What is histamine? - Looks simple. Made from aminoacid histidine.

\[
\text{histamine} \quad \xrightarrow{pK_a's = 5.7, 9.8} \quad \text{histidine} \quad \xrightarrow{pK_a's = 1.9, 6.0, 9.3}
\]

How is it made – Handout.

What does it do? – Four different receptors known now. All part of G protein-coupled family.

H1 – immune response that causes hives, makes blood vessels leaky
H2 – stimulates stomach acid secretion,
H3 – found in CNS and can inhibit release of other neurotransmitters,
H4 - found in bone marrow and white blood cells and regulates neutrophil release from bone marrow. It is also expressed in the colon, liver, lung, small intestine, spleen, testes, thymus, tonsils, and trachea

Hives also known as urticaria, is a kind of skin rash with red, raised, itchy bumps. They may also burn or sting. Often the patches of rash move around.

Hives often occur following an infection or as a result of an allergic reaction such as to medication, insect bites, food, psychological stress, cold temperature, or vibrations. In half of cases the cause remains unknown. Risk factors include having conditions such as hay fever or asthma. Diagnosis is typically based on the appearance. Patch testing may be useful to determine the allergy. Prevention is by avoiding whatever it is that causes the condition. Typically they last a few days and do not leave any long-lasting skin changes. Fewer than 5% of cases last for more than six weeks. The condition frequently recurs.

Treatment is typically with antihistamines such as diphenhydramine and ranitidine. In severe cases, corticosteroids or leukotriene inhibitors may also be used. Antihistamines that block the histamine H1 receptors are the first line of therapy.

About 20% of people are affected. Cases of short duration occur equally in males and females while cases of long duration are more common in females. Cases of short duration are more common among children while cases of long duration are more common among those who are middle aged. Hives have been described at least since the time of Hippocrates. The term urticaria is from the Latin urtica meaning "nettle".
Peptic ulcer disease (PUD), is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus. An ulcer in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as a duodenal ulcer. Common symptoms include upper abdominal pain that improves with eating. Other symptoms include belching, vomiting, weight loss, or poor appetite. About a third of older people have no symptoms. Complications may include bleeding (15% of people) with an ulcer perforation, and blockage of the stomach.

Common causes include the bacteria Helicobacter pylori and non-steroidal anti-inflammatory drugs (NSAIDs). Other less common causes include tobacco smoking, stress due to serious illness, Crohn disease and liver cirrhosis, among others. H. pylori can be diagnosed by testing the blood for antibodies or a biopsy of the stomach.

Diet does not play an important role in either causing or preventing ulcers. Treatment includes stopping smoking, stopping NSAIDs, stopping alcohol, and medications to decrease stomach acid. The medication used to decrease acid is usually either a proton pump inhibitor (PPI) or an H2 blocker. Ulcers due to H. pylori are treated with a combination of medications such as amoxicillin, clarithromycin, and a PPI.

Peptic ulcers are present in around 4% of the population. They newly began in around 87.4 million persons worldwide in 2015. About 10% of people develop a peptic ulcer at some point in their life. They resulted in 267,500 deaths in 2015 down from 327,000 deaths in 1990.

In the early 1960s only one class of antihistamine was known (H1 now)

First generation antihistamines

Clinically, H1-antihistamines are used to treat allergic reactions and mast cell-related disorders. Sedation is a common side effect of H1-antihistamines that readily cross the blood–brain barrier; some of these drugs, such as diphenhydramine and doxylamine, are therefore used to treat insomnia. H1-antihistamines can also reduce inflammation.
Second generation antihistamines

Mepyramine crosses the blood–brain barrier to a much lower degree than the first-generation antihistamines. Their main benefit is they primarily affect peripheral histamine receptors (as opposed to the CNS) and therefore are less sedating. However, high doses can still induce the central nervous system drowsiness. The reason for their peripheral selectivity is that most of these compounds are zwitterionic at physiological pH (around pH 7.4). As such, they are very polar, meaning that they do not easily cross the blood–brain barrier and act mainly outside the central nervous system.

Possible synthesis

Ketotifen is a noncompetitive H1-antihistamine and mast cell stabilizer. It is most commonly sold as a salt with fumaric acid, ketotifen fumarate, and is available in two forms. In its ophthalmic form, it is used to treat allergic conjunctivitis, or the itchy red eyes caused by allergies. In its oral form, it is used to prevent asthma attacks. Ketotifen relieves and prevents eye itchiness and/or irritation associated with most seasonal allergies. It starts working within minutes after administering the drops. The mean elimination half life is 12 hours.

