Introduction of Anti-Histamine

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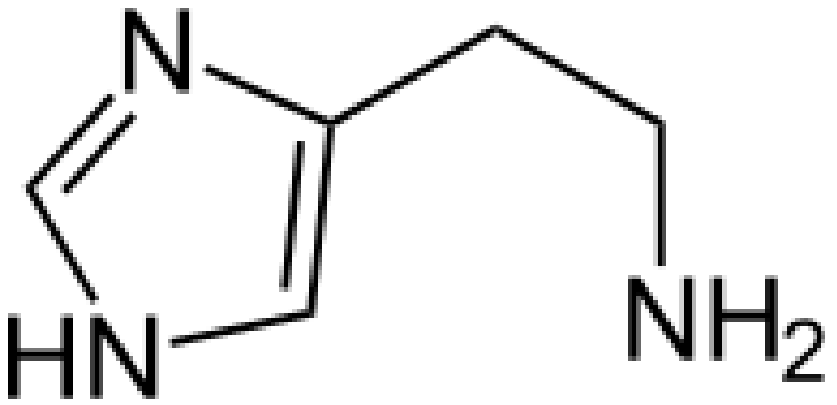
Histamine

- Local hormone.

- A chemical messenger component of various biological pathways. It is involved in mediation of allergic and hypersensitivity reactions as well as regulation of gastric acid secretion.

- Source?

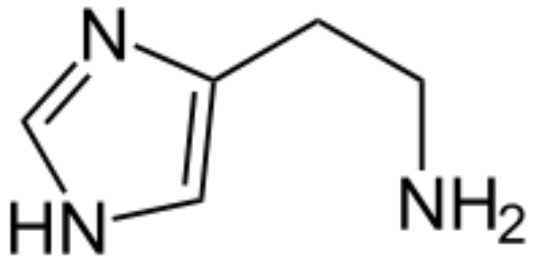


Histamine Properties

Notes

- **Two possible tautomers**
- **pK_a for the α-NH_2 group = 9.80.**
- **% ionisation at pH 7.4 = 99.6**
- **pK_a for the imidazole ring = 5.74**
- **Imidazole ring is not ionised at blood pH.**
- **SAR studies suggest that the (α)- NH3+ monocation is important for agonist activity at H-receptors**

- **What type of interactions do you expect to see?**

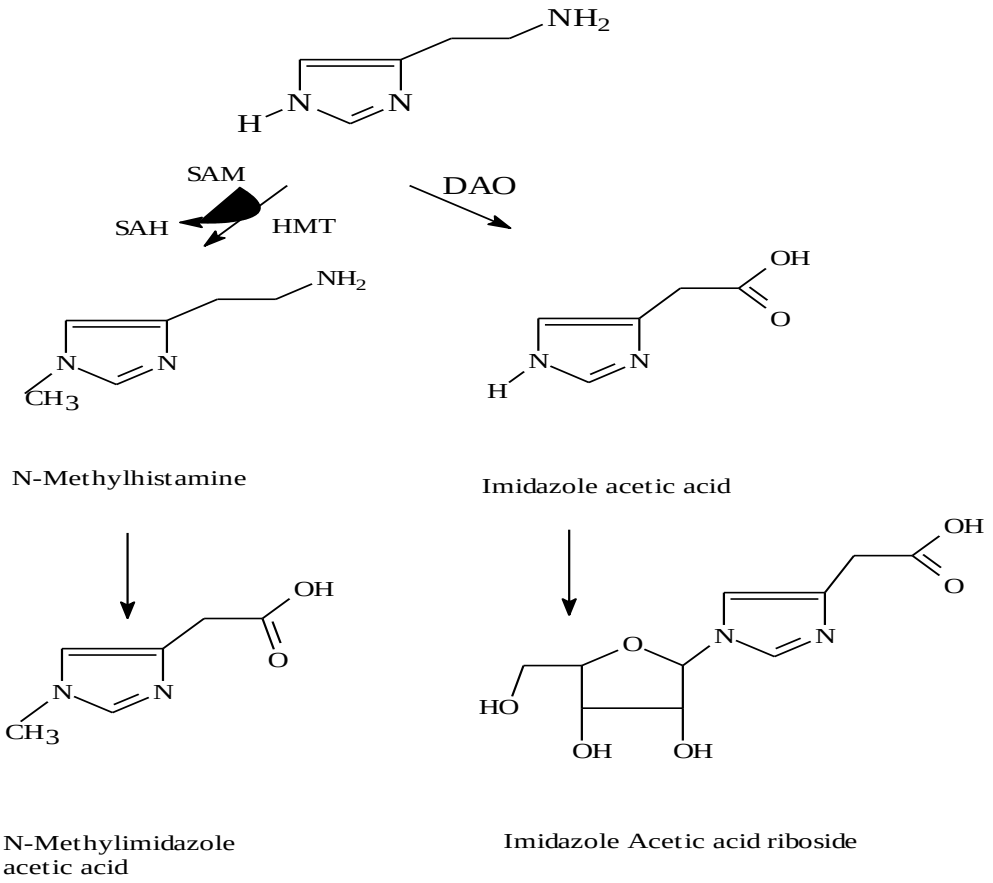


Receptors

- ***H1- receptors mediate:***
  - smooth muscle contraction
  - increased vascular permeability
  - pruritus
  - prostaglandin generation
  - decreased AV conduction time+ tachycardia
- ***H2-receptors mediate:***
  - Gastric acid secretory action of histamine
- ***H3-receptors***
  - Neural auto receptors which modulate histamine synthesis and release in the CNS.
- ***H4-receptor:***
  - *WBCs*, They have been shown to mediate mast cell chemota.xis

- **Termination of histamine action :**

  Three principal ways exist for terminating the physiological effects of histamine
- cellular uptake
- desensitization of cells
- metabolism (the most common pathway)



[HMT: histamine N-methyl transferase . SAM: S-adenosyl-L-methionine
SAH: S-adenosyl-L-homocysteine . DAO: Diamine oxidase]

Histamine H1-receptor Antagonists: Antihistaminic agents

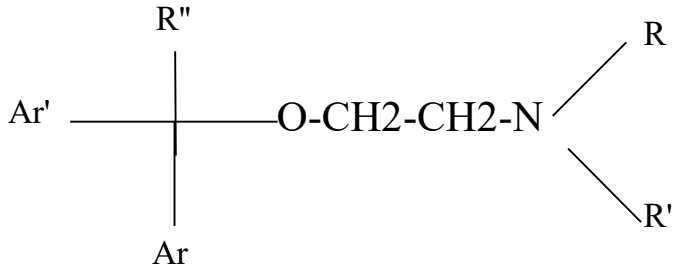
Mechanism of action:

H1- antagonists are defined as those drugs that competitively inhibit the action of histamine on tissues containing these receptors.

H1-antagonists are subdivided into two groups: the first generation or classical histamines & second generation or non-sedating antihistamines.

First Generation H1-Antagonists:

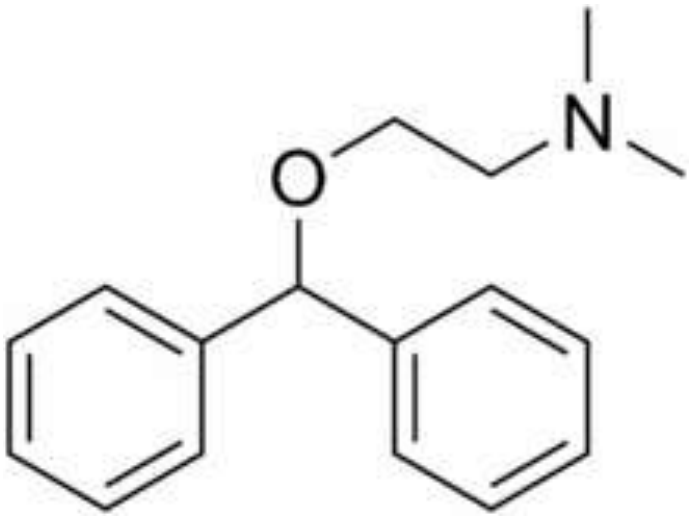
- ***Aminoalkyl ethers (ethanolamines)***
- The drugs in this group possess significant anticholinergic activity.
- Drowsiness is a common side effect as a result of the ability of these compounds to penetrate the BBB and occupy central H1-receptors.
- GI side effects are relatively low compared to the ethylenediamines.



