Medicinal Chemistry - II

Antihistamines, Antiallergic and Antiulcer Agents

Dr. Heba Abdel Halim

Histamine

- Synthesized in the Golgi apparatus of mast cells and basophils by enzymatic decarboxylation of histidine
- Also synthesized in the gastric mucosa, and neurons of the central nervous system (CNS) and in the periphery
- Effects include: massive bronchial spasm and effects on smooth muscle and the vasculature, anaphylactic shock

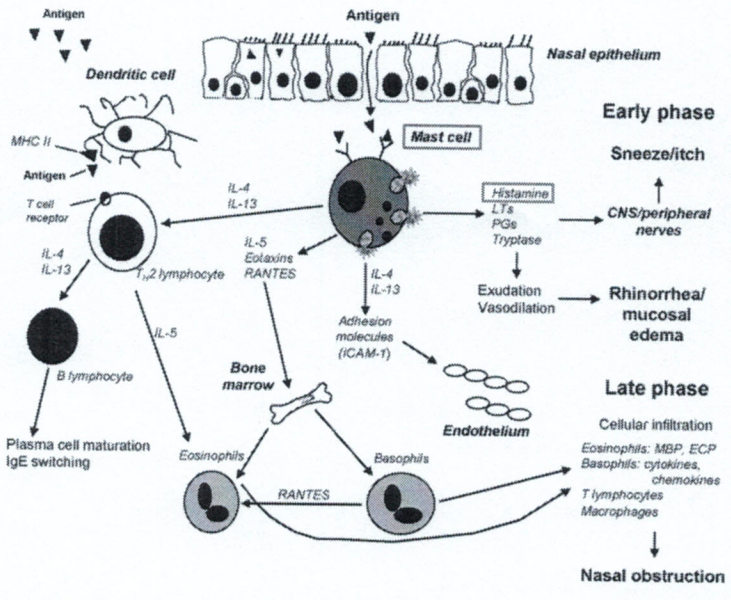
➢ **Histamine receptors**

- H_1, H_2 and H_3 and most recently H_4
- G protein-coupled receptors
- H_1 receptors:
  - ✓ Allergic inflammatory responses
  - ✓ Contraction of smooth muscles in gut, uterus and bronchi
  - ✓ Smooth muscle relaxation in fine blood vessels resulting in vasodilation, may result in severe hypotension
- H_2 receptors
  - ✓ Regulation of gastric acid secretion

Histamine

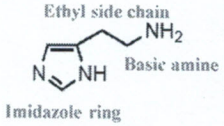
- CNS, H_1 and H_2 receptors, predominantly localized on postsynaptic membranes:
  - ✓ Physiologic role at axons in several regions of the CNS
  - ✓ Role in the regulation of sleeping and waking, in energy and endocrine homeostasis and in cognition and memory
- H_3 receptors:
  - ✓ Modulates the release of neurotransmitters
  - ✓ Function predominantly as presynaptic receptors
  - ✓ Detected in some peripheral organs
- H_4 receptor:
  - ✓ Very restricted locations in intestinal tissue, spleen and immune active cells, e.g., mast cells, eosinophils and T-cells
  - ✓ Proinflammatory mediators

Allergic Cascade



Histamine Structure

- pK_a values of 5.80 (imidazole) and 9.40 (aliphatic primary amine)
- At physiologic pH, equilibrium mixture of tautomeric cations:
  - ✓ 96% exists as monocation
  - ✓ 3% exists as dication about
  - ✓ Very small amount of the nonprotonated species



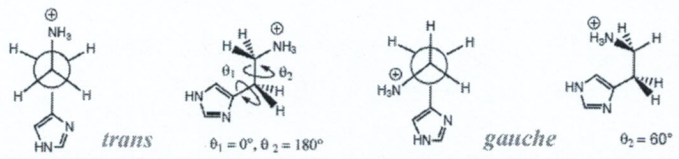
pK_a: 9.40 pK_a: 5.80

- At lower pHs increase the proportion of the dication
- The monocation and dication are the biologically active form
- Penetration of membranes via the nonprotonated species
- Changing the aromatic rings of histamine to weakly and very weakly basic heteroaromatic rings maintained the histamine agonist activity (less potent than histamine) which suggest that the monocation is sufficient for agonist activity

Histamine Structure

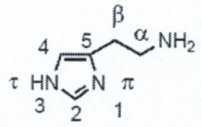
- In aqueous solutions, the tautomeric equilibrium of the imidazole ring favors the N^{τ}-H tautomer by about 4:1

- H on τ nitrogen permits binding with the receptors
- Tautomerism is not important in H_1 binding and important in the H_2 interaction
- Both *trans* and *gauche* conformations exist in solution
- The *trans* conformer has less steric hindrance but the *gauche* conformer is stabilized by an ion–dipole interaction, intramolecular



SAR of Histamine

➢ **Side Chain**



- *Trans* conformation of histamine is preferred at both H_1 and H_2 receptors
- Branching the side chain, addition of other alkyl substituents onto the histamine molecule, produces compounds with decreased potency at H_1 and H_2 receptors
- α- and β-methylhistamine exist predominantly as *gauche* conformers, very weak H_1 and H_2 agonists
- Aliphatic amine nitrogen substitution results in decreasing activity at both H_1 and H_2 receptors:

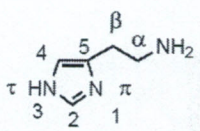
$$NH_2 > NHMe > NMe_2 > N^+Me_3 \text{ (quaternary ammonium salt)}$$

- *Gauche* conformation is favoured at the H_3 receptor because α-methyl-histamine and other more conformationally restricted analogs are potent H_3 agonists

SAR of Histamine

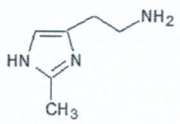
➢ **Ring modifications:**

- Imidazole N-methyl substitution:
  - ✓ N1-methyl substitution leads to inactive agents
  - ✓ N3-methyl substitution very weak at H_1 & H_2

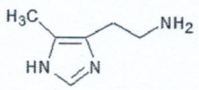


- C2-methylhistamine is a selective H_1 agonist
- C4-methylhistamine, a selective H_2 agonist

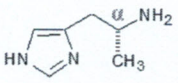
  The *trans* conformation of 4-methylhistamine cannot adopt the fully extended *trans* conformation due to the interaction of the 4-methyl group with the aliphatic two-carbon chain
- 4-Substitution causes H_2 selective where electron donor favor τ tautomer
- 5-Substitution causes H_2 selective, electron withdrawer favor τ tautomer



H_1 agonist

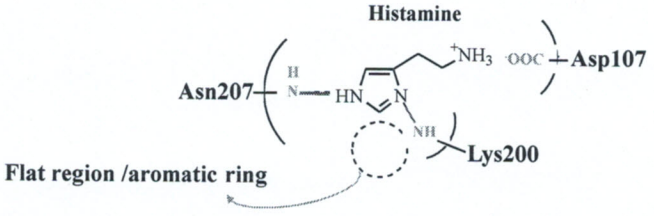


H_2 agonist



H_3 agonist

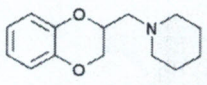
Histamine Receptor Binding



- Anionic center (Asp107) provide the initial interaction binding with the protonated amine
- The area surrounding the ionic site is small or nonexistent, *N*-methyl substitution decrease potency
- Flat region and/or aromatic amino acid residue to interact with the imidazole ring
- Asn207 interacting with the N^{τ}-nitrogen of imidazole ring
- Lys200 interacts with the nucleophilic N^{π}-nitrogen
- Between the two there is no stereoselectivity, no chirality

