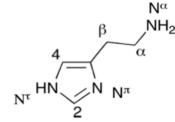


**PHAR3817 Notes – Respiratory**

**Histamine**

- Imidazole ring + ethyl amine side chain
- Formed by decarboxylation reaction of histidine (via histidine decarboxylase)
- Secreted from mast cells and some CNS neurons – accounts for *some* allergy symptoms
  - o Similar to autocooid, but lacks endocrine gland

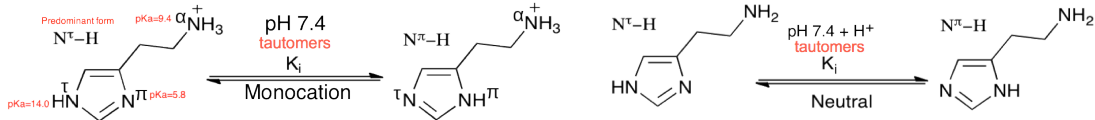


**Allergies**

- Due to hypersensitivity reaction of IgE antibodies
- Allergen binds to IgE → excessive activation of mast cells/basophils → excess histamine release
- Histamine causes inflammation by ↑ vasodilation, capillary permeability, smooth muscle contraction, mucus secretion, PNS stimulation

**Tautomerism**

- Histamine is a basic organic compound with two nitrogens that can be protonated
- pH 7.4 – exists 96.6% as monocationic conjugate species (N<sup>α</sup> as NH<sub>3</sub><sup>+</sup>)
  - o 80% N<sup>τ</sup>-H (tele-tautomer) – enhances receptor-binding

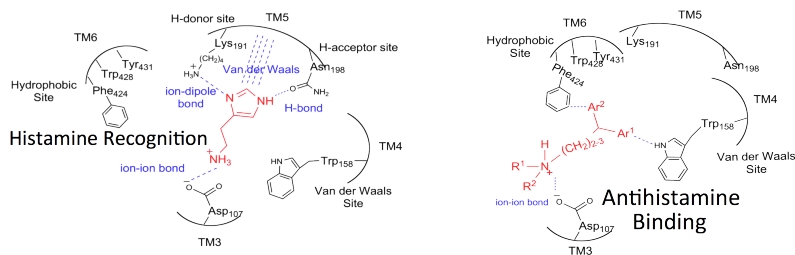


Receptor	Location
H <sub>1</sub>	- Smooth muscle of intestine, bronchi, blood vessels, uneven distribution in CNS neurons
H <sub>2</sub>	- Gastric parietal cells, myocytes (heart), guinea pig atria, uterus - Control release of gastric acid from parietal cells; modulates heart rate/contractility
H <sub>3</sub>	- Mainly in basal ganglia, hippocampus and cortical areas - Presynaptic autoreceptors to regulate histamine synthesis/release - Modulates release of other neurotransmitters (ACh, dopamine, NAd, serotonin)
H <sub>4</sub>	- Wide expression in lung and immune system – spleen, thymus, leukocytes - Possible benefits in allergy and autoimmune disease (IBS, arthritis) treatment

**Histamine receptor**

- GPCRs – seven-transmembrane domain receptors
- Antihistamines are actually inverse agonists – bind and stabilise the *inactive* form of the receptor
  - o Aromatic rings should be *unsubstituted* (otherwise too bulky to fit in binding sites)
- Histamine *activates* H<sub>1</sub> receptor via electron donations
- Stereochemistry affects receptor-binding – can affect steric hindrance, e.g. chlorpheniramine:
  - o Pyridine ring binds to sterically-hindered H<sub>1</sub>R hydrophobic site
  - o Chlorophenyl ring binds to van der Waals site as Cl is too large for hydrophobic pocket
  - o Thus only R-isomer is active (S-isomer is inactive)
    - Administering only the active isomer may result in less side-effects

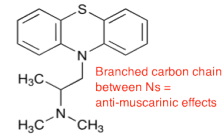
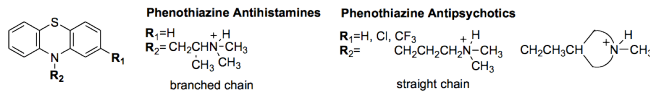
Bond type	H <sub>1</sub> R location	Histamine	H <sub>1</sub> R location	Antihistamine
Van der waals	TM5 residues	Pi electrons of imidazole ring	TM6 hydrophobic site Phe424	Aromatic ring
Ion dipole	TM5 Lys191 NH <sub>3</sub> <sup>+</sup>	Pi electrons of ring nitrogen	TM4 Trp158	Aromatic ring
Ion-ion	TM3 Asp107 COO <sup>-</sup>	Terminal nitrogen	TM3 Asp107 COO <sup>-</sup>	N (ion-ion bond)
Hydrogen	TM5 Asn198 C=O	Proton on tele-nitrogen		