It was known that histamine stimulated stomach acid, but none of the known antihistamines inhibited acid secretion.
**ANTI-ULCER AGENTS - HISTAMINE ANTAGONISTS**

**Ulcers**
- Localised erosions of the mucous membranes of the stomach and duodenum
- Potentially fatal if untreated
- Caused by stress, infection (H. Pylori), smoking and drugs (NSAIDS)
- Aggravated by gastric acid (HCl) in the stomach
- Estimated 1 out of 10 people will have one sometime in their life

**Therapy of ulcers**
- Old days: antacids, bland diet (crackers, milk), surgery on stomach
- New days:
  - Lower the levels of gastric acid
    - a. histamine antagonists and
    - b. proton pump inhibitors
  - Antibacterial agents vs. H. Pylori
  - Herbal remedies

---

**Parietal cells and gastric acid release**

**Notes**
- Release of gastric acid is promoted by acetylcholine, gastrin and histamine
sulfonated tyrosine

\[
\text{modified Glu}
\]

\[
\text{gastrin - peptide hormone (made by G cells)}
\]

acetyl choline

histamine

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Biosynthesis of histamine from the amino acid histidine (with vitamin B6)

Histidine (pK\textsubscript{a} = 3.8, 6.1, 9.3)

\[ \text{PLP - vitamin B6 (aldheyde version)} \]

Histamine (pK\textsubscript{a} = 8.6)

\[ \text{PLP - vitamin B6 (amine version)} \]

A similar process occurs with many other amino acids, including synthesis of neurotransmitters serotonin and dopamine (which forms epinephrine and norepinephrine). Glutamate can react in a similar manner.

Histamine is released when cells are damaged. It increases the permeability of small blood vessels and allows white blood cells into that area to defend against infection. Allergic reactions and irritation are common side effects.

Histamine - Properties

- A chemical messenger released by cells
- Acts as a local hormone

Histamine - Properties

Notes

- Two possible tautomers
  - pK\textsubscript{a} for the \( \alpha-NH_2 \) group = 9.80.
  - 96\% ionisation at pH 7.4 = 99.6
  - pK\textsubscript{a} for the imidazole ring = 5.74
  - Imidazole ring is slightly ionized at blood pH

Percent conjugate acid and conjugate base

\[ \text{plasma pH = 7.4} \]

\[ \begin{align*}
\text{pK}\textsubscript{a1} &= 5.7 \\
\text{pK}\textsubscript{a2} &= 9.8
\end{align*} \]

What could make the pK\textsubscript{a} go higher or lower?
The conjugate acid is positive and the conjugate base is neutral.

\[ \begin{align*}
\text{pH} - \text{pK}\textsubscript{a} &= \log \frac{[B]}{[HB^+]} \\
7.4 - 5.7 &= \log \frac{[B]}{[HB^+]}
\end{align*} \]

\[ \begin{align*}
[B] &= 10^{7.4 - 5.7} = 50 / 1 = 98\% / 2\%
\end{align*} \]

\[ \begin{align*}
\text{pH} - \text{pK}\textsubscript{a} &= \log \frac{[B]}{[HB^+]} \\
7.4 - 9.8 &= \log \frac{[B]}{[HB^+]}
\end{align*} \]

\[ \begin{align*}
[B] &= 10^{7.4 - 9.8} = 1 / 250 = 0.4\% / 99.6\%
\end{align*} \]

Two tautomer possibilities

- \( \pi \) is closer to the side chain

How does the pK\textsubscript{a} of imidazole compare to pK\textsubscript{a1} of histamine? (higher, lower or similar)?
**Histamine Actions**

Histamine is released by cell damage

- Stimulates dilation of blood vessels with increased permeability
- White blood cells escape blood vessels and access area of tissue damage
- White blood cells combat infection

**BUT**

Histamine is also released by allergies, asthma, hay fever and insect bites

---

**Classical antihistamines**

Commonly used to treat symptoms such as inflammation & itching

- Mepyramine
- Diphenhydramine (Benadryl)

• But no effect on gastric acid release
• Casts doubt on histamine receptors being present on parietal cells
• Histamine may promote gastric acid release indirectly
• SK&F propose two types of histamine receptor (H₁ and H₂)
  (SKF = Smith, Kline & French)
• H₁ - responsible for classical actions of histamine
• H₂ - proposed as the receptor on the parietal cells in the stomach
• Claim that H₂ receptors are unaffected by classical antihistamines
• Implies classical antihistamines are H₁ specific
Histamine used as the lead compound

- No known H₂ antagonist at the time - no lead compound
- SK&F decide to use histamine itself as the lead compound
- Aim is to alter an agonist into an antagonist
- Compare development of propranolol (β-blocker) from adrenaline
- Need to know SAR requirements for H₂ agonists
- Analogues tested by their ability to promote gastric acid release
- Does not prove existence of H₂ receptor

S-epinephrine (adrenaline) was used as a lead compound for labetalol. SKF proposed to follow a similar strategy to find an antagonist for histamine stomach acid secretion.

