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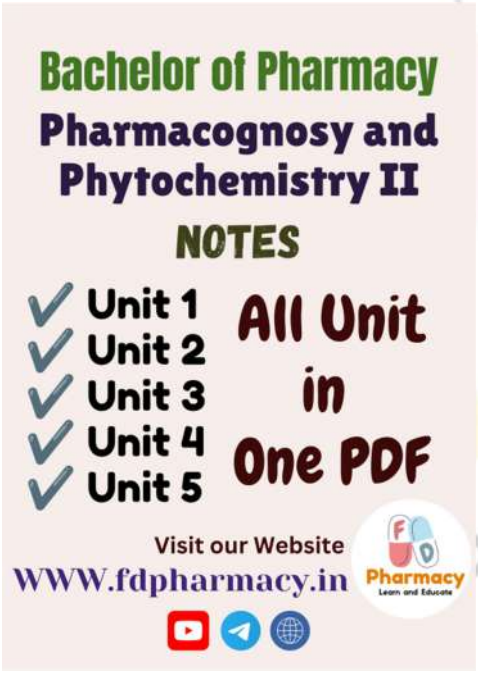
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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Antihistaminic agents :** Histamine, receptors and their distribution in the humanbody
- **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

Antihistaminic Agents

- Antihistaminic agents (commonly called antihistamines) are drugs that block the action of histamine, a chemical mediator involved in allergic and inflammatory reactions.
- Histamine is released during immune responses (e.g., allergies, asthma, anaphylaxis) and causes itching, swelling, redness, increased mucus secretion, bronchoconstriction, and gastric acid secretion.
- Antihistaminic agents work by blocking histamine receptors and are used in treatment of allergic rhinitis, urticaria, hay fever, asthma, anaphylaxis, peptic ulcers, and motion sickness.

Histamine

- Histamine is a biogenic amine autacoid (local hormone) that exerts its action near the site of synthesis.
- It is stored in an inactive form inside granules of mast cells and basophils and released when triggered.

Chemical Nature

- Histamine is an organic nitrogenous compound.
- Molecular formula: $C_5H_9N_3$.
- Structure: Imidazole ring + ethylamine side chain.

Synthesis of Histamine

- Precursor : Amino acid Histidine.
- Enzyme : Histidine decarboxylase.
- Reaction : Decarboxylation of histidine (removal of –COOH group) → formation of histamine.

$$\text{Histidine} \xrightarrow{\text{Histidine Decarboxylase}} \text{Histamine} + CO_2$$

Storage of Histamine

- Stored primarily in mast cells and basophils inside membrane-bound granules.
- Granules also contain other inflammatory mediators.
- In mast cells → histamine is stored in complex with Heparin.
- In basophils → stored in complex with Chondroitin sulfate.

Release Mechanism of Histamine

- **Process:** Degranulation of mast cells and basophils.
- **Trigger:** Mainly IgE-mediated antigen–antibody reaction.

Steps of release:

1. Allergen enters body.
2. B-lymphocytes produce IgE antibodies.
3. IgE attaches to the surface receptors of mast cells/basophils.
4. Allergen binds to IgE → cross-linking occurs.
5. Mast cell undergoes degranulation, releasing histamine + other mediators.

$$\text{Allergen} + \text{IgE (on Mast Cell)} \Rightarrow \text{Degranulation} \Rightarrow \text{Histamine Release}$$

Histamine Receptors

- Histamine exerts its actions through four types of receptors – H_1, H_2, H_3, H_4.
  All are G-protein coupled receptors (GPCRs) but linked to different intracellular pathways.

Histamine Receptors, Location & Effects

Receptor	Location	Type of G-Protein & Intracellular Action	Physiological Effect
H_1	Smooth muscles, vascular endothelial cells, heart, CNS	Coupled to Gq protein → activates Phospholipase C (PLC) → ↑ IP_3, DAG, Ca^{2+}	- Vasodilation (via NO) - Increased vascular permeability (edema) - Bronchoconstriction (asthma) - Increased intestinal motility - Itching, pain (via sensory nerves)
H_2	Gastric parietal cells, vascular smooth muscle, neutrophils, heart, uterus, CNS	Coupled to Gs protein → stimulates Adenylate cyclase → ↑ cAMP	- Increased gastric acid secretion - Vasodilation - Cardiac stimulation (↑ heart rate, contractility)
H_3	Mainly CNS (high in hypothalamus, thalamus, cortex, caudate nucleus); also in intestine, testis, prostate	Coupled to Gi protein → inhibits adenylate cyclase → ↓ cAMP	- Inhibits release of histamine (autoreceptor) - Modulates release of other neurotransmitters (ACh, dopamine, serotonin, norepinephrine) - Role in sleep–wake cycle, appetite, cognition
H_4	Immune system tissues: thymus, spleen, small intestine, colon, bone marrow, basophils, eosinophils, mast cells	Likely coupled to Gi protein → ↓ cAMP	- Chemotaxis of immune cells - Regulates inflammatory and immune response - Involved in autoimmune & chronic inflammatory diseases

ACTION OF HISTAMINE

Histamine is a biogenic amine that plays important roles in immune response, gastric secretion, and neurotransmission. Its effects depend on the type of histamine receptor (H_1, H_2, H_3, H_4) activated.

1. Immune Response

- Released from mast cells and basophils during allergic reactions.
- Causes itching, redness, swelling, and increased mucus secretion.
- Contributes to inflammation and allergic symptoms (e.g., hay fever, urticaria, asthma).

2. Blood Vessels

- Causes vasodilation (widening of blood vessels).
- Increases vascular permeability, allowing immune cells and plasma to move into tissues.
- Results in edema, heat, redness, and swelling at the site of infection or injury.

3. Respiratory System

- Produces bronchoconstriction by acting on H_1 receptors in airway smooth muscle.
- This can lead to difficulty in breathing, especially in asthma and hypersensitivity.

4. Gastrointestinal Tract

- Stimulates H_2 receptors on gastric parietal cells, leading to increased secretion of gastric acid (HCl).
- Plays a role in digestion but excess secretion causes ulcers, GERD, and acidity.

5. Central Nervous System

- Acts as a neurotransmitter in the brain.
- Regulates sleep–wake cycle, appetite, learning, memory, and cognitive functions.
- High concentration in hypothalamus, cortex, and thalamus.

HISTAMINE METABOLISM

Histamine is not stored for long once released; it is rapidly metabolized by two major pathways:

1. Oxidative Pathway

- Enzyme: Diamine Oxidase (DAO, also called Histaminase).
- Reaction: Histamine → Imidazole Acetic Acid (an inactive metabolite).
- Mainly occurs in intestinal mucosa, kidney, placenta.
- Important in detoxification of ingested histamine (e.g., from food).

2. Methylation Pathway

- Enzyme: Histamine N-Methyltransferase (HNMT).
- Reaction: Histamine → N-Methylhistamine.
- Further oxidized to N-Methylimidazole Acetic Acid.
- Occurs mainly in the liver and central nervous system.

CLASSIFICATION OF ANTIHISTAMINES

Antihistaminic drugs are mainly classified based on the type of histamine receptor they block:

1. **H_1 Receptor Antagonists (H_1 Blockers)** – primarily used for allergic conditions.
2. **H_2 Receptor Antagonists (H_2 Blockers)** – primarily used for gastric acid-related disorders.

