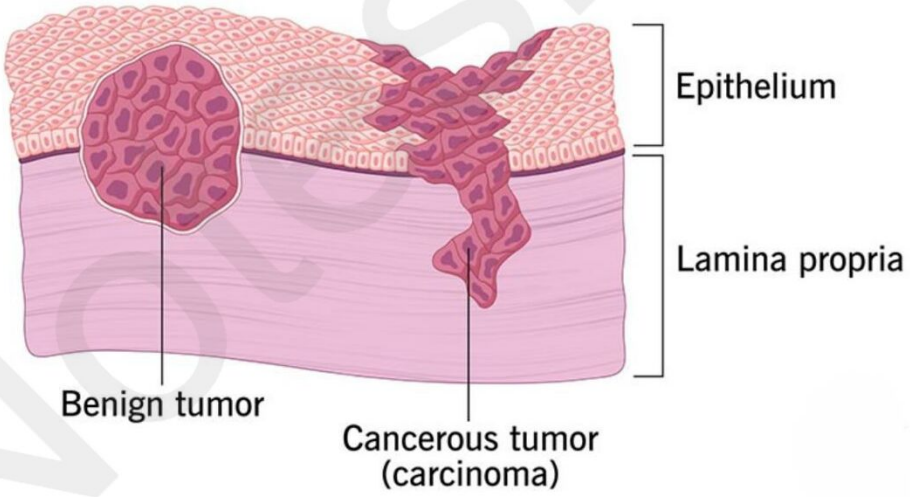
- **Mechanism of Action**: It inactivates the **(H+, K+)-ATPase function** in the stomach, suppressing gastric acid secretion.
- **Uses**:
  - **GERD**: Manages **erosive esophagitis**.
  - **Ulcer Prevention**: Protects against recurrence of stomach ulcers due to NSAID use.
  - **Hypersecretory Conditions**: Treats **Zollinger-Ellison Syndrome** and other pathological hypersecretory conditions

Anti-neoplastic agents

- **Alkylating agents:** Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa
- **Antimetabolites:** Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine
- **Antibiotics:** Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin
- **Plant products:** Etoposide, Vinblastin sulphate, Vincristin sulphate
- **Miscellaneous:** Cisplatin, Mitotane.

Neoplastic:

- A neoplasm is a type of abnormal and excessive growth of tissue.
- The process that occurs to form or produce a neoplasm is called neoplasia.
- The growth of a neoplasm is uncoordinated with that of the normal surrounding tissue, and persists in growing abnormally, even if the original trigger is removed.



Reason:

- The main cause of cancer is mutations, or changes to the DNA in your cells. Genetic mutations can be inherited. They can also occur after birth as a result of environmental forces.

These external causes, called carcinogens, can include:

- **Physical carcinogens** like radiation and ultraviolet (UV) light

- **Chemical carcinogens** like cigarette smoke, asbestos, alcohol, air pollution, and contaminated food and drinking water
- **Biological carcinogens** like viruses, bacteria, and parasites

Types of Cancer:

There are also several clinical terms used for certain general types of cancer:

- **Carcinoma** is a cancer that starts in the skin or the tissues that line other organs.
- **Sarcoma** is a cancer of connective tissues such as bones, muscles, cartilage, and blood vessels.
- **Leukemia** is a cancer of the bone marrow, which creates blood cells.
- **Lymphoma** and myeloma are cancers of the immune system.

Learn more about specific types of cancer with the resources below.

- Appendix cancer
- Bladder cancer
- Bone cancer
- Brain cancer
- Breast cancer
- Cervical cancer
- Rectal cancer
- Colon or colorectal cancer
- Duodenal cancer
- Ear cancer
- Endometrial cancer
- Esophageal cancer
- Heart cancer
- Gallbladder cancer

Treatment:

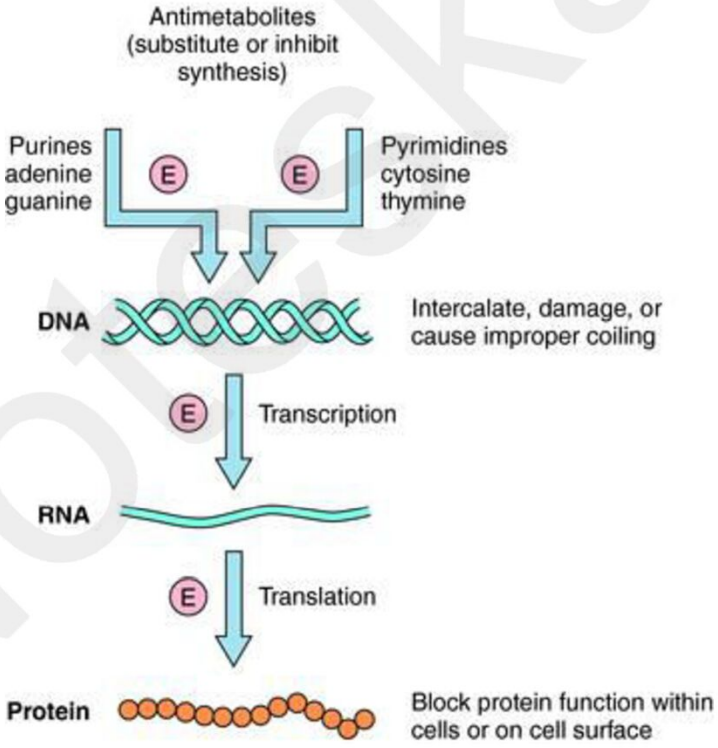
- **Localized treatment.** Localized treatment usually involves using treatments like surgery or local radiation therapy at a specific area of the body or tumor.
- **Systemic treatment.** Systemic drug treatments, such as chemotherapy, targeted therapy, and immunotherapy, can affect the entire body.
- **Palliative treatment.** Palliative care involves relieving health symptoms associated with cancer, such as trouble breathing and pain.

