Structure-Activity Relationships of Histamine H_1-Receptor Agonists

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Abstract: Significant progress in the development of potent and selective histamine H_1-receptor agonists has been achieved since 1990. Optimisation of the class of 2-phenylhistamines has furnished 2-[3-(trifluoromethyl)phenyl]histamine and its N^{α}-methyl derivative. The discovery of histaprodifen (2-[2-(3,3-diphenylpropyl)-1*H*-imidazol-4-yl]ethanamine) and the novel lead compound suprahistaprodifen (N^{α}-2-[(1*H*-imidazol-4-yl)ethyl]histaprodifen) represents additional milestones in the H_1-receptor agonist field.

Keywords: Histaprodifen, suprahistaprodifen, H_1-receptor agonist, partial agonist, guinea-pig ileum, guinea-pig aorta, guinea-pig trachea, rat aorta.

INTRODUCTION

Histamine exerts its pharmacological effects via activation of four histamine receptors, H_1–H_4 [1, 2]. Stimulation of smooth muscles and vasodilation by histamine were described for the first time in 1910 by Dale and Laidlaw [3]. Later, the receptor that mediates these effects was named histamine H_1 receptor. Histamine H_1 receptors are coupled via $G_{q/11}$ proteins to phosphoinositide hydrolysis, which results in the formation of inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). The production of these second messengers results in an increase of the intracellular Ca^{2+} concentration, which explains a variety of cellular responses such as NO production, cGMP and cAMP accumulation and phospholipase A_2 as well as phospholipase D activation [4].

The first highly effective histamine H_1-receptor antagonists have been introduced in the forties of the last century by Bovet's group [5]. Nowadays H_1-receptor antagonists play a prominent role in the symptomatic treatment of allergy, motion sickness and vertigo, and they are used as mild sedatives [6]. Therapeutic applications of H_1-receptor agonists, however, have not yet been established. Different reasons may be responsible for the deficit in H_1-receptor agonists for clinical uses: (i) H_1 receptors are mainly involved in pathological processes (vide infra); (ii) our knowledge of H_1-receptor-mediated physiological and pathophysiological functions, especially in the central nervous system (CNS), is still limited; and (iii) until recently highly potent and selective H_1-receptor agonists were not available. At present the practical applications of histamine as an H_1-receptor agonist are limited to its use as a diagnostic agent. Histamine is used to determine airway hyper-responsiveness in asthmatic subjects [7] and to elicit the wheal and flare response in the skin [8].

There is a substantial evidence that histamine is involved in various physiological and pharmacological processes and functions as a neurotransmitter in the CNS [1, 9]. The histamine H_1 receptor plays an important role in allergic conditions like rhinitis, asthma, anaphylaxis and urticaria [1]. In the CNS histamine H_1 receptors are particularly enriched in neocortex, hippocampus, nucleus accumbens, thalamus and posterior hypothalamus [1]. Histamine, acting through H_1 receptors, has been shown to operate as an endogenous anticonvulsant [10–13] and antidepressant [14]. In addition, histamine seems to modulate pain [15, 16] and to regulate food and water intake [17–19] and cognitive processes *via* activation of H_1 receptors [20, 21]. Furthermore, H_1 receptors seem to be involved in the central thermoregulation [22], the circadian rhythm of sleep and wakefulness [23, 24], and the regulation of the cardiovascular [25] and neuroendocrine system [26]. Histamine also induces migraine via activation of H_1 receptors [27]. Recently it has been reported that histamine produces dilation of meningeal blood vessels that could be blocked by H_1- and H_2-receptor antagonists. It could be demonstrated that H_1 receptors may also be present on trigeminal neurones while H_2 receptors are not [28].

Based on structure-activity relationship (SAR) studies, this review would like to show the attempts that were made to obtain potent and selective H_1-receptor agonists. Such compounds may help to increase our knowledge of the diverse physiological and pathophysiological functions of histamine and of the histamine H_1 receptor. In addition, such compounds may help to understand the molecular mechanism of H_1-receptor activation. Recently, a few reviews have been published which have treated SAR of H_1-receptor agonists [1, 4, 29, 30].