1. H_1 Receptor Antagonists

First Generation H_1 Blockers

- Cross the blood-brain barrier, causing sedation.
- Examples:

Drug Name
Diphenhydramine Hydrochloride
Triprolidine Hydrochloride
Promethazine Hydrochloride
Dimenhydrinate
Doxylamine Succinate
Clemastine Fumarate
Diphenylpyraline Hydrochloride
Tripelennamine Hydrochloride
Chlorcyclizine Hydrochloride
Meclizine Hydrochloride
Buctizine Hydrochloride
Chlorpheniramine Maleate
Phenidamine Tartarate
Trimeprazine Tartarate
Cyproheptadine Hydrochloride
Azatadine Maleate

Second Generation H_1 Blockers

- **Less sedating**, longer acting.
- Examples:
  - Astemizole
  - Loratadine
  - Cetirizine
  - Levocetirizine
  - Cromolyn Sodium (mast cell stabilizer – often included in anti-allergic therapy)

2. H_2 Receptor Antagonists

- Used mainly to reduce gastric acid secretion **in** peptic ulcers, GERD, Zollinger–Ellison syndrome**.**
- Examples:
  - Cimetidine
  - Famotidine
  - Ranitidine

STRUCTURE–ACTIVITY RELATIONSHIP (SAR) OF ANTIHISTAMINES

The general structure of antihistamines consists of:

Aryl group (Ar) – Connecting atom (X) – Alkyl chain – Terminal nitrogen (NR')

1. Aryl Groups (Ar)

- Diaryl substitution is essential for significant H_1 receptor affinity.
- Maximum antihistaminic activity depends on the planarity of the two aryl rings.
- Types of aryl groups:
  - Ar = Phenyl or Heteroaryl (e.g., 2-furyl)
  - Ar' = Alkyl or Alkyl-methyl group

2. Connecting Atom (X)

- The atom/group linking the aryl ring to the alkyl chain is called X.
- Common connecting groups:
  - O → Alkyl ether (–O–)
  - NH → Ethylene diamine derivative (–NH–CH_2–CH_2–NH–)
  - C → Monoamine propyl analog (–CH_2–)

3. Alkyl Chain

- Usually consists of 2–3 carbon atoms.
- Most antihistamines have an ethylene chain (–CH_2–CH_2–).
- Branching generally decreases activity (exception: Promethazine).
- Chain length and flexibility influence lipophilicity and CNS penetration.

4. Terminal Nitrogen Atom (NR')

- Terminal nitrogen is usually a tertiary amine for maximum antihistaminic activity.
- Can be part of a heterocyclic ring.
- Dimethyl substitution on nitrogen → highest H_1 receptor activity.
- Plays a role in solubility, receptor binding, and side-effect profile.

H_1 ANTAGONISTS (H_1 Blockers)

- H_1 antagonists are classical antihistaminic agents that block the physiological effects of histamine by selectively antagonizing H_1 receptors.
- Mainly used in allergic conditions to reduce symptoms such as itching, sneezing, runny nose, hives, and bronchoconstriction.

First Generation H_1 Blockers

- Cross the blood-brain barrier, causing sedation.
- Examples:

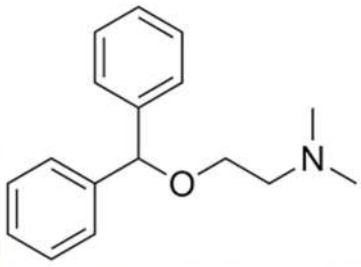
Drug Name
Diphenhydramine Hydrochloride
Triprolidine Hydrochloride
Promethazine Hydrochloride
Dimenhydrinate
Doxylamine Succinate
Clemastine Fumarate
Diphenylpyraline Hydrochloride
Tripelennamine Hydrochloride
Chlorcyclizine Hydrochloride
Meclizine Hydrochloride
Buctizine Hydrochloride
Chlorpheniramine Maleate
Phenidamine Tartarate
Trimeprazine Tartarate
Cyproheptadine Hydrochloride
Azatadine Maleate

Diphenhydramine Hydrochloride

- Diphenhydramine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is commonly used for allergic conditions, motion sickness, insomnia, and Parkinsonian symptoms due to its antihistaminic, sedative, and anticholinergic properties.
- It is a ethanolamine derivative, structurally related to other classic antihistamines.
- Being a first-generation H_1 blocker, it crosses the blood-brain barrier, which accounts for central nervous system (CNS) effects, such as sedation.

Chemical Structure

- IUPAC Name: 2-(diphenylmethoxy)-N,N-dimethylethanamine hydrochloride
- Molecular Formula: $C_{17}H_{21}NO \cdot HCl$
- Molecular Weight: 291.82 g/mol
- Chemical Structure:



Mechanism of Action

- Diphenhydramine acts primarily as a competitive antagonist at H_1 histamine receptors.
- By blocking H_1 receptors:
  1. Prevents histamine-induced smooth muscle contraction in the bronchi, gut, and uterus.
  2. Inhibits vasodilation and increased vascular permeability, reducing edema, itching, and redness.
  3. Blocks histamine-mediated neurotransmission in the CNS, causing sedation.
- Additional anticholinergic action contributes to relief from motion sickness and parkinsonian symptoms.

Synthesis

1. Preparation of 2-(Diphenylmethoxy)ethyl chloride:
    - Diphenylmethanol reacts with 2-chloroethanol in the presence of acid catalyst to form 2-(diphenylmethoxy)ethyl chloride.
2. Amination:
    - The intermediate 2-(diphenylmethoxy)ethyl chloride is reacted with dimethylamine to produce Diphenhydramine.
3. Formation of Hydrochloride Salt:
    - The free base Diphenhydramine is treated with hydrochloric acid to give Diphenhydramine hydrochloride, a crystalline and water-soluble salt suitable for pharmaceutical formulations.

Uses

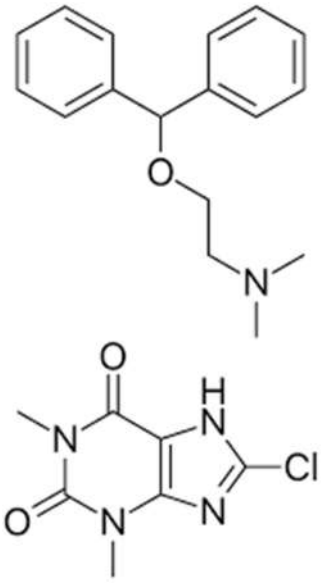
1. Allergic conditions:
    - Rhinitis, urticaria, angioedema, and other histamine-mediated allergies.
2. Motion sickness and nausea:
    - Effective due to anticholinergic action on vestibular system.
3. Insomnia:
    - Sedative effect makes it useful as short-term sleep aid.
4. Parkinsonism and extrapyramidal symptoms:
    - Anticholinergic activity helps reduce tremors and rigidity.
5. Cold and cough preparations:
    - Often included for its sedative and antihistaminic effects.

Dimenhydrinate

- Dimenhydrinate is a first-generation H_1 histamine receptor antagonist.
- It is primarily used as an antiemetic and anti-motion sickness agent.
- Chemically, Dimenhydrinate is a salt composed of diphenhydramine and 8-chlorotheophylline.
- The combination balances diphenhydramine's sedative effect with the mild CNS stimulant effect of 8-chlorotheophylline, reducing drowsiness.
- It also exhibits anticholinergic activity, which contributes to its antiemetic action.

Chemical Structure

- Components:
  1. Diphenhydramine: 2-(diphenylmethoxy)-N,N-dimethylethanamine
     - Molecular formula: $C_{17}H_{21}NO$
  2. 8-Chlorotheophylline: a xanthine derivative
     - Molecular formula: $C_7H_7ClN_4O_2$
- Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Diphenhydramine component blocks H_1 histamine receptors in the vestibular system and GI tract.
  - Reduces nausea, vomiting, and motion sickness symptoms.
- Anticholinergic Activity:
  - Inhibits muscarinic receptors in the vestibular system, reducing vertigo and motion-induced nausea.
- CNS Effects:
  - Diphenhydramine causes sedation, while 8-chlorotheophylline partially counteracts drowsiness, balancing CNS effects.

Synthesis of Dimenhydrinate

1. Diphenhydramine Preparation:
    - Synthesized via alkylation of diphenylmethanol with 2-dimethylaminoethyl chloride.
2. 8-Chlorotheophylline Preparation:
    - Derived from theophylline by chlorination at position 8.
3. Salt Formation:
    - Equimolar amounts of diphenhydramine base and 8-chlorotheophylline are combined to form Dimenhydrinate, a stable crystalline salt suitable for tablets and oral solutions.

Uses

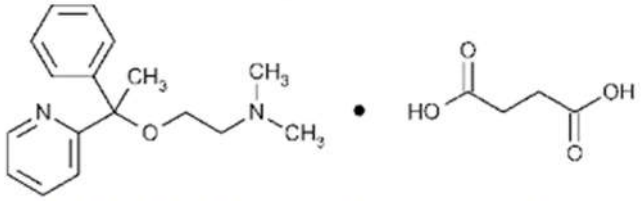
1. Motion sickness:
    - Prevention and treatment of nausea, vomiting, and vertigo due to motion.
2. Nausea and vomiting:
    - Post-operative or drug-induced emesis.
3. Vertigo:
    - Symptomatic relief of dizziness associated with vestibular disorders.
4. Mild sedation:
    - Can cause drowsiness due to the diphenhydramine component.