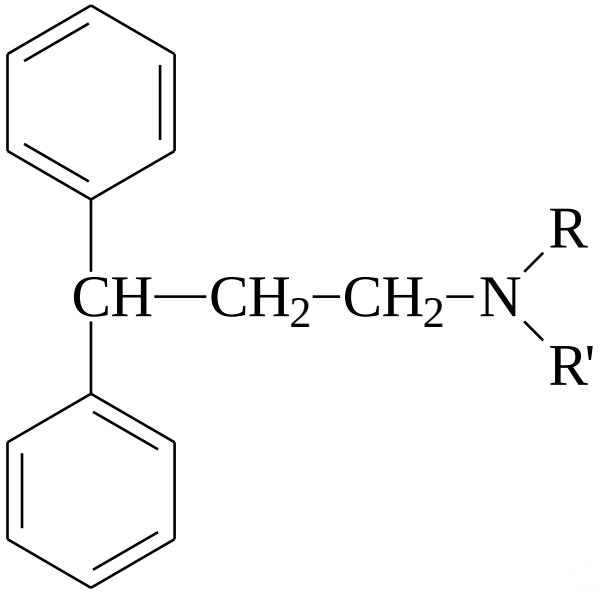
(General Sructure of the Aminoalkyl ethers)

Diphenhydramine (Benadryl®)

- pka of 3ry amine?
- Ionization at pH=7
- 5% unionized
- CNS effect
- Mixtures : Pectolyn antitussive contains dextromethorphan + diphenhydramine + sodium citrate.
- Uses: Sleep aid, allergy, anxiolytic.
- No addiction but dependence.

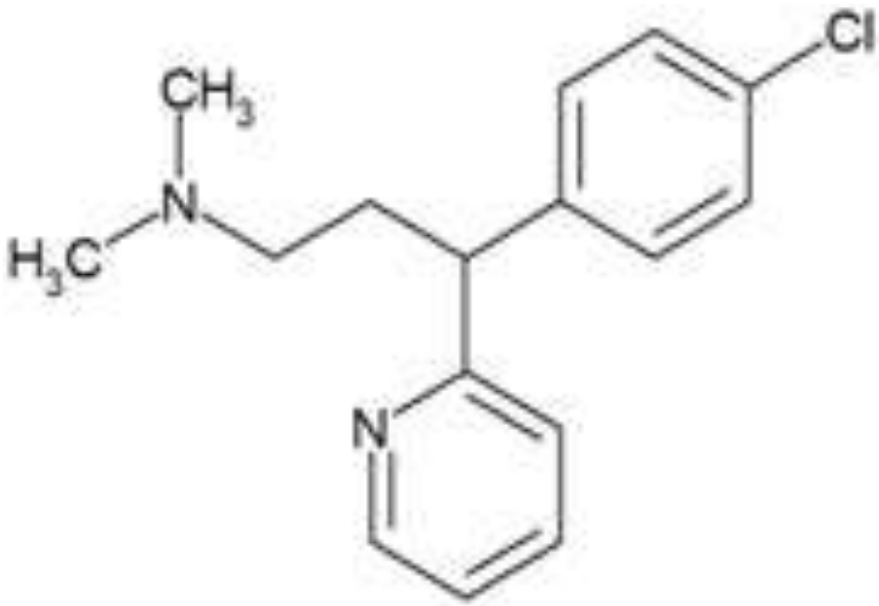


- ***Propylamines :***
- Characterized structurally by an sp3 or sp2 carbon connecting atom with a carbon chain of two additional carbons linking the key tertiary amino and diaryl pharmacophore moieties.
- Those Propylamines with a saturated carbon connecting moiety are commonly referred to as the Pheneramines.
- The halogenated ones are more potent and have a longer duration of action.
- All Pheneramines are chiral molecules, and the anti-histaminic activity resides almost exclusively in the S-stereoisomers.



Chlorpheniramine(Polaramine, Allerfin)

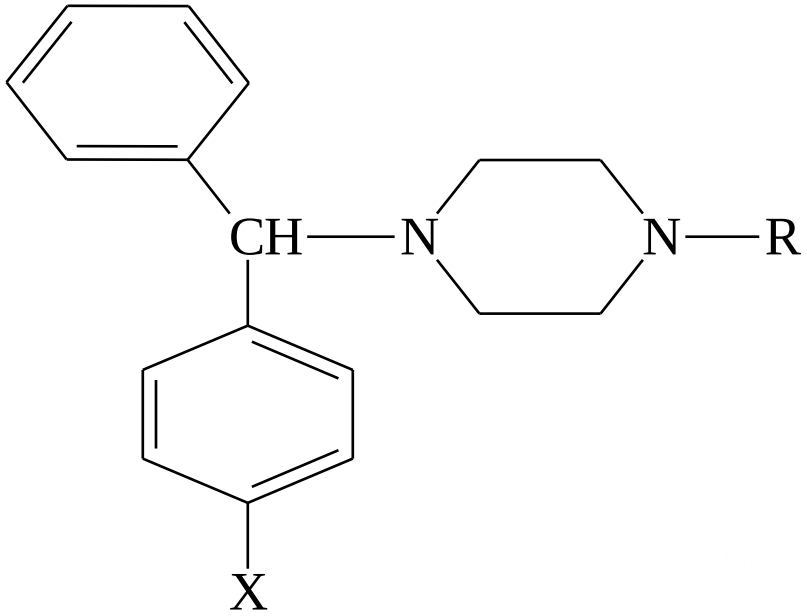
- 3ry amine, side effects?
- Both **Cl** and Pyridine increase potency.
- Mixtures: Tussifin contains chlorpheniramine + codeine + glyceryl guaiacolate + potassium citrate + sodium benzoate + liquorice



- ***Piperazine (cyclizines):***

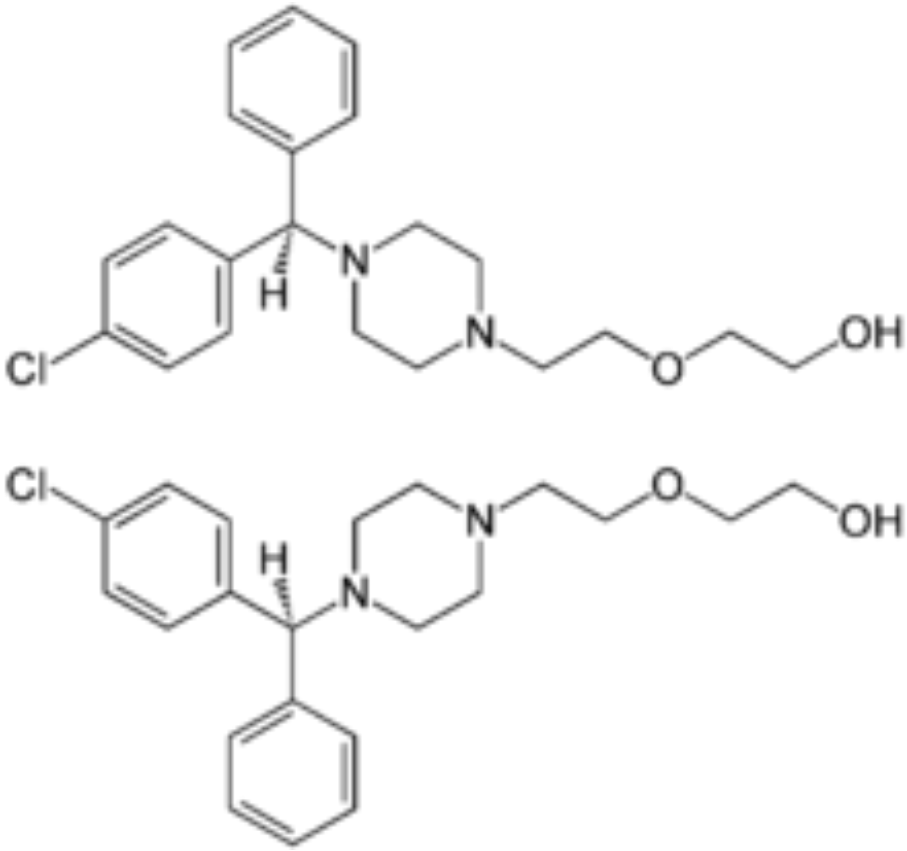
- In this series the connecting moiety is a CHN group, and the carbon chain, terminal amine functionality as well as the nitrogen atom of the connecting group are all part of the Piperazine moiety.

