



ANTI HISTAMINES

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An Allergic Reaction

- **Early phase reaction:**

occurs within minutes of exposure to an allergen and lasts for 30-90 minutes

- **Late phase reaction:**

begins 4-8 hours later and can last for several days, often leading to chronic inflammatory disease

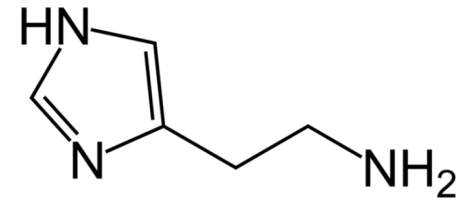
Common Allergens

- Tree Pollen and Grass
- Pet Danders
- Mold
- Dust Mites
- Foods

Symptoms

- Allergic Rhinitis
- Conjunctivitis
- Bronchoconstriction
- Urticaria
- Atopic Dermatitis
- Anaphylaxis

Histamine



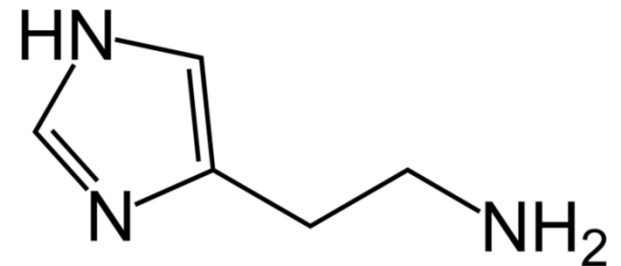
- One of the key mediators released from mast cells and basophils
- Histamine is an important chemical mediator of hypersensitivity
- Plays a major role in the pathophysiology of allergic diseases,
- Histamine exerts its effects through its interaction with one of four distinct receptors (H₁, H₂, H₃, H₄).

Histamine

- Signal involved in local immune response, also a neurotransmitter
- synthesized by the decarboxylation of histidine
- Either stored or quickly inactivated by histamine-N-methyltransferase and diamine oxidase
- Release of histamine from mast cells is stimulated by IgE antibodies which respond to foreign antigens in the body

Histamine Receptors

- **H1 histamine receptor**
 - Found on smooth muscle, endothelium, and central nervous system tissue
 - Activation results in vasodilatation, bronchoconstriction, smooth muscle activation
- **H2 histamine receptor**
 - Found on parietal cells
 - Regulates gastric acid secretion
- **H3 histamine receptor**
 - Found in the central nervous system
 - Regulates the release of other neurotransmitters
- **H4 histamine receptor**
 - Recently discovered in different parts of the body including organs of the digestive tract, basophils, and bone marrow cells



An Overview of Antihistamines

- **Antihistamine** historically refers to drugs that antagonize the actions of histamine at H₁ receptors.
- Block the binding of Histamine to its receptors
- Three generations of Antihistamines
 - Each generation improved on the previous one
 - Share general characteristics and properties

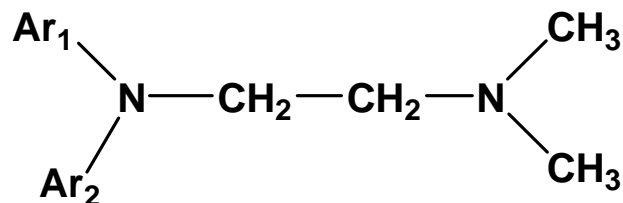
Classes of first generation H₁ receptor antagonist antihistamines

- Small, lipophilic molecules that could cross the BBB
- Not specific to the H₁ receptor
- Ethylenediamines
- Ethanolamines
- Alkylamines
- Piperazines
- Tricyclics



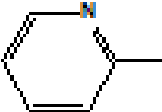
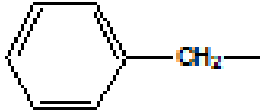
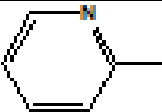

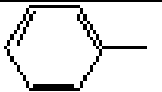
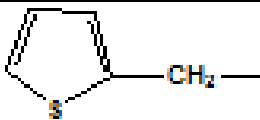
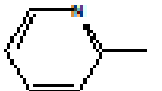
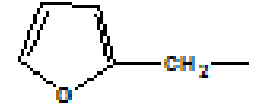
Common Structural Features

- 2 aromatic rings, connected to a central carbon, nitrogen, or oxygen
- Spacer between central atom and the amine, usually 2-3 carbons in length. (Can be linear, ring, branched, saturated or unsaturated)
- The amine is substituted with small alkyl groups
- Chirality at X increases potency of the drug
- For maximum potency, the two aromatic rings should be orientated in different planes