Doxylamine Succinate

- Doxylamine succinate is a first-generation H_1 histamine receptor antagonist.
- It is commonly used as a sedative, sleep aid, and antiemetic, especially in combination with pyridoxine for nausea and vomiting of pregnancy (morning sickness).
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing sedation and CNS depressant effects.
- Chemically, it is a ethanolamine derivative, similar to diphenhydramine.

Chemical Structure

- IUPAC Name: 2-(1-ethylpyrrolidin-2-yl)-1-(phenylmethylsulfanyl)ethanol succinate
- Molecular Formula: $C_{17}H_{21}NO \cdot C_4H_6O_4$ (Doxylamine succinate)
- Molecular Weight: 380.49 g/mol (salt)
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks H_1 receptors in the respiratory tract, skin, and GI tract, reducing allergic symptoms like itching, swelling, and redness.
- CNS Effects:
  - Crosses blood-brain barrier, causing sedation, which makes it effective as a sleep aid.
- Anticholinergic Effects:
  - Inhibits muscarinic receptors in the vestibular system, reducing nausea, vomiting, and motion sickness.
- Used in combination with vitamin B6 (pyridoxine) for morning sickness, leveraging its antiemetic and sedative effects.

Synthesis of Doxylamine Succinate

1. Formation of Doxylamine base:
    - Alkylation of diphenylmethylsulfanyl ethanol derivative with N-ethyl-2-pyrrolidinemethanamine.
2. Conversion to Succinate Salt:
    - The free base of Doxylamine is reacted with succinic acid to form Doxylamine succinate, a stable, water-soluble salt suitable for oral formulations.

Uses

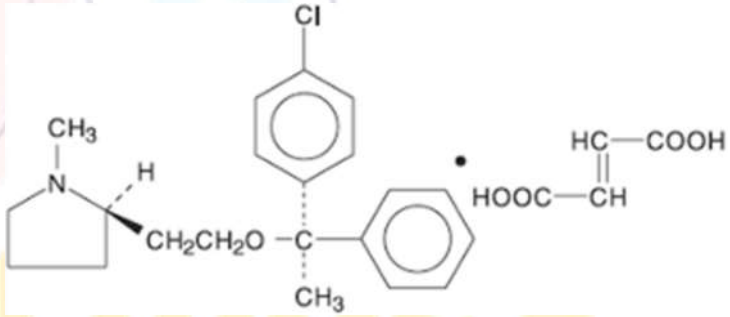
1. Insomnia:
    - Short-term management of sleep disturbances due to sedative properties.
2. Allergic conditions:
    - Relief from rhinitis, urticaria, and other H_1-mediated allergies.
3. Nausea and vomiting:
    - Used in morning sickness (often combined with pyridoxine).
4. Cold and cough preparations:
    - Included for antihistaminic and sedative effects in OTC multi-symptom remedies.
5. Motion sickness:
    - Anticholinergic effect reduces vertigo and emesis.

Clemastine Fumarate

- Clemastine fumarate is a first-generation H_1 histamine receptor antagonist.
- It is primarily used to treat allergic conditions, such as rhinitis, urticaria, and conjunctivitis, and also for pruritus relief.
- As a first-generation antihistamine, it crosses the blood-brain barrier, producing sedation, though less than diphenhydramine.
- It is a ethanolamine derivative with high H_1 receptor selectivity.

Chemical Structure

- IUPAC Name: 2-[2-[(R)-1-(4-chlorophenyl)-1-phenylethyl]aminopropyl]-1-methoxyethanol fumarate
- Molecular Formula: $C_{22}H_{26}ClNO \cdot C_4H_4O_4$ (fumarate)
- Molecular Weight: 426.94 g/mol (salt)
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 receptors in the respiratory tract, skin, and GI tract.
  - Reduces allergic responses like edema, itching, redness, and rhinorrhea.
- CNS Effects:
  - Crosses the blood-brain barrier, causing sedation, although milder than diphenhydramine.
- Anticholinergic Effects:
  - Mild inhibition of muscarinic receptors, reducing nasal and vestibular symptoms in allergies.

Synthesis of Clemastine Fumarate

1. Formation of Clemastine Base:
    - The key intermediate 2-[2-(diphenylmethylamino)propyl]-1-methoxyethanol is prepared via alkylation and reductive amination reactions.
2. Chlorophenyl Substitution:
    - Introduce the 4-chlorophenyl group to the diphenylmethane moiety via electrophilic aromatic substitution.
3. Formation of Fumarate Salt:
    - The free base of clemastine is reacted with fumaric acid to form Clemastine fumarate, a stable, water-soluble salt suitable for oral formulations.

Uses

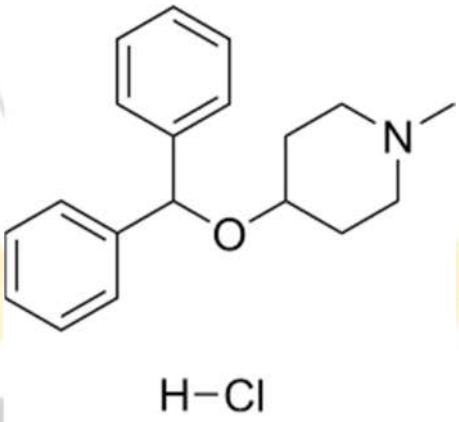
1. Allergic conditions:
    - Rhinitis, conjunctivitis, urticaria, pruritus, and other H_1-mediated allergies.
2. Cold and flu symptoms:
    - Relief of sneezing, runny nose, and watery eyes.
3. Mild sedation:
    - Provides sedative effect for sleep in some formulations.
4. Combination therapy:
    - Sometimes combined with decongestants in OTC cold remedies.

Diphenylpyraline Hydrochloride

- Diphenylpyraline hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used for allergic conditions like rhinitis, urticaria, pruritus, and sometimes in cold preparations.
- Being a first-generation H_1 blocker, it crosses the blood-brain barrier, which can produce mild sedation.
- Chemically, it is a diphenylpiperidine derivative, structurally related to other classic antihistamines.

Chemical Structure

- IUPAC Name: 1-(Diphenylmethyl)-4-(2-dimethylaminoethoxy)piperidine hydrochloride
- Molecular Formula: $C_{21}H_{28}N_2O{\cdot}HCl$
- Molecular Weight: 349.91 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Competitively blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces edema, itching, redness, and other allergic symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, producing mild sedation.
- Anticholinergic Effects:
  - Mild inhibition of muscarinic receptors can help reduce nasal secretions and motion sickness symptoms.

Synthesis of Diphenylpyraline Hydrochloride

1. Formation of Diphenylmethyl Piperidine Intermediate:
    - Piperidine is reacted with diphenylmethyl halide to form the core structure.
2. Introduction of Ethanolamine Side Chain:
    - The hydroxylated 2-dimethylaminoethyl group is attached via ether linkage to the piperidine nitrogen.
3. Formation of Hydrochloride Salt:
    - The free base is treated with HCl to yield Diphenylpyraline hydrochloride, a crystalline, water-soluble salt suitable for oral or injectable formulations.

Uses

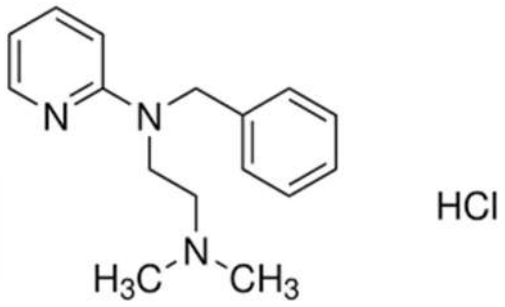
1. Allergic conditions:
    - Urticaria, rhinitis, pruritus, and other H_1-mediated reactions.
2. Cold symptoms:
    - Relief of sneezing, runny nose, and watery eyes.
3. Mild sedation:
    - Provides sedative effect in formulations.
4. Adjunct therapy:
    - Can be combined with decongestants or cough suppressants in multi-symptom cold preparations.

