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Histamine Receptors

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Histamine is an important chemical mediator and neurotransmitter on a broad spectrum of physiological and pathophysiological conditions in central and peripheral tissues which exerts its specific effects by four different aminergic G-protein coupled receptor (GPCR) subtypes ($H_1 - H_4$). The biogene amine, 2-(1H-imidazol-4-yl)ethanamine, is known to participate in allergic and inflammatory reactions, gastric acid secretion, immunomodulation, and neurotransmission.

Introduction

Histamine is produced by decarboxylation (E.C. 4.1.1.22 or E.C. 4.1.1.26) of the semi-essential amino acid L-histidine and stored in mast cells, basophils, some neurons etc [1,2]. Its synthesis in Golgi apparatus can be blocked by α-fluoromethylhistidin[3].

Since the first synthesis of histamine by Windaus and Vogt, the anaphylactic reaction of histamine with Dale and Laidlaw, and the detection of blockers of histamine effects by D. Bovet[1], different advances in histamine receptors ligands have ever attracted pharmaceutical developments and are still highly topical[6].
While H_1 and H_2 receptors have been successful targets of blockbuster drugs for treating allergic diseases and gastric ulcer, respectively, the developments of H_3 and H_4 receptor ligands are still on their way to market[7]. The different histamine receptor subtypes are named in chronological order as H_1, H_2, H_3, and H_4 receptors. Though the first three subtypes have firstly been characterized by classical pharmacological methods, meanwhile every one of corresponding genes are cloned in humans as well as in many other species (Figure 2) [8-13].
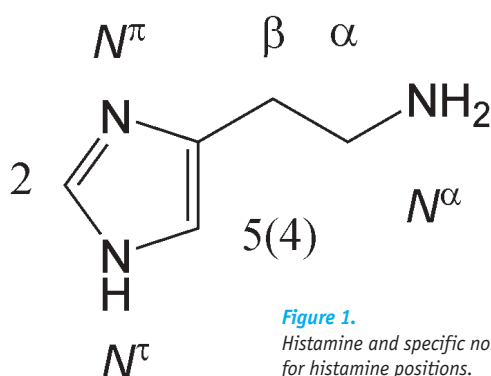

Figure 1.
Histamine and specific nomenclature for histamine positions.

Histamine possesses two basic functionalities (primary aliphatic amine (pK_{a1} 9.4) and imidazole (pK_{a2} 5.8)) making the monocation with different tautomers the preferred form at physiologic pH value (96%) with a minor dicationic fraction (3%) and only a very small amount of the neutral form (Figure 1)[4]. On metabolic pathway one can distinct two major initial inactivation mechanisms in which imidazole methylation by histamine N^{τ}-methyltransferase (E.C. 2.1.1.8) is ubiquitously found whereas oxidation by diamine oxidase (E.C. 1.4.3.6) is mainly located in the periphery. Following oxidations by monoamine oxidases, aldehyde dehydrogenase or xanthine oxidase maybe with conjugation to ribose led a small amount only (2-3%) of the released histamine excreted unchanged[3,5].
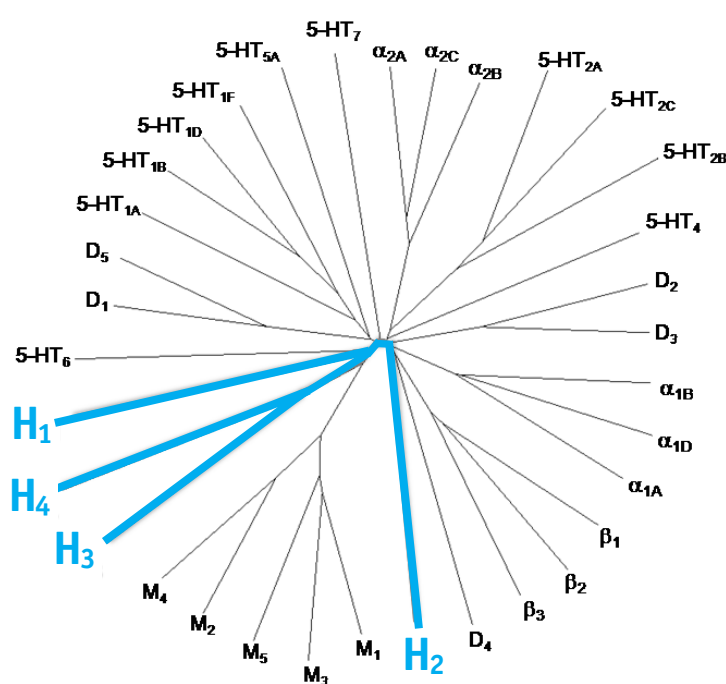

Figure 2.
Phylogenetic tree of five subfamilies of human aminergic GPCRs (modified from Ref. 12).