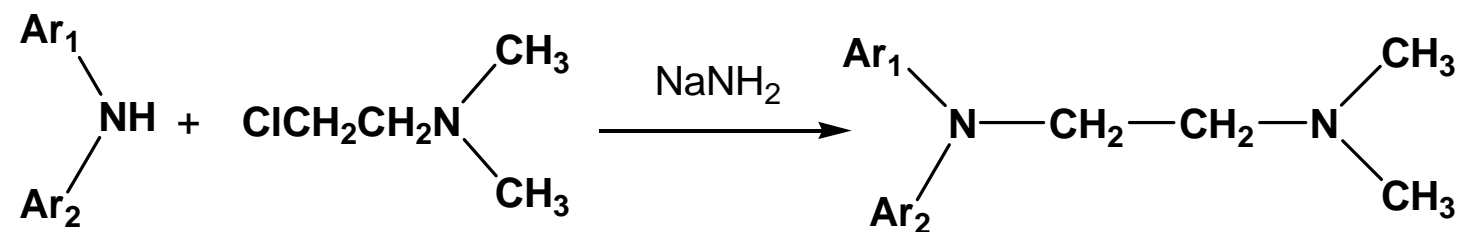
Ethylenediamines



These were the first group of clinically effective H₁-antihistamines

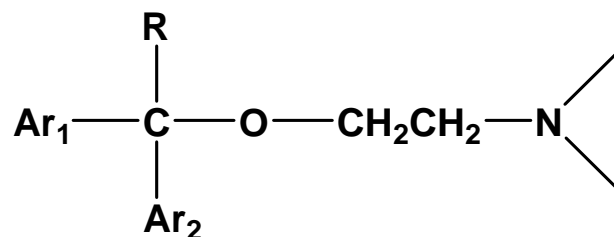
Compound	Ar ₁	Ar ₂
Phenbenzamine (N,N-dimethyl-N ¹ -benzyl-N ² -phenylethylenediamine)		
Triproleamine		
Mepyramine (Pyrilamine) (N,N-dimethyl-N ¹ -(4-methoxybenzyl)-N ² -(2-pyridyl)ethylenediamine)		
Metaphenylene (N,N-dimethyl-N ¹ -(2-thienylmethyl)-N ² -phenylethylenediamine)		
Metafurilene (N,N-dimethyl-N ¹ -(2-furilmethyl)-N ² -(2-pyridyl)ethylenediamine)		

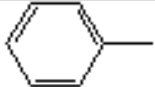

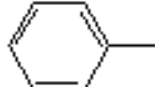
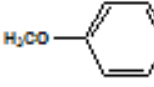
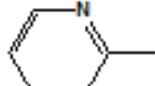
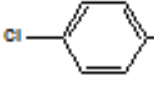
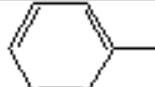
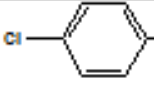
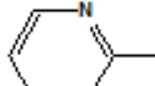

Synthesis



Ethanolamines

- This class has significant anticholinergic side effects and sedation, however reduced the gastrointestinal side effects

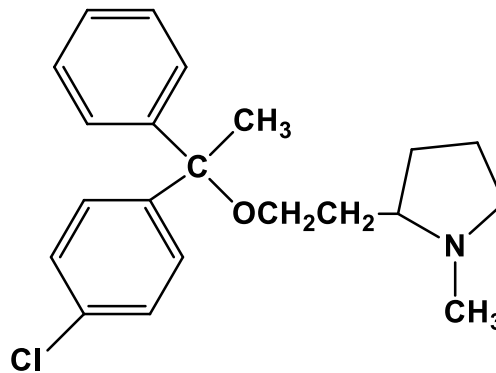


Compound	Ar ¹	Ar ²	R
Diphenhydramine (Benedryl) 2-(Diphenylmethoxy)-N,N-dimethylethanamine			H
Medrylamine 2-[(4-Methoxyphenyl)phenylmethoxy]-N,N-dimethylethanamine HCl			H
Carbinoxamine (Clistine) 2-[(4-chlorophenyl)-pyridin-2-yl-methoxy]-N,N-dimethyl-ethanamine			H
Chlorphenoxamine 2-[1-(4-chlorophenyl)-1-phenylethoxy]ethyl}dimethylamine			CH ₃
Doxylamine N,N-dimethyl-2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethanamine			CH ₃

Diphenhydramine (Benedryl)

- Oldest and most effective antihistamine on the market
- Available over the counter
- Because it induces sedation, it's used in nonprescription sleep aids such as Tylenol.

