

Antihistamines and anti ulcer drugs

Abdu Tuha

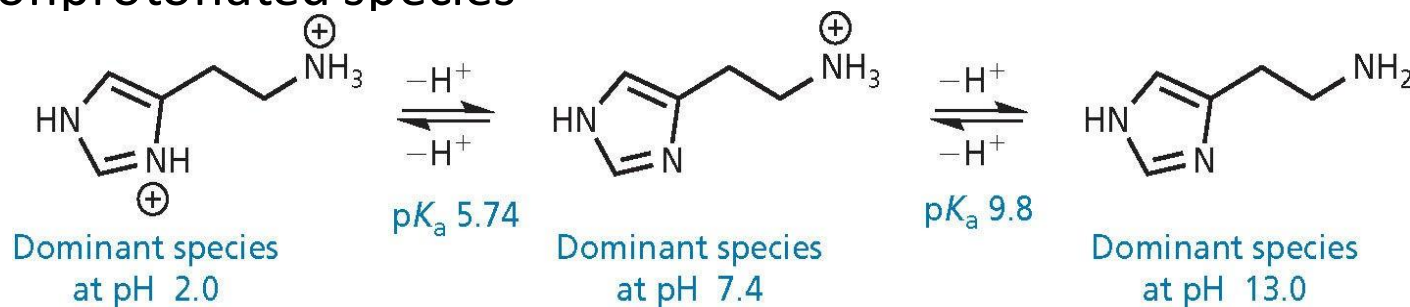
Antihistamines

Histamine

- Histamine consists of imidazole and ethylamine side chain
- Imidazole N at 3 is designated as *pros* (π) N, N at 1 is termed *tele* (τ) N
 - Side chain N is distinguished as $N\alpha$
- Histamine has pK_a of 5.74 (imidazole) and 9.40 (aliphatic primary amine)
- At physiological pH , it exists as an equilibrium mixture of tautomeric cations

Histamine cont.

- Monocation making up > 96% and dication \approx 3%, only very small amount of nonprotonated species
- Penetration of membranes by histamine would be expected to occur via the nonprotonated species



Histamine cont.

- The two-protonated species are considered as active forms
- Aromatic ring congeners of histamine with weakly and very weakly basic heteroaromatic rings (4-chloroimidazole, 1,2,4-triazole and pyridine) exhibit agonist activity, less potent than histamine
 - Monocation (protonated aliphatic amine) is sufficient for agonist activity and protonation of the heterocyclic ring is not an absolute requirement

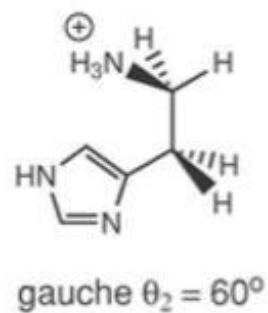
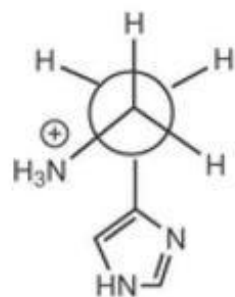
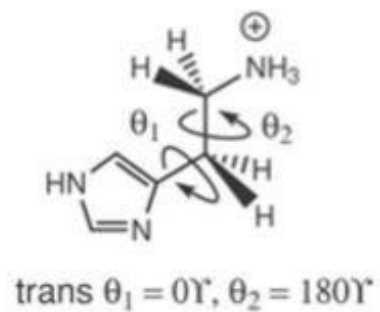
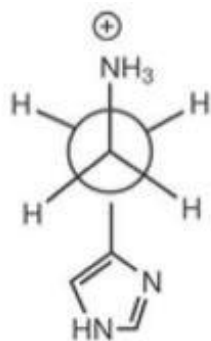
Histamine cont.

- In aqueous sol, tautomeric equilibrium of imidazole favors N^T-H tautomer by 4:1
- Change in tautomeric composition occurs with changes in the 4-substituent
 - CH_3 vs. Cl ; proportion of N^T-H tautomer decreased in the chlorine substituted congener to 12% vs. 70% for 4-methylhistamine and decreased potency is observed
 - Tautomeric composition might be important in receptor interaction

Histamine cont.

- Conformational studies indicate both *trans* and *gauche* conformations exist in solution
- *Trans* conformation of 4-methylhistamine, selective H₂ agonist, cannot readily adopt the fully extended *trans* conformation because of interaction of 4-methyl with aliphatic chain
- α - and β -methylhistamine exist predominantly as *gauche* conformer and both are very weak H₁ and H₂ agonists

Histamine cont.

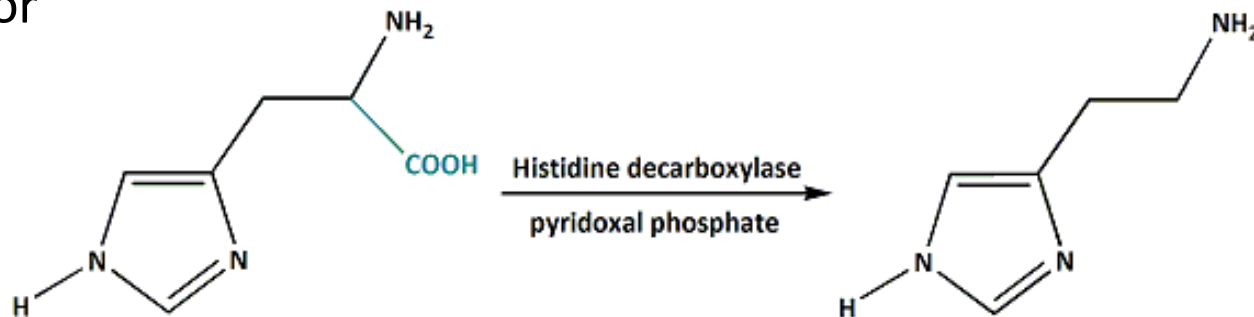


Histamine cont.

- Suggested that *trans* of histamine is preferred at both H₁ and H₂
- *Gauche* conformation suggested for histamine at H₃ receptor, because α -~~meth~~ylhistamine and some conformationally restricted analogues are potent H₃ agonists
- Imidazole N-substitution with methyl result in nearly inactive analogs
- Similarly aliphatic amine substitution result in decreasing activity NH₂ > NHMe > NMe₂ > N⁺Me₃ at both H₁ and H₂

Physiological characteristics of histamine

- Histamine is synthesized in the Golgi apparatus of mast cells and basophils by enzymatic decarboxylation of L-histidine
 - Catalyzed by L-histidine decarboxylase with pyridoxal phosphate serving as cofactor

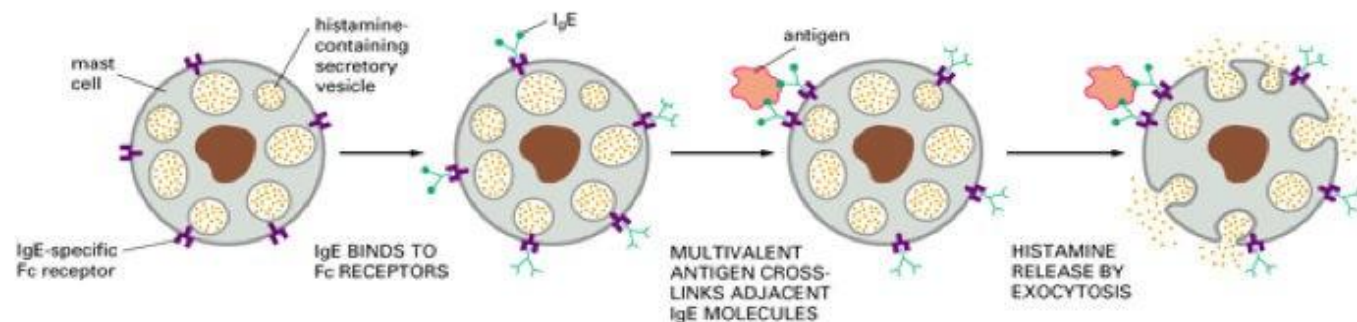


Physiological cont.

- Initial contact of an antigen leads to antigen specific IgE by B cells
- Fc region of IgE binds to FcεRI located on the surface of mast cells in tissues and on basophils in the blood
 - IgE bound in turn serve as receptors for antigen
- Re-introduction of antigen causes cross-linking of Fab components of adjacent IgE antibodies, triggers the release of histamine

Physiological cont.