Histamine H_1-Antagonists

- Piperoxan protected guinea pigs against histamine-induced bronchospasm
- Isosteric modifications of piperoxan resulted in the classical H_1 antagonists
- Effective in the treatment of allergic responses



Piperoxan

➢ **First-generation H_1-antihistamines**

- Cholinergic, adrenergic, dopaminergic and serotonergic effects
- High logP
- CNS effects include: sedation, drowsiness, decreased cognitive ability and somnolence
- Other effects include appetite stimulation, muscle spasm, anxiety, confusion, and occasionally irritability, tremor and tachycardia

➢ **Second-generation H_1-antihistamines**

- Separation of CNS depressant and anticholinergic effects from peripheral antihistaminic effects
- Low logP, nonsedating
- Less anticholinergic and antiadrenergic

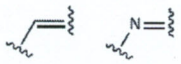
Isosteres

- **Atoms or groups of atoms which share the same valency and which have chemical or physical similarities**
- **Similarities in size, polarity, electronic distribution and bonding**
- **Bioisostere is a group that can be used to replace another group while retaining the desired biological activity**

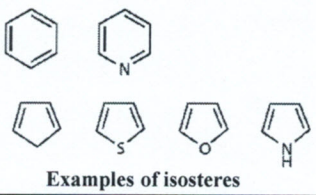
Univalent isosteres CH_3, NH_2, OH, F, Cl, SH
Br, I-Pr
I, t-Bu

Bivalent isosteres CH_2, NH, O, S

Trivalent isosteres



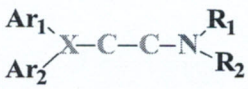
Ring equivalents



Examples of isosteres

Histamine H_1-Antagonists General Structure

➢ **General structural:**

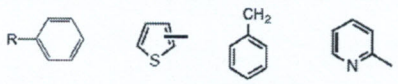


- ✓ **Two aromatic groups**
- ✓ **Connecting atom X**
- ✓ **Carbon chain**
- ✓ **Aliphatic amine (N)**

- **Variations in the different groups account for the differences observed in potency, pharmacologic, metabolic and adverse effects**

➢ **Ar_1 and Ar_2 substituents**

- **Diaryl pattern present in first- and second- generation antihistamines**
- **Phenyl or substituted phenyl, thienyl, benzyl or pyridyl**



Histamine H_1-Antagonists General Structure

➢ **Ar_1 and Ar_2 substituents, Cont**

- **Provide bulk, antagonistic activity**
- **Pyridyl generally results in more potent compounds than phenyl**
- **If fused must be non–coplanar (tricyclic antidepressant 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**

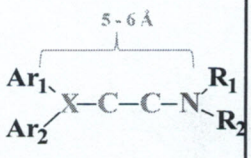
➢ **Connecting atom (X)**

- **Atom X can be an oxygen, nitrogen or carbon**
- **The nature of atom X is the basis for the structural classification of H_1 antagonists:**
  - ✓ **X = C–O: (Aminoalkyl Ethers) ethanolamines ether and propanolamines**
  - ✓ **X = C : Alkylamines (Saturated and Unsaturated)**
  - ✓ **X = N : Ethylenediamines, piperazines (cyclizines), tricyclic antidepressant and miscellaneous compounds (newer compounds that do not fall into one of the older, traditional, classes)**

Histamine H_1-Antagonists General Structure

➢ **Connecting chain**

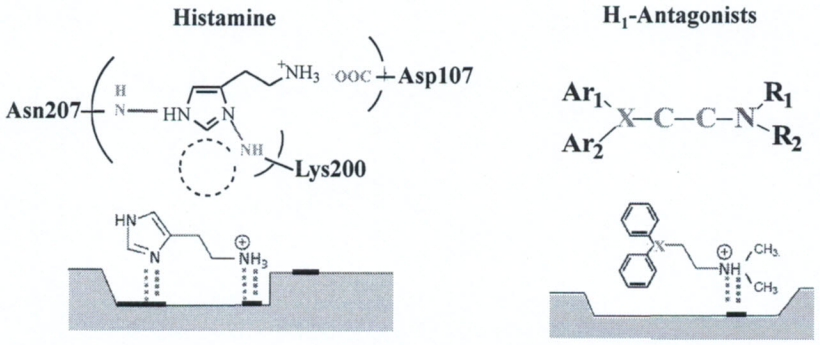
- **Function to separate the nitrogen from the rings by 5-6 Å**
- **Usually two or three carbons in length**
- **May be saturated, unsaturated, branched or part of a ring**
- **Branching decreases antihistaminic potency except for the phenothiazines where β-carbon branching increases antihistaminic potency**



➢ **Aliphatic amine**

- **Must be basic at physiological pH, protonation**
- **Simple alkyl or aralkyl groups**
- **Dimethyl is the optimum configuration**
- **R_1 and R_2 : Potency order is 3° > 2° > 1°, quaternization (4°) does not increase antihistaminic but increase anticholinergic activity**
- **Larger substituents 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**

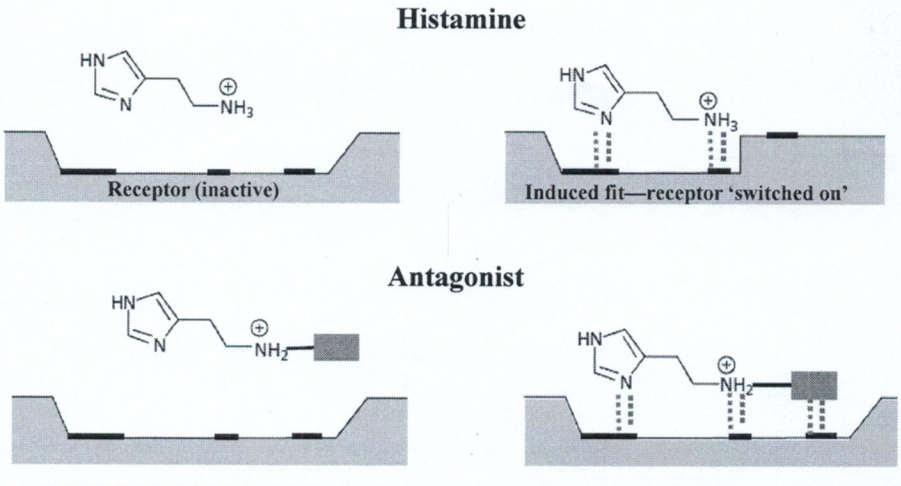
Histamine H_1-Antagonists Receptor Interaction



- The H_1 antagonists do not occupy the same area or space as the natural receptor substrate (histamine)
- Only the protonated nitrogen binds the same anionic site as Histamine (Asp107)
- The aromatic tail binds adjacent to the histamine binding site leading to nonspecific conformational perturbation of the receptor, this changes the shape of the receptor thus decreasing the affinity for histamine
- Sites adjacent to the binding site may be chiral because steroselectivity is observed with some H_1 antagonists