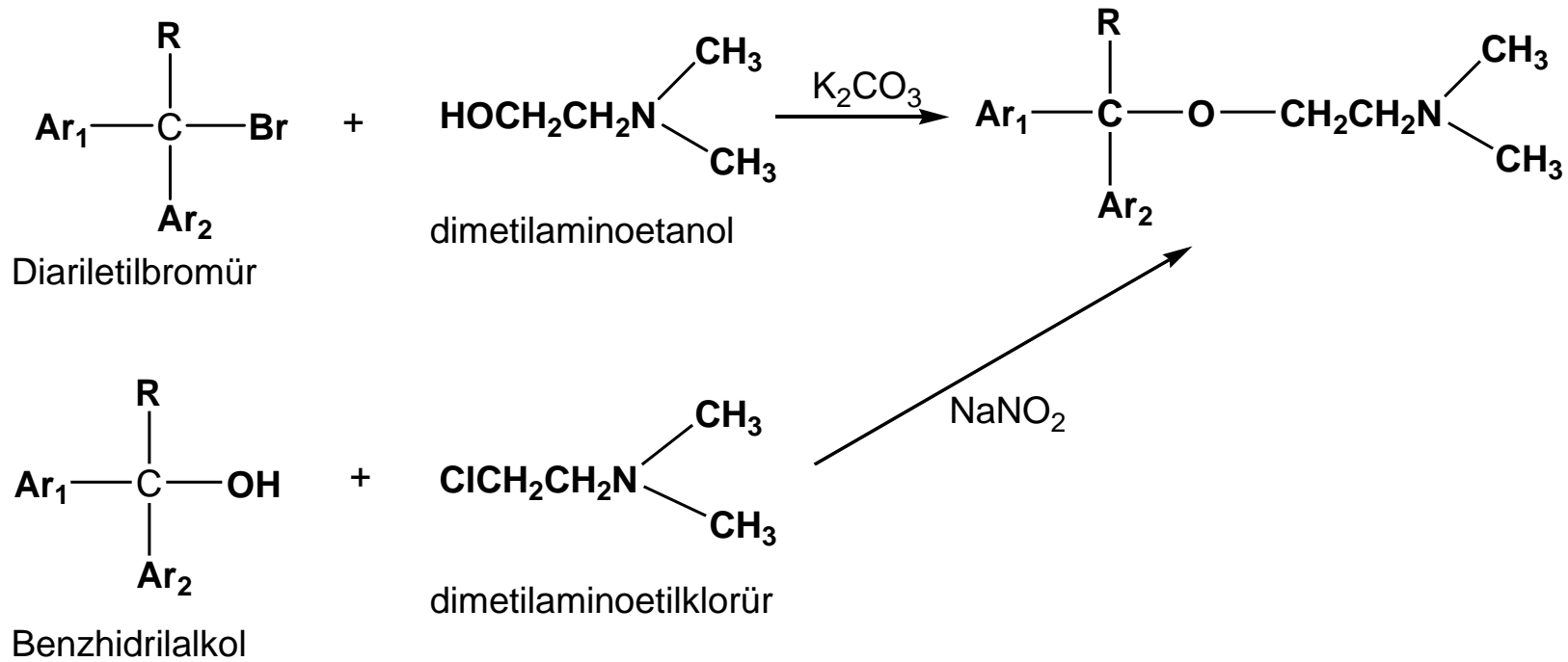
Clemastine (Tavist)



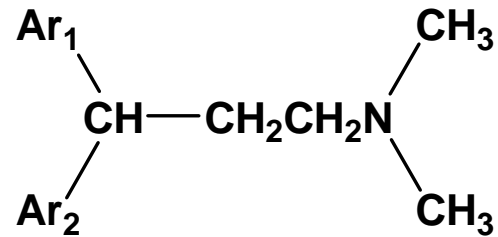
2-(2-(1-(4-chlorophenyl)-1-phenylethoxy)ethyl)-1-methylpyrrolidine

- Exhibits fewer side effects than most antihistamines
- Widely used as an antipruritic (stops itching)

