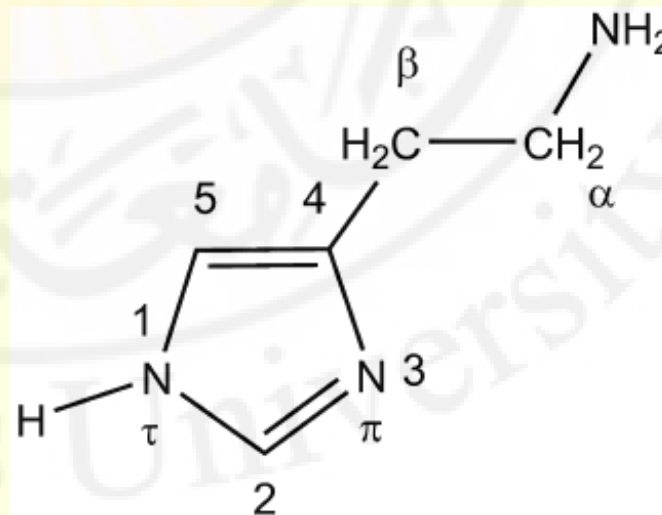


The background features a large, faint watermark of the Damascus University logo. The logo is circular, containing a central emblem with a sunburst and Arabic calligraphy. The words "Damascus University" are written in English at the bottom of the circle, and Arabic text is at the top.

Antihistamine

Histamine

- Histamine, known as 4(5-)(2-aminoethyl)imidazole
- structurally is composed of an imidazole heterocycle and ethylamine side chain.
- The methylene groups of the aminoethyl side chain are designated α and β
- The side chain is attached, via the $-\text{CH}_2$ group, to the 4-position of an imidazole ring.



Histamine

- ❖ Histamine exerts its diverse biologic effects through four types of receptors H_1 , H_2 , H_3 , and H_4
- The involvement of histamine in the mediation of :
 - A. immune and hypersensitivity reactions
 - B. the regulation of gastric acid secretion
- has led to the development of important drug classes such as :
 - I. Drugs used in the treatment of **Symptoms Associated With Allergic**
 - II. Drugs used in the treatment of **Gastric Hypersecretory Disorders.**

Storage and Release of Histamine

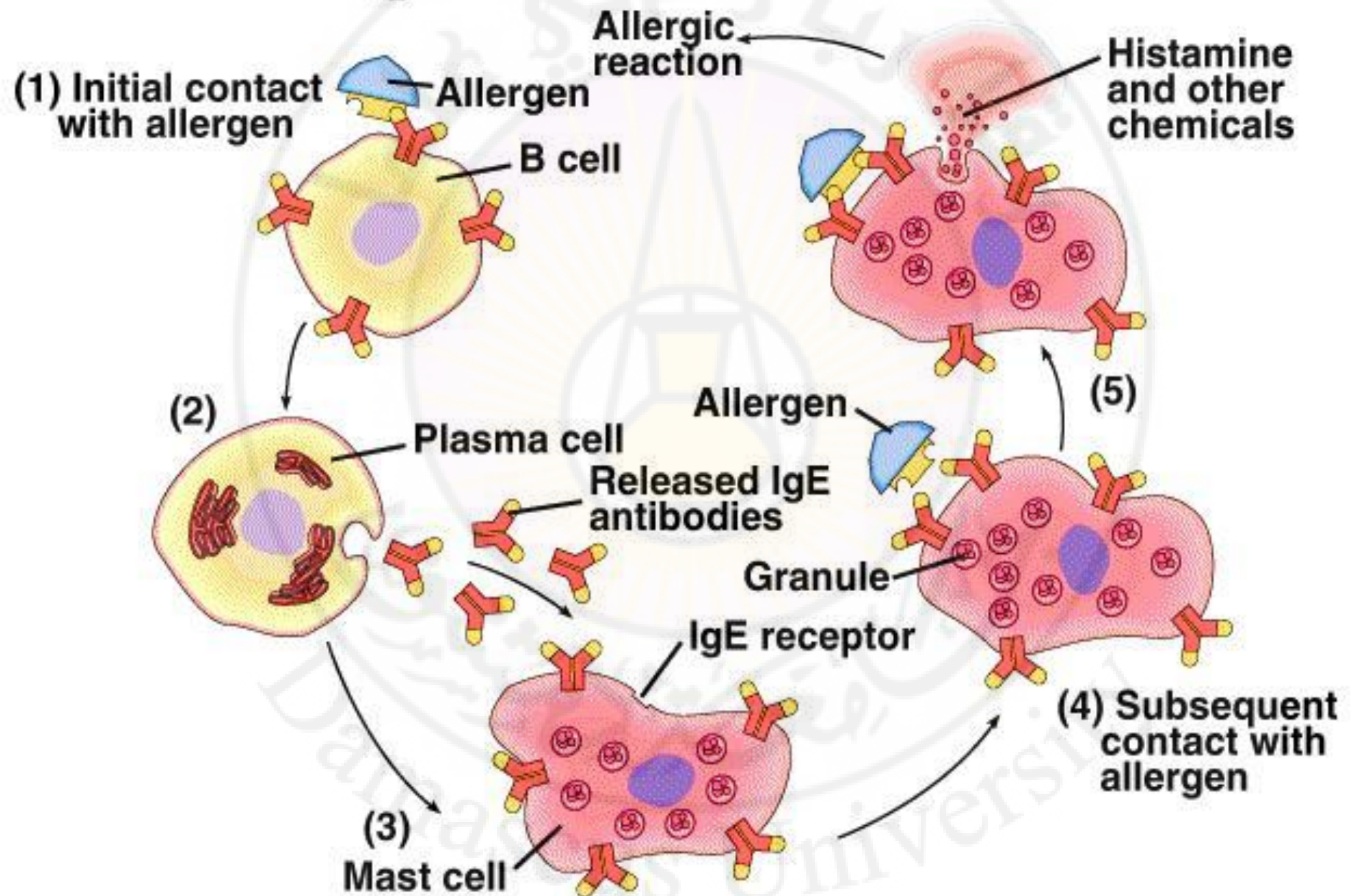
- Most histamine is biosynthesized and stored as protein complexes in mast cells and basophilic granulocytes
- Protein complexed histamine is released by exocytosis in response to :

I. Immune Stimuli (antigen and antibody)

The release of histamine as one of the mediators of hypersensitivity reactions is initiated by the interaction of an antigen-IgE complex with the membrane of a histamine storage cell.

II. Nonimmune Stimuli (bacterial products, physical effects, and cholinergic effects).

An Allergic Reaction — Overview



Histamine H₁-Receptors

➤ H₁-receptors mediate a host of physiologic processes including:

- 1) Pruritus
- 2) Pain
- 3) Vasodilation
- 4) Vascular Permeability
- 5) Hypotension
- 6) Flushing
- 7) Headache
- 8) Tachycardia
- 9) Bronchoconstriction
- 10) stimulation of airway vagal afferent nerves and cough receptors
- 11) decreased atrioventricular-node conduction time.

Histamine H1-Receptors

- the CNS H1-receptor activation influences
 1. Cycles of Sleeping and Waking
 2. Food Intake
 3. Thermal Regulation
 4. Emotions and Aggressive Behavior
 5. Locomotion
 6. Memory, and Learning

Histamine H₂-Receptors

- H₂-receptors are expressed in various tissues where they mediate
 1. Gastric Acid Secretion
 2. Vascular Permeability
 3. Hypotension
 4. Flushing
 5. Headache
 6. Tachycardia
 7. Bronchodilatation and Respiratory Mucus Production.

The actions of Histamine

- Histamine exhibits a wide variety of both physiological and pathological functions in different tissues and cells.
- The actions of histamine that are of interest from both a pharmacological and therapeutic point of view include
 1. its role as a **chemical mediator of Hypersensitivity and Allergic Inflammatory Reactions**
 2. a major role in the **Regulation Of Gastric Acid Secretion**
 3. an emerging role as a **Neurotransmitter in the CNS.**

Antihistamine

- The term *Antihistamine* historically has referred to drugs that block the actions of Histamine at H₁-receptors rather than other histamine receptor subtypes.
- These *Antihistamines*, referred to now as the *First-generation* or *Classical Antihistamines*, are related structurally and include:
 - 1) *Aminoalkyl Ethers* (referred to also as *Ethanol Amine*)
 - 2) *Ethylenediamines*
 - 3) *Propylamines* (referred to also as *Alkyl Amine*)
 - 4) *Piperazines*
 - 5) *Phenothiazines*
 - 6) *Dibenzocycloheptenes*

Structures

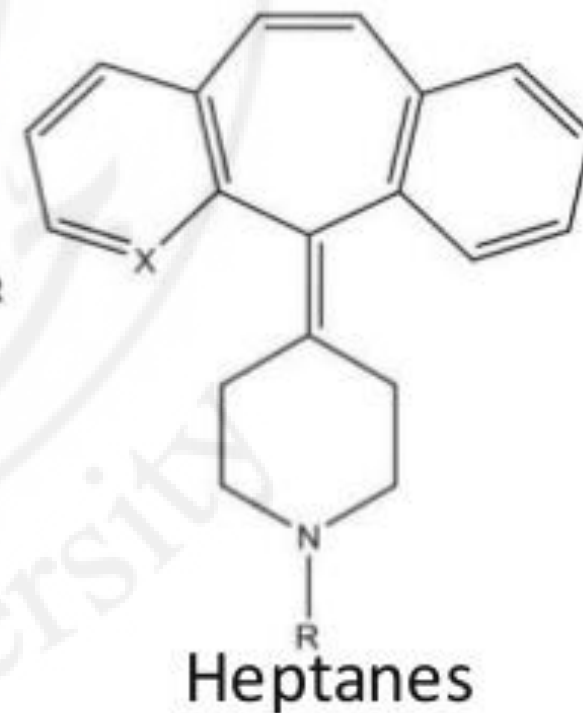
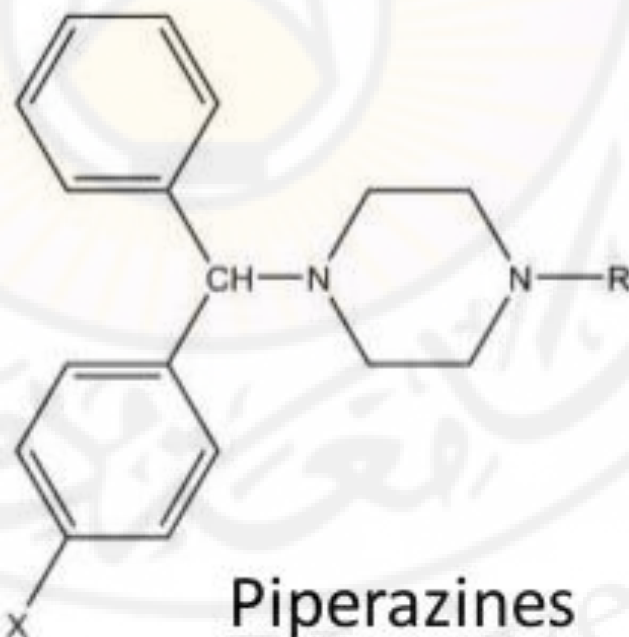
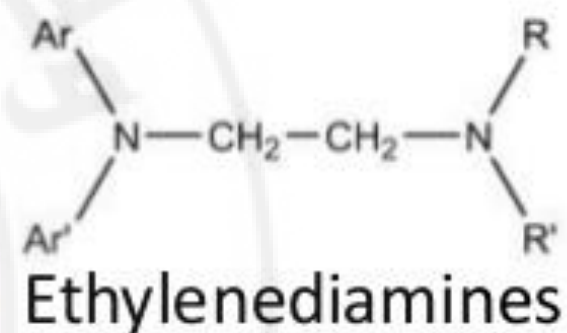
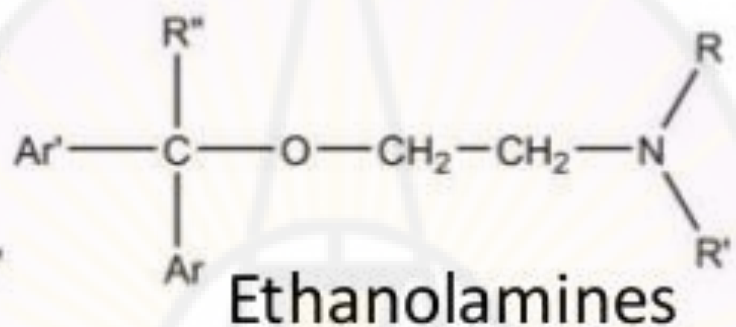
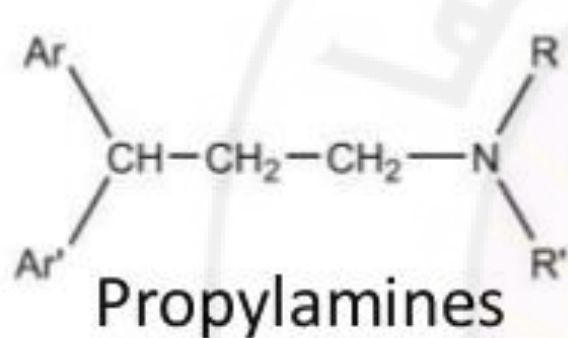


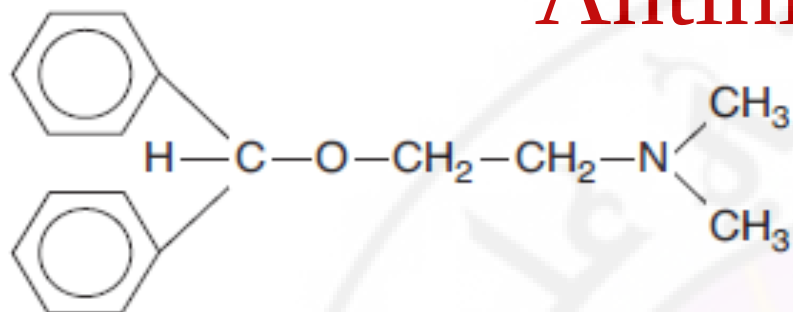
CHART 3: Chemical classification of H1 antihistamines

Alkylamines	Ethanolamines	Ethylenediamines	Phenothiazines	Piperazines	Piperidines
Bromopheniramine ¹	Carbinoxamine ¹	Antazoline ¹	Promethazine ¹	Bucizine ¹	Azatadine ¹
Chlorpheniramine ¹	Clemastine ¹	Pyrilamine ¹	Mequitazine ¹	Cyclizine ¹	Cyproheptadine ¹
Dexchlorpheniramine ¹	Dimenhydrinate ¹	Tripelenamine ¹	Trimepazine ¹	Meclizine ¹	Ketotifen ¹
Pheniramine ¹	Diphenhydramine ¹			Oxatomide ¹	Loratadine ²
Dimethindene ¹	Doxylamine ¹			Hydroxyzine ¹	Desloratadine ²
Triprolidine ¹	Phenyltoxamine ¹			Cetirizine ²	Bilastine ²
Acrivastine ¹				Levocetirizine ²	Ebastine ²
					Terfenadine ²
					Fexofenadine ²
					Levocabastine ²
					Mizolastine ²
					Rupatadine ²

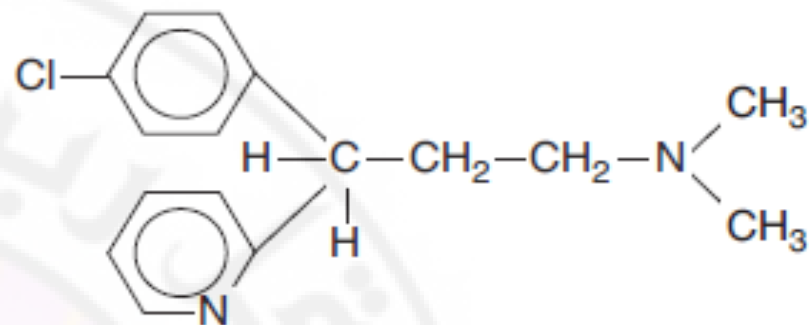
¹ classical or first-generation H1 antihistamines; ² second-generation H1 antihistamines

Adapted source: de Benedictis FM, et al.²⁶

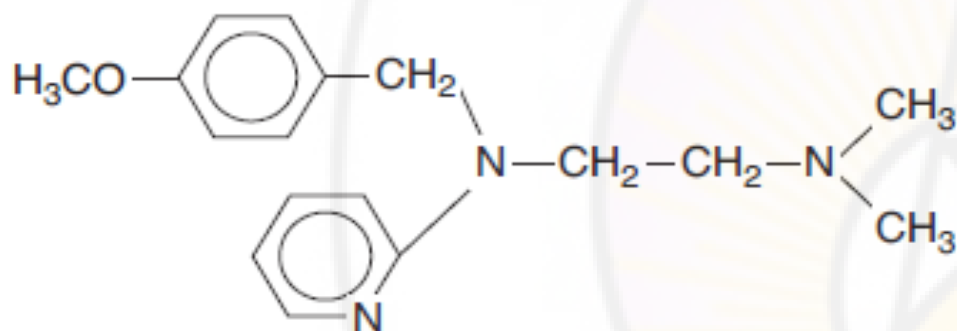
Antihistamine



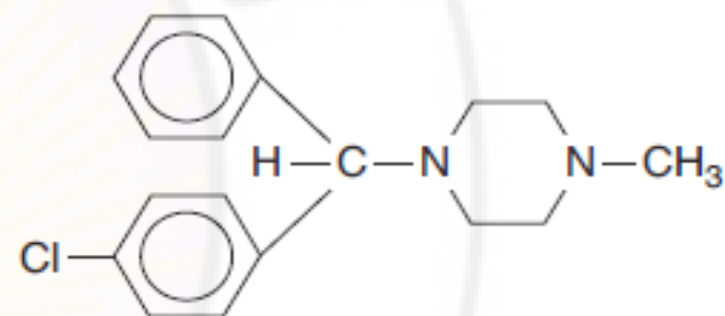
DIPHENHYDRAMINE (an ethanolamine)



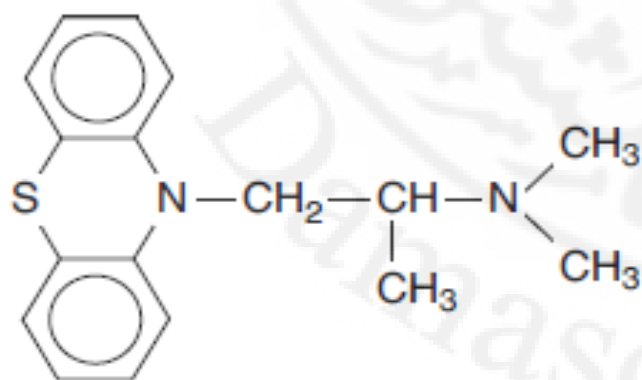
CHLORPHENIRAMINE (an alkylamine)



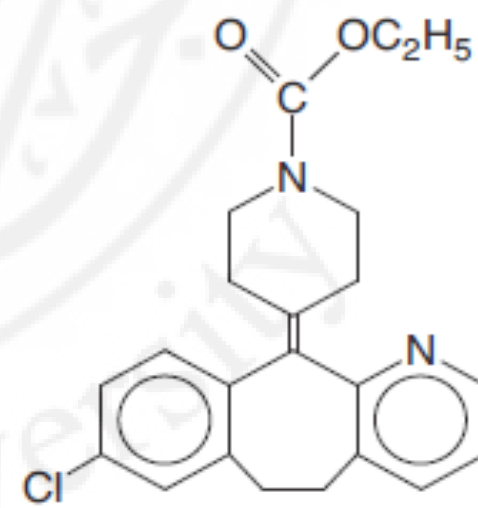
PYRILAMINE (an ethylenediamine)



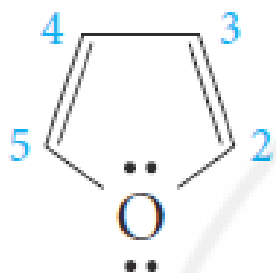
CHLORCYCLIZINE (a piperazine)



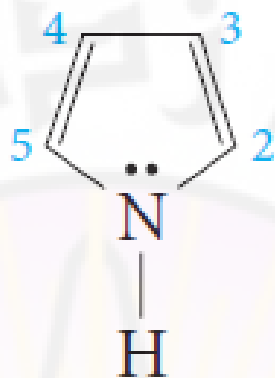
PROMETHAZINE (a phenothiazine)



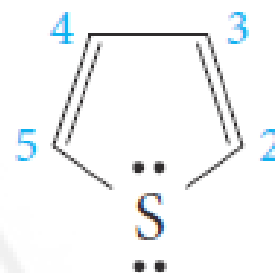
LORATADINE (a tricyclic piperidine)



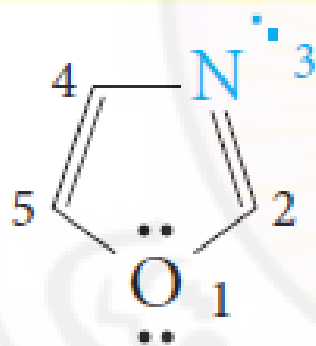
furan



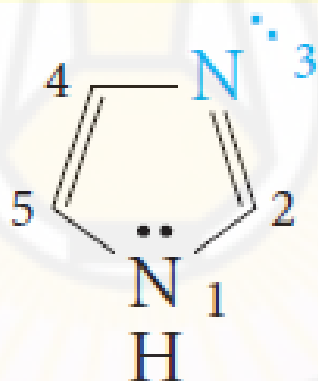
pyrrole



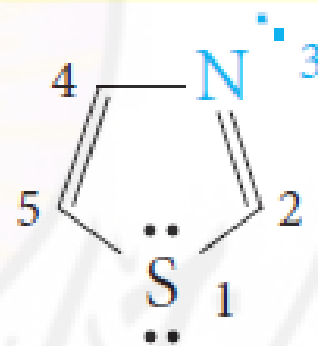
thiophene



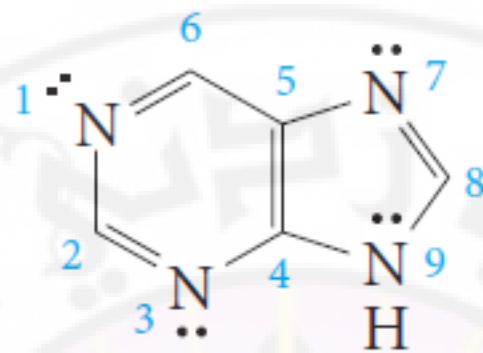
oxazole



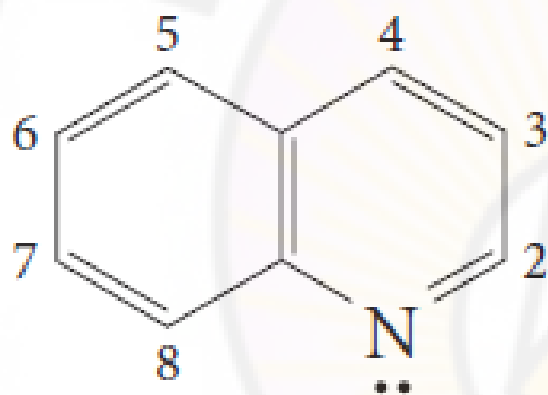
imidazole



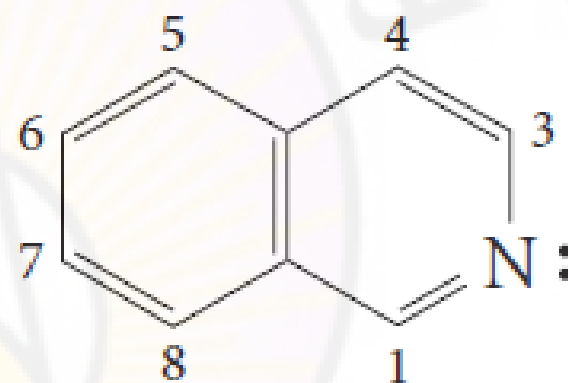
thiazole



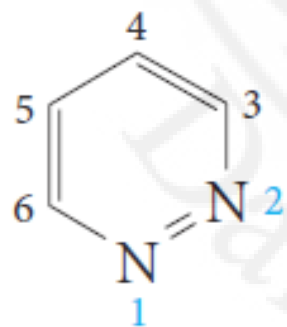
purine



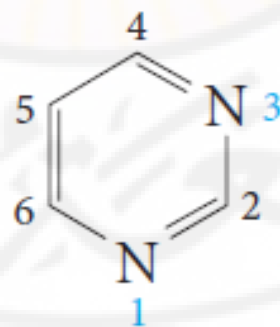
quinoline



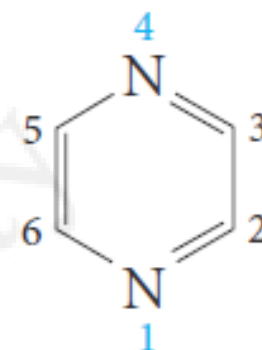
isoquinoline



pyridazine



pyrimidine



pyrazine

Antihistamine

- ❖ **First-Generation or Classical Antihistamines** display an array of other pharmacological activities that contribute either toward additional therapeutic applications, or limit use as adverse reactions
- ❖ **Second-Generation Agents** are **derivatives of several first-generation agents**, but have been modified to be more specific in pharmacologic action and limited in their tissue distribution or accumulation profiles.

