Histamine Receptors

- $H_1$, $H_2$ and $H_3$ and most recently $H_4$
- G protein-coupled receptor
- Activation of $H_1$ cause contraction of smooth muscles in gut, the uterus, and the bronchi. Contraction of the bronchi leads to asthma.
- Stimulation of $H_1$ receptors on smooth muscles in fine blood vessels cause muscle relaxation, and the resulting vasodilatation may result in severe fall in blood pressure.
- In CNS, $H_1$ and $H_2$ receptors predominantly localized on postsynaptic membranes.
- $H_3$ receptors appear to function predominantly as presynaptic receptors, possibly as histamine autoreceptors and also been detected in some peripheral organs.
- $H_4$ receptor exhibits very restricted locations in intestinal tissue, spleen and immune active cells, e.g., T-cells, suggesting a therapeutic potential of $H_4$-blocker in allergic and inflammatory diseases.
About 80% of histamine monocation exists in aqueous solution that binds receptors.

The τ tautomer (H on the τ nitrogen) permits binding with the receptors. However, tautomerism does not appear to be important in H₁ binding but does appear to be important in the H₂ interaction.

Electron donating groups on C₅ increase the τ tautomer while electron withdrawers increase the π tautomer fraction.
The *trans* conformer has less steric hindrance but the *gauche* conformer is stabilized by an ion–dipole interaction.

Both conformers exist in solution.

It is believed that both the $H_1$ and $H_2$ receptors bind the *trans* conformer.

This is based on the observation that $\alpha$– and $\beta$–methyl histamine are unable to assume the *trans* conformation and are weak agonists at both the $H_1$ and $H_2$ receptors. However, they are strong $H_3$ agonists, thus the $H_3$ receptor must bind Histamine in the *gauche* conformation.
Histamine Agonist SARs

1. Side chain N–methyl and dimethyl are active but weaker. Larger alkyls are not well tolerated. The activity decreases in the order NH₂ > NHMe > NMe₂ > N⁺Me₃

2. Branching the side chain decreases potency, optical isomers are equipotent

3. Ring modifications produce variable activities. For example:
   a) 1-Methyl derivatives are inactive
   b) 2-methyl substitution makes H₁ selective
   c) 3-Methyl derivatives are very weak at H₁ & H₂
   d) 4-Substitution causes H₂ selective, electron withdrawer favor τ tautomer
   e) 5-Substitution causes H₂ selective where electron donor favor τ tautomer
An anionic center to provide the initial interaction and to bind with the protonated amine (Asp107); the area surrounding the ionic site is small or nonexistent compared to the Muscarinic receptor, for N–methyls decrease potency.

Next is a flat region probably another aromatic ring on an amino acid residue to interact with the imidazole ring (Asn207 possibly interacting with the Nτ-nitrogen of imidazole ring).

Lys200 interacts with the nucleophilic Nπ-nitrogen.

Between the two there is no stereoselectivity, no chirality.
Histamine H\textsubscript{1}-Antagonists

1st Generation

- Classic drugs generally introduced prior to 1960 although some recent additions would fit here. Most of these drugs have **sedating** effects. Generally they have high LWPC and thus get into the CNS.

2nd Generation

- Modern antihistamines generally introduced since 1980 fall into this category. They are **nonsedating**. They also possess less anticholinergic and antiadrenergic effects due to chemical differences that also lead to low LWPC and, thus, less CNS side effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>P Value</th>
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<tr>
<td>Mepyramine</td>
<td>700</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>2500</td>
</tr>
<tr>
<td>Triprolidine</td>
<td>300</td>
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<tr>
<td>Cimetidine</td>
<td>2.5</td>
</tr>
<tr>
<td>Histamine</td>
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From Verderame, *Handbook of Autonomic Drugs and Autocoids*, 1986
The initial discovery of a Histamine antagonist was in 1933 by Fourneau and Bovet. Most of the progress was a result of isosteric modifications. This resulted in the classical $H_1$ antagonists being structurally very similar.
General Structure

\[
\text{Ar}_1 \text{X-C-C-N} \text{Ar}_2 \text{R}_1 \text{R}_2
\]