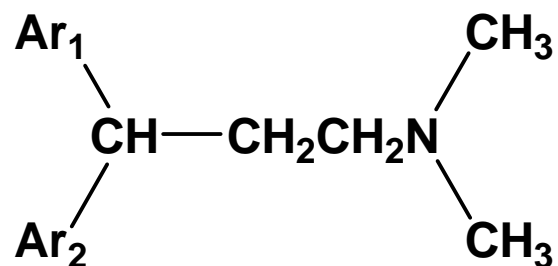
Synthesis

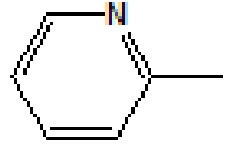
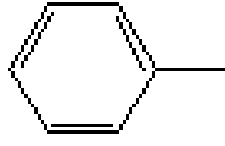
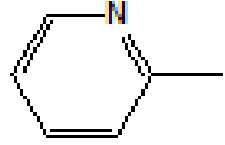
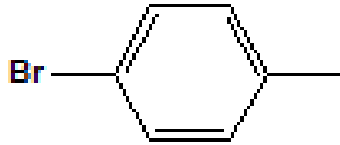
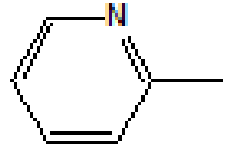
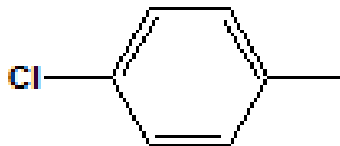


Alkylamines

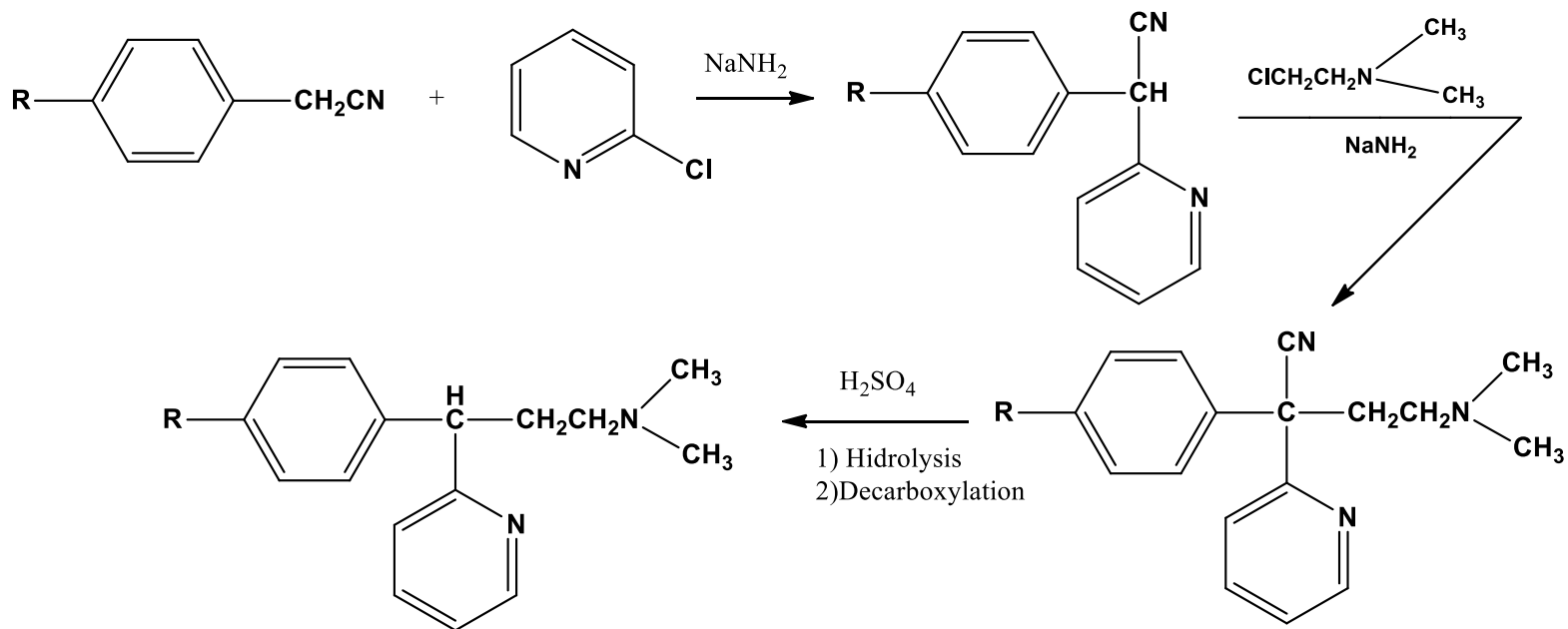


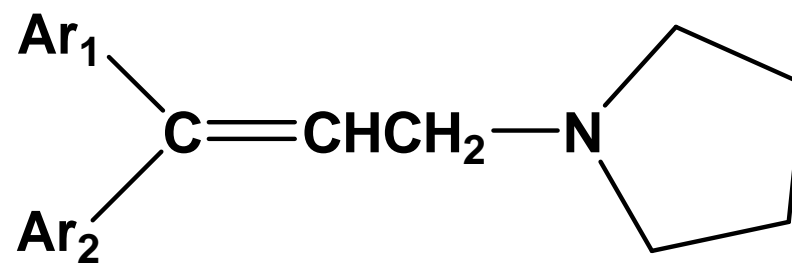
- Isomerism is an important factor in this class of drugs, which is due to the positioning and fit of the molecules in the H₁-receptor binding site
- These drugs have fewer sedative and GI adverse effects, but a greater incidence of CNS stimulation
- These drugs lack the “spacer molecule” (which is usually a nitrogen or oxygen) between the two aromatic rings
- At least one of the rings has nitrogen included in the aromatic system