- They are moderately potent anti-histaminic with lower incidence of drowsiness, and characterized by a slow onset and long duration of action. These agents exhibit central and peripheral antimuscarinic activity and this may be responsible for the anti-emetic and anti-vertigo effects. Some members exhibit a strong teratogenic potential.



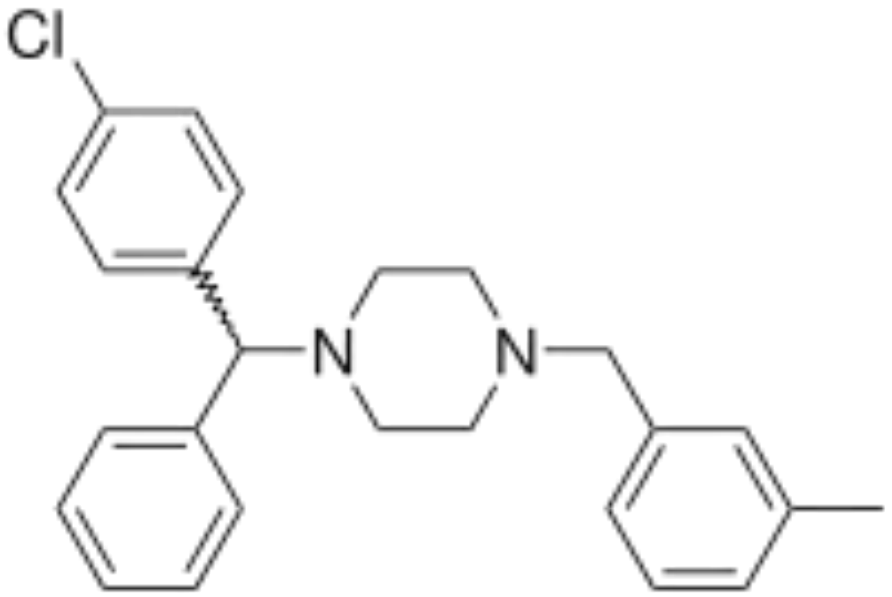
Hydroxyzine (Atarax)

- Potency compared to diphenylhydramine, chlorpheniramine?
- Piprezine ring?



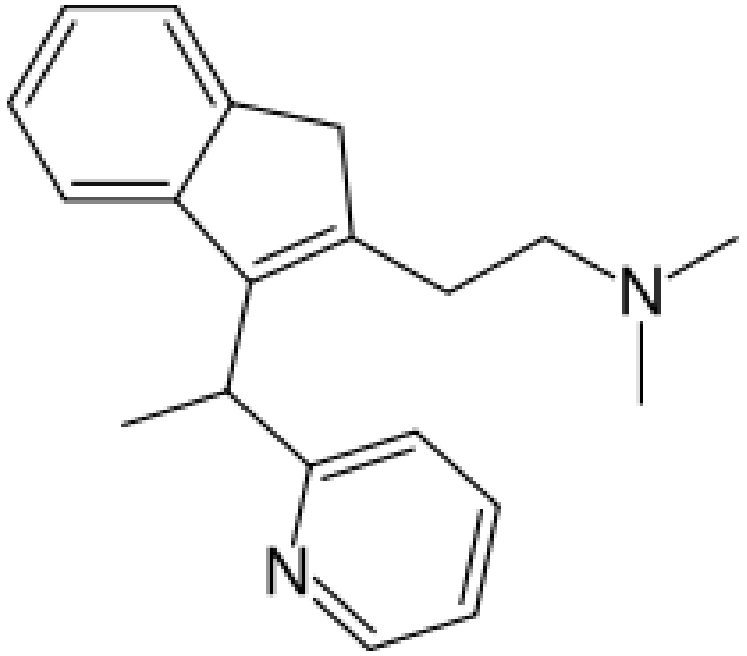
Meclozine (Navidoxine with B6)

- Sedation
- Anticholenregic effect
- Motion sickness and morning sickness



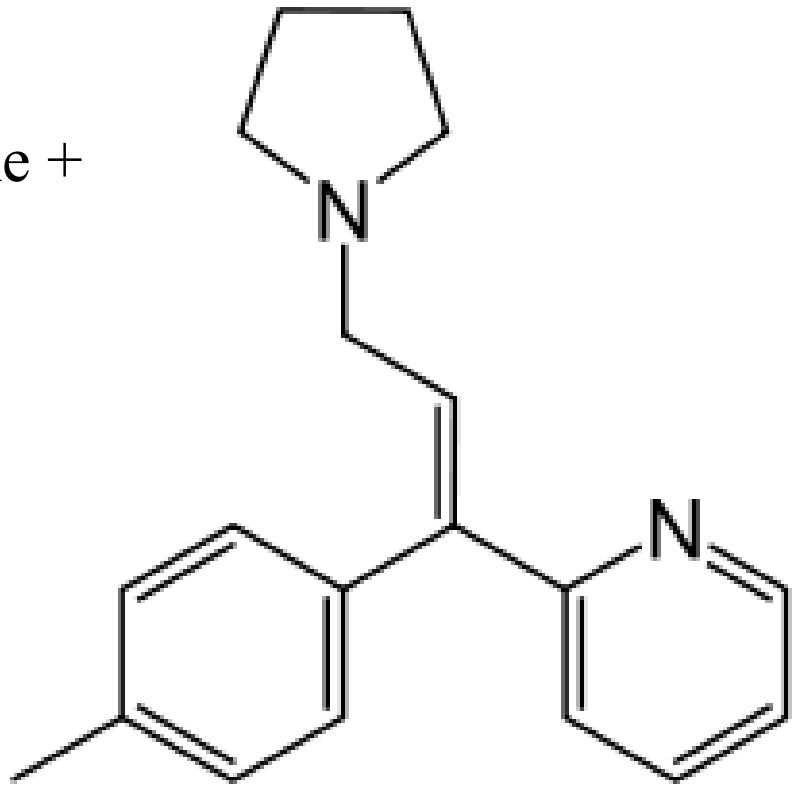
Dimetindene (Fenistil)

- Potency due to pyridine(H-π)
- Indene group, hypnotic



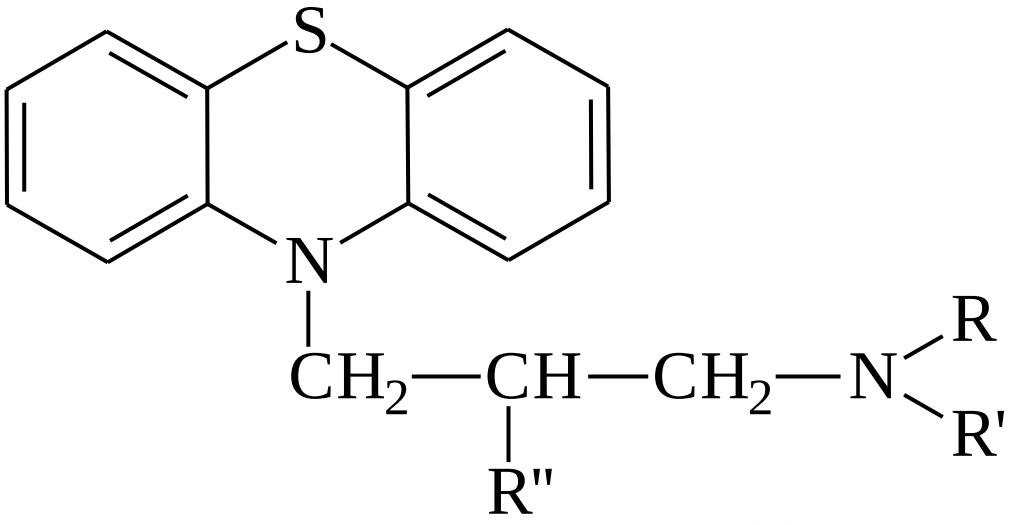
Triprolidine (Trifed)

- 3ry amine(Pyrrolidine)
- Mixtures : Trifed.. Conatins guaiphenesin + pseudoephdrine + triprolidine.