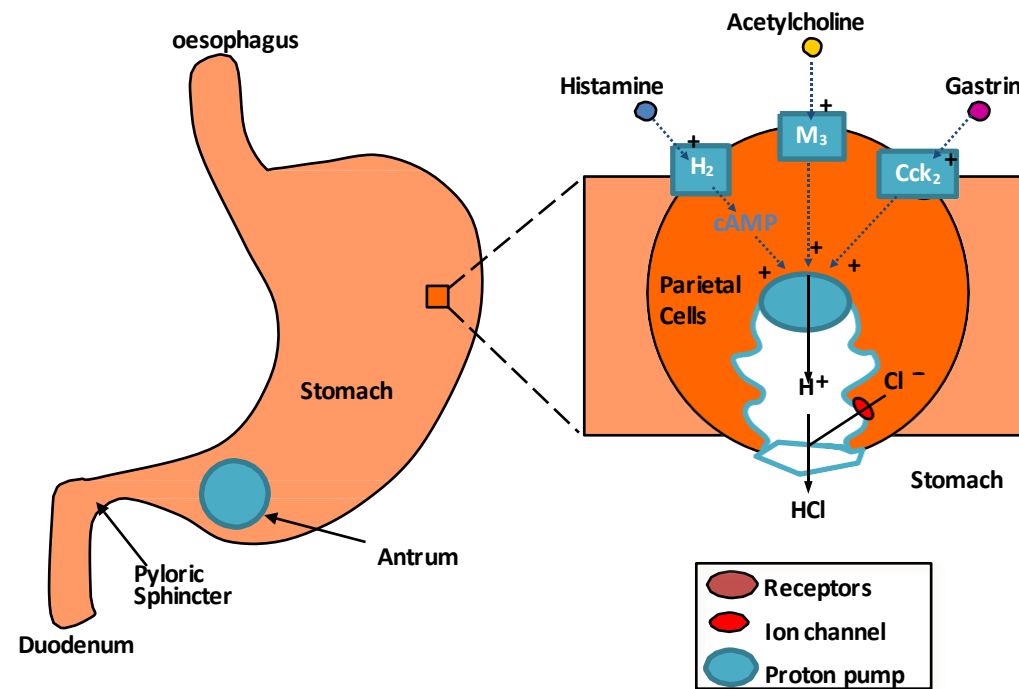
- Histamine released bind to H_1 to cause dilation and an increase in the permeability of blood vessels
 - Are largely responsible for the clinical manifestations of allergic reactions as hay fever, asthma, and hives



Physiological cont.

- Three agonists stimulate parietal cells: **gastrin**, histamine and Ach
 - Gastrin binds to CCK_B receptors on the parietal cell to evoke an increase in intracellular calcium
 - Histamine binds to H_2 that primarily signal through increased cAMP
 - Ach binds to M_3 to stimulate an increase in intracellular calcium
- Parietal cell stimulation results in movement of $\text{H}^+/\text{K}^+-\text{ATPase}$ to the apical membrane to secrete acid

Physiological cont.



Physiological cont.

- Histamine is released from ECL cells
 - In response to gastrin stimulation and
 - Neuronal stimulation via **PACAP** by binding to PACAP-1
- **Somatostatin** released from D cells inhibits acid secretion by reducing
 - ECL cell's histamine release
 - Blocking gastrin release and
 - Directly inhibiting parietal cell acid secretion

Physiological cont.

- Unstimulated state; parietal cells contain abundant intracellular tubulovesicles that sequester proton pumps beneath the cell surface
- Stimulation; tubulovesicles fuse with apical membrane of the parietal cell, exposing proton pumps to lumen and thus enabling acid secretion
- Cessation of acid secretion occurs upon internalization of H^+/K^+ -ATPase and the re-establishment of the intracellular tubulovesicles

Histamine receptors

- H_1 -receptors mediate smooth muscles contraction, increased vascular permeability, pruritus, prostaglandin generation, decrease in AV conduction time accompanied by tachycardia and activation of vagal reflex
- Human H_1 is GPCR (7 TMs) and contain 487-amino-acid
- Signal transduction processes begin with $G_{q/11}$ -coupled hydrolysis of phosphatidylinositide to IP_3 and DAG, via activation of phospholipase C

Receptors cont.

- **H₂-receptors** are coupled via G_{αs} to activate adenylyl cyclase for synthesis of cAMP
 - In some systems it is coupled to G_q to stimulate PLC
- Aspartate in third TM is highly conserved, suggested to be a recognition site for the protonated aliphatic amine at both H₁ and H₂
- Threonine and/or asparagine in fifth TM of both H₁ and H₂ suggested to be sites of binding of imidazole

Receptors cont.

- **H₃-receptors** function as a neuronal autoreceptor (Presynaptic) serving to modulate histamine synthesis and release in the CNS
 - Activation leads to a decrease in histamine release
 - Activated via G_{αi/o}, coupled negatively to AC
- **H₄ receptors** are limited to hematopoietic system
 - Histamine stimulation results in a chemotactic response, cell migration, suggests a role in the inflammatory response

H₁-antagonists

First generation H₁-antagonists

- Are useful in treatment of allergic responses; hay fever, rhinitis, urticaria and conjunctivitis
- Have additional effects on cholinergic, adrenergic, dopaminergic and serotonergic receptors



General structure

1G cont.

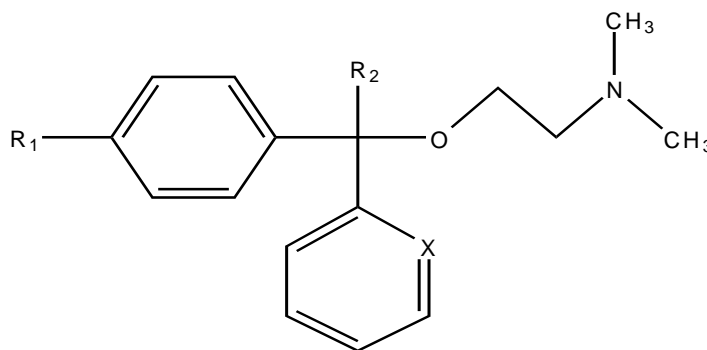
- The nitrogen should be 3° for maximum activity
- The nitrogen may also form a part of heterocyclic moieties like piperidine or piperazine
- The R groups attached to aliphatic amine are usually simple alkyl group
- The spacer is usually two or three carbon in length and it may be in a ring, may be branched, and may be saturated or unsaturated

1G cont.

- Aromatic groups (Ar_1 , Ar_2) may be aryl or heteroaryl, which may be substituted
- The group (X) can be carbon, CHO or nitrogen
- Most antihistamines are inverse agonists rather than neutral antagonists
- Inverse agonists bind to the inactive conformation of the receptor, shifting the equilibrium toward the inactive state
 - Neutral antagonists interact with both conformations of the receptor

Ethanolamine ethers

- The general structure for ethanolamine ethers



- The aromatic groups may be phenyl, substituted phenyl or heterocyclic for good antihistaminic activity

Ethanolamine cont.

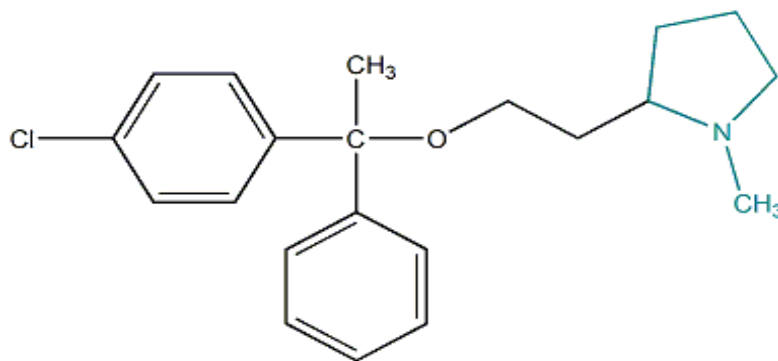
Drugs	R ₁	R ₂	X
Diphenhydramine	H	H	CH
Bromodiphenhydramine	Br	H	CH
Chlorodiphenhydramine	Cl	H	CH
Carbinoxamine	Cl	H	N
Doxylamine	H	CH ₃	N

Ethanolamine cont.

- **Diphenhydramine** was the first clinically useful ethanolamine series and serve as the prototype
- The compound with the aryls *p*-Cl-Ph and 2-pyridyl is **carbinoxamine**, a potent antihistamine
- Substitution of a methyl at carbon α to ether affords the related compound **doxylamine**, in which the aryls are phenyl and 2-pyridyl

Ethanolamine cont.

- **Clemastine**, a homologue with an additional carbon between oxygen and the basic nitrogen, which is incorporated into a ring
 - Is a recent addition to the group with less sedative properties



Ethanolamine cont.

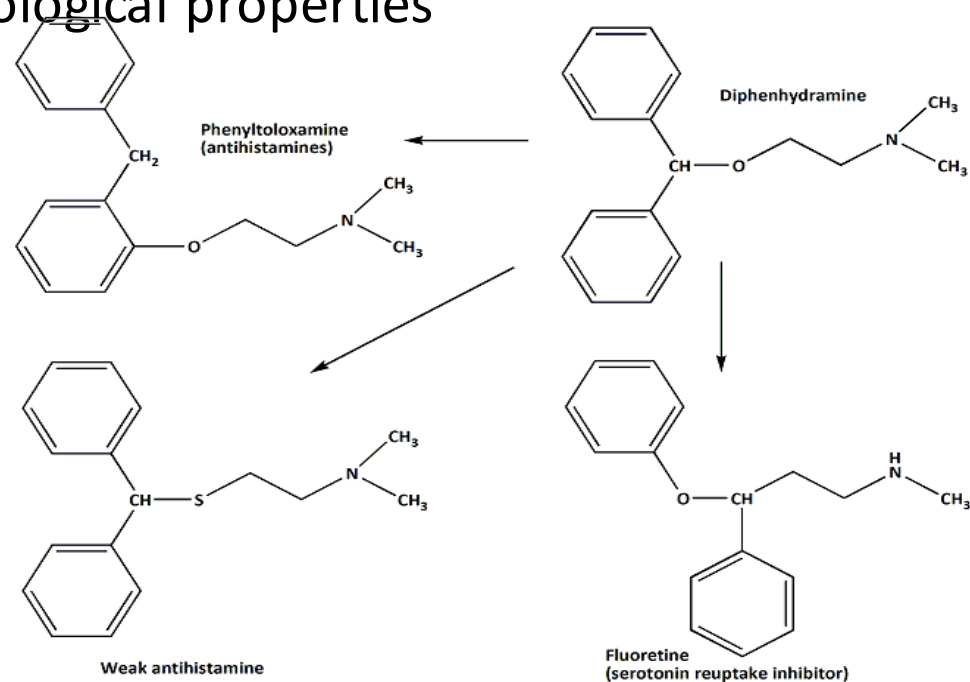
- Clemastine is marketed as R,R-enantiomer, more potent than either R,S- and S,R-enantiomers
- Diphenhydramine is used in treatment of Parkinsonism because of its central cholinergic property
- **Dimenhydranate** is 8-chlorotheophylline salt of diphenhydramine and is recommended for nausea of motionsickness and hyperemesis gravidarum

Ethanolamine cont.