SIMPLE HISTAMINE DERIVATIVES AS H_1-RECEPTOR AGONISTS

In the histamine molecule (**1**, Fig. **1**) two structural portions can be distinguished: the imidazole ring and the ethanamine side chain. Modification of the ethanamine side chain, which comprised methylation at the α- or β-position, alkylation of the amino group, and elongation or shortening of the side chain, did not provide compounds with enhanced selectivity for H_1 vs. H_2 and H_3 receptors, respectively [4]. Modification of the imidazole moiety of histamine was first achieved by the replacement of the imidazole ring by another

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five- or six-membered nitrogen containing heterocyclic ring (e.g., 2-thiazolyl, 2-pyridyl, 3-isoxazolyl). This approach yielded the first selective H_1-receptor agonists and indicated that the presence of the tautomeric N^{π}-N^{τ} system of the imidazole ring is not obligatory [4, 29, 30]. Despite its moderate potency, the most prominent representative of this class of compounds, 2-(thiazol-2-yl)ethanamine (2-TEA, **2**, (Fig. **1**), is still used as a selective H_1-receptor agonist in numerous pharmacological studies.

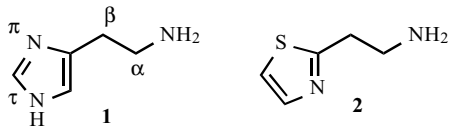


Fig. (1). Chemical structure of histamine (**1**) and 2-(thiazol-2-yl)ethanamine (2-TEA, **2**).

A promising approach to enhance H_1-receptor selectivity was the introduction of an alkyl or an aryl (phenyl, aromatic heterocyclic) substituent at the 2-position of the imidazole ring [4, 29, 30]. It could be shown that histamine derivatives with lower alkyl substituents (methyl, ethyl) at C-2 displayed diminished agonist potency but enhanced selectivity for H_1 vs. H_2 and H_3 receptors, respectively [4, 30]. Based on an early observation that 2-phenylhistamine behaved as a full H_1-receptor agonist in guinea-pig ileum with approximately 3–10-fold lower potency than histamine [31], numerous derivatives were synthesised [29], which showed increased potency if various substituents were introduced at the *meta* position of the phenyl ring. 2-[3-(Trifluoromethyl)phenyl]histamine (**3**) and 2-(3-bromophenyl)histamine (**4**) justify special mention since these compounds were the first full agonists in guinea-pig ileum showing a potency that equals that of histamine [32] (Fig. **2**). In addition, when studied under the same experimental conditions as **3** and **4**, the *meta*-substituted fluoro, chloro, and iodo analogue of **4** displayed similar relative potencies (85%, 96%, 96% vs. 112% (**4**) and 128% (**3**) [32]).

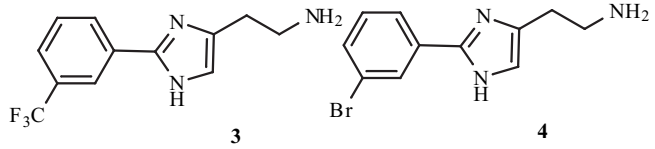


Fig. (2). Chemical structure of 2-[3-(trifluoromethyl) phenyl]histamine (**3**) and 2-(3-bromophenyl)histamine (**4**).

The activity of **3** as a histamine H_1-receptor agonist was slightly enhanced by *mono*-methylation of N^{α} but this derivative behaved as a high-efficacy partial agonist in guinea-pig ileum (intrinsic activity (i.a.) 0.97) [33]. In accordance with this observation in the guinea-pig ileum assay, *meta*-substituted 2-phenylhistamine derivatives were partial agonists in guinea-pig aorta and in DDT_1MF-2 smooth muscle cells [32–34]. The micromolar affinity observed for **3**, **4** and related compounds was confirmed by inhibition of the [^{3}H]mepyramine binding to H_1 receptors from guinea-pig cerebellar membranes where **3** and **4** were approximately 40-fold more potent than histamine [32]. Variations in receptor reserve and/or in the efficiency of receptor-effector coupling may be responsible for the differences in potency and efficacy in various functional H_1-receptor assays [35]. In addition, it has been proposed that histamine and 2-phenylhistamine derivatives interact in different ways with the guinea-pig H_1-receptor protein. In contrast to histamine, the N^{τ} atom of 2-phenylhistamine seems not to be essential for H_1-receptor binding [36]. Nevertheless, **3** and **4** were the first relatively potent H_1-receptor agonists, which were selective due to their low affinities for H_2, H_3, M_3, α_{1D}, β_1, and 5-HT_{2A} receptors, respectively [32]. If the imidazole ring of *meta*-substituted 2-phenylhistamine derivatives was exchanged by a thiazole ring, 2-substituted 2-(thiazol-4-yl)-ethanamines were obtained, which behaved as weak partial H_1-receptor agonists in guinea-pig ileum. Agonist potencies were 23–240-fold lower than that of histamine. Based on this observation it was suggested that the sulphur atom does not interact with a site of the H_1 receptor [37].