Epinephrine is a nonselective agonist of a variety of adrenergic receptors, including the major subtypes α₁, α₂, β₁, β₂, and β₃, triggering a number of metabolic changes. Binding to α- adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle, and stimulates glycolysis and inhibits insulin-mediated glycogenesis in muscle. β adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together, these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body.

Labetalol is used to lower blood pressure and heart rate. It was the first drug created that combined both alpha- and beta- adrenergic receptor blocking properties. It was postulated that weak blocking of both alpha- and beta-receptors could work together to decrease blood pressure. Labetalol was not found to cross the blood-brain-barrier.

SAR for H₁ and H₂ agonists

Two nitrogen atoms are required for H₁ agonist activity - hives
All three nitrogen atoms are required for H₂ agonist activity – stomach acid


**Strategies for converting agonists to antagonists**

- Add extra functional groups to find extra binding interactions with the binding site
- Extra binding interactions may result in a different mode of binding resulting in a different induced fit for the receptor
- Different induced fit may fail to activate the receptor
- As a result, analogue binds but fails to activate the receptor
- Antagonist is likely to bind more strongly than an agonist

*Histamine*

![Diagram showing the conversion of histamine to an agonist and antagonist](image)

**Examples** - extra hydrophobic groups? Over 200 compounds were made without any antagonist using hydrophobic groups.

![Diagram showing possible changes in the histamine molecule](image)

But 2 of them made SKF believe there were 2 different receptors for “hives” vs. “stomach acid”.

![Diagram showing the 2-methylhistamine and 4-methylhistamine](image)
Next step was to try adding extra hydrophilic groups instead
• Aim was to search for extra polar binding regions

*N*-Guanylhistamine

Biological properties
• Partial agonist - promotes HCl release but less strongly than histamine (possible reason?)
• Prevents histamine from fully promoting the release of HCl
• SK&F suggested that *N*-guanylhistamine was binding to the proposed H2 receptor, resulting in weak activation
• While present, *N*-guanylhistamine blocks histamine from binding

*N*-Guanylhistamine - Structure and chemical properties
• The guanidine group is basic and ionized
• Different tautomers are possible
• The positive charge can be delocalized over 3 resonance structures
• There are many possible shapes

The positive charge is more diffuse and can be further away from the imidazole ring. SKF also tried several derivatives without the imidazole ring, but none showed antagonist activity. A decision was made that the imidazole ring was necessary for receptor recognition. This proved to be a very costly mistake when a few years later competitors, Glaxo (ranitidine/Zantac) and Yamanouchi (famotidine/Pepcid) made even more active H2 antihistamines without the imidazole ring that made even more money.
Binding theory for agonists and antagonists
Possible binding regions

• Three binding regions are proposed for the H₂ receptor - an imidazole binding region (H bonds) and two polar binding regions
• Two binding modes are proposed - one for agonists and one for antagonists
• The imidazole binding region is common to both binding modes
• Proposed that one of the polar binding regions is accessed by agonists and the other by antagonists. The antagonist polar region is further from the imidazole binding region

Binding of histamine

• Histamine has a short chain
• Charged α-nitrogen can only reach the polar agonist region
• The antagonist binding region is out of range
• Histamine can only bind as an agonist, so acts as a pure agonist
Binding of $N^\alpha$-guanylhistamine

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

Chelation binding theory - The proposal

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

The evidence

Structures A, B and B’ are all partial agonists, but structure A has greater antagonist properties. What does that suggest?
Chelation binding theory

Binding modes for analogues

Positive charge is localized further out leading to better interactions with the antagonist binding region

Only one H-bond is possible with the antagonist binding region. Charge is also directed away from the carboxylate ion - weaker antagonist property.

The chelation binding theory was eventually disproved, but it served a purpose in explaining results and pushing the project forward on rational grounds.

Another possibility considered was altering the side chain to make it more conformationally rigid. How could it be made more rigid?

However, when the more rigid analog was found to be less potent it was felt that side chain flexibility was necessary. Could have tried different ring sizes (but we don’t know all of the compounds). Probably wanted minimal changes possible.
Chain extension strategy

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

**Results**

- Partial agonist.  
  Antagonist activity increases

- Partial agonist  
  Antagonist activity decreases!

- Antagonist activity of the extended guanidine analogue increases as expected.
- Isothiourea analogue might have been expected to have increased antagonist activity since the charge is further out, but it didn’t.