Clinical Uses of Antihistamines

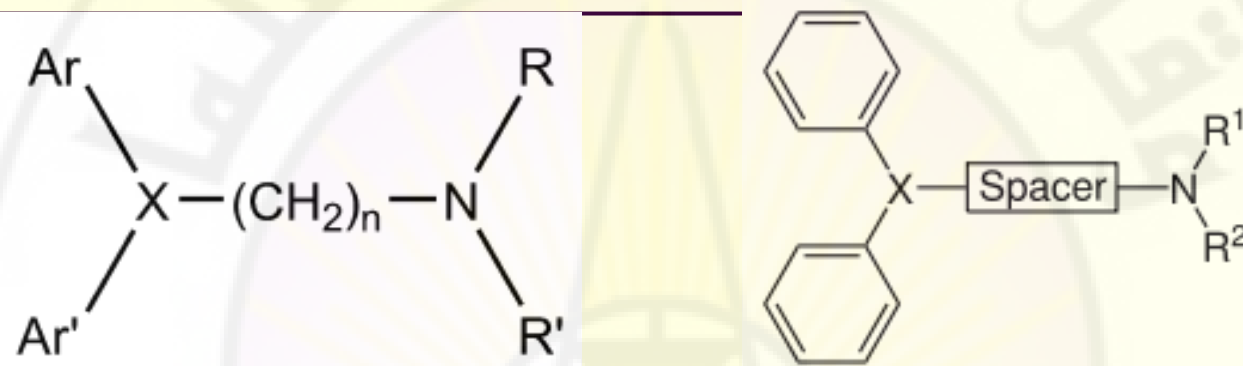


1. Allergic Rhinitis (common cold)
2. Allergic Conjunctivitis (pink eye)
3. Allergic dermatological conditions
4. Urticaria الشرى (hives)
5. Angioedema (swelling of the skin)
6. Pruritus (insect bites)
7. Anaphylactic reactions (severe allergies)
8. Nausea and vomiting (first generation H₁ antihistamines)
9. Sedation (first generation H₁-antihistamines)

Mechanism of Action of H₁-Antihistamines

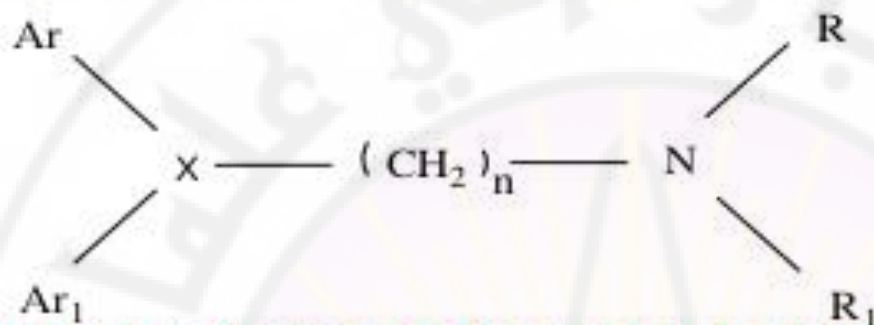
1. H1-antihistamines antagonists combine with the H1-receptor
2. Some H1-antihistamines can also block histamine release
3. The H1-antihistamines do not block antibody production or antigen–antibody interactions

Structure–Activity Relationships for H1-antihistamines



- the structural requirements for H1-antihistaminic action were identified as shown in Figure :
- I. Ar is aryl (including phenyl, substituted phenyl, and heteroaryl groups such as 2-pyridyl)
 - II. Ar' is a second aryl or arylmethyl group
 - III. X is a connecting atom of O, C, or N
 - IV. (CH₂)_n represents a carbon chain, usually ethyl
 - V. NRR' represents a basic, terminal amine function.

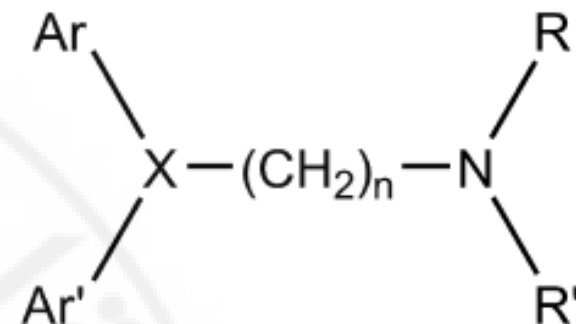
GENERAL STRUCTURE OF ANTIHISTAMINES



STRUCTURAL REQUIREMENTS:

- **Ar is aryl:** Phenyl, substituted phenyl, hetero aryl groups like 2-pyridyl.
- **Ar₁:** Second aryl (or) aryl methyl group.
- **X:** Connecting atom of O, C, (or) N.
- **(CH₂)_n:** Carbon chain usually ethyl.
- **NRR₁:** Basic, terminal amine functional group.

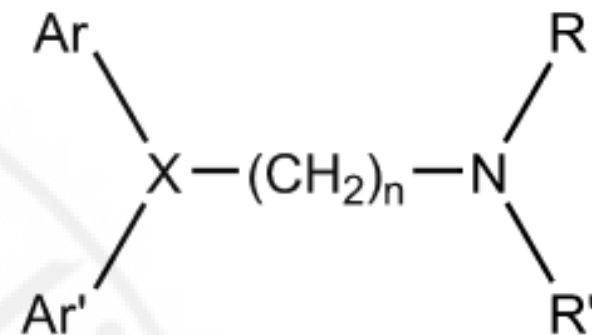
Structure–Activity Relationships for H1-antihistamines



The two aromatic rings:

1. is present in both the first- and second-generation antihistamines
2. is essentially a significant H1-receptor affinity
3. must be able to adopt a noncoplanar conformation relative to each other for optimal interaction with the H1-receptor.
4. may be linked as in the tricyclic antihistamines phenothiazines, dibenzocycloheptanes, dibenzocycloheptenes.
5. may by contain substituents in one of the aryl rings (usually benzene), and these influence histamine potency as well as biodisposition

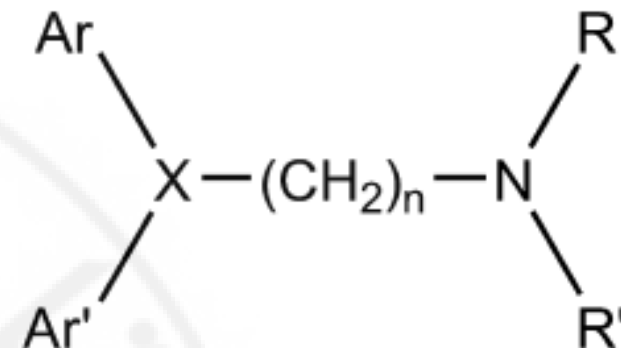
Structure–Activity Relationships for H₁-antihistamines



The terminal nitrogen atom

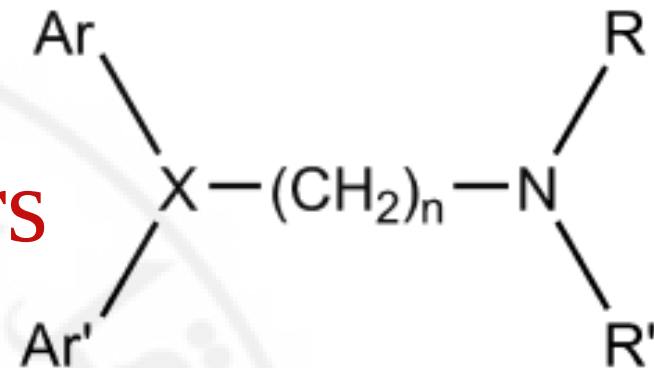
6. is a simple dimethyl moiety in many of the first-generation antihistamines
 7. may be part of a heterocyclic structure (piperazines)
 8. is basic ($pK_a = 8.5 - 10$) in all cases, and thus is presumed to be protonated when bound on the receptor.
- ✓ The terminal nitrogen atom is also important in the development of stable, solid dosage forms through salt formation.

Structure–Activity Relationships for H₁-antihistamines



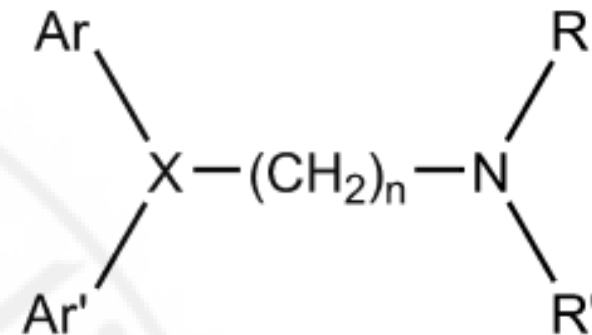
9. The carbon chain of typical H₁-antihistamines consists of two or three atoms.
 10. The X connecting moiety of typical H₁-antihistamines may be a saturated carbon–oxygen, or simply a carbon atom or nitrogen atom.
- ✓ Many antihistamines containing a carbon atom in the connecting moiety are chiral and exhibit stereoselective receptor binding. in vitro analyses indicate that enantiomers with the S configuration have higher H₁-receptor affinity

Structure–Activity Relationships at H₁-Receptors



- Generally, the **First-** and **Second-Generation Antihistamines** are substantially more lipophilic than the histamine (or the H₂-antagonists).
- This lipophilicity difference results primarily from the presence of the two aryl rings and the substituted amino moieties

Structure–Activity Relationships for H₁-antihistamines



- ✓ The nature of the connecting moiety and the structural nature of the aryl moieties have been used to classify the Antihistamines
- ✓ The variations in the diaryl groups, X-connecting moieties, and the nature of substitution in the alkyl side chain or terminal nitrogen among the various drugs account for differences observed in :
 - i. Antihistaminic Potency.
 - ii. Pharmacological, Biodisposition.
 - iii. Adverse Reaction Profiles.

General Pharmacological and Therapeutic Considerations

- The classical antihistamines have been used extensively for:
 1. the Symptomatic Treatment (sneezing, rhinorrhea, and itching of eyes, nose, throat) Allergic Rhinitis (Hay fever, Pollinosis).
 2. Chronic Idiopathic Urticaria.
 3. relieve the symptoms of Asthma.
 4. relieve the symptoms of Upper Respiratory Infections including (The Common Cold الرشح, Otitis Media التهاب الأذن الوسطى, Sinusitis التهاب الجيوب).

General Pharmacological and Therapeutic Considerations

- These uses are clearly attributed to their ability to counter the action of histamine at peripheral H1-receptors, which mediate the **Immune** and **Inflammatory Processes** characteristic of these pathologies.
- Most clinical evidence does not support such use unless Asthma or infection is accompanied by allergic inflammation.
- the **Antihistamines** should not be used alone in **Anaphylaxis**, but may be used with **Epinephrine** to relieve any H1-receptor–mediated symptoms.

General Pharmacological and Therapeutic Considerations

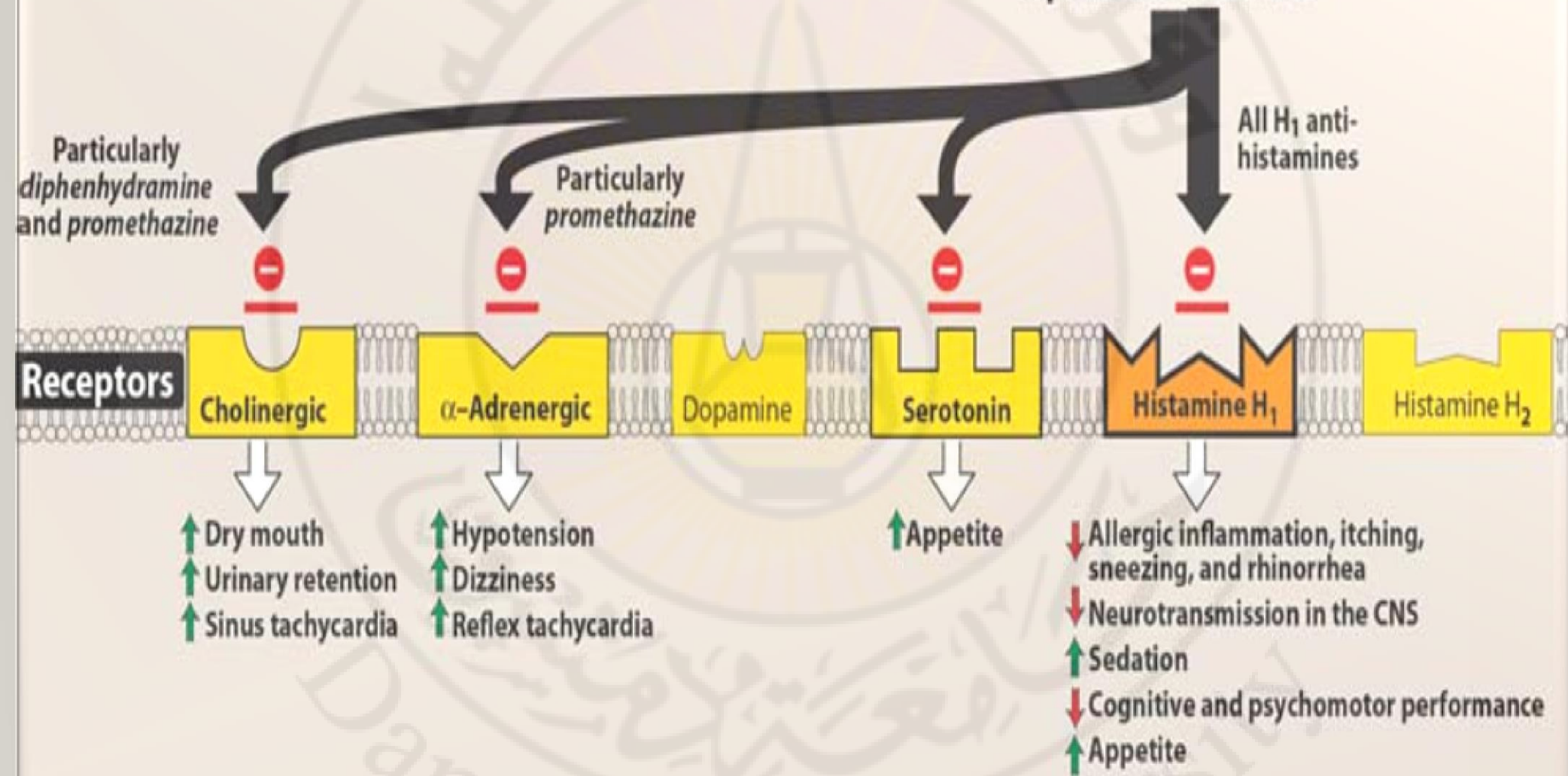
- Several first-generation antihistamines (Phenothiazines , Piperazines, Aminoalkyl Ethers) have antiemetic actions and thus may be useful in the treatment of
 1. Nausea and Vomiting
 2. Vertigo
 3. Motion Sickness
 4. Hyperemesis Gravidarum (nausea of pregnancy)
- Antihistamines including Promethazine, Pyrilamine, Tripeleennamine, and Diphenhydramine display local anesthetic activity that may be therapeutically useful.

General Pharmacological and Therapeutic Considerations

- The ability of H1-antihistamines to display an array of pharmacological activities is largely because they can interact with :
 1. H1-receptors throughout the body
 2. Muscarinic receptors
 3. Adrenergic receptors
 4. Serotonergic receptors

- H1-antihistamines contain the basic pharmacophore required for binding to muscarinic as well as adrenergic and serotonergic receptors

H₁ Antihistamines



General Pharmacological and Therapeutic Considerations

- Most clinical evidence suggests that there is no significant difference in therapeutic efficacy for first- and second-generation agents in the treatment of these conditions.
- The first-generation agents also tend to achieve and maintain higher levels in the brain than the second-generation agents, resulting in CNS-based pharmacologic actions:
 1. Sedation
 2. Fatigue
 3. Dizziness

General Pharmacological and Therapeutic Considerations

- Many of the first-generation antihistamines readily penetrate the **Blood-Brain Barrier** (BBB) because of their lipophilicity, and maintain significant CNS concentrations
 - Blockade of central H1-receptors results in sedation, an effect that has contributed to the historical use of antihistamines as **nonprescription sleep aids**, as well as drugs for **perioperative sedation**.
 - the blockade of central H1-receptors also results in
 1. **Decreased Cognitive**
 2. **Decreased Psychomotor Performance**
 3. **Increased Appetite and Weight Gain**
- all considered to be therapy-limiting adverse effects

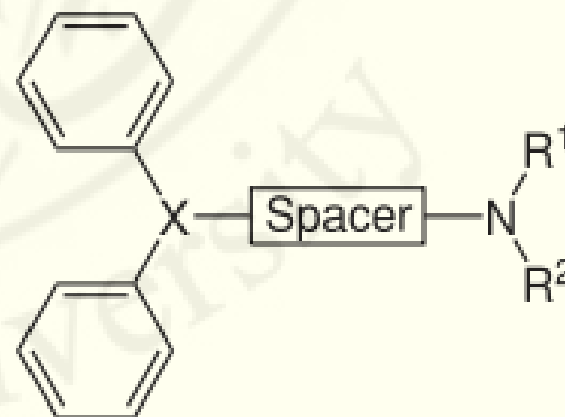
General Pharmacological and Therapeutic Considerations

- The H1-antihistamines display various significant drug interactions when coadministered with other therapeutic agents :
 1. **MAO inhibitors** prolong and intensify the **Anticholinergic** actions of the **Antihistamines**.
 2. the sedative effects of H1-antihistamines may potentiate the depressant activity of
 - I. **Barbiturates**
 - II. **Alcohol**
 - III. **Narcotic Analgesics**
 - IV. **Other Depressants**

First-Generation Antihistamine Classes

Aminoalkyl Ethers (Ethanolamines)

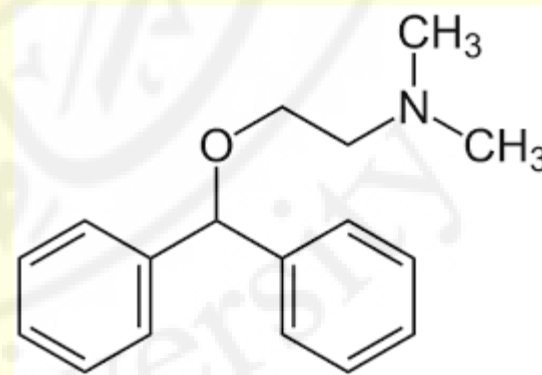
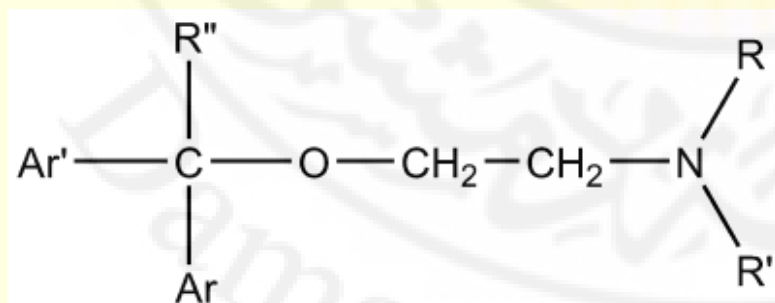
- Aminoalkyl Ethers Antihistamines are characterized by the presence of
 1. CHO connecting moiety (X)
 2. Two or Three carbon atom chain as the linking moiety (between the diaryl and tertiary amino groups)
 3. Tertiary amino groups
 4. Most compounds in this series are simple *N, N*-dimethylethanolamine derivatives



First-Generation Antihistamine Classes

Aminoalkyl Ethers (Ethanolamines)

- The basic nitrogen in all of these compounds is not only essential for binding affinity, but also serves as a moiety for the formation of stable, solid salts.
- The simple diphenyl derivative **Diphenhydramine** was the first clinically useful member of the ethanolamine series and serves as the prototype.



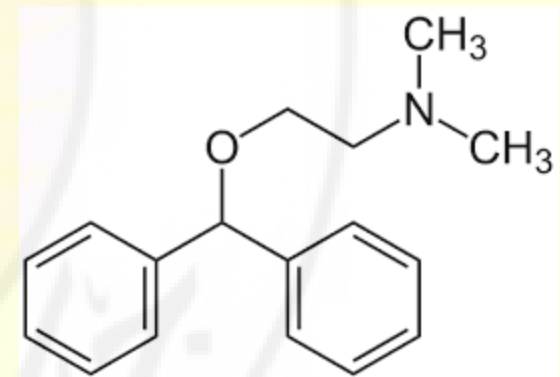
Diphenhydramine

First-Generation Antihistamine Classes

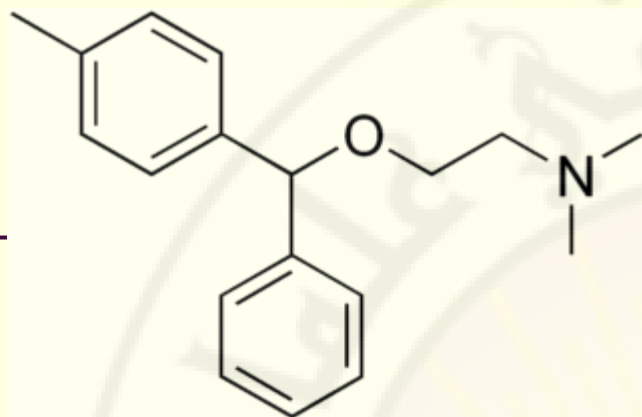
Aminoalkyl Ethers (Ethanolamines)

- Other therapeutically useful derivatives of **Diphenhydramine** have been obtained by **para substitution** on one of the phenyl rings:

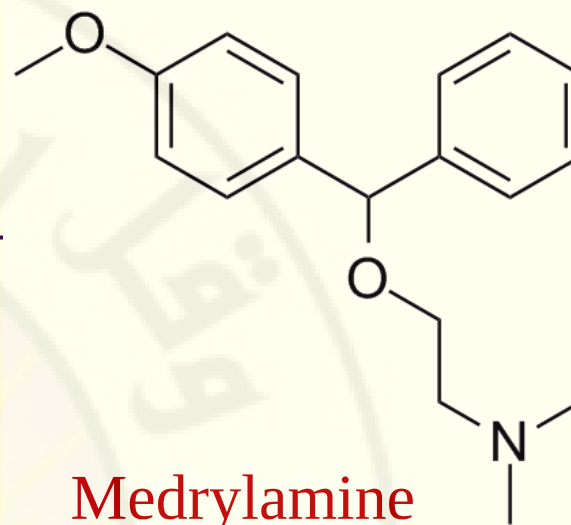
- ✓ **Methyl** (**Methyldiphenhydramine**)
- ✓ **Methoxy** (**Medrylamine**)
- ✓ **Chloro** (**Chlorodiphenhydramine**)
- ✓ **Bromo** (**Bromodiphenhydramine**)



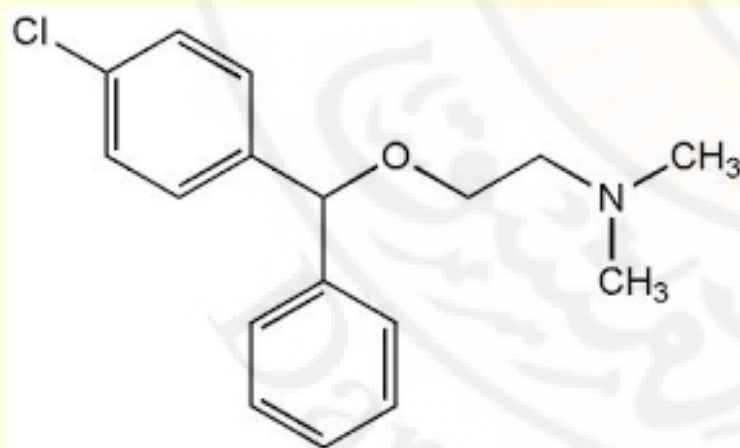
- These derivatives have better therapeutic profiles than **Diphenhydramine** because of reduced adverse effects.



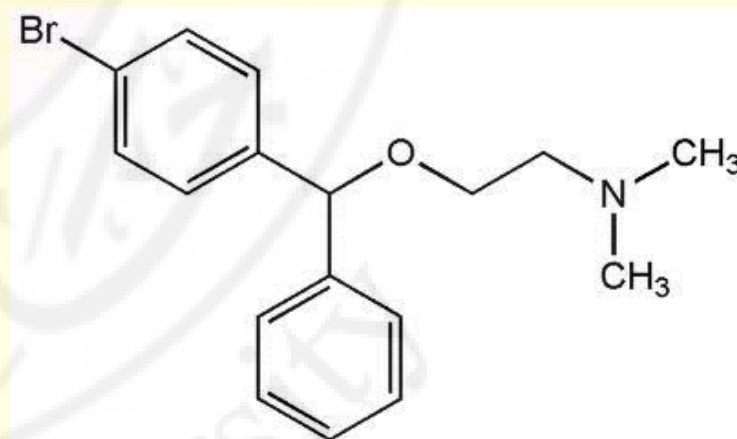
Methyldiphenhydramine



Medrylamine



Chlorodiphenhydramine



Bromodiphenhydramine

First-Generation Antihistamine Classes

Aminoalkyl Ethers (Ethanolamines)

- Replacement of one of the phenyl rings of the diphenhydramine with a 2-pyridyl group, as in Doxylamine and Carbinoxamine, enhances antihistaminic activity
- As a result of an asymmetrically substituted benzylic carbon, most of the aminoalkyl ethers are optically active.
- the individual enantiomers differ significantly in antihistaminic activity, with activity residing predominantly in the S-enantiomers.

First-Generation Antihistamine Classes

Aminoalkyl Ethers (Ethanolamines)

Aminoalkyl Ethers possess significant **Anticholinergic Activity** which contributes to :

➤ Their Therapeutic Use as

1. Antiemetic
2. Motion Sickness
3. Anti-parkinson Drugs

➤ Their Adverse Effects

- 1) Dry Mouth
- 2) Blurred Vision
- 3) Urinary Retention
- 4) Constipation
- 5) Tachycardia

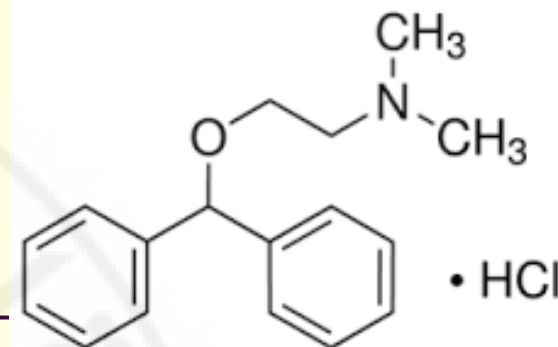
First-Generation Antihistamine Classes

Aminoalkyl Ethers (Ethanolamines)

- **Drowsiness**, as well as other CNS effects, is a common side effect to the tertiary aminoalkyl ethers, presumably as a result of the ability of these compounds to penetrate the BBB and occupy central H₁-receptors.
- Although this central action is exploited in over the counter (OTC) **Sleeping Aids**, it may interfere with the performance of tasks requiring mental alertness.

Aminoalkyl Ethers (Ethanolamines)

Diphenhydramine (Benadryl)



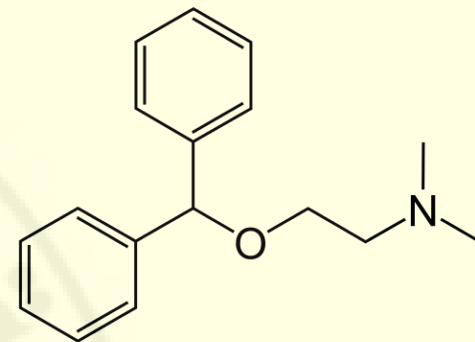
2-(diphenylmethoxy)- *N,N*-dimethyl ethanamine

It is a bitter-tasting hydrochloride salt

- In addition to Antihistaminic action, Diphenhydramine possesses:
 1. Anticholinergic
 2. Antitussive
 3. Antiemetic
 4. Sedative Properties
- Conversion to a quaternary ammonium salt does not alter the antihistaminic action greatly but does increase the anticholinergic action

Aminoalkyl Ethers (Ethanolamines)

Diphenhydramine (Benadryl)



1) As an antihistaminic agent

It is recommended in various **Allergic Conditions** and, to a lesser as an **Antitussive** and **Parkinsonism drug**.

2) It is also used in **OTC sleep-aid products**.