- Increasing alkyl size at C2' of one of the aromatic ring, large decreases in antihistaminic activity and increases in anticholinergic activity
 - With larger alkyl, spatial orientations between the two aromatic rings are limited because of increasing rotameric restrictions
- Introduction of these alkyl substituents at C-4' decreases anticholinergic activity and yields small increases in antihistaminic activity

Ethanolamine cont.

- Very small changes in the arrangement of aromatic groups significantly alter pharmacological properties



Ethylenediamines

- R' and R are usually methyl, Ar may be phenyl, benzyl or heterocyclic and Ar' may biphenyl or heterocyclic for antihistaminic activity
- All compounds have two 3° nitrogens separated by a two carbon chain
- Exhibit high frequency CNS depression and GI SEs
- **Phenbenzamine** serve as the prototype for the development of more effective derivatives

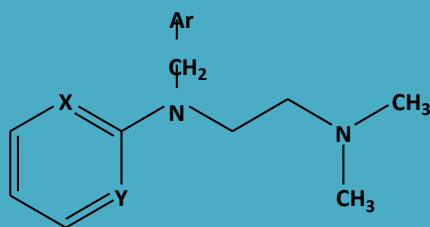
Ethylenediamines cont.

- Replacement of the phenyl of phenbenzamine with a 2-pyridyl yielded **tripelennamine**, a more effective histamine blocker
- Substitution of a para methoxy (**pyrilamine** or **mepyramine**), chloro (**chloropyramine**), or bromo (**bromotripelennamine**) resulted in further enhancement in activity
- **Methapyrilene** and **thonzylamine** are potent H₁ antagonists

Ethylenediamines cont.

- Replacement of benzyl of tripeleennamine with 2-thienylmethyl provided methapyrilene
- Replacement of tripeleennamine's 2-pyridyl with pyrimidinyl yielded thonzylamine

Ethylenediamines cont.



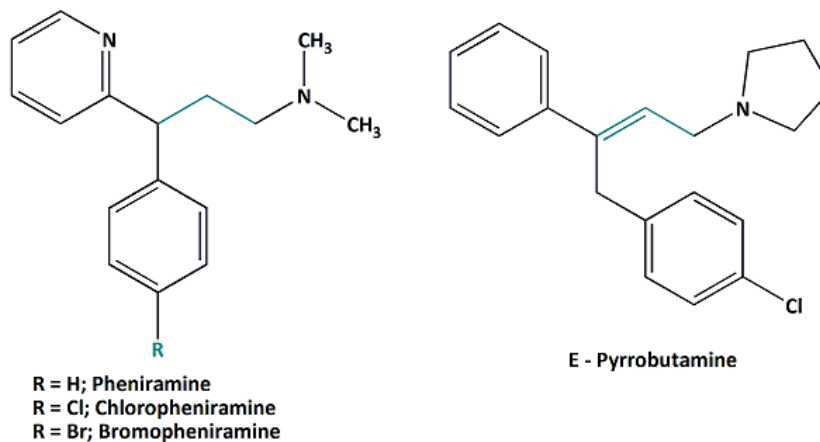
Drugs	X	Y	Ar
Phenbenzamine	CH	CH	
Tripelennamine (pyribenzamine)	N	CH	
Methapyrilene	N	CH	
Thonzylamine	N	N	

Alkyl amines

- A carbon replaces the heteroatom spacer in the general structure
- Characterized by long duration and decreased incidence of central sedative SEs compared to ethylenediamines and ethanolamine ether
- This structural change introduces a chiral carbon when the two aromatic rings are different, activity resides almost exclusively in S-enantiomer
- Most extensively used until the more 2G antihistamines appeared

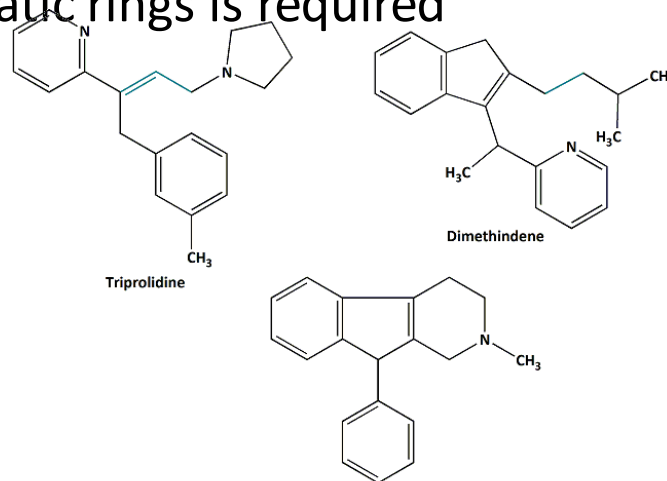
Alkyl cont.

- E- and Z-isomers show large potency differences in tissue-based assays
 - E-pyrrobutamine is more potent than its Z-isomer by 165-fold, and E-triprolidine is more potent than its Z-isomer by ~1,000-fold



Alkyl cont.

- Difference in potency between E- and Z-isomers shows that the two aromatic rings probably have quite different binding at the receptor
 - Evidence suggesting that 5–6 Å distance between tertiary aliphatic amine and one of the aromatic rings is required

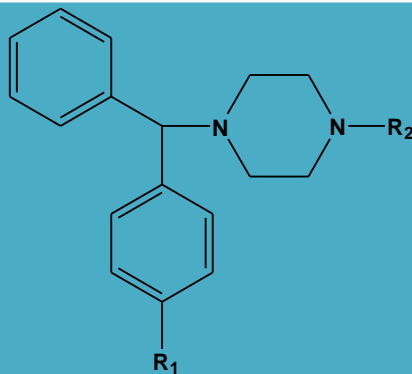


Antihistamine and antiulcer agents

Piperazines

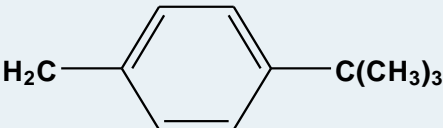
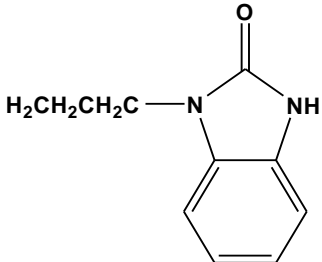
- Are structurally related to both the ethylenediamines
- Their structures include the 2-carbon separation between nitrogen atoms, which is incorporated into piperazine
- Diarylmethylene groups are attached to one of the nitrogen, and an alkyl or aralkyl is attached to the other nitrogen
- Early compounds, such as [cyclizine](#), [chlorcyclizine](#), [meclizine](#), [buclizine](#), and [hydroxyzine](#), have been widely used against motion sickness, because they have useful central antiemetic effects

Piperazine cont.



Drugs	R ₁	R ₂
Cyclizine	H	CH ₃
Chlorcyclizine	Cl	CH ₃
Meclizine	Cl	

Piperazine cont.

Drug	R ₁	R ₂
Bucizine	Cl	
Oxatomide	H	
Hydroxyzine	Cl	CH ₂ CH ₂ OCH ₂ CH ₂ OH
Cetirizine	Cl	CH ₂ CH ₂ OCH ₂ CH ₂ COOH

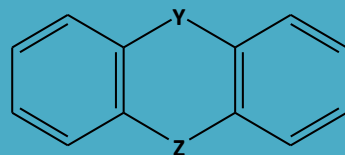
Piperazines cont.

- Have significant anticholinergic and antihistaminic properties
- The acid metabolite of hydroxyzine, **cetirizine**, formed from oxidation of primary alcohol to the corresponding carboxylic acid, is classified with the 2G non-sedating antihistamines
- Amphoteric nature of cetirizine, having both aliphatic amine and carboxylic acid, associated with decreased but not absent sedative SEs

Tricyclic antihistamines

- Earliest potent tricyclic antihistamines were **phenothiazines** (Y=S, X=N)
- Phenothiazine antihistamines contain a 2- or 3-carbon, branched alkyl chain between the nonbasic phenothiazine nitrogen and the aliphatic amine
 - Differ from the antipsychotic phenothiazine in which the chain usually is three carbons long, unbranched, and without substituents in aromatic ring
- Besides useful antihistaminic effects, most have pronounced sedative effects and long durations

Tricyclic cont.