Although all the receptor subtypes belong to one family of rhodopsin-like class A GPCRs with a highly conserved aspartate residue in the third transmembrane helix, they strongly differ in receptor distribution, ligand binding, signaling pathways and functions (Table 1).

	hH$_1$	hH$_2$	hH$_3$	hH$_4$
Chromosomal gene location	3p25	5q35.2	20q13.33	18q11.2
Amino acids	487	359	445	390
Isoforms			+	+
G-protein coupling	G$_{q/11}$	G$_s$	G$_i$/G$_o$	G$_i$/G$_o$
Principal signal transduction	PLC ↑, Ca^{2+} ↑	cAMP ↑	cAMP ↓, Ca^{2+} ↑, MAPK ↑	cAMP ↓, Ca^{2+} ↑, MAPK ↑
Tissues	Lung, brain, vessels	Heart, stomach, brain	Neurones (CNS, PNS)	Mast cells, eosinophils
Physiological relevance	Contraction of smooth muscles, food intake, sleep-wake regulation	Gastric acid secretion	Sleep, food intake	Chemotaxis
Pathophysio-logical relevance	Allergic reaction	Gastric ulcer	Cognitive impairment, seizure, metabolic syndrome?	Inflammation, immune reaction

Table 1. Molecular pharmacology profiles of histamine receptor subtypes.

Some signaling mechanisms or G-protein couplings remain unclear and are still subject of actual investigations. Additional non-GPCR binding properties have also been observed like the allosteric modulation of glutamatergic ion channels of the NMDA receptor class[14]. Histamine reuptake mechanism comparable to that of the other aminergic neurotransmitters has not been observed and is discussed in different points[15].

Histamine H$_1$ receptor

Histamine H$_1$ receptors are distributed in a wide variety of tissues, e.g. central nervous system[16], smooth muscles, gastrointestinal tract, cardiovascular system, endothelial cells and lymphocytes[17]. Upon activation a stimulation of phospholipase C (PLC) (and phospholipases A$_2$ and D) via Gα$_{q/11}$ leads to an increase of inositol-1,4,5-trisphosphate (IP$_3$) and 1,2-diacylglycerol (DAC) and thereby via increased Ca^{2+} concentration and/or cAMP, cGMP, NO formation to contraction of smooth muscles, dilatation of arterioles and capillaries, vascular permeability in vessels as well as stimulation of afferent neurons (Table 1)[18].
Wakening status and vomiting are observed as central effects. Histamine is stimulation signaling cascade of nuclear factor kappa B (NF-κB) leading to (pro)inflammatory mediators.
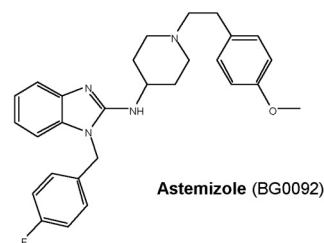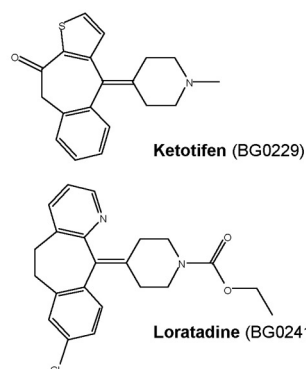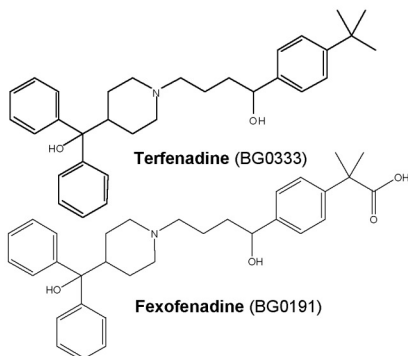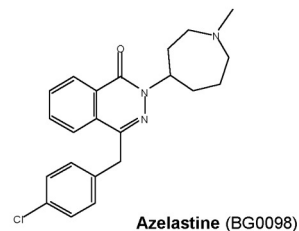Typical immediate responses of allergic reaction typ I like redness, itching and swelling ("triple response") are mainly caused by H$_1$ receptor activation. Rhinitis, asthma, anaphylaxis and urticaria can also be taken as peripherially H$_1$ receptor-mediated effects as food and water intake, convulsion, attention and sleep regulation are taken as central ones.

Histamine H$_1$ receptor agonists are mainly used as pharmacological tools instead of therapeutically active drugs[19]. The moderate potent H$_1$ receptor agonist betahistine for Ménière's disease is also exhibiting H$_3$ receptor antagonist properties. Replacement of the imidazole nucleus led to thiazol-2-yl- or pyridine-2-yl ethanamin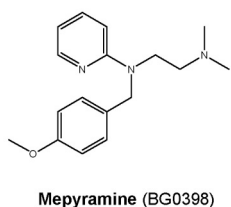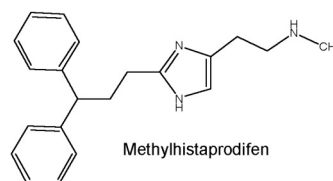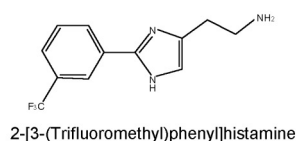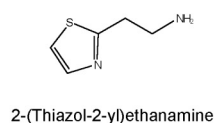e compounds with some H$_1$ receptor preference (Figure 3). The 2-substituted histamine derivatives (e.g. 2-[3-(trifluoromethyl)phenyl]histamine or the histaprodifen series) led to compounds with higher affinity and efficacy. Surprisingly some compounds of other lead structures like lisuride or proxifan also showed some H$_1$ receptor agonist properties.