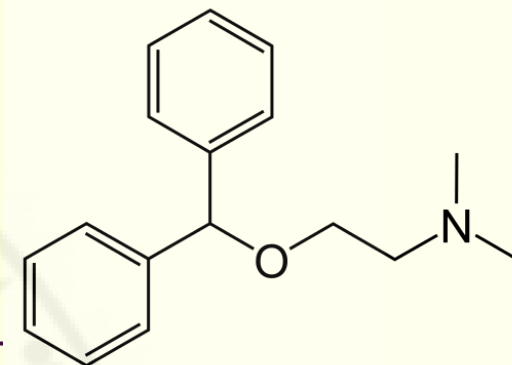
3) It is administered in the treatment of **Urticaria**, **Seasonal Rhinitis** (hay fever), and some **Dermatoses**.

■ The most common side effect is drowsiness, and the concurrent use of alcohol and other CNS depressants should be avoided.

Aminoalkyl Ethers (Ethanolamines)

Diphenhydramine Hydrochloride

(Benadryl)



- Diphenhydramine used to treat a number of conditions including
 1. Allergic Symptoms
 2. Itchiness
 3. The Common Cold
 4. Insomnia
 5. Motion Sickness
 6. Drug-Induced Parkinsonism
 7. Diphenhydramine also has **Local Anesthetic** properties, and has been used as such in people allergic to common local anesthetics such as lidocaine.

Aminoalkyl Ethers (Ethanolamines)

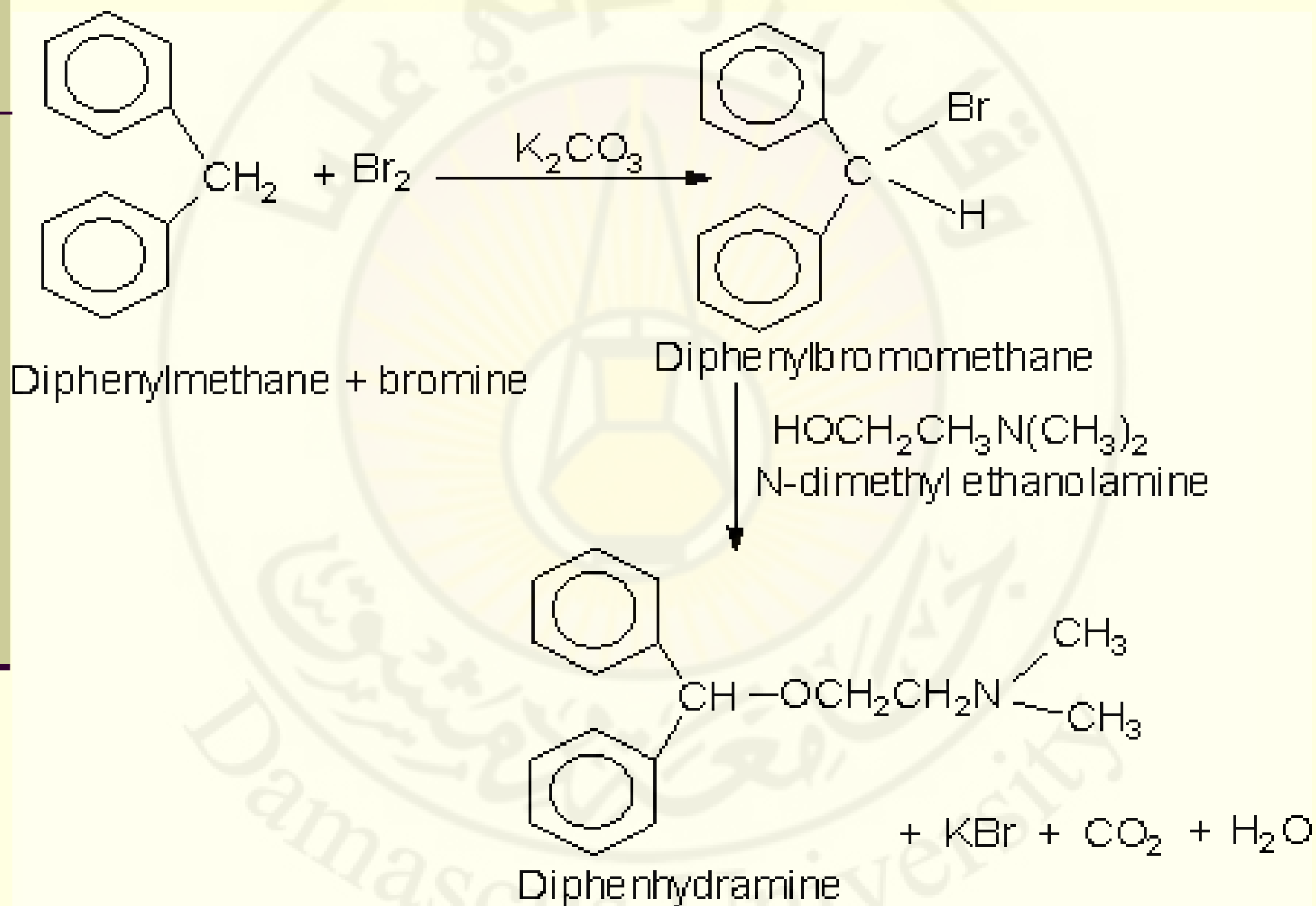
Diphenhydramine Hydrochloride (Benadryl)

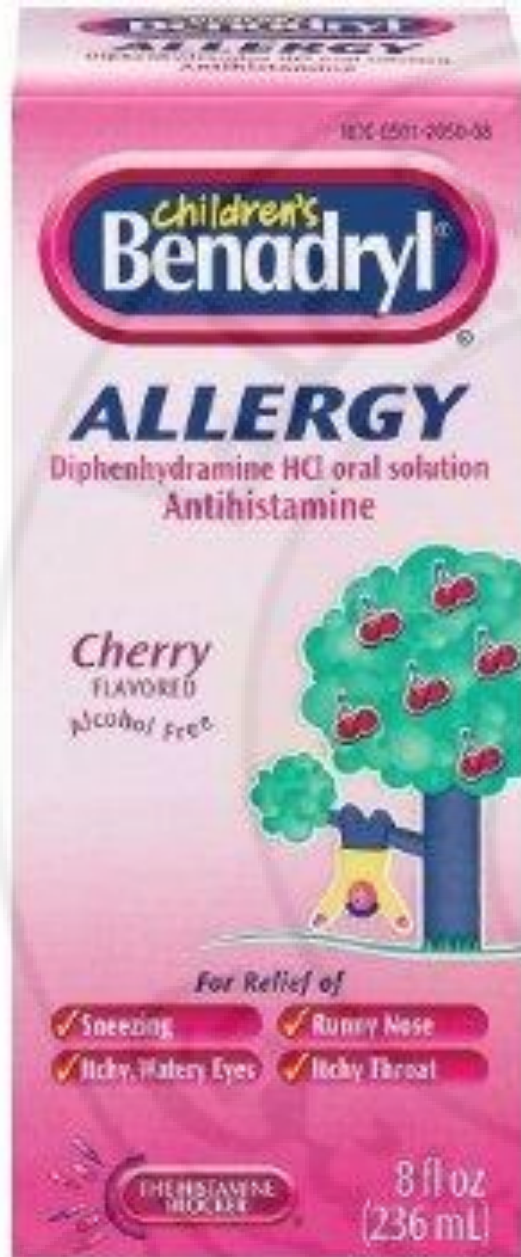
➤ Dosage forms:

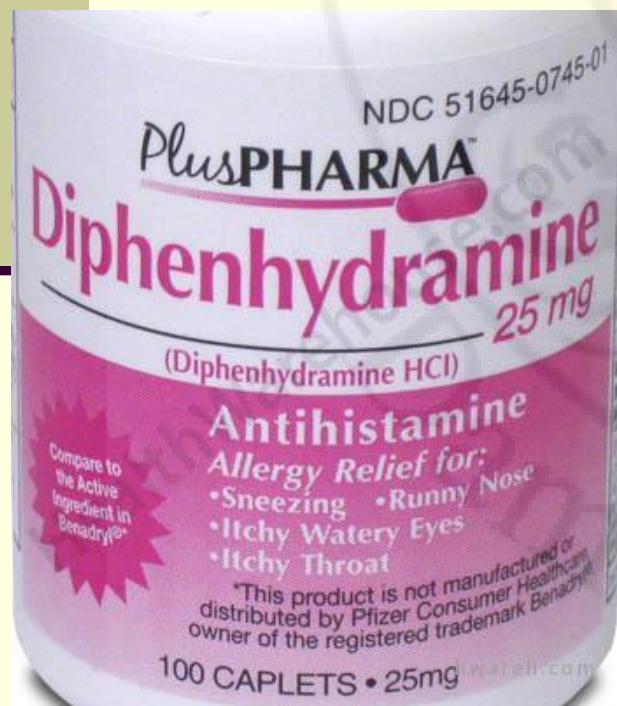
- 1) Tablets (12.5, 25, and 50 mg);
- 2) Capsules (25 and 50 mg);
- 3) oral disintegrating strips (12.5 and 25 mg);
- 4) solutions, elixirs, and syrups (12.5 mg/5 mL);
- 5) suspension (25 mg/5 mL);
- 6) and injection (50 mg/mL).

➤ Usual adult doses:

- I. **Antihistamine:** 25 to 50 mg every 4 to 6 hours (maximum of 300 mg/day)
- II. **Antitussive liquid:** 25 to 50 mg every 4 hours (liquid) or 25 mg every 4 hours (syrup); do not exceed 300 mg/day
- III. **Motion sickness:** 25 to 50 mg every 4 to 6 hours (maximum of 300 mg/day)



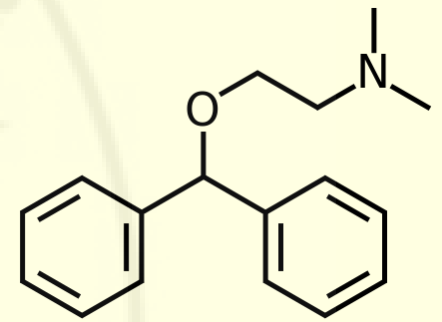




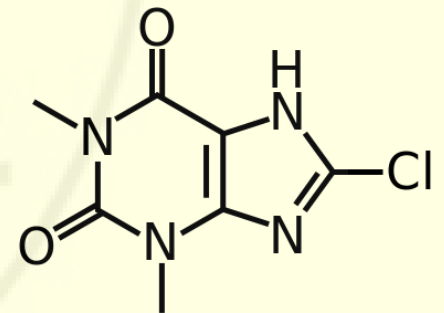
Aminoalkyl Ethers (Ethanolamines)

Dimenhydrinate (Dramamine)

- **Dimenhydrinate** is The 8-chlorotheophyllinate (theoclate) salt of diphenhydramine
- 8-chlorotheophylline 2-(diphenylmethoxy)-*N,N*-dimethylethylamine
- is a white crystalline, odorless powder
- 8-Chlorotheophylline, a chlorinated derivative of **theophylline**, was added in order to counteract Drowsiness.
- Theophylline is very closely related to caffeine and theobromine, mild central nervous system stimulants.



diphenhydramine

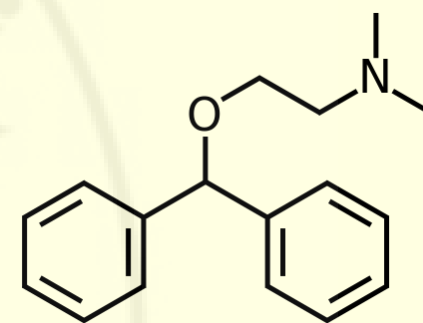


8-chlorotheophyllinate

Aminoalkyl Ethers (Ethanolamines)

Dimenhydrinate (Dramamine)

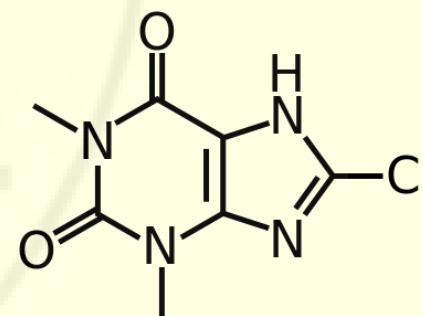
➤ It was thought that by combining the **Antiemetic Effects** of **Diphenhydramine** with a **Stimulant**, the extreme drowsiness induced by the former could be mitigated somewhat by the latter.



diphenhydramine

➤ **Dimenhydrinate** is recommended for

- 1) **Nausea of Motion Sickness** (the dose should be taken at least 0.5 hour before beginning a trip)
- 2) **Hyperemesis Gravidarum** (nausea of pregnancy).



8-chlorotheophyllinate

Aminoalkyl Ethers (Ethanolamines)

Dimenhydrinate (Dramamine)

➤ Dosage forms:

- 1) Tablets (50 mg),
- 2) liquid (12.5 mg/5 mL, 15.62 mg/5 mL),
- 3) injection (50 mg/mL)

➤ Usual dosage (motion sickness):

- Adult/children 12 years of age: 1 to 2 chewable tablets or tablets (50–100 mg) every 4 to 6 hours
- Children 6 to younger than 12 years of age: 1/2 to 1 chewable tablet or tablet (25–50 mg) every 6 to 8 hours.
- Children 2 to younger than 6 years of age: 1/4 to 1/2 chewable tablet or tablet (12.5–25 mg) every 6 to 8 hours



Features:

- ☒ Chewable
- ☒ Great Taste
- ☒ Easy to Take
- ☒ Portable
- ☒ Take with or without Water



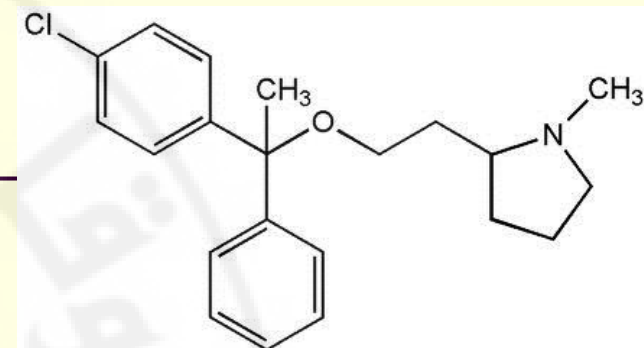


Features:

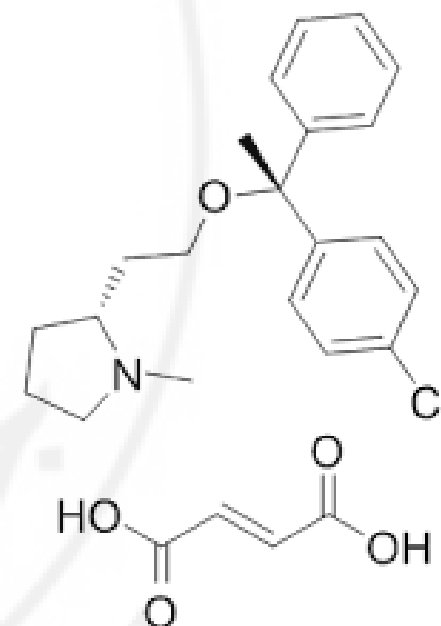
- ☒ Comfort Shaped
- ☒ Portable
- ☒ Ideal When Vomiting Due to Motion Sickness is Present

Aminoalkyl Ethers (Ethanolamines)

Clemastine Fumarate (Tavist)

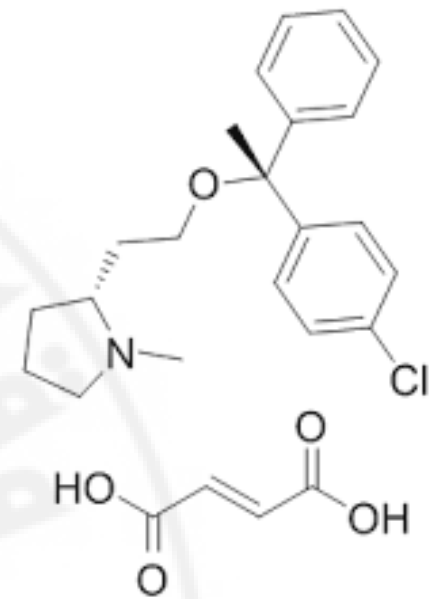


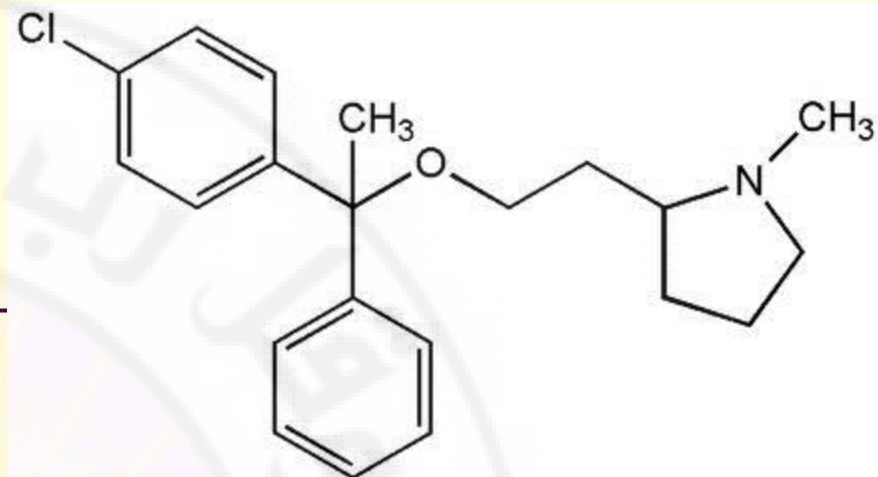
- Dextrorotatory **Clemastine**: R,R-2[2[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine hydrogen fumarate
- It has two chiral centers, each of which has the (*R*) absolute configuration.
- **Clemastine** is characterized by a long duration of action, with an activity that reaches a maximum in 5 to 7 hours and persists for 10 to 12 hours.
- The side effects are those usually encountered with this series of antihistamines.



Clemastine Fumarate (Tavist)

- **Clemastine** is closely related to chlorphenoxamine, which is used for its central cholinergic-blocking activity.
- **Clemastine** has significant antimuscarinic activity
- Dosage forms:
 - 1) Tablets (1.34 and 2.68 mg)
 - 2) Syrup (0.67 mg/5 mL)
- Usual adult dose:
 - 1) **Allergic Rhinitis**: 1.34 mg twice daily for adults; 0.67 mg twice daily for children 6 to 12 years of age
 - 2) **Urticaria/Angioedema**: 2.68 mg twice daily





Original Prescription Strength
TAVIST-1[®]
Antihistamine (Clemastine Fumarate)

**12 Hour Relief of
Allergy & Hay Fever Symptoms**

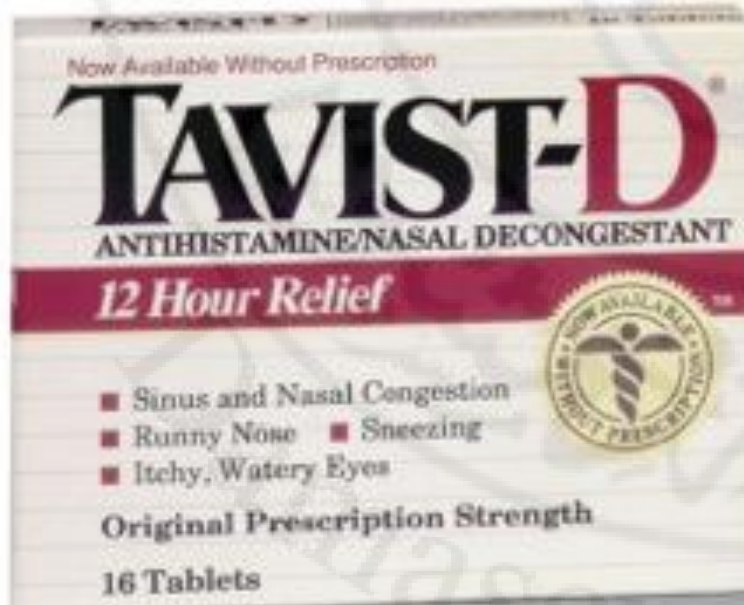


16 TABLETS



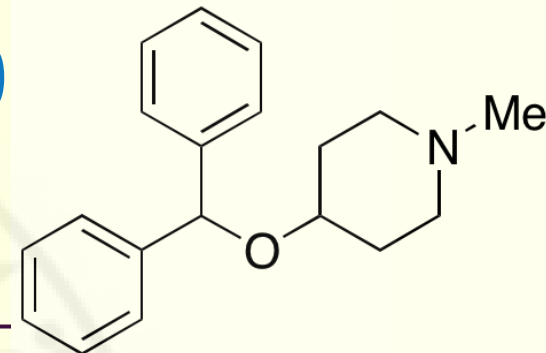
- Itchy, Watery Eyes
- Sneezing
- Runny Nose





Aminoalkyl Ethers (Ethanolamines)

Diphenylpyraline Hydrochloride.



- 4-(diphenylmethoxy)-1-methylpiperidine hydrochloride (Hispril, Define)
- is a white or slightly off white crystalline powder that is soluble in water or alcohol.
- **Diphenylpyraline** is structurally related to **Diphenhydramine** with the aminoalkyl side chain incorporated in a piperidine ring.
- It is a potent antihistaminic, and the usual dose is 2 mg 3 or 4 times daily.

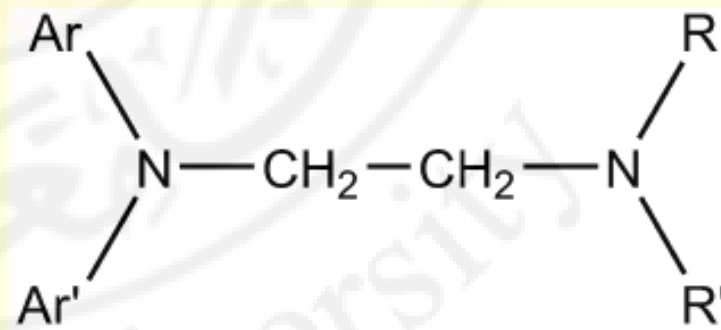
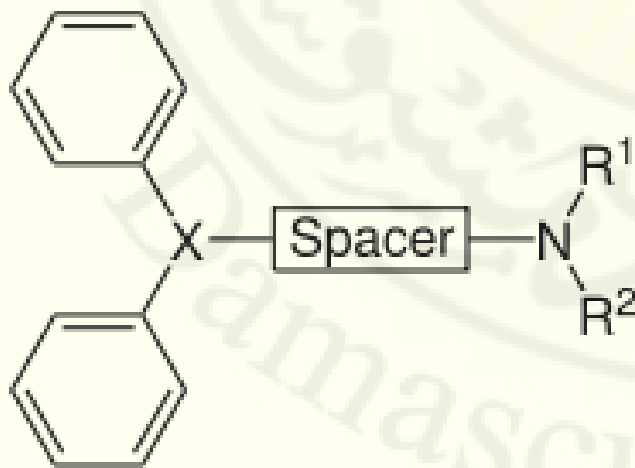
Dosage forms: Extended-release capsules (5 mg)

Usual adult dose: Oral, 5 mg/12 hours

First-Generation Antihistamine Classes

Ethylenediamines

- The **Ethylenediamine Antihistamines** are characterized by the presence of a
 - 1) **Nitrogen-connecting atom (X)**
 - 2) **two-carbon atom chain** as the linking moiety between the key diaryl and the **Tertiary amino** moieties

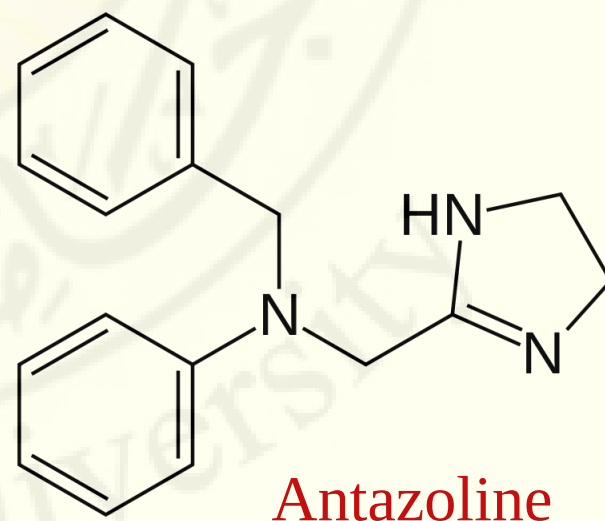
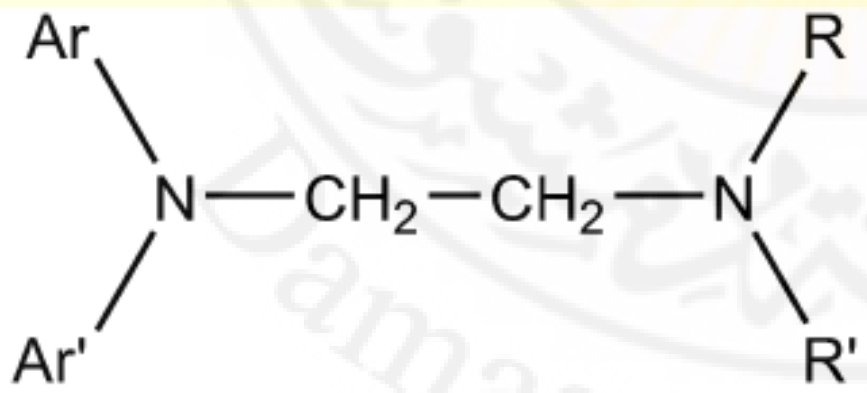


Ethylenediamines

First-Generation Antihistamine Classes

Ethylenediamines

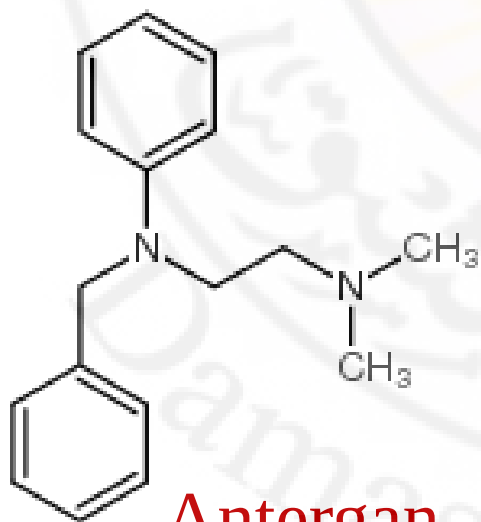
- All compounds in this series are simple diarylethylenediamines except **Antazoline**
- in **Antazoline** the terminal amine and a portion of the carbon chain are included as part of an **imidazoline** ring system.
- **Antazoline** is not always classified as an ethylenediamine derivative.