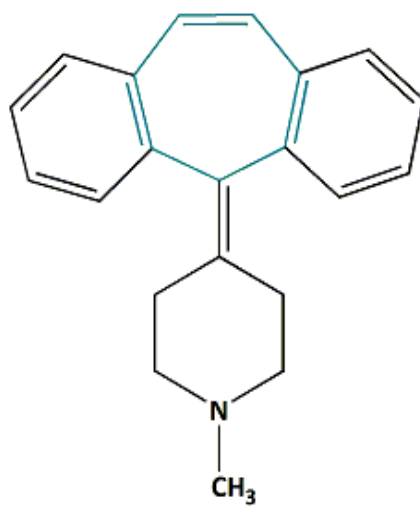


Drugs	Y	Z
Promethazine	S	
Pyrathiazine	S	
Trimeprazine	S	
Methdilazine	S	

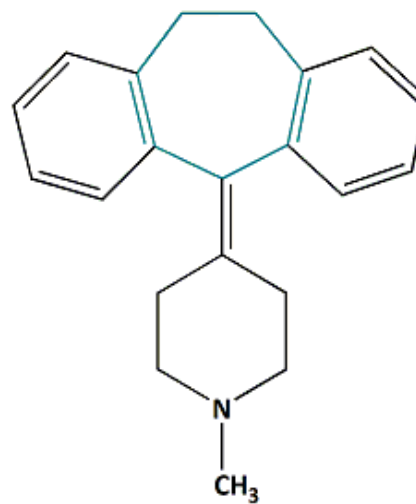
Tricyclic cont.

- **Dibenzocycloheptanes** are phenothiazine analogues in which the sulfur is replaced with two methylene
- Enantiomers of 3-methoxycyproheptadine have different potency as antihistamines, antiserotonin and anticholinergic agents
 - (–)-isomer retained antihistaminic, antiserotonin, and appetite-stimulating effects similar to cyproheptadine, (+)-enantiomer had greater anticholinergic potency
 - Pyridine analogue apparently lacks most of these qualities

Tricyclic cont.



Cyproheptadine



Azatadine

Second generations

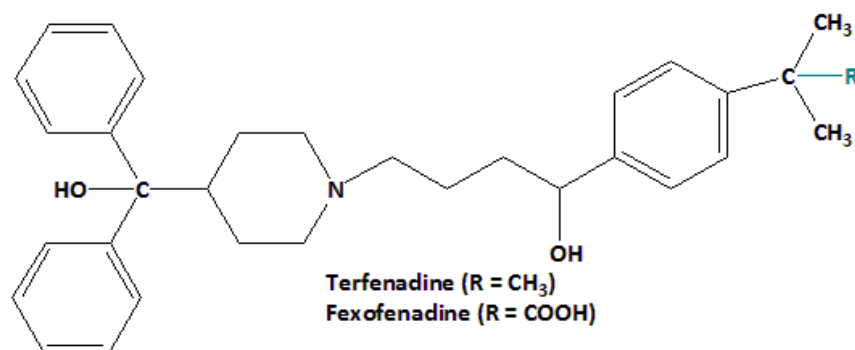
- 2G antihistamines bind only to peripheral H₁, reduce allergic response with little or no sedation due to poor BBB penetration
 - Due to their amphiprotic nature (most are zwitteronic at physiologic pH) or because they are substrate for drug efflux P-glycoprotein transporter or organic anion transporter protein
- Have prolonged antihistaminic effects due to slow dissociation from H₁
- Possess selective peripheral H₁ antihistaminic effects, have less anticholinergic, adrenergic and serotonergic activity

Fexofenadine and terfenadine

- The histamine receptor affinity of terfenadine is believed to be primarily to the presence of diphenylmethyloperidine
- Lack of anticholinergic, adrenergic and serotogenic action appear to be linked to N-phenylbutanol substituent
 - This substitution also limits distribution of to CNS
- Terfenadine is no longer available because extensive clinical reports of life threatening cardiac arrhythmias

Fexofenadine cont.

- The cardiac effects are associated with blockade of **hERG** (human ether-a-go-go) gene product, α -subunit of an inward rectifying cardiac K^+ channel
- Terfenadine is very rapidly metabolized via CYP3A4 to give fexofenadine, the carboxylic acid metabolite of terfenadine with no antiarrhythmic SEs

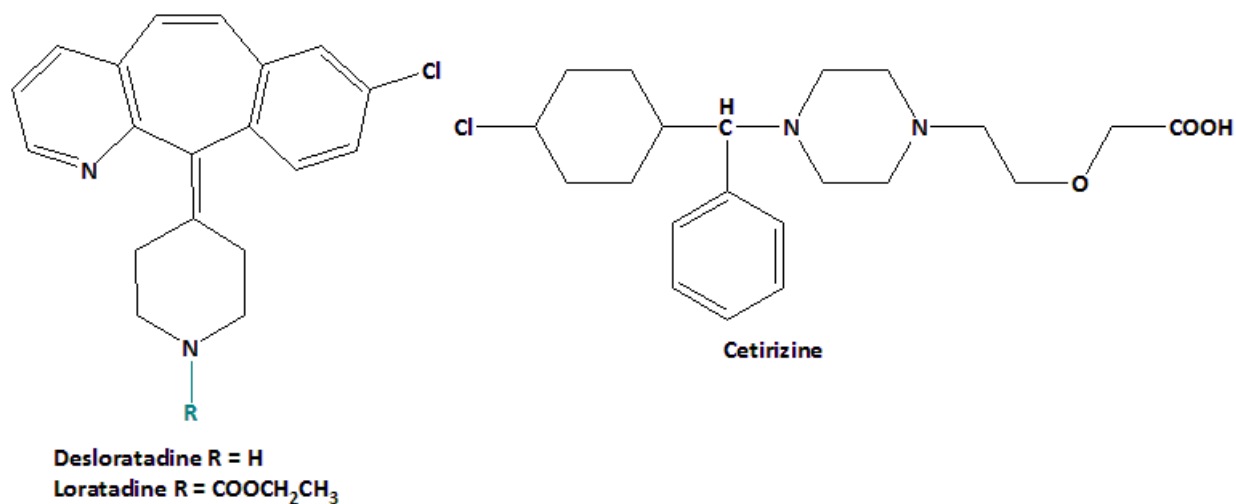


Loratadine

- Is structurally related to azatadine and cyproheptadine
- Differs from azatadine in that a neutral carbamate has replaced the basic tertiary amino and the phenyl has been substituted with chlorine
 - Replacement of the basic group with a neutral functionality is believed to preserve antihistaminic activity while reducing CNS SEs
- Loratadine is extensively metabolized to form the descarboethoxy metabolite, [desloratadine](#)

Loratadine cont.

- Desloratadine is the active metabolite of loratadine and has a very similar receptor binding and safety profile



Cetirizine

- It is zwitteronic (tertiary aliphatic amine and carboxylic acid) and relatively polar, does not penetrate BBB readily
- Has a long duration of action and is highly selective for H₁
- No cardiotoxicity has been reported, but some drowsiness occurs
- **Levocetirizine**, the R-enantiomer, has higher affinity than its S-enantiomer for H₁ (>30-fold) and is more slowly dissociated by more than 20-fold from the receptor

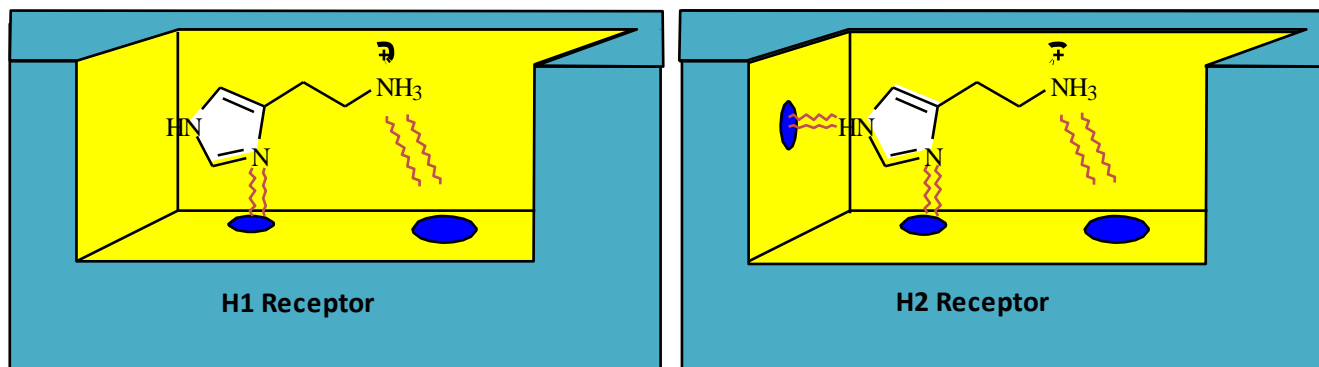
H₂-antagonists

Lead compound

- Conventional antihistamines fail to inhibit all known action of histamines
- SK&F scientists proposed a different kind of histamine receptors
- No lead compound for H₂ antagonist, so SK&F decide to use histamine itself as the lead
 - Alter an agonist into an antagonist
- Exploring how histamine bind to its receptors was important

Lead cont.