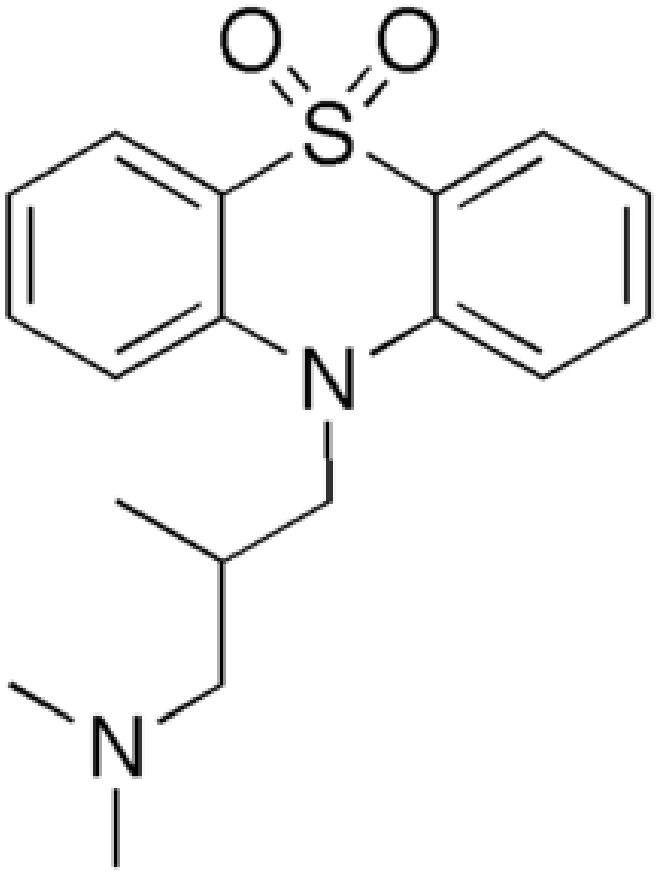
- ***Phenothiazines:***

- Differs from the phenothiazine antipsychotics which requires an unbranched propyl chain.
- The enantiomers have similar anti-histaminic and other pharmacologic properties.
- Lengthening of the side chain and substitution of lipophilic groups in 2-position of the aromatic ring decrease anti-histaminic activity and increase psychotherapeutic properties.



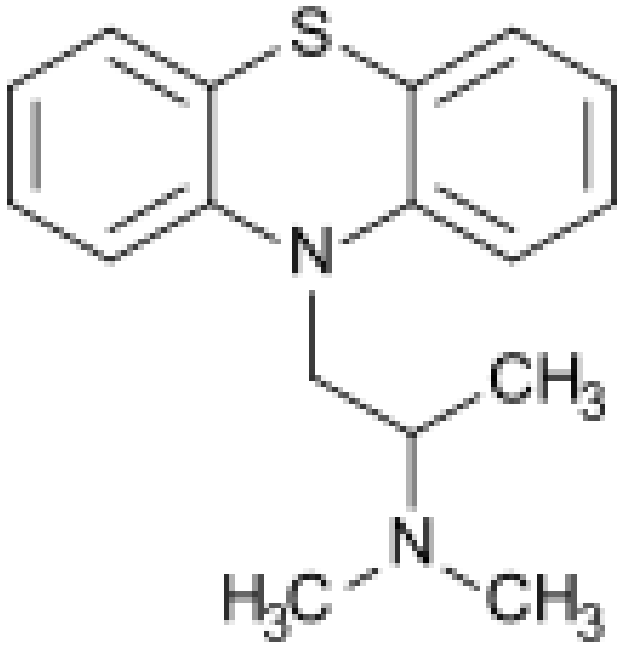
Oxomemazine (Rectolyn, Rictamol)

- Rectolyn?
- Phenothiazine ring?
- Used for psycosis



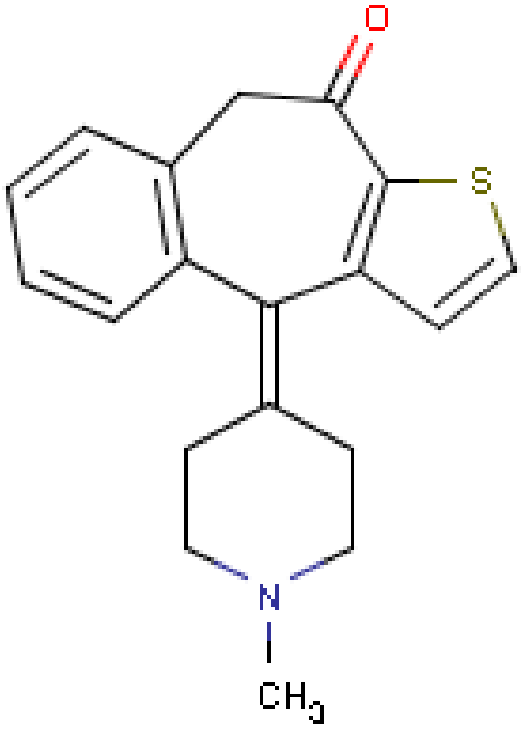
Promethazine (Histazin)

- I.M
- Subcutaneous or intra-arterial injection are contraindicated!



Ketotifen (Zaditen)

- Isosteres.

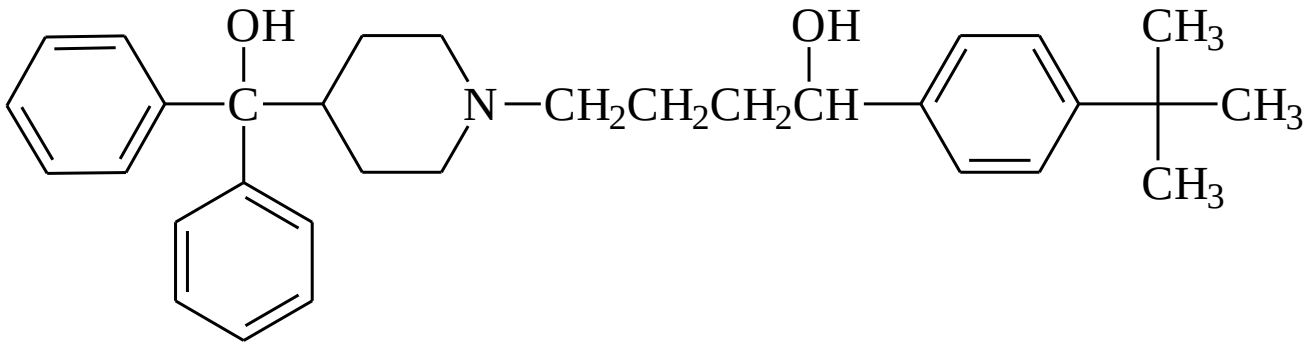


Second generation H1-Antagonist drug classes:

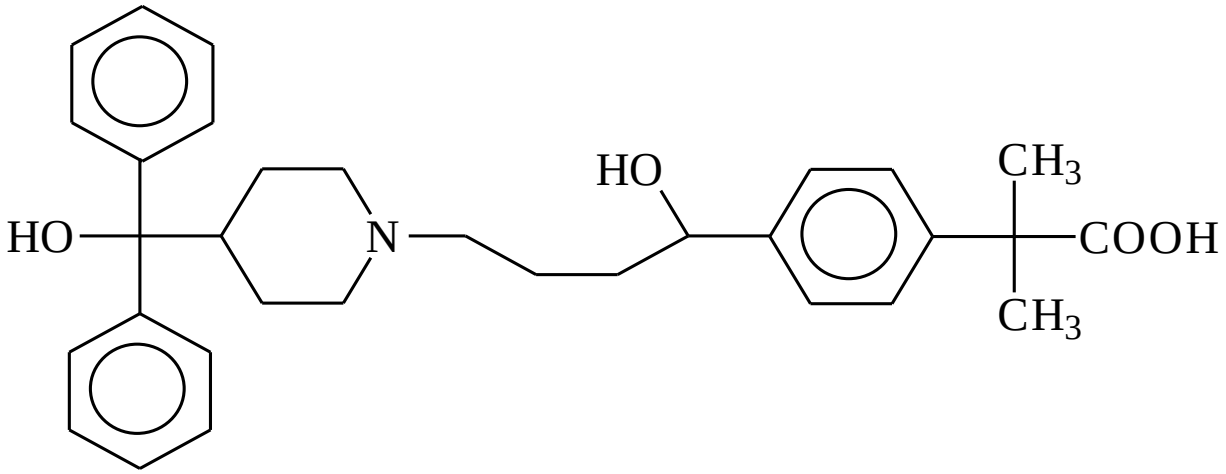
- Second generation agents have little affinity for muscarinic, adrenergic or serotonergic receptors, therefore they produce less side effects.