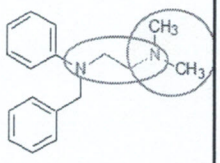
Histamine H_2-Antagonists / Antiulcer Agents

Receptor interactions of histamine and an antagonist



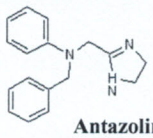
First Generation Histamine H_1-Antagonists

➢ Ethylenediamines

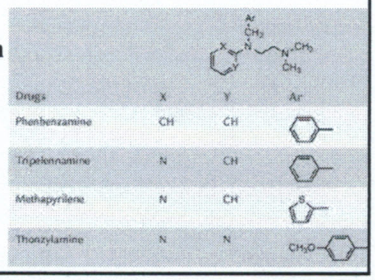


Phenbenzamine

- First clinically useful H_1 antagonist, Phenbenzamine
- Two nitrogens, only one is basic enough to be protonated at physiological pH
- Two-carbon spacers between the two nitrogen atoms
- Compounds with several different but closely related aromatic rings and include: phenyl, 2-pyridyl, halogen- and methoxy-substituted phenyl, or pyrimidyl
- Methyl groups are usually the alkyl substituents on basic nitrogen and ethylenediamine spacer
- Antazoline: the tertiary amine is replaced with an imidazoline group, less potent but lack of irritation and has local anesthetic properties, ideal for ophthalmic use



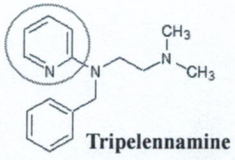
Antazoline



Drugs	X	Y	Ar
Phenbenzamine	CH	CH	
Tripelennamine	N	CH	
Methapyrilene	N	CH	
Thonzylamine	N	N	

SAR of Ethylenediamines

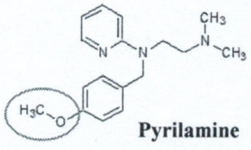
❖ Isosteric replacement



Tripelennamine

- 2-pyridyl group replacing one of the phenyl groups:
- More potent, Tripelennamine
- 3-or 4-pyridyl are not considered isosteres and produced less potent compounds

❖ Aromatic ring substitution

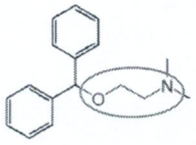


Pyrilamine

- *Para* substitution (lipophilic, e.g., Cl, Br, CH3) can increase potency
- *Ortho* substitution is highly undesirable, interferes with the ring conformation
- *Meta* substitution is either ineffective or unfavorable, due to electronic effect and increased lipophilicity
- *Para* methoxy on tripelennamine produces pyrilamine, a more potent less toxic drug

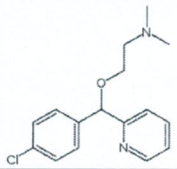
Histamine H_1-Antagonists

➢ Ethanolamine Ethers

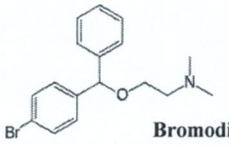


Diphenhydramine

- The prototype is diphenhydramine
- Significant anticholinergic side effects
- Sedative properties are very common
- Structural analogs with various ring substituents (Me, OMe, Cl, Br) in one of the aromatic rings
- 2-pyridyl group can replace one of the phenyl groups:
  Isosteric replacement of phenyl by a 2-pyridyl result in slight increase in potency
- Combination of 2-pyridyl and *para* chloro phenyl, carbinoxamine, 39 fold increase in potency, the chloro increases logP and metabolic stability
- The *para* substitution with Br, bromodiphenhydramine, twice as potent as the parent compound



Carbinoxamine

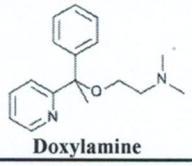


Bromodiphenhydramine

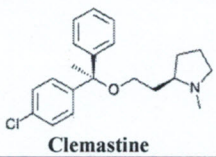
First Generation Histamine H_1-Antagonists

➢ Ethanolamine Ethers, Cont

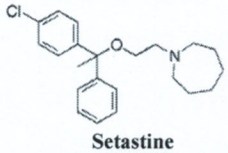
- *Para* substituents decrease anticholinergic activity and yields small increases in antihistaminic activity
- Increasing *ortho* alkyl group size (Me, Et, iPr, tBu) leads to large decreases in antihistaminic activity and increases in anticholinergic activity due to spatial orientations of the two aromatic rings with regard to each other
- Doxylamine: methyl group at the α-carbon to the ether, slight increase in potency
- Clemastine: additional carbon atom between the oxygen and the basic nitrogen (incorporated into a ring), *propanolamines*, less sedative properties:
  Lengthening the chain increases potency and duration of action (up to 12 hours)
- Setastine: alkyl amine in a seven-membered hexahydroazepine ring



Doxylamine



Clemastine



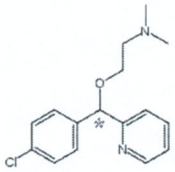
Setastine

First Generation Histamine H_1-Antagonists

➢ Ethanolamine Ethers, Cont

- Chiral center due to differences in the two aromatic rings
  - ✓ Levo (*S*) isomers are more potent than the dextro (*R*):
  - ✓ Levo (*S*) carbinoxamine is 24 times more potent than the dextro (*R*)

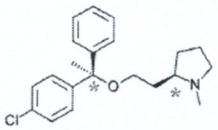
    Implies that the receptor must possess a degree of asymmetry in the area of rings binding



Carbinoxamine

  - ✓ Clemastine, with two chiral centers, potency order is: *R,R* > *R,S* > *S,R* > *S,S*

    The configuration of the chiral center at the benzhydryl carbon * (close to the rings) has a more significant influence on potency than the centre close to the nitrogen * (pyrrolidine ring)

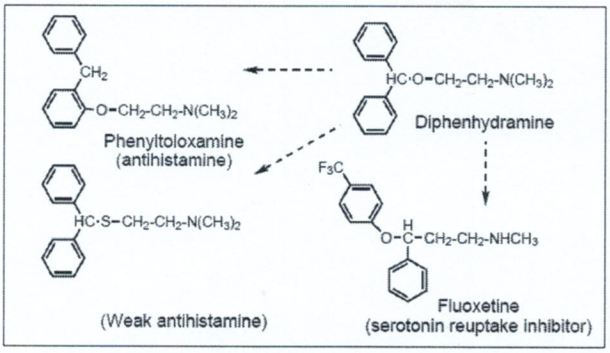


Clemastine

First Generation Histamine H_1-Antagonists

➢ Ethanolamine Ethers, Cont

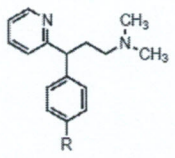
- Retro arrangement of carbon and oxygen atoms led to a series of very important selective serotonin reuptake inhibitors
- Conversion of the oxygen atom to a sulfur atom results in a great decrease in antihistaminic activity