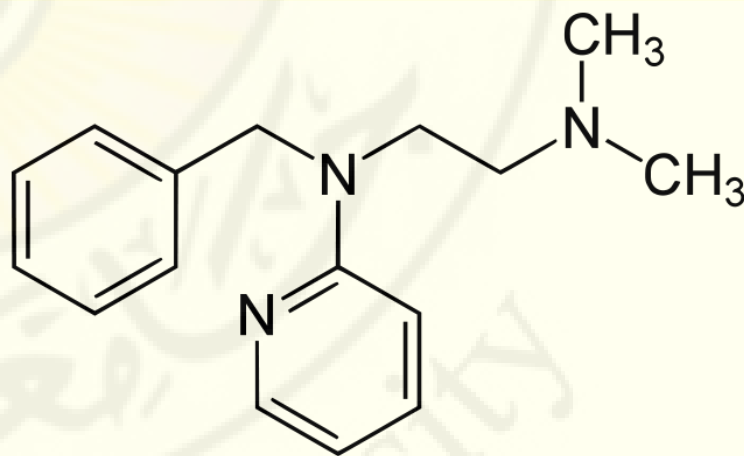
First-Generation Antihistamine Classes

Ethylenediamines

- The **Phenbenzamine** (**Antergan**) was prototype for the development of more effective derivatives.
- Replacement of the phenyl moiety of **Phenbenzamine** with a 2-pyridyl system yielded **Tripelennamine**, a significantly more effective histamine receptor blocker



Antergan
(Phenbenzamine)

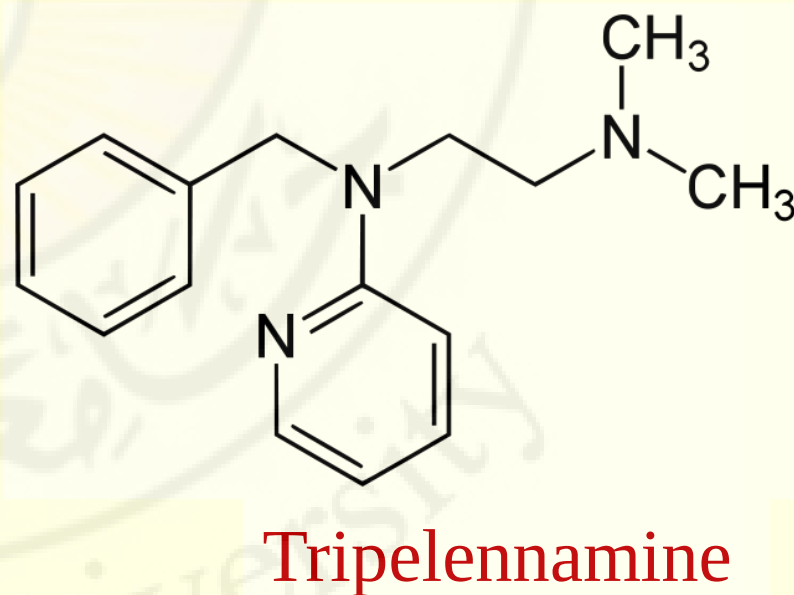
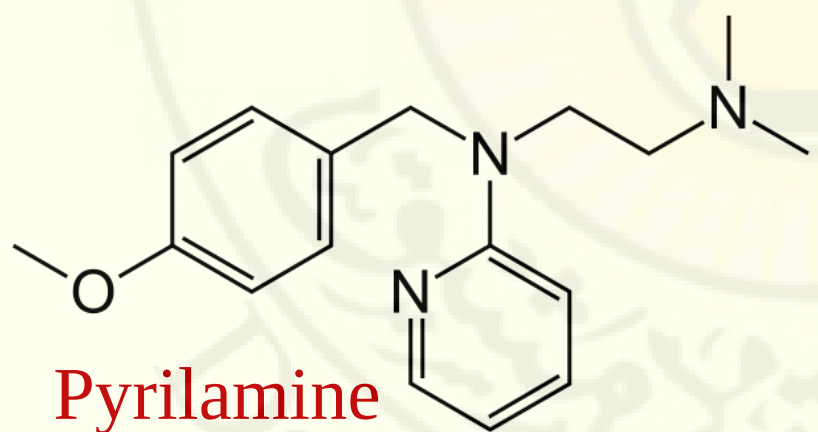


Tripelennamine
(Pyribenzamine)

First-Generation Antihistamine Classes

Ethylenediamines

- Substitution of a **para** at **benzyl group** enhances activity
- ✓ para methoxy (**Pyrilamine** or **Mepyramine**)
- ✓ para chloro (**Chloropyramine**)
- ✓ para bromo (**Bromtripelennamine**)



First-Generation Antihistamine Classes

Ethylenediamines

- In all of **Ethylenediamines**, the aliphatic or terminal amino group is required for H1-blocking activity and is significantly more basic than the nitrogen atom bonded to the diaryl moiety.
- The aliphatic amino group in the **Ethylenediamines** is sufficiently basic for the formation of pharmaceutically useful salts.
- **Ethylenediamines** are moderately effective H1-antihistamines

First-Generation Antihistamine Classes

Ethylenediamines

- **Ethylenediamines** display a relatively high frequency of CNS depressant
- The anticholinergic and antiemetic actions of **Ethylenediamines** are relatively low compared with those of most other classical, first-generation antihistamines

Ethylenediamines

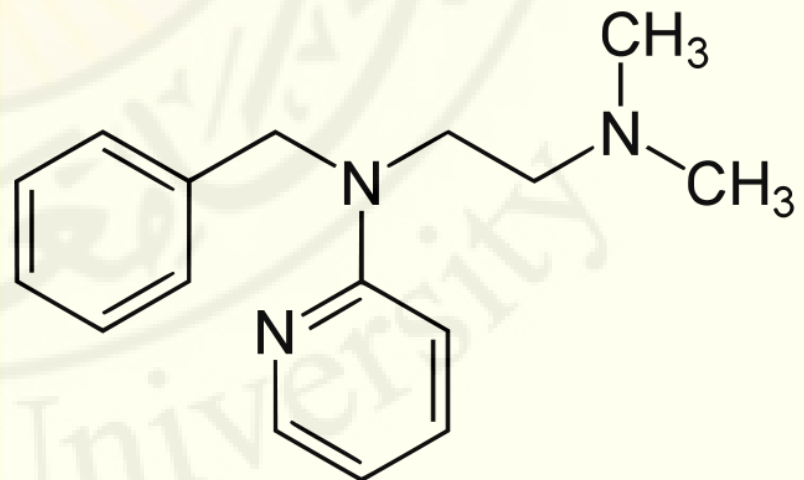
Tripelennamine hydrochloride

N,N-dimethyl-N-(Benzyl)-N-(pyridin-2-yl) ethane-1,2-diamine

- **PBZ** (PyriBenZamine Citrate), is available as a monocationic salt, which is a white crystalline powder freely soluble in water and in alcohol.
- For oral administration in liquid dose forms, the citrate salt is less bitter and thus more palatable than the hydrochloride.

Dosage forms: Elixir

Usual adult dose: Oral, 25 to 50 mg/4 to 6 hours



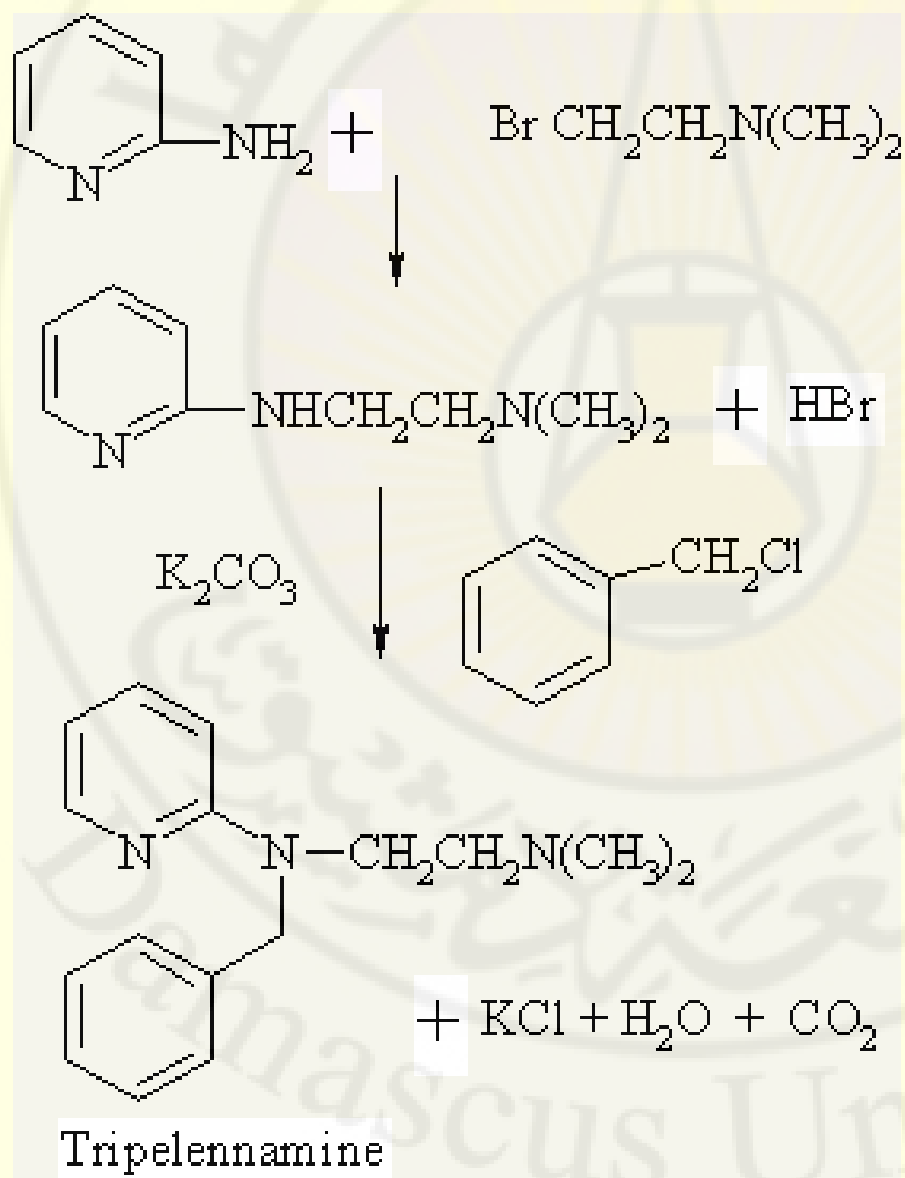
Ethylenediamines

Tripelennamine hydrochloride

- **Tripelennamine** hydrochloride is a salt is soluble in water. It was the first ethylenediamine developed in the United States
- It appears to be as effective as **Diphenhydramine** and may have the advantage of fewer and less severe side reactions.
- **Drowsiness** may occur and may impair the ability to perform tasks requiring alertness.
- The concurrent use of alcoholic beverages should be avoided.
- **Dosage forms:** Tablets, extended-release tablets
- **Usual adult dose:** Oral tablets, 25 to 50 mg/4 to 6 hours; extended-release tablets, 100 mg/8 to 12 hours

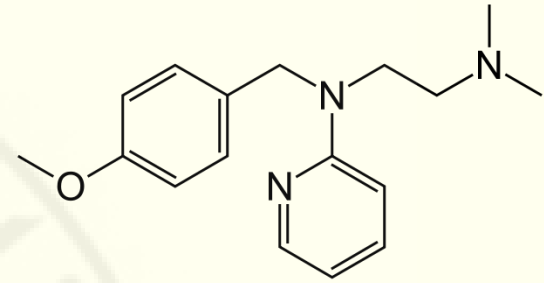
Ethylenediamines

Tripelennamine hydrochloride



Ethylenediamines

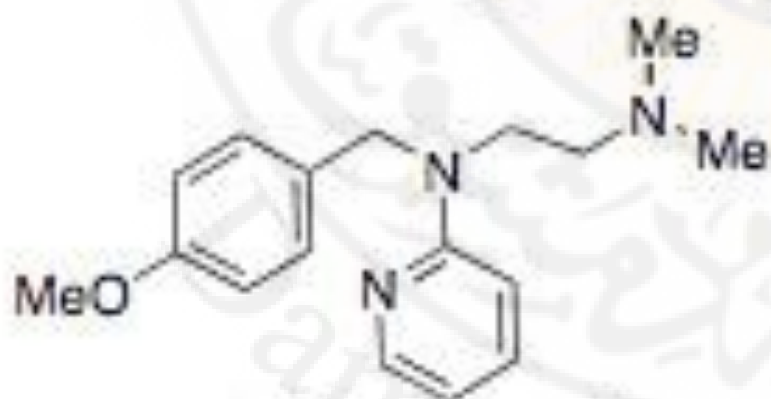
Pyrilamine Maleate (Mepyramine)



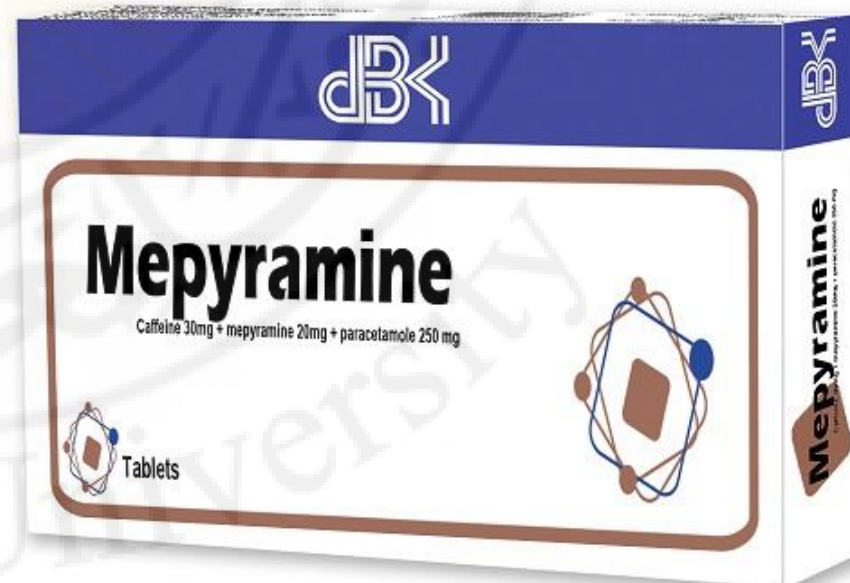
- **Pyrilamine Maleate.** 2-[4-methoxybenzyl [2-dimethylamino)ethyl]-amino]pyridine, is available as the acid maleate salt
- **Pyrilamine** differs structurally from **Tripelennamine** by having a methoxy group in the *para* position of the benzyl radical.
- It differs from its more toxic and less potent precursor **phenbenzamine** (**Antergan**) by having a 2-pyridyl group on the nitrogen atom in place of a phenyl group.
- Because of the pronounced local anesthetic action, the drug should not be chewed, but taken with food.
- **Dosage forms:** Tablets
- **Usual adult dose:** Oral, 25 to 50 mg/6 to 8 hours

Ethylenediamines

Pyrilamine Maleate (Mepyramine)

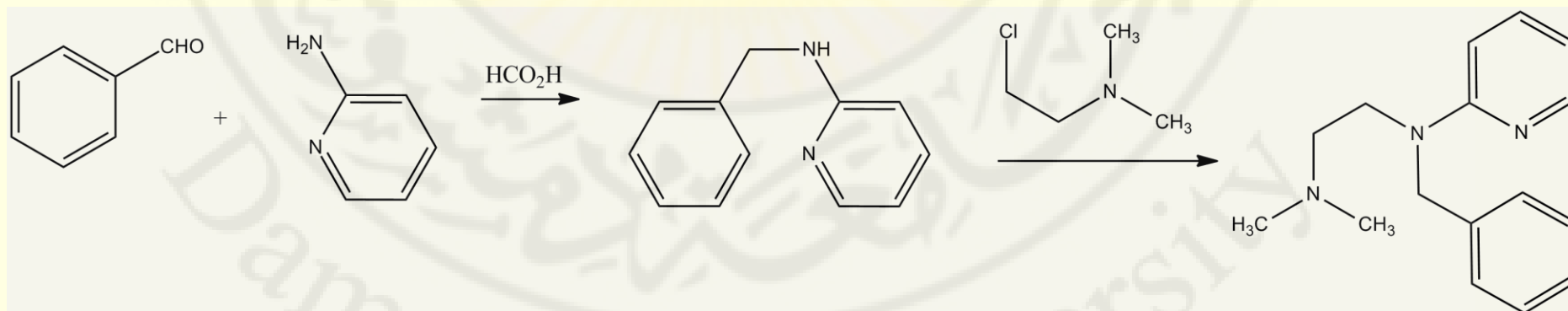
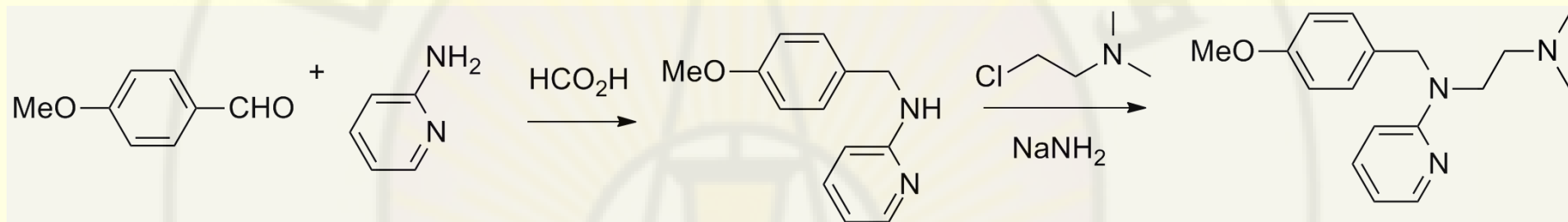


Mepyramine
(Pyrilamine)



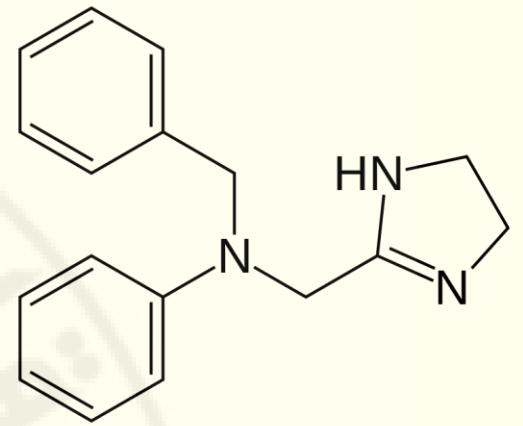
Ethylenediamines

Pyrilamine Maleate (Mepyramine)



Ethylenediamines

Antazoline Phosphate



2-[(*N* benzylnilino) methyl]-2-imidazoline

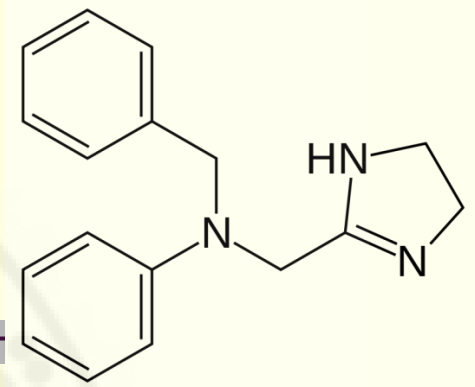
- **Antazoline** phosphate is a bitter, white to off-white crystalline powder soluble in water.

Antazoline phosphate salt is more soluble in water than **Antazoline hydrochloride** salt

- **Antazoline** is **less active** than most of the other antihistaminic drugs, but it is characterized by **the lack of local irritation**.

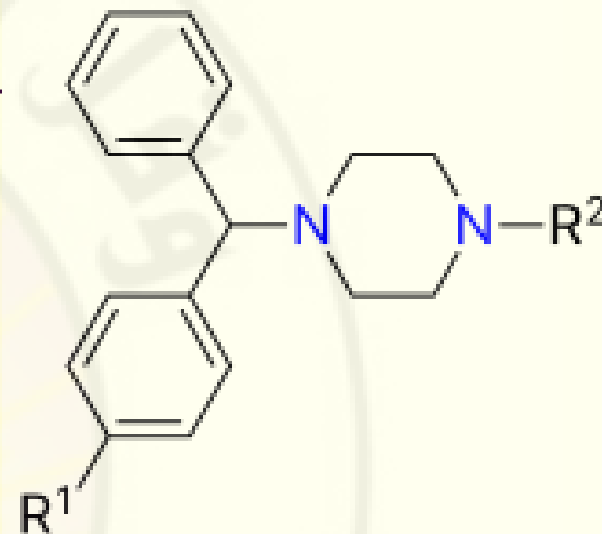
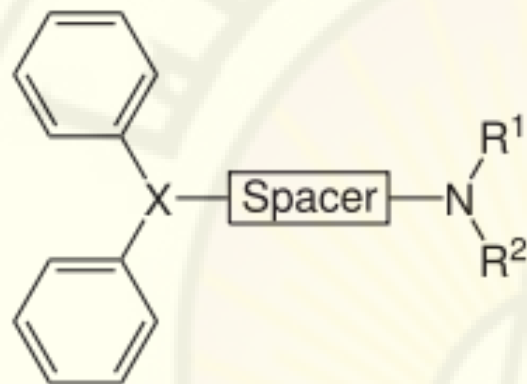
Ethylenediamines

Antazoline Phosphate



- **Antazoline phosphate** is applied topically to the eye in a 0.5% solution.
- The less soluble hydrochloride is given orally.
- In addition to its use as an antihistamine, **Antazoline** has more than twice the local anesthetic potency of **procaine** and also exhibits anticholinergic actions.

Piperazines (Cyclizines)



- The **Piperazines (Cyclizines)** can also be considered **ethylenediamine derivatives** or **cyclic ethylenediamines** (cyclizines).
- in this series
 - 1) the connecting moiety (X) is a CHN group
 - 2) the carbon chain, terminal amine functionality, and the nitrogen atom of the connecting group are all part of a piperazine moiety.

Piperazines (Cyclizines)

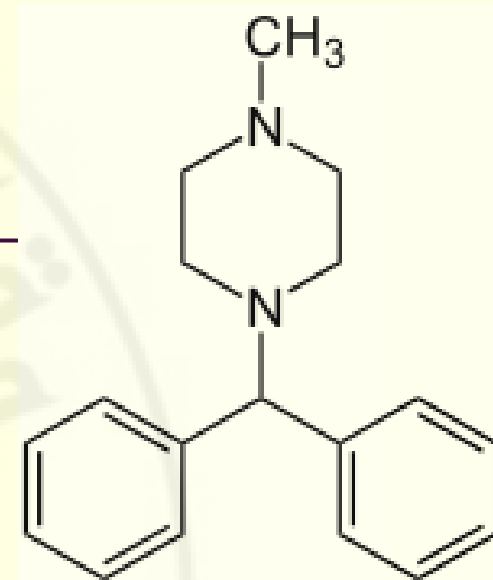
- Both nitrogen atoms in Piperazines Antihistamines are aliphatic and thus display comparable basicities.
- The primary structural differences within this series involve the
 1. nature of the para aromatic ring substituent (H or Cl) and
 2. nature of the terminal piperazine nitrogen substituent.
- The Piperazines are moderately potent Antihistaminics with a relatively high potential to cause drowsiness and psychomotor and cognitive dysfunction

Piperazines (Cyclizines)

- The activity of the Piperazines Antihistamines is characterized by a slow onset, but a long duration of action
- Piperazine Antihistamines have found significant use as Antiemetics and Antivertigo agents and in the treatment of Motion Sickness
- Some members of this series have exhibited a strong teratogenic potential, inducing several malformations in animal models.

Piperazines (Cyclizines)

Cyclizine Hydrochloride



1-(diphenylmethyl)-4-methylpiperazine

or

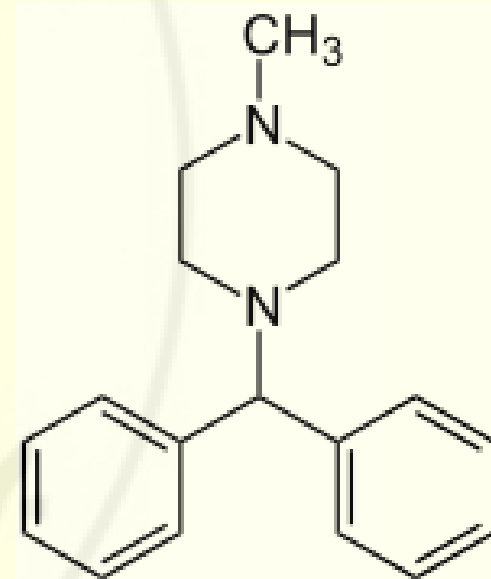
1-benzhydryl-4-methyl-piperazine

- **Cyclizine** is a **First-Generation Antihistamine** of the **Piperazines Class** of Antihistamines
- The lactate salt is used for intramuscular (IM) injection because of the limited water solubility of the hydrochloride
- The injection should be stored in a cold place, because if it is stored at room temperature for several months, a slight yellow tint may develop. This does not indicate a loss in biologic potency.

Piperazines (Cyclizines)

Cyclizine Hydrochloride

- Cyclizine is an antihistamine drug used to treat:
 1. Nausea
 2. Vomiting
 3. Dizziness
- associated with
 1. Motion Sickness
 2. Vertigo
 3. post-operatively following administration of general anaesthesia and opioids



Piperazines (Cyclizines)

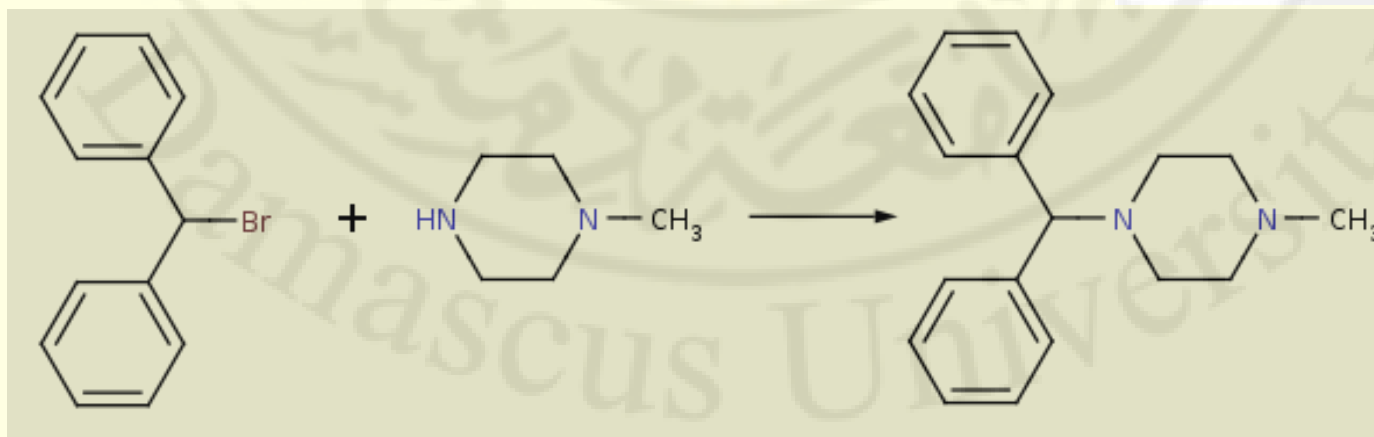
Cyclizine Hydrochloride

➤ Dosage forms:

- 1) Tablets HCl (25 and 50 mgHCl)
- 2) and injection (lactate)

➤ Usual adult dose:

- 1) 1 tablet every 4 to 6 hours for adults
- 2) children 12 years of age and older; 1/2 tablet every 6 to 8 hours

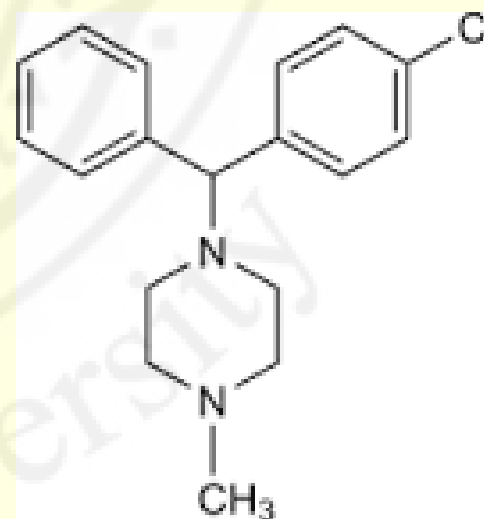


Piperazines (Cyclizines)

Chlorcyclizine hydrochloride

1-[(4-Chlorophenyl)(phenyl)methyl]-4-methylpiperazine

- Chlorcyclizine is a First-Generation Antihistamine of the Piperazine Class of Antihistamines
- Disubstitution or substitution of halogen in the 2 or 3 position of the benzhydryl rings results in a much less potent compound.
- Chlorcyclizine is used primarily to treat allergy symptoms such as
 1. Rhinitis
 2. Urticaria
 3. Pruritus
 4. may also be used as an Antiemetic



Lot: #Pxxxx Exp. Date: xx/xxxx

NDC 63717-333-08

bicloral-D
LIQUID

**Antitussive • Antihistamine
• Nasal Decongestant**

Each teaspoonful (5 mL) contains:

Chlophedianol HCl.....	12.5 mg
Chlorcyclizine HCl.....	12.5 mg
Pseudoephedrine HCl.....	30 mg

For professional use.