- All these agents are devoid of sedating effects at therapeutic concentrations due to poor CNS penetration and lowered affinities for central histaminic, cholinergic and adrenergic receptors.

- **Terfenadine:**
- Selective long acting (>12 hr) H1-antagonist (first generation).
- Histamine receptor affinity is related primarily to the diphenylmethylpiperidine moiety.
- Oxidative demethylation yields COOH.
- CA pka=4, completely ionized and does not pass BBB.
- Long duration of action due to slow dissociation from receptor.
-

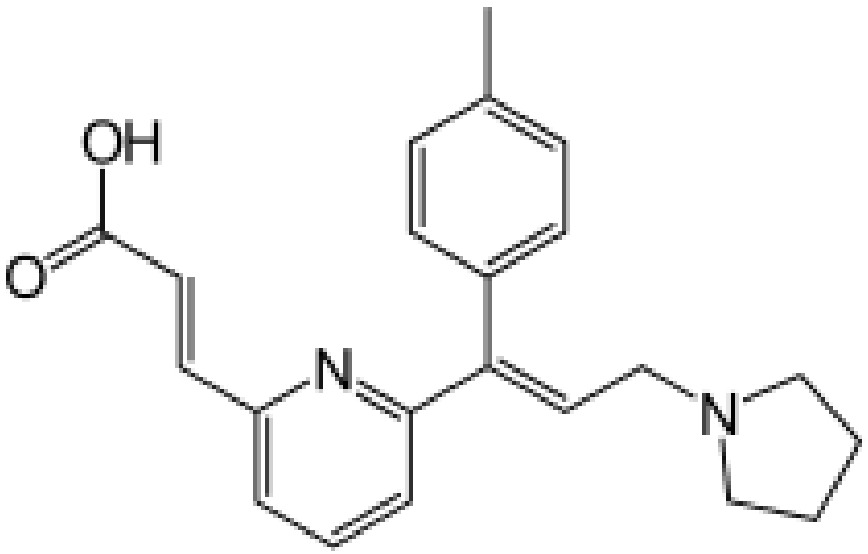


- **Fexofenadine HCl (TelFast):**
- It is a metabolite of terfenadine, not only active and effective in allergic disorders, but also less cardio toxic than terfenadine.
- Selective H1-receptor blocker with no clinically significant cholinergic or adrenergic receptor blockade.
- No sedative or other CNS effects. (doesn't cross BBB)



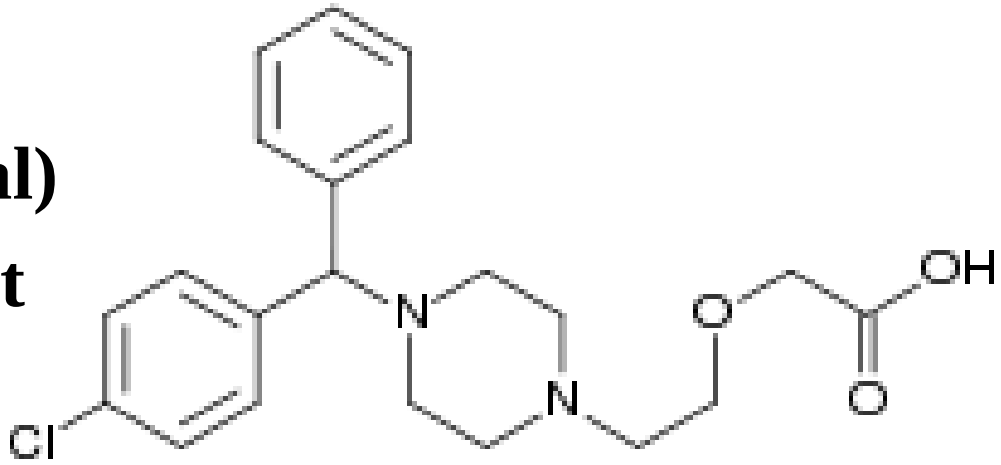
Acrivastine (Semprex capsules)

- 2nd generation H1-blocker.
- $t_{0.5}$ increased, due to increased protein binding, lysine!
- Binding, potency regions?



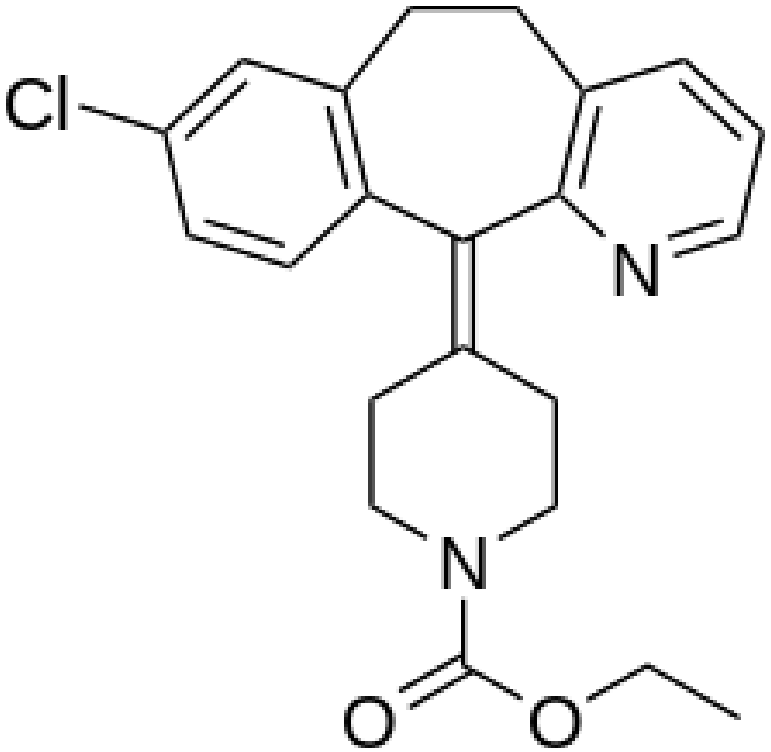
Cetirizine (zyrtec)

- High potency, longer duration of action?
- Chiral?
- **Levocetrizine(xyzal)**
- **6 times more potent**