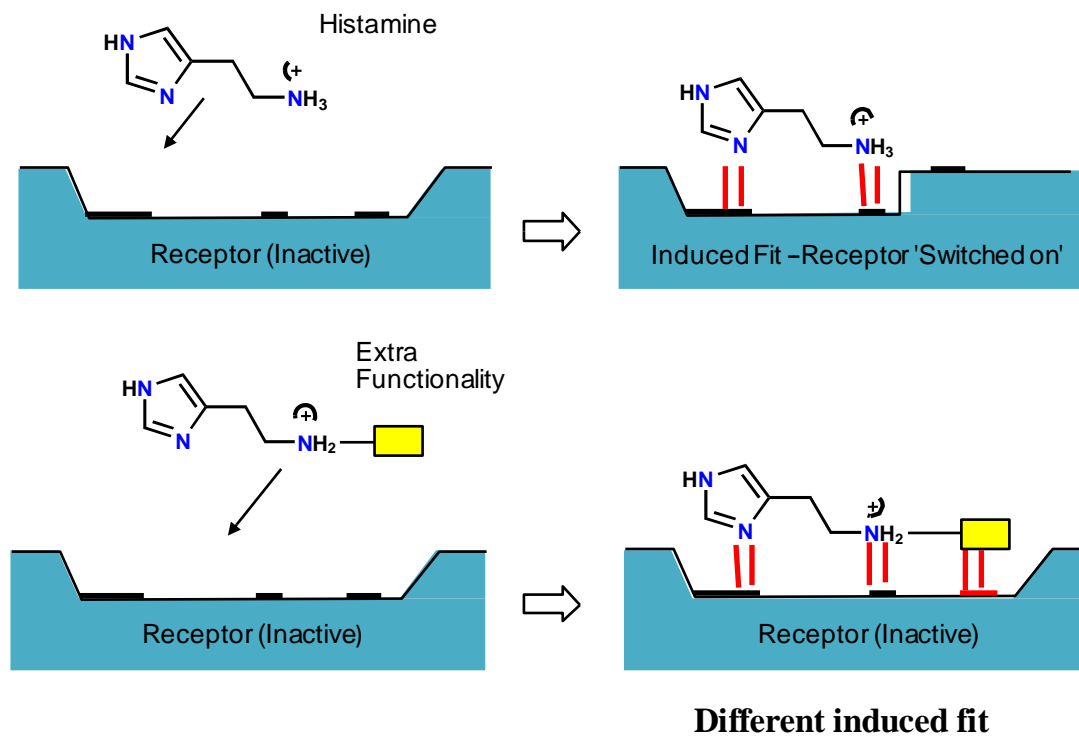
- SAR studies on histamine and its analogues showed
 - Two nitrogen atoms are required for H₁ agonist activity
 - All three nitrogen atoms are required for H₂ agonist activity



Lead cont.

- Histamine fit into its binding site and induce a change in shape that switch on the receptor
- An antagonist can be found by adding extra functional groups to find extra binding interactions
 - Extra binding interactions may result in a different induced fit, fail to activate the receptor
- Antagonist is likely to bind more strongly than an agonist

Lead cont.



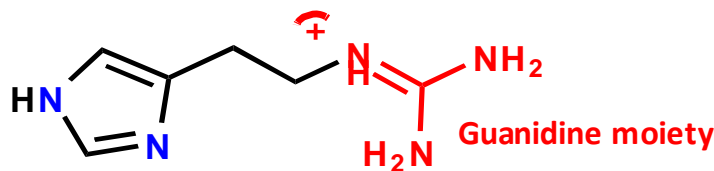
N^{α} -guanylhistamine

- Fusing an aromatic ring on to NA had been successful tactic in the design of adrenergic antagonists
 - This tactic was tried with histamine, but none of those compounds proved to be antagonist
- The focus switch to the effect of varying polar group, particularly the terminal $\alpha\text{-NH}_3^+$ was replaced by different polar groups



N^{α} -guanylhistamine cont.

- The reason being such group could bond to the same binding region as NH_3^+ , but geometry of binding might be altered to produce antagonist
 - Led to N^{α} -guanylhistamine, partial agonist of gastric acid secretion
 - N^{α} -guanylhistamine prevents histamine from fully promoting the release of HCl

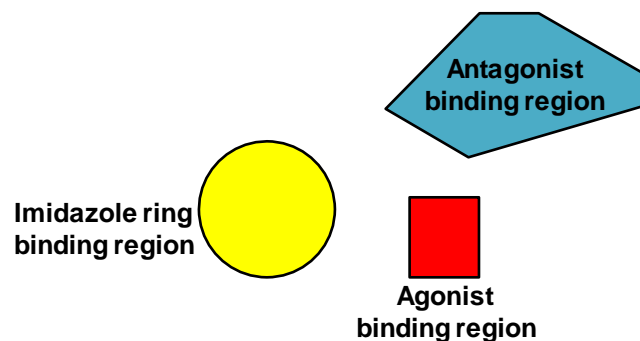


N^{α} -guanylhistamine cont.

- SK&F suggest that N^{α} -guanylhistamine is binding to the proposed H_2 , resulting in weak activation by blocking histamine from binding
- **Three binding regions** are proposed for H_2 , an imidazole binding region and two polar binding regions
- **Two binding modes** are proposed, one for agonists and one for antagonists

N^{α} -guanylhistamine cont.

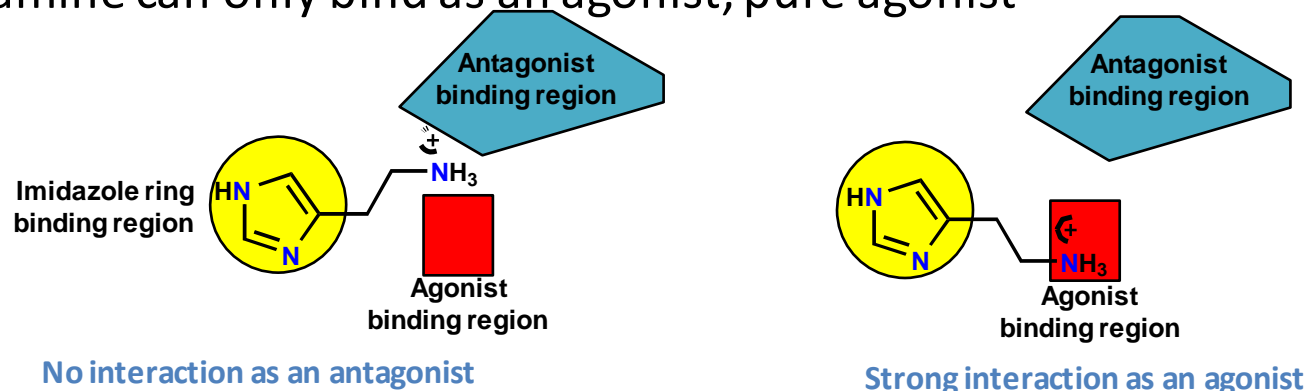
- Imidazole binding region is common to both binding modes
- One of the polar binding regions is accessed by agonists and the other by antagonists
- Antagonist polar region is further from the imidazole binding region



N^{α} -guanylhistamine cont.

Binding of histamine

- Histamine has a short chain, charged α -nitrogen can only reach the polar agonist region
- Antagonist binding region is out of range, not be accessed by histamine
 - Histamine can only bind as an agonist, pure agonist

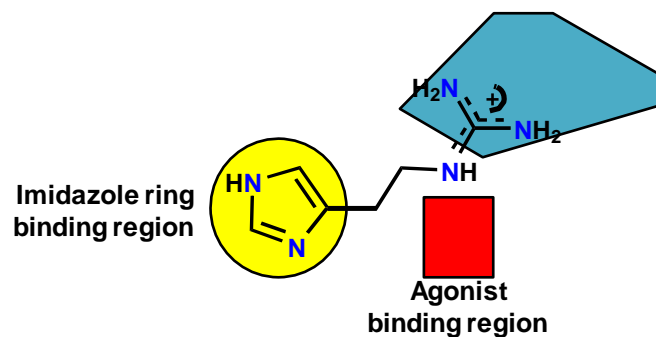
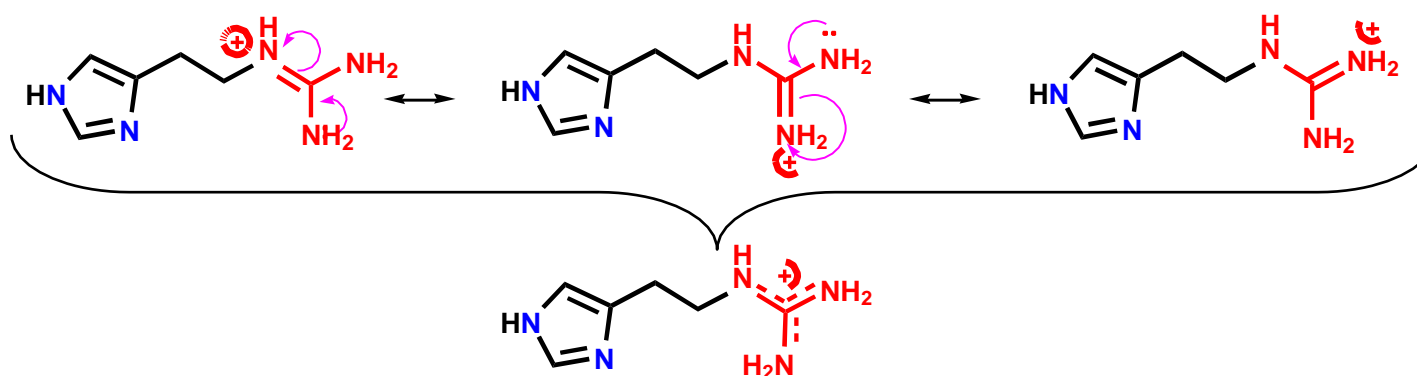


N^{α} -guanylhistamine cont.

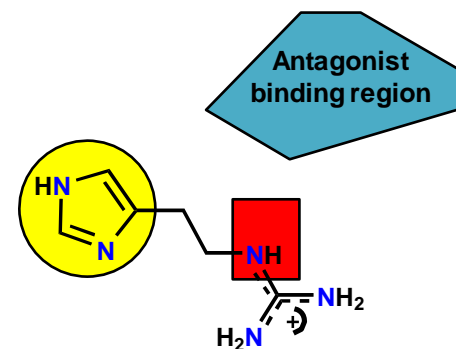
Binding of N^{α} -guanylhistamine

- Guanidine is basic and protonated at pH 7.4
- The charge on guanidine can be spread around the planar arrangement of three nitrogens and can be further away from the imidazole
 - Allows N^{α} -guanylhistamine to bind in two modes
- Structure binds as an agonist in one mode and as an antagonist in the other mode, partial agonist

N^{α} -guanylhistamine cont.