Anti-neoplastic agents:

- Antineoplastic agents, also known as anti-cancer or chemotherapy drugs, are medications used to treat various types of cancer.
- These agents target and kill rapidly dividing cells, a hallmark of cancer, but can also affect normal cells, leading to side effects.
- They are important role in the management of cancer, often in combination with other treatment modalities such as surgery and radiation therapy.

Mechanism Of Action:

Basic mechanisms by which antineoplastic drugs selectively kill tumor cells. *E* stands for enzymes, some of which are inhibited by these drugs. Inhibition of DNA or RNA synthesis or replication, production of miscoded nucleic acids, and formation of modified proteins are key mechanisms of action for many of these drugs.



Classification:

- **Alkylating agents:** Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa

- **Antimetabolites:** Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine
- **Antibiotics:** Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin
- **Plant products:** Etoposide, Vinblastin sulphate, Vincristin sulphate
- **Miscellaneous:** Cisplatin, Mitotane.

1. Alkylating agents:

- Alkylating agents came to be used for cancer therapy as a result of observations of the effects of the mustard gases on cell growth.
- Alkylation takes place through chemical formation of a positively charged carbonium ion that reacts with an electron-rich site, particularly on DNA or RNA, to form modified nucleic acids.
- Most clinically used alkylating drugs have two active groups, which enable them to form **covalent links** between adjacent nucleic acid strands that are more difficult to repair than monofunctional adducts.
- These cross-links also prevent separation of the dual strands of DNA during cell cycling. For maximal kill, it is important to administer the maximally tolerated dose.

Mechanism Of Action:

Alkylating agents

↓

Produce Carbonium ion (C+) (highly reactive)

↓ Alkylation

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

↓

Cross linking/abnormal base pairing/scission of DNA strand

↓

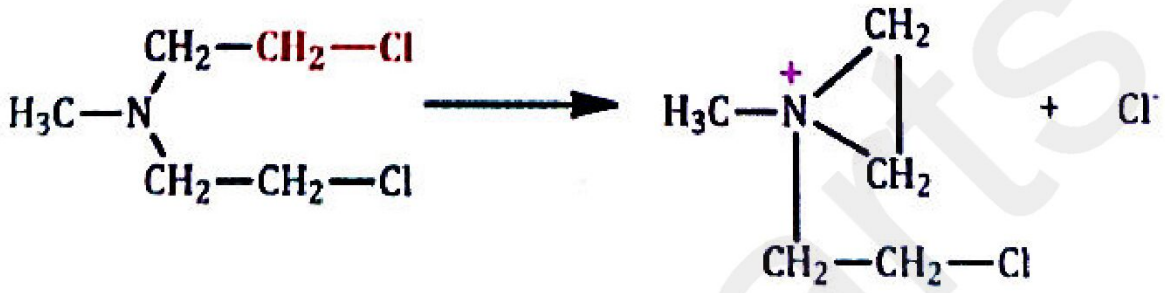
Inhibition of DNA synthesis.

Mechanism of Action:

These compounds produce highly reactive carbonium ion intermediates that transfer alkyl group to cellular macromolecules by forming covalent bonds.

It alkylates the 7th nitrogen atom of guanine residue in DNA, and results in cross-linking or abnormal base pairing.

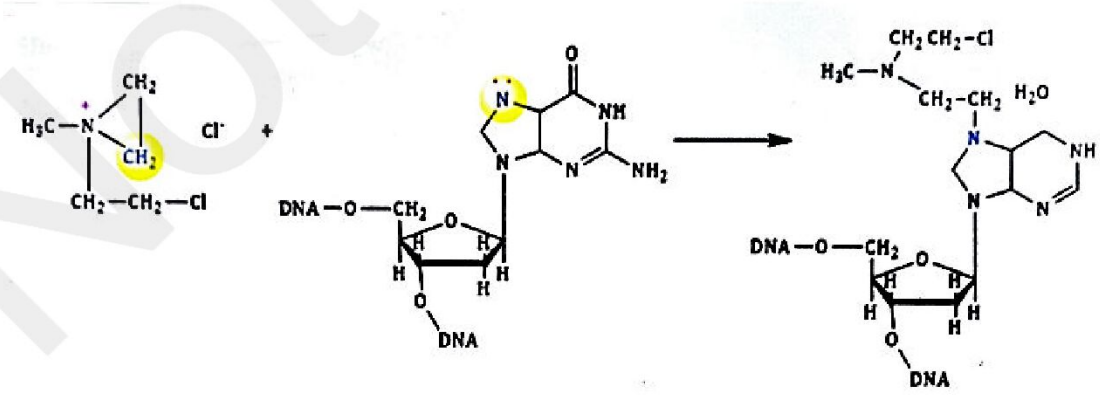
STEP-1- Intramolecular cyclization



Initially, one of the 2-chloro ethyl side chain undergoes a first-order (SN,) intramolecular cyclization with the release of Cl- and formation of highly reactive ethyleniminium intermediate (Step I).