Compound	Ar ₁	Ar ₂
Pheniramine (Avil) <i>N,N</i> -dimethyl-3-phenyl-3-pyridin-2-yl-propan-1-amine		
Brompheniramine (±) 3-(4-bromophenyl)- <i>N,N</i> -dimethyl-3-pyridin-2-yl-propan-1-amine		
Chlorpheniramine (±) 3-(4-chlorophenyl)- <i>N,N</i> -dimethyl-3-pyridin-2-yl-propan-1-amine		

Synthesis

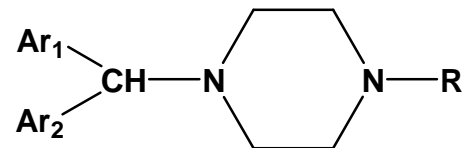




Compound	Ar ₁	Ar ₂
Pyrrambutamine 1-[(2 <i>E</i>)-4-(4-chlorophenyl)-3-phenylbut-2-en-1-yl]pyrrolidine		
Triprolidine 2-[(<i>E</i>)-1-(4-methylphenyl)-3-pyrrolidin-1-yl-prop-1-enyl]pyridine		

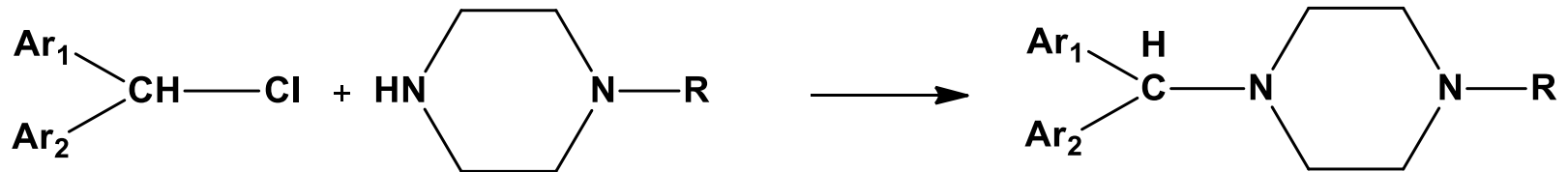
Piperazines

- Structurally related to the ethylenediamines and the ethanolamines and thus produce significant anti-cholinergic effects
- Used most often to treat motion sickness, vertigo, nausea and vomiting



Compound	Ar ₁	Ar ₂	R
Cyclizine 1-difenilmetil-4-metilpiperazin			-CH ₃
Meclizine 1-[(4-chlorophenyl)(phenyl)methyl]-4-(3-methylbenzyl)piperazine			
Bucizine 1-[(4-chlorophenyl)-phenyl-methyl]-4-[(4-tert-butylphenyl)methyl]piperazine			
Cinnarizine 1-benzhydryl-4-cinnamyl-piperazine			
Hydroxyzine 2-(2-{4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl}ethoxy)ethanol			HO-CH ₂ CH ₂ -O-CH ₂ CH ₂ -

Synthesis



Meclizine;

- It is most commonly used to inhibit nausea and vomiting as well as vertigo, however it does cause drowsiness

•Cyclizine;

- Nausea, vomiting and dizziness associated with motion sickness, vertigo and post-operatively following administration of general anaesthesia and opioids

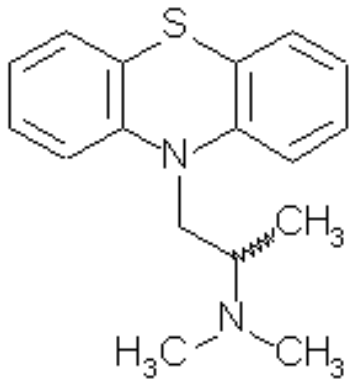
Hydrozine;

- In addition to treating itches and irritations, its an antiemetic, a weak analgesic and an anxiolytic (treat anxiety)

Tricyclics

- These drugs are structurally related to tricyclic antidepressants, which explains why they have cholinergic side effects

Promethazine (Phenegan)