Tripelennamine Hydrochloride

- Tripelennamine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used for allergic conditions, including rhinitis, urticaria, and pruritus, and sometimes in cold and cough preparations.
- Being a first-generation H_1 blocker, it crosses the blood-brain barrier, leading to sedation, though milder than diphenhydramine.
- Chemically, it is an ethylenediamine derivative, similar to other classic H_1 blockers.

Chemical Structure

- IUPAC Name: N^1-(2-(pyridin-2-yl)ethyl)-N^2,N^2-dimethylethane-1,2-diamine hydrochloride
- Molecular Formula: $C_{13}H_{21}N_3 \cdot HCl$
- Molecular Weight: 245.79 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Tripelennamine competitively blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces allergic symptoms like itching, swelling, redness, and sneezing.
- CNS Effects:
  - Crosses the blood-brain barrier, causing mild sedation, less than diphenhydramine or promethazine.
- Minimal Anticholinergic Effects:
  - Compared to ethanolamine derivatives, Tripelennamine has lower anticholinergic activity, reducing dry mouth and drowsiness.

Synthesis of Tripelennamine Hydrochloride

1. Preparation of Pyridylethylamine Intermediate:
    - 2-bromoethylpyridine is reacted with dimethylamine to form the substituted ethylenediamine intermediate.
2. Formation of Tripelennamine Base:
    - The intermediate undergoes secondary amine formation with ethylenediamine derivatives to yield Tripelennamine free base.
3. Formation of Hydrochloride Salt:
    - The free base is treated with HCl to form Tripelennamine hydrochloride, a water-soluble, crystalline salt suitable for pharmaceutical formulations.

Uses

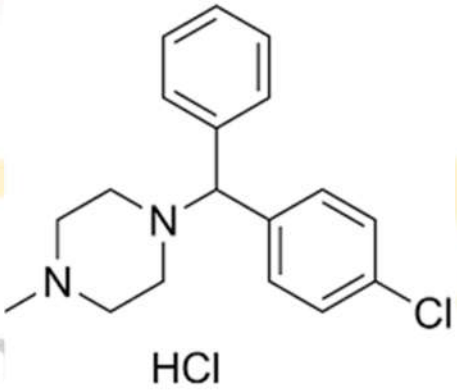
1. Allergic conditions:
    - Urticaria, rhinitis, pruritus, and other H_1-mediated reactions.
2. Cold and cough preparations:
    - Relief from sneezing, runny nose, and watery eyes.
3. Mild sedation:
    - Provides sedative effect, though weaker than other first-generation antihistamines.
4. Combination therapy:
    - Sometimes combined with decongestants in OTC multi-symptom cold remedies.

Chlorcyclizine Hydrochloride

- Chlorcyclizine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used for allergic conditions such as rhinitis, urticaria, and pruritus, and sometimes for motion sickness.
- As a first-generation antihistamine, it crosses the blood-brain barrier, causing mild sedation.
- Chemically, it is a piperazine derivative, structurally related to cyclizine.

Chemical Structure

- IUPAC Name: 1-[(4-chlorophenyl)(phenyl)methyl]-4-methylpiperazine hydrochloride
- Molecular Formula: $C_{17}H_{20}ClN_2 \cdot HCl$
- Molecular Weight: 303.81 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces edema, itching, redness, and other allergic symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, producing mild sedation.
- Anticholinergic Effects:
  - Mild muscarinic receptor inhibition helps reduce nasal secretions and motion sickness symptoms.

Synthesis of Chlorcyclizine Hydrochloride

1. Formation of Diphenylmethylpiperazine Intermediate:
    - React 4-chlorobenzhydryl chloride with 4-methylpiperazine to form the intermediate.
2. Formation of Hydrochloride Salt:
    - The free base is treated with HCl to produce Chlorcyclizine hydrochloride, a crystalline, water-soluble salt suitable for oral formulations.

Uses

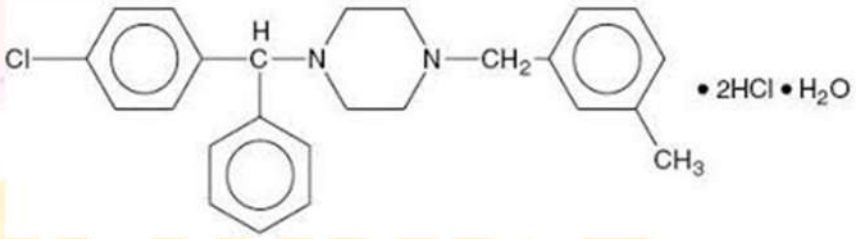
1. Allergic conditions:
    - Rhinitis, urticaria, pruritus, and other H_1-mediated reactions.
2. Cold symptoms:
    - Relief from sneezing, runny nose, and watery eyes.
3. Motion sickness:
    - Mild antiemetic effect due to anticholinergic activity.
4. Mild sedation:
    - Can cause drowsiness, useful in formulations for night-time allergy relief.

Meclizine Hydrochloride

- Meclizine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used as an antiemetic, antivertigo, and anti-motion sickness agent, and also for allergic conditions.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing mild sedation, although less than diphenhydramine.
- Chemically, it is a piperazine derivative related to cyclizine and hydroxyzine.

Chemical Structure

- IUPAC Name: 1-[(4-chlorophenyl)(phenyl)methyl]-4-(3-methylbenzyl)piperazine hydrochloride
- Molecular Formula: $C_{23}H_{27}ClN_2 \cdot HCl$
- Molecular Weight: 382.93 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 receptors in the vestibular system and the GI tract.
  - Reduces allergic responses, nausea, and vomiting.
- CNS Effects:
  - Crosses the blood-brain barrier, causing mild sedation.
- Anticholinergic Effects:
  - Mild inhibition of muscarinic receptors helps reduce motion sickness and vertigo.
- Vestibular System Action:
  - Reduces neuronal excitability in the inner ear and chemoreceptor trigger zone (CTZ) to prevent nausea and vomiting.

Synthesis of Meclizine Hydrochloride

1. Formation of Diphenylmethylpiperazine Intermediate:
    - React 4-chlorobenzhydryl chloride with piperazine to form the intermediate.
2. Introduction of Benzyl Group:
    - Alkylation of the piperazine nitrogen with 3-methylbenzyl chloride forms the Meclizine base.
3. Formation of Hydrochloride Salt:
    - Treat the free base with HCl to yield Meclizine hydrochloride, a crystalline, water-soluble salt suitable for oral administration.

Uses

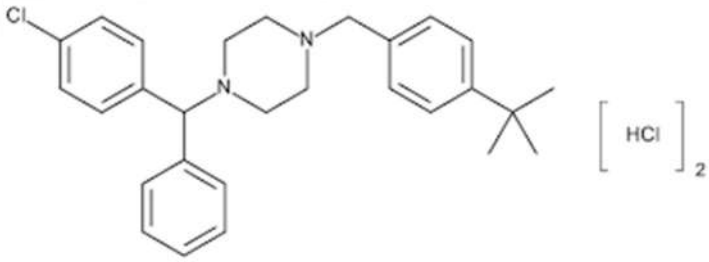
1. Motion sickness and vertigo:
    - Prevention and treatment of nausea, vomiting, and dizziness.
2. Allergic conditions:
    - Rhinitis, urticaria, pruritus.
3. CNS sedative effect:
    - Mild sedation, though less pronounced than diphenhydramine or promethazine.
4. Combination therapy:
    - Sometimes included in multi-symptom cold and allergy formulations.

Buctizine Hydrochloride

- Buctizine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used for allergic conditions such as rhinitis, urticaria, and pruritus.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing mild sedation.
- Chemically, it is a piperazine derivative, similar in structure to cyclizine and meclizine, with potent antihistaminic activity and low anticholinergic effects.