Therapeutically H$_1$ receptor antagonists are much more important than the agonists. Generally a basic nitrogen functionality is connected via different linkers to a aromatic lipophilic moiety (e.g. ethylenediamine, colamine, propylamine typ)[20]. Stereochemical differentiation can be made with several enatiomeric/diastereomeric compounds. Actually differentiation of distinct generations of H$_1$-antihistamines is mainly done by selection criteria based on the central or missing central effects. Sedation was one of the main problems with the application of first generation H$_1$-antihistamines like bamipine, dimetindene, diphenhydramine, doxylamine, mepyramine (also named pyrilamine) etc. (Figure 3). Many of these compounds are nowadays used as sedatives or antikinetose compounds or have a local application way avoiding this side effect[21]. Newer second generation H$_1$-antihistamines do not or only poorly penetrate the blood-brain barrier. In some cases high hydrophilicity seems to be the reason for this whereas other show affinity for efflux systems like P-glycoprotein or organic anion transporter polypeptide. Some of the newer non-sedating compounds are the active metabolites of long time known antagonists: astemizole → norastemizole, hydroxyzine → ceterizine, terfenadine → fexofenadine, ebastine → carebastine, loratidine → desloratidine. Terfenadine and astemizole have at high plasma concentration like many other compounds some affinity at voltage-dependent human ERG1 potassium channels (hERG1-K$^+$) leading to prolonged QT time and *Torsades de pointes*[22,23]. Due to the danger of metabolic accumulation by CYP3A4 inhibition these compounds have been withdrawn from market or at least reduced availability. Many neuroleptic drugs like ketanserine, promethazine, cyproheptadien, olanzapine, cinnarizine etc. possess high antagonist H$_1$ receptor potency[24]. The increase in weight gain can be directly correlated to their H$_1$ antagonist receptor occupancy mediated by a hypothalamic AMP kinase[25,26]. Many of the compounds described above show high species differences with affinity making the development of radioligands problematic[27].

Although many of these compounds are described as histamine H$_1$ receptor antagonists they are pharmacologically better described as inverse agonists due their reduction of the constitutive activity level[28]. Therefore, the term "H$_1$-antihistamines" should be used instead of H$_1$ receptor antagonists which also includes the neutral antagonists. Constitutive activities have been found in all histamine receptor subtypes and most antagonists have to be defined as inverse agonists whereas only a small number of antagonists are neutral antagonists in some test systems.

Agonists

2-(Thiazol-2-yl)ethanamine

2-[3-(Trifluoromethyl)phenyl]histamine

Methylhistaprodifen

Mepyramine (BG0398)

Diphenhydramine (BG0169)

Cetirizine (BG0436)

Azelastine (BG0098)

Terfenadine (BG0333)

Fexofenadine (BG0191)

Ketotifen (BG0229)

Loratadine (BG0241)

Astemizole (BG0092)
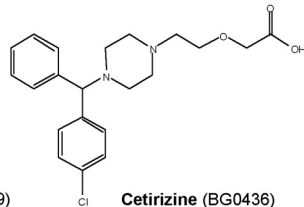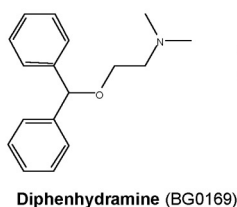
Antagonists

Some pharmaceutical companies claim for their new marketed compounds the belonging to a third generation of H_1-antihistamines owed to reduced effects at hERG or some additional properties at supporting targets, e.g. mast cell stabilization or PAF, 5-LO, neurokinines, thromboxane A_2, bradykinin B_2 etc. antagonisms[29]. Presently the clinical data of most new candidates do not show a clear optimized profile in this direction in comparison to that of the best first or second generation H_1-antihistamine allowing any claim of third generation H_1-antihistamines[30]. Many histamine-mediated effects cannot be blocked by H_1-antihistamines[31].

Histamine H_2 receptor

Histamine H_2 receptors are found in a variety of tissues including brain, gastric parietal cells and cardiac tissues. H_2 receptor stimulation can mediate positive inotropic and chronotropic effects on atrial and ventricular tissues, but the most prominent effect is the stimulation of gastric acid secretion. In the central nervous system (CNS) H_2 receptor activation can inhibit nerve cells and block the long-lasting after-hyperpolarization and thereby increase working memory. Second messenger is cAMP via G_S stimulation of adenylyl cyclase. In some cell system $G\alpha_q$ coupling to PLC and intracellular Ca^{2+} has also been observed (Table 1).