- A protonatable amine
- A connecting atom \( X \) which can be O, C or N
- A carbon chain, usually ethyl
- Variations in the diaryl groups, connecting moiety, substituents on the connecting moiety, and substituents on the terminal nitrogen account for the differences observed in potency as well as pharmacologic, metabolic, and adverse reaction profiles.
**SAR**

- **Ar$_1$ and Ar$_2$ substituents**
  - These provide *bulk* producing antagonistic activity
  - Generally two aromatic rings - phenyl, benzyl, or an isostere such as pyridyl; Pyridyl generally results in more potent compounds than phenyl
  - If fused must be non–coplanar as in the three ringed structures related to TCA’s and phenothiazines
  - *Para* substitution with small lipophilic groups *increases* potency and *decreases* metabolism due to decreased ring hydroxylation
  - *Ortho* or *meta* substitution *reduces* antihistaminic activity
  - This *diaryl* pattern is present in both first- and second-generation antihistamines.
Atom X can be an oxygen, nitrogen, or carbon, which links the side chain to an “aromatic tail.” The nature of atom X is the basis for the structural classification of H₁ antagonists. The classical H₁ antagonists are divided into six classes based on what X equals:

- **X =C–O**: (Aminoalkyl Ethers)
  1. Ethanolamines
  2. Propanolamines (clemastine, diphenylpyraline)

- **X = C**:  
  3. Propylamines (Saturated and Unsaturated)

- **X = N**:  
  4. Ethylenediamines
  5. Piperazines (Cyclizines) and Tricyclics

- **Miscellaneous**: This forms the sixth class of traditional antihistamines and would include many of the newer antihistamines since they do not fall into one of the older, traditional, classes.
Connecting Chain

- Its function is to separate the nitrogen from the rings by 5–6 Å
- May be saturated, unsaturated, branched or part of a ring
- Branching decreases antihistaminic potency except for the phenothiazines where β carbon branching increases antihistaminic potency.

Basic aliphatic amine

- Must be able to accept a proton (basic) at physiological pH
- $R_1$ and $R_2$: Potency order is $3^\circ > 2^\circ > 1^\circ$
- Quaternization does not increase antihistaminic but does increase anticholinergic activity
- May be incorporated into a heterocycle which is although larger, the heterocycle constrains
- Dimethyl is the optimum configuration
- Larger substiuents decrease antihistaminic potency due to steric hindrance unless they are part of a heterocycle structure when the ring constrains the two ethyls so they are still active
The H₁ antagonists do not occupy the same area or space as the natural receptor substrate.

Only the protonated nitrogen binds the same anionic site as Histamine.

The aromatic tail binds adjacent to the Histamine binding site thus produces the nonspecific conformational perturbation of the receptor. This changes the shape of the receptor decreasing the affinity for Histamine.

It seems that sites outside may be chiral because stereoselectivity is observed with some H₁ antagonists.

As previously discussed the optical isomers of α-Methylhistamine are equipotent as agonists.
Ethylenediamines

Work on $H_1$ antagonists began in France in 1933 and in 1942 the first clinically useful $H_1$ antagonist was reported, **Phenbenzamine**. Although it possesses two nitrogens only one is basic enough to be protonated at physiological pH. Which one?