Chemical Structure

- IUPAC Name: 1-[4-(1,3-benzodioxol-5-yl)-1-methylbutyl]-4-methylpiperazine hydrochloride
- Molecular Formula: $C_{19}H_{27}N_2O_2 \cdot HCl$
- Molecular Weight: 354.89 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces edema, itching, redness, and other allergic symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, producing mild sedation, though weaker than diphenhydramine.
- Minimal Anticholinergic Effects:
  - Compared to ethanolamine and ethylenediamine derivatives, Buctizine has lower anticholinergic activity, reducing dry mouth and drowsiness.

Synthesis of Buctizine Hydrochloride

1. Formation of Piperazine Intermediate:
    - Methylpiperazine is reacted with an appropriate alkyl halide containing the benzodioxole moiety.
2. Side Chain Attachment:
    - The substituted alkyl chain is attached to the piperazine nitrogen to yield the Buctizine free base.
3. Formation of Hydrochloride Salt:
    - Treat the free base with HCl to form Buctizine hydrochloride, a stable, water-soluble crystalline salt suitable for oral administration.

Uses

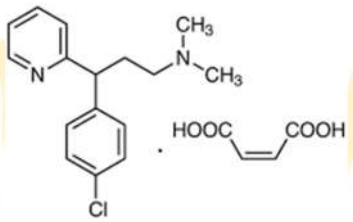
1. Allergic conditions:
    - Rhinitis, urticaria, pruritus, and other H_1-mediated reactions.
2. Mild sedation:
    - Useful in night-time allergy relief or in multi-symptom formulations.
3. Cold symptoms:
    - Relief of sneezing, runny nose, and watery eyes.
4. Combination therapy:
    - Sometimes combined with decongestants in OTC cold remedies.

Chlorpheniramine Maleate

- Chlorpheniramine maleate is a first-generation H_1 histamine receptor antagonist.
- It is widely used to treat allergic conditions such as rhinitis, urticaria, conjunctivitis, and pruritus.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, leading to mild sedation.
- Chemically, it is a alkylamine derivative, structurally related to tripelennamine, with high H_1 receptor selectivity.
- The maleate salt form increases water solubility for oral or injectable formulations.

Chemical Structure

- IUPAC Name: 3-(4-chlorophenyl)-N,N-dimethyl-3-pyridin-2-ylpropan-1-amine maleate
- Molecular Formula: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ (maleate)
- Molecular Weight: 274.79 g/mol (salt)
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Chlorpheniramine competitively blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces edema, itching, redness, and allergic responses.
- CNS Effects:
  - Crosses the blood-brain barrier, causing mild sedation, useful in nighttime relief of allergy symptoms.
- Minimal Anticholinergic Effects:
  - Compared to ethanolamine derivatives, it has low anticholinergic activity, reducing dry mouth and drowsiness.

Synthesis of Chlorpheniramine Maleate

1. Formation of Alkylamine Intermediate:
    - 4-chlorophenylacetonitrile reacts with 2-chloropyridine under basic conditions to form the intermediate.
2. Reductive Amination:
    - The intermediate undergoes reduction with dimethylamine to yield Chlorpheniramine free base.
3. Formation of Maleate Salt:
    - The free base is reacted with maleic acid to form Chlorpheniramine maleate, a crystalline, water-soluble salt suitable for oral and injectable dosage forms.

Uses

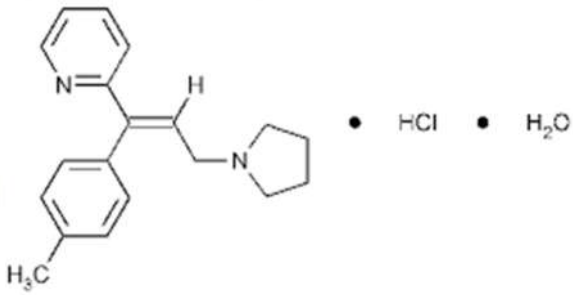
1. Allergic conditions:
    - Hay fever, rhinitis, conjunctivitis, urticaria, pruritus.
2. Cold and flu symptoms:
    - Relief of sneezing, runny nose, watery eyes.
3. Mild sedation:
    - Useful in nighttime allergy relief.
4. Combination therapy:
    - Often included with decongestants or cough suppressants in OTC cold remedies.

Triprolidine Hydrochloride

- Triprolidine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It is primarily used to relieve allergic symptoms such as hay fever (seasonal allergic rhinitis), urticaria, and conjunctivitis.
- Being a first-generation antihistamine, it can cross the blood-brain barrier, leading to sedative effects.
- Chemically, it is a pyridine derivative and structurally related to other classic H_1 blockers.

Chemical Structure

- IUPAC Name: (Z)-N,α-dimethyl-α-[4-(methylsulfanyl)phenyl]-2-pyridinepropan-2-amine hydrochloride
- Molecular Formula: $C_{16}H_{20}N_2 \cdot HCl$
- Molecular Weight: 264.81 g/mol
- Chemical Structure



Mechanism of Action

- Triprolidine is a competitive antagonist at H_1 histamine receptors.
- Action at H_1 receptors:
  1. Blocks histamine-induced smooth muscle contraction in bronchi, gut, and uterus.
  2. Inhibits vascular permeability and vasodilation, reducing edema, itching, and redness.
  3. Crosses the CNS, causing mild sedation.
- Compared to diphenhydramine, Triprolidine has relatively less sedative effect, but still exhibits anticholinergic properties.

Synthesis of Triprolidine Hydrochloride

1. Alkylation of Pyridine Derivative:
    - Start with α-bromopropylamine derivative of pyridine.
2. Formation of Substituted Phenyl Linkage:
    - React with 4-methylthiophenyl compound to attach the phenyl group at the α-position.
3. Methylation of Amino Group:
    - N-Methylation is performed to obtain the N,N-dimethylamine structure.
4. Formation of Hydrochloride Salt:
    - Treat the free base with HCl to form Triprolidine hydrochloride, a crystalline, water-soluble salt suitable for pharmaceutical use.

Uses

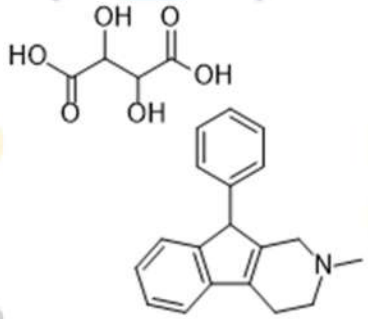
1. Allergic disorders:
    - Hay fever, seasonal rhinitis, conjunctivitis, urticaria, and other histamine-mediated allergic reactions.
2. Cold symptoms:
    - Sometimes included in multi-symptom cold preparations for relief of sneezing, runny nose, and itching.
3. Combination therapy:
    - Often combined with decongestants or cough suppressants in OTC formulations.
4. Sedative effect:
    - Provides mild CNS depressant effect, helpful in relieving allergy-induced insomnia.

Phenidamine Tartarate

- Phenidamine tartarate is a first-generation H_1 histamine receptor antagonist.
- It is primarily used for allergic conditions, such as rhinitis, urticaria, and pruritus, and sometimes in cold preparations.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing mild sedation.
- Chemically, it is a phenylpiperazine derivative, with high selectivity for H_1 receptors.
- The tartarate salt enhances solubility and stability for pharmaceutical use.

Chemical Structure

- IUPAC Name: 1-(2-phenylpropyl)-4-methylpiperazine tartrate
- Molecular Formula: $C_{15}H_{24}N_2 \cdot C_4H_6O_6$ (tartarate)
- Molecular Weight: 324.39 g/mol (salt)
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Phenidamine competitively blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces edema, itching, redness, and allergic symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, causing mild sedation, useful for nighttime allergy relief.
- Minimal Anticholinergic Effects:
  - Lower anticholinergic activity compared to ethanolamine derivatives, reducing dry mouth and drowsiness.

Synthesis of Phenidamine Tartarate

1. Formation of Phenylpiperazine Intermediate:
    - Methylpiperazine reacts with 2-phenylpropyl halide under basic conditions to form the substituted piperazine.
2. Formation of Tartarate Salt:
    - The free base is treated with tartaric acid to yield Phenidamine tartarate, a crystalline, water-soluble salt suitable for oral or injectable formulations.

