## Design and Preparation of New Ligands Interacting with the Histamine H4 Receptor

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# Chapter 2

## A NEW GENERATION OF ANTI-HISTAMINES: HISTAMINE $H_4$ RECEPTOR ANTAGONISTS ON THEIR WAY TO THE CLINIC.

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The current chapter provides an overview on the status of the $H_4$R field in 2009 which formed the basis of the investigations provided in the following chapters. It was aimed to provide an up to date overview on the available chemical diversity and the knowhow of the receptor ligand interactions. A more recent overview of the field can be found in Current Topics in Medicinal Chemistry [1a].

## Abstract

At the turn of the millennium, the DNA sequence encoding the histamine $H_4$ receptor ($H_4R$) was identified in data from human genome databases. Considering the clinical importance of $H_1R$ and $H_2R$ ligands, and the clinical trials that are ongoing for $H_3R$ ligands, the latest addition to the histamine receptor family was noted with interest by the pharmaceutical industry. Initial studies describing the expression of the $H_4R$, and the activity of this receptor in (patho)physiology, suggested that the $H_4R$ played a role in the immune system. The introduction of the reference $H_4R$ antagonist JNJ-7777120 (Johnson & Johnson Pharmaceutical Research & Development LLC/Abbott Laboratories), and proof of this agent's efficacy in models of asthma, allergic rhinitis and pruritis, highlighted the $H_4R$ as a novel drug target. The first clinical candidates targeting the $H_4R$ have been identified, and new $H_4R$ antagonists are expected to enter the clinic in the near future.

## Introduction

The construction of the human genome database enabled the identification of the sequence of the histamine $H_3$ receptor ($H_3R$), and the subsequent discovery of the $H_4R$ [1-5]. The latter receptor exhibits a low levels of overall homology with other members of the histamine receptor subfamily (~ 20% homology with $H_1R$ and $H_2R$, and 31% homology with $H_3R$) [6,7]. Although many of the known imidazole ligands of the $H_3R$ bind to the $H_4R$ with comparable affinities, the $H_4R$ exhibits distinct expression and pharmacology profiles [6]. The $H_4R$ was initially described as being expressed mainly in the periphery [8]. However, recent research has demonstrated that the $H_4R$ is present in several regions of the CNS [9,10]. This receptor has also been identified in the bone marrow and on cells such as eosinophils, mast cells, basophils and dendritic cells, and on synovial cells from patients with rheumatoid arthritis [11-14]. The expression levels of the $H_4R$ appear to be modulated by proinflammatory mediators, linking this receptor with the inflammatory process [2,15]. A role of the $H_4R$ in the inflammatory process was demonstrated by the ability of this receptor to mediate the chemotaxis of immunocompetent cells such as eosinophils and mast cells [11,12]. The histamine-driven recruitment of such cells toward sites of inflammation contributes to the inflammatory process.

In the mouse, the chemotaxis of mast cells in the lung is mediated by histamine, and can be blocked by a selective $H_4R$ antagonist [16]. Histamine-induced mast cell chemotaxis also occurs in vitro, where this process can be blocked by an $H_4R$ inverse agonist [12]. Histamine-induced chemotaxis of eosinophils has also been demonstrated in vitro. Upon treatment with histamine, eosinophils undergo $H_4R$-mediated shape change and increase the expression of the adhesion molecules CD11b/CD18 and CD54, events that are required for the migration of eosinophils into tissues [11]. The expression of the human $H_4R$ ($hH_4R$) on monocyte-derived dendritic cells also stimulates the chemotactic response in vitro, and the activation of the $H_4R$ in this system inhibits the production of IL-12p70 [13]. Other evidence for the role of the $H_4R$ in the immune response is the histamine-mediated regulation of IL-16 release from CD8+ T-cells [17]. This cytokine is a chemoattractant for CD4+ cells that play an important role in the adaptive immune response.

The role of the $H_4R$ in the immune response was also demonstrated in a murine model of airway inflammation [18]. In this model, ovalbumin was administered intraperitoneally in the sensitization phase and the mice were then challenged with a 5% aerosol of ovalbumin, which resulted in an inflammatory response that resembled human asthma. $H_4R$ antagonists blocked the inflammatory response to ovalbumin when administered during either the sensitization or the challenge phase [18]. This observation demonstrated that the $H_4R$ was not only able to suppress the inflammatory response to an allergen, but that this receptor was also involved in an adaptive immune response, possibly by educating helper type 2 (Th2) T-cells.

Another *in vivo* anti-inflammatory effect of an $H_4R$ antagonist was demonstrated in a murine model of human allergic rhinitis [19]. Mice that were sensitized for ovalbumin exhibited a dose-dependent decrease of allergic rhinitis symptoms, such as sneezing and rubbing, after the administration of a selective $H_4R$ antagonist. The serum levels of IL-4 and total IgE in these mice decreased, while IFNγ levels in nasal lavage fluid increased, thereby contributing to the inhibition of the allergic response.

$H_4R$ antagonists have been used to block pain responses in rat models of carrageenan-induced acute hyperalgesia, post carrageenan thermal hypersensitivity and a spinal cord ligation model of neuropathic pain [20-23]. The site of action of the $H_4R$ blockers on the pain response has not been established; however, $H_4R$ receptors are expressed in the spinal

cord and CNS, which may explain the antinociceptive and antipruritic activities of $H_4R$ antagonists [9,10].

The role of the $H_4R$ in a murine model of pruritis was first described in 2004 [24]. Subsequently, the $H_4R$ was demonstrated to cause itch in mice, induced by either histamine or selective $H_4R$ agonists, and this effect could be blocked by the administration of an $H_4R$-selective antagonist [25]. Histamine $H_1R$ antagonists were also able to reduce histamine-induced itch. Additionally, the co-administration of $H_4R$ and $H_1R$ antagonists potently reduced the pruritic response. Similar synergistic effects following the co-administration of $H_1R/H_4R$ antagonists to mice were observed in the toluene-2,4-diisocyanate (TDI)- or 2,4-dinitrochlorobenzene (DNCB)-induced models of allergic contact dermatitis [26]. However, a selective $H_4R$ antagonist was unable to inhibit the inflammatory response in the TDI- and DNCB-induced models, suggesting that the $H_4R$ does not control inflammation in all circumstances [26].

## Chemistry Histamine $H_4$ receptor antagonists – Clinical candidates

Pfizer Inc is investigating a series of 2-amino-pyrimidines as $H_4R$ antagonists, including PF-2988403, for the potential treatment of inflammation [27]. Although the structure of PF-2988403 has not been disclosed, the related patent application claims the general structure for this compound (Figure 1) [101]. PF-2988403 displayed a $pK_i$ value at the $hH_4R$ of 8.02, and was approximately 200-fold selective for the $hH_4R$ versus the other human histamine receptors ($pK_i$ values < 5.7 for the $H_1R$, $H_2R$ and $H_3R$). PF-2988403 exhibited a range of functional effects in various species: an inverse agonist in humans, a partial agonist in monkeys and dogs, and a full agonist in rats. This variability in activity has made the preclinical profiling of PF-2988403 particularly challenging, as demonstrated by an *in vivo* study in rats, in which the compound displayed proinflammatory effects [27].