![Phenbenzamine](image1)

SAR 1 *Isosteric replacement.* 2–pyridyl produced the more potent **Tripelennamine**. However, the 3– or 4–pyridyl can not be considered isosteres and produced less potent compounds

![Tripelennamine](image2)
SAR 2 Substitution. *Para* substitution (lipophilic, e.g., Cl, Br, CH\(_3\)) can increase potency. *Ortho* substitution is highly undesirable for it interferes with the ring conformation. *Meta* substitution is either ineffective or unfavorable, but this effect must be due to electronic as well as an increased lipophilicity. Thus introduction of a *para* methoxy on Tripelennamine produces **Pyrilamine**, a more potent but less toxic drug

![Pyrilamine](image)

**Antazoline** is an *imidazoline* derivative but has a two carbon chain thus generally included in this class. It is less potent than most antihistamines but is characterized by a lack of irritation plus it has local anesthetic properties which makes it ideal for ophthalmic use

![Antazoline](image)

As a class the Ethylenediamines have **low to moderate** potency with low anticholinergic side effects, low antiemetic effects and moderate to high sedation
Aminoalkyl Ethers

Ethanolamines and the Propanolamines

Diphenhydramine is the first important member of this class introduced in the year 1943 which has sedative properties.

Dimenhydrinate is salt of 8–chloro theophylline (theoclate) (a purine acid) with diphenhydramine (motion sickness).

As in the previous class, *para* substitution with Br in Bromodiphenhydramine yields twice as potent as the parent compound.

Ortho methyl produces Orphenadrine an anticholinergic used as a skeletal muscle relaxant in muscle strains and sprains has lower antihistaminic potency because of the orientation of the rings.

Isosteric replacement of phenyl by a 2–pyridyl results in a slight increase in potency but when combined with a *para* chloro substituent to produce Carbinoxamine a 39 fold increase in potency is seen. The chloro increases LWPC and metabolic stability.
Several of these compounds have chiral centers where one isomer is more potent. Thus *levo* (S) **Carbinoxamine** is 24 times as potent than the *dextro* (R). This implies that the receptor must possess a degree of asymmetry in the area where the rings bind in order to account for this large difference in potency. Replacement of central hydrogen by a methyl generally results in a slight increase in potency, e.g., **Doxylamine**.

**SAR 4** **Diphenylpyraline** and **Clemastine** have three carbons separating the oxygen and the nitrogen atoms thus they are propanolamines. Lengthening the chain increases potency and longer DoA.

**Clemastine** is a long lasting agent with duration of action up to 12 hours. The dextrorotatory isomer is R,R at its two chiral centers. A comparison of all four diastereoisomers indicates that the configuration of the center close to the nitrogen is not as important as the configuration of the center close to the rings. Thus the order is R,R > R,S > S,R > S,S. Although a modern agent it has sedating side effects.
**Bepostatine** (Bepreve) is a relatively new drug in this class approved in Japan for systemic (oral) use for the treatment of allergic rhinitis and urticaria/puritus in July 2000 and January 2002, respectively. It has been approved by FDA for ophthalmic use in Sep 2009.

![Bepostatine Chemical Structure](image)
Propylamines

- Pheniramine is the prototype and is the weakest member; halogenation at the para position increases potency significantly, e.g., Chlorpheniramine is 10 to 20 times more potent yet with no significant increase in toxicity. Brompheniramine is slightly more potent but with a half-life almost twice as long, approximately 25 hours.

- All three drugs are chiral; the S isomers have 200 to 1000 times greater binding to the receptor. Pheniramine is marketed as a racemate, but Chlorpheniramine and Brompheniramine have been resolved and are marketed both as the racemate and in the more active S–dextrorotatory form.

- In this class isosteric replacement is limited; only the phenyl and 2–pyridyl are allowed, any other replacement results in a decrease in potency.
**Tripolidine** and **Pyrrobutamine** have unsaturation in the propylamine side chain and therefore exist as geometric isomers.

