Therapeutics of Histamine Receptors

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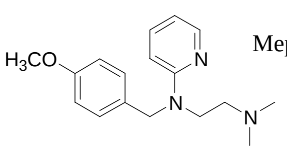
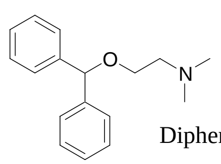
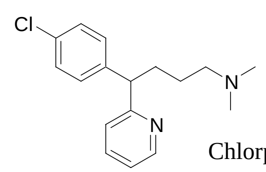
The biogenic amine, histamine, has a rich history in medicinal chemistry. It was first detected as a uterine stimulant in ergot extracts, almost one hundred years ago, by Barger and Dale.[1] This was followed by an intensive pharmacological evaluation of the role of histamine by Dale and Laidlaw.[2] In a series of papers, the powerful effect of histamine in stimulating smooth muscle contractions and its actions in reducing blood pressure were noted. These early studies demonstrated a similarity between the effects of histamine and the symptoms that appear during inflammation and with the characteristic symptoms produced by trauma or allergic reactions. Only later was it determined by Best et. al.[3] that histamine is a natural constituent of the body. It then became widely assumed that histamine was the principal mediator of inflammation and shock and consequently prompted a search for substances capable of counteracting these effects. This ultimately led to the development of antihistamines by Bovet et al at the Pasteur Institute in the 1940's. Using several epinephrine analogues as a chemistry starting point the group at the Pasteur Institute were able to identify compounds capable of blocking the actions of histamine. Exploitation of these observations by Rhone-Poulenc and other pharmaceutical companies led to the introduction of antihistamines for the treatment of allergic conditions such as hay fever. Over the years this afforded numerous commercially successful drugs including mepyramine, diphenhydramine and chlorpheniramine, many of which are used to this day.



Mepyramine

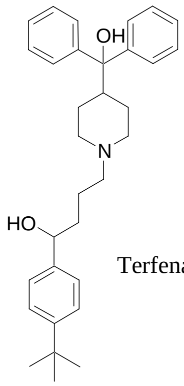


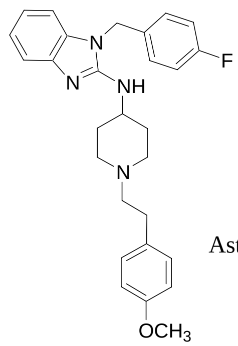
Diphenhydramine

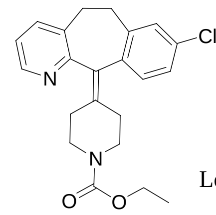


Chlorpheniramine

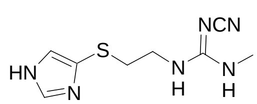
Much later, in the 1970's, non-sedating antihistamines were identified by several pharmaceutical companies; terfenadine from Merrell,[4] astemizole from Janssen[5] and loratadine from Schering-Plough.[6,7] Although terfenadine and astemizole became associated with cardiac arrhythmias leading to the withdrawal of terfenadine from the U.S. market, loratadine achieved "blockbuster" status with annual sales in excess of a billion dollars.[8]

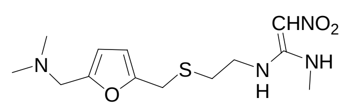

Terfenadine


Astemizole

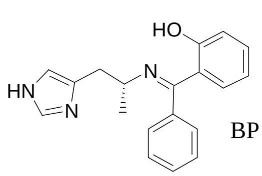

Loratadine

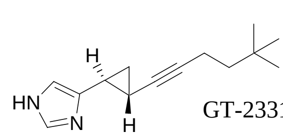
Continued examination of the physiological role of histamine using the early antihistamines (H_1-antagonists) led to the observation that not all the actions of histamine could be blocked by these drugs, prompting the suggestion that there may be two types of histamine receptor by Folkow et. al.[9] In particular the failure of antihistamines to block histamine stimulated gastric acid secretion led Black et. al. (circa 1964) to search for antagonists of this effect of histamine. Their medicinal chemistry efforts began by considering the endogenous ligand as a template. Thus Black's now classical pharmacological approach[10] was to modify the endogenous ligand by reducing efficacy whilst retaining and eventually increasing affinity to obtain a competitive antagonist. Ultimately this led to the discovery of the first marketed histamine H_2 antagonist cimetidine[11,12] which was followed by ranitidine[13] and both these drugs became "blockbusters". The H_2-antagonists revolutionized the treatment of gastric and duodenal ulcers.


Cimetidine

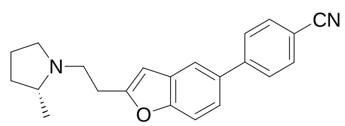

Ranitidine

A third histamine receptor was described by Schwartz et al in 1983 as an autoreceptor controlling histamine release in the brain. Subsequently it was shown to presynaptically inhibit the release of other mono-amines in the brain and peripheral tissue. However despite the availability of numerous H_3 agonists and antagonists, the clinical evaluation of these ligands only occurred recently. Prior to the cloning of the H_3 receptor there were few reports of compounds entering the clinic. The (*R*)-alpha-methyl histamine prodrug BP 2.94[14] and GT-2331[15] which were evaluated for pneumoallergic disorders, and attention deficit hyperactive disorder, respectively.

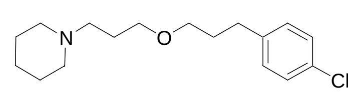

BP 2.94


GT-2331

The cloning of the H_3 receptor by Lovenberg et al[16] prompted a renaissance in the H_3 arena allowing pharmaceutical companies in particular to apply high throughput screening technology to identify new templates for medicinal chemists. This in turn initiated a move away from imidazole-based ligands and their inherent liabilities and the discovery of numerous non-imidazole-based antagonists.[17] Despite these events in the late 1990's it is only recently that compounds have entered clinical trials where the therapeutic targets include sleep disorders, obesity, schizophrenia and cognitive disorders. Companies acknowledging a clinical presence include, Abbott,[18] Bioprojet,[19] GlaxoSmithKline[20] and Johnson and Johnson.[21]



ABT-239



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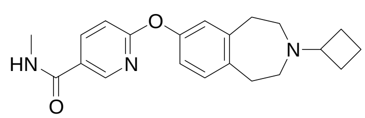
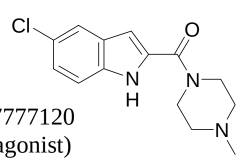
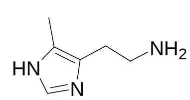


GSK-189254A

The fourth histamine receptor, H_4, was identified by several laboratories in 2000 and was discovered as part of programs aimed at the identification of ligands for orphan GPCR's.[22] The H_4 receptor is primarily located in the immune system and H_4 antagonists may offer the potential to treat a range of allergic and immunological disorders. Shortly after the characterization of the receptor a potent non-imidazole antagonist ligand[23] was described and more recently an imidazole-based selective agonist was described.[24] These ligands will be important tools to determine the role of the H_4 receptor as a target for therapeutic intervention.



JNJ-7777120
(Antagonist)



4-Methylhistamine
(Agonist)

Over the last 100 years histamine research has provided many important drugs for the treatment of allergic (H_1 mediated) and gastrointestinal disorders (H_2 mediated) and with the more recent characterization of the histamine H_3 and H_4 receptors novel therapies for CNS and immune disorders have become a distinct possibility.

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