Cellzome Inc was investigating a series of benzofuropyrimidines, including CZC-13788, as $H_4R$ antagonists for the potential treatment of inflammatory conditions such as allergic rhinitis and asthma [28]. In the hit-to-lead phase, Cellzome collaborated with Argenta Discovery Ltd [28]. By September 2007, CZC-13788 was in preclinical development, and, at that time, the first clinical trials were expected to commence in mid-2008, primarily for

allergic rhinitis [28]; however no further development has been reported and this agent is presumed to be no longer in active development. The structure of CZC-13788 has not been disclosed, but was described in a patent application from Cellzome, which included the generic structure indicated in Figure 1 [102]. The compound was a potent and selective inverse $hH_4R$ agonist, demonstrated a pharmacokinetic profile that was consistent with once daily dosing and exhibited a good toxicological profile. CZC-13788 inhibited histamine-induced shape changes in human eosinophils and was active in animal models [28].

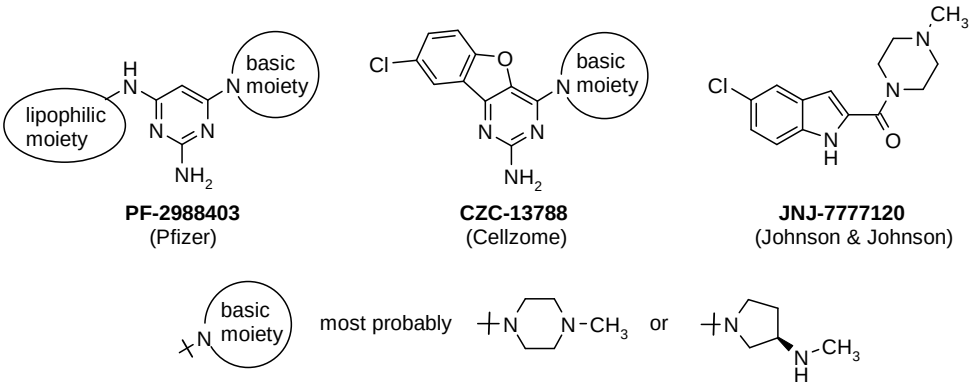



**Figure 1.** The structures of selected histamine H receptor antagonists that are clinical candidates.

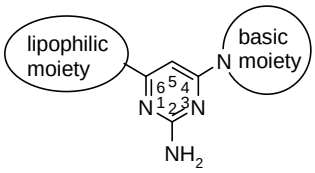
Johnson & Johnson Pharmaceutical Research & Development LLC is investigating a series of indole-carboxamides, including JNJ-7777120, which is being co-developed by Abbott Laboratories, as $H_4R$ antagonists for the potential treatment of inflammation [29]. By April 2008, JNJ-7777120 had been nominated as a clinical candidate, but no date for the initiation of clinical trials was disclosed [30]. The compound displayed a $pK_i$ value for the $hH_4R$ of 8.4, which translated into functional antagonistic activity in $hH_4R$ transfected cells with a $pA_2$ value of 8.1. The $pA_2$ value is the determination of antagonism of histamine inhibition of forskolin-stimulated cAMP-mediated reporter gene activity in SK-N-MC cells expressing the $hH_4R$. Additionally, JNJ-7777120 exhibited more than 1000-fold selectivity for the $H_4R$ versus other histamine receptors. JNJ-7777120 was minimally active against a panel of more than 50 receptor targets representing the major classes of bioaminergic receptors, neuropeptide receptors, ion channel binding sites and transporters, which is indicative of high selectivity for the $H_4R$ [29]. JNJ-7777120 exhibited poor stability in rat

liver microsomes and medium stability in human liver microsomes [31]. The administration of JNJ-7777120 (10 mg/kg po) to rats resulted in an AUC value of 7 h•µM/l and a t½ value of 2.3 h, which corresponded to a bioavailability of 22%. JNJ-7777120 inhibited both human eosinophil and murine bone-marrow mast cell chemotaxis with $IC_{50}$ values of 86 nM and 40 nM, respectively [29,31]. Treatment with JNJ-7777120 significantly reduced inflammatory indicators in a murine model of asthma [30]. JNJ-7777120 also demonstrated antipruritic efficacy in two murine models of contact dermatitis. In these models, the abdominal skin of BALB/c and NMRI mice were sensitized to the haptens TDI or DNCB. The systemic administration with JNJ-7777120 did not reduce hapten-induced inflammatory responses in the ear swelling test, but did reduce both TDI- and DNCB-induced scratching in a dose-dependent manner in both models. The co-administration of the $H_1R$ antagonist cetirizine with JNJ-7777120 produced the most pronounced inhibition of hapten-induced scratching. These results suggest that $H_4R$ antagonism does not reduce the allergic inflammatory response, but does inhibit allergen-induced itch [32].

Various chemical classes that are structurally similar to the clinical candidates discussed in the previous paragraphs in the *$H_4R$ antagonists – Clinical candidates* section have been described. A literature overview in which these structurally similar compounds have been classified based on their scaffolds is provided in the *Pyrimidines*, *Fused pyrimidines*, *Indole carboxamide analogs* and *Other compound classes* sections. A general SAR for each of these scaffolds will be discussed.

## Pyrimidines

The structures of pyrimidine-based $H_4R$ antagonists can be clustered by the nature of the lipophilic moieties at position 6 (compound **1**; Figure 2), that is, whether the structures have aryl, alkyl or amino substituents at this position.




**1**

**Figure 2.** General structure of pyrimidines.

**6-Aryl-pyrimidines**

In the patent applications from Bayer Healthcare AG that describe the pyrimidine scaffold, the activities of the compounds at the $hH_4R$ are divided into categories. The most potent category (A) was defined as those compounds with $pK_i$ values > 7.70. The most common moiety at position 4 of the pyrimidines in category A was methylpiperazine, but other basic residues were well tolerated (eg, compounds **2** to **5**; Figure 3). The importance of the orientation of the basic center was demonstrated by compounds **3** and **6** (Figure 3), which differ only in the chiral aminopyrrolidine group at the 4-position, but have significantly different activities. While the S-enantiomers of these compounds have $pK_i$ values > 7.70, the R-enantiomers have $pK_i$ values between 7.70 and 7.00, and are classed as category B. Compounds bearing a 3-aminomethyl azetidine moiety at the 4-position of the pyrimidine also tolerated a substituent at the 5-position without a significant reduction in potency (e.g., compounds **4**, **7** and **8**; Figure 3) [103,104].