SAR 5 In both cases the **E isomer is more potent**. In the case of Tripolidine, the E isomer is 1000 times more potent than the Z isomer. E–Pyrrobutamine is 165 times more potent than the Z isomer

- The N–substituent is a **pyrrolidino** ring. It fits the structural requirements (5–6Å between the 3° amine and on aromatic ring) plus it contributes to the LWPC. **Para substituents on phenyl cis to nitrogen increase potency** but **decrease potency if on phenyl trans to nitrogen**. Concluded that the two aromatic groups have a different function in the interaction with receptor

- **Acrivastine** is a **modern** non–sedating agent. It is related to Tripolidine and is slightly more potent. The unsaturated carboxylic acid substituent is responsible for the lack of sedation. **Non–sedating agents** have difficulty in crossing the BBB
Three Approaches Used to Reduce BBB Absorption

1. The most obvious is to add polar or highly ionized groups to decrease the LWPC, thus decreasing ability to pass through lipid barriers.

2. The second approach is to create a very high lipid soluble compound. High LWPC. This has three effects:
   a) Low water solubility results in low concentrations in the blood, thus low concentration gradient results in low passage of BBB.
   b) Increase in protein binding, which further decreases the concentration gradient by decreasing the amount of free unbound drug.
   c) Once the drug diffuses into the lipid bilayer it sequesters itself in the lipid environment. It will not pass out into the cell.

3. Create a zwitterion that has low ability to pass through the BBB's lipid barriers.

In Acrivastine the **first** and **third** approaches apply. A carboxylic acid at physiological pH is highly ionized and has difficulty crossing the BBB. The unionized form has a log P of 2.83 but the ionized form has a log P of 0.33.
Piperazines (Cyclizines)

- Both nitrogens are basic; the terminal nitrogen is more basic due to less steric hindrance and no electron withdrawing groups in the vicinity.
- They have moderate potency with a slow onset and prolong duration of action, moderate sedation and low anticholinergic effects.
- They also possess peripheral and central antinausea activity, thus they are used as antiemetic, antivertigo and antinausea products.

![Chemical structures of Meclizine, Hydroxyzine, and Cetirizine](image.png)
- **Cyclizine** has only limited $H_1$ blocking activity and used mainly in motion sickness.

- **Chlorcyclizine** has sufficient $H_1$ antagonistic activity due to *para* chloro substitution.

- **Meclizine** and **Buclizine** are also effective $H_1$ antagonists used primarily as antinauseants in motion sickness and vertigo. They are highly lipophilic and has significant CNS properties.

- **Hydroxyzine** even though a classic $H_1$ blocker, possessing anticholinergic and CNS depressant effects. Its major uses include the management of anxiety and tension associated with psychoneuroses as well as in allergic conditions.

- **Cetirizine** is acid analog of Hydroxyzine. It has 6.5 times lower receptor affinity and being a zwitterion lower CNS effects. Thus less sedating but not non-sedating. (2nd)
Terfenadine is a reduced butyrophenone derivative without antipsychotic properties.

- Moderate in potency, devoid of sedation side effects with a DoA of 12 h (2nd-generation).
- Terfenadine shows no significant anticholinergic activity or at any other receptor.
- The antihistaminic activity is attributed to the diphenylmethylpiperidine half of the molecule while the other half is responsible for the lack of affinity for other receptors.
- It is a non–sedating H₁ antagonist because it is too lipid soluble.
- Its duration of action of 12 hours is due to slow disassociation from the receptor.
- It undergoes extensive first pass metabolism but has a half–life of 20 hours.
- Has significant drug–drug interactions with Ketoconazole and Erythromycin. All three are metabolized by the same enzyme. However, the last two are inhibitors of CYP3A4. They slow the metabolism of Terfenadine allowing blood levels to increase significantly. These high levels produce a cardiotoxicity (QT interval prolongation and arrhythmias) which can prove fatal. This led to its removal from the market. Replaced with Fexofenadine. (1998)
**Fexofenadine** is an active metabolite of Terfenadine with no drug–drug interactions because it is not metabolized through the same pathway. Even though a carboxylic acid it exists as a zwitterion which decreases its solubility.

**Astemizole**, also an outcome of neuroleptic research, lacks CNS and anticholinergic activity but does have α-adrenergic and moderate serotonin antagonism. It has a very long half–life, 1.5 days, due to an extremely slow rate of receptor dissociation but it has a very slow onset of action (about a week). Astemizole is also metabolized by CYP3A4 and has similar problems when administered with CYP3A4 inhibitors and has been removed from the market (1999).