First agonists of histamine H_2 receptors were also structurally closely related to the endogeneous ligand[32]. Dimaprit and its rigid aromatic analogue amthamine have been developed, of which the later shows improved selectivity and potency as compared to that of histamine (Figure 4).

The guanidine derivatives like impromidine or arpromidine have much higher affinities and possess positive inotropic vasodilatatory effects. Due to their polar in physiological medium quantitatively protonated guanidinium moiety for oral application prodrugs with strong electron withdrawing groups have been applied. With side chain branching stereochemical differentiation can be observed comparable to that of H_1 receptor antagonists.

The discovery of the first histamine H_2 receptor antagonists and their pharmacological characterizations is strongly associated with Sir James Black and coworkers[33]. The thiourea derivative burimamide has been the first selective compound for at that time called "non-H_1-receptor antagonists" leading to the definition of H_2 receptors (Figure 4). Ironically, burimamide was later detected as potent histamine H_3 receptor antagonist and then also as H_4 receptor agonist. Further developments led to metiamide and then to cimetidine as the first compound for therapy of gastric ulcer. Ranitidine, nizatidine, famotidine, and roxatidine were compounds with much higher affinities and a largely improved interaction potential. Whereas the imidazole derivative cimetidine is a potent inhibitor of CYP3A4 the later compounds have to be applied in much smaller dosage and possess less than 10% of the effects on cytochrom P450 metabolism than cimetidine. The safety of the newer H_2 receptor antagonists led to the availability of some of the compounds as OTC (over-the-counter) drugs. Nowadays due to the improved therapeutic profile proton pump inhibitors like omeprazole have replaced the H_2 receptor antagonists as first line therapy. Within the group of histamine H_2 receptor antagonists one can clearly observe the concept of bioisosteric replacement of the thiourea element in burimamide as polar moiety.

Antagonists with special properties are the slightly brain penetrating zolantidine and as one of the most potent compounds the radioligand [^{125}I]iodoaminopotentidine.

Whereas antagonists for H_1 and H_2 receptors have been introduced into market for a long time, the run for the first selective H_3 or H_4 receptor ligand in the market is highly topical. Numerous pharmaceutical companies and academic institutions have programs with diverse lead structures and some even with first candidates into clinical trials.
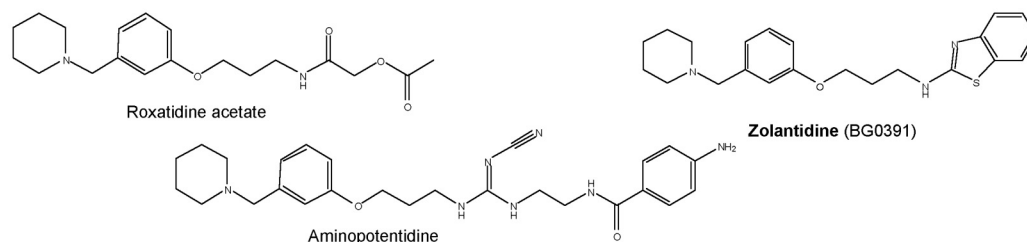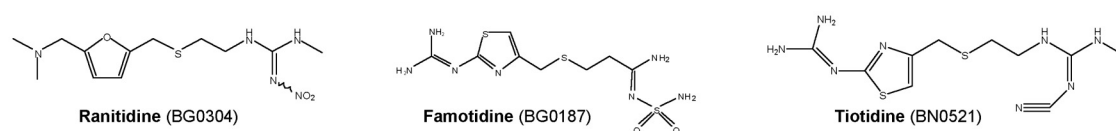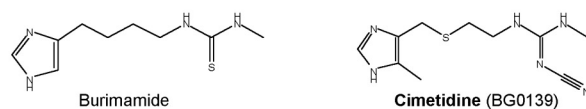
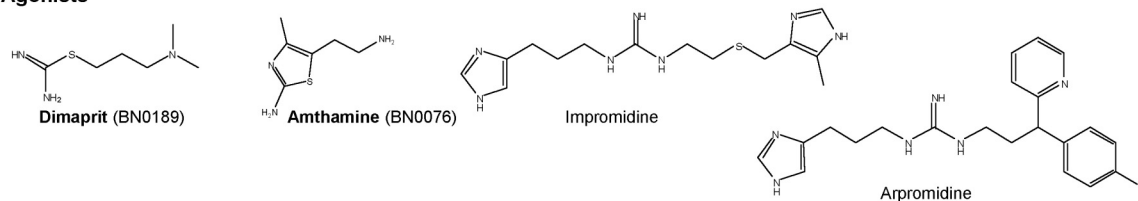### Histamine H_3 receptor