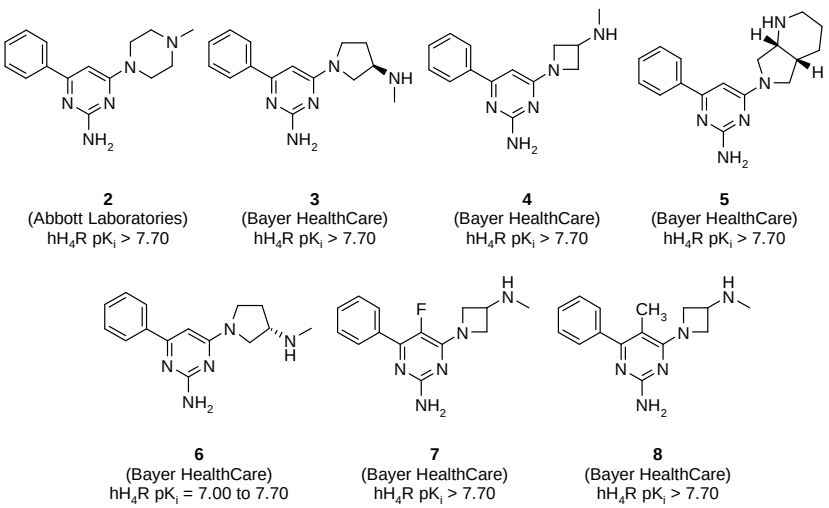



**Figure 3.** Selected 6-aryl-pyrimidines from Bayer Healthcare AG.

Researchers from Abbott reported that pyrimidines with sterically demanding groups in the 4-position, such as a piperazine moiety, exhibited a significant reduction in potency at the $hH_4R$ after the introduction of substituents at the 5-position (e.g., compounds **9** to **11**; Figure 4) [33]. Substituents at the 4- and 3-position of the 6-phenyl moiety were well tolerated, but activity at the $hH_4R$ was significantly reduced with the introduction of a 2-

position substituent (compounds **9**, **12** to **16**; Figure 4). The exception to this general trend was the 2-methoxyphenyl moiety, which had a $pK_i$ value of 8.86 (compound **16**; Figure 4) and was more active at the $hH_4R$ than the 4- and 3-substituted derivatives [33]. Changing the pyrimidine core to the three pyridine regioisomers, as indicated in compounds **17** to **19** (Figure 4), significantly reduced potency at the $hH_4R$. This series demonstrated that the N1-ring nitrogen of the aminopyrimidine scaffold is key for potent $hH_4R$ activity [33].

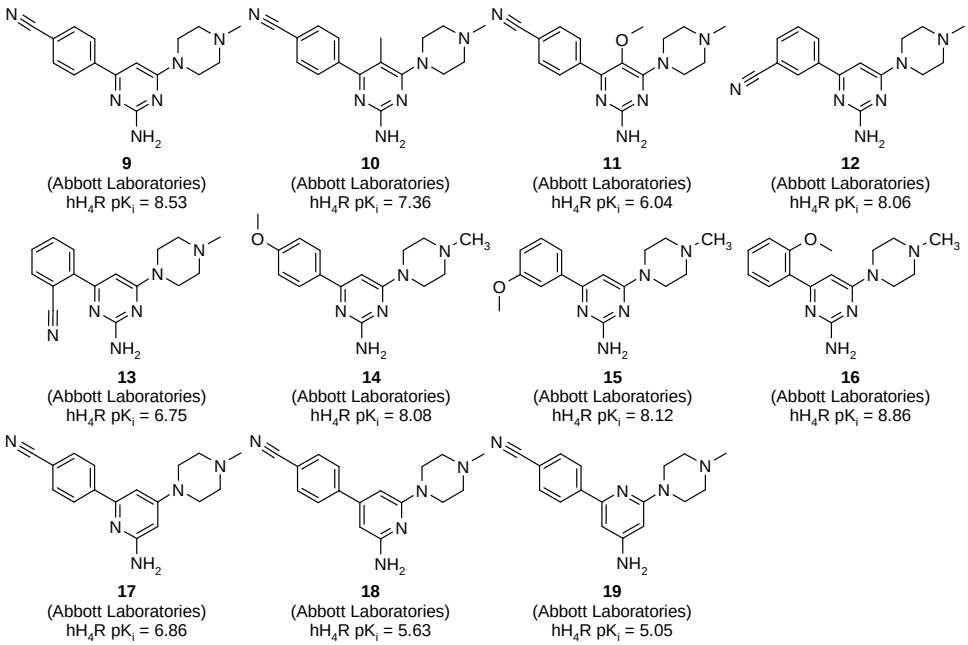



**Figure 4.** Selected 6-aryl-pyrimidines published by Abbott Laboratories.

The highlight of the optimization campaign from Abbott was compound **9** (pKi = 8.53), which acted as an antagonist on the $hH_4R$ and as a partial agonist on the rat $H_4R$ [33]. In the rat, compound **9** (1 mg/kg, iv) demonstrated a t½ value of 0.4 h and a Cmax value of 32 ng/ml at 0.4 h post-administration, which was equivalent to a bioavailability of 31%. This compound was active in a zymosan-induced peritonitis model of inflammation, as well as in a murine itch model, with potencies at the $hH_4R$ similar to those of JNJ-7777120 [33].

### 6-Alkyl-pyrimidines

In addition to the 6-aryl-pyrimidines, researchers from Abbott also investigated 6-alkyl pyrimidines, and demonstrated that an increase in lipophilicity at the 6-position improved the affinity of the compounds for the $hH_4R$ (eg, compounds **20** and **21**; Figure 5) [33].

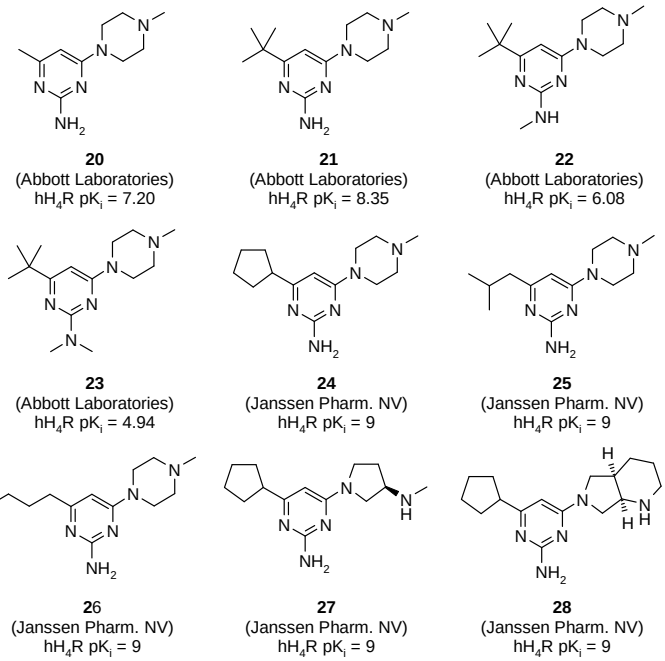



**Figure 5.** Selected 6-alkyl-pyrimidines from Abbott Laboratories and Janssen Pharmaceutica NV.

In the series of 6-alkyl pyrimidines from Abbott, the SAR for the 2-position of this scaffold was steep; the introduction of a methyl group at this position reduced the activity of the resulting compound at the $hH_4R$ by 100-fold, and a further log unit of activity was lost by the introduction of a second methyl group (eg, compounds **21** to **23**; Figure 5) [33].