Structural similarities among diphenhydramine related structures

First Generation Histamine H_1-Antagonists

➢ **Alkyl Amines**

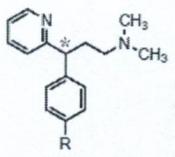


R = H; Pheniramine
R = Cl; Chlorpheniramine
R = Br; Brompheniramine

- X: carbon atom
- Classical H_1-antagonists with low anticholinergic side effects
- Most widely used
- OTC antihistamines for mild seasonal allergies
- Pheniramine is the prototype, weakest member
- Pheniramine, chlorpheniramine, brompheniramine, and the *E*-isomers of olefinic (C=C) homologs
- Halogen- substituted ring compounds, *para* position increases potency:
  - ✓ Chlorpheniramine is 10 to 20 times more potent with no increase in toxicity
  - ✓ Brompheniramine is slightly more potent but with doubled half-life
- Long duration of action and decreased incidence of central sedative side effects compared to ethylenediamines and ethanolamine ethers
- Ring isosteric replacement is limited; only the phenyl and 2-pyridyl are allowed, other replacements result in decrease in potency

First Generation Histamine H_1-Antagonists

➢ **Alkyl Amines, Cont**



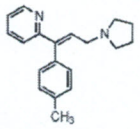
R = H; Pheniramine
R = Cl; Chlorpheniramine
R = Br; Brompheniramine

- <u>Chiral carbon</u>
- Two different aromatic rings (Ar = *p*-X-Ph, 2-pyridyl)
- The *S*-enantiomers have greater affinity for H_1-histamine receptors versus muscarinic and adrenergic receptors
- Pheniramine, chlorpheniramine and brompheniramine *S*-isomers have 200 to 1000 times greater binding to the receptor
- (+)-*S*- vs. (−)-*R*-chlorpheniramine: the (+)-enantiomer being more potent
- Single enantiomers of these agents are available:
  Dexchlorpheniramine and dexbrompheniramine

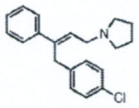
First Generation Histamine H_1-Antagonists

➢ **Alkyl Amines, Cont**

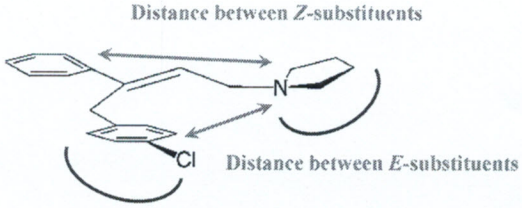
- **Olefinic (C=C) homologs of pheniramine**
- **Double bond**
- ***E*- and *Z*- isomers of the alkenes show very large differences in potency:**
  - ✓ ***E*-isomer is more potent than *Z*-isomer**
  - ✓ ***E*-pyrobutamin is 1,000-fold more potent than its *Z*-isomer**
  - ✓ **The two aromatic rings have quite different binding environments at the receptor**



***E*-Triprolidine**



***E*-pyrobutamin**

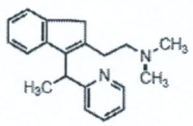


Potential binding sites based on *E/Z*-configurations

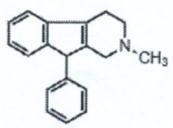
First Generation Histamine H_1-Antagonists

➢ **Alkyl Amines, Cont**

- **Dimethindene and Phenindamine, cyclic analog**

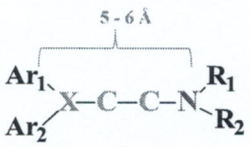


Dimethindene



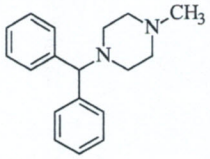
Phenindamine

- **5 - 6 Å distance between the tertiary aliphatic amine and one of the aromatic rings is required for receptor binding**



First Generation Histamine H_1-Antagonists

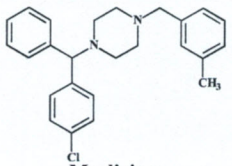
➢ Piperazines



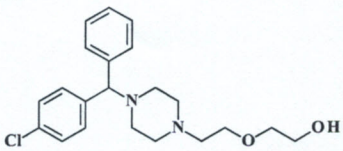
Cyclizine

- Two-carbon separation between nitrogen atoms
- The two nitrogens are basic
- Nitrogen atoms incorporated into the piperazine ring
- Diarylmethylene groups are attached to one of the nitrogens
- Alkyl or aralkyl substituent is attached to the other nitrogen
- Early compounds: cyclizine, chlorcyclizine, meclizine, buclizine, and hydroxyzine:
  - ✓ antihistamines
  - ✓ motion sickness, vertigo and for suppression of nausea and vomiting (central antiemetic effects, highly lipophilic), Main use
  - ✓ significant anticholinergic side effects and drowsiness

Chlorcyclizine



Meclizine



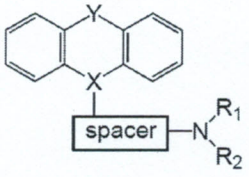
Hydroxyzine

First Generation Histamine H_1-Antagonists

➢ Tricyclic H_1-Antihistamines

- Connected aromatic through additional atoms such as: sulfur, oxygen or a short one- or two-carbon chain

  General structure:



X: C, CH, N

Y : CH_2, S, O, NH, CH_2O, CH_2CH_2, CH=CH

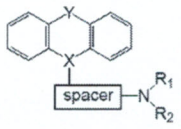
Spacer : two or three carbons

R_1, R_2 = CH_3 or five membered ring

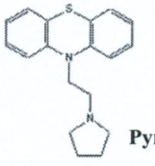
First Generation Histamine H_1-Antagonists

➢ **Tricyclic H_1 Antihistamines**

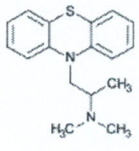
❖ **Phenothiazines**



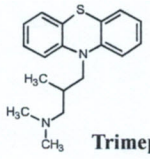
- ✓ **Y = S and X = N**
- ✓ **Two- or three-carbon branched alkyl chain between the non-basic phenothiazine nitrogen and the aliphatic amine**
- ✓ **Promethazine: antihistamine, antiemetic and anticholinergic**
- ✓ **Pronounced sedative effects and long durations of action**
- ✓ **Branching of ethyl side chain increases potency, promethazine**
- ✓ **Increasing side chain to 3 carbons decreases antihistamine potency and increases dopamine antagonism**
- ✓ **Branching of propyl side chain increases antihistamine potency but decreases dopamine antagonism, e.g., trimeprazine**



Pyrathiazine



Promethazine

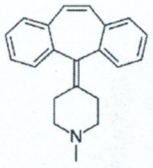


Trimeprazine

First Generation Histamine H_1-Antagonists

➢ **Tricyclic H_1 Antihistamines**

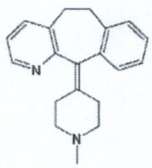
❖ **Dibenzazepine**



Cyproheptadine

- **Cyproheptadine very potent H_1-antagonist**
  - ✓ **Antipruritic**
  - ✓ **Pronounced sedation**
  - ✓ **High affinity for cholinegric and serotonin receptors**
  - ✓ **Enhances appetite thus promote weight gain, anorexia nervosa**

- **Azatadine**
  - ✓ **Phenyl replaced by a 2–pyridyl and the double bond saturated**
  - ✓ **More Potent than Cyproheptadine**
  - ✓ **H_1-antagonist, anti-serotonin and high anticholinergic potency**



Azatadine

Then:

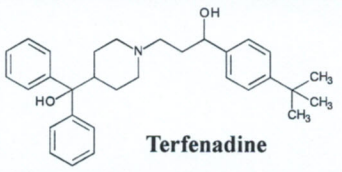
- **Second-generation antihistamines**

Second Generation Histamine H_1-Antagonists

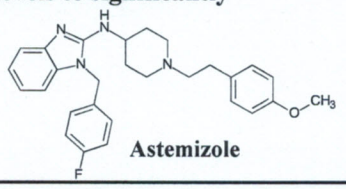
- Nonsedating H_1 Antihistamines
- Selective peripheral H_1 antihistaminic effects
- less anticholinergic activity
- Less affinity for adrenergic and/or serotonergic receptors
- Diverse in chemical structure
- Similar peripheral pharmacologic properties
- Structural resemblance to first-generation H_1 antagonists
- Limited CNS effects, do not penetrate the blood–brain barrier
- Amphoteric (*Zwitterionic* at physiologic pH)
- Drug efflux P-glycoprotein or organic anion transporters
- Very slow rates of dissociation from H_1 receptors
- Long duration of action: parent drug or its active metabolites
- Fexofenadine, terfenadine, astemizole, cetirizine and loratadine

Second Generation Histamine H_1-Antagonists

- Terfenadine, astemizole, grepafloxacin, thioridazine, sertindole, and cisapride
- No longer marketed
- Lipophilic aliphatic amines containing one or more aromatic groups
- Life-threatening cardiac arrhythmias
- Binding to the hERG K^+ ion channel
- Inhibition of K^+ ion channel leads to fatal cardiotoxicity (QT interval prolongation and arrhythmias)
- Metabolized by the same enzyme, CYP3A4:
  - ✓ Ketoconazole and erythromycin are inhibitors of CYP3A4
  - ✓ Significant drug-drug interactions with ketoconazole and erythromycin
  - ✓ Slow the metabolism increases blood levels to significantly



Terfenadine

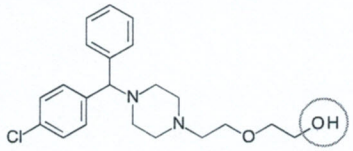


Astemizole

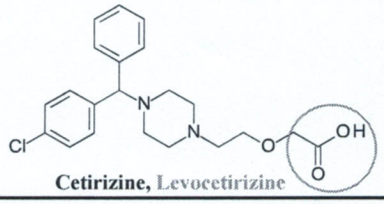
Second Generation Histamine H_1-Antagonists

➢ Piperazines

- Cetirizine, acid analog of hydroxyzine (first generation):
  Oxidation of the terminal primary alcohol to the corresponding carboxylic acid
- 6.5 times lower receptor affinity
- Highly selective for H_1 receptors
- *Zwitterion*, lower CNS effects
- Decreased, but not absent, sedative side effects, some drowsiness
- Long duration of action
- No cardiotoxicity
- The *R*-enantiomer of cetirizine, levocetirizine has higher affinity than the *S*-enantiomer for the H_1 receptor



Hydroxyzine (first generation)

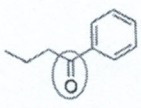


Cetirizine, Levocetirizine

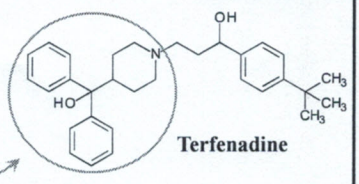
Second Generation Histamine H_1-Antagonists

➢ Butyrophenone

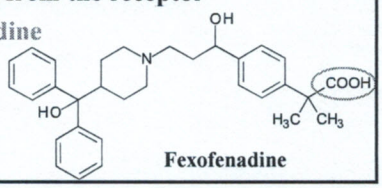
- Reduced derivative (e.g; haloperidol)
- No antipsychotic properties
- Terfenadine
- Moderate in potency
- No sedative side effects
- No significant anticholinergic activity or on any other receptor
- Antihistaminic activity is attributed to diphenylmethylpiperidine part
- Other part responsible for the lack of affinity for other receptors
- 12 hours duration of action, slow disassociation from the receptor
- Removal from market, replaced with Fexofenadine
- Carboxylic acid metabolite of terfenadine
- Antihistaminic properties of terfenadine
- No antiarrhythmic side effects



Butyrophenone



Terfenadine



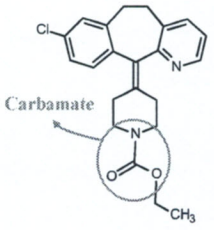
Fexofenadine

Second Generation Histamine H_1-Antagonists

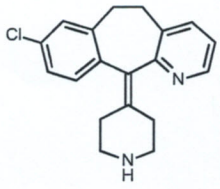
➢ Tricyclic H_1 Antihistamines

❖ Dibenzazepine

- Loratadine and Desloratadine
- Related to the first-generation tricyclic antihistamines
- Non-sedating H_1 antagonist, no anticholinergic side effects
- Cl and carboxyethyl increase potency
- Carbamate nitrogen, neutral, rapidly absorbed and quick acting
- Metabolized by CYP3A4 and 2D6 directly to desloratadine via an oxidative process without hydrolysis
- No cardiotoxic effects
- The desloratadine metabolite is more potent and with longer half-life
- Desloratadine has a slow off-rate from the H_1 receptor



Loratadine



Desloratadine

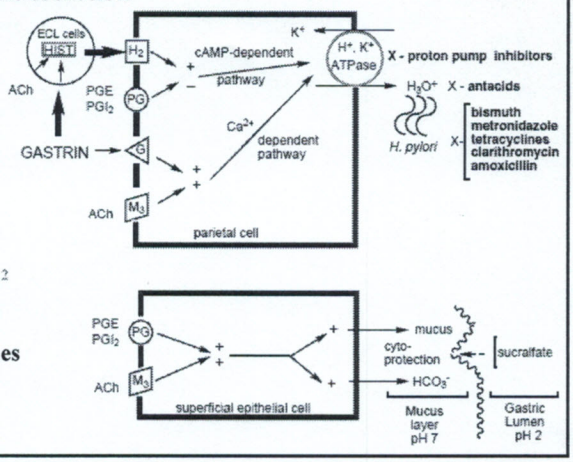
Gastric Secretions

- Secretion of gastric acid occurs at the level of parietal cells of the oxyntic gland in the gastric mucosa
- Occurs via an H^+/K^+-ATPase that exchanges hydronium ion ($H3O^+$) with uptake of K^+
- Several mediators regulate this secretion by way of receptor systems:

✓ Histamine is secreted from endochromaffin-like (ECL) cell, which is innervated by muscarinic receptors (M) via the enteric nervous system and by gastrin receptors (G)

✓ Agonist occupation of histamine H_2 receptors in parietal cells leads to gastric acid secretion (H_2)

✓ Other input at parietal cells includes the prostaglandins (PGs), gastrin, and muscarinic receptors



Histamine H_2-Antagonists / Antiulcer Agents

- Used in the treatment of duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD)
- Included in multidrug treatment protocols for eradication of *H. pylori*
- H_2 antihistamines designed to decrease the secretion of gastric acid

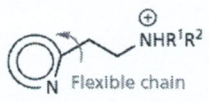
➢Rational Drug Design

- Based on an extensive investigative approach to drug design came the first breakthrough in anti-ulcer therapy with the design of the H_2 antagonist cimetidine (Tagamet®)
  - Early example of rational drug design
  - No lead compounds, natural product
  - No known target, histamine receptor
  - The idea started to find a block for the gastrin effect
  - Conventional antihistamines failed to inhibit gastric acid release, not all the actions of histamine