Function of histamine as neurotransmitter has been proven with the discovery of the H_3 receptor[34]. It is presynaptically located as autoreceptor controlling the synthesis and release of histamine[35]. As heteroreceptor it modulates with presynaptical localization the release of numerous other neurotransmitters, e.g. acetylcholine, norepinephrine, dopamine, serotonin, glutamate, γ-aminobutyric acid. With activation via $G\alpha_i$ and $G\alpha_0$ inhibition of adenylyl cyclase, activation of mitogenactivated protein kinase (MAPK), phospholipase A_2 (release of arachidonic acid), and Akt/GSK-3β kinases as well as inhibition of Na^+/H^+ antiporter and K^+-induced Ca^{2+} mobilization take place (Table 1). Numerous different isoforms are found in different species and different tissues leading to the assumption that signaling fine tuning may be controlled by formation of isoforms or receptor oligomerization[36]. The histamine H_3 receptor is anatomically localized primarily to the CNS with prominent expression in basal ganglia, hippocampus, cortex and striatal area. In the periphery H_3 receptor can be found with low density in gastrointestinal, bronchial and cardiovascular system.

As H_3 autoreceptor activation stimulates the negative feed-back mechanism, reduced central histaminergic activity is observed[37]. Involvement in cognition, sleep-wake status, energy homeostatic regulation, inflammation etc. has attracted pharmaceutical research for numerous so far unmet therapeutic approaches in different peripheral, but mainly central diseases[38,39].

Potent stimulation of H_3 receptors has been observed by imidazole derivatives only[40]. The methylated histamine derivatives, N^α-methylhistamine and the more selective and potent (R)-α-methylhistamine, are used for a long time for receptor characterization and are also available as tritiated radioligands (Figure 5). The distomeric (S)-configured isomer is about 100-times less potent than the eutomeric (R)-α-methylhistamine and allows useful control experiments. Although uncountable experiments with these tools have been reported, selectivity concerning H_4 receptors may be a problem with some investigations. Imetit, immepip, imifuramine and recently immethridine have been introduced as useful alternatives. As simple histamine derivatives are rapidly metabolized by histamine N-methyltransferase (HMT) orally available prodrugs[41,42] like the anti-inflammatory azomethine BP2.94 have been developed and introduced into clinical trials[43].

The floating change from agonist to antagonist behavior is even more complex with histamine H_3 receptors than with any other of the histamine receptor subtypes. Due to high constitutive activity of H_3 receptors inverse agonists can be found as well as neutral antagonists[44,45]. Based on theoretical aspects of receptor theory compounds with protean agonist properties have been described showing the whole spectra of pharmacological responses from inverse agonist to neutral antagonist to (partial) agonist in one molecule depending on the test system[46].

Agonists

Dimaprit (BN0189)   Amthamine (BN0076)   Impromidine   Arpromidine

Burimamide   Cimetidine (BG0139)

*Figure 4. Chemical structures of some histamine H_2 receptor agonists and antagonists. (Bold text denotes compounds available from **BIOTREND**).*

Ranitidine (BG0304)   Famotidine (BG0187)   Tiotidine (BN0521)

Roxatidine acetate   Zolantidine (BG0391)

Aminopotentidine

Antagonists

Agonists

(R)-α-Methylhistamine (BN0332)   *N*α-**Methylhistamine** (BN0366)   **Imetit** (BN0270)   **Immepip** (BN0271)   **Immethridine** (BN0272)

Proxyfan

GT-2331 (Cipralisant)

FUB 407

Thioperamide (BN0519)

Clobenpropit (BN0152)