Researchers from Janssen Pharmaceutica NV demonstrated that a broad range of lipophilic moieties were tolerated at the 6-position of the pyrimidine, and several resulted in compounds that were highly active against the $hH_4R$ (eg, compounds **24** to **26**; Figure 5) [105]. Similar to the compounds from Bayer [103,104], the use of a broad range of basic residues could generate potent $hH_4R$ ligands (eg, compounds **24**, **27** and **28**; Figure 5) [105].

**6-Amino-pyrimidines**

The SAR of the 4-position of the 6-amino-pyrimidine scaffold disclosed in a patent application from Pfizer (eg, compounds **29** to **31**; Figure 6) [101] was similar to that of the aryl and alkyl-pyrimidine derivatives discussed previously in the Pyrimidines section. In addition to the common N-methylpiperazine substituent, the use of several other cyclic diamines also generated highly potent $H_4R$ ligands.

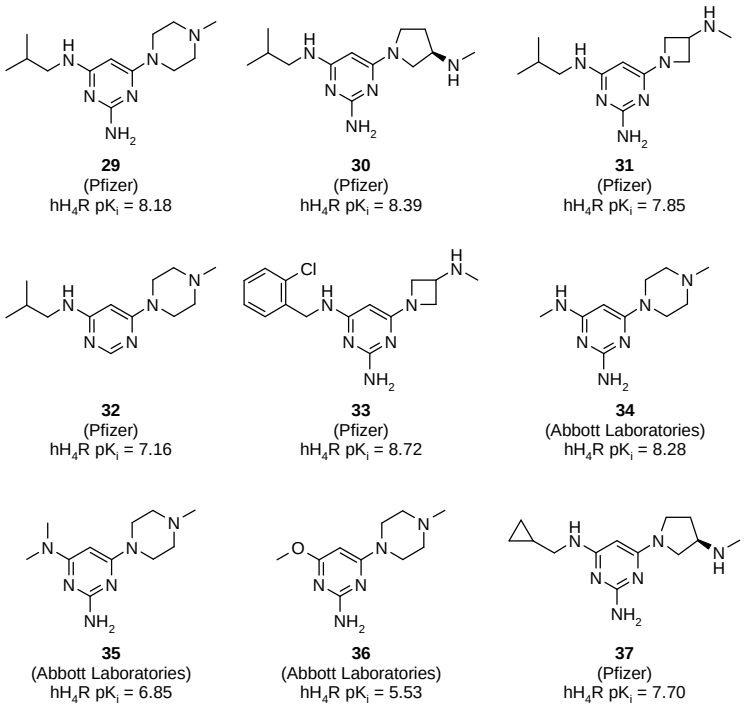



**Figure 6.** Selected 6-alkyl-pyrimidines from Pfizer Inc and from Abbott Laboratories.

The importance of the amino substituent at the 2-position, which increased activity at the $hH_4R$ by 10-fold, is illustrated by compounds **29** and **32** (Figure 6). In addition to lipophilic alkyl amines, benzylamine and aniline were also tolerated at the 6-position without a significant reduction in potency (eg, compound **33**; Figure 6). Affinity for the $hH_4R$ was reduced significantly if N,N-dialkylamino or alkyloxy substituents were introduced at the 6-position (eg, compounds **34** to **36**; Figure 6) [33].

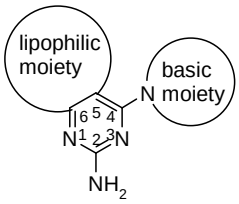
For compound **37** (Figure 6), two different synthetic routes and two different salt forms have been described, which could indicate that this compound has been advanced to

preclinical development [101]. The affinity of compound **37** for the $hH_4R$ has been determined in two different assays ($pK_i$ = 7.70 and 8.57) [101].

Two patent applications from Palau Pharma [106] and UCB Pharma SA [107] have also claimed 6-amino-pyrimidines, but no $hH_4R$ activity data have been disclosed.

**Fused pyrimidines**

Fused pyrimidines are substituted at positions 5 and 6, and the substituents form a lipophilic cycle (eg, compound **38**; Figure 7). The structures of this class can be categorized by the nature of the lipophilic cycles.




**38**

**Figure 7.** General structure of fused pyrimidines.

**Benzofuropyrimidines**

Patent applications from Argenta Discovery [108], Cellzome [102] and UCB Pharma [109] that described benzofuropyrimidines (see the general structure of compound **39** and example compounds **40** and **41**; Figure 8) did not disclose any $hH_4R$ affinity data.However, some SAR for this class of compounds can be extracted from several other disclosures.

Researchers from Janssen Pharmaceutica reported that the introduction of a chlorine atom at the 8-position of benzofuropyrimidine improved $hH_4R$ affinity by 10-fold (e.g., compounds **42** and **43**; Figure 8) [110]. Further improvements in $hH_4R$ affinity were achieved by changing the basic moiety to methylpiperazine (eg, compound **44**; Figure 8) [110]. No data on the SAR for the 6- and 7-positions have been reported. Substitutions at the 9-position were unfavorable (compound **45**; Figure 8), reducing activity at the $hH_4R$ by 500-fold [100]. Only compounds with an unsubstituted amine at the 2-position exhibited

high activity at the $hH_4R$. The mono-substitution of the amine group reduced activity at the $hH_4R$ by 10-fold (eg, compound **46**; Figure 8) [110]. A loss of activity at the $hH_4R$ of more than 1000-fold was observed when dimethylamine was introduced at the 2-position (eg, compound **47**; Figure 8) [110]. The replacement of the oxygen atom at the 6-position by a sulphur atom reduced the activity of the compounds at the $hH_4R$. The extent of the reduction was dependent on the nature of the residue at the 4-position; in the case of N-methylpiperazine, activity at the $hH_4R$ was reduced by 100-fold (eg, compound **48**; Figure 8), whereas the activity of compound **49** (aminopyrrolidine-substituted; Figure 8) was reduced by 2-fold [110].