Uses

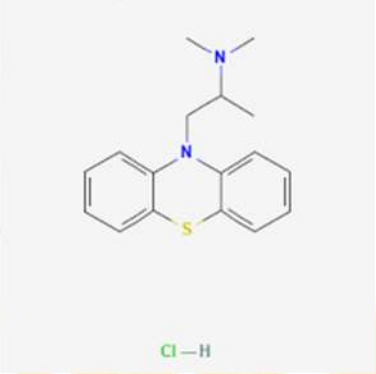
1. Allergic conditions:
    - Rhinitis, urticaria, pruritus, and other H_1-mediated reactions.
2. Cold and flu symptoms:
    - Relief of sneezing, runny nose, and watery eyes.
3. Mild sedation:
    - Useful for night-time allergy relief.
4. Combination therapy:
    - Sometimes included with decongestants or cough suppressants in OTC cold remedies.

Promethazine Hydrochloride

- Promethazine hydrochloride is a first-generation H_1 histamine receptor antagonist.
- It belongs to the phenothiazine class of compounds, structurally related to antipsychotic agents, but used primarily for antihistaminic, sedative, antiemetic, and anticholinergic effects.
- It is used for allergic conditions, motion sickness, nausea/vomiting, sedation, and pre-anesthetic medication.
- As a first-generation H_1 blocker, it crosses the blood-brain barrier, causing sedation.

Chemical Structure

- IUPAC Name: N,N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine hydrochloride
- Molecular Formula: $C_{17}H_{20}N_2S{\cdot}HCl$
- Molecular Weight: 284.87 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 re+ceptors in the respiratory tract, skin, and GI tract.
  - Reduces edema, itching, redness, and allergic symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, leading to sedation and antiemetic action.
  - Acts on the chemoreceptor trigger zone (CTZ) in the medulla to prevent nausea and vomiting.
- Anticholinergic Effects:
  - Mild inhibition of muscarinic receptors helps in motion sickness prevention.

Synthesis of Promethazine Hydrochloride

1. Preparation of 10-chlorophenothiazine:
    - Phenothiazine is chlorinated at position 10 to form the reactive intermediate.
2. Side-chain Alkylation:
    - React 10-chlorophenothiazine with 2-dimethylaminopropyl chloride via nucleophilic substitution, forming Promethazine free base.
3. Formation of Hydrochloride Salt:
    - The free base is treated with HCl to obtain Promethazine hydrochloride, a water-soluble, crystalline salt suitable for oral, parenteral, or rectal formulations.

Uses

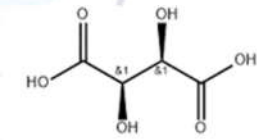
1. Allergic conditions:
    - Hay fever, urticaria, angioedema, and pruritus.
2. Motion sickness and nausea:
    - Prevents emesis from motion sickness, post-operative nausea, or drug-induced nausea.
3. Sedation:
    - Used as a short-term sedative or pre-anesthetic medication.
4. Cold and cough preparations:
    - Included in OTC formulations for antihistaminic and sedative effects.
5. Adjunct in Parkinsonism:
    - Reduces extrapyramidal side effects due to anticholinergic action.

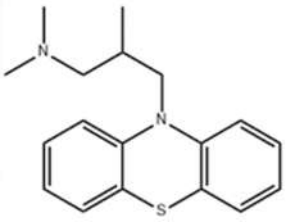
Trimeprazine Tartarate

- Trimeprazine tartarate is a first-generation H_1 histamine receptor antagonist.
- It is primarily used as an antiallergic, sedative, and antipruritic agent.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing sedation, which makes it useful in pruritic and allergic conditions requiring CNS calming effects.
- Chemically, it is a phenothiazine derivative, structurally related to promethazine, with potent H_1 receptor antagonism.
- The tartarate salt improves solubility and stability for pharmaceutical formulations.

Chemical Structure

- IUPAC Name: N,N-dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine tartarate
- Molecular Formula: $C_{18}H_{22}N_2S \cdot C_4H_6O_6$ (tartarate)
- Molecular Weight: 368.44 g/mol (salt)
- Chemical Structure





Mechanism of Action

- H_1 Receptor Antagonism:
  - Trimeprazine blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract.
  - Reduces pruritus, edema, erythema, and allergic reactions.
- CNS Effects:
  - Crosses the blood-brain barrier, producing sedation, which helps in sleep disturbances caused by itching or allergy.
- Anticholinergic Effects:
  - Mild inhibition of muscarinic receptors, reducing nasal and vestibular secretions.

Synthesis of Trimeprazine Tartarate

1. Formation of Phenothiazine Intermediate:
    - Phenothiazine is reacted with appropriate haloalkane to form the substituted aminopropyl derivative.
2. Introduction of Dimethylamino Group:
    - Alkylation of the side chain nitrogen with methyl groups forms the Trimeprazine base.
3. Formation of Tartarate Salt:
    - The free base is reacted with tartaric acid to yield Trimeprazine tartarate, a crystalline, water-soluble salt suitable for oral and injectable dosage forms.

Uses

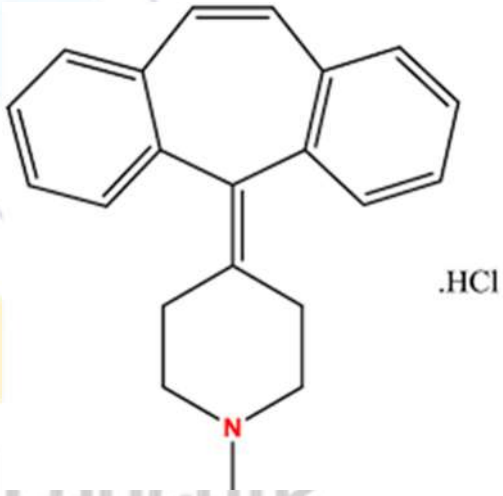
1. Allergic conditions:
    - Urticaria, pruritus, rhinitis, and other H_1-mediated reactions.
2. Sedative use:
    - Provides CNS calming effect in conditions aggravated by itching or anxiety.
3. Cold and flu symptoms:
    - Relieves sneezing, runny nose, and watery eyes.
4. Combination therapy:
    - Occasionally combined with decongestants or antitussives in OTC cold remedies.

Cyproheptadine Hydrochloride

- Cyproheptadine hydrochloride is a first-generation H_1 histamine receptor antagonist with additional antiserotonergic properties.
- It is used for allergic conditions, such as rhinitis, urticaria, and pruritus, and also as an appetite stimulant in certain clinical conditions.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing sedation.
- Chemically, it is a piperidine derivative with a tricyclic ring system similar to phenothiazines but lacking the sulfur atom.

Chemical Structure

- IUPAC Name: 4-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride
- Molecular Formula: $C_{21}H_{21}N \cdot HCl$
- Molecular Weight: 309.86 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Blocks histamine at H_1 receptors in the skin, respiratory tract, and GI tract, reducing edema, itching, and redness.
- Antiserotonergic Activity:
  - Inhibits serotonin (5-HT) receptors, which contributes to appetite stimulation and reduction of migraine and carcinoid symptoms.
- CNS Effects:
  - Crosses the blood-brain barrier, causing sedation.
- Anticholinergic Effects:
  - Mild anticholinergic activity can lead to dry mouth and mild drowsiness.

Synthesis of Cyproheptadine Hydrochloride

1. Formation of Tricyclic Ketone:
    - Dibenzo[a,d]cycloheptene is prepared via Friedel-Crafts cyclization of appropriate biphenyl derivatives.
2. Amination:
    - The ketone is reacted with methylpiperidine under basic conditions to form Cyproheptadine base via reductive amination.
3. Formation of Hydrochloride Salt:
    - The free base is treated with HCl to form Cyproheptadine hydrochloride, a crystalline, water-soluble salt suitable for oral formulations.

Uses

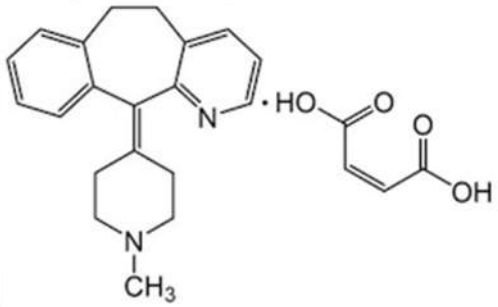
1. Allergic conditions:
    - Hay fever, rhinitis, urticaria, pruritus, and other H_1-mediated reactions.
2. Appetite stimulant:
    - Used in cachexia or weight loss conditions to increase appetite.
3. Migraine and serotonin-mediated conditions:
    - Reduction of carcinoid syndrome symptoms and migraine due to antiserotonergic activity.
4. CNS sedative effect:
    - Mild sedation helps in night-time allergy relief.