There are many possible substituents, shapes and polar interactions. Remember, decisions are made by how much acid gets secreted in a rats stomach based on pH reading.

- many, many possibilities

- possibilities

- possibilities

- possibilities
Chain extension strategy
Proposed binding for 3C extension analogues

Is there a different form of hydrogen bonding taking place?

Compare 2C bridged analogues.

Summarize effects

Imidazole ring binding region

Agonist binding region

Partial agonists with good antagonist activity (X=Me or SMe)
Partial agonists with good antagonist activity (X= Me or SMe)

Stronger interaction

Receptor
X=NH₂, SMe, Me

Poor binding as an antagonist

Good binding as an antagonist

Emphasis now switches to the types of binding interactions at the polar binding regions

Distinguishing between the polar binding regions

1 Strategy
Replace the ionic guanidine group with a neutral H-bonding group

2 Rationale
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.
It may not be crucial for the antagonist binding region.

3 Method
Replace the basic guanidine moiety with a neutral thiourea group

SK&F 91581

Thiourea

No agonist activity
Very weak antagonist
Distinguishing between the polar binding regions

Comparison between the thiourea and guanidine groups

**Similarities** - Planarity, geometry, size, polarity, H-bonding ability

**Differences** - Thiourea is neutral while guanidine is basic and ionised

![Thiourea and Guanidine Comparison](image-url)

R = 2C = weak antagonist
R = 3C = better antagonist

**Conclusions** -
- Agonist polar region involves ionic and H-bonding interactions
- Antagonist polar region may not require ionic interactions. H-bonding may be sufficient

Chain extension (again), and addition of N-methyl group

**Strategy**
Extend the carbon bridge to 4 carbons (another CH₂ in the side chain)
Pushes thiourea group further out
May increase the interaction with the antagonist binding region

**Results**
Discovery of burimamide

**Properties of burimamide**
- 100 times more active as an antagonist compared to N*-guanylhistamine
- No antagonist activity at H₁ receptors
- Activity still too low for oral use

**Conclusions**
- Chain extension leads to a pure antagonist with good activity
- Chain extension allows a better overlap of the thiourea group with the antagonist binding region
- N-methyl effect (hydrophobic pocket or desolvation?)
- Establishes the existence of H₂ receptors
The imidazole ring
Structures – more complicated than appears at first look

[Diagram showing the imidazole ring in tautomers I, II, and III]

- Imidazole ring can exist as two tautomers (I) and (II) as well as an intermediate with two resonance forms (III)
- Which of these is preferred?
- Which nitrogen atom in III is more positive? (Depends on what “R” is)

The imidazole ring basicity

Percent ionization of imidazole ring at physiological pH \( \approx 7.4 \)

- Histamine (pK_a = 5.74)
  - Ionization = 2% of imidazole ring
- Imidazole (pK_a = 6.80)
  - Ionization = 25% (H is reference group)
- Burimamide (pK_a = 7.25)
  - Ionization = 40% of imidazole ring

Conclusions

- The imidazole ring of histamine is not ionized when it interacts with the imidazole binding region
- The ionized form of burimamide is unlikely to bind well
- Decreasing the basicity and ionization of the imidazole ring in burimamide closer to that of histamine may increase the binding interactions to the imidazole binding region
- An extra methyl on the end thiourea group made it a stronger antagonist (probably tried many variations)
Varying basicity of the imidazole ring

**Strategy**

Convert the side chain of burimamide to a more \( \text{e-}\)-withdrawing group

Thiaburimamide – S has slightly longer bonds, slightly more polar

\( K_p = \text{partition coefficient, more later} \)

\[
pK_a = 6.25
\]

Increase in antagonist activity

Non-ionised imidazole is favoured

Ionization \( \approx 7\% \)

**Compare:**

- **Histamine** (\( pK_a = 5.74 \))
  - Ionization \( \approx 2\% \) of imidazole ring

- **Imidazole** (\( pK_a = 6.80 \))
  - Ionization \( \approx 25\% \)
  - (H is reference group)

- **Burimamide** (\( pK_a = 7.25 \))
  - Ionization \( \approx 40\% \) of imidazole ring

**Tautomer studies of the imidazole ring**

**Tautomer I vs tautomer II**

- Favoured tautomer for histamine is I
- Inductive effect decreases with distance
- \( \text{N}^\varphi \) is less basic than \( \text{N}^\tau \)
- \( \text{N}^\tau \) is more likely to be protonated
- Favoured tautomer for thiaburimamide is also tautomer I

**Strategy**

- Increase the basicity of \( \text{N}^\tau \) relative to \( \text{N}^\varphi \) to further increase the percentage population of tautomer I vs tautomer II
- Add an electron-donating group to the imidazole ring closer to \( \text{N}^\tau \) than to \( \text{N}^\varphi \)
Tautomer studies