The labeling for this product includes professional labeling which is not intended for use by the general public.

Patent
Pending



HAWTHORN
PHARMACEUTICALS, INC.

8 fl oz (240 mL)

Grape Flavor
Alcohol Free • Dye Free

Usual Dosage: See Drug Facts
for full dosage information.

Store at Controlled Room Temperature
20°-25°C (68°-77°F); excursions permitted
15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Tamper evident by foil seal under cap. Do not use if foil seal is
broken or missing.

This bottle is not to be dispensed to the consumer.

Dispensed in a tight, light-resistant container with a child-resistant
cap.

**KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.
IN CASE OF OVERDOSE, GET MEDICAL HELP OR CONTACT A
POISON CONTROL CENTER IMMEDIATELY.**

Patent Pending

Mfg for:
Hawthorn Pharmaceuticals, Inc.
Madison, MS 39110
HL229 Rev. 12/11



NDC 16477-152-01

Dallergy[®]
CHEWABLE TABLETS

New
Improved
Formula

Antihistamine • Nasal Decongestant
For Professional Use

Each tablet contains:

Chlorcyclizine HCl	12.5 mg
Phenylephrine HCl	5 mg

GRAPE FLAVOR



100 Tablets
Rev 9/11



Lot No.:
Exp. Date:

Lift Here
for
Drug Facts

AHIST™

Chlorzoxazone HCl	_____	25 mg
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MAGNA
INTERNATIONAL, INC.
Lansdale, PA 19380

30 Tablets



AMIST

Keywords: *workplace spirituality, organizational commitment, organizational citizenship behavior, turnover intention, organizational trust, organizational identification*

Novel

THE UNIVERSITY OF CHICAGO

1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific requirements of the task.

POLY-TUSSIN
LIQUID 

**Antihistamine • Antitussive**

Sugar Free / Alcohol Free / Dye Free / Gluten Free

Each 5 mL (1 teaspoonful) contains:

Chlorcyclizine HCl	9.375 mg
--------------------------	----------

Codeine Phosphate	10 mg
--------------------------------	--------------

(WARNING: May be habit forming)



Cherry Flavor

C

Distributed by:
Poly Pharmaceuticals
Quilman, MS 39355
16 fl oz. (473 mL)

Lift
Here

Active Ingredients	Purpose
(In each 5 mL teaspoonful)	

Chlorcyclizine
Hydrochloride 9.375 mg Antihistamine
Codeine Phosphate 10 mg Antitussive
(WARNING: May be habit forming)

Uses

Temporarily relieves these symptoms due to the common cold, hay fever (allergic rhinitis) or other upper respiratory allergies:

- runny nose
- sneezing
- itching of the nose or throat
- itchy, watery eyes
- cough due to minor throat and bronchial irritation

Warnings

Ask a doctor before use if you have

- a breathing problem such as emphysema or chronic bronchitis
- glaucoma
- difficulty in urination due to the enlargement of the prostate gland
- a cough that lasts or is chronic such as occurs with smoking, asthma or emphysema
- a cough that occurs with too much phlegm (mucus)
- a chronic pulmonary disease or shortness of breath, or children who are taking other drugs

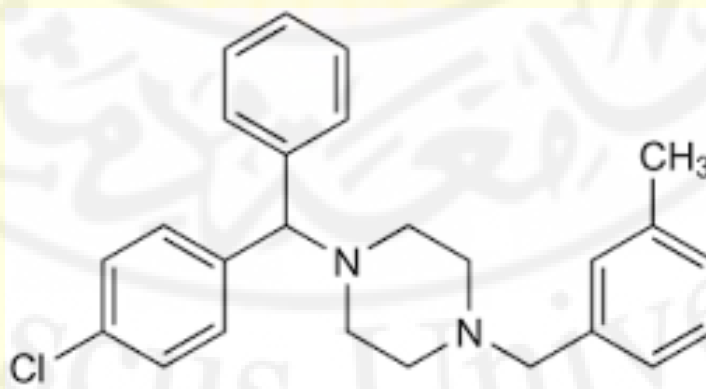
Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.

Piperazines (Cyclizines)

Meclizine hydrochloride

1-[(4-chlorophenyl)(phenyl)methyl]-4-(3-methylbenzyl)
piperazine

- Meclizine is a **first-generation antihistamine** of the **Piperazine Class**
- It differs from **Chlorcyclizine** in having an *N*-(*m*-methyl benzyl group) in place of the *N*-methyl group.



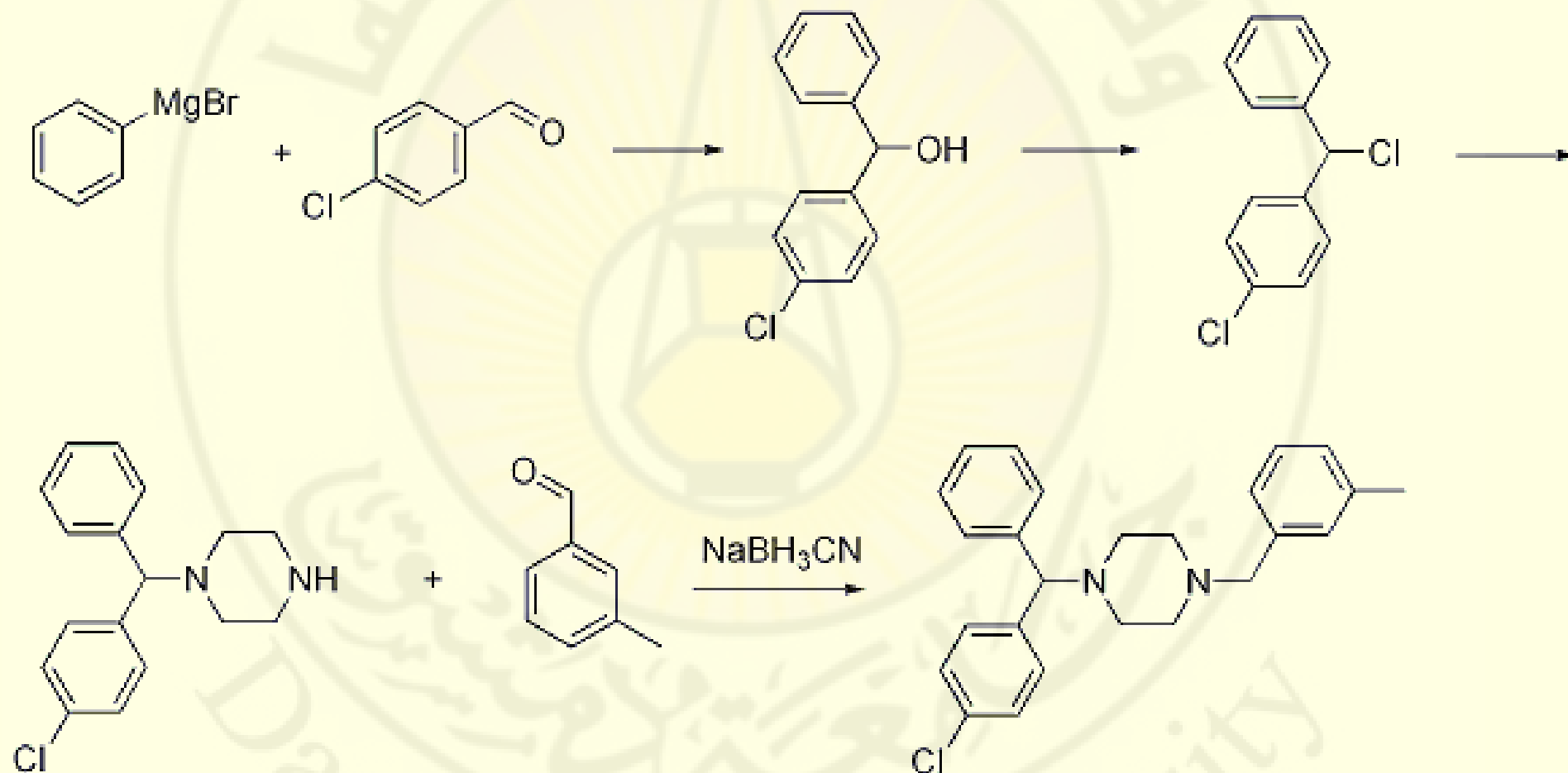
Piperazines (Cyclizines)

Meclizine hydrochloride

- Meclizine is an antihistamine drug used to treat:
 1. Nausea
 2. Vomiting
 3. Dizziness
- associated with
 1. Motion Sickness
 2. Vertigo

Piperazines (Cyclizines)

Meclizine hydrochloride



Piperazines (Cyclizines)

Meclizine hydrochloride

- **Dosage forms:** Tablets (12, 5, 25, 50 mg) and capsules (25 mg)
- **Usual adult dose:**
 - ❖ **Motion sickness:** 25- to 50-mg meclizine HCl should be taken 1 hour prior
 - ❖ **Vertigo:** 25 to 100 mg daily in divided doses

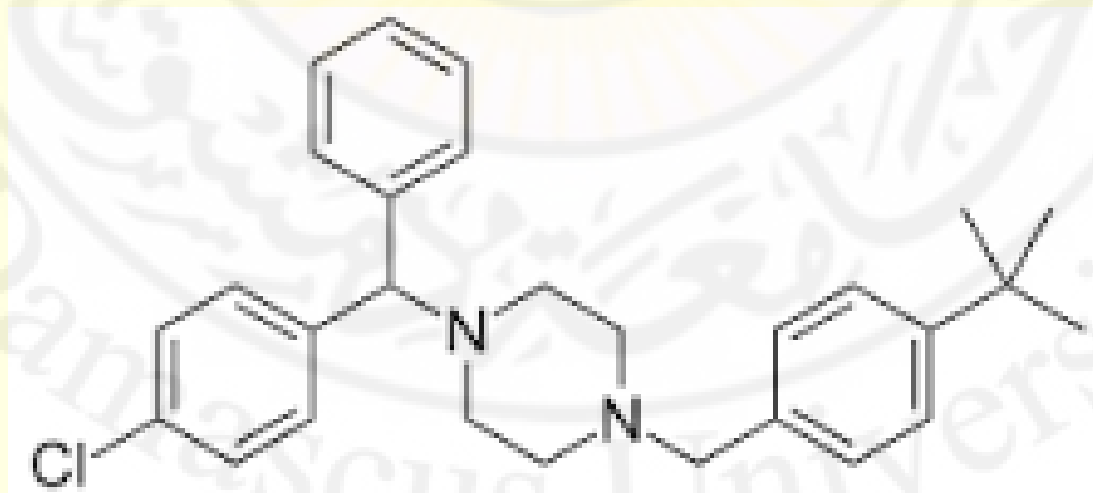


Piperazines (Cyclizines)

Buclizine hydrochloride

1-[(4-chlorophenyl)- phenyl-methyl]-4- [(4-tert-butylphenyl) methyl] piperazine

- The highly lipid-soluble **Buclizine** has CNS depressant, antiemetic, and antihistaminic properties.
- This drug has been discontinued in the United States.



Piperazines (Cyclizines)

Bucazine hydrochloride



Propylamines (Alkylamine Derivatives)

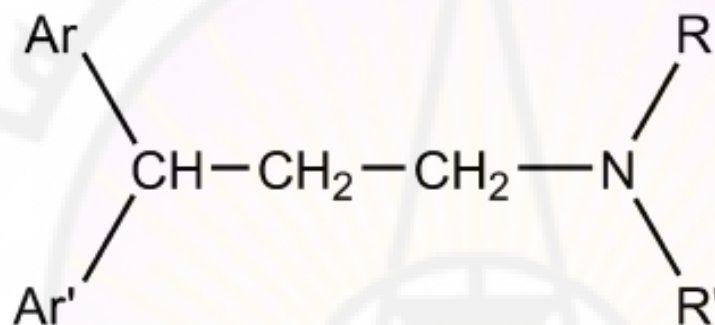


Figure 23.10 • General structure of the propylamines.

- The **Propylamine Antihistamines** are characterized structurally by an sp³ or sp² carbon-connecting atom with a carbon chain of two additional carbons linking the key tertiary amino and diaryl pharmacophore moieties
- **propylamines** with a **saturated carbon-connecting moiety** are commonly referred to as the **Pheniramines**.

Propylamines (Alkylamine Derivatives)

- All of the **Pheniramines** consist of a:
 1. phenyl and a 2-pyridyl aryl group and
 2. terminal dimethylamino moiety

- **Pheniramines** differ only in the phenyl substituent at the *para* position:
 1. H (**pheniramine**)
 2. Cl (**chlorpheniramine**)
 3. Br (**brompheniramine**)

Propylamines (Alkylamine Derivatives)

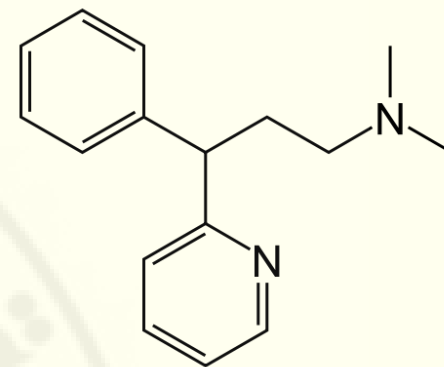
- The halogenated pheniramines are significantly more potent (20–50 times) and have a longer duration of action than Pheniramine
- All pheniramines are chiral molecules
- Antihistaminic activity resides almost exclusively in the *S*-stereoisomers (200 –1000 times higher H₁-receptor binding affinities)
- The pheniramines are widely used in OTC products for seasonal allergies.

Propylamines (Alkylamine Derivatives)

- The propylamines with an **unsaturated connecting moiety** In the open-chain propylamines, **the *E*-isomers are significantly more potent than the *Z*-isomers.**
- The **Propylamines Class** of antihistamines have:
 1. **most active H1-antagonists**
 2. **Greater Receptor Selectivity**
 3. **Fewer Anticholinergic** and CNS side effects than other first generation antihistamines.
 4. relatively **long half-lives** and are in many OTC preparations for once a- day treatment of mild allergy symptoms
 5. They produce **less sedation**

Propylamines

Pheniramine maleate (Trimeton)

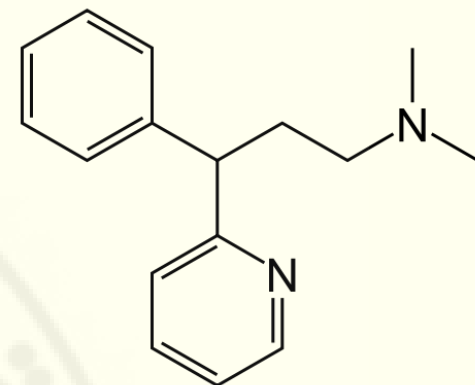


N,N-dimethyl-3-phenyl-3-(pyridin-2-yl)-propan-1-amine

- Pheniramine is a **first-generation antihistamine** of the **Propylamine Class** of Antihistamines
- **Pheniramine** is a **chiral compound** and it is marketed as the racemate
- ✓ **Pheniramine** has Antihistamine with Anticholinergic properties
- Derivatives of Pheniramine differ only in the phenyl substituent at the **para position**:
 1. **Chlorphenamine**
 2. **Brompheniramine**

Propylamines

Pheniramine maleate (Trimeton)



- Pheniramine is the least potent member of the series
- The halogenation of Pheniramine increases its potency by 20-fold
- ✓ Pheniramine is used
 1. to treat allergic conditions such as hay fever or urticaria
 2. Off-label as an over-the-counter sleeping pill in a similar manner to other sedating antihistamines such as Diphenhydramine
 3. in eye drops used for the treatment of Allergic conjunctivitis

Propylamines

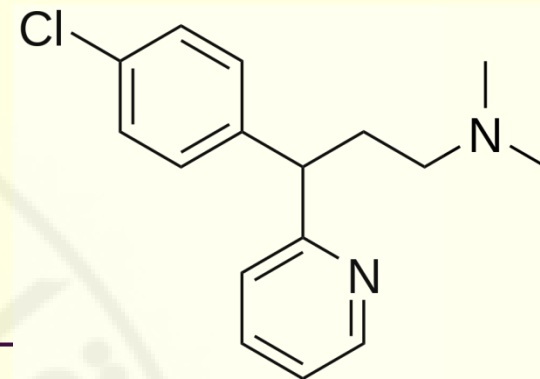
Pheniramine maleate (Trimeton)



Propylamines

Chlorpheniramine maleate

(Chlor Trimeton)



3-(4-chlorophenyl)-*N,N*-dimethyl-3-(pyridin-2-yl)-propan-1-amine

- Chlorphenamine is a **first-generation antihistamine** of the **Propylamine Class** of Antihistamines
- **Chlorination** of pheniramine in the ***para* position** of the phenyl ring increases potency 10-fold with no appreciable change in toxicity.
- The usual dose is 2 to 4 mg 3 or 4 times a day
- **chlorphenamine** in the indicated products is racemic chlorphenamine maleate, whereas

Propylamines

Chlorpheniramine maleate

- **Dexchlorpheniramine** is the dextrorotary stereoisomer
- Most of the antihistaminic activity resides with the **dextro isomer**
- **Dexchlorpheniramine** (**Polaramine**) is the dextrorotatory enantiomer of chlorpheniramine.
- the **Dextro isomer** has the **S configuration**

Propylamines

Chlorpheniramine maleate

■ Dosage forms:

1. Tablets (2, 4, 8, and 12 mg)
2. Extended release capsules (8 and 12 mg)
3. syrup (2 mg/5 mL)
4. oral suspension (4 and 8 mg/5 mL)

■ Usual adult dose: Oral, 4 mg/4 to 6 hours; extended release, 8 to 12 mg/8 to 12 hours; IM, intravenous (IV), or subcutaneous, 5 to 40 mg

■ Dosage forms: Extended-release tablets (4 and 6 mg), syrup (2 mg/5mL)

■ Usual adult dose: 4 or 6 mg at bedtime or every 8 to 10 hours

Propylamines

Chlorpheniramine maleate



See New Warnings Information

NDC 42507-393-62

Does Not Contain
Pseudoephedrine

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**NIGHT
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Multi-Symptom

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PE

- Headache/Sore Throat > **Acetaminophen**
- Nasal Congestion > **Phenylephrine HCl**
- Coughing > **Dextromethorphan HBr**
- Runny Nose > **Chlorpheniramine Maleate**

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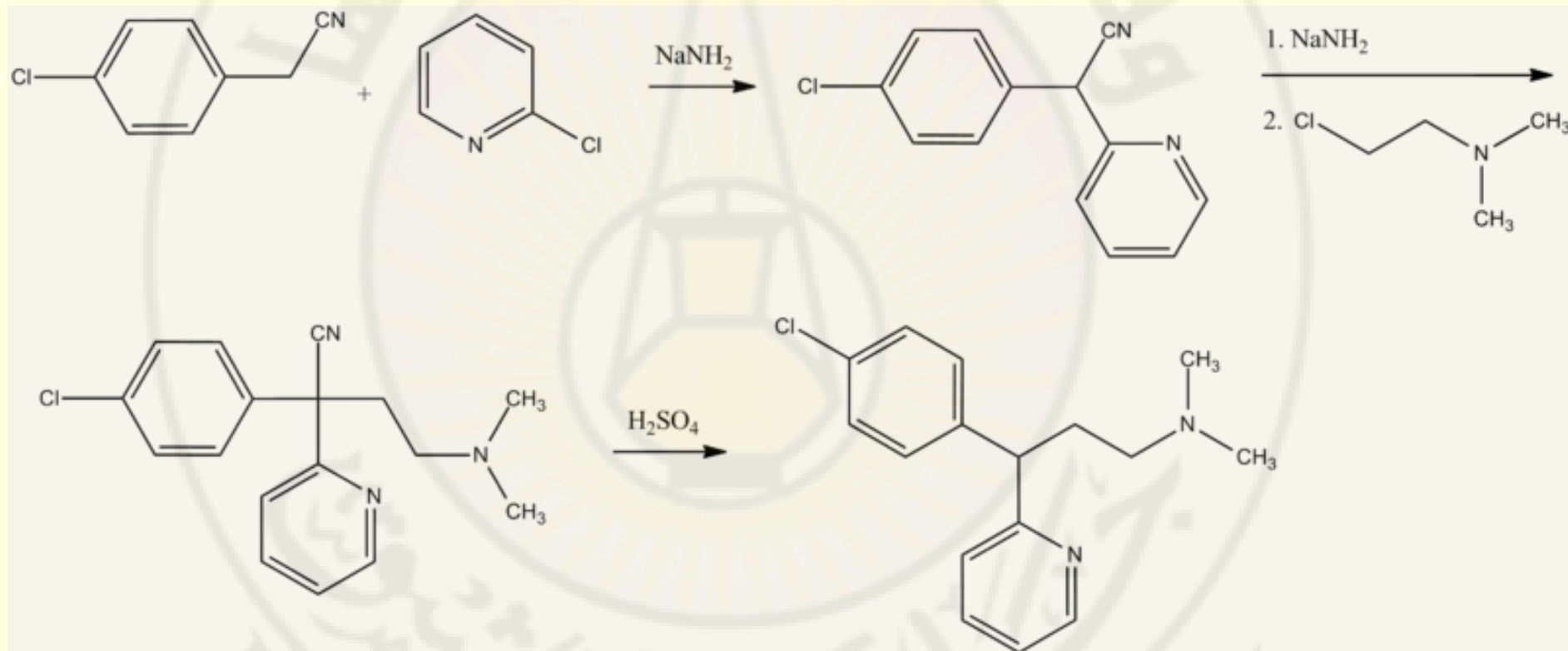
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Propylamines

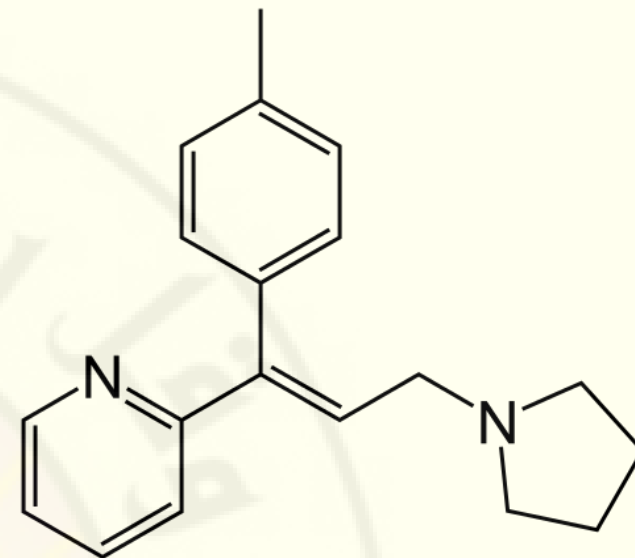
Chlorpheniramine maleate



Propylamines

Triprolidine hydrochloride

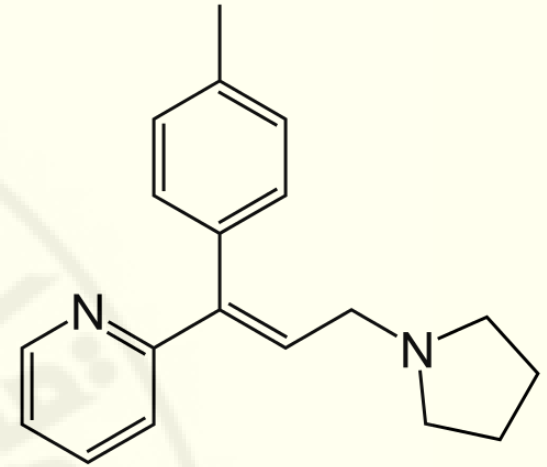
2-[(*E*)-1-(4-methylphenyl)-3-pyrrolidin-1-yl-prop-1-enyl]pyridine



- Triprolidine is a **first-generation antihistamine** of the **Propylamine Class** of Antihistamines
- The antihistaminic activity is confined mainly to the **geometric isomer** in which the **pyrrolidinomethyl group is *trans* to the 2-pyridyl group**.
- Pharmacological studies confirm the high activity of **Triprolidine** and the superiority of (*E*) over corresponding (*Z*) isomers as H₁-antihistamines.

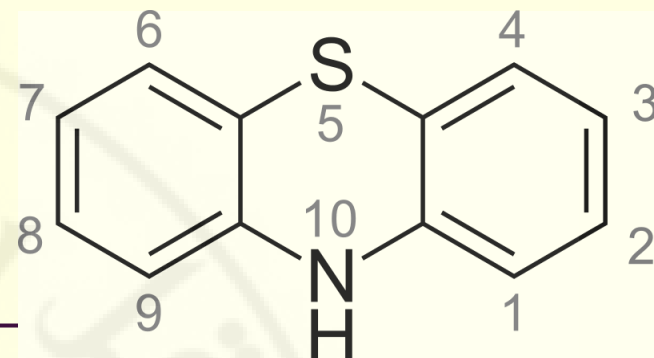
Propylamines

Triprolidine hydrochloride



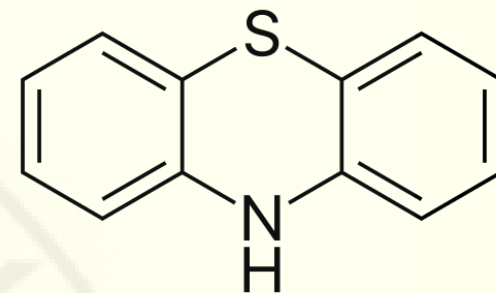
- **Triprolidine** is an over-the-counter antihistamine with anticholinergic properties.
- **Triprolidine** is used to treat the symptoms associated with allergies
- **Triprolidine** is sometimes combined with other **cold medications** designed to provide general relief for **flu-like symptoms**.
- Like many antihistamines, the most common side effect is drowsiness.