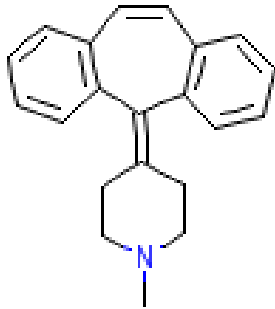


- This drug has extremely strong anticholinergic and sedative effects
- It was originally used as an antipsychotic, however now it is most commonly used as a sedative or anti-nausea drug (also severe morning sickness) and requires a prescription

10-(2-N,N-dimethylamino)propylphenothiazin

Tricyclics

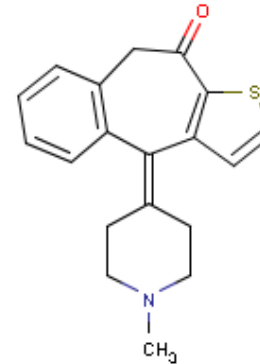
Cyproheptadine



5-(1-metil-4-piperidiniliden)-5H-dibenzo[a,d]siklohepten

- This drug both an antihistamine and an antiserotonergic agent
- It is a 5-HT₂ receptor antagonist and also blocks calcium channels
- Used to treat hay fever and also to stimulate appetite in people with anorexia

Ketotifen (Zaditor)

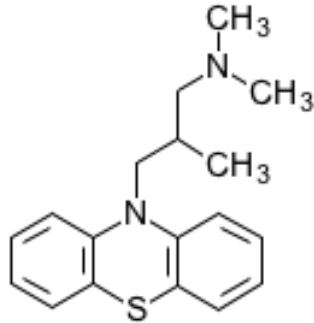


4,9-Dihidro-4-(1-metil-4-piperidiniliden)-10H-benzo[4,5]siklohepta[1,2-b]tiyofen-10-on

- This drug is available in two forms: an ophthalmic form used to treat allergic conjunctivitis or itchy red eyes and an oral form used to prevent asthma attacks
- It has several adverse side effects including drowsiness, weight gain, dry mouth, irritability and increased nosebleeds

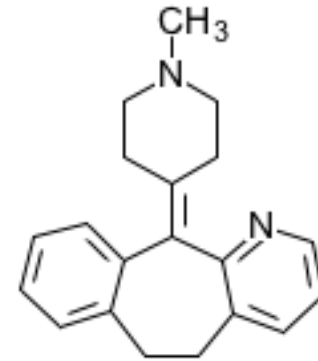
Tricyclics

Alimemazine (Vallergan)



- This drug is used to treat itchiness and hives that results from allergies
- Since it causes drowsiness, it is useful for rashes that itch worse at night time
- It is also used to sedate young children before operations

Azatadine (Optimine or Trinalin)

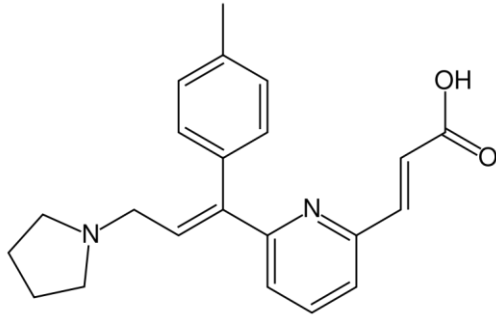


- This drug is used to treat symptoms of allergies and the common cold such as sneezing, runny nose, itchy watery eyes, itching, hives and rashes

Second generation H₁-receptor antagonists

- These are the newer drugs and they are much more selective for the peripheral H₁-receptors involved in allergies as opposed to the H₁-receptors in the CNS
- Therefore, these drugs provide the same relief with many fewer adverse side effects
- The structure of these drugs varies and there are no common structural features associated with them
- They are however bulkier and less lipophilic than the first generation drugs, therefore they do not cross the BBB as readily
- Recent studies have also showed that these drugs also have anti-inflammatory activity and therefore, would be helpful in the management of inflammation in allergic airways disease.

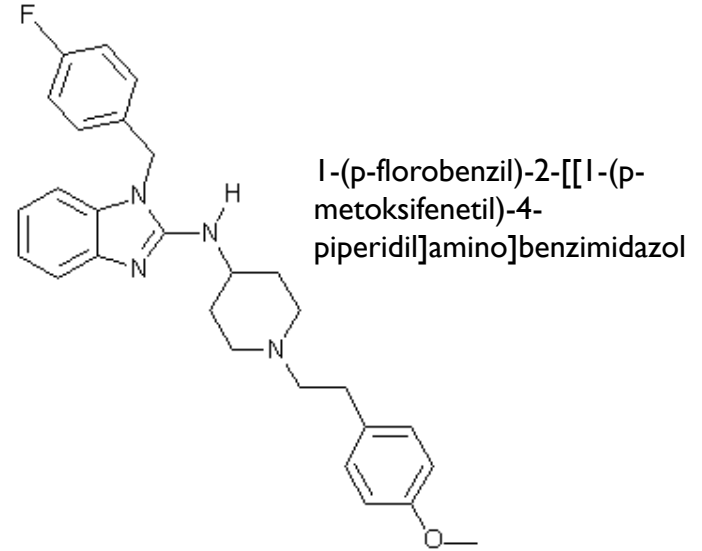
Acrivastine (Semprex-D)



