CLASSIC ANTIHISTAMINE STRUCTURE-ACTIVITY RELATIONSHIP SUMMARIES

PROPYLAMINE (ALKYLAMINE) ANTIHISTAMINES

 Pheniramine Maleate

 Brompheniramine Maleate Dextrobrompheniramine Maleate

 Chlorpheniramine Maleate Dextrochlorpheniramine Maleate

"Pheniramines"

 PYRROBUTAMINE PHOSPHATE

 TRIPROLIDINE HYDROCHLORIDE

 ACRIVASTINE

"Propenylpyrrolidines"

 DIMETHINDENE MALEATE

 PHENINDAMINE TARTRATE

PROPERTIES OF THE PROPYLAMINES

- Sub-classified based on connecting atom (sp3 or sp2), terminal amino group and connecting chain
- "Pheniramines" have aromatic and pyridine ring and thus are chiral. S-isomer are active
  * "Para-substituted pheniramines have superior histamine receptor affinity.
- Propenylpyrrolidines" active in the "cis" configurations
- Generally among the "most potent" first generation antihistamines: Dosage: 2.5-4 mg
- Sedation: Less than ethanolamines, ethylendiamines
- Anti-Muscarinic Activity: Moderate
- Anti-Emetic Activity: Very Low
- Relatively low affinity for other NT receptors (adrenergic, 5-HT, DA, etc)
- Relatively low GI side effects (compared to ethylendiamine antihistamines)
- Metabolism mainly by successive oxidation N-dealkylation, followed by aldehyde oxidation and conjugation (glycine) of the resultant acid.
**ETHANOLAMINE (AMINOALKYL ETHER) ANTIHISTAMINES**

![General Structure](image)

- **DIPHENHYDRAMINE HCl**
- **DIMENHYDRINATE** (Xanthine salt)
- **CARBINOXAMINE MALEATE**
- **BROMODIPHENHYDRAMINE HCl**
- **DOXYLAMINE SUCCINATE**
- **CLEMASTINE FUMARATE**
  (not a "true" ethanolamine)
- **DIPHENYLPYRALINE HCl**
  (not a "true" ethanolamine)

**PROPERTIES OF THE ETHANOLAMINES**

- All have connecting group of CHO and two carbon connecting chain except diphenylpyraline and clemastine
- All are dimethylamino derivatives except diphenylpyraline (Piperidine) and clemastine (pyrrolidine)
- "Para"-halo-substituted diphenhydramines have superior therapeutic efficacy to diphenhydramine
- Pyridyl derivatives (carbinoxamine, doxylamine) have enhanced antihistaminic activity relative to diphenhydramine
- Chiral derivatives: bromodiphenhydramine, carbinoxamine, doxylamine, clemastine; S > R
- Overall antihistaminic Activity: High (Clemastine) to moderate (Carbinoxamine) to low (Diphenhydramine)
- **Sedation Potential**: Moderate to high: Penetration to CNS (lipophilic) and binding to H-1 receptor
- **Anti-Emetic Activity**: Moderate to High (Dimenhydrinate)
- **Anti-Muscarinic Actions**: High to due high affinity for muscarinic receptors
- Relatively low affinity for other NT receptors (adrenergic, 5-HT, DA, etc)
- Relatively low GI side effects (compared to ethylenediamine antihistamines)
- Metabolized by N-oxidation, successive N-dealkylation to aldehydes followed by oxidation to the acid and glycine conjugation of the acid
ETHYLENEDIAMINE ANTIHISTAMINES

**General Structure**

- **PYRILAMINE MALEATE**
- **METHAPYRILENE HCl**
- **TRIPLENNAMINE (CITRATE OR HCl)**
- **THONZYLAMINE HCl**
- **ANTAZOLINE PHOSPHATE** (not a "true" ethylenediamine)

**PROPERTIES OF THE ETHYLENEDIAMINES:**
- All have connecting group of N and two carbon connecting chain.
  - Less basic nitrogen due to electron delocalization
- All have at least one heterocyclic aryl ring (pyridyl or pyrimidine) which enhances activity
- "Para"-sunstituents (pyrilamine, etc) enhance antihistaminic activity
- No chirality in these compounds
- Lower antihistaminic potency than the ethanolamines (doses of 25-50 mg)
- Sedation Potential: Relatively low to moderate (more polar, less CNS distribution and lower H-1 affinity)
- Anti-Muscarinic Activity: Lower affinity for MACHRs, thus lower anticholinergic activity than ethanolamine
- Anti-emetic activity: Low
- Relatively low affinity for other NT receptors (adrenergic, 5-HT, DA, etc)
- Relatively HIGH incidence of GI side effects (compared to ethanolamine antihistamines)
- Metabolized by N-glucuronidation, N-oxidation and pyridyl oxidation followed by phenol glucuronidation
**PROPERTIES OF THE PIPERAZINES**