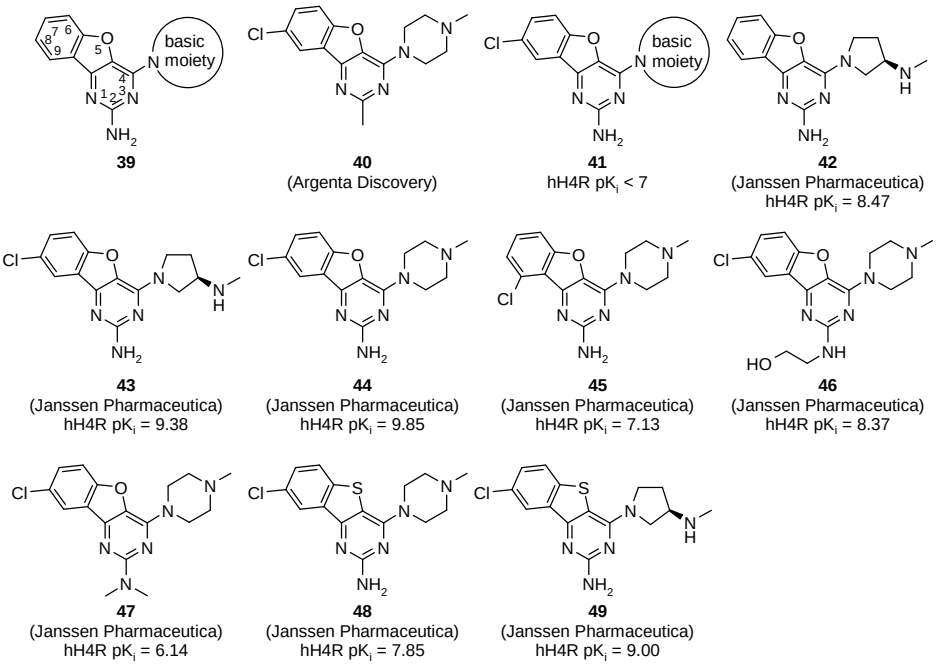



**Figure 8.** Selected benzofuropyrimidines from Argenta Discovery Ltd, Cellzome Inc, Janssen Pharmaceutica NV and UCB Pharma SA.

**Cycloalkyl-pyrimidines**

Researchers at Abbott further developed the aryl-pyrimidines described in the Pyrimidines section, and discovered that condensed cycloalkyl-pyrimidines were potent

$H_4R$ ligands [21,111]. Also, researchers at UCB Pharma SA investigated this type of pyrimidines, but no data related to these compounds have been published [112]. Compound **50** (Figure 9), which has a 5-membered ring, exhibited a $pK_i$ value of 7.89 at the $hH_4R$, while acting as a full agonist (96% receptor activation) at the rat $H_4R$ [21]. Increasing the ring size to seven (eg, compound **51**; Figure 9) improved activity at the $hH_4R$ by 6-fold, and conferred antagonist activity at the rat $H_4R$ [21]. However, compound **51** demonstrated low microsomal stability in rats, which may have been caused by the rapid demethylation of the N-methylamino-pyrrolidine moiety [21]. Compared with compound **51**, A-943931 (Abbott; Figure 9), which contains an unsubstituted aminopyrrolidine moiety, exhibited improved stability in rat and human liver microsomes, high aqueous solubility and no interaction potential with cytochrome P450 isoenzymes, and demonstrated similar activity at the $hH_4R$ [21]. A-943931 exhibited high in vitro potency in functional across species assays ($pK_b$ = 8.24 for the $hH_4R$ and mouse $H_4R$, and 8.00 for the rat $H_4R$) [21]. Additionally, this compound exhibited good selectivity for $hH_4R$ compared with other histamine receptor family members and a large panel of various receptors and kinases [21]. A-943931 demonstrated antagonist activity in an in vitro assay of bone marrow-derived mast cells natively expressing $hH_4R$ receptors, with an $IC_{50}$ value of 0.38 µM for the blockade of histamine-induced shape change [21]. The intraperitoneal administration of this compound (33 µmol/kg) also potently blocked $H_4R$-agonist-induced itch in mice [21]. A-943931 (34 µmol/kg), administered intraperitoneally, reduced inflammation in a murine model of peritonitis, and was effective in a rat model of inflammatory pain ($ED_{50}$ = 72 µmol/kg). The efficacy of this compound was also demonstrated in a neuropathic pain model in rats, with an $ED_{50}$ value of 100 µmol/kg [21].

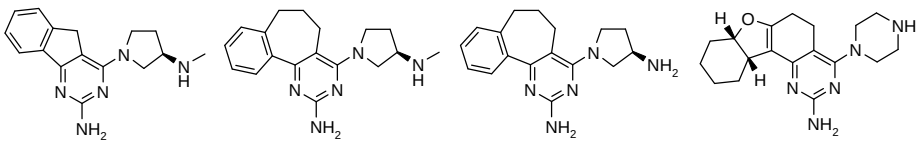
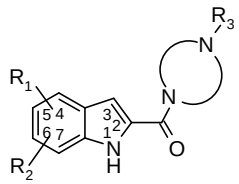



**Figure 9.** Selected condensed cycloalkyl-pyrimidines from Abbott Laboratories.

A-987306 (Abbott; Figure 9), which has a $pK_i$ value of 8.24, is representative of another series of condensed cycloalkyl-pyrimidines discovered by Abbott [22]. This compound demonstrated antagonist activity and blocked *in vivo* $H_4R$ agonist-induced scratching in mice. Interestingly, A-987306 was particularly potent in a pain assay in rats, blocking carrageenan-induced thermal hyperalgesia with an $ED_{50}$ value of 42 µmol/kg [22].

## Indole carboxamide analogs

The starting point for the optimization of the indolecarboxamide series (for the general structure of this class, see compound **52**; Figure 10) developed by Johnson & Johnson was compound **53** ($hH_4R$ pKi = 7.42; Figure 11), which was identified during a HTS of their corporate compound collection [29].




**52**

**Figure 10.** General structure of indole carboxamides.

The $hH_4R$ activity of compound **53** was improved by the methylation of the nitrogen atom on the piperazine ring (eg, compounds **53** and **54**, and compounds **55** and JNJ-7777120; Figures 1 and 11) [29]. The piperazine moiety could be displaced by several different basic residues without a significant reduction in activity at the $hH_4R$ (eg, compounds **56** to **59**; Figure 11); for example, compound **58** (containing an octahydro-pyrrolo[3,4-b]pyridine) exhibited a $hH_4R$ activity comparable with that of JNJ-7777120 [115,117]. A comparison of compounds **56** and **57** demonstrated that the orientation of the basic nitrogen was important for $hH_4R$ activity [29]. The SAR observed for this region of the molecule was similar to that previously discussed for the pyrimidines (see Pyrimidines section).

A SAR investigation of the indole ring suggested that lipophilic residues were tolerated at the 4-, 5- and 7-positions (eg compounds **60** to **63**; Figure 11) [29,31]. Significant improvements in activity with respect to the unsubstituted compound **54** were observed

with lipophilic substituents at the 5-position (eg, JNJ-7777120 and compound **61**) and with small lipophilic residues, such as methyl, or with polar residues, such as an amino group, at the 7-position) [29,31].