## First-generation antihistamines

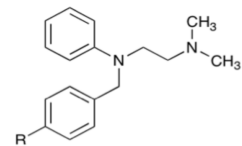
General structure	Possible substituents	X
	Ar <sup>1</sup> = aryl, substituted phenyl, heteroaryl	N = ethylenediamine
	Ar <sup>2</sup> = aryl, benzyl (ArCH <sub>2</sub> )	CH-O = aminoalkyl ether
	R = tertiary acyclic (NMe <sub>2</sub> ) or cyclic	CH or C=C = alkyl amine
	Ar-N <sup>+</sup> distance ~5-6Å	

- First generation antihistamines have similar structure to anti-cholinergics
- Branching of side chain enhances selectivity for H<sub>1</sub>-receptors
  - o Straight chain = antipsychotics (dopaminergic receptors)



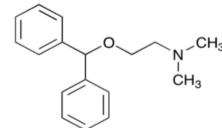
## Ethylenediamines

- Two aromatic rings + terminal tertiary amine
- Sedative effects, GI disturbances, CNS effects (inhibit serotonin and dopamine reuptake), weak anticholinergic effects, strongest antiemetic activity
- E.g. mepyramine (R=OCH<sub>3</sub>), tripelemamine (R=H)



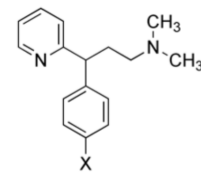
## Aminoalkyl ethers

- AKA ethanolamines – differs from ethylenediamines by replacing N with O
- Sedation, low GI irritation, strongest anticholinergic side effects
- Diphenhydramine maleate – Benadryl, Unisom SleepGels (sedation)
- Dimenhydrinate – antiemetic for travel sickness
- Doxylamine succinate (Mersyndol) – antiemetic + mild sedative
- Clemastine – antipuritic (stops itching)



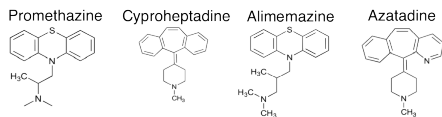
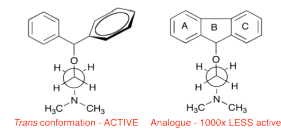
## Aminopropyl compounds

- Two aromatic rings and terminal amine (no N/O)
  - o X = H (pheniramine), Br (brompheniramine), Cl (chlorpheniramine)
- Low sedation/GI irritation/anticholinergic effects, strong CNS stimulation
- Mainly used for cold and flu – dexchlorpheniramine



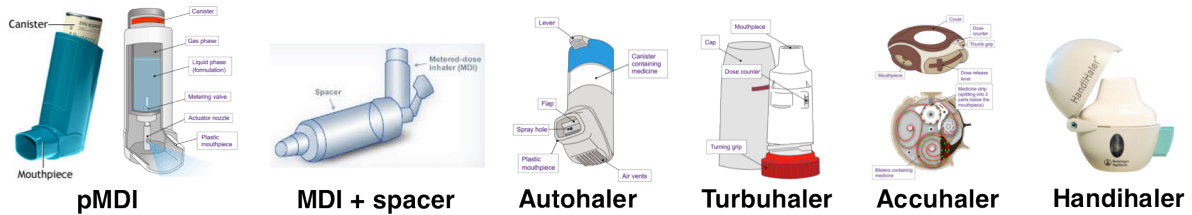
## Tricyclic antihistamines

- Non-planar rings – B (centre) ring adopts boat conformation so rings A and C are not in same plane
  - o Enhances potency and binding to H<sub>1</sub>R
- Anticholinergic, CNS and sedative effects (low GI irritation)
- Promethazine – anti-emetic
- Cyproheptadine – allergy, migraine prophylactic, appetite stimulant
- Alimemazine/azatadine – antipuritic (eczema, poison ivy), sedative, antiemetic