Metiamide

Notes
• 10 fold increase in antagonist activity versus burimamide
• Electron-donating effect of methyl group is more significant at N°
• Increases basicity of N°
• Favours tautomer I over tautomer II
• But, increases in pK_a to 6.80
• Increase in ionization to 20%
• Increase in the population of tautomer (I) outweighs the increase in population of the ionised structures (III)
• Unacceptable side effects - kidney damage

Alternative rationales
• The increases in activity for thiaburimamide and metiamide may be due to a conformational effect
• The thioether link increases the length and flexibility of the side chain
• This may lead to increased binding
• The methyl substituent may orientate the side chain into the active conformation – i.e. the methyl group acts as a conformational blocker

Substituted oxygen for sulfur in the side chain to make it more electron withdrawing

Less potent than burimamide despite the side chain being more electron withdrawing, should be less ionized

Possible explanations
• The ether link is smaller and less flexible
• The ether may be involved in a ‘bad’ hydrogen bond
• There may be an energy penalty involved in desolvating the oxygen prior to binding
From metiamide to cimetidine

- The side effects of metiamide (decrease in white blood count) may be due to the thiourea group
- The thiourea group is not a natural functional group
- Replacing thiourea with a natural functional group may remove the side effects

![Chemical structures of metiamide, cimetidine, and guanidinium](image)

**Thiourea** - Toxic side effects, few out of 700 patients had granulocytopenia (low white blood cells)

**Urea** - Drop in activity ~ 5% as active

**Guanidinium** - Drop in activity (~ 5% as active) but no agonist activity!

**Conclusions**
- First guanidine analogue to be a pure antagonist
- The longer 4C chain pushes the guanidine unit beyond the agonist binding region, but not beyond the antagonist binding region

![Diagram of binding interactions for the 4C extended guanidine](image)

**From metiamide to cimetidine**

**Wrong compounds**

Binding as an antagonist was good

Not binding as an agonist was good
**Strategy:**
- Retain the guanidine group, but try to remove the positive charge (use dipoles instead)
- Guanidine is a natural group present in the amino acid arginine
- Increase activity of drug by making the guanidine group neutral
- Add a strong electron-withdrawing group to decrease basicity (many tried)
  - (NO₂ and CN), both showed similar antagonist activity

**From metiamide to cimetidine**

**Properties**
- Comparable activity to metiamide
- Fewer side effects
- Inhibits H₂-receptors and lowers levels of gastric acid released
- Marketed in 1976, greatly reduced surgeries
- Biggest selling prescription drug until ranitidine (1981)
- Metabolically pretty stable
- Inhibits cytochrome p450 enzymes (side effect)
- Drug-drug interactions with diazepam, lidocaine and warfarin (side effect)
- More recent studies suggest it may help chronic tendenitis of the shoulder and as a supplemental drug in colorectal cancer
Cimetidine (Tagamet)

- The cyanoguanidine group acts as a bio-isostere for the thiourea group

- Both groups are planar and of similar geometry
- Both groups are polar but essentially neutral
- Both groups have high dipole moments
- Both groups have low partition coefficients (K_p values, more water soluble)
- The cyanoguanidine group is weakly acidic and weakly basic - amphoteric
- The cyanoguanidine group is not ionised at pH 7.4

New Consideration - Possible tautomers of the cyanoguanidine group (Cimetidine = Tagamet)

- The favoured tautomer is the imino tautomer

- The electron-withdrawing effect of the CN group is an inductive effect
- The inductive effect is felt most at the neighbouring nitrogen
- The neighboring nitrogen is least likely to form a bond to hydrogen
- The imino tautomer allows pi resonance with the cyano substituent (and N lone pairs below)
The cyanoguanidine group – possible conformational isomers (and configurational?)

- Notes
  - The E, E and Z,Z conformations are not favoured because of steric interactions (X-ray and NMR evidence support this)
  - Bad news for the chelation bonding theory because Z,Z conformation is not favored
  - Chelation to the one carboxylate group requires the E,E or the Z,Z conformation

The cyanoguanidine group – new idea as to possible binding modes

Old idea for interaction at active site had 2 H bonds, steric interaction - not favored

New idea for interaction at active site has 2 H bonds in different directions.
**Rigidification nitropyrrrole analogue**

- Unable to adopt the *E,E* or *Z,Z* conformation
- Strongest analogue of cimetidine (antagonist)
- Locked into the active conformation
- Can only interact with two separate H-bond acceptors in the antagonist binding region