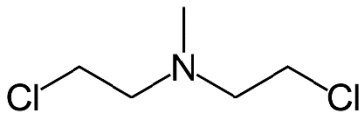
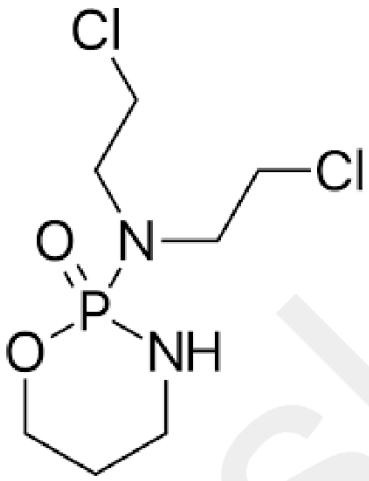
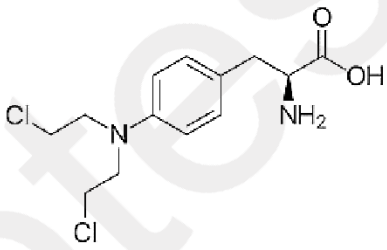
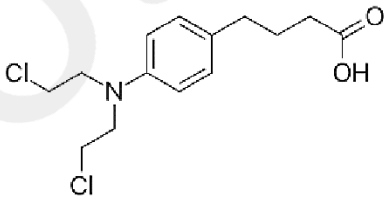
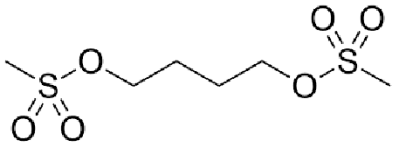
By this reaction, tertiary amine is converted to an unstable quaternary ammonium compound, which react by forming carbonium ion.

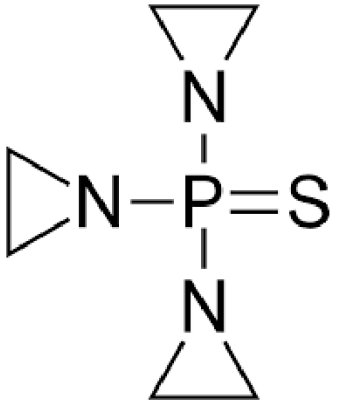
STEP-2- Nucleophilic attack of unstable aziridine



This precedes a second-order reaction (SN,) nucleophilic substitution and alkylates the 7th N atom in guanine (Step II).

Drugs:

Drug	Structure	Mechanism of Action	Uses
Mechlorethamine		Alkylates DNA by forming cross-links between DNA strands, leading to cell death.	Used to treat Hodgkin's disease and other types of lymphomas.
Cyclophosphamide		Prodrug converted to active metabolites in the liver; alkylates DNA, leading to cell death.	Used to treat various cancers including lymphomas, leukemias, and breast cancer; also used as an immunosuppressant.
Melphalan		Alkylates DNA, forming cross-links between DNA strands, leading to cell death.	Used to treat multiple myeloma and ovarian cancer.
Chlorambucil		Alkylates DNA, forming cross-links between DNA strands, leading to cell death.	Used to treat chronic lymphocytic leukemia and lymphomas.
Busulfan		Alkylates DNA, leading to cross-linking of DNA strands and subsequent cell death.	Used to treat chronic myelogenous leukemia.

Thiotepa		Alkylates DNA, leading to cross-linking of DNA strands and subsequent cell death.	Used to treat breast cancer, ovarian cancer, and bladder cancer.

Synthesis of Mechlorethamine:

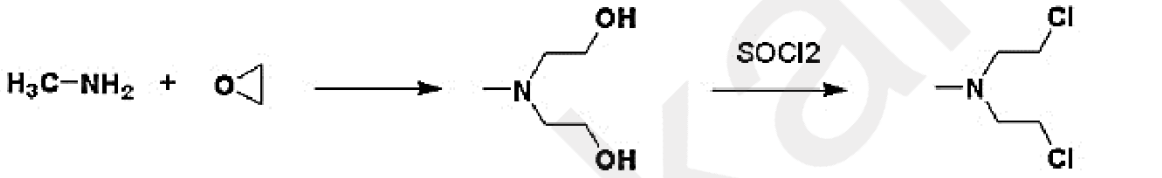


fig: synthesis of mechlorethamine

Ethylene oxide is treated with methanamine. Product so formed is further treated with SOCl2 to obtain mechlorethamine.

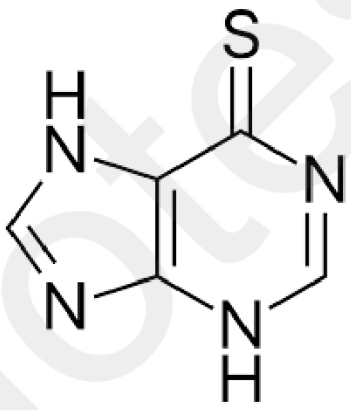
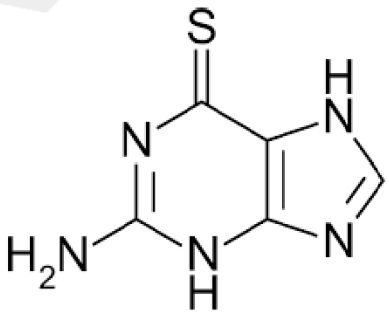
Structural Activity Relationship