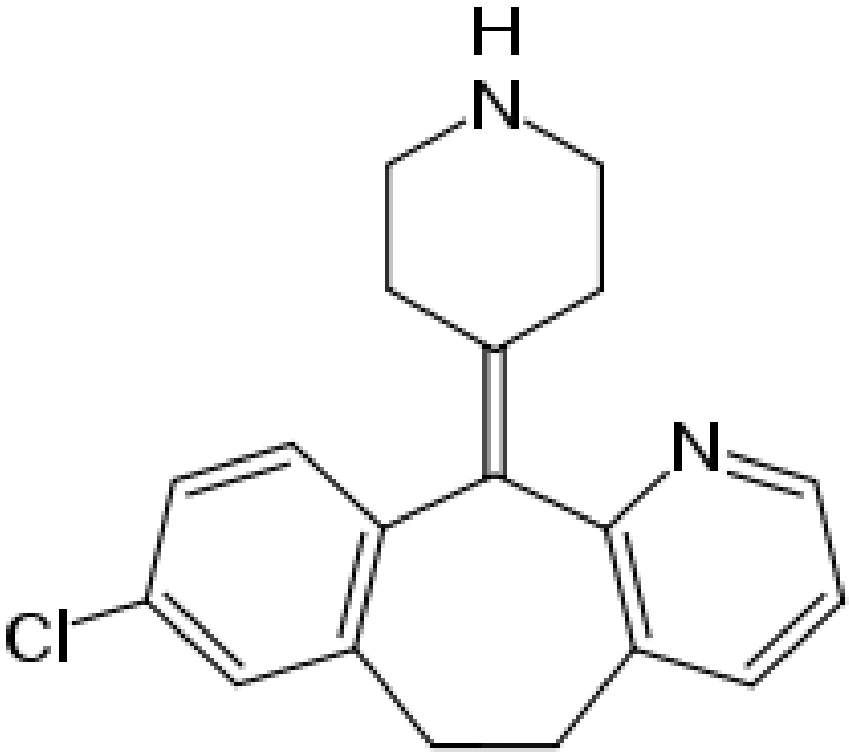
Loratadine (Claritine)

- Amide not amine?
- Prodrug
- Long duration of action, late onset of action



Desloratadine (Aerius)

2nd amine, CNS?



Histamine H2-Receptor Antagonist:

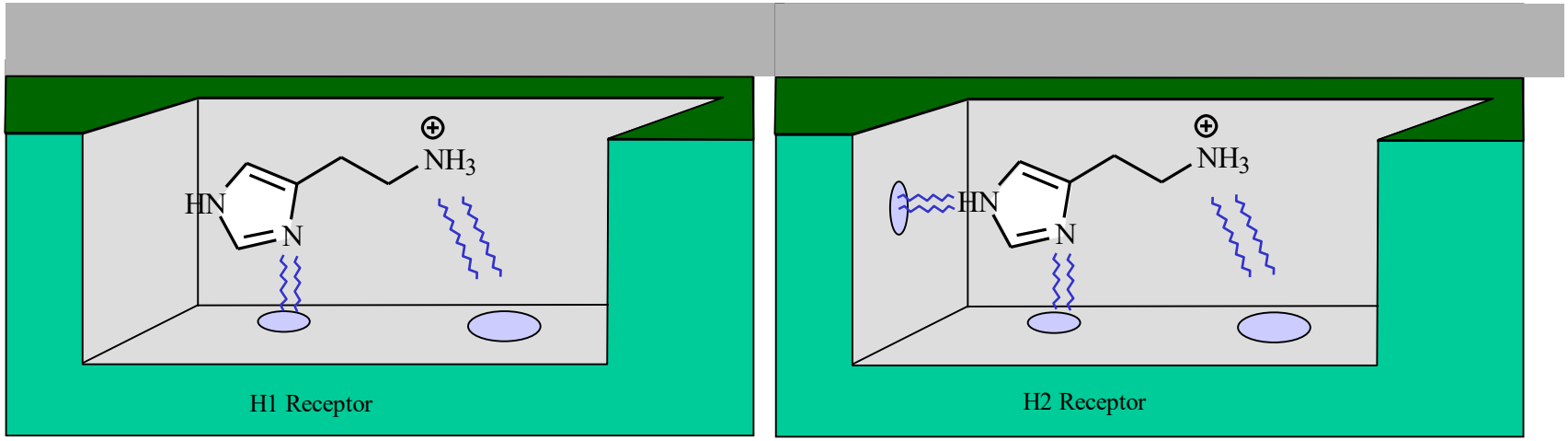
- Their primarily pharmacological action involves antagonism of the action of histamine at its H2-receptors.
- Used in the treatment of acid peptic disorders including:Heartburn to peptic ulcer disease, Zollinger – Ellison syndrome, GERD, Acute stress ulcers and erosions.

Histamine as a lead compound

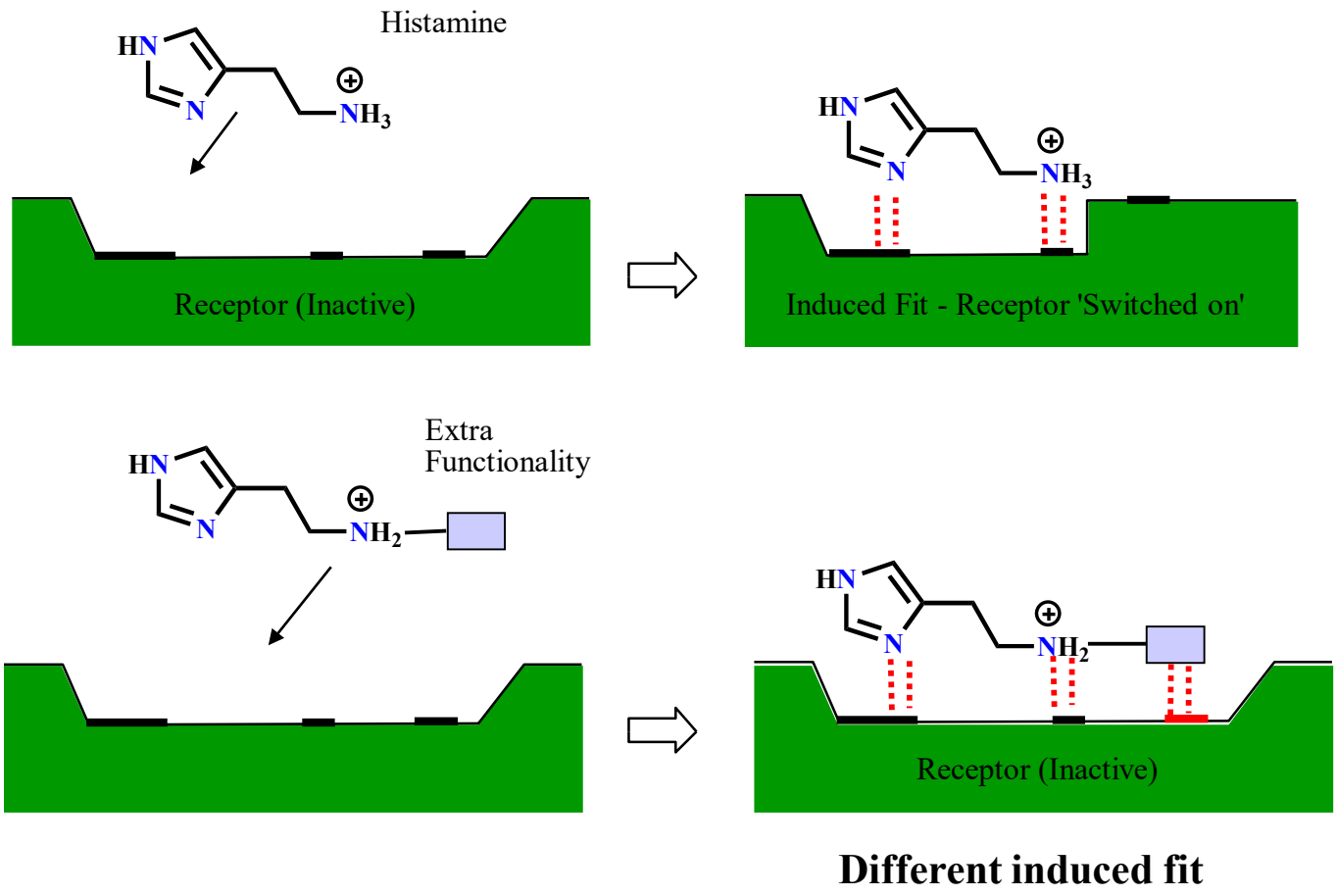
- **No known H_2 antagonist at the time - no lead compound**
- **SK&F decide to use histamine itself as the lead compound**
- **Aim is to alter an agonist into an antagonist**
- **Need to know SAR requirements for H_2 agonists**
- **Analogues tested by their ability to promote gastric acid release**

SAR for H_1 and H_2 agonists

Two nitrogen atoms are required for H_1 agonist activity
All three nitrogen atoms are required for H_2 agonist activity