---

**Desolvation theory – would an increase in hydrophobic character help activity?**

- A guanidine unit is highly polar and highly solvated
- Solvated water must be removed prior to binding
- An energy penalty is involved
- The ease of desolvation may affect strength of binding and activity
- A urea group is more hydrophilic than a cyanoguanidine group
- May explain lower activity of the urea analogue
Reminder – partition coefficient

\[
\log P_{\text{oct/H2O}} = \log \frac{[\text{neutral compound}]_{\text{octanol}}}{[\text{neutral compound}]_{\text{water}}}
\]

at specific pH values

\[
\log D_{\text{oct/H2O}} = \log \frac{[\text{all forms compound}]_{\text{octanol}}}{[\text{all forms compound}]_{\text{water}}}
\]

The partition-coefficient (P) or distribution-coefficient (D) is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium.

These ratios are a measure of the difference in solubility of the compound in two phases (water and 1-octanol).

The partition-coefficient generally refers to the concentration ratio of un-ionized species of compound whereas the distribution-coefficient refers to the concentration ratio of all species of the compound (ionized plus un-ionized) and depends on pH.

The distribution coefficient is a partition coefficient at a specific pH value.

The partition coefficient measures how hydrophilic or hydrophobic a chemical substance is.

Hydrophobic drugs with high octanol/water partition coefficients are mainly distributed to hydrophobic areas such as lipid bilayers of cells, while low octanol/water partition coefficients are found primarily in aqueous regions such as blood serum.

Solubility and partition coefficients of straight chain functional groups in 100 g water

<table>
<thead>
<tr>
<th>Solubility</th>
<th>( \log P_{\text{oct/H2O}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% miscible</td>
<td>0.54</td>
</tr>
<tr>
<td>100% miscible</td>
<td>0.32</td>
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<td>2.6</td>
</tr>
<tr>
<td>100% miscible</td>
<td>3.05</td>
</tr>
</tbody>
</table>


There is good correlation of calculated partition coefficients with experimental partition coefficients.

\[ \log P_{\text{oct/H}_2\text{O}} = \log \frac{[\text{compound}]_{\text{octanol}}}{[\text{compound}]_{\text{water}}} \]

What might a distribution coefficient curve look like for the following compound?

![Chemical Structure](image)

**Desolvation theory - hydrophobic analogues**

**Strategy**
- Increase the hydrophobic character of the planar aminal system
- Implies less solvation by water
- Implies less of an energy penalty associated with desolvation
- Implies easier binding at active site and a stronger activity

**Result**
- Antagonist activity of analogues increases as hydrophobic character increases

**Lipinski’s rules**
- No more than 5 hydrogen bond donors (the total number of N-H and O-H)
- No more than 10 hydrogen bond acceptors (all N and O atoms)
- A molecular mass less than 500 daltons (some say < 300)
- An 1-octanol/water partition coefficient, \( \log P < 5 \) (some say \( \log P < 3 \))
- There are many exceptions to Lipinski’s Rules.
- Lipinski said, in general, an orally active drug has no more than one violation and Veber’s rules
  - Polar surface area (all the O and N < 140Å² and < 90Å² for the BBB) and
  - The number of rotatable bonds (< 7-10)
    has been found to better discriminate between compounds that are orally active and those that are not

https://pdfs.semanticscholar.org/8493/576a7927322ebbb79c353bc1e1100a186eb50.pdf
Desolvation theory - hydrophobic analogues

**Result**

- Antagonist activity of analogues increases as hydrophobic character increases

![Diagram showing log (activity) vs. log \( P \) of HZ relationship]

\[ \log (\text{activity}) = 2.0 \log P + 7.4 \]

Desolvation theory - hydrophobic analogues vs. activity

<table>
<thead>
<tr>
<th>Structure</th>
<th>Activity (log A)</th>
<th>Polarizability (log P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>5.0</td>
<td>-0.95</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>4.6</td>
<td>-1.35</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>6.1</td>
<td>-0.8</td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
<td>5.8</td>
<td>-0.8</td>
</tr>
<tr>
<td><img src="image5" alt="Structure 5" /></td>
<td>6.0</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure</th>
<th>Activity (log A)</th>
<th>Polarizability (log P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6" alt="Structure 6" /></td>
<td>4.1</td>
<td>-1.6</td>
</tr>
<tr>
<td><img src="image7" alt="Structure 7" /></td>
<td>3.9</td>
<td>-1.5</td>
</tr>
<tr>
<td><img src="image8" alt="Structure 8" /></td>
<td>5.3</td>
<td>-1.15</td>
</tr>
<tr>
<td><img src="image9" alt="Structure 9" /></td>
<td>5.4</td>
<td>-0.9</td>
</tr>
<tr>
<td><img src="image10" alt="Structure 10" /></td>
<td>5.3</td>
<td>-1.1</td>
</tr>
</tbody>
</table>

\[ \log (\text{activity}) = 2.0 \log P + 7.4 \]