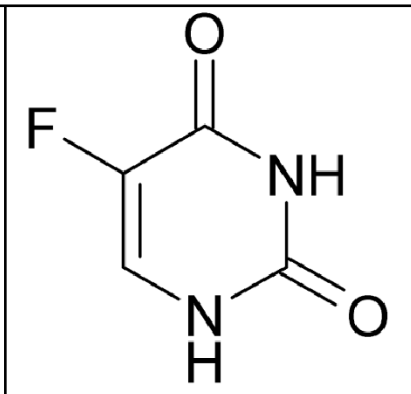
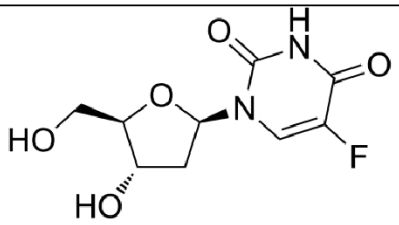
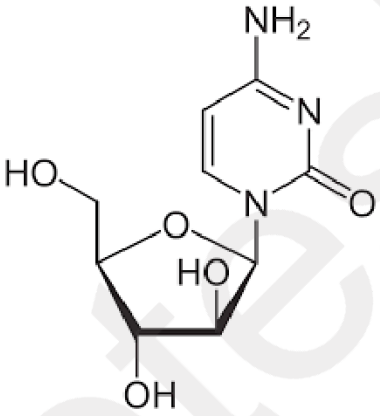
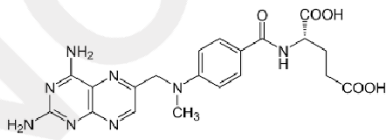
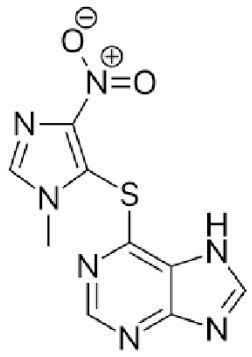
- Replacement of the sulfur atom by nitrogen will lower the toxicity.
- 2-chloroethyl group is essential for the activity as the aziridine cation is formed by this only. Aziridine cation will attach with the alkylates of the DNA later.
- Binding with the amino group will increase the oral route availability o the drug
- The introduction of the substituted phenyl group will also increases the oral route availability of the drug.
- Aromatic ring introduction will increase the stability of the drug.
- Aromatic ring will further increase the distribution of the drug throughout the body.
- Benzimidazole ring can provide the local and faster action of the drug.
- Benzimidazol will further decrease the half life of compound.

2. Antimetabolites: Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine

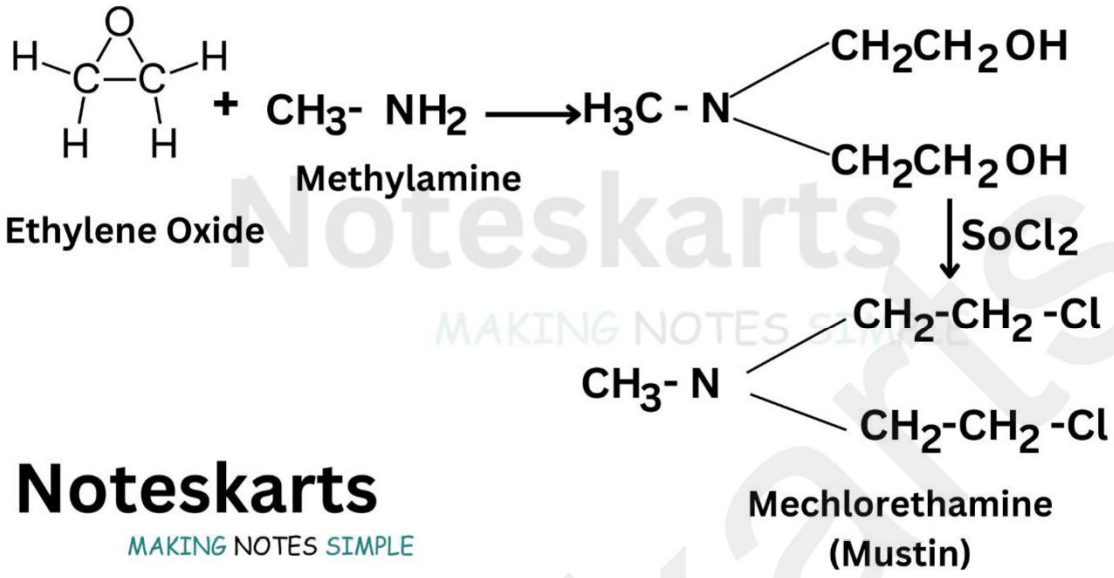
Antimetabolites:

- Antimetabolites are a class of chemotherapy drugs that are used to treat cancer.
- They are cytotoxic drugs that mimic the molecules cells need to grow, and are most effective against fast-growing tumors.
- Antimetabolites are similar to natural chemicals in biochemical reactions, but are different enough to interfere with cell division and functions.
- They disrupt the formation or use of natural compounds, inhibiting metabolic pathways like nucleic acid synthesis.
- Antimetabolites can also incorporate into nucleic acids, which inhibits their normal function and triggers apoptosis.