Ciproxifan

BP2.649

GSK-189254

ABT-239

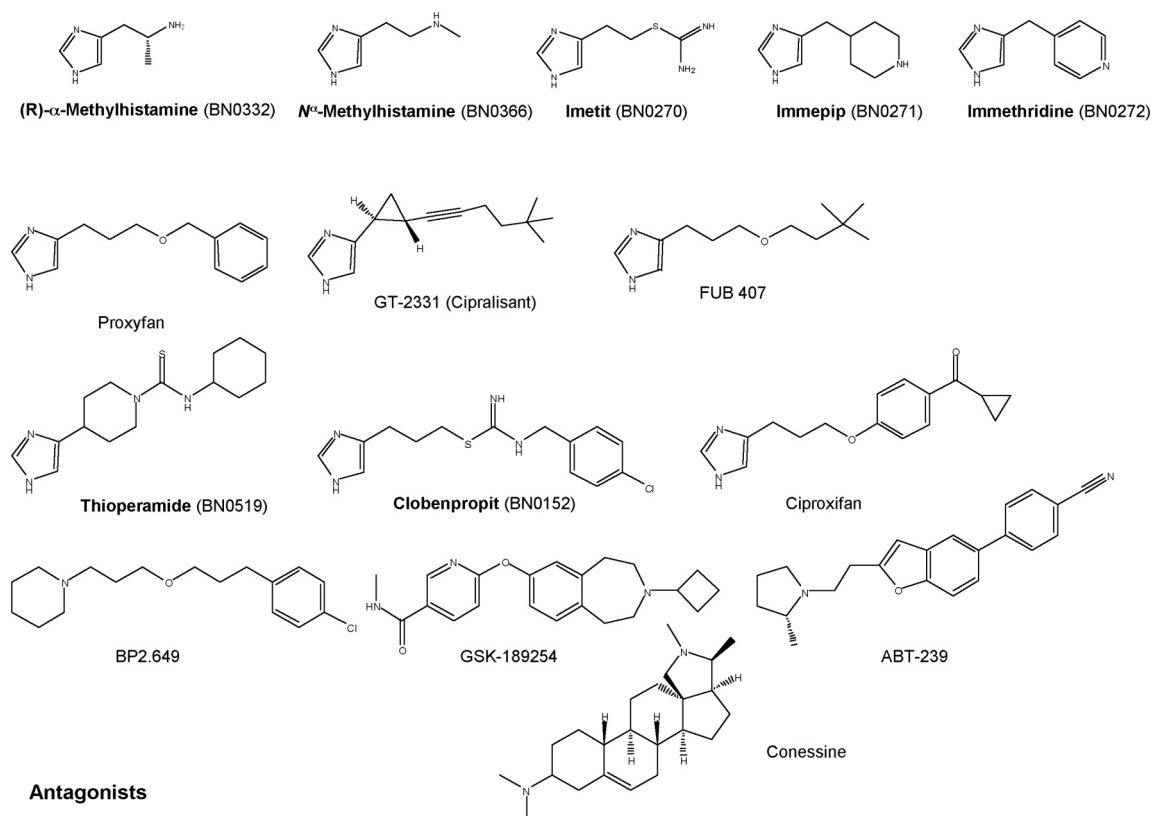Conessine

Antagonists

*Figure 5. Chemical structures of some histamine H₃ receptor agonists and antagonists. (Bold text denotes compounds available from **BIOTREND**).*

Proxyfan was the first compound as protean agonist for H₃ receptors (Figure 5)[47]. Different degrees of partial (ant)agonist properties were later also found in other series of non-amine imidazole derivatives like GT-2331 (cipralisant) or FUB 407.

First generation of H₃ receptor antagonists were monoalkyl-substituted imidazole-based derivatives like thioperamide, clobenpropit or ciproxifan (Figure 5)[48]. Claimed interaction potential to CYP isoenzymes caused by the imidazole moiety related to elements of the porphyrine cycle and sometimes complex pharmacological behavior led to imidazole replacements. A general pharmacophor element of these non-imidazole derivatives has been described which is nowadays shown in numerous variations and combinations: A basic moiety is linked by a spacer to a central, mostly aromatic core structure which then is connected to further affinity enhancing elements, e.g. another basic moiety or hydrophilic/ lipophilic groups or a combination thereof[49-52]. Distance and orientation of functionalities are of special importance as seen with the untypical antagonist conessine. Within the developments of the last decade pharmacokinetic properties and pharmacological profile have been attributed with further optimization (e.g. ABT-239). With the first compounds species specific affinities have been a problem as the preclinical evaluation included different in vivo assays in a variety of animals although receptor homology across species has been greater than 90%. Exchange of only two amino acids in transmembrane domain changed rodent binding behavior to human one and vice versa[53,54]. Development problems like selectivity, blood/brain concentration ratio, central nervous system clearance or phospholipidosis have been attributed. Numerous therapeutic indication are claimed in which cognitive impairment, attention-deficit hyperactivity disorder,

schizophrenia, narcolepsy, seizure, and obesity are mostly mentioned. Promising compounds like BP2.649, GSK-189254, and JNJ-17216498 have already entered clinical phase[51]. Others are on their line (e.g., GSK-239512, CEP-16795, CEP-26401, SAR-110894). Further properties have been put into the molecules depending on their potential therapeutic use (e.g., acetylcholine esterase[55], HMT[56], serotonin re-uptake[57])or on their use as pharmacological tool (e.g.,fluorescence, radioactivity) maintaining or even improving their H₃ receptor affinities.

Histamine H₄ receptor
The histamine H₄ receptor shows 31 − 43% overall homology to the related H₃ receptor depending on species which rise to 54% identity in transmembrane domains. The genomic structure is comparable to that of the H₃ receptor with two large introns and three exons with large interspecies variations from 65 − 72% homology in sequences. Activation of H₄ receptor via Gα$_i$ and Gα$_0$ leads to an inhibition of adenylyl cyclase and downstream of cAMP responsive elements (CRE) as well as activation of mitogen-activated protein kinase (MAPK) and phospholipase C with Ca²⁺ mobilization (Table 1). Receptor distribution has been found in bone marrow and leukocytes, particularly eosinophils, mast cells, dendritic cells, basophils and T cells, with moderate levels in spleen and small intestine. Although first expression studies showed the absence of H₄ receptors in the CNS, in situ hybridization studies confirmed evidence for human brain localization in low density.