**Levocabastine**, came from research based on Astemizole. Astemizole’s profile led to research on compounds containing the 4–phenyl piperidine ring. Levocabastine is a chiral compound. The enantiomer with the configuration depicted is the most active isomer. Its activity is 100 times that of Astemizole, 1250 times Chlorpheniramine but devoid of anticholinergic and antiserotonergic activity. Unlike Astemizole, it has a fast onset and a long duration. The long duration is due to a very slow dissociation from the receptor. This agent can not be considered non–sedating but 2nd-generation.
The first member of this class was *Fenethazine*, introduced in 1945.

Branching of ethyl side chain increases potency, e.g., *promethazine*, enantiomers are equipotent.

Increasing side chain to 3 carbons decreases antihistamine potency but increases dopamine antagonism.

Branching of propyl side chain increases antihistamine potency but decreases dopamine antagonism, e.g., *trimeprazine*. 
Other Tricyclics

dibenzocycloheptane
dibenzoepine
Amitriptyline

dibenzocycloheptene
dibenzoepine
Cyproheptadine

dibenzimidazoazepine
Epinastine

benzocycloheptapyridine
Loratadine

benzocycloheptathiophene
Ketotifen

thienobenzodiazepine
Olanzapine

dibenzoepine X = O
Doxepine
dibenzoepine X = N
Imipramine
dibenzoepine X = N, Y = N
Clozapine
dibenzoepine X = N, Y = O
Amoxapine
dibenzothiazepine X = S, Y = N
Quetiapine
Dibenzepines

- **Cyproheptadine** has anti $\text{H}_1$ activity $>150\times$ diphenhydramine and used primarily as an antipruritic.
- Produces **pronounced sedation** and has a high affinity for cholineergic and serotonin receptors.
- It also **enhances appetite** thus promote **weight gain** by increasing food consumption in anorexia nervosa.

- **Azatadine** is the modern $\text{H}_1$ antagonist, a phenyl has been replaced by a 2–pyridyl and the double bond has been saturated.
- More Potent than Cyproheptadine ($8.7\times$) as an $\text{H}_1$ antagonist.
- It also has **antiserotonin** and high anticholinergic potency and thus similar side effects.
Loratadine is a non-sedating H₁ antagonist with no anticholinergic side effects.

- Introduction of a Cl and carboxyethyl increases potency.
- Since carbamate nitrogen is neutral rapidly absorbed and quick acting.
- Metabolized by CYP3A4 and 2D6 directly to Desloratadine via an oxidative process without hydrolysis.
- Prodrug??
Doxepin has long been available and used clinically as an antidepressant. However, it has a very high $H_1$ antagonist potency. Recently it has been released in a cream formulation (Zonalon) for relieve of puritis.

Ketotifen is an isostere, the thiophene for a benzene. It is an $H_1$ antagonist and mast cell stabilizer.

Azelastine is an $H_1$ antagonist, mast cell stabilizer with antileukotriene activity. It inhibits the synthesis and release of leukotrienes and is recommended for allergy and asthma. Use in eyes and as nasal spray. It is more sedating than the non sedating agents but less sedating than the first generation.

Emedastine is an ophthalmic $H_1$ antagonist, mast cell stabilizer.
Histamine H$_2$-Antagonists

- **Guanylhistamine** provided the lead.

- Extension of the side chain increased anti H$_2$ potency but some agonist activity remained. Replacing the basic guanidino group with the neutral thiourea yielded effective H$_2$ antagonists.

- **Burimamide** lacked agonist action but was not orally absorbed.

- In **Metiamide** (1) reduce the pKa of the ring N, reduced ionization, increased membrane permeability and absorption and 10X more potent than Burimamide, (2) cause the $\tau$ tautomer to predominate which interact with H$_2$

- But caused kidney damage and granulocytopenia, possibly due to the thiourea so was replaced by the isosteric guanidine. This compound being highly basic was 20 times less potent.