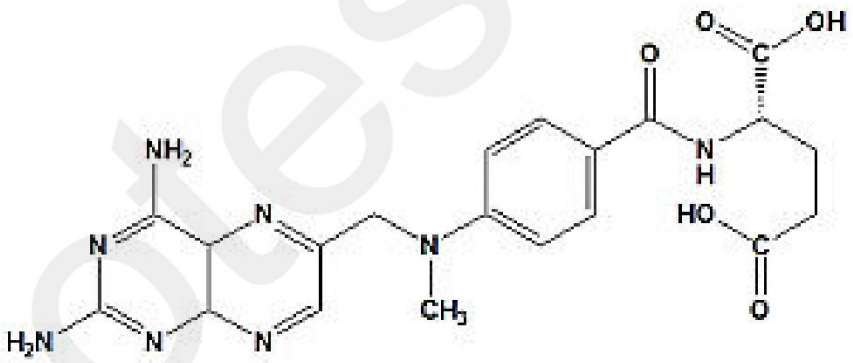
Drug	Structure	Mechanism of Action	Uses
Mercaptopurine		Inhibits purine synthesis, interfering with DNA and RNA synthesis and function.	Used to treat acute lymphoblastic leukemia (ALL) and other types of leukemia.
Thioguanine		Incorporates into DNA and RNA, leading to cell death; inhibits purine synthesis.	Used to treat acute myeloid leukemia (AML).

Fluorouracil		Inhibits thymidylate synthase, leading to a decrease in DNA synthesis and cell death.	Used to treat various cancers, including colorectal, breast, and skin cancers.
Floxuridine		Metabolized to fluorouracil, inhibiting DNA synthesis by blocking thymidylate synthase.	Used to treat liver metastases from gastrointestinal adenocarcinoma.
Cytarabine		Inhibits DNA synthesis by incorporating into DNA and inhibiting DNA polymerase.	Used to treat acute myeloid leukemia (AML) and other types of leukemia.
Methotrexate		Inhibits dihydrofolate reductase, leading to a decrease in DNA synthesis.	Used to treat various cancers, rheumatoid arthritis, and psoriasis.
Azathioprine		Metabolized to mercaptopurine, inhibiting purine synthesis and leading to cell death.	Used as an immunosuppressant in organ transplantation and autoimmune diseases.

Synthesis of Mercaptopurine:



Methotrexate:

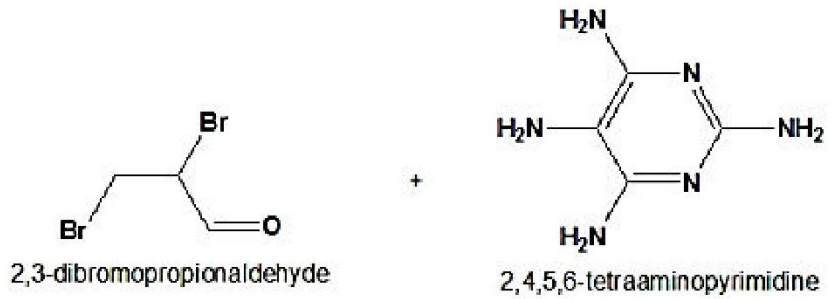


Methotrexate

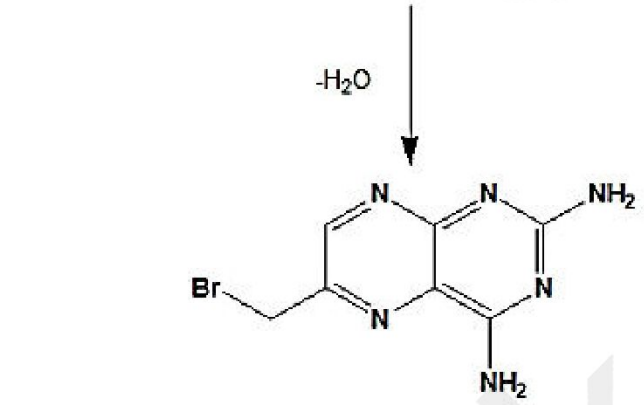
Synthesis of Methotrexate:

i. Condensation of 2,3-dibromopropionaldehyde with 2,4,5,6-tetraaminopyrimidine to produce 6-bromomethyl-2,4-diaminopteridine.

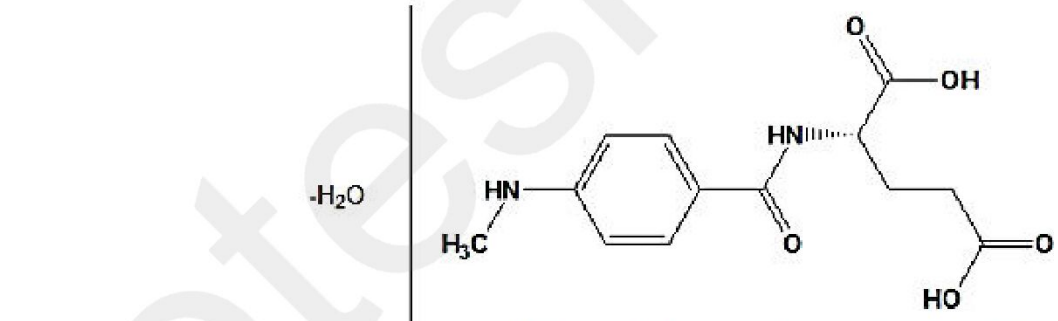
ii. 6-bromomethyl-2,4-diaminopteridine will undergo further condensation with N-(para-(methylamino)benzoyl)glutamic acid. This will lead to the synthesis of methotrexate.