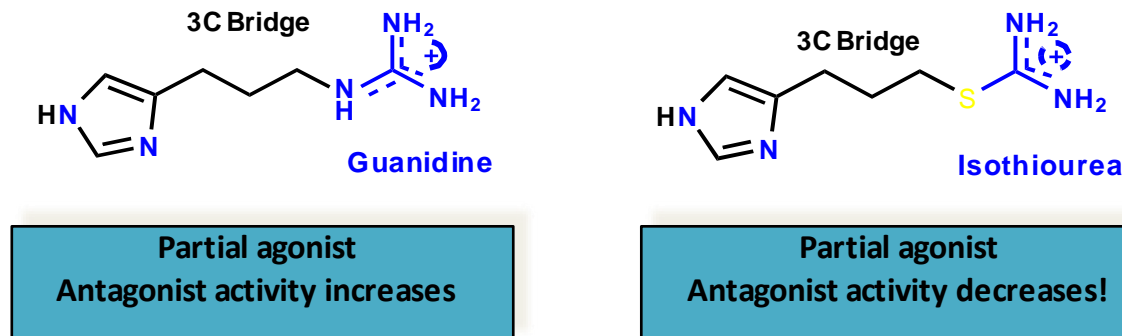
Binding as an antagonist



Binding as an agonist

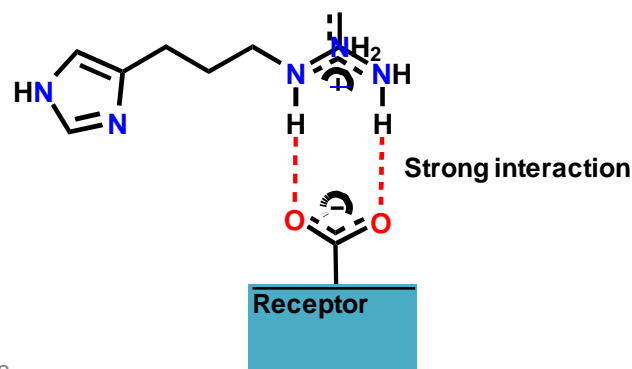
Chain extension

- Chain was extended from two-carbon to three-carbon to push the guanidine further out and to increase interaction with the antagonist region
 - Antagonist activity of the extended guanidine analogue increases as expected



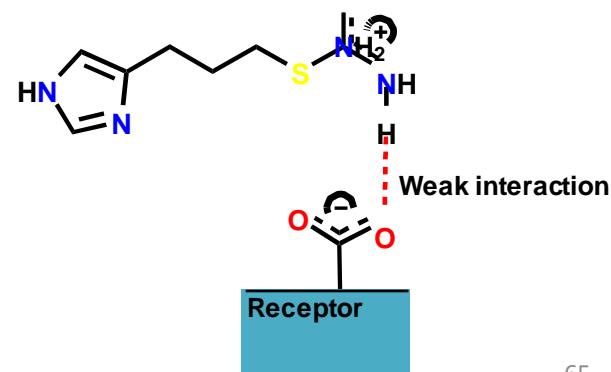
Chain cont.

- But Isothiourea analogue, expected to have increased antagonist activity since the charge is further out, produced decreased antagonist activity
 - Proposed that HB involve one terminal NH_2 along with NH within the chain



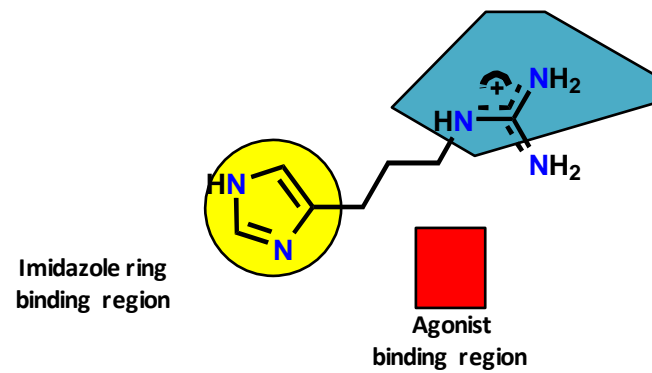
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Antihistamine and antiulcer agents

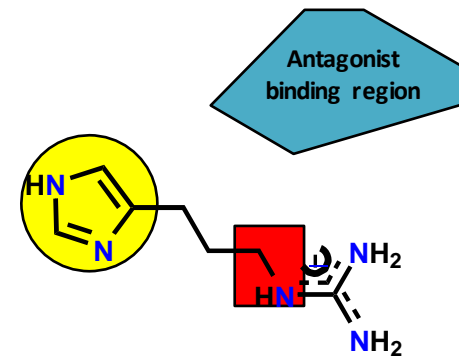


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Chain cont.



Good binding as an antagonist



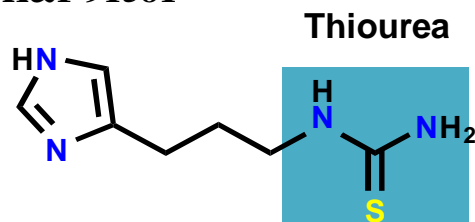
Binding as an agonist

Development of burimamide

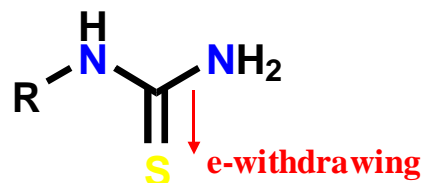
- Replace the ionic guanidine with a neutral H-bonding group may allow a distinction to be made between the two polar binding regions
- Ionic bonding is known to be crucial for the agonist-binding region, which may not be crucial for the antagonist-binding region
- Replacing the basic guanidine with neutral thiourea result in **SK&F 91581**, a weak antagonist with no agonist activity

Burimamide cont.

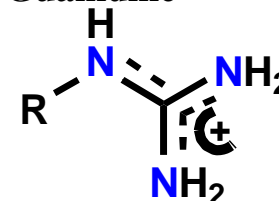
SK&F 91581



Thiourea



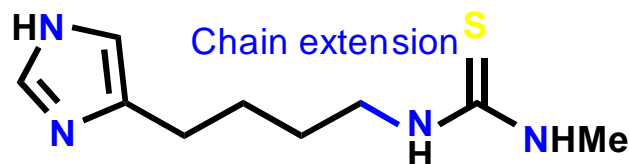
Guanidine



- Guanidine and thiourea group
 - Similarities; planarity, geometry, size, polarity, HB ability
 - Differences; thiourea is neutral while guanidine is basic and ionised

Burimamide cont.

- Established that antagonist-binding region involves only HB
- Further chain extension and addition of N-methyl lead to **burimamide**, enhanced activity suggesting thiourea moved closer to the antagonist binding site
- Benefit of N-methyl is due to an increase in hydrophobicity (desolvation penalty)

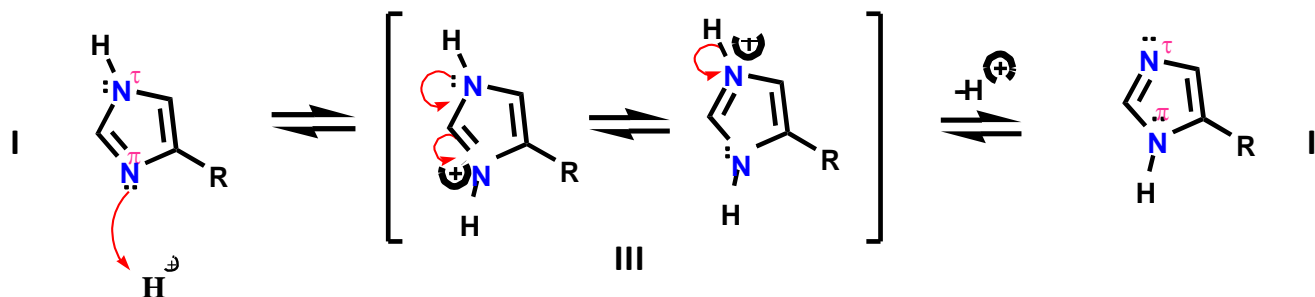


Burimamide cont.

- Burimamide is 100x more active in inhibiting gastric release compared to N^{α} -guanylhistamine with no antagonist activity at H_1
 - Proved the existence of H_2 -receptors
- Burimamide was not suitable for clinical trials since its activity was too low for oral use
- Imidazole can exist as two tautomers (I) and (II) as well as two ionised forms (III)

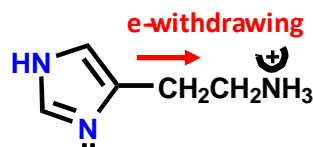
Development of metiamide

- If bonding involves only one of the tautomer form or the protonic form
 - Antagonism can be increased if structure was varied to prefer that form over the others

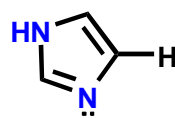


Metiamide cont.