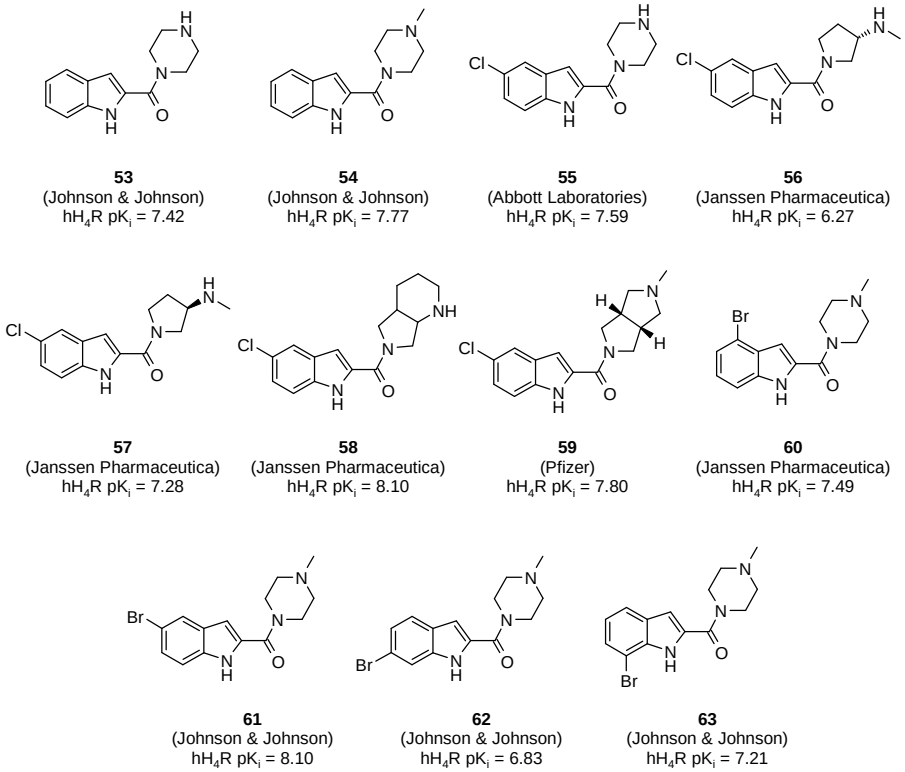



**Figure 11.** Selected indole carboxamides from Johnson & Johnson.

The simultaneous introduction of lipophilic residues, such as chlorine atoms, at the 4-and 5-positions, or at the 5- and 7-positions generated compounds with $hH_4R$ activities comparable to that of JNJ-7777120 [29,31]. JNJ-7777120 was selected as the most promising candidate from this optimization program. This drug exhibited a high turnover rate in rat and mouse liver microsomes (179 and 143 [pmol/min]/mg, respectively), but was stable in human liver microsomes (19 [pmol/min]/mg) [21]. Interestingly, the metabolite (the demethylated derivative, compound **55**) exhibited a significantly improved metabolic stability in rat and mouse (95 and 43 [pmol/min]/mg, respectively) compared with JNJ-7777120 [21]. In a pharmacokinetic study in the mouse, the methylpiperazine moiety of JNJ-7777120 was rapidly demethylated, and yielded compound **55** as an active metabolite;

the AUC value of compound **55** was 4.2-fold higher than the AUC value of JNJ-7777120 [21]. Researchers at Johnson & Johnson also investigated whether the indole moiety of the scaffold could be replaced by a thienopyrrole or a benzimidazole [31,118]. The replacement of the benzene portion of the indole with thiophene reduced $hH_4R$ activity 5-fold (eg, compounds **64** and **65**; Figure 12). The introduction of a chlorine atom in the thiophene ring increased $hH_4R$ activity in the series in which both hetero atoms are on the same site ('head-to-head'), more than in the series in which the sulfur and the nitrogen are oriented in the opposite direction ('head-to-tail'; eg, compounds **66** and **67**; Figure 12). A pronounced difference between the 'head-to-head' and the 'head-to-tail' series was observed in a functional assay to determine the $pA_2$ value, in which compound **66** exhibited a 4-fold higher activity as an antagonist than compound **67** [31].

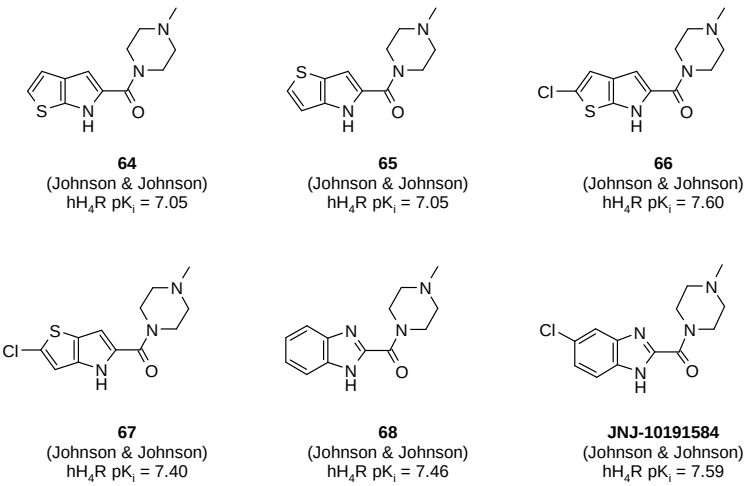



**Figure 12.** Selected indole carboxamide analogs from Johnson & Johnson.

The unsubstituted benzimidazole carboxamide, compound **68** (Figure 12), exhibited a reduced activity at the $hH_4R$ compared with the corresponding indole derivative (compound **54**; Figure 12) [31]. In contrast to the behavior of the indole series, the introduction of a chlorine atom to the benzimidazole carboxamides increased the $hH_4R$ activity, but a 3-fold increase in antagonism activity was observed in a functional assay to determine the $pA_2$ value [31,34].

The benzimidazole JNJ-10191584 (Figure 12) exhibited an increased metabolic stability compared with the indole-based JNJ-7777120 and the thienopyrrole-based compound **66**

[31]. JNJ-10191584 demonstrated 2- to 4-fold and 1.5- to 2-fold increases in $t_{½}$ values in human liver microsomes and in the rodent S9 fraction, respectively, compared with either JNJ-7777120 or compound **66** [31]. However, a similar trend was not observed *in vivo*; JNJ-7777120 or compound **66** exhibited similar bioavailability, but the AUC value of JNJ-10191584 was reduced by 3.5-fold compared with compound **66** [31]. The thienopyrrole compound **66** lacked oral bioavailability in rats [31]. The 6-fold decrease in the affinity for the $hH_4R$ of JNJ-10191584 compared with JNJ-7777120 was reflected in the eosinophil and mast cell in vitro chemotaxis assay [31].