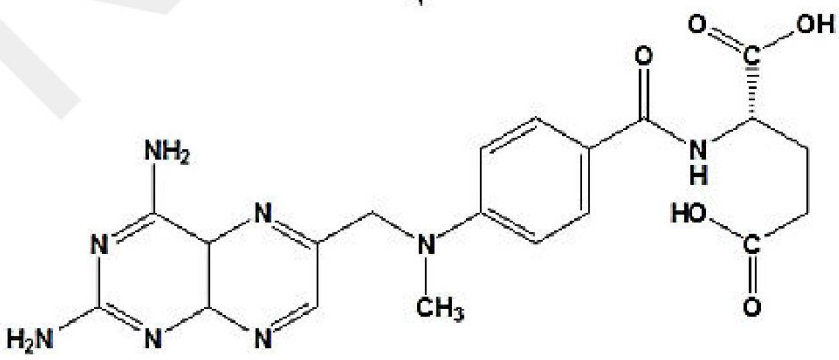
2,3-dibromopropionaldehyde + 2,4,5,6-tetraaminopyrimidine



6-bromomethyl-2,4-diaminopteridine



N-(para-(methylamino)benzoyl)glutamic acid

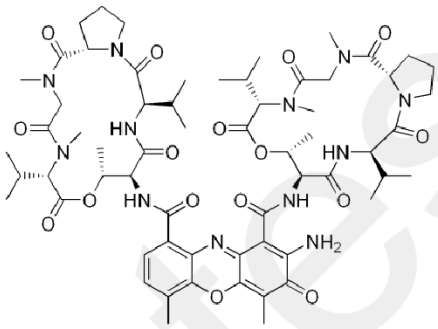
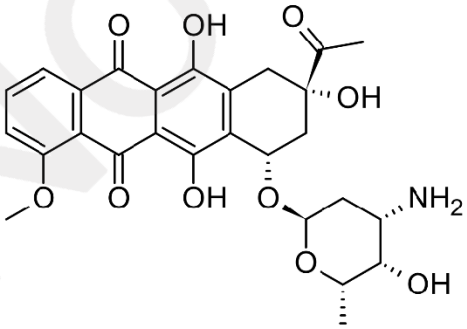


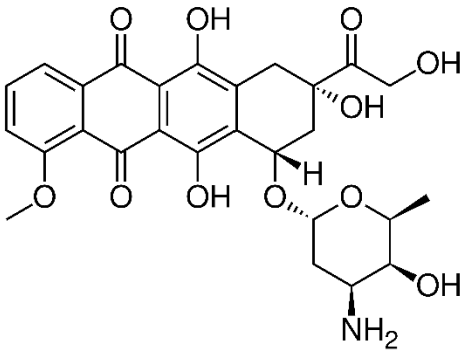
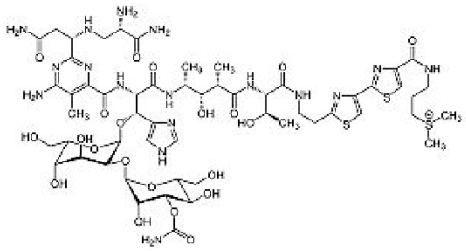
3. Antibiotics: Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin

Antibiotics:

- An antibiotic is a type of antimicrobial substance active against bacteria.
- It is the most important type of antibacterial agent for fighting bacterial infections, and antibiotic medications are widely used in the treatment and prevention of such infections.
- They may either kill or inhibit the growth of bacteria.

Drugs:

Drug Name	Structure	Mechanism of Action	Uses
Dactinomycin		Mechanism of Action: Intercalates into DNA, inhibiting RNA synthesis.	Uses: Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma, testicular cancer
Daunorubicin		Mechanism of Action: Intercalates into DNA, inhibiting topoisomerase II and causing strand breaks.	Uses: Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL)

Doxorubicin		Mechanism of Action: Intercalates into DNA, inhibiting topoisomerase II and causing strand breaks.	Uses: Breast cancer, bladder cancer, Kaposi's sarcoma, lymphomas, acute lymphoblastic leukemia (ALL)
Bleomycin		Mechanism of Action: Induces DNA strand breaks through free radical formation.	Uses: Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular cancer, ovarian cancer, cervical cancer

4. Plant products: Etoposide, Vinblastin sulphate, Vincristin sulphate

Plant products:

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

Classification of Plant Products:

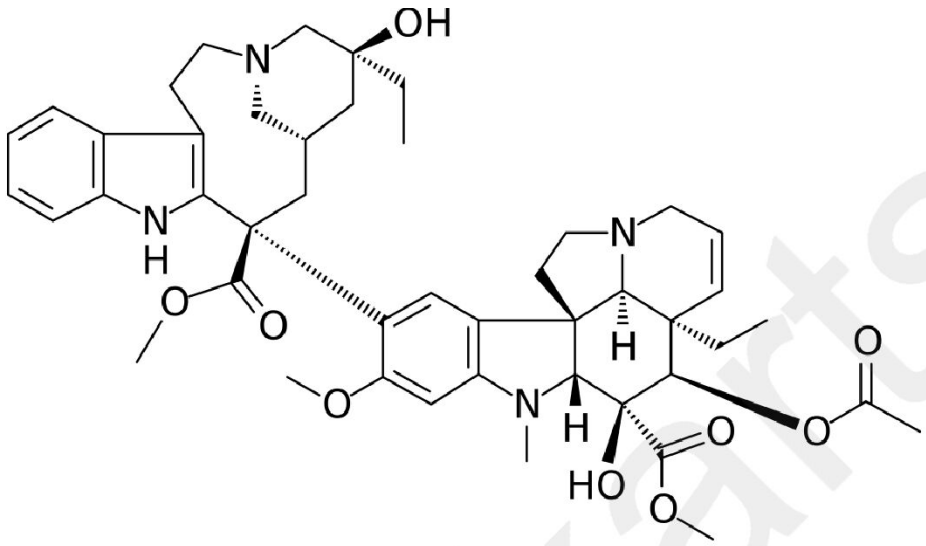
1. Vinca Alkaloids: (Vinblastine, Vincristine and Vindesine)
2. Epipodophyllotoxin: (Etoposide and Teniposide)
3. Taxanes: (Paclitaxel and Docetaxel)
4. Camptothecin derivatives (Camptotecin and Irinotecan)

Vinblastine:

- Vinca alkaloids are obtained from the Madagascar periwinkle plant Catharanthus roseus (Vincarosea).

This plant is known for hypoglycemic activity, which is of little importance compared to their cytotoxic effects.

Structure:



Mechanism of Action:

- It binds to microtubular protein tubulin, prevents polymerization and assembly of microtubules, and causes mitotic spindle destruction.
- The chromosomes fail to move apart during mitosis and lead to metaphase arrest.

Microtubules

↓

Free tubulin dimer

↓ Vinca Alkaoid

Vinca Bound Tubulin

↓

Paracrystaline aggregates

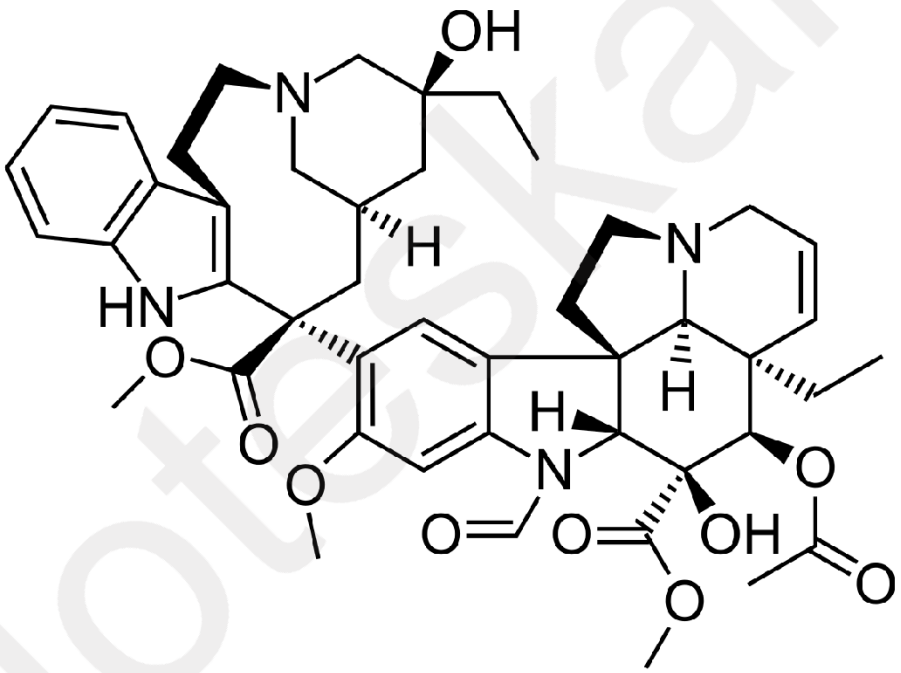
Uses:

- Generalized Hodgkin's disease
- Mycosis fungoides
- Letterer-Siwe disease
- Lymphocytic lymphoma

Vincistin:

- Vincristine, also known as Leurocristine.
- Vincristine was first isolated in 1961.
- It is given intravenously It is extracted from Catharanthus roseus.

Structure:



Mechanism of Action:

- It binds to microtubular protein tubulin, prevents polymerization and assembly of microtubules, and causes mitotic spindle destruction.
- The chromosomes fail to move apart during mitosis and lead to metaphase arrest.

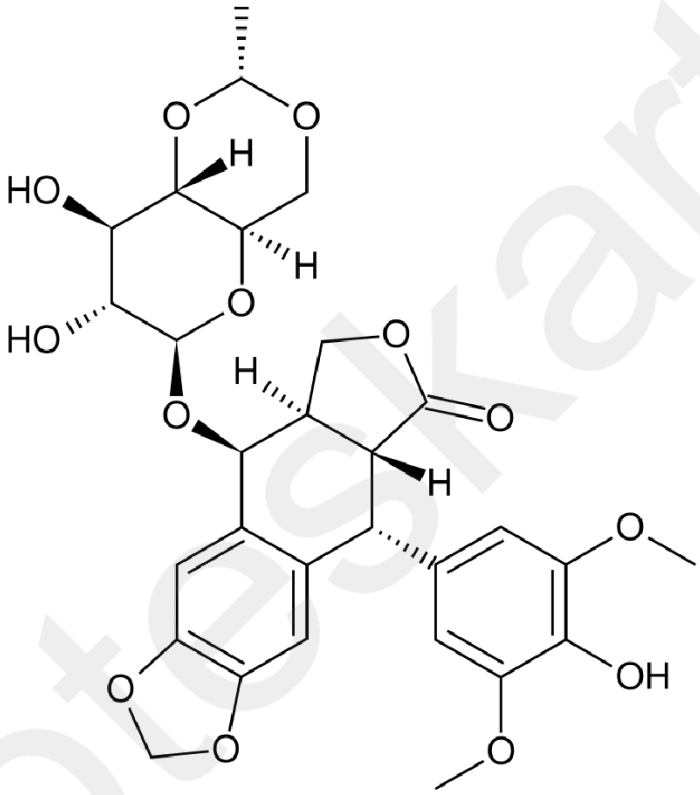
Used:

- Vincristine is a vinca alkaloid used to treat acute leukemia, malignant lymphoma, Hodgkin's disease, acute erythraemia, and acute panmyelosis.

Etoposide:

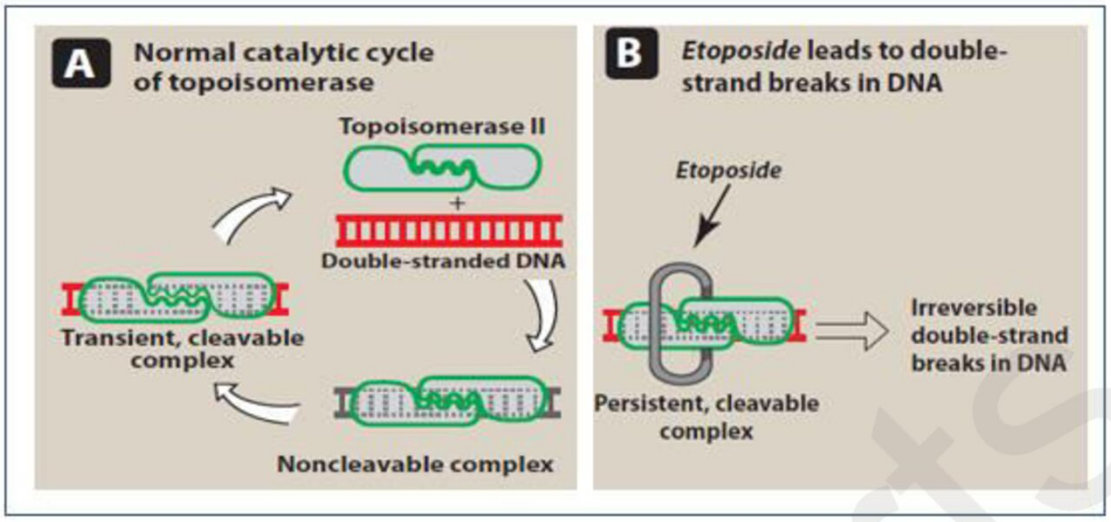
- Etoposide is a beta-D-glucoside, a furonaphthodioxole and an organic heterotetracyclic compound.
- It has a role as an antineoplastic agent and a DNA synthesis inhibitor.
- It is functionally related to a podophyllotoxin and a 4'-demethylepipodophyllotoxin.

Structure:



Mechanism of Action:

- It is phase-specific cytotoxic drug which blocks cells in late S to G2 phase of cell cycle. Its major target is topoisomerase II. Topoisomerase II forms transient break in double strand DNA to manage DNA tangles and supercoils which is followed by resealing of the transient break.
- They form complex with topoisomerase II and DNA and prevent resealing of the DNA break. The enzyme remains bound to free end of broken DNA strand which results in transient, cleavable form of complex. This is susceptible to irreversible double strand DNA break. Hence, there occurs accumulation of double strand DNA break and cell death.



Uses:

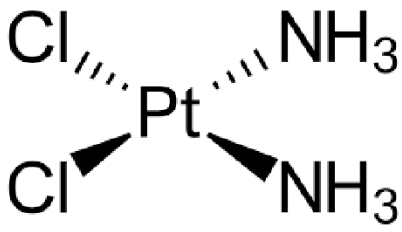
- Used in treatment of lung cancer, germ-cell tumor and Kaposi's sarcoma associated with acquired immunodeficiency syndrome (AIDS).
- To treat non- Hodgkin lymphoma.
- Used in combination with bleomycin and cisplatin for testicular carcinoma.

5. Miscellaneous: Cisplatin, Mitotane

Cisplatin:

Cisplatin is a platinum based chemotherapy agent used to treat various sarcomas, carcinomas, lymphomas, and germ cell tumors.

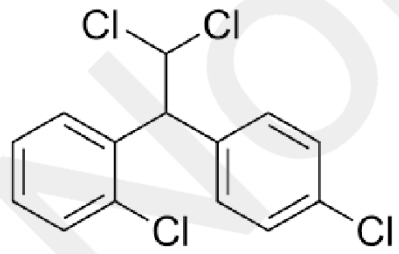
Structure:



Uses:

- Cisplatin injection is used to treat advanced cancer of the bladder, ovaries, or testicles.
- Cisplatin is an antineoplastic agent (cancer medicine).
- It interferes with the growth of cancer cells, which are eventually destroyed by the body.

Mitotane:



MOA:

- It works by slowing growth or reducing the size of the tumor.

Uses:

- Mitotane is used to treat cancer of the adrenal gland that can not be treated with surgery.
- Mitotane is in a class of medications called antineoplastic agents.