Phenothiazines



- ✓ Beginning in the mid-1940s, several **antihistaminic drugs** were discovered as a result of **bridging the aryl units of agents related to the Ethylenediamines**
- ✓ The search for effective **Antimalarials** led to the investigation of **phenothiazine derivatives** in which the **bridging entity is sulfur**.
- ✓ Subsequent testing found that the **Phenothiazine Class** of drugs **had not only Antihistaminic activity but also Antipsychotics activity** considerably different from that of the Ethylenediamines.

Phenothiazines



- The Phenothiazine derivatives that display therapeutically useful antihistaminic actions

1) contain a two- or three-carbon, branched alkyl chain between the ring system and terminal nitrogen atom

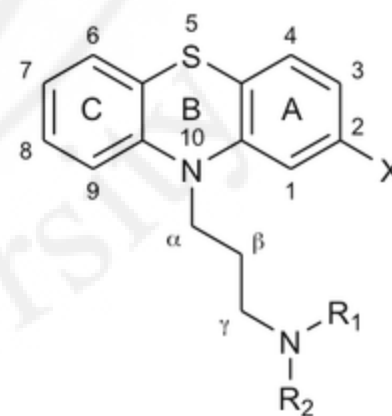
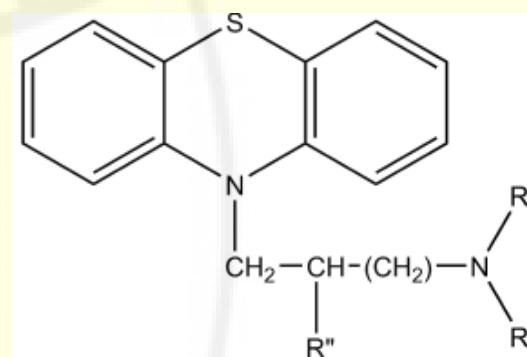
2) the Heterocyclic Ring is unsubstituted

Whereas

✓ Phenothiazine Antipsychotic series

1) contain an unbranched propyl chain

2) the Heterocyclic Ring is substituted

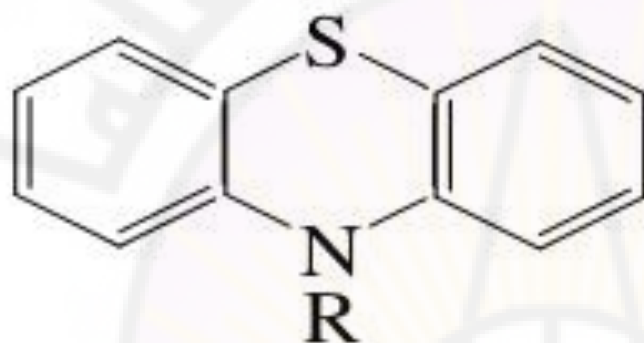


Phenothiazines

- ✓ In general the combination of
 - 1) lengthening of the side chainand
 - 1) substitution of lipophilic groups in the 2-position of the aromatic ring
- ✓ results in compounds with decreased antihistaminic activity and increased psychotherapeutic properties
- ✓
- ✓ Promethazine is the prototype of Phenothiazine Antihistaminic class and the parent member of this series

d) PHENOTHIAZINE DERIVATIVES:

GENERAL STRUCTURE:



DRUG	R	CHEMICAL NAME
PROMETHAZINE	$\text{—CH}_2\text{—}\underset{\text{CH}_3}{\text{—}}\text{N(CH}_3)_2$	(±)10-[2-(Dimethylamino)propyl]phenothiazine
TRIMEPRAZINE	$\text{—CH}_2\text{—}\underset{\text{CH}_3}{\text{—}}\text{CH}_2\text{N(CH}_3)_2$	(±)10-[3-(Dimethylamino)-2-methylpropyl]phenothiazine. 7/10/2014

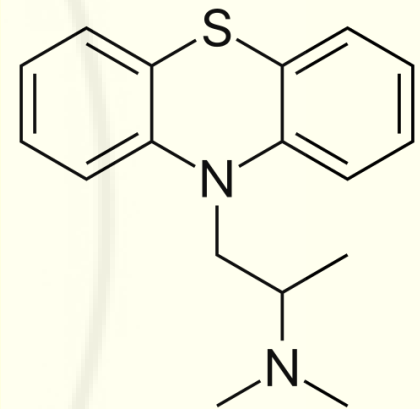
Phenothiazines

Promethazine hydrochloride (Phenergan)

- ✓ *N,N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine

or

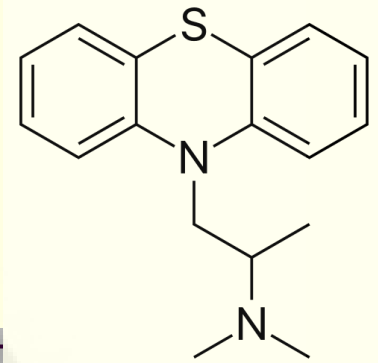
- ✓ 10-[2-(dimethylamino)-propyl]phenothiazine
- ✓ **Promethazine** is a **first-generation antihistamine** of the **phenothiazine** family.
- ✓ Promethazine is a **neuroleptic medication** and has strong Sedative and weak **Antipsychotic** effects.
- ✓ It also reduces motion sickness and has antiemetic and anticholinergic properties
- ✓ Promethazine is the parent member of this series



Phenothiazines

Promethazine hydrochloride

(Phenergan)

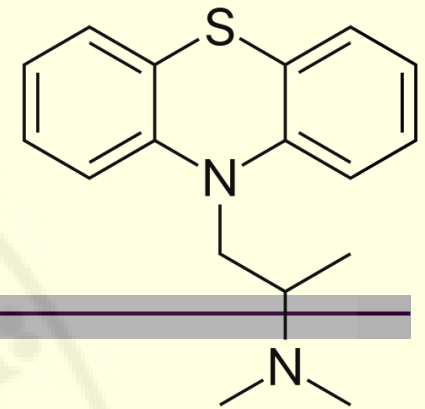


- It is a relatively long-acting antihistamine as a result of slow metabolic inactivation.
- In addition to its antihistaminic and sedating action Promethazine is a potent **Antiemetic**, anticholinergic
- Promethazine potentiates the action of analgesic and other sedative drugs
- Promethazine may cause drowsiness and impair the ability to perform tasks requiring alertness

Phenothiazines

Promethazine hydrochloride

(Phenergan)

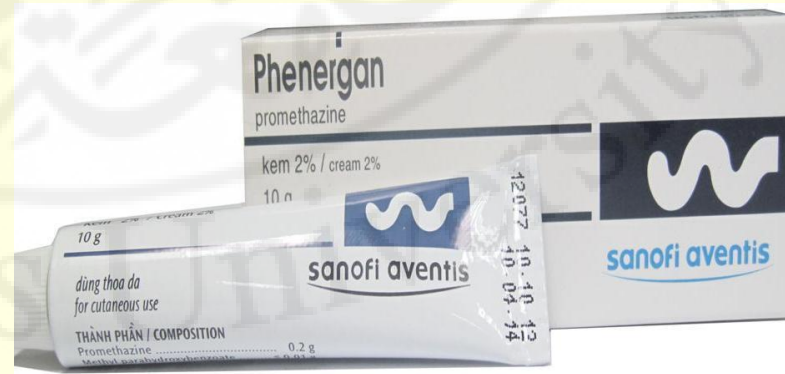
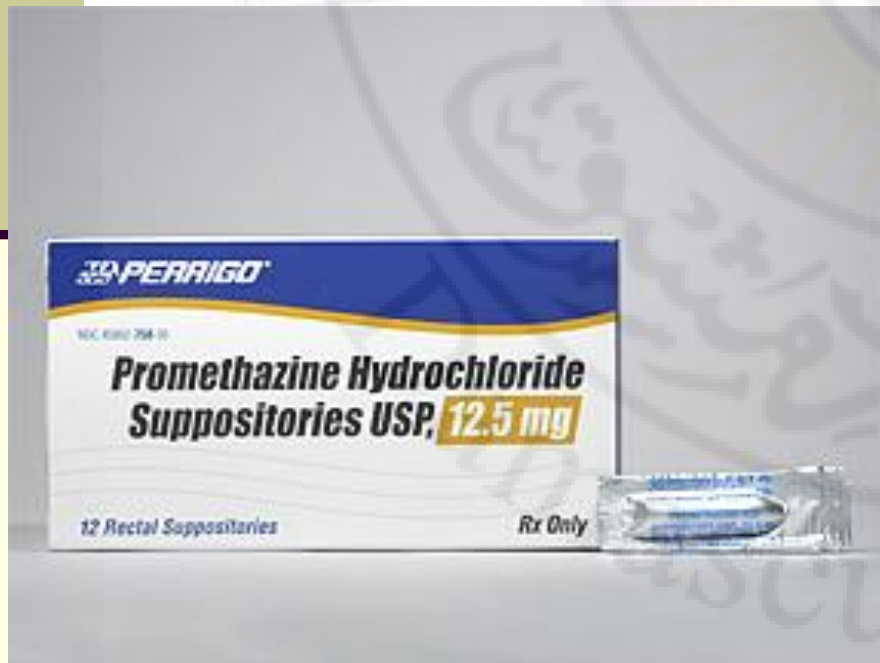


It is a phenothiazine derivative that is used

- 1) As a Sedative
- 2) preoperative sedation and to counteract post narcotic nausea
- 3) As Antiallergic medication (allergic rhinitis), or to treat **allergic reactions**, alone or in combination with oral decongestants such as pseudoephedrine
- 4) treatment for anaphylactoid conditions (IM/IV)
- 5) Together with codeine or dextromethorphan against Cough
- 6) As a Motion **Sickness** or **Seasickness** remedy when used with ephedrine or pseudoephedrine
- 7) moderate to severe Morning Sickness and Hyperemesis Gravidarum

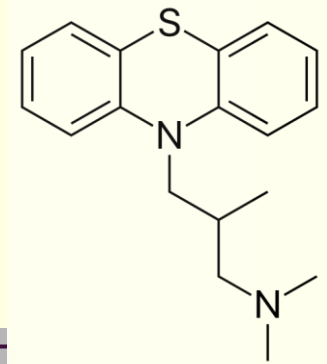
Phenothiazines

Promethazine hydrochloride(Phenergan)



Phenothiazines

Trimeprazine (Alimemazine) tartrate (Temaril)



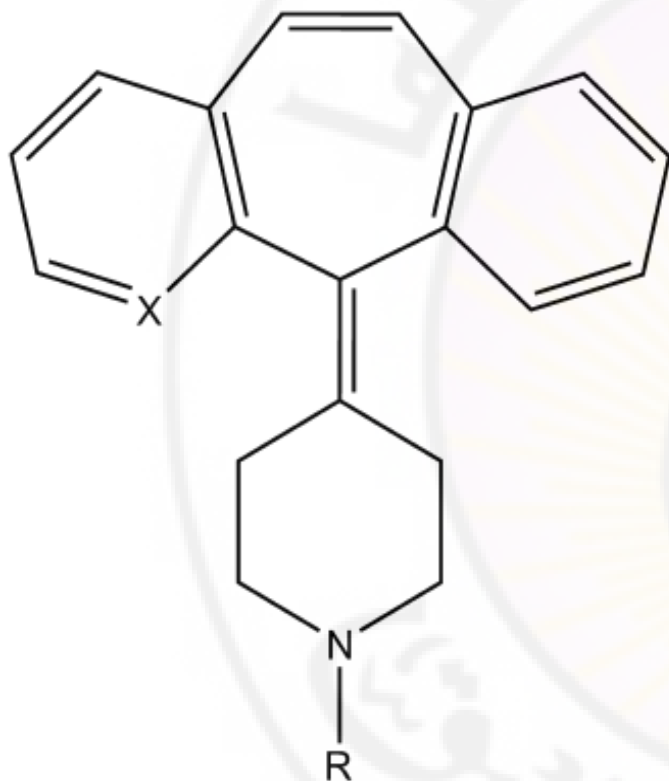
N,N,2-trimethyl-3-(phenothiazin-10-yl) propan-1-amine

Or

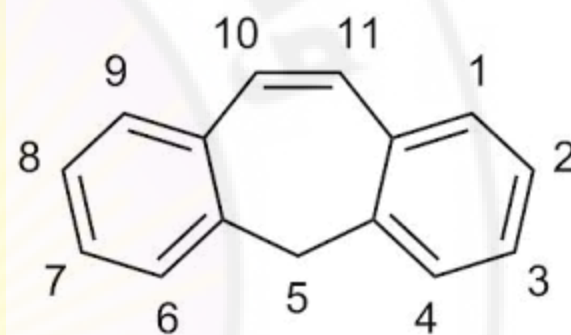
10-[3-(dimethylamino)-2-methylpropyl] phenothiazine

- Alimemazine is a first-generation antihistamine of the phenothiazine family
- Alimemazine is used as
 - 1) Antipruritic (it prevents itching from causes such as eczema or poison ivy, by acting as an antihistamine)
 - 2) Sedative
 - 3) Hypnotic
 - 4) Antiemetic for prevention of motion sickness

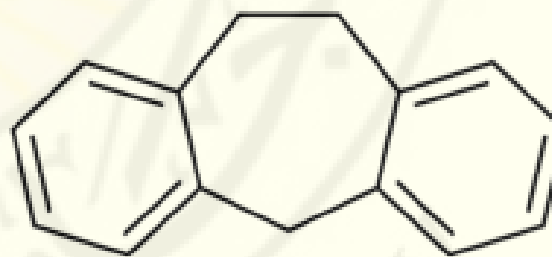
Dibenzocycloheptenes & Dibenzocycloheptanes



General structure of
Dibenzocycloheptenes and
Dibenzocycloheptanes



Dibenzocycloheptene

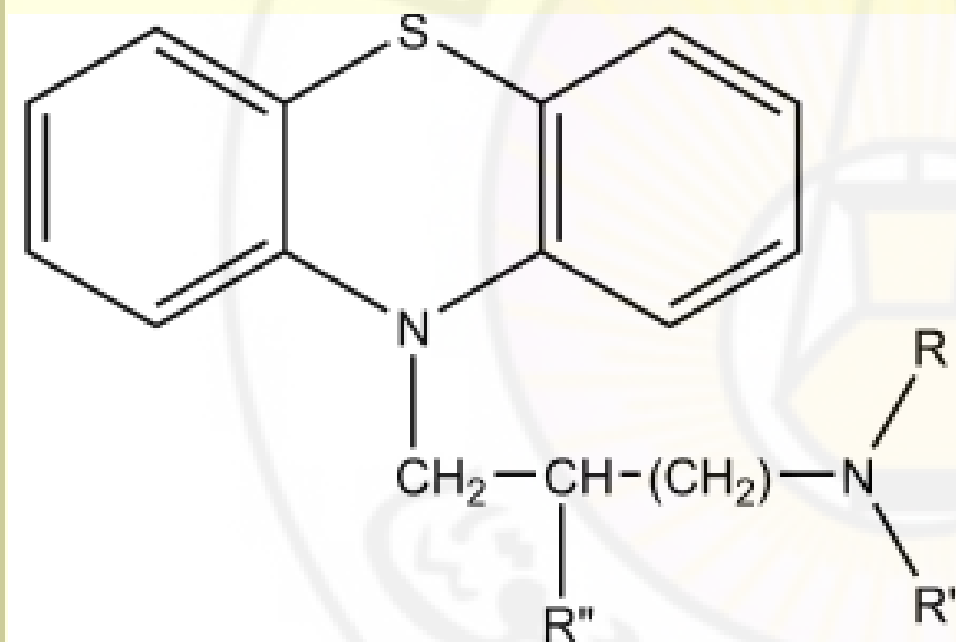


Dibenzocycloheptane

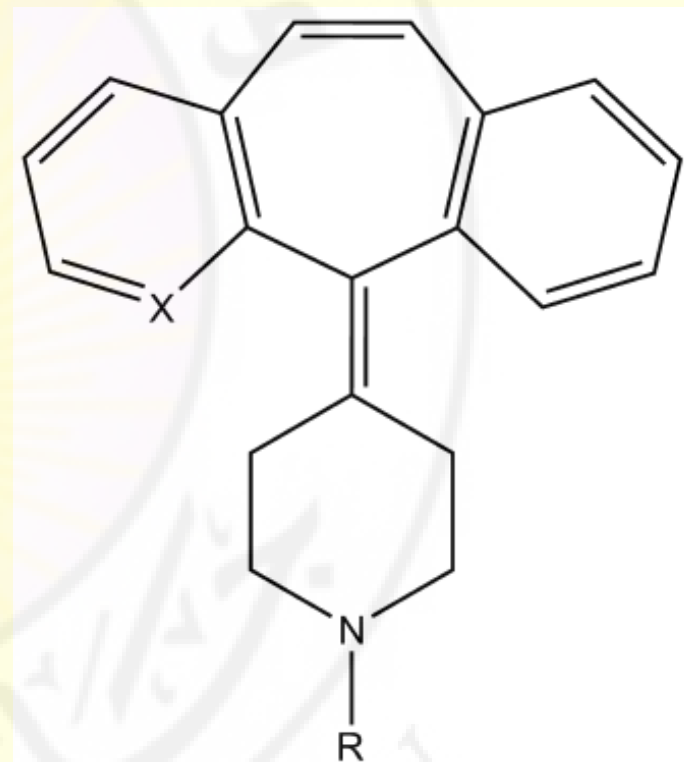
Dibenzocycloheptenes & Dibenzocycloheptanes

- The **dibenzocycloheptene** and **dibenzocycloheptane** antihistamines may be regarded as phenothiazine analogs in which the
 - 1) the **Sulfur Atom** has been replaced by an **isosteric vinyl group** (**Cyproheptadine**) or a **saturated ethyl bridge** (**Azatadine**)and
 - 2) the **Ring Nitrogen** has been replaced by an **sp² carbon atom**

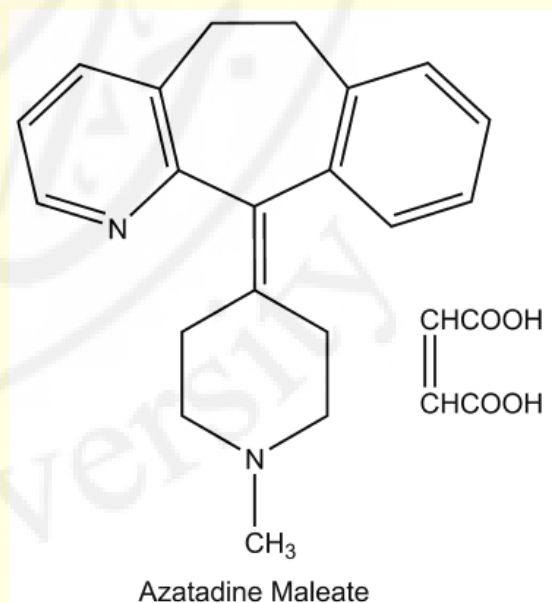
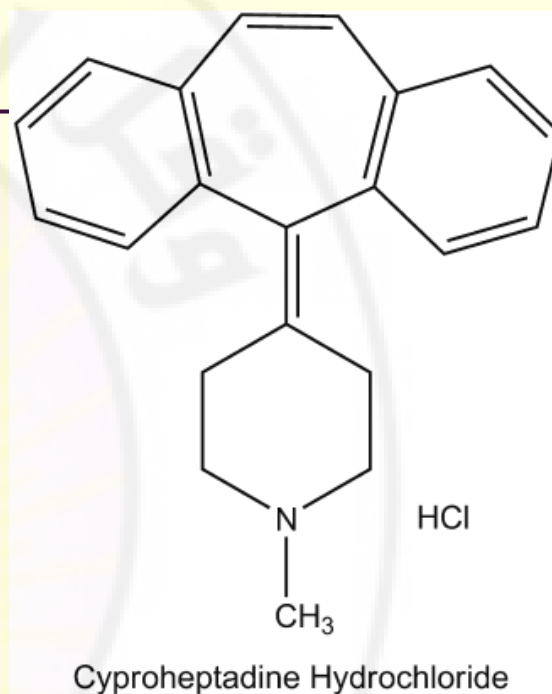
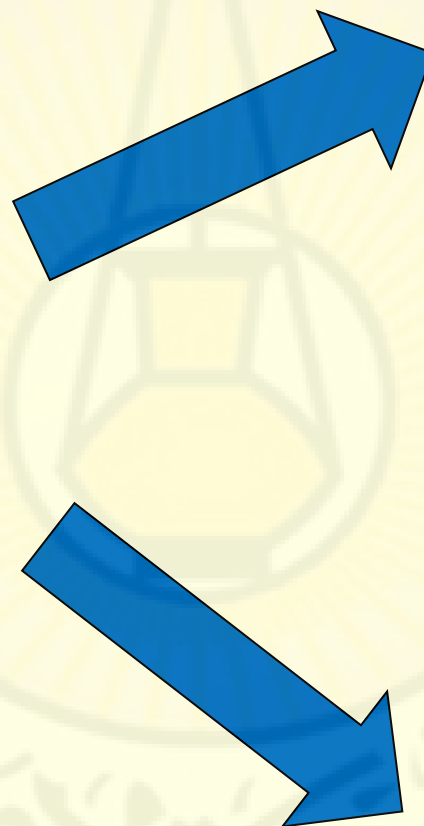
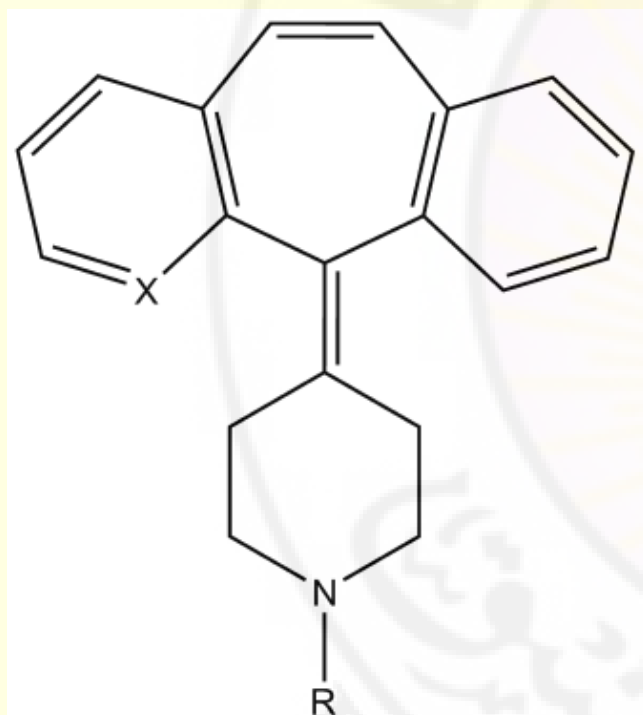
Dibenzocycloheptenes & Dibenzocycloheptanes



Phenothiazines



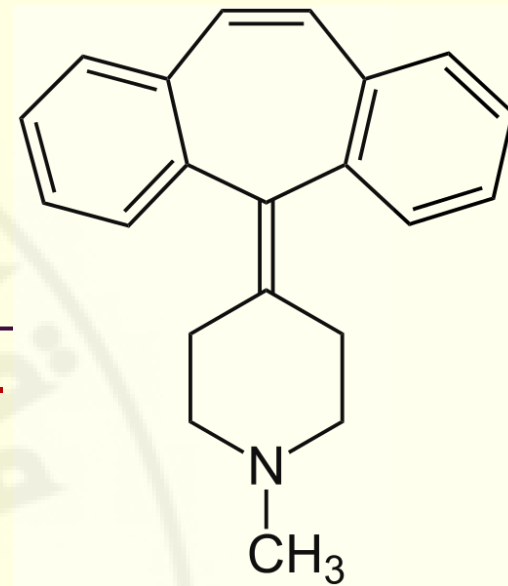
Dibenzocycloheptene
& Dibenzocycloheptane



Dibenzocycloheptene and
Dibenzocycloheptane

Cyproheptadine hydrochloride

4-(5*H*-dibenzo [a,d] cyclohepten-5-ylidene)-1-methylpiperidine



- Cyproheptadine is a first-generation antihistamine of the dibenzocycloheptenes Class of Antihistamines with additional Anticholinergic, Antiserotonergic, and local anesthetic properties
- Cyproheptadine possesses both Antihistamine and Antiserotonin activity and is used as an antipruritic agent

Cyproheptadine hydrochloride

- Cyproheptadine is indicated for the treatment of
 - 1) hypersensitivity reactions
 - 2) allergic rhinitis (perennial, seasonal)
 - 3) vasomotor rhinitis
 - 4) allergic conjunctivitis
 - 5) uncomplicated allergic skin manifestations of urticaria and angioedema
 - 6) amelioration of allergic reactions to blood or plasma
 - 7) cold urticaria

Cyproheptadine hydrochloride

- Cyproheptadine is also used off-label for
 - 1) Nightmares associated with posttraumatic stress disorder (PTSD)
 - 2) prevention of Migraine
 - 3) Suppression of vascular headaches
 - 4) appetite stimulation
- Sedation is the most prominent side effect
- **Dosage forms:** Tablets (4 mg) and syrup (2 mg/5 mL)
- **Usual adult dose:** Oral, 4 mg 3 or 4 times a day



Restore the Joy of eating food

APITISE Syrup

Cyproheptadine 2 mg + Tricholine 275 mg

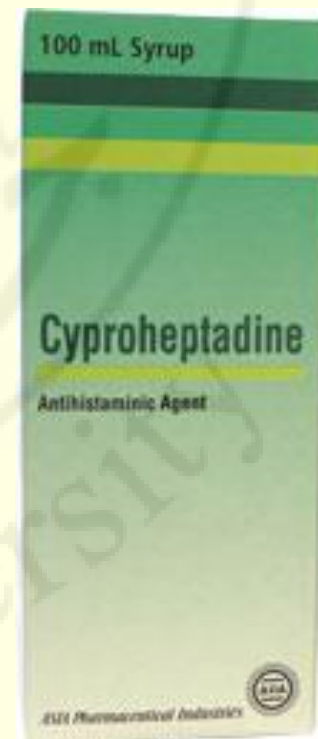
- ☺ Accepted Clinical combination for stimulating appetite & growth
- ☺ Shows stimulatory effects on growth hormones
- ☺ Tones up the entire digestive system

In

- ☺ Loss of Appetite
- ☺ Anorexia
- ☺ Weight Loss
- ☺ Intestinal mal absorption
- ☺ Underweight Children