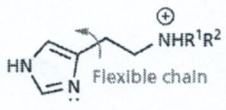
Histamine H_2-Antagonists / Antiulcer Agents

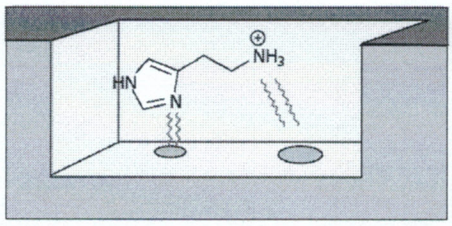
Histamine binding

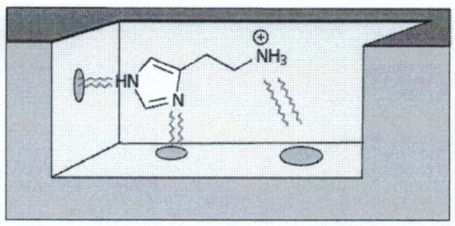
H_1 receptor



H_2 receptor



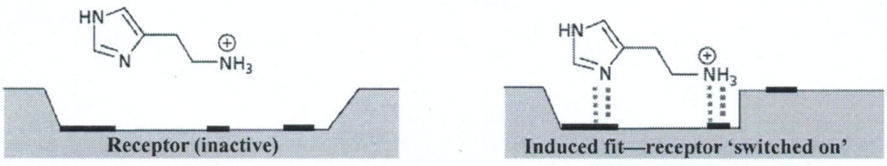




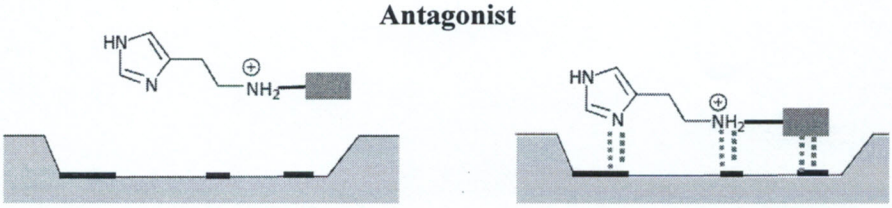
Histamine H_2-Antagonists / Antiulcer Agents

Receptor interactions of histamine and an antagonist

Histamine

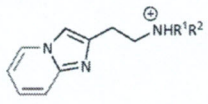


Antagonist

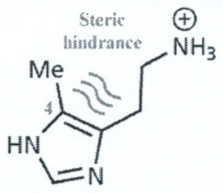


Histamine H_2-Antagonists / Antiulcer Agents

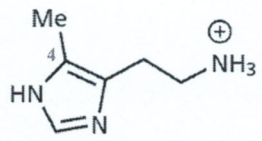
- **Alterations on histamine**
- **Fusing an aromatic ring on histamine, not antagonist**



- **Substituents to different locations of the histamine skeleton, not antagonist:**
  4-methylhistamine selective H_2 agonist, stimulated gastric acid release
  4-methyl group is acting as a conformational blocker
  This conformation is required for:



H_1 receptor

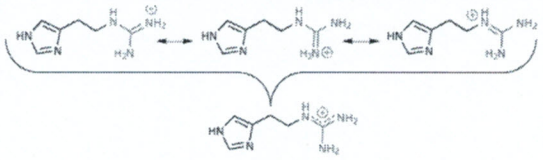


H_2 receptor

Histamine H_2-Antagonists / Antiulcer Agents

- Adding hydrophobic groups, two hundred compounds, no antagonist activity
- Then studied the effect of varying polar groups on the terminal α-NH 3^+: Binding to the same region as the histamine -NH 3^+ group but with different the geometry of bonding to produce an antagonist lead to:

  N^{α}-guanylhistamine, weak antagonist of gastric acid release



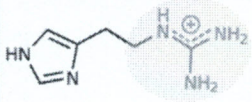
N^{α}-guanylhistamine

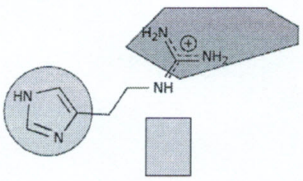
- Guanidine structures with no imidazole ring, no antagonist activity
- Both imidazole ring and the guanidine group are required
- Similarity between of N^{α}-guanylhistamine and histamine:
  1. imidazole ring
  2. positively charged group, guanidine group is basic and protonated
  3. two-carbon bridge

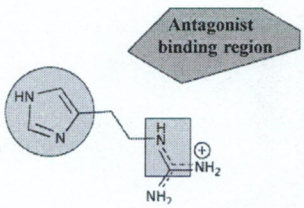
Histamine H_2-Antagonists / Antiulcer Agents

- N^{α}-guanylhistamine is <u>partial</u> agonist:
  - ✓ activates the H_2 receptor, not to the same extent as histamine, week agonist
  - ✓ histamine would be prevented from binding, antagonist

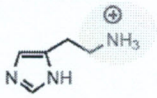
N^{α}-guanylhistamine

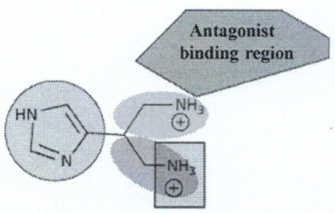






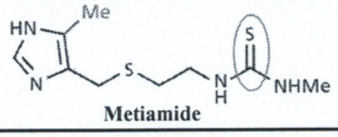
Histamine



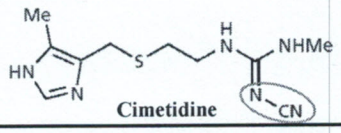


Histamine H_2-Antagonists / Antiulcer Agents

- N^{α}-guanylhistamine, lead compound
- Extension of the side chain
- Replacing the basic guanidino group with the neutral thiourea
- Further chain extension led to burimamide
- Burimamide is 100 times more potent than N^{α}-guanylhistamine, lacked agonist action, not orally absorbed
- Burimamide imidazole ring pK_a value of 7.25, modify structure to favour N^{τ}-hydrogen
- Thiaburimamide, lower pK_a of 6.25 and enhanced H_2-antagonist potency
- N^{τ}-hydrogen tautomer, 4-methylhistamine: metiamide
- Metiamide side effects associated with the thiourea group
- Replacement of this group with strong electron withdrawer but more lipophilic cyano derivative yielded the metiamide cyanoguanidine analogue: cimetidine
- Cimetidine inhibits the cytochrome P-450 enzymes in the liver, drug - drug interactions and has antiandrogenic action