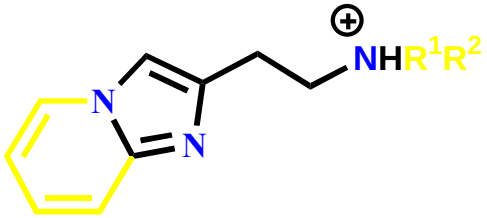
Strategies for converting agonists to antagonists

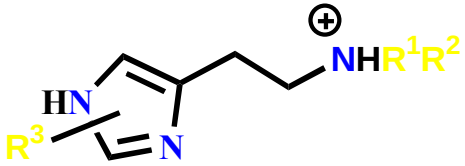


Different induced fit

Strategies for converting agonists to antagonists

Examples - extra hydrophobic groups

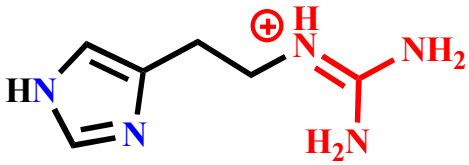




Results

- No antagonist activity observed with extra hydrophobic groups
- Try adding extra hydrophilic groups instead
- Aim is to search for extra polar binding regions

N^{α}-Guanylhistamine



Guanidine moiety

7.1 Biological properties

- Partial agonist - promotes HCl release but less strongly than histamine

- Prevents histamine from fully promoting the release of HCl

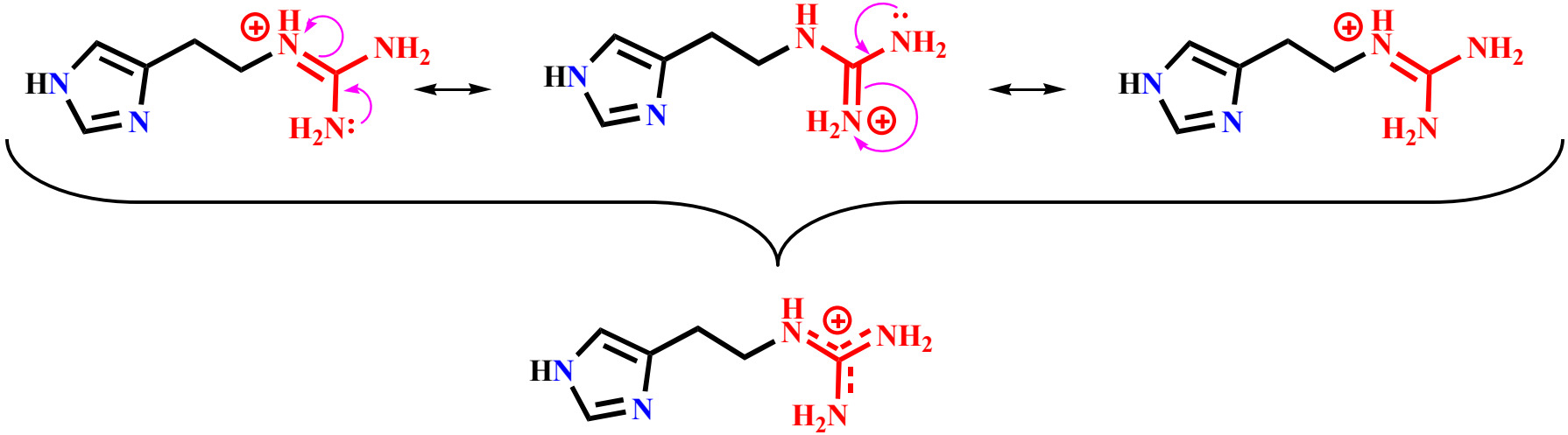
- SK&F suggest that N^{α}–guanylhistamine is binding to the proposed H_2 receptor, resulting in weak activation

- Whilst present, N^{α}–guanylhistamine blocks histamine from binding

N^{α}-Guanylhistamine

Structure and chemical properties

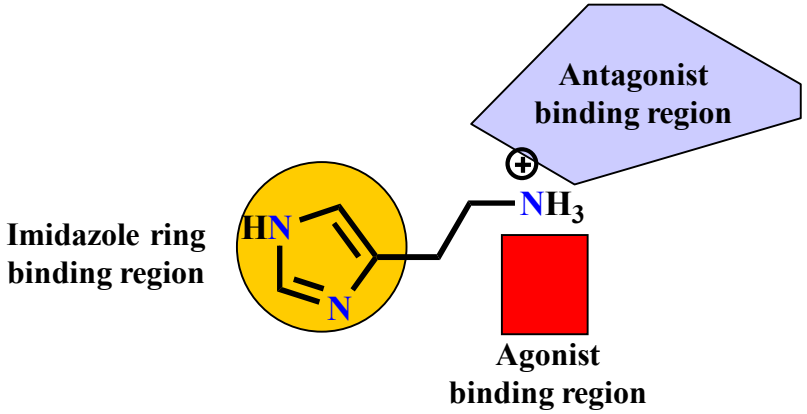
- The guanidine group is basic and ionised
- Different tautomers are possible
- The positive charge can be delocalised



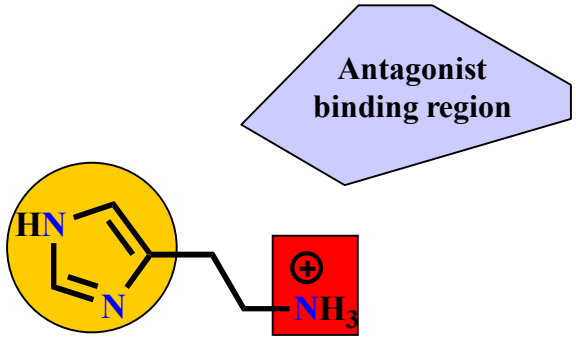
The positive charge is more diffuse and can be further away from the imidazole ring

Binding theory for agonists and antagonists

Binding of histamine



No interaction as an antagonist

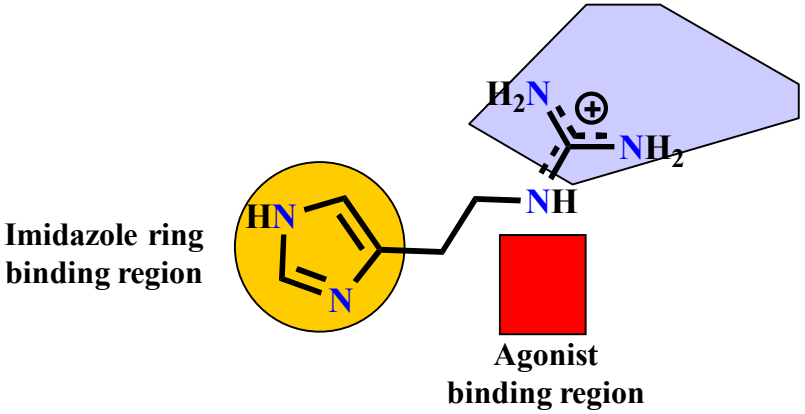


Strong interaction as an agonist

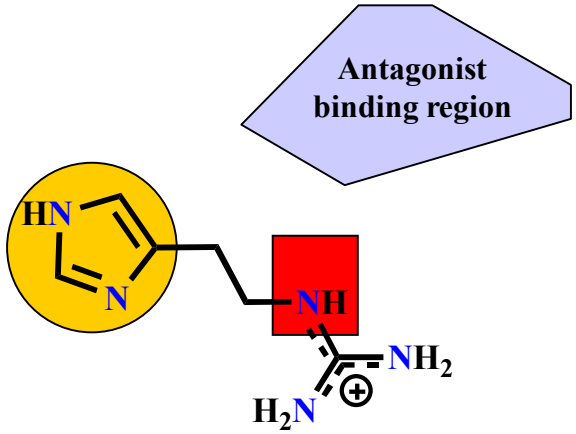
- **Histamine has a short chain**
- **Charged α-nitrogen can only reach the polar agonist region**
- **The antagonist binding region is out of range**
- **Histamine can only bind as an agonist**
- **Histamine acts as a pure agonist**