APITISE FOR THE JOY OF FOOD



Rhinitis

Vasomotor Rhinitis

- **Rhinitis** is a condition that includes a runny nose, sneezing, and nasal stuffiness.
- When hay fever or allergies are not causing these symptoms, the condition is called **Nonallergic Rhinitis**.
- One type of **nonallergic rhinitis** is called **vasomotor rhinitis**.
- Vasomotor rhinitis is not caused by an infection or allergy. The exact cause is unknown. Symptoms are triggered by something that irritates the nose, such as:
 - 1) **Dry Atmosphere**
 - 2) **Air Pollution**
 - 3) **Alcohol**
 - 4) **Certain Medications**
 - 5) **Spicy Foods**
 - 6) **Strong emotions**

Rhinitis

Allergic Rhinitis

- Allergic rhinitis is an allergic reaction that happens when your immune system overreacts to substances that you have inhaled, such as pollen
- The two types of Allergic Rhinitis are
 - I. Seasonal Allergic Rhinitis Hay fever is caused by outdoor allergens.
 - II. Perennial allergic rhinitis occurs year-round and it is caused by indoor allergens such as
 - 1) Dust Mites عث الغبار
 - 2) Pet Dander وبر الحيوانات الأليفة
 - 3) Cockroaches الصراصير
 - 4) Molds



Second-Generation Antihistamines

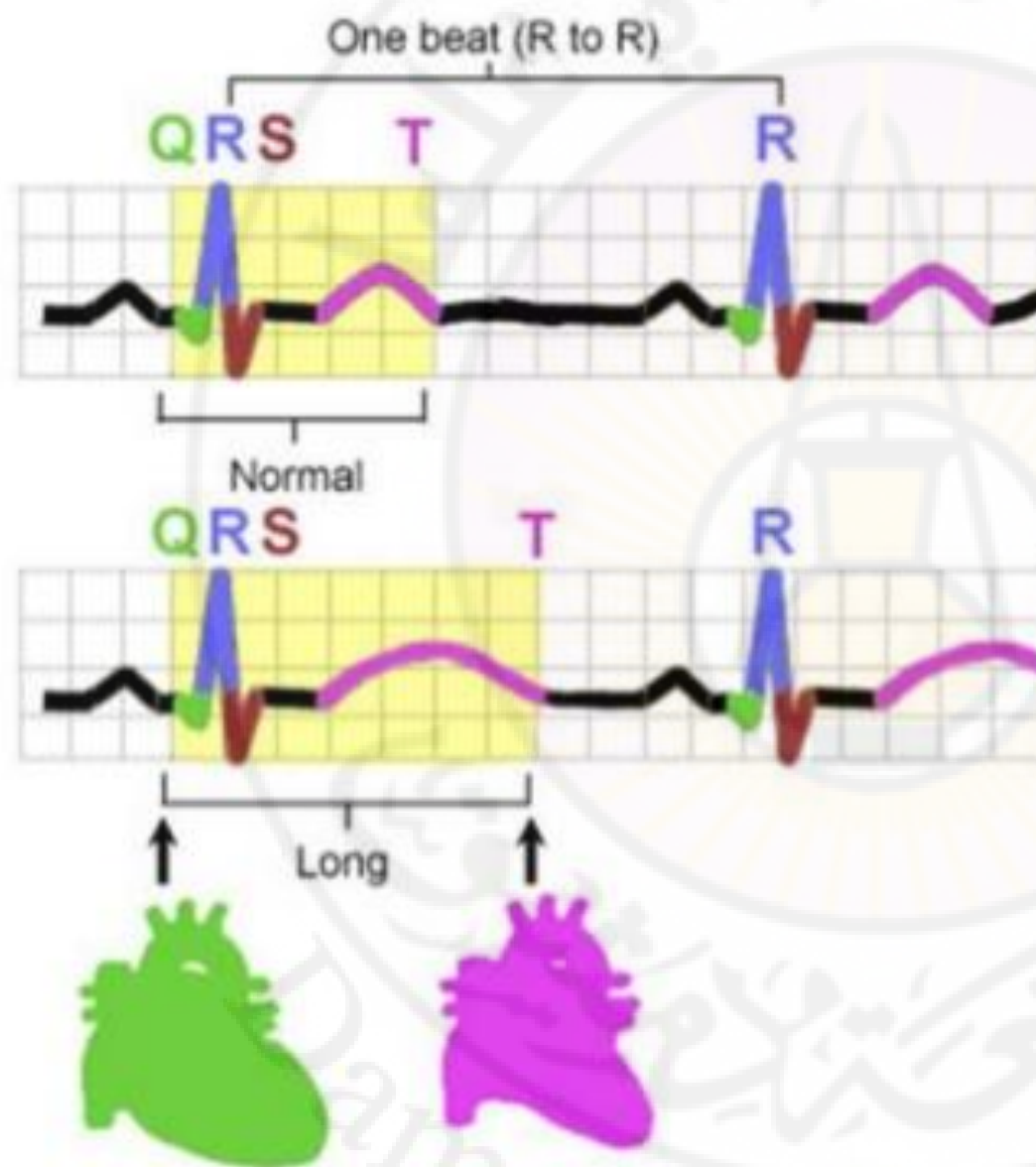
- Initial design efforts toward new or second-generation antihistamines focused on developing agents with
 - Nonsedating properties
 - H₁-receptor selectivity
- These efforts led to the introduction of
 - 1) Astemizole
 - 2) Terfenadine
- derivatives of the first-generation agents with substantially larger *N*-tertiary amine substituents

Second-Generation Antihistamines

- **Astemizole** and **Terfenadine** proved to be
 - 1) Nonsedating
 - 2) H1-receptor selective
 - 3) but they have cardiovascular toxicities (QT prolongation)

- Further drug design efforts resulted in the discovery of new second-generation agents, which retained:
 - 1) the nonsedating
 - 2) and receptor-selectivity properties
 - 3) but lacked the cardiotoxicity of **Astemizole** and **Terfenadine**.

ECG of heart and prolonged QT interval

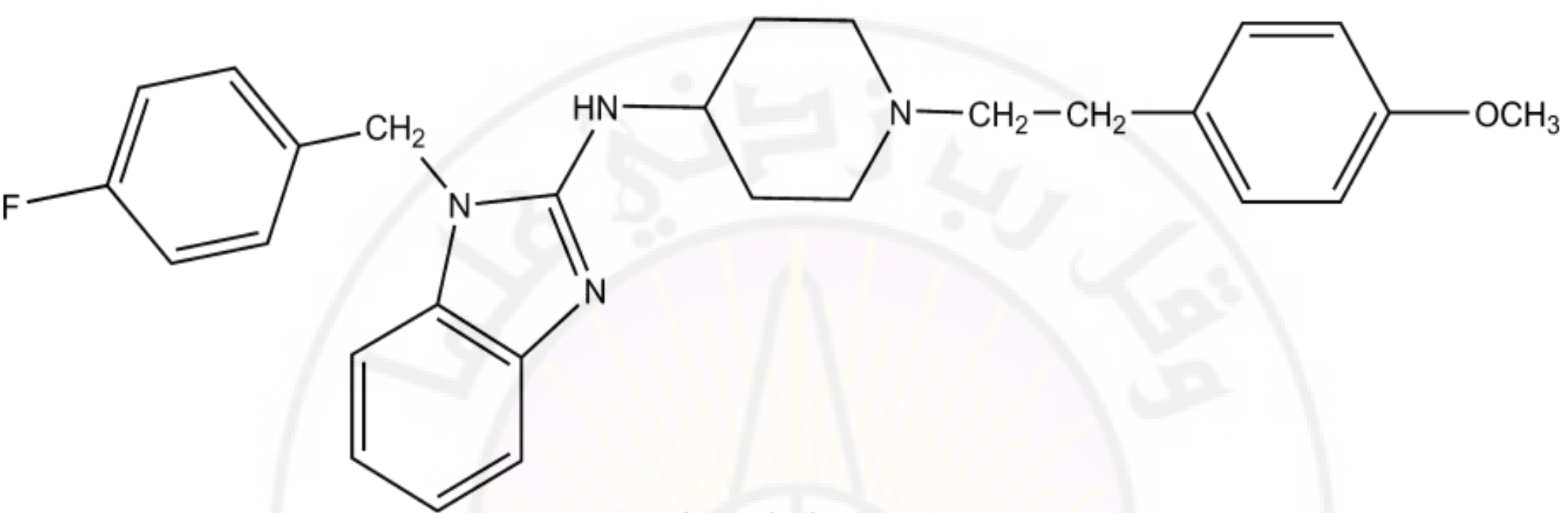


- The QT interval denotes time period taken by heart to empty it's blood.

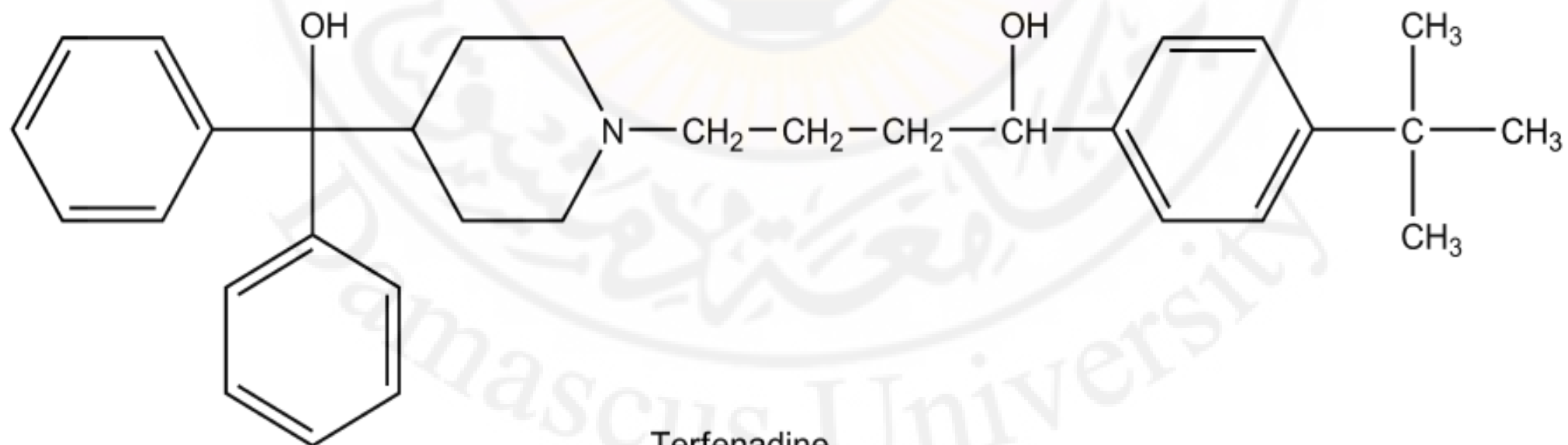
- Prolonged QT interval Suggests problem in cardiac muscle's repolarization mechanism after each contraction.

- It is a **dangerous side effect** that can cause 'Ventricular Fibrillation' which will **lead to sudden death** unless a defibrillator is used to reset heart's normal rhythm

Heart is full of blood at Q. Heart contracts at end of T.



Astemizole



Terfenadine

Second-Generation Antihistamines

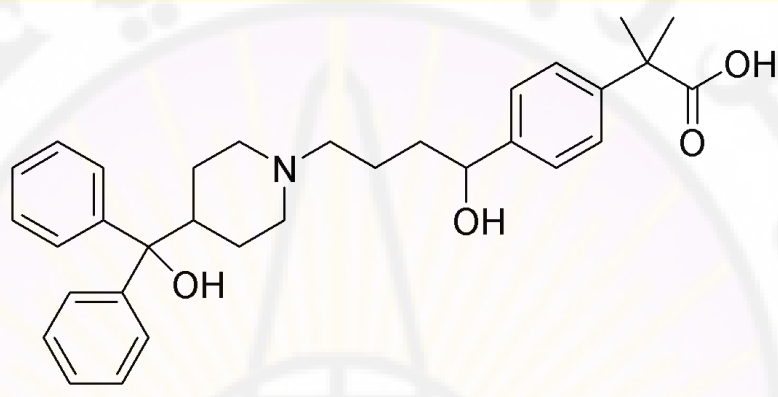
- The new second-generation drugs include
 - 1) **Acrivastine**, an alkene-acid derivative of **Triprolidine**
 - 2) **Cetirizine** and **Levocetirizine**, oxidation metabolites of **Hydroxyzine**
 - 3) **Desloratadine**, an oxidation–hydrolysis metabolite of **Loratadine**;
 - 4) **Fexofenadine**, an oxidativebmetabolite of **Terfenadine**
- These newer agents are **structurally diverse**, but are **derivatives of first-generation drugs**, containing **larger, polar functionality** connected either to the **terminal tertiary amine**, or as a substituent of one of the **aromatic rings**.

Second-Generation Antihistamines

- second-generation agents **do not accumulate in the CNS** because their
 - ❖ **Hydrophilicity** (in some cases)
 - ❖ **And high affinity for P-glycoprotein efflux pumps** of cells associated with the BBB

Second-Generation Antihistamines

Fexofenadine Hydrochloride (Allegra)



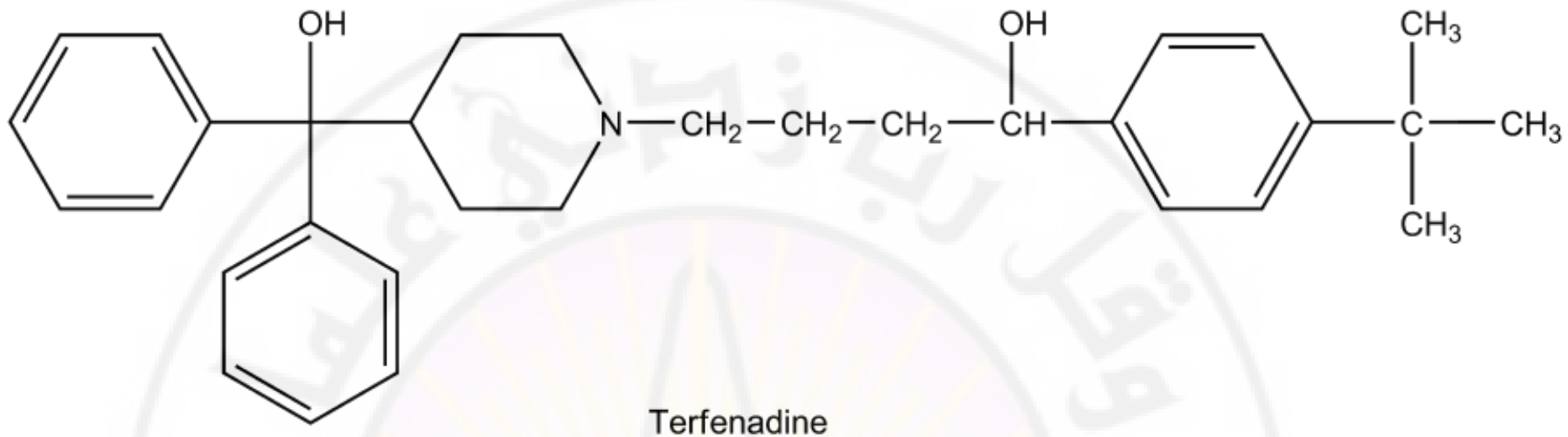
4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzene acetic acid

- Fexofenadine is a second-generation antihistamine because it is less able to pass the blood-brain barrier and cause sedation, compared to first-generation antihistamines.
- Fexofenadine is marketed as a **racemate** and exists as a **zwitterion** in aqueous media at physiological pH

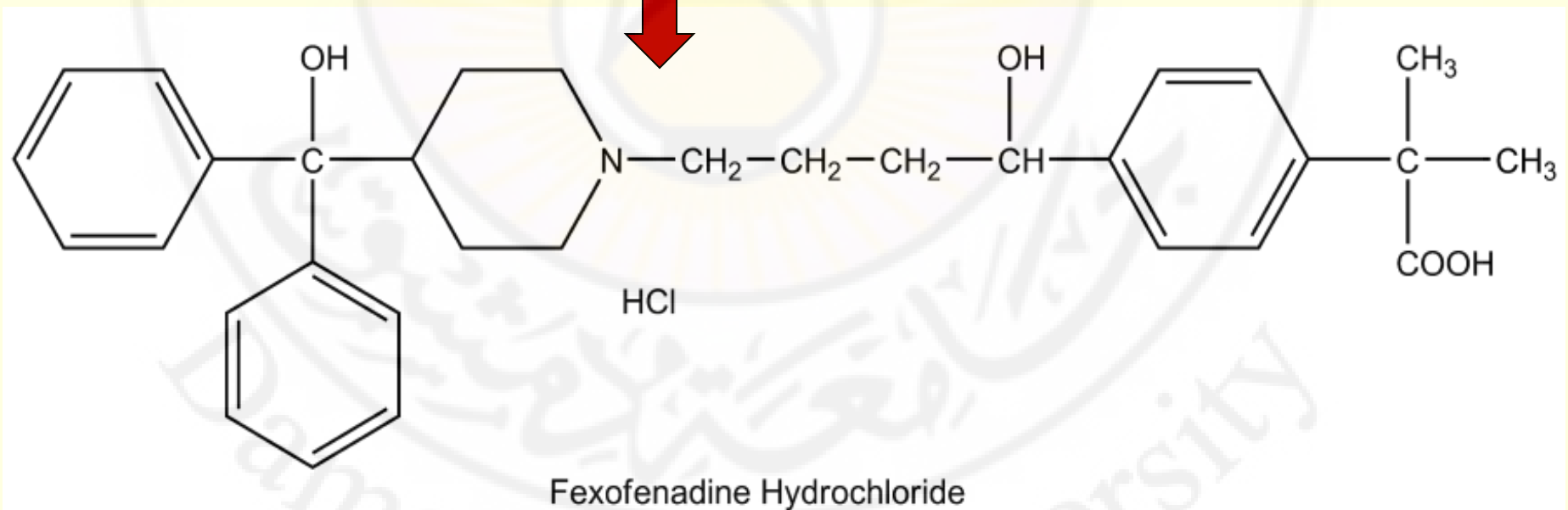
Second-Generation Antihistamines

Fexofenadine Hydrochloride (Allegra)

- Fexofenadine is a **primary oxidative metabolite of Terfenadine**
- Fexofenadine is a selective peripheral H₁-receptor ligand that produces
- No anticholinergic effects
- **No sedative** or other CNS effects because it **does not cross** the BBB
- Fexofenadine does not block potassium channels in cardiocytes
- **no prolongation of the QT interval** or related heart rhythm abnormalities were detected when fexofenadine was administered concurrently with erythromycin or ketoconazole



**cytochrome P450
(CYP)-based metabolism**

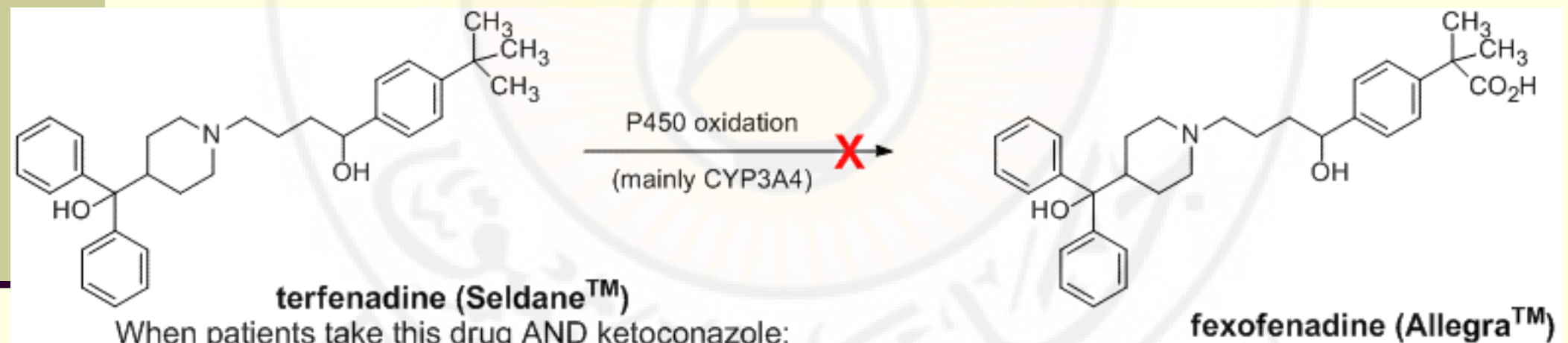
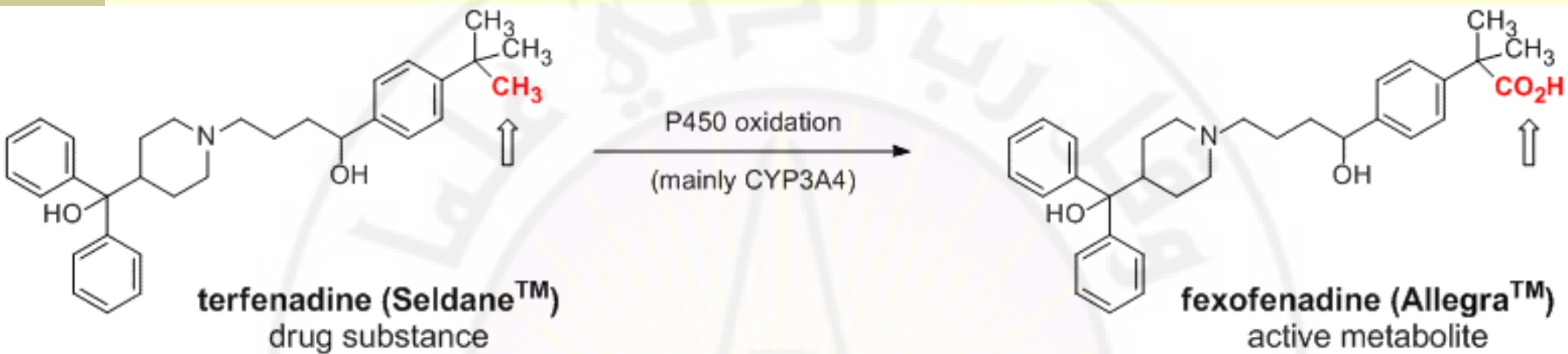


Fexofenadine is indicated for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria.

Second-Generation Antihistamines

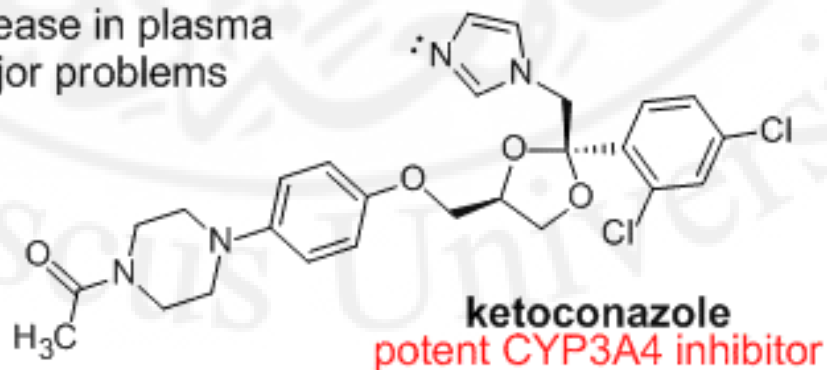
Fexofenadine Hydrochloride (Allegra)

- Fexofenadine is a selective H1-antihistamine with little affinity for muscarinic, serotonergic, or adrenergic receptors.
- ✓ The histamine receptor affinity of Fexofenadine is related primarily to the presence of the Diphenylmethyl Piperidine Moiety
- ✓ The lack of anticholinergic, adrenergic, or serotonergic actions is related to the presence of the N-Phenylbutanol Substituent



When patients take this drug AND ketoconazole:

- substance concentrations increase in plasma
- adverse events become major problems

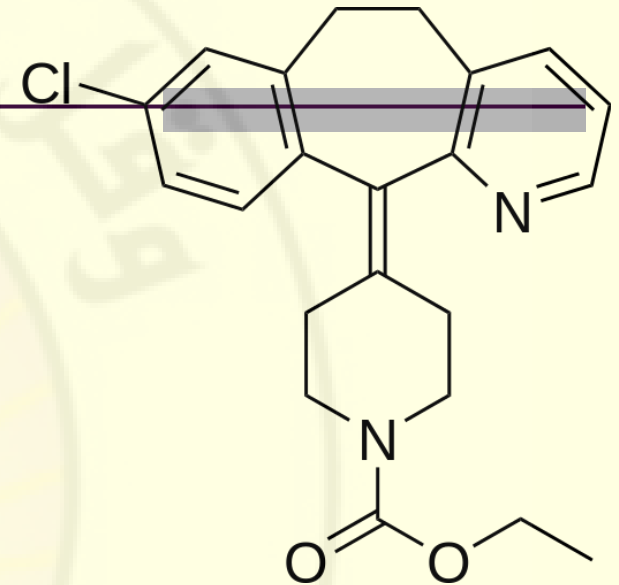




Second-Generation Antihistamines

Loratadine

Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate

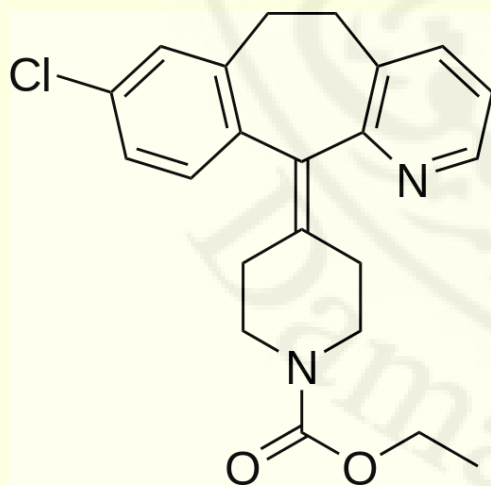


- Loratadine is a second-generation antihistamine of the dibenzocycloheptanes Class of Antihistamines
- Loratadine produces no substantial CNS or autonomic side effects or cardiac toxicity

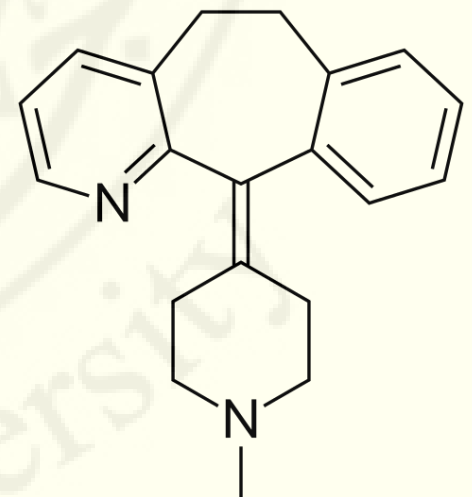
Second-Generation Antihistamines

Loratadine

- Loratadine is structurally related to the antihistamines **Azatadine** and **Cyproheptadine**, and to some tricyclic antidepressants.
- It differs from **Azatadine**, in that a neutral **carbamate** group has replaced the basic tertiary amino moiety, and a **phenyl** ring has been substituted with a **chlorine atom**.