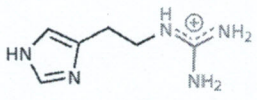


Metiamide



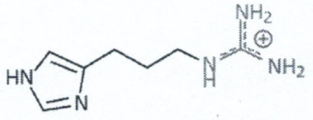
Cimetidine

Histamine H_2-Antagonists / Antiulcer Agents



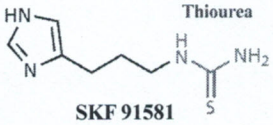
N^{α}-guanylhistamine

Chain extension



Increased H_2-antagonist activity
Some agonist activity

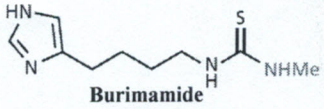
Thiourea



SKF 91581

Weak H_2-Antagonists
No agonist activity

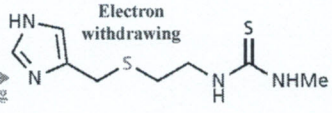
Chain extension
N-methyl group



Burimamide

Specific competitive H_2-antagonist activity
No agonist activity
pK_a: 7.25

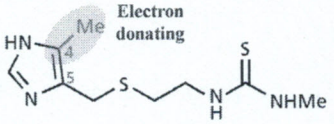
Electron withdrawing group



Thiaburimamide

Increases H_2-antagonists activity
pK_a: 6.25

Electron donating group

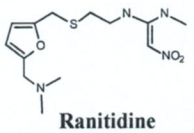


Metiamide

Histamine H_2-Antagonists / Antiulcer Agents

➢ Ranitidine

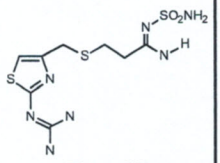
- Furan derivative, isostere of the imidazole
- 4-10 times more potent than cimetidine
- Longer duration of action
- The tertiary amine side chain allows of salt formation
- Weak inhibitor of cytochrome P-450 enzymes



Ranitidine

➢ Famotidine

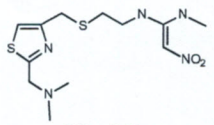
- Thiazole derivative
- 9-15 more potent than ranitidine and 40–60 than cimetidine
- Salts can easily be prepared for this compound
- Weak inhibitor of cytochrome P-450 enzymes



Famotidine

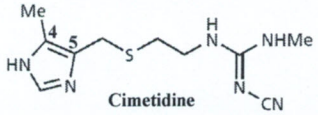
➢ Nizatidine

- Thiazole derivative similar to Famotidine
- 5-18 more potent than cimetidine
- No antiandrogenic or enzyme inhibition
- No inhibition of cytochrome P-450 enzymes



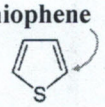
Nizatidine

SAR of Histamine H_2-Antagonists



Cimetidine

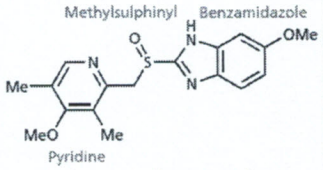
- Aromatic ring, imidazole ring is not required for activity
- Replacing the ring with more hydrophobic rings such as phenyl or thiophene reduces activity



- Imidazole ring: predominant N^{τ}-hydrogen
- The terminal nitrogen group should be polar but not basic for maximal potency
- Electron donor methyl at C4 and electron withdrawing side chain at C5
- Replacing the sulphur atom with a $-CH_2$ leads to a drop in activity in cimetidine and ranitidine
- Placing the sulphur next to the ring lowers activity
- Replacement of sulphur by a $-CH_2$ group increase activity of famotidine and nizatidine
- Side chain: separation of the ring from the nitrogen group by 4 atoms gives maximal potency

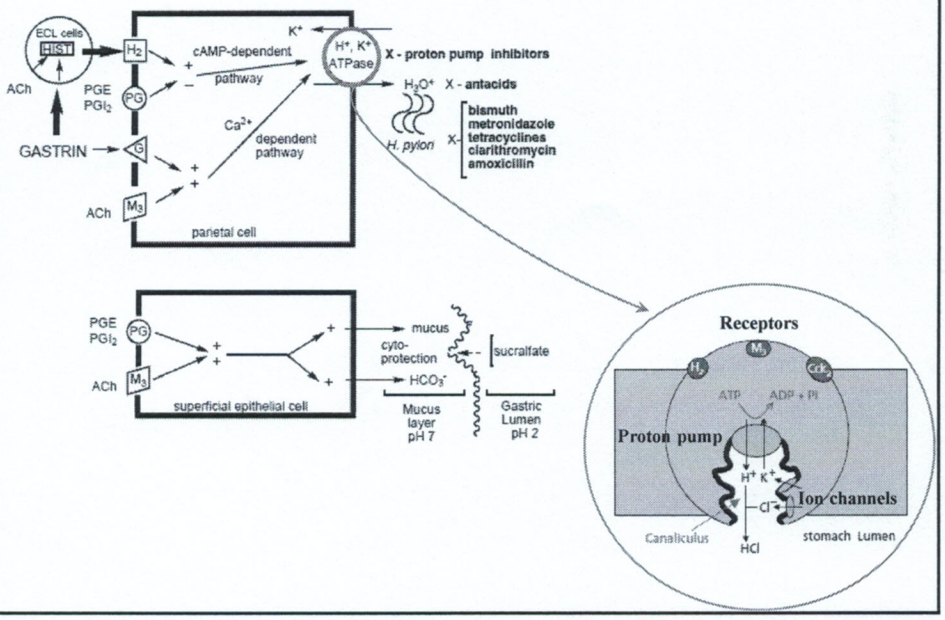
Proton Pump Inhibitors

- PPIs
- Omeprazole , lansoprazole, pantoprazole and rabeprazole
- Irreversibly inhibiting the enzyme complex: proton pump or H^+/K^+-ATPase, export of protons from the parietal cell
- Superior to the H_2 antagonists
- Used alone and in combination for *H. pylori* treatment
- Pyridyl methylsulphinyl benzamidazole skeleton
- Prodrugs, activated in the acidic canaliculi of parietal cells
- Bind irreversibly to exposed cysteine (Cys) residues of the proton pump and prevent further release of hydrochloric acid
- 'Downstream' in the acid secretion of hydrochloric acid release
- Very few side effects:
  1. Target enzyme (H^+/K^+-ATPase) is only present in parietal cells
  2. Drug is inactive at neutral pH
  3. Drug is rapidly activated close to the target
  4. As activated the drug reacts rapidly with the target