- This drug relieves itchy rashes and hives
- It is non-sedating because it does not cross the BBB

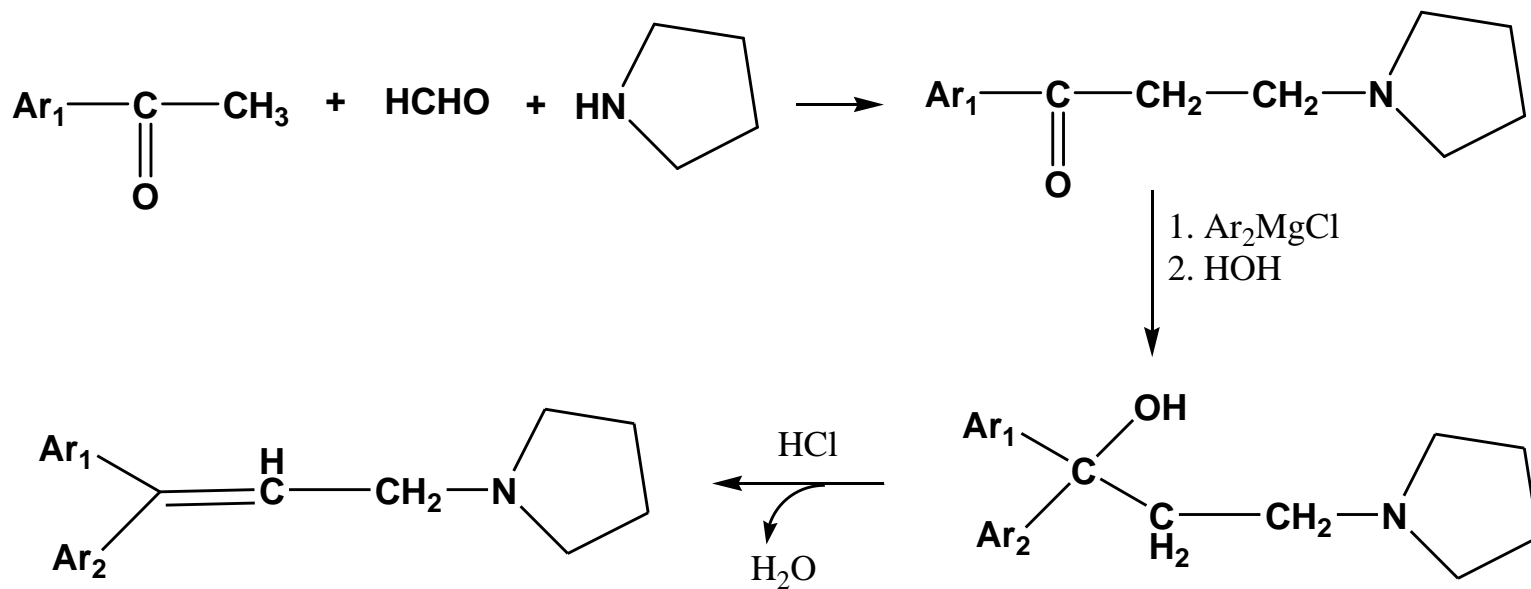
The activity of E-isomer is great higher than that of Z-isomer.

Astemizole (Hismantol)

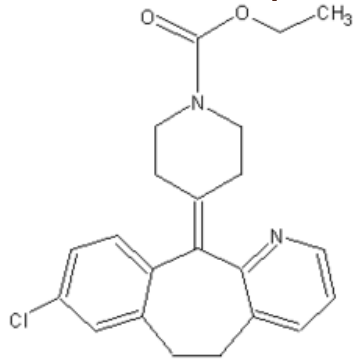


- This drug has a long duration of action
- It suppresses the formation of edema and pruritus
- It doesn't cross the BBB
- It has been taken off the market in most countries because of adverse interactions with erythromycin and grapefruit juice

Synthesis of Acrivastine



Loratadine (Claritin)