Azatadine Maleate

- Azatadine maleate is a first-generation H_1 histamine receptor antagonist.
- It is used for allergic conditions, including rhinitis, urticaria, and conjunctivitis.
- Being a first-generation antihistamine, it crosses the blood-brain barrier, producing mild sedation.
- Chemically, it is a tricyclic azepine derivative, structurally related to phenothiazine and trimeprazine, with high H_1 receptor selectivity.
- The maleate salt enhances water solubility and stability for pharmaceutical formulations.

Chemical Structure

- IUPAC Name: 4-(4-chlorophenyl)-1-methyl-2-piperazin-1-yl-3H-benzo[b][1,4]oxazin-3-one maleate
- Molecular Formula: $C_{21}H_{23}ClN_2O \cdot C_4H_4O_4$ (maleate)
- Molecular Weight: 420.90 g/mol (salt)
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Azatadine competitively blocks histamine at H_1 receptors in the skin, respiratory tract, and conjunctiva.
  - Reduces pruritus, edema, redness, and allergic reactions.
- CNS Effects:
  - Crosses the blood-brain barrier, causing mild sedation, helpful in nighttime allergy relief.
- Minimal Anticholinergic Effects:
  - Low anticholinergic activity reduces dry mouth and drowsiness.

Synthesis of Azatadine Maleate

1. Formation of Tricyclic Azepine Intermediate:
    - Condensation of 4-chlorobenzaldehyde with an appropriate piperazine-substituted ketone forms the tricyclic core.
2. Methylation:
    - The secondary amine is methylated to give the Azatadine free base.
3. Formation of Maleate Salt:
    - The free base is treated with maleic acid to yield Azatadine maleate, a crystalline, water-soluble salt suitable for oral formulations.

Uses

1. Allergic conditions:
    - Rhinitis, urticaria, conjunctivitis, and other H_1-mediated reactions.
2. Cold symptoms:
    - Relief of sneezing, runny nose, and watery eyes.
3. Sedative effect:
    - Mild sedation is beneficial for nighttime allergy relief.
4. Combination therapy:
    - Occasionally included in multi-symptom OTC cold remedies.

Second Generation H_1 Antagonists

Second generation H_1 antagonists are the newer class of antihistamines developed to reduce allergic symptoms while minimizing sedation. Unlike first generation H_1 blockers, these drugs have limited ability to cross the blood-brain barrier, which results in minimal central nervous system (CNS) side effects like drowsiness.

They are primarily used for allergic conditions such as rhinitis, urticaria, and conjunctivitis, providing effective relief from symptoms like sneezing, itching, and runny nose without significant sedation.

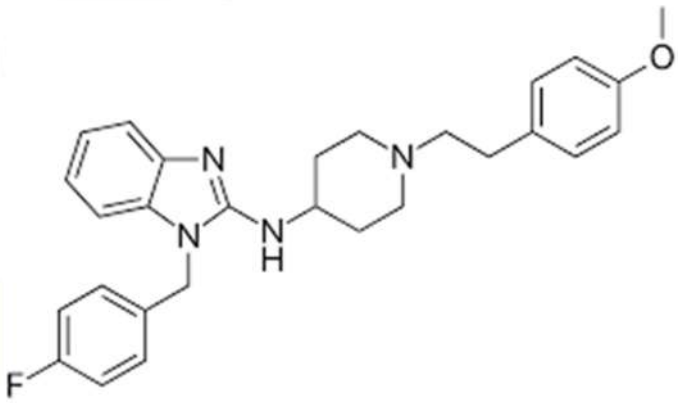
- Examples :
  - Astemizole
  - Loratadine
  - Cetirizine
  - Levocetirizine
  - Cromolyn Sodium

Astemizole

- Astemizole is a second-generation H_1 histamine receptor antagonist.
- Unlike first-generation H_1 blockers, it is non-sedating because it does not significantly cross the blood-brain barrier.
- It was primarily used to treat allergic conditions such as rhinitis, urticaria, and pruritus.
- Astemizole has a longer duration of action (12–24 hours) compared to first-generation antihistamines.
- Chemically, it is a piperidyl-benzimidazole derivative.

Chemical Structure

- IUPAC Name: 1-(4-(1H-benzimidazol-2-yl)phenyl)-4-(4-chlorobenzyl)piperazine
- Molecular Formula: $C_{28}H_{31}ClN_4$
- Molecular Weight: 461.03 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Astemizole selectively blocks histamine at peripheral H_1 receptors, preventing allergic symptoms such as itching, sneezing, and nasal congestion.
- CNS Effects:
  - Very low CNS penetration, so sedation is minimal compared to first-generation H_1 blockers.
- Cardiac Considerations:
  - Astemizole can prolong QT interval and may cause arrhythmias (torsades de pointes) in overdose or drug interactions, which led to its withdrawal in many countries.

Synthesis of Astemizole

1. Formation of Piperazine Intermediate:
    - N-substituted piperazine is prepared by reacting piperazine with 4-chlorobenzyl chloride.
2. Coupling with Benzimidazole:
    - The substituted piperazine is then coupled with 4-(2-bromophenyl)benzimidazole to form Astemizole base.
3. Final Purification:
    - The base is purified for pharmaceutical use; it is usually formulated as tablets or capsules.

Uses

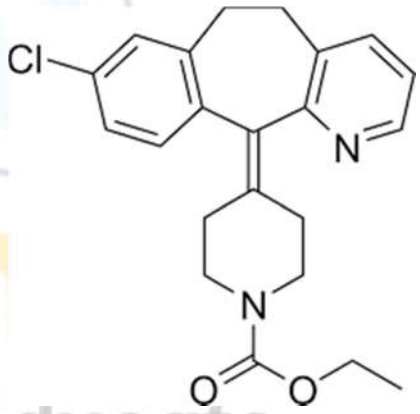
1. Allergic conditions:
    - Rhinitis, urticaria, pruritus, and other H_1-mediated reactions.
2. Long-acting antihistamine:
    - Provides 12–24 hours symptom relief with once-daily dosing.
3. Non-sedating therapy:
    - Useful for patients needing allergy relief without drowsiness.

Loratadine

- Loratadine is a second-generation H_1 histamine receptor antagonist.
- It is non-sedating because it does not significantly cross the blood-brain barrier.
- Primarily used for allergic conditions such as rhinitis, urticaria, and pruritus.
- Loratadine has a long duration of action (up to 24 hours), allowing once-daily dosing.
- Chemically, it is a tricyclic piperidine derivative with high H_1 receptor selectivity and minimal anticholinergic activity.

Chemical Structure

- IUPAC Name: ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate
- Molecular Formula: $C_{22}H_{23}ClN_2O_2$
- Molecular Weight: 382.88 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Loratadine selectively blocks peripheral H_1 receptors, preventing allergic symptoms such as itching, sneezing, and nasal congestion.
- CNS Effects:
  - Minimal blood-brain barrier penetration, so sedation is negligible.
- Metabolite Activity:
  - Active metabolite desloratadine contributes to prolonged antihistaminic action.
- Anticholinergic Effects:
  - Negligible, so fewer side effects like dry mouth or blurred vision.

Synthesis of Loratadine

1. Formation of Tricyclic Core:
    - Synthesize the cycloheptapyridine ring system via cyclization of appropriate biphenyl derivatives.
2. Attachment of Piperidine Ester:
    - Introduce ethyl piperidine-1-carboxylate at the tricyclic core through nucleophilic substitution.
3. Chlorination:
    - Chlorine atom is introduced on the aromatic ring to yield Loratadine base.
4. Purification:
    - The base is purified for oral formulations; it is formulated as tablets, syrup, or capsules.