Binding theory for agonists and antagonists

Binding of *N*α-guanylhistamine



Binding as an antagonist
Receptor not activated

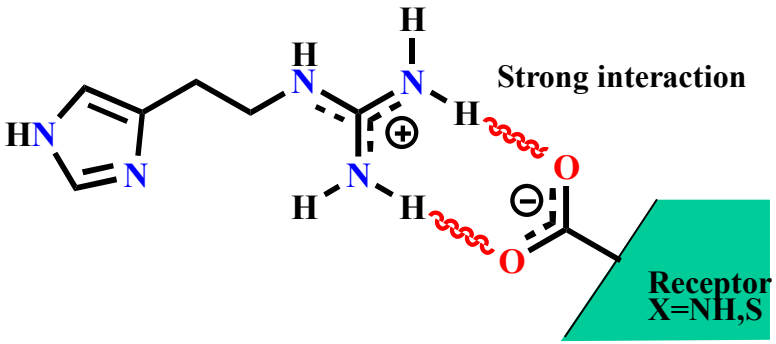


Binding as an agonist
Receptor activated

- Positive charge on the structure is more diffuse and further out
- Allows *N*α-guanylhistamine to bind in two different modes
- Structure binds as an agonist in one mode and as an antagonist in the other mode, making it a partial agonist

Chelation binding theory

The proposal

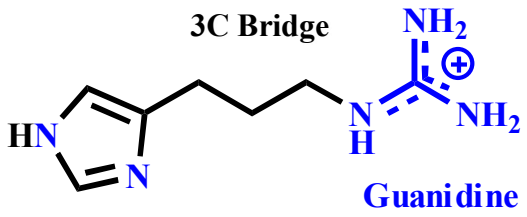


SK&F propose that the guanidine moiety interacts with a carboxylate ion in the antagonist binding region by means of two H-bonds and an ionic interaction

Chain extension strategy

Aim To push the polar guanidine group further out and to increase the interaction with the antagonist binding region

Results

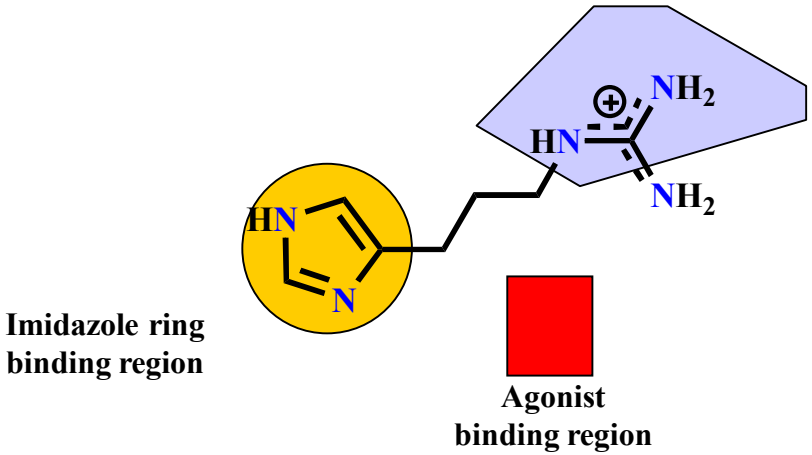


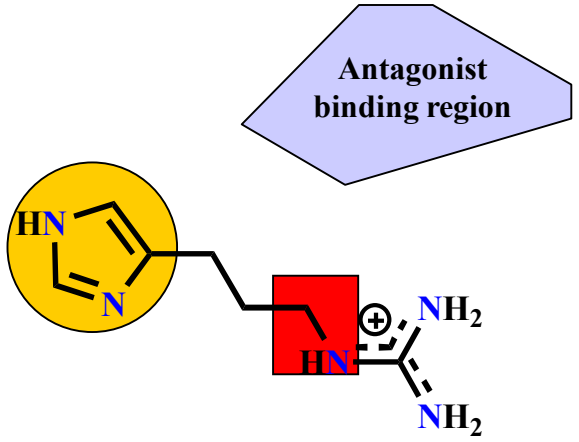
Partial agonist
Antagonist activity increases

- **Antagonist activity of the extended guanidine analogue increases as expected**

Chain extension strategy

Proposed binding for 3C extension analogues





Good binding as an antagonist

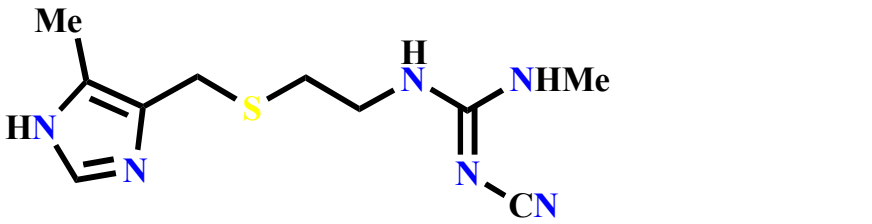
Binding as an agonist

Cimetidine

Strategy:

- Retain the guanidine group
- Guanidine is a natural group present in the amino acid arginine
- Increase activity by making the guanidine group neutral
- Add a strong electron-withdrawing group to decrease basicity (e.g. NO_2 or CN)

Cimetidine



Electron-withdrawing cyanide group

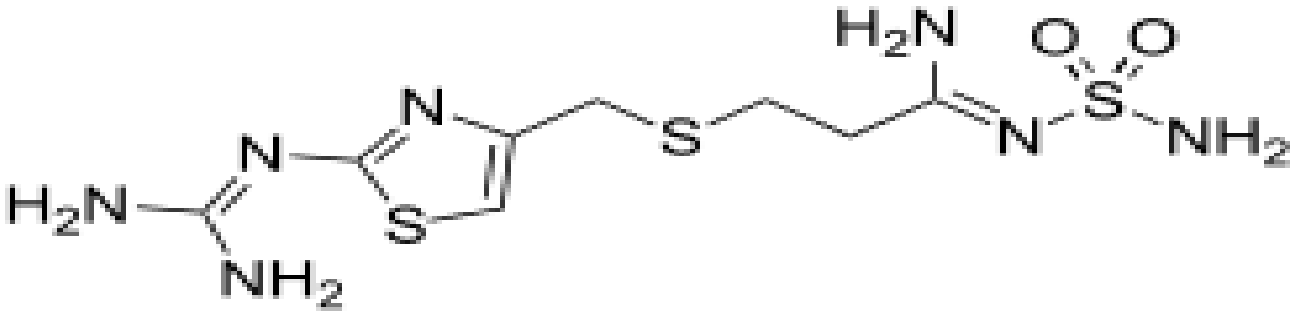
Cimetidine (Tagamet)

Properties

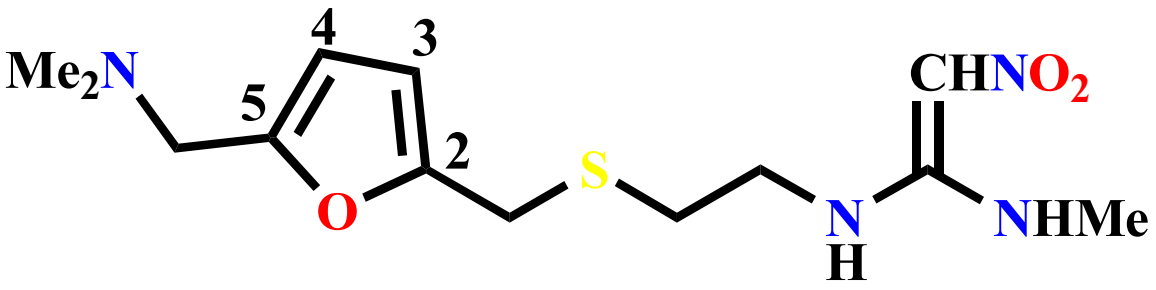
- Inhibits H_2-receptors and lowers levels of gastric acid released
- Marketed in 1976
- Biggest selling prescription drug until ranitidine
- Metabolically stable
- Inhibits cytochrome p450 enzymes
- Drug-drug interactions with diazepam, lidocaine and warfarin

Famotidine (Pepcidin, Famodar)

- More potent than
  Cimetidine (2 guanido gps)



Ranitidine (Zantac)



- Contains a nitroketeneaminal group
- Different heterocyclic ring
- Took over from cimetidine as the most widely sold prescription drug in the world