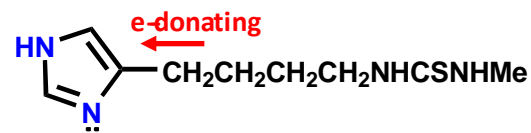
- pK_a for imidazole of histamine is 5.74, meaning it is weak base and not ionised (3% at physiological pH) when it interacts with imidazole region
- pK_a of imidazole in burimamide is 7.25, more basic and 40% ionized at physiological pH
 - Ionised form of burimamide is unlikely to bind well



Histamine $pK_a = 5.74$
Ionisation = 3%



Imidazole $pK_a = 6.80$



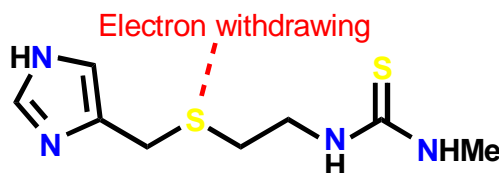
Burimamide $pK_a = 7.25$
Ionisation = 40%

Metiamide cont.

- Decreasing the basicity and ionisation of imidazole in burimamide closer to histamine may increase binding interactions
- It was necessary to make the side chain electron withdrawing rather than electron donating
 - Can be done by replacing methylene unit in the side chain with an isostere, which is more electronegative but same size and properties as methylene; sulfur

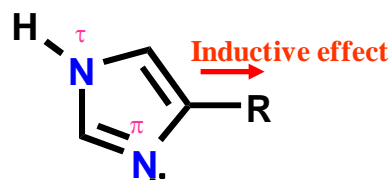
Metiamide cont.

- The resulting compound, **thiaborimamide**, has a significantly lower pK_a of 6.25 and was found to have enhanced antagonist activity
 - Supports non-ionised imidazole is favoured
- Thiaborimamide favors unionized imidazole over the ionized, but there are two possible unionized tautomers



Metiamide cont.

- The preferred tautomer for histamine is I
- The side chain of histamine has positively charged amino, means the side chain has electron-withdrawing effect on the imidazole
- Since this inductive decreases with distance, nitrogen closer to the side chain (N^π) experience greater electron withdrawn effect than one away (N^τ)

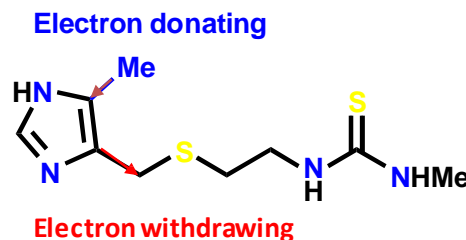


Metiamide cont.

- N^π is less basic than N^τ , N^τ is more likely to bond to hydrogen
- Since the side chain in thiaburimamide is electron withdrawing, then tautomer I will be favored
- Increase the basicity of N^τ relative to N^π to further increase the percentage population of tautomer I vs. tautomer II
- Electron donating was placed at position 4 of the imidazole, inductive effect will be felt more strongly at the neighbouring nitrogen (N^τ)

Metiamide cont.

- Methyl was chosen because it was known that 4-methylhistamine was highly selective for H_2
 - Resulted in **metiamide**, has 10x increase in antagonist activity compared to burimamide
- pK_a of imidazole increased to 6.80 compared to 6.25 to thiaburimamide, result in ionisation to 20%

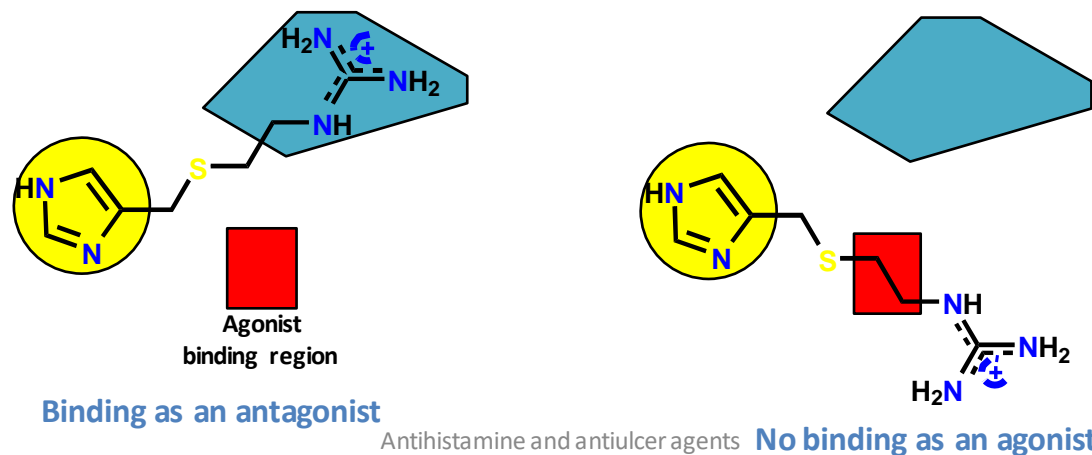


Metiamide cont.

- Increase in population of tautomer (I) outweighs the increase in population of the ionised structures (III)
- Metiamide produces unacceptable kidney damage
- SEs of metiamide may be due to the thiourea
 - Thiourea is not a natural functional group and replacing thiourea with a natural functional group may remove the SEs

Cimetidine

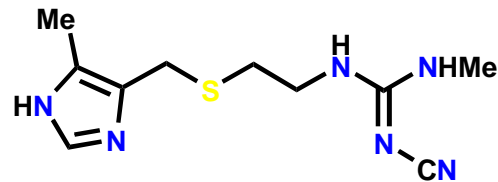
- Guanidine was less active, but interesting that this compound has no agonist activity
- One possible explanation is the longer 4C chain pushes the guanidine unit beyond the agonist-binding region, but not beyond the antagonist-binding region



Cimetidine cont.

- Guanidine is a natural group present in arginine
- Making the guanidine neutral can increase the activity since the low activity was probably due to full ionization at pH 7.4
- Strong EWGs was added to decrease basicity (e.g. NO₂ or CN)
- Cyanoguanidine analogue (**cimetidine**) was the more potent analogue and was chosen for clinical studies

Cimetidine cont.



Electron-withdrawing
cyanide group

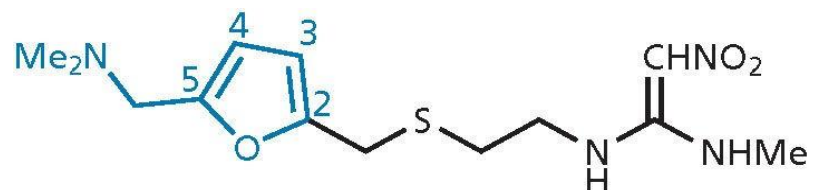
- Cimetidine was marketed in 1976 and has the following properties
 - Comparable activity to metiamide but lesser SEs
 - Inhibits H₂-receptors and lowers gastric acid released
 - Metabolically stable
 - Inhibits CYP-450

Further H₂ antagonists

Ranitidine

- Cimetidine inhibits CYP1A2, CYP2D6 and most importantly CYP3A4
 - Slow metabolism and elimination of other drug
- Further studies on cimetidine showed that imidazole could be replaced
- Glaxo replaced the imidazole with furan bearing nitrogen-containing substituent, leads to the introduction of ranitidine
 - Has fewer SEs, last longer and 10x more active

Further cont.



- Ranitidine inhibits only CYP2D6, which is less crucial in the metabolism of common drugs
- SAR studies for ranitidine include:
 - Replacing the sulfur or placing it next to the ring lowers activity

Further cont.

- 2,5-disubstitution is the best substitution pattern for furan
- Replacing furan with more hydrophobic ring such as phenyl or thiophene reduce activity
- Heterocyclic rings of cimetidine and ranitidine are not interacting in the same way with H₂ receptor
 - Supported by the fact that dimethylaminomethylene attached to cimetidine leads to drop in activity

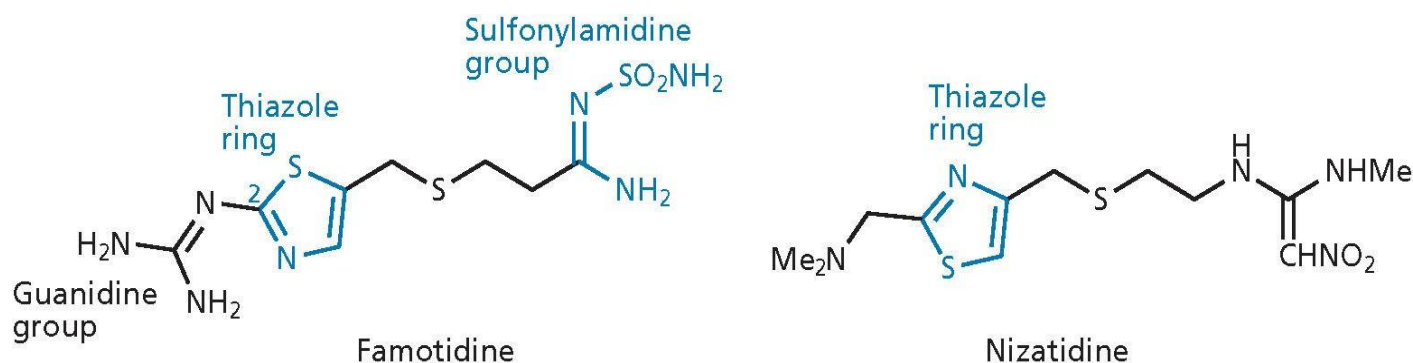
Further cont.

Famotidine and nizatidine

- Famotidine is 30x more active than cimetidine
- The side chain contains sulfonylamidine and the imidazole of histamine has been replaced by 2-guanidinothiazole
- Methyl on the heterocyclic ring, *ortho* to the chain leads to a drop in activity (unlike cimetidine series)
- Three of four hydrogen in the two amidine NH_2 are required for activity

Further cont.