The H_4 receptor seems to be present in most tissues at low level and connected to cells of hematopoietic lineage. This suggests a role in inflammatory processes and immune responses supported by the regulation of H_4 receptor expression by stimuli such as interferon, cytokines (e.g. TNF-α) and IL- 6, -10 and -13. The H_4 receptor mediates chemotaxis of mast cells and eosinophils as well as controlling cytokine release from dendritic cells and T cells[58-61]. Antagonists show general anti-inflammatory potency in models of asthma, arthritis, colitis, and pruritis[62,63]. Further results in autoimmune disorders, allergic conditions and nociceptive responses can be expected in the near future.

Many compounds with reported affinity for H_3 receptors do also have affinity for H_4 receptors. This is especially true for imidazole-containing compounds although there are numerous exceptions. The tetrahydrofuran derivative imifuramine and its cyanoguanidine analogue OUP-16 show H_4 receptor preferred activity. Compounds like clozapine, burimamide and clobenpropit behave as partial agonists at H_4 and as antagonists at H_3 receptors showing some functional selectivity[64]. Once more, a methylated histamine derivative is used as pharmacological tool. 4(5)-Methylhistamine has been developed as H_2 receptor agonist but shows higher affinity at H_4 receptor (Figure 6)[65,66].
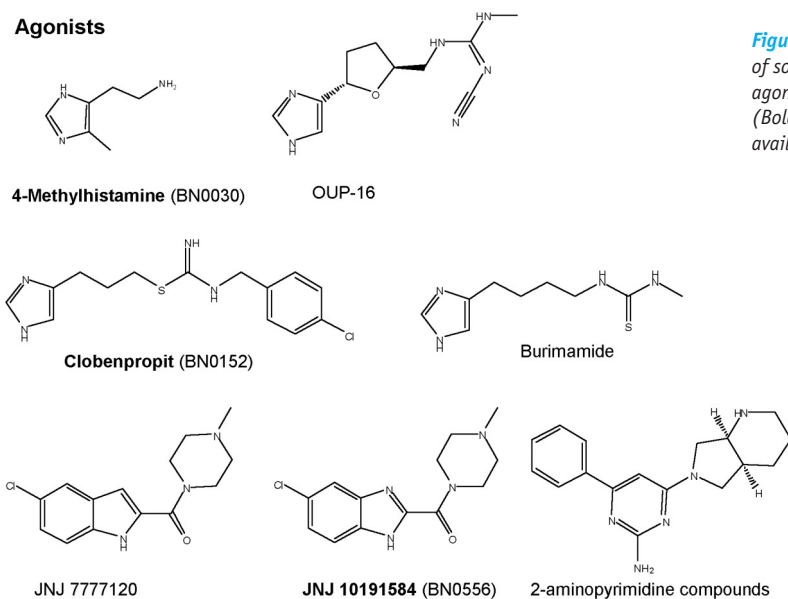
The first highly selective and orally active H_4 receptor ligand described has been the antagonist JNJ7777120 (Figure 6)[4]. Unfortunately, this compound is rapidly metabolized in liver microsomes and has a limited half-life of about 1 - 2 hours in vivo. Numerous heterocyclic compounds related to the indoloylpiperazines have been developed. Several new leads are claimed with the 2-aminopyrimidine moiety as an interesting heterocyclic scaffold[68]. It may be assumed that further lead structures are already claimed by different pharmaceutical companies in patents, but have not been put into public[69].

Perspective

Histamine receptor subtypes have been important drug targets for many decades. Histamine H_3 and recently H_4 receptors have led to a strong renewal of the interest in this biogene amine as well as to intensified research on the ligands and the potential therapeutic indications. It is assumed that within the next few years the first histamine H_3 receptor antagonist will go into market and developments on H_4 receptor antagonists will quickly follow. Reports on further details are eagerly awaited.

Although at present histamine-related development in pharmaceutical industry is mainly fixed on these receptor subtypes, basic research on re-uptake mechanism, isoform activation, receptor cross-talk etc. may open new fields for novel therapeutic applications of new ligands.

Agonists

4-Methylhistamine (BN0030)   OUP-16

Clobenpropit (BN0152)   Burimamide

JNJ 7777120   JNJ 10191584 (BN0556)   2-aminopyrimidine compounds

*Figure 6. Chemical structures of some histamine H_4 receptor agonists and antagonists. (Bold text denotes compounds available from **BIOTREND**).*

Antagonists

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Histamine receptor compounds

In brackets: pK_i/pK_D values followed by Cat. Nos. (Radioligands: see BIOTREND Radiochemicals-Catalogue).