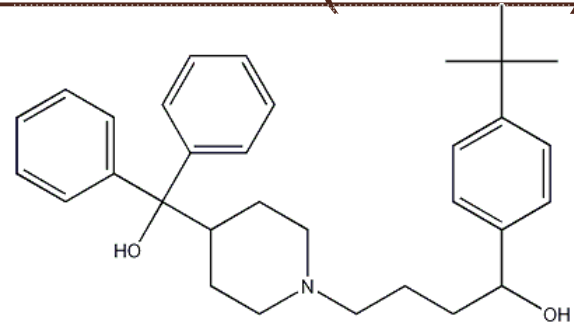


4-(8-kloro-5,6-dihidro-11H-benzo[5,6]silohepta[1,2-b]piridin-11-iliden)-1-piperidinkarboksilik asit etil ester

Strong selective H₁ receptor antagonist, but no anticholinergic activity and central nerve system inhibition,

- It has long lasting effects and does not cause drowsiness because it does not cross the BBB

Terfenadine (Seldane)

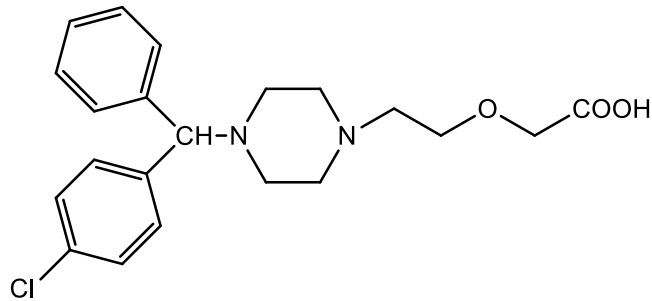


1-(4-Tert-butilfenil)-4-[4-(hidroksidifenilmetil)-1-piperidil]butan-1-ol

- It was formerly used to treat allergic conditions

- In the 1990's it was removed from the market due to the increased risk of cardiac arrhythmias

- **Cetirizine**
- This drug treats indoor and outdoor allergies and is safe to use in children as young as 2

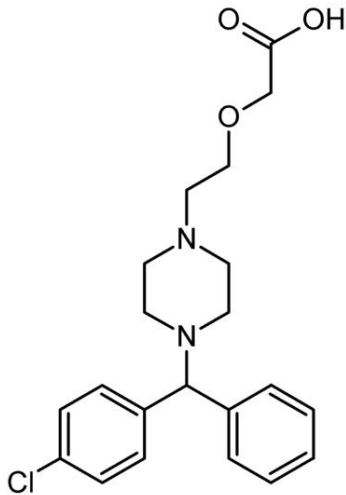


2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)acetic acid

Third generation H₁-receptor antagonists

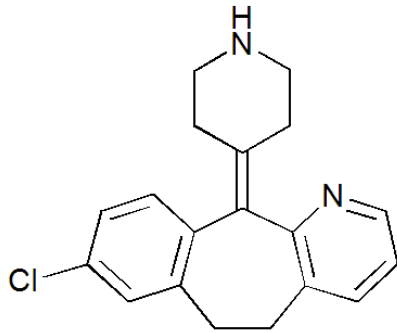
- These drugs are derived from second generation antihistamines
- They are either the active enantiomer or metabolite of the second generation drug designed to have increased efficacy and fewer side effects

Levocetirizine (Zyral)



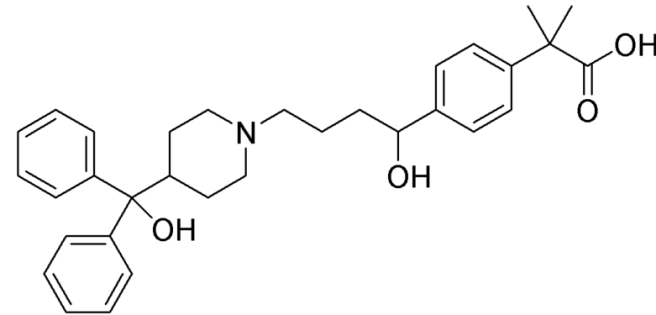
- This drug is the active enantiomer of cetirizine and is believed to be more effective and have fewer adverse side effects.
- It does not cross the BBB and does not cause significant drowsiness
- It has been shown to reduce asthma attacks by 70% in children

Deslortadine (Clarinet)



- It is the active metabolite of Loratadine
- Even though it is thought to be more effective, there is no concrete evidence to prove this

Fexofenadine (Allegra)



- It was developed as an alternative to Terfenadine
- Fexofenadine was proven to be more effective and safe

Side Effects

- **First Generation Drugs:**
 - Anticholinergic CNS interactions
 - Gastrointestinal reactions
 - Common side effects: sedation, dizziness, tinnitus, blurred vision, euphoria, lack of coordination, anxiety, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough
- **Second Generation Drugs:**
 - Common side effects: drowsiness, fatigue, headache, nausea and dry mouth
- Side effects are far less common in Second Generation drugs