Omeprazole

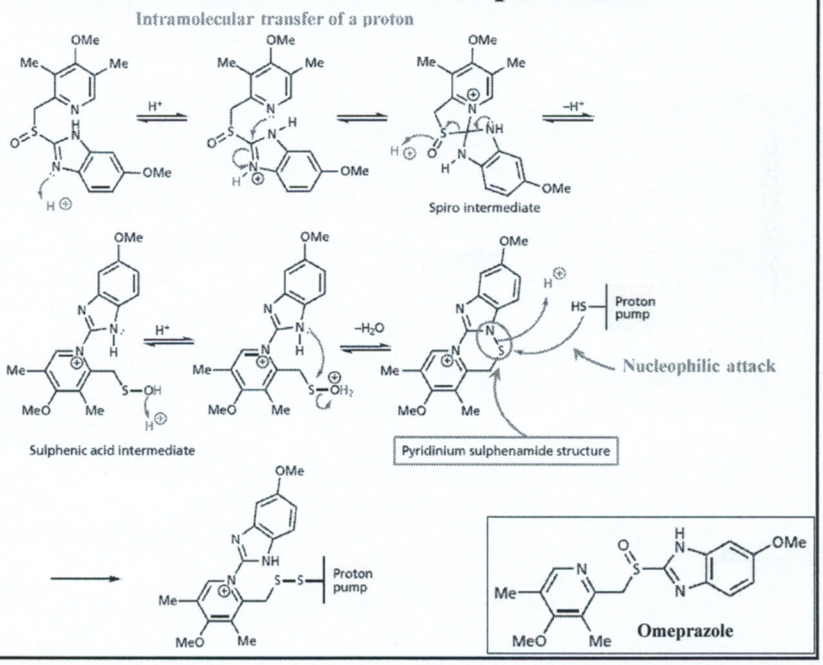
Proton Pumps



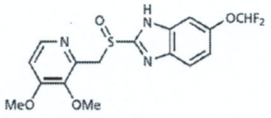
Mechanism of Proton Pump Inhibition

- Weak bases, pK_a 4.0
- Ionized only in the secretory canaliculus of the parietal cell (pH:2)
- The consequences of this:
  - ✓ Ionized drug is too polar to cross back into the cell, a 1000-fold accumulation of the drug in the site of action (canaliculi)
  - ✓ Protonation triggers an acid-catalysed conversion that activates the drug
- Protonation on the benzimidazole ring
- Cationic, tetracyclic pyridinium sulphenamide is formed, rate of enzyme inhibition corresponds to the rate of sulfenamide formation
- Sulfenamide reacts with thiol groups in the enzyme, forming a disulfide link (-S-S-), irreversible enzyme inactivation
- Forming a covalent bond with a accessible cysteine residues on the proton pump (Cys-813, Cys-892 and Cys-821)
- Long duration of action, depends on new pumps generation by the cell

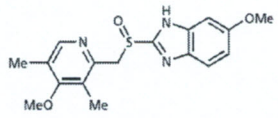
Mechanism of Proton Pump Inhibition



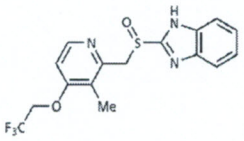
Proton Pump Inhibitors



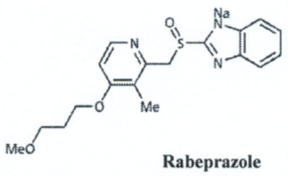
Pantoprazole



Omeprazole

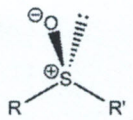


Lansoprazole



Rabeprazole

- All PPIs have similar potencies
- Differences in structure result in differences in pharmacokinetics
- Differences in oral bioavailability are not clinically important
- All the PPIs are chiral, chiral sulfur

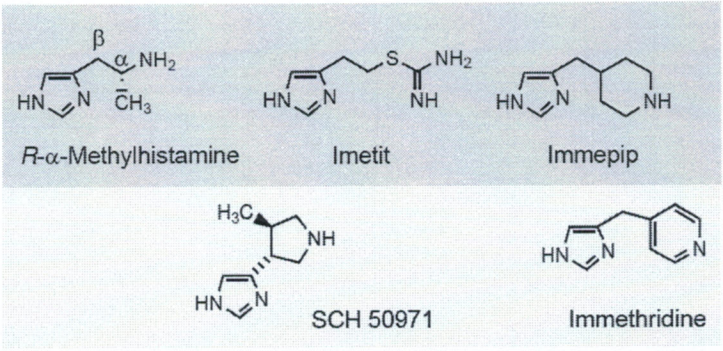


- Both isomers are converted into the nonchiral active species at the same rate
- First pass metabolism primarily by CYP3A4 and CYP2C19

Histamine H_3- Agonists and Antagonists

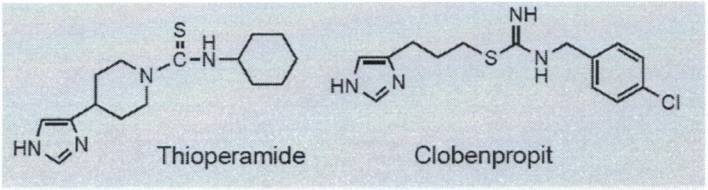
- Several H_3 receptor agonists and antagonists have been studied
- Potential for treating asthma, migraine, hypertension, septic shock, depression, mild, cognitive impairment, Alzheimer disease, schizophrenia, narcolepsy, obesity, and attention-deficient hyperactivity disorder
- Selective agonists are the isothiourea imetit, immepip and its N-methyl analog methimep, all retain the imidazole ring of histamine
- Thioperamide and clobenpropit are examples of potent and selective H_3 receptor antagonist, retain the imidazole group but possess widely varying N-substituent
- Some of the imidazole containing agonist and antagonist analogs have affinity for other receptors (e.g., some α-adrenergic receptor subtypes)
- Centrally acting H3 antagonists are under study by several drug companies
- Lead compounds, some have entered clinical trial, are tiprolisant, JNJ 1018146, and GSK-189254

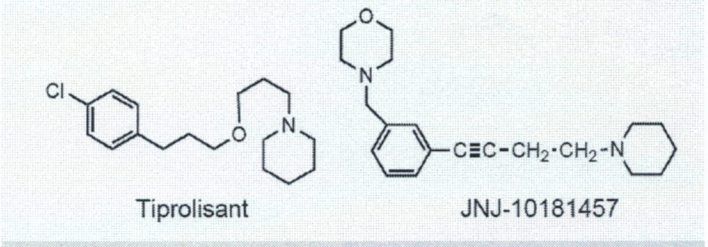
Histamine H_3- Agonists

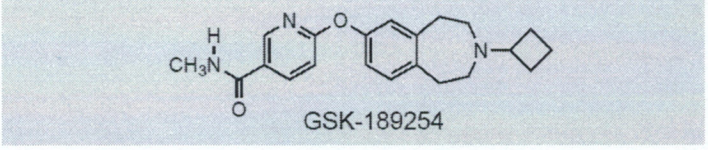


R-α-Methylhistamine Imetit Immepip

Histamine H_3- Antagonists







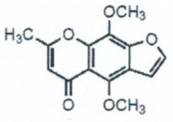
Inhibitors of Histamine Release

- **Bronchodilatory activity of khellin:**

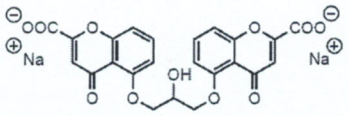
  Plant chromone (*Ammi visnaga*) used by ancient Egyptians for spasmolytic activity
- **Cromolyn sodium and Nedocromil sodium, bischromones**
- **Mast cell stabilizers, prevent the release of histamine from mast cells**
- **Inhibit function of other cells, may occur in later stages of inflammatory responses**
- **Cromolyn has no intrinsic antihistaminic or anti-inflammatory activity**
- **Used prophylactically for bronchial asthma and prevention of exercise-induced bronchospasm, and for seasonal and perennial allergic rhinitis (nasal solution)**
- **Used as eye drops for allergic conjunctivitis and keratitis**
- **Very low oral bioavailability**

Chromone

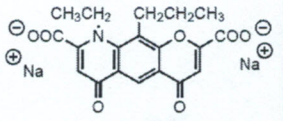
Khellin



Khellin



Cromolyn sodium



Nedocromil sodium

Mandatory Reading

Foye's principles of medicinal chemistry
7th edition, Thomas L. Lemke and David A. Williams, LWW, 2013

Chapter 32:

Antihistamines, Related Antiallergic and Antiulcer Agents