Uses

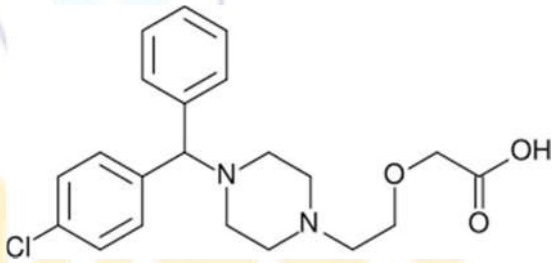
1. Allergic conditions:
    - Allergic rhinitis, chronic urticaria, pruritus, and other H_1-mediated reactions.
2. Long-acting antihistamine:
    - Provides 24-hour symptom relief with once-daily dosing.
3. Non-sedating therapy:
    - Suitable for patients needing allergy relief without drowsiness, e.g., drivers, students, and professionals.
4. Active metabolite:
    - Desloratadine enhances efficacy and prolongs duration of action.

Cetirizine

- Cetirizine is a second-generation H_1 histamine receptor antagonist.
- It is non-sedating because it minimally crosses the blood-brain barrier, unlike first-generation antihistamines.
- Used for allergic conditions, such as allergic rhinitis, chronic urticaria, and pruritus.
- It is the carboxylic acid metabolite of hydroxyzine, providing high selectivity for H_1 receptors.
- Cetirizine has a long duration of action (~24 hours), allowing once-daily dosing.

Chemical Structure

- IUPAC Name: (±)-[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]acetic acid
- Molecular Formula: $C_{21}H_{25}ClN_2O_3$
- Molecular Weight: 388.90 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Cetirizine selectively blocks histamine at peripheral H_1 receptors, preventing itching, sneezing, rhinorrhea, and other allergic symptoms.
- CNS Effects:
  - Minimal blood-brain barrier penetration → very low sedation.
- Anti-inflammatory Effects:
  - Inhibits release of pro-inflammatory mediators such as leukotrienes and cytokines in allergic reactions.
- Anticholinergic Effects:
  - Negligible, so dry mouth and other anticholinergic side effects are minimal.

Synthesis of Cetirizine

1. Hydroxyzine Intermediate:
    - Cetirizine is synthesized from hydroxyzine, which is first prepared via reaction of piperazine derivatives with appropriate chlorophenylmethyl compounds.
2. Conversion to Carboxylic Acid:
    - Hydroxyzine is oxidized to produce Cetirizine, introducing the carboxylic acid group, which improves H_1 selectivity and reduces CNS penetration.
3. Purification:
    - The final product is purified and formulated as cetirizine hydrochloride or as the free acid in tablets, syrup, or oral solutions.

Uses

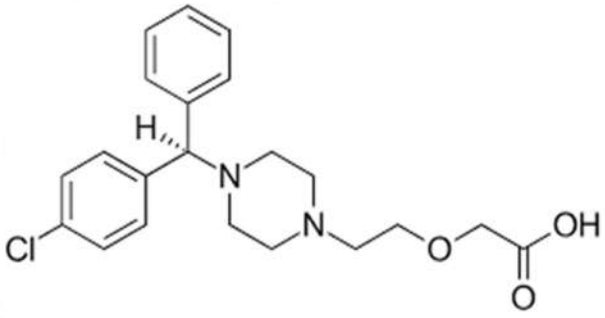
1. Allergic conditions:
    - Allergic rhinitis, chronic urticaria, pruritus, and other H_1-mediated reactions.
2. Non-sedating antihistamine:
    - Suitable for patients who require daytime relief without drowsiness.
3. Once-daily dosing:
    - Long-acting, providing 24-hour symptom control.
4. Adjunct therapy:
    - Sometimes used with nasal corticosteroids in severe allergic rhinitis.

Levocetirizine

- Levocetirizine is a second-generation H_1 histamine receptor antagonist.
- It is the active (R)-enantiomer of Cetirizine, providing more potent and selective H_1 blockade.
- It is non-sedating due to minimal blood-brain barrier penetration.
- Used for allergic conditions, including allergic rhinitis, chronic urticaria, and pruritus.
- Levocetirizine has a rapid onset of action and a duration of effect of ~24 hours, allowing once-daily dosing.

Chemical Structure

- IUPAC Name: (R)-[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]acetic acid
- Molecular Formula: $C_{21}H_{25}ClN_2O_3$
- Molecular Weight: 388.90 g/mol
- Chemical Structure



Mechanism of Action

- H_1 Receptor Antagonism:
  - Levocetirizine selectively blocks peripheral H_1 receptors, preventing allergic symptoms such as itching, sneezing, rhinorrhea, and nasal congestion.
- CNS Effects:
  - Minimal blood-brain barrier penetration → very low sedation.
- Anti-inflammatory Effects:
  - Inhibits release of pro-inflammatory mediators (leukotrienes, cytokines) in allergic responses.
- Anticholinergic Effects:
  - Negligible, minimizing dry mouth or blurred vision.

Synthesis of Levocetirizine

1. Preparation of Cetirizine:
    - Racemic cetirizine is synthesized from hydroxyzine via oxidation to introduce the carboxylic acid group.
2. Resolution of Enantiomers:
    - The (R)-enantiomer (Levocetirizine) is separated using chiral resolution methods, producing the pure active enantiomer.
3. Purification:
    - Levocetirizine is purified and formulated as levocetirizine dihydrochloride for oral administration.

Uses

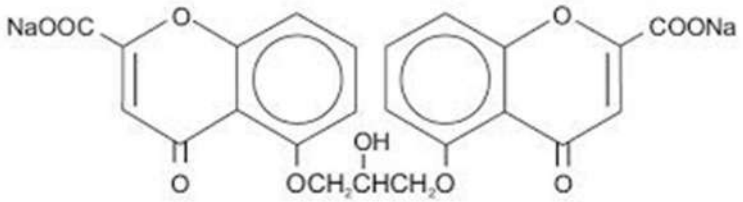
1. Allergic conditions:
    - Allergic rhinitis, chronic urticaria, pruritus, and other H_1-mediated reactions.
2. Non-sedating therapy:
    - Suitable for daytime relief without drowsiness.
3. Once-daily dosing:
    - Provides 24-hour symptom control.
4. Pediatric and adult use:
    - Safe for both adults and children in approved dosages.

Cromolyn Sodium

- Cromolyn sodium is a mast cell stabilizer and non-antihistamine anti-allergic drug.
- Unlike H_1 antihistamines, it does not block histamine receptors directly, but prevents the release of histamine and other mediators from mast cells.
- It is used for allergic conditions, including asthma, allergic rhinitis, conjunctivitis, and food allergies.
- Administered via inhalation, nasal spray, or eye drops.
- It is non-sedating and has minimal systemic absorption.

Chemical Structure

- IUPAC Name: Disodium 5-(1-hydroxy-1-methylethyl)-1,3-benzenedicarboxylate
- Molecular Formula: $C_{15}H_{10}Na_2O_8$
- Molecular Weight: 512.21 g/mol
- Chemical Structure



Mechanism of Action

- Mast Cell Stabilization:
  - Prevents degranulation of mast cells, inhibiting release of histamine, leukotrienes, and prostaglandins.
  - Reduces bronchoconstriction, mucus secretion, and inflammation in allergic responses.
- No H_1 receptor antagonism:
  - Does not block histamine receptors directly; thus, it is preventive rather than therapeutic for acute allergic symptoms.
- Anti-inflammatory Effects:
  - Reduces inflammatory cell infiltration and airway hyperreactivity in asthma.

Synthesis of Cromolyn Sodium

1. Preparation of Benzopyrone Derivative:
    - 1,3-benzenedicarboxylic acid is reacted with 1-hydroxy-1-methylethyl groups to form the chromone derivative.
2. Formation of Sodium Salt:
    - The free acid is neutralized with sodium hydroxide to produce cromolyn sodium, a water-soluble salt suitable for inhalation, nasal, or ophthalmic use.

Uses

1. Asthma prophylaxis:
    - Prevents exercise-induced and allergen-induced bronchospasm.
2. Allergic rhinitis:
    - Nasal spray reduces sneezing, itching, and runny nose.
3. Allergic conjunctivitis:
    - Eye drops preven+t ocular itching and redness.
4. Food allergies:
    - Reduces mediator release in mild food allergy reactions.
5. Non-sedating preventive therapy:
    - Safe for long-term prophylaxis, including in children.