- All have connecting group of CHN and the N is part of the piperazine ring
- Can be considered "cyclic" ethylenediamine derivatives; terminal N and connecting chain are part of the ring
- Contain either N-methyl, N-aralkyl or N-oxyalkyl piperazine substituents.
- All have two aromatic aryl moieties, and most have a p-Cl substituent. Thus most are chiral
- **Antihistaminic Potency:** Moderate to High: Piperazine N-substituents enhance histamine receptor affinity
- Slow onset, but long duration of action (high receptor affinity)
- **Sedation:** Moderate due to CNS distribution and H-1 receptor affinity
- **Anti-Muscarinic Activity:** Moderate
- **Anti-Emetic Action:** Moderate-High (Motion Sickness use)
- Relatively low affinity for other NT receptors (adrenergic, 5-HT, DA, etc)
- Metabolized by N-glucuronidation, N-oxidation and oxidative N-dealkylation
- OND metabolism to norcyclizines has been linked to teratogenic activity of these compounds
PHENOTHIAZINE ANTIHISTAMINES

General Structure

PROMETHAZINE HCl

TRIMEPRAZINE TARTRATE

METHDILAZINE HCl

PROPERTIES OF THE PHENOTHIAZINES

- All are "tricyclic" derivatives, but the aryl rings are not coplanar
- All are dimethylamino derivatives except Methdilazine (pyrrolidine with side chain)
- Differ from Phenothiazine DA antagonists in the length of the connecting chain, the branching in the side chain, and the lack of aromatic ring substituents: Very low DA receptor affinity
- Chirality in connecting chain: Enantiomers appear to be equipotent
- Antihistaminic Potency: Moderate to high: Doses Trimepraznie>Methdilazine>Promethazine
- Relatively long action, especially Promethazine
- Sedation: Low (Methdilazine) to High (Promethazine)
- Anti-Muscarinic: High
- Anti-Emetic: Very high (Utility in motion sickness, etc)
- Relatively low affinity for other NT receptors (adrenergic, 5-HT, DA, etc)
- Relatively low GI side effects (compared to ethylenediamine antihistamines)
- Metabolized by successive N-dealkylation (like other antihistamines), S-oxidation, aromatic ring oxi and N-oxidation.
**DIBENZOCYCLOHEPTENES/HEPTANE ANTIHISTAMINES**

**General Structure**

- All are "tricyclic" derivatives, but the aryl rings are not coplanar
- Similar to the phenothiazines with a C-C fragment in place of the S and C=C in place of N.
- All are methylpiperideinyl compounds.
- Azatadine is the pyridinyl biosostere of cyproheptadine with a partially saturated central ring
- **Antihistaminic Potency**: Relatively high (Doses of 1-4 mg)
- **Sedation Potential**: Low (cuproheptadine) to moderate (azatadine)
- **Antimuscarinic Activity**: Moderate
- **Anti-Emetic Activity**: Low
- **High 5-HT receptor Antagonoist activity**

**CYPROHEPTADINE HCl**  
(DIBENZOCYCLOHEPTENE)

**AZATADINE MALEATE**  
(DIBENZOCYCLOHEPTANE)
NON-SEDATING ANTIHISTAMINE SAR RELATIONSHIP SUMMARIES

General Properties:
- General Pharmacophore: Diaryl-X-Piperidine/Piperazine-N-Aralkyl/Polar Group
  - Diaryl-X-Piperidine-N-Aralkyls: Terfenadine, Fexofenadine, Astemizole
  - Diaryl-X-Piperazine-N-Polar Group: Loratadine
  - Diaryl-X-Piperazine-N-Polar group: Cetirizine
- Relatively high H-1 receptor affinity: contributes to long duration
- Relatively high H-1 receptor Selectivity: N-Aralkyl/Polar results in decreased affinity for muscarinic, adrenergic and serotonergic receptors
- Low Sedation due to low CNS penetration (?), lower affinity for central H-1 receptors (?) and high selectivity for H-1 versus other receptors.
- Life-threatening arrhythmias with terfenadine and astemizole: Drug interactions between drugs that inhibit astemizole and terfenadine metabolism (imidazole antifungals, macrolide antibiotics, etc).

- Terfenadine: R = CH₃
  - Reduced butyrophenone derivatives (antipsychotic)
  - Terfenadine (base)/Fexofenadine (Amphoteric)
  - Terfenadine CV toxicity: Drug Interactions!
  - Fexofenadine: active metabolite of terfenadine
  - High H-1 affinity and selectivity (see notes)
  - Long duration due to high receptor affinity, active metabolites and biliary+renal elimination
  - Fexofenadine not metabolized!

- Fexofenadine: R=COOH
- Analog of dibenzocycloheptene H-1 blocker
- High H-1 affinity and selectivity (see notes)
- Some anti-5HT activity
- Long duration due to high receptor affinity, active metabolite and biliary+renal elimination
- Metabolized by hydrolysis to active metabolite

- Astemizole
  - Diaryl-X-Piperidine-aralkyl derivative
  - Astemizole CV toxicity: Drug Interactions!
  - High H-1 affinity and selectivity (see notes)
  - Long duration due to high receptor affinity, active metabolites and biliary+renal elimination
  - Astemizole metabolized by AH and OND.
  - The desmethyl metabolite from OND is active and has a long half-life

- Loratadine

- Cetirizine
  - Diaryl-X-Piperazine: Acid metabolite of hydroxyzine
  - High H-1 affinity and selectivity (see notes)
  - Long duration due to high receptor affinity and biliary+renal elimination
  - Not significantly metabolized