## Other compound classes

In addition to the compound classes described in the previous sections of this review, which are similar to the clinical candidates in this field, several other compound classes have been identified as potential $H_4R$ antagonists.

### Quinoxalines

The quinoxaline scaffold as a potential source of $H_4R$ antagonists has been reported in both the patent [119] and the scientific literature [35]. The description of the SAR of this series in the patent literature is limited, with an emphasis on variations in small lipophilic substituents on the 5- to 8- positions of the quinoxaline [119]; the scaffold has been described in more detail elsewhere [35]. The quinoxalines were identified by researchers at the VU University in Amsterdam after the construction of a pharmacophore model based on the $H_4R$ antagonist JNJ-7777120 and the $H_4R$ full agonist VUF-6884, which is a close analog of the promiscuous G-protein coupled receptor ligand clozapine [36]. The initial pharmacophore model was used to design a series of fragments with micromolar affinity for the $hH_4R$, which included 2-(4-methylpiperazin-1-yl) quinoxaline. The optimization of the quinoxaline fragment led to the discovery of the benzyl-substituted quinoxaline compound **69** and the chloro-quinoxaline(1H)2-one compound **70** (both in Figure 13). The addition of a second chlorine atom to compound **70** resulted in the discovery of the potent dichloro-substituted compound **71** (Figure 13), which bound to the $hH_4R$ with a $pK_i$ value of 8.25. Several analogs from this series tolerated 2-phenoxy or 2-benzyloxy subsitutents (eg,

compounds **72** and **73**; Figure 13), although the affinity for the $hH_4R$ decreased by approximately 8-fold and these compounds were only moderately active. The alteration of the N-methylpiperazine moiety resulted in a large decrease in $hH_4R$ binding affinity, as illustrated by the homopiperazine analog **74** (Figure 13; compare this with compound **70**). The subcutaneous administration of compounds **69** (10 mg/kg) and **70** (30 mg/kg) elicited significant anti-inflammatory effects in carrageenan-induced paw edema in the rat [35].

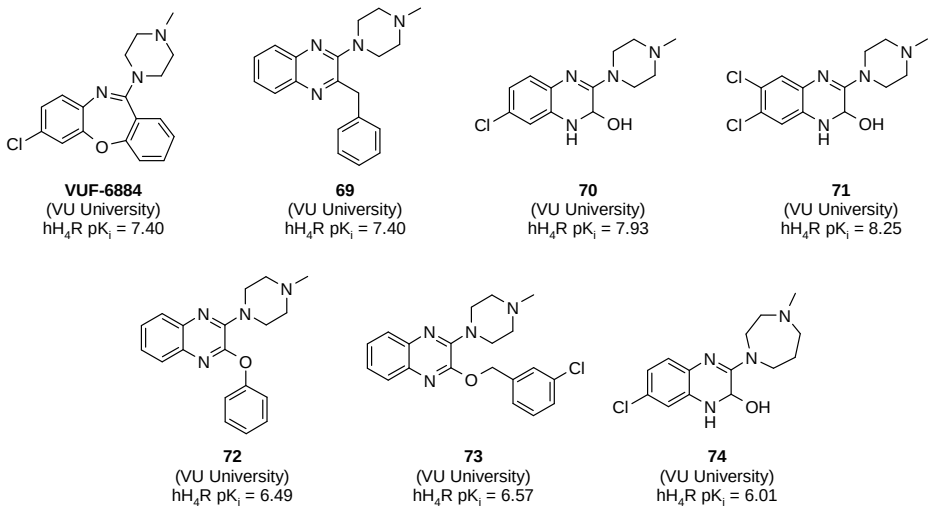



**Figure 13.** Selected histamine $H_4R$ ligands from Janssen Pharmaceutica NV and the VU University.

**Quinazolines**

In a scaffold-hopping approach, the SAR of the quinoxalines was extrapolated and a quinazoline scaffold was developed [37]. The introduction of hydrophobic groups at the 4-position of quinazoline led to the discovery of compound **75** (Figure 14), which was moderately active at the $hH_4R$. The replacement of the benzyl group by a 2-thiophenyl group to yield compound **76** (Figure 14) significantly increased the potency of this series. The SAR of the hydrophobic side chain of this series was steep. The replacement of the thiophene sulfur atom with an oxygen atom reduced the affinity for the $hH_4R$ by more than 10-fold (eg, compound **77**; Figure 14) [37]. The introduction of small substituents, such as a chlorine atom at the 6-position of the quinazoline scaffold, increased $H_4R$ affinity by

approximately 10-fold [37,38]. Further optimization at the 4-position identified aminoethylsulfonamide-containing compounds. Interestingly, the sulfonamide side chain tolerated various substituents on the sulfonamide nitrogen without significant loss of $hH_4R$ affinity, as illustrated by aniline and morpholine analogs (eg, compounds **78** to **80**; Figure 14) [38]. Similar to compounds from the quinoxaline series, the subcutaneous administration of compound **78** (30 mg/kg) demonstrated significant anti-inflammatory effects in the carrageenan-induced paw edema model of acute inflammation.

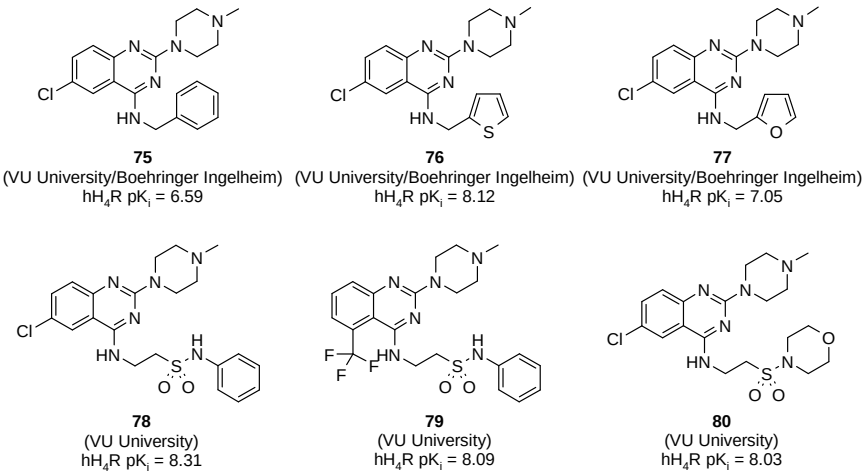



**Figure 14.** Quinazoline compounds from the VU University.

**Aryl imidazoles**

The initial lead compound of the aryl imidazole series, compound **81** (Figure 15), was identified as a HTS hit from the corporate compound collection of Johnson & Johnson and displayed moderate affinity for the $hH_4R$ ($pK_i$ = 6.91) [39]. The aryl imidazole pharmacophore is significantly different to all of the compound classes discussed in previous sections. The investigation of more rigid linker moieties between the phenyl group and the piperazine, such as cis- or trans- alkenes, alkynes or phenyl, did not improve the potency of these compounds at the $hH_4R$ (eg, compound **82**; Figure 15) [39]. The $hH_4R$ activity of the series was significantly improved by the introduction of a chlorine atom on the phenyl moiety (eg, compound **83**; Janssen; Figure 15) [121]. In addition to 5-