Loratadine



Azatadine

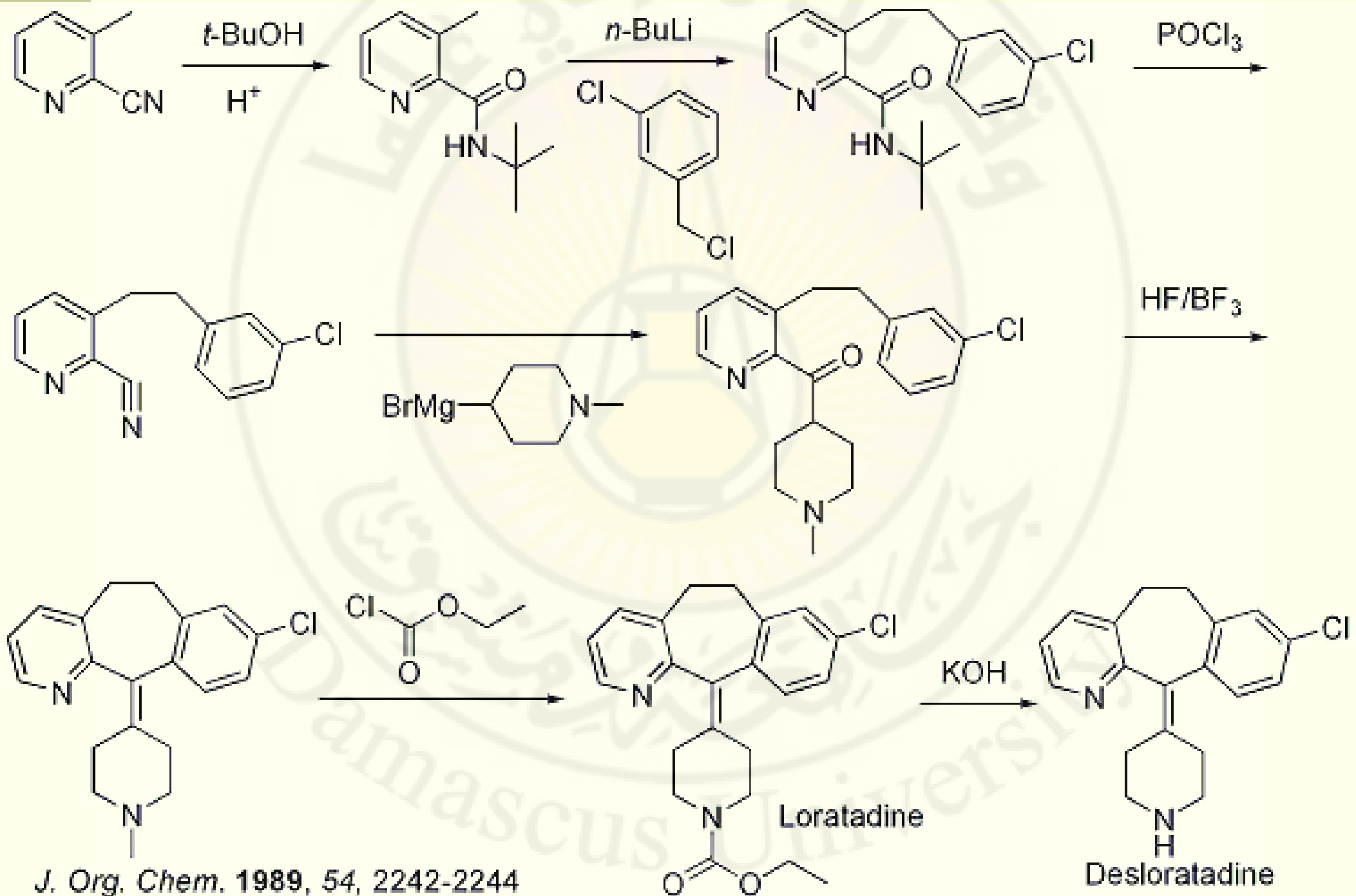


**30 Tablets
10 mg**

**LONG-ACTING,
NON-SEDATING
ANTIHISTAMINE**

*Trademark



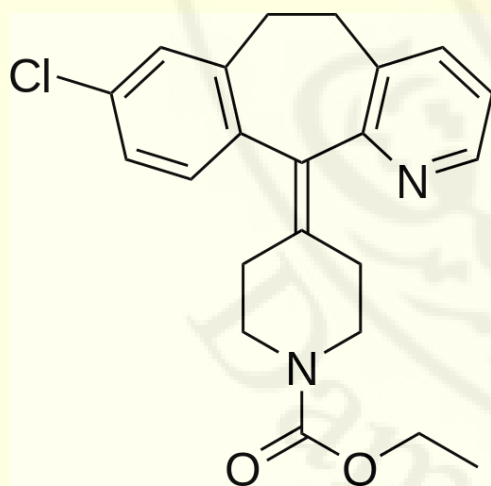


Second-Generation Antihistamines

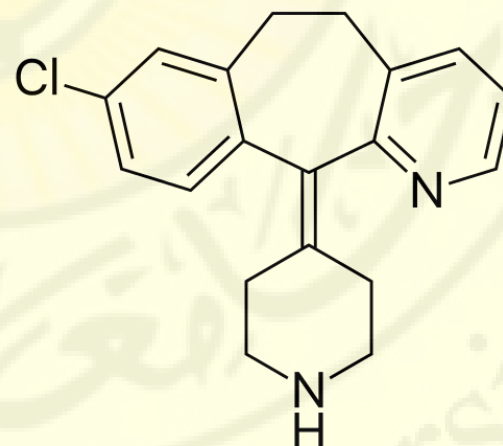
Desloratadine (Clarinex)

8-chloro-6,11-dihydro-11-(4-piperdinylidene)- 5H-benzo[5,6]cyclohepta[1,2-b]pyridine

- Desloratadine is a second-generation antihistamine of the Dibenzocycloheptanes Class of Antihistamines
- Desloratadine is an active metabolite of Loratadine



Loratadine



Desloratadine

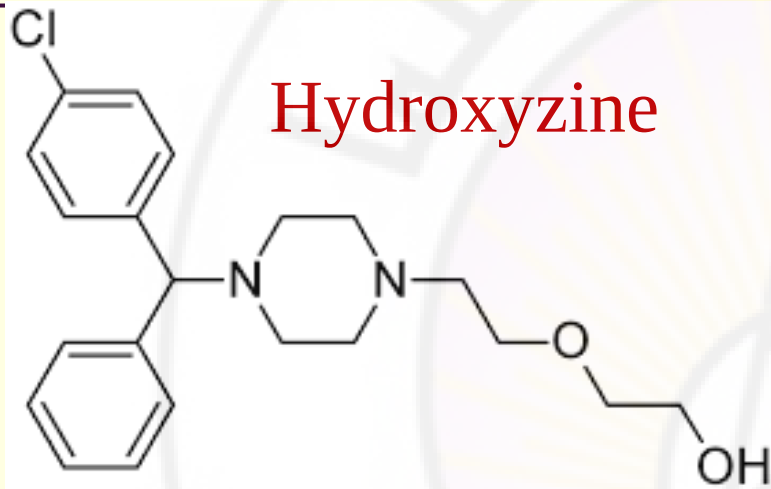
Second-Generation Antihistamines

Desloratadine (Clarinx)

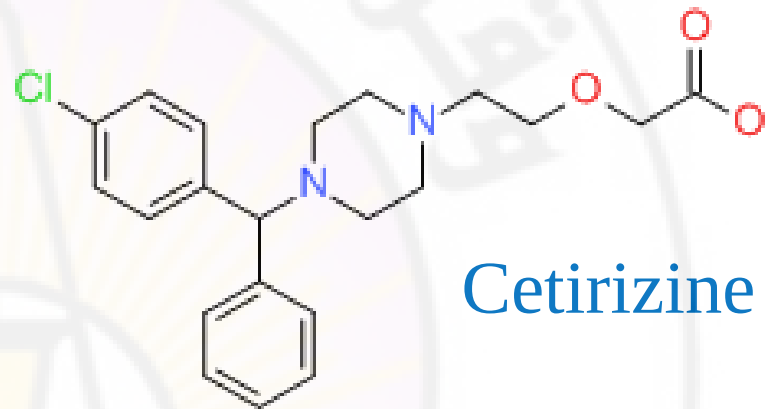
- ✓ **Desloratadine** is extensively metabolized to 3-hydroxydesloratadine, also an active metabolite
- ✓ Co administration of Desloratadine with **cytochrome P450** inhibitors results in no cardiac toxicity
- **Desloratadine** is indicated for
 - 1) the symptomatic relief of pruritus and
 - 2) reduction in the number and size of hives in chronic idiopathic urticaria patients
 - 3) to treat allergic rhinitis and nasal congestion
 - 4) To relief of the nasal and nonnasal symptoms of perennial allergic rhinitis and seasonal allergic rhinitis

Second-Generation Antihistamines

Cetirizine (Zyrtec)



Hydroxyzine

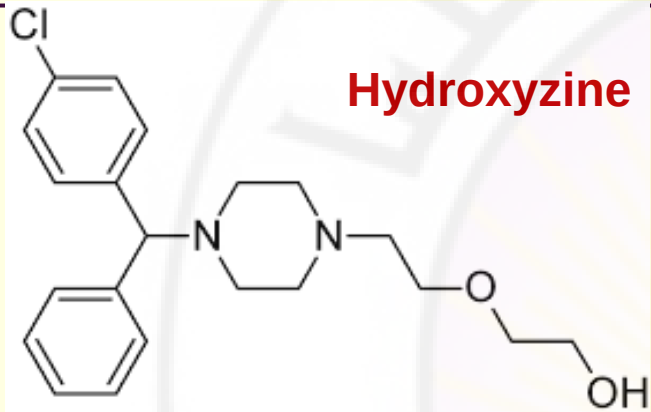


Cetirizine

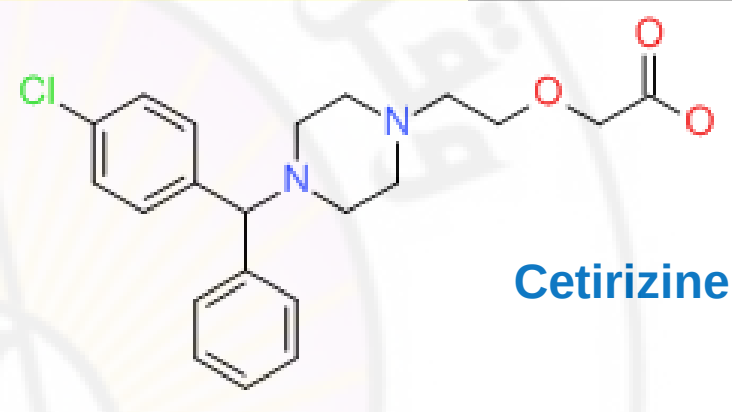
- [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid
- Cetirizine is a **Second-Generation Antihistamine** of the **Piperazine Class** of Antihistamines
- Cetirizine is the primary acid metabolite of **Hydroxyzine**
- It is a racemic selective H_1 receptor antagonist

Second-Generation Antihistamines

Cetirizine (Zyrtec)

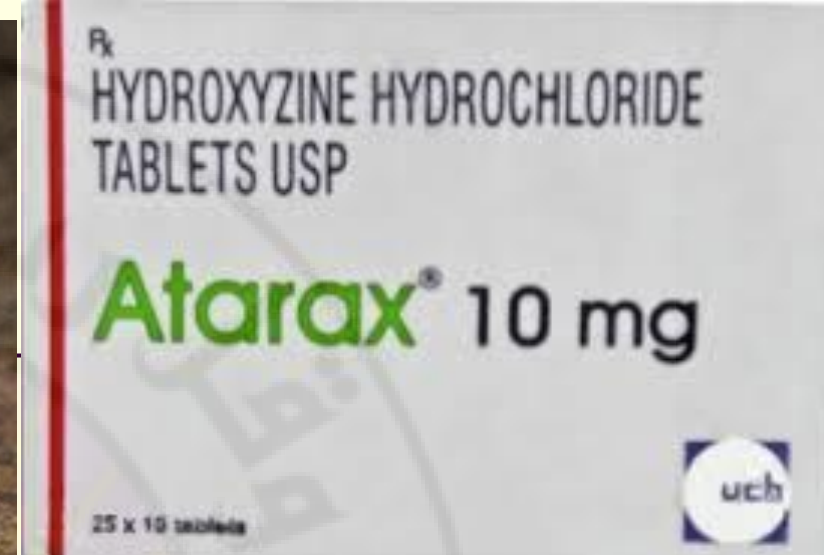
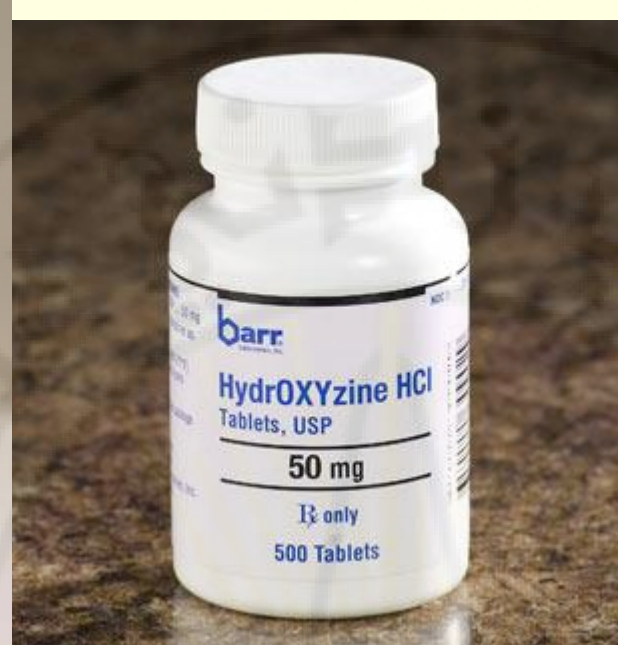


Hydroxyzine



Cetirizine

- **Cetirizine** is zwitterionic and relatively polar and thus does not penetrate or accumulate in the CNS
- ❖ The advantages of this compound appear to be its
 - 1) long action (once-daily dosing)
 - 2) rapid onset of activity
 - 3) minimal CNS effects
 - 4) lack of effects on cardiac rhythm



Second-Generation Antihistamines

Cetirizine (Zyrtec)

- The drug has been associated with dose-related **somnolence** (cetirizine may interfere with the performance of certain jobs or activities)
- Other effects of this drug include **fatigue**, **dry mouth**, **pharyngitis**, and **dizziness**
- **Cetirizine is indicated for**
 - ❖ runny nose, sneezing, itching of the nose or throat, and/or itchy
 - ❖ watery eyes caused by hay fever or other upper respiratory allergies

Cetirizine Hydrochloride
5 mg/5 ml Oral Solution
(as Cetirizine hydrochloride)



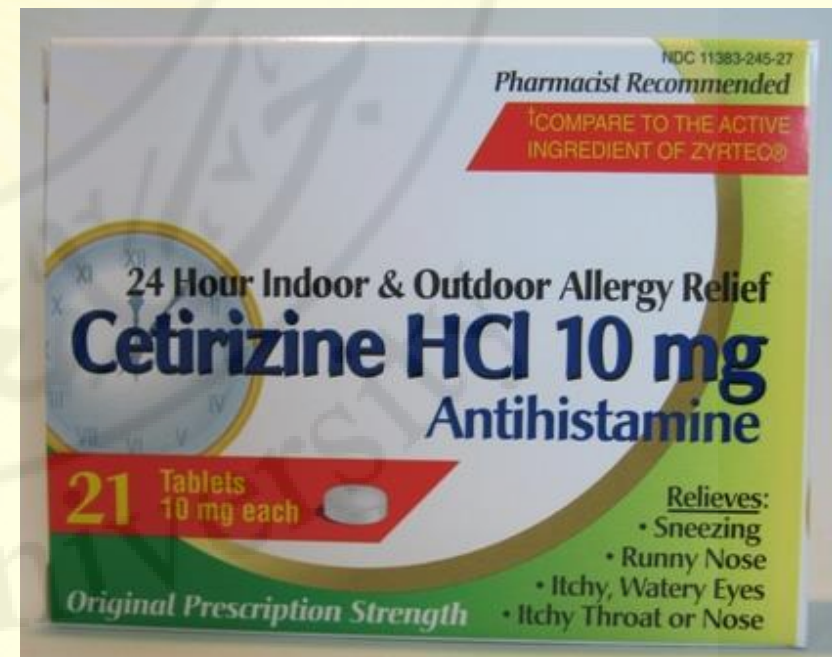
Once Daily Allergy Relief
Adults and children over 6 years

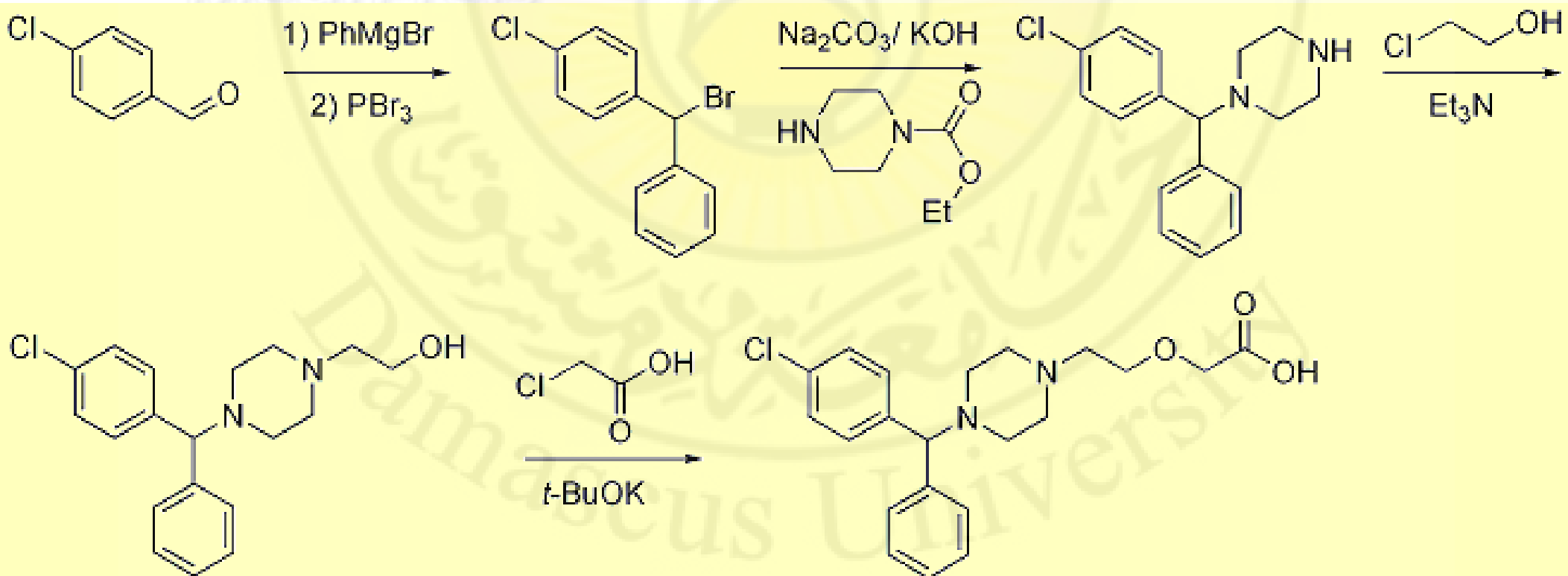
- Hayfever
- Pet allergy
- Dust allergy
- Skin allergy

Children 2 - 5 years

- Hayfever

200 ml

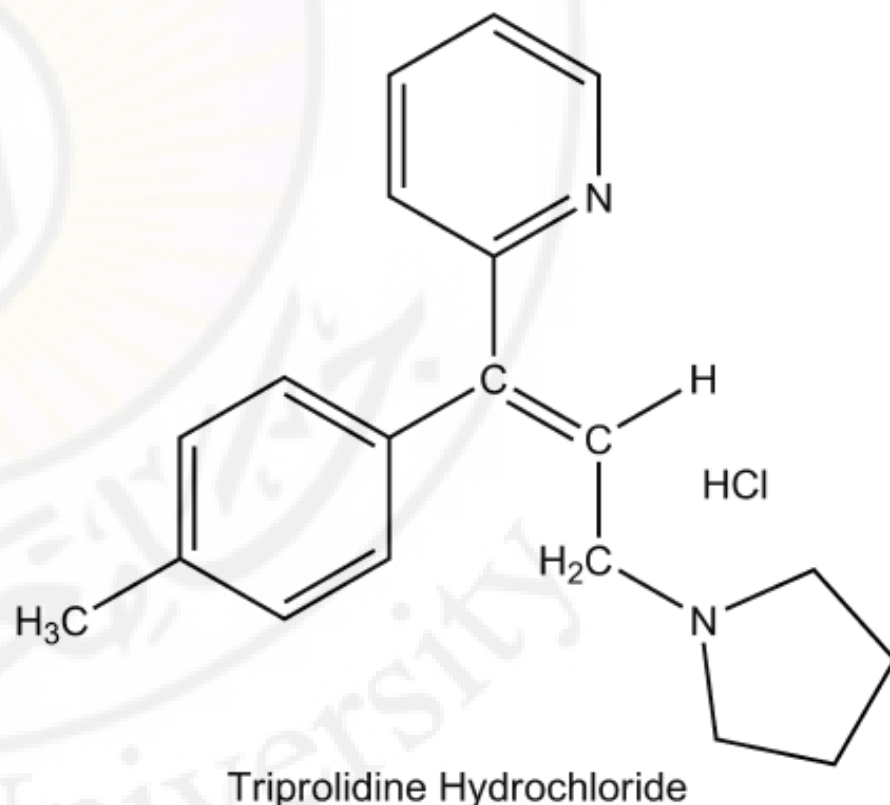
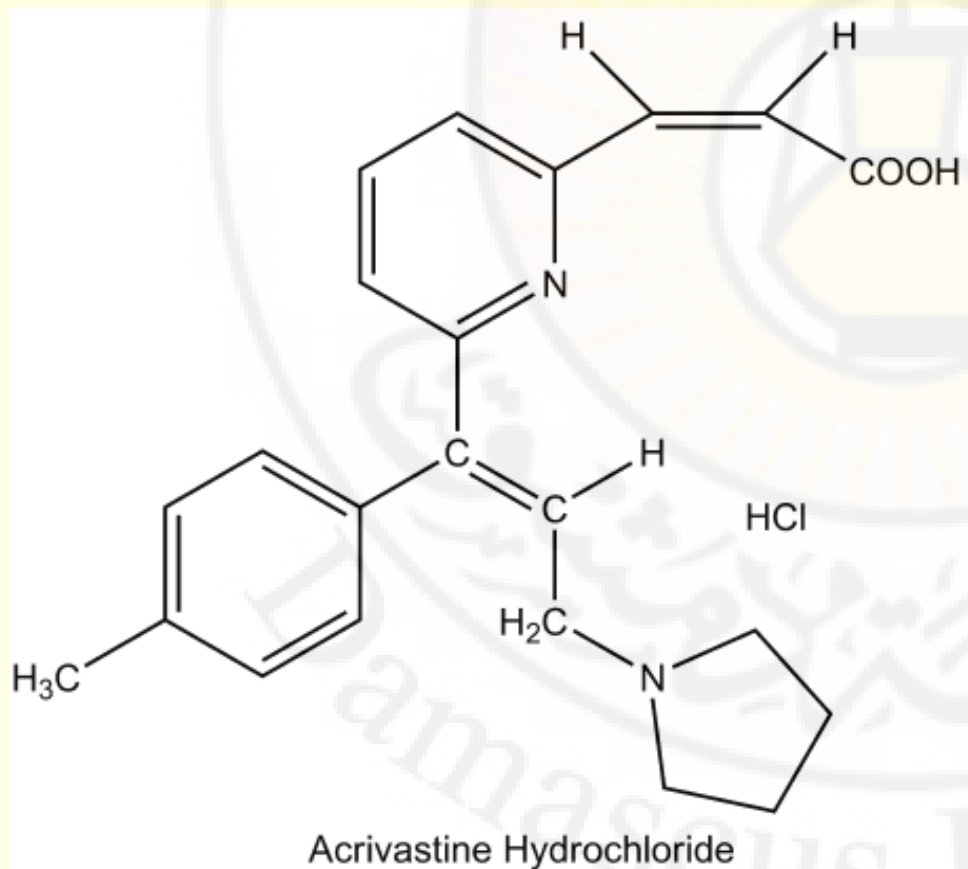




Second-Generation Antihistamines

Acrivastine (Semprex)

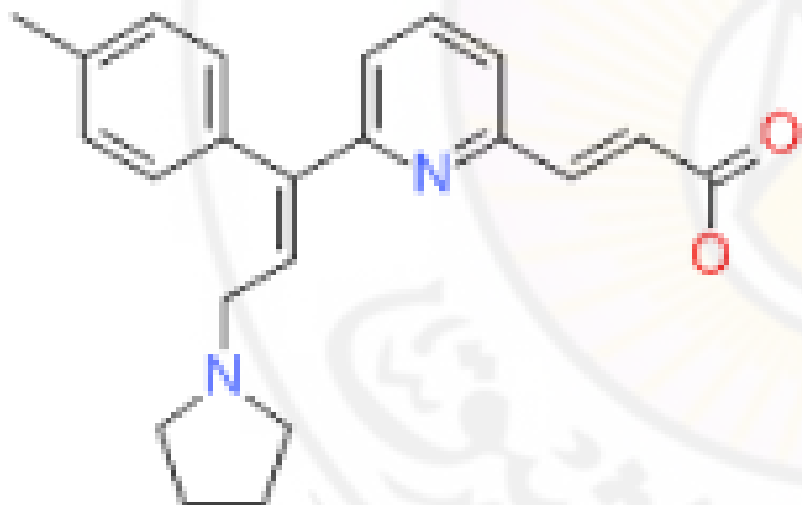
- **Acrivastine** is an analog of **Triprolidine** containing a carboxyethenyl moiety at the 6-position of the pyridyl ring



Second-Generation Antihistamines

Acrivastine (Semprex)

- Acrivastine is a fixed-combination product of the antihistamine Acrivastine (8 mg) with the decongestant pseudoephedrine (60 mg).



Second-Generation Antihistamines

Acrivastine (Semprex)

- Acrivastine shows antihistaminic potency and duration of action comparable to those of **Triprolidine**
- Unlike **Triprolidine**, acrivastine does not display significant anticholinergic activity at therapeutic concentrations.
- **Acrivastine** displays limits BBB accumulation because of the enhanced polarity of this compound resulting from carboxyethenyl
- this compound produces less sedation than **Triprolidine**
- **Dosage forms:** Tablets: various combination products
- **Usual adult dose:** Oral, 8mg 3 to 4 times a day