Greater activity than expected?  
Lower activity than expected?
Dipole moment theory – dipole-dipole interactions

- A dipole-dipole interaction takes place between the drug and the binding site on approach of the drug.
- The dipoles line up and orientate the drug.
- Good interaction with the binding site occurs if the binding groups are positioned correctly with respect to the binding regions - results in good activity.
- Poor interaction occurs if the binding groups are not positioned correctly with respect to the binding regions - leads to poor activity.

QSAR study including dipole-dipole interactions

- The orientation of the dipole is more important than its strength.
- $\log (\text{activity}) = 9.12 \cos \theta + 0.6 \log P - 2.71$

- Activity increases as hydrophobicity increases ($\log P$).
- The ideal angle of the dipole moment = 30°.
- At 30°, $\theta = 0°$ and $\cos \theta = 1$.
- At 30°, $\log (\text{activity}) = 9.12 + 0.6 \log P - 2.71$
- When dipole moment does not equal 30°, $\cos \theta < 1$ and activity falls.
\[
\log A = 9.12 \cos \theta + 0.6 \log P - 2.7
\]

\[A = \text{activity}\]

\[\theta = \text{deviation of angle of dipole moment from vertical (receptor site?)}\]

\[P = \text{partition coefficient (related to solubility in water vs. 1-octanol)}\]

---

**Cimetidine**

- Contains a nitroketeneaminal group (other flat groups will work too)
- Different heterocyclic ring, has a furan ring
- Fewer side effects
- 10 times more active
- Longer duration of action
- Replacing sulfur with methylene (CH₂) reduces activity
- Placing sulfur next to ring reduces activity
- Replacing furan with a more hydrophobic ring lowers activity
- 2,5-disubstitution pattern works best
- The methyl groups on the nitrogen can be varied without lowering activity
- That same N,N-dimethylaminomethylene substituent on Cimetidine lowers activity
- Methyl substitution at position 3 on the furan ring eliminates activity
- Methyl substitution at position 4 increases activity (indicates a different sort of interaction than Cimetidine)
- Introduced in 1981, was making over $7,000,000 per day
- Took over from Cimetidine as the most widely sold prescription drug in the world

---

**Ranitidine (Zantac, Glaxo) Glaxo merged with SmithKline**

- Contains a nitroketeneaminal group (other flat groups will work too)
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- Fewer side effects
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Famotidine (Pepcid)

• Different heterocyclic ring, thiazole ring
• 30 times more active than Cimetidine
• Side chain of sulfonlamidine group, but not essential, needs to have a dipole moment and be able to hydrogen bond, more variety possible
• Side chain length can be 4-5 atoms
• Replacing S with CH$_2$ in side chain increases activity
• Methyl group at position 4 decreases activity
• 3 of the 4 hydrogen atoms on the guanidine group are required for activity
• Has no effect on cytochrom P450 and does not appear interact with other drugs
• Pepcid is also used with dogs and cats with acid reflux
• Pepcid is used with H1 antagonists for severe urticaria
• Relief of heartburn, acid indigestion, and acid reflux (GERD)
• Part of a multidrug regimen for Helicobacter pylori eradication (in combination with antibiotics)
• Given to surgery patients before operations to reduce the risk of aspiration pneumonitis.
• It has even been used as a co-drug in treatment-resistant schizophrenia
• About 80% of stomach ulcers are healed in 4-6 weeks of treatment with all of these drugs

Parietal Cells, the Proton Pump and Inhibitors (PPI)

The proton pump
• Pumps protons out of the parietal cell and potassium ions back in
  \((\text{H}^+ \text{, outside}) / (\text{H}^+ \text{, inside}) \sim 3,000,000 / 1\) [highest ion differential in the body]
• Requires energy - provided by hydrolysis of ATP to ADP, catalysed by ATPase
• The proton pump is also called H$^+/K^+$-ATPase
• Chloride ions depart through a separate ion channel
• HCl is formed in the canaliculus
• The potassium ions exit the parietal cell as counter ions for the chloride ions and are then pumped back in
• A separate potassium ion channel is used for K$^+$ ions leaving the cell
Proton Pump Inhibitors

- All of these are prodrugs, minimal side effects until they reach their target
- Activated by the strongly acidic conditions (pH < 4) found in the canaliculae of parietal cells in the stomach wall

Mechanism of inhibition

- Irreversible inhibition (covalent binding)
- Pyridinium sulphenamide structure
Design of omeprazole (Losec)