- The furan in ranitidine is replaced by thiazole to give nizatidine, equipotent with ranitidine

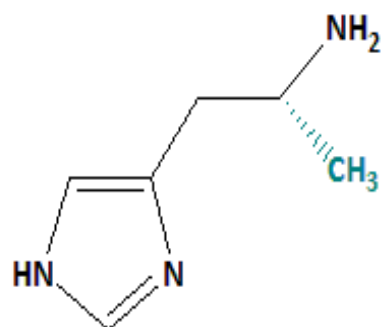


H₃ and H₄ antagonists

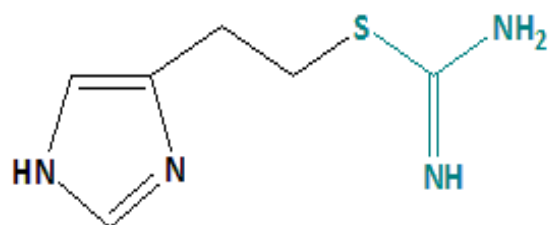
H₃-receptor ligands

- Alteration of histamine resulted in potent and selective H₃-agonist; (R)- α -methylhistamine
- Replacement of amino with isothioureia has yielded the potent and selective H₃-agonist, imetit
- Immepip, contain piperidine, is comparable in potency to (R)- α -methylhistamine
- Thioperamide, a cyclohexylthioureia derivative of immepip, is a potent and competitive H₃-antagonist both *in vivo* and *in vitro*

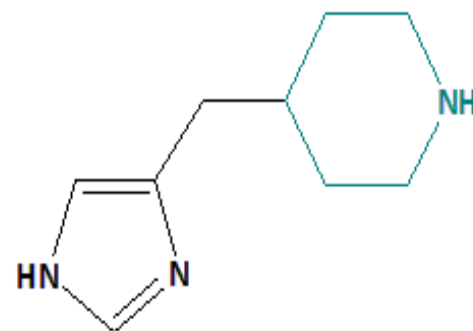
H₃-receptor cont.



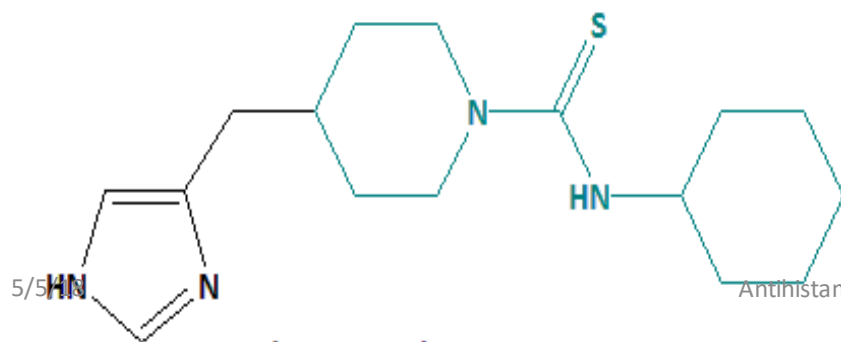
(R)-α-methylhistamine



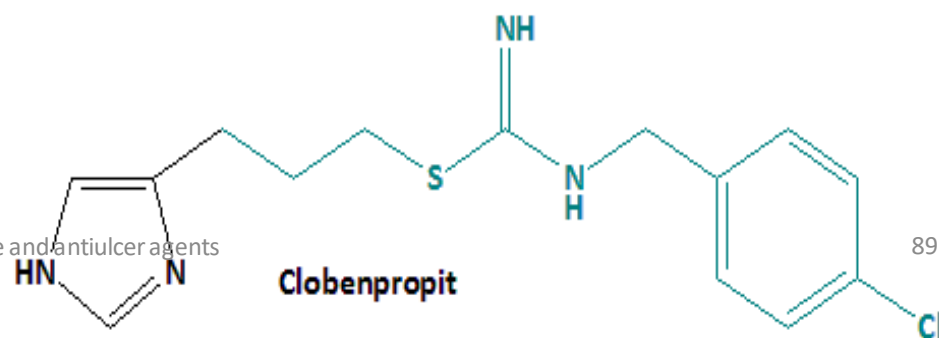
Imetit



Immepip



Thioperamide



Clobenpropit

H₃-receptor cont.

- Centrally acting H₃ antagonists are under study by several companies
- Agents are sought for a variety of disorders
 - Depression, mild cognitive impairment, AD, schizophrenia, narcolepsy, obesity, and attention-deficient hyperactivity disorder
- JNJ 5207852, a compound that increases wakefulness, and ABT-239, a compound that is being evaluated for cognition related disorders

H₄-receptor ligands

- R- α -methylhistamine and imetit are also agonists at H₄, but they have lower affinity than at H₃
- Clobenpropit is a partial agonist at H₄, but it is an H₃ inverse agonist
- Thioperamide is an inverse agonist at H₄ and H₃
- 4-Methylhistamine has greater affinity (>100-fold) for H₄ than other histamine receptor subtypes

H₄-receptor cont.

- A selective H₄ antihistamine has recently been reported, [JNJ 7777120](#)
 - Blocks histamine-induced chemotaxis in mast cells and eosinophils
- H₄ antagonists might be useful against autoimmune inflammatory and allergic disorders, including rheumatoid arthritis, asthma and allergic rhinitis
- Nasal stuffiness and blockage in allergic rhinitis, poorly treated with H₁ and H₂ antihistamines, possible use of H₄ antihistamines

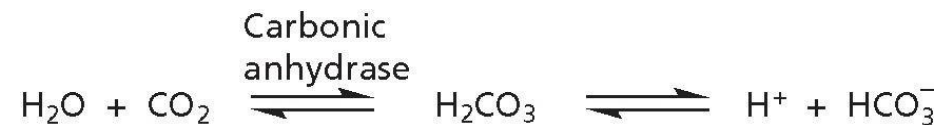
Antiulcer agents

Peptic ulcer

- Peptic ulcer is a localised erosions of the mucous membranes of the stomach and duodenum
 - Pain is due to irritation of the exposed surface by stomach acid
- If left untreated, ulcer could result in severe bleeding and even death
- Caused by stress, *H. Pylori* and NSAIDs
- Once ulcer erupted, HCl aggravates the problem and delay recovery

Parietal cell and proton pump

- When parietal cell are secreting HCl, they form invagination, canaliculi
 - Increase the amount of surface area available to the cell, across which it can release HCl
- Proton for HCl are generated from water and CO₂, by carbonic anhydrase
- Once proton generated, have to be exported out of cell for two reasons



Parietal cell cont.

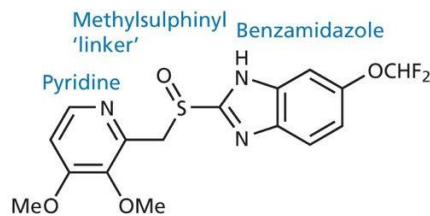
- Build up of acid within cell would be harmful
- The enzyme catalyzed reaction that generates the protons is reversible
- Export of proton from parietal cell is achieved by proton pump or H^+/K^+ ATPase because
 - Pumps protons out of cell at the same time pumps potassium ions back in
 - Energy is required as both ions are being moved against concentration gradient; hydrolysis of ATP

Parietal cell cont.

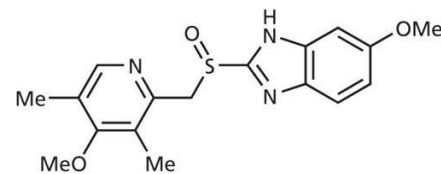
- Chloride ions depart through chloride ion channel, this outflow closely matches the efflux of protons
- HCl is formed in the canaliculus
- Potassium ions exit the parietal cell as counter ions for chloride ions and are then pumped back in by proton pump
 - Potassium undergo a cyclic movement

Proton pump inhibitors

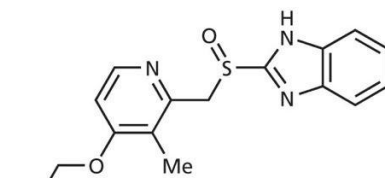
- There are 4 PPIs in clinical use: omeprazole, lansoprazole, pantoprazole and rabeprazole
 - S-enantiomer (esomeprazole) of omeprazole has also been approved



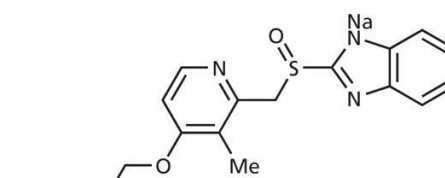
Pantoprazole



Omeprazole



Lansoprazole



Rabeprazole

Antihistamine and antiulcer agents

MOA

- PPIs are weak bases, pK_a of about 4.0
 - Only ionized in strongly acidic environment, $pH < 4$
 - Conditions found only in secretory canaliculus, $pH \leq 2$
- The drug is absorbed into blood after oral administration and transported throughout the body until they reach the parietal cells
 - Since they are un-ionized this stage and lipophilic, they are able to cross the cell membrane of the parietal cell

MOA cont.

- Canaliculus is highly acidic, drug becomes protonated
- Consequence of this are two fold:
 - Ionized drug is too polar to cross back into the cell through cell membrane
 - Lead to 1000 fold accumulation of the drug in the canaliculi where it is intended to act
 - Protonation triggers an acid-catalyzed conversion, which activates the drug