First gen	Mediated through	Effects
<b>Benefits</b>	H <sub>1</sub> -receptor	↓ Allergic inflammation, itch, sneezing, rhinorrhoea, wheezing
	Nuclear factor κB	↓ Antigen presentation, chemotaxis, proinflammatory cytokines
	Ca <sup>2+</sup> ion channels	↓ Mediator release
<b>Side effects</b>	H <sub>1</sub> -receptor	Crosses BBB, ↓ neurotransmission in CNS, ↑ sedation and appetite, ↓ cognitive and psychomotor performance
	Muscarinic receptor	Anticholinergic – dry mouth, urinary retention, sinus tachycardia
	α-Adrenergic receptor	Hypotension, dizziness, reflex tachycardia
	Serotonin receptor	Increased appetite
	Cardiac-ion channels	Prolonged QT intervals (potential ventricular arrhythmias)

General steps	Explanation
Remove inhaler cap	Protects from dust/moisture
Shake well	Mixes drug with propellant
Exhale to residual volume	Assists coordination and timing
Keep head upright, lift chin slightly	Prevent aerosol hitting mouth and throat
Place mouthpiece between teeth and seal with lips	Prevent drug from escaping or hitting teeth
Hold breath for ~10 seconds	Allow particles to settle in lungs
Exhale away from inhaler mouthpiece	Moisture/particles in breath affect medication
Wait between doses	Time for sedimentation, diffusion, less loss of fines



### Pressurised metered dose inhalers (pMDIs)

- Uses propellant – requires low airflow rate, but requires coordination/timing
- Includes press-activated devices (MDI), and breath-activated devices (Easi-breathe, Autohaler)
- Spacer – simplifies coordination and timing of inhalation, minimises risk of adverse effects
  - o Slows down particles and reduces particle size – only need regular deep breath

	pMDI	pMDI + spacer	Autohaler
<b>1</b>	Remove cap and shake well	Remove cap and shake well Insert inhaler into spacer	Remove cap and shake well Raise lever to prepare dose
<b>2</b>	Exhale completely	Exhale completely	Exhale completely
<b>3</b>	Head upright, lift chin slightly	Head upright, lift chin slightly	Head upright, lift chin slightly
<b>4</b>	Place mouthpiece between teeth and seal with lips	Place spacer mouthpiece between teeth, seal with lips	Place mouthpiece between teeth, seal with lips, do not cover air vents at the base
<b>5</b>	Inhale <i>slowly</i> and deeply, pressing canister early	Press canister once, and inhale <i>slowly</i> and deeply from spacer	Inhale <i>slowly</i> and deeply (breath activates drug release)
<b>6</b>	Hold breath for 10 seconds	Breathe in/out through spacer for 4 breaths	Hold breath for 10 seconds
<b>7</b>	Exhale away from mouthpiece		Exhale away from mouthpiece
<b>8</b>	Replace cap; repeat if needed	Wait; repeat for second dose	Push lever down; replace cap

### Dry powder inhalers (DPIs)

- Rely on force of inhalation to deliver drug – no need for coordination/timing
- Multi-dose devices (Accuhaler, Diskhaler, Turbuhaler) and single-dose (Aeroliser, Handihaler)
- Hold DPIs upright to ensure accurate dose

	Turbuhaler	Accuhaler	Handihaler
<b>1</b>	Remove cap	Slide thumb grip to open inhaler	Remove cap and mouthpiece
<b>2</b>	Keep inhaler upright to ensure correct dose	Push lever back completely to load dose (“click”)	Place capsule into centre chamber and close mouthpiece
<b>3</b>	Rotate grip until “click”	Hold inhaler horizontally	Press green button then release
<b>4</b>	Exhale completely	Exhale completely	Exhale completely
<b>5</b>	Keep head upright	Keep head upright	Keep head upright
<b>6</b>	Mouthpiece between teeth/lips	Mouthpiece between teeth/lips	Mouthpiece between teeth/lips
<b>7</b>	Inhale <i>forcefully</i> /fast and deeply	Inhale <i>forcefully</i> and deeply	Inhale <i>forcefully</i> and deeply
<b>8</b>	Hold breath for 10 seconds	Hold breath for 10 seconds	Hold breath for 10 seconds
<b>9</b>	Exhale away; replace cap	Exhale normally; close inhaler	Tip out used capsule; close