substitution, substituents at the 4- and 6-positions of the benzimidazole were tolerated without a significant reduction in activity (compound **84**; Johnson & Johnson; Figure 15) [39]. Improvements in affinity for the $hH_4R$ by more than 10-fold were observed by replacing the piperazine moiety with a homopiperazine moiety (eg, compound **85**; Johnson & Johnson; Figure 15) [39]. The benzimidazole moiety could also be replaced by a diphenyl-substituted imidazole residue (eg, compound **86**; Janssen; Figure 15), although the $hH_4R$ activity of this compound was reduced by 6-fold compared with the equivalent benzimidazole-containing compound [120].

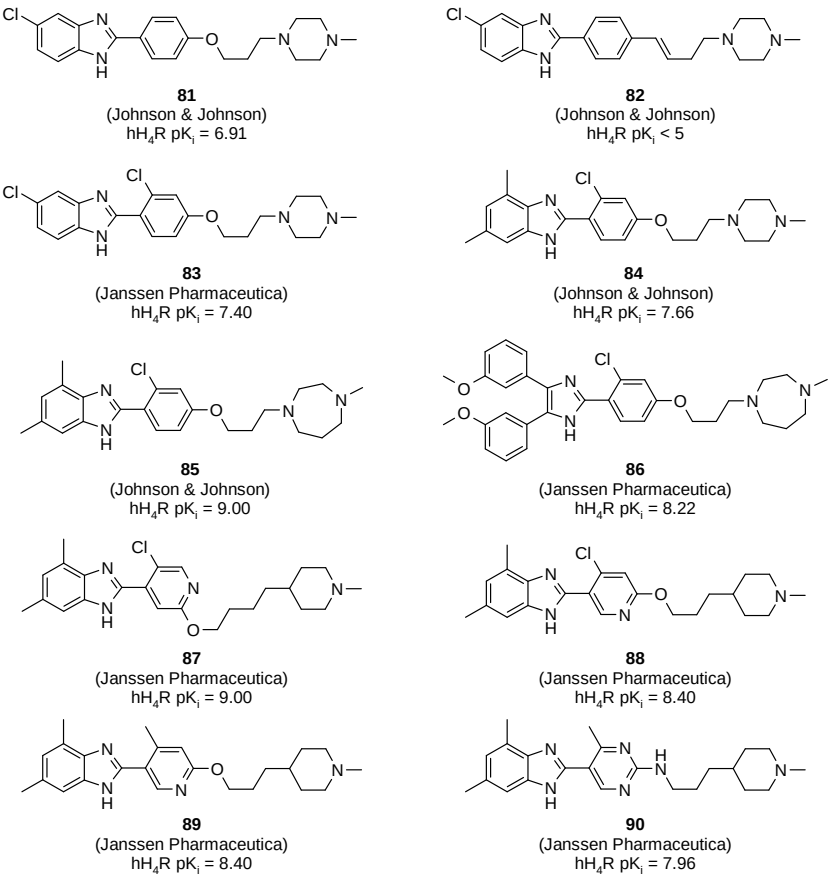



**Figure 15.** Selected arylimidazoles from Johnson & Johnson and Janssen Pharmaceutica NV.

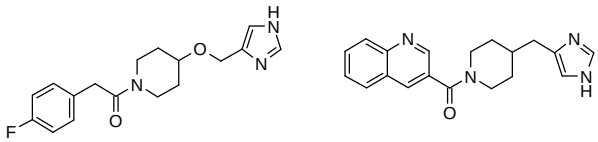
The central phenyl moiety of the compounds in this series could be replaced by a pyridine and, notably, compound **87** (containing a 3-substituted pyridine group; Figure 15) displayed

the highest $hH_4R$ affinity of all the compounds investigated in this series [121]. The 4-substituted pyridines also exhibited a high affinity for the $H_4R$ (eg, compound **88**; Figure 15) [121]. The $H_4R$ activity of compounds in this series was maintained when the chlorine atom at the pyridine moiety was replaced by methyl group (eg, compound **89**; Figure 15) [121]. In addition to pyridines, pyrimidines were also well tolerated. The ether oxygen atom could be replaced by a basic amine, as in compound **90** (Figure 15), which resulted in a potent ligand containing the $H_4R$ privileged 2-aminopyrimidine moiety [122]. No data on the *in vivo* or DMPK properties of compounds from this series were available at the time of publication.

## Piperidine carboxamides

AstraZeneca plc disclosed a series of piperidine carboxamides, which were substituted at the 4-position of the piperidine ring with a hydroxymethylimidazole (eg, compound **91**; Figure 16) [123]. Compound **91** exhibited $hH_4R$ activity at concentrations of < 10 µM.

Schering Corp claimed the use of a series of compounds that displayed activity at the $hH_3R$ and $hH_4R$ for the treatment of pulmonary inflammation. For example, compound **92** (Figure 16) exhibited comparable activity at the $hH_4R$ ($pK_i$ = 7.42) and the $hH_3R$ ($pK_i$ = 7.26) [124].



**91**
(AstraZeneca)

**92**
(Schering Corp)
$hH_4R$ $pK_i$ = 7.42

**Figure 16.** Selected piperidine carboxamides from AstraZeneca plc and Schering Corp.

## Histamine $H_4$ receptor agonists

Although little is known regarding the potential clinical use of $H_4R$ agonists, an important discovery provided a warning that not all $H_4R$ ligands may be suitable for clinical

development [27]. Researchers from Pfizer demonstrated that a high dose of an agonistic $H_4R$ ligand in the rat depleted cells from the thymus and bone marrow, and caused a shift in the number of circulating blood cells [27]. $H_4R$ ligands that did not exhibit full agonism were devoid of this effect. These results indicate that the future clinical use of $H_4R$ agonists may be limited.

## Conclusion

Several large pharmaceutical companies have initiated $H_4R$ drug discovery efforts. The search for $H_4R$ ligands has resulted in several new compounds that are being used to study the clinical potential of this newest histamine receptor subtype. Promising preclinical results are being reported, especially for the treatment of inflammation and itch. For the $H_4R$ ligands, the selectivity profiles, metabolic stability and species differences are being evaluated, and there remain an interest in novel $H_4R$ compounds. However, IP must be carefully navigated, and there is an increasingly crowded IP space for certain scaffolds (eg, pyrimidine-containing $H_4R$ ligands).

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