Nomenclature	H_1	H_2	H_3	H_4
Agonists	HTMT BN0256	Dimaprit BN0189, Amthamine BN0076	Imetit (9.5) BN0270, Immepip (9.4) BN0271, R-α-Methylhistamine (9.2) BN0332, Immethridine (9.1) BN0272	Imetit (8.6) BN0270, Immepip (8) BN0271, Clobenpropit (7.9, partial agonist) BN0152, 4-Methylhistamine (7.3) BN0030
Antagonists	Doxepin (9.6) BG0175, Ketotifen (9.2) BG0229, Mepyramine (9) BG0398, Astemizole (7.7) BG0092, Antazoline (6.2) BG0041	Famotidine (pA_2 8.3) BG0187, Tiotidine (7.5) BN0521, Ranitidine (7.3) BG0304, Cimetidine (6.5) BG0139	Clobenpropit (9.4) BN0152, Iodophenpropit (9) BN0605, Thioperamide (7.6) BN0519	JNJ 10191584 (7.6) BN0556, Thioperamide (7.6) BN0519
Radioligands	[³H]-Mepyramine (9) ART-1431	[³H]-Tiotidine ART-1433	[³H]-R-α-Methylhistamine (9.2), ART-1342 [³H]-$N^α$-Methylhistamine (8.7) ART-1435	

Histamine H_1 selective

Cat. No.	Product	Category
BN0256	HTMT dimaleate	Histamine H_1/H_2 agonist
BG0041	Antazoline hydrochloride	Histamine H_1 antagonist, I ligand, neuroprotective agent
BG0092	Astemizole	Histamine H_1 antagonist, anti-allergic agent, P450 substrate
BG0098	Azelastine hydrochloride	Histamine H_1 antagonist, anti-allergic agent
BG0436	Cetirizine dihydrochloride	Histamine H_1 antagonist, anti-allergic agent
BG0140	Cinnarizine	Histamine H_1 antagonist
BG0169	Diphenhydramine hydrochloride	Histamine H_1 antagonist, anti-allergic agent
BG0175	Doxepin hydrochloride	Potent histamine H_1 antagonist, also binds to H_4
BG0191	Fexofenadine hydrochloride	Histamine H_1 antagonist, anti-allergic agent
BG0229	Ketotifen fumarate	Potent histamine H_1 antagonist, anti-allergic agent
BG0136	Levocetirizine dihydrochloride	Histamine H_1 antagonist, anti-allergic agent, active enantiomer
BG0241	Loratadine	Peripheral histamine H_1 antagonist, anti-allergic agent
BG0398	Mepyramine maleate	Potent, selective histamine H_1 antagonist
BN0638	Mirtazepine	Potent histamine H_1 antagonist, 5-$HT_{2,3}$ and $α_2$ antagonist
BG0299	Promethazine hydrochloride	Histamine H_1 antagonist
BG0333	Terfenadine	Histamine H_1 antagonist, anti-allergic agent

Histamine H$_2$ selective

Cat. No.	Product	Category
BN0076	Amthamine dihydrobromide	Highly selective histamine H$_2$ agonist
BN0189	Dimaprit dihydrochloride	Histamine H$_2$ agonist, moderatly potent H$_3$/H$_4$ antagonist
BN0256	HTMT dimaleate	Histamine H$_2$/H$_1$ agonist
BG0139	Cimetidine	Histamine H$_2$ antagonist, I$_1$ ligand
BG0187	Famotidine	Selective, potent histamine H$_2$ antagonist
BN0604	ICI 162,846	Potent histamine H$_2$ antagonist
BG0304	Ranitidine dihydrochloride	Selective, potent histamine H$_2$ antagonist
BN0521	Tiotidine	Selective, potent histamine H$_2$ antagonist
BG0391	Zolantidine dimaleate	Selective, potent histamine H$_2$ antagonist

Histamine H$_3$ and H$_4$ selective

Cat. No.	Product	Category
BN0270	Imetit dihydrobromide	Histamine H$_3$/H$_4$ agonist (H$_3$> H$_4$)
BN0271	Immepip dihydrobromide	Histamine H$_3$/H$_4$ agonist
BN0272	Immethridine dihydrobromide	Potent histamine H$_3$ agonist, highly selective over H$_4$
BN0332	(R)-(-)-α-Methylhistamine dihydrobromide	Potent histamine H$_3$ agonist
BN0333	(S)-(+)-α-Methylhistamine dihydrobromide	Histamine H$_3$ agonist, less active enantiomer
BN0030	4-Methylhistamine dihydrochloride	Potent, selective histamine H$_4$ agonist
BN0366	N$^\alpha$-Methylhistamine dihydrochloride	Non-selective histamine H$_3$ agonist
BN0152	Clobenpropit dihydrobromide	Potent histamine H$_3$ antagonist, partial H$_4$ agonist
BN0605	Iodophenpropit dihydrobromide	Potent, selective histamine H$_3$ antagonist
BN0556	JNJ 10191584 maleate	Potent, selective histamine H$_4$ antagonist
BN0519	Thioperamide maleate	Potent histamine H$_3$/H$_4$ antagonist

Histamine-related compounds

Cat. No.	Product	Category
BN0582	DPPE fumarate	Intracellular antagonist of histamine
BN0490	SKF 91488 dihydrochloride	Histamine N-methyltransferase (HMT) inhibitor

Related Radioligand

Cat. No.	Product	Category
ART-0234	[^{3}H]-L-Histidine	Precursor of histamine

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