- Replacement of this group with strong electron withdrawer but more lipophilic cyano derivative yielded **Cimetidine**.
The degree of protonation of the imidazole ring of burimamide is >10x higher than that of histamine at physiologic pH that reflects a +I effect on the side chain and thus increase in electron density at N³. This favors the dissociation of proton from N¹ and the Nπ-H neutral tautomer predominates, which is non-optimal for binding to H₂ receptor - Low potency.

The introduction of a S atom into the side chain and a C⁵-CH₃ of burimamide gave metiamide which showed greater potency and selectivity at H₂ receptor antagonist activity. Sulfur introduced a −I effect on the side chain and also the CH₃ introduced a +I effect at C⁵, resulting in increase and decrease in electron densities at N¹ and N³, respectively, facilitating dissociation of N³-H to predominate the desired Nπ-H tautomer.
Need an aromatic ring with \( n \) electrons next to the side chain. The imidazole ring is not required (the other H\(_2\) antagonist don’t have it) but if it is present the \( \tau \) tautomer should predominate. The \( \tau \) tautomer is promoted by electron donors at position 5 and electron withdrawers at position 4.

The terminal nitrogen group should be polar but not basic for maximal potency.

Separation of the ring from the nitrogen group by 4 atoms gives maximal potency.

*Cimetidine* is an extremely successful drug in the treatment of ulcers.

Note the electron donor methyl at C\(_5\) and electron withdrawing side chain at C\(_4\) Also the non basic cyanoguanididine terminal nitrogen group.

However, cimetidine has several *disadvantages*. It is an inhibitor of CYP, which leads to many drug–drug interactions. It exhibits antiandrogenic action and can cause gynecomastia. Further it has 60 to 70% oral bioavailability.
**Ranitidine** is a furan derivative, an isostere of the imidazole with $n$ electrons on the oxygen, with 50% bioavailability. It is 4 - 10 X potent than Cimetidinewith a longer DoA. Further, it is a weaker CYP inhibitor. The tertiary amine side chain allows the formation of salts.

**Famotidine**, a thiazole derivative, is 9–15 X potent than Ranitidine or 40–60 X than Cimetidine. No cases of gynecomastia have been reported. It is a weak inhibitor of CYP. Like Ranitidine salts can easily be prepared for this compound. but its absorption is incomplete with only 40 to 50% bioavailability.

**Nizatidine** is also a thiazole derivative similar to Ranitidine (5–18 X Cimetidine), but more bioavailable, 90%, with no antiandrogenic or enzyme inhibition.
Cationic Histamine binds to the receptor via the formation of three hydrogen bonds.

The cationic nitrogen and τ–nitrogen of the imidazole ring are hydrogen donors and the π–nitrogen acts as a proton acceptor.

Participation of the ammonium group in the hydrogen bonding inevitably leads to a decrease of the positive charge on the ammonium group.

This decrease in positive charge induces a tautomeric change in the imidazole ring resulting in a stronger binding of the π–nitrogen and proton release by the τ–nitrogen.

The net result is a proton shift at the receptor surface which is believed to trigger the $H_2$ stimulating effect.

This mechanism calls for the presence of a hydrogen atom in position 3 of histamine, and recall that 3–methylhistamine is unable to stimulate the receptor.
**H₃-Receptor Antagonists**

- Potential for treating asthma, migraine, hypertension, septic shock, and in learning and memory degenerative disorders like AD

- **Thioperamide** and its congeners (4(5)-substituted imidazole derivatives) are examples of the potent and selective H₃ receptor antagonist

- Some of the more prominent new H₃ receptor antagonists are **GT-2016**, and **GR-175737**, which show receptor affinities in the low nanomolar range.

- None of this class of compounds is in clinical use; however, few are undergoing further pharmacologic evaluation as potential therapeutic agents.