The lead compound

- Originally an antiviral drug
- Inhibited gastric acid secretion (side effect)
- Liver toxicity due to the thioamide group (side effect)
- Many derivatives were made to try and overcome this

Modification of the thiourea group

- Also inhibited gastric acid secretion (desired effect)
- The pyridine ring and bridging CH₂S moiety are important to activity
- Many “heterocycle-X-Y-heterocycle” two atom bridges were tried
- Left side pyridine and -CH₂-S- bridge worked best, but right heterocycle was changed to benzimidazole

Design of omeprazole (Losec)

Modify the imidazole ring

Increase in activity due to the benzimidazole ring
Sulfoxide metabolite had increased activity over H 124/26

Drug metabolism studies

- Timoprazole formed by oxidation of sulfur on of H124/26
- Timoprazole was the active drug (prodrug)
- Pyridinylmethylsulfanyl benzimidazole structure
- Side effect – inhibited iodine uptake by the thyroid gland, so no clinical trials
- More analogs were synthesized to get around the iodine problem
Design of omeprazole (Losec)

- Potent antisecretory properties over long periods of time
- No toxic side effects on the thyroid
- No other serious side effects using animal studies
- Picoprazole was found to be the most effective antisecretory compound ever tested in humans
- At this point (1977) the proton pump was discovered and identified as the target of picoprazole
- Various substituents were tried on the pyridine ring to make it more basic/nucleophilic

Add substituents to the heterocyclic rings

Design of omeprazole (Losec)

Substituents varied on the pyridine ring

- Substituents which increase the basicity/nucleophilicity of the pyridine ring are good for activity
- Consistent with the mechanism of activation
- Methyl substituents at the meta position have an inductive effect
- Methoxy substituent is more effective at para position than meta position because of resonance effect

- H159/69 is potent but chemically too labile (unstable in vivo)
Design of omeprazole (Losec)
Substituents varied on the benzimidazole ring

• Substituents were varied to get the right balance of potency, chemical stability and synthetic accessibility
• Omeprazole was found to have the best balance

![Diagram of Omeprazole]

• Launched in 1988 by Astra
• World’s biggest selling drug (over $6 billion in 2000 alone, > $16,000,000 per day)
• Patents ran out in 2001 (Europe and US)

Esomeprazole (Nexium)

• Omeprazole has an asymmetric centre
• The S-enantiomer has better potency and pharmacokinetic profile
• Undergoes less metabolism than the “R” enantiomer so maintains higher levels of the drug in the body
• Example of chiral switching, started a new patent
• The “R” enantiomer was approved in the U.S. In 2009 as Dextansoprazole (another patent)

![Diagram of Nexium and Metabolites]
Synthesis of Omeprazole

Features of *Helicobacter pylori*

• Spiral, curved bacterium
• Grows best in oxygen concentrations of 5%
• Naturally present in the stomachs of many people
• Attaches to a sugar molecule on the surface of the cells lining the stomach wall
• The organism secretes proteins and toxins that inflame the stomach lining
• Responsible for the recurrence of ulcers
• The organism is protected by the mucus layer
• A pH gradient across the mucus layer means that the pH is near neutral at the stomach lining
• The helicobacter pylori bacteria was discovered in the contents of Otzi’s stomach (5000 year old frozen ice man).

Helicobacter pylori, is a gram-negative, microaerophilic bacterium found usually in the stomach. It was identified in 1982 and found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause. It is also linked to the development of duodenal ulcers and stomach cancer. Over 80% of individuals infected with the bacterium are asymptomatic, and it may play an important role in the natural stomach ecology.

More than 50% of the world’s population harbor *H. pylori* in their upper gastrointestinal tract. *H. pylori*’s helical shape is thought to have evolved to penetrate the mucoid lining of the stomach.

Individuals infected with *H. pylori* have a 10 to 20% lifetime risk of developing peptic ulcers and a 1 to 2% risk of acquiring stomach cancer.
Features of *Helicobacter pylori*

- Bacterium produces urease enzyme, releases basic ammonia
- Neutralises any acid in the local environment of the bacteria

\[
\text{NH}_2 \quad \text{NH}_2 \\
\text{Urea} \quad \xrightarrow{\text{Urease}} \quad \text{H}_2\text{O} \\
2 \text{NH}_3 \quad + \quad \text{CO}_2
\]

Treatment of *Helicobacter pylori*

- Triple therapy of a proton pump inhibitor and two antibiotics
- Antibiotics work better at a higher pH than is normally present in stomach
- The proton pump inhibitor is present to raise the pH

Example

- Omeprazole
- Amoxicillin
- Metronidazole