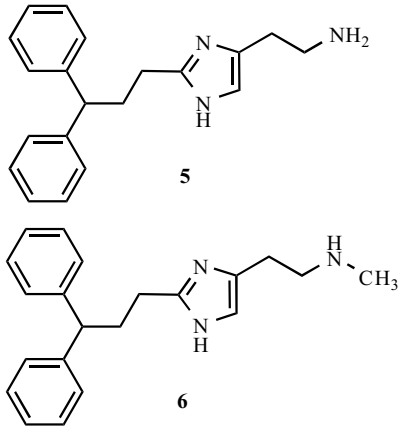


Fig. (3). Chemical structure of histaprodifen (**5**) and methylhistaprodifen (**6**).

HISTAPRODIFEN AND METHYLHISTAPRODIFEN ARE POTENT AND SELECTIVE H_1-RECEPTOR AGONISTS

It has recently been reported that a number of 2-substituted histamine derivatives, including 2-(3-bromophenyl)histamine, stimulate G-proteins in a receptor-independent manner [38–40]. The identification of histaprodifen (2-[2-(3,3-diphenylpropyl)-1*H*-imidazol-4-yl]ethanamine) (**5**, Fig. **3**) as a potent H_1-receptor agonist from a series of potential G-protein-stimulatory compounds, however, represents a substantial progress in histamine chemistry [41]. The design of histaprodifen had its origin in the idea to attach a diphenylalkyl substituent (*viz*. diphenylmethyl up to diphenylpentyl) to the 2-position of the imidazole ring of histamine. A diphenylmethyl substituent, for example, is a common feature of therapeutically used high-affinity H_1-receptor antagonists such as diphenhydramine, oxatomide, cetirizine, and fexofenadine. Consequently, it has been speculated that high affinity might be provided by the two phenyl rings and efficacy by the histamine fragment. While the attachment of a diphenylmethyl and a diphenylethyl substituent to the 2-position of the imidazole ring of histamine resulted in weak partial agonists of low efficacy, the attachment of a diphenylbutyl and a diphenylpentyl substituent afforded low affinity antagonists at guinea-pig and rat H_1 receptors. In contrast, the linkage with the diphenylpropyl substituent

Table 1. Pharmacological Parameters of Histaprodifen (5) and Methylhistaprodifen (6) Obtained from Functional Studies[a]

Receptor	Tissue	Effect	5		6	
			pEC_{50}	pA_2	pEC_{50}	pA_2
H_1	gp ileum	contraction	6.7 (1.0)	6.0[b]	7.2 (0.99)	6.5[b]
H_1	gp aorta[c]	contraction	6.5 (0.84)	–	7.1 (0.89)	–
H_1	rat aorta	relaxation	6.1 (0.50)	–	6.8 (0.61)	–
H_2	gp right atrium	heart rate↑	n.a.	4.5	n.a.	4.9
H_3	gp ileum[d]	relaxation	n.a.	<5.8	n.a.	<5.8
M_3	gp ileum	contraction	n.a.	5.6	n.a.	5.5
α_{1D}	rat aorta	contraction	n.a.	5.5	n.a.	5.2
β_1	gp right atrium	heart rate↑	n.a.	4.3	n.a.	4.8
5-HT_{1B}	gp iliac artery	contraction	n.a.	4.9	n.a.	5.1
5-HT_{2A}	rat tail artery	contraction	n.a.	5.2	n.a.	5.4
5-HT_3	gp ileum[d]	contraction	n.a.	<5.7	n.a.	<5.8
5-HT_4	rat esophagus	relaxation	n.a.	<5.5	n.a.	<5.8

[a]Data from [41], [b]pK_P, [c]moderately precontracted with $PGF_{2\alpha}$, [d]myenteric plexus preparation, n.a. not active, gp guinea-pig, i.a. is given in parentheses.

yielded a potent H_1-receptor agonist, histaprodifen [41]. Histaprodifen (**5**) was equipotent with histamine in guinea-pig ileum and behaved as a full agonist in this tissue [41]. Equipotency with histamine and partial agonism (i.a. 0.84) was observed for **5** in endothelium-denuded rings of guinea-pig aorta moderately precontracted with $PGF_{2\alpha}$. In addition, **5** induced an endothelium-dependent relaxation of precontracted rings of rat aorta. In this assay **5** also behaved as a partial agonist (i.a. 0.50) with potency being 5-fold higher than that of histamine [41]. The fact that **5** can display a range of intrinsic activities depends on the species, the extent of receptor reserve and variations in the efficiency of receptor-effector coupling in the different H_1-receptor bioassays used [35] (vide supra).

A further enhancement of the potency could be achieved by N^{α}-methylation of histaprodifen. Methylhistaprodifen (N^{α}-methyl-2-[2-(3,3-diphenylpropyl)-1*H*-imidazol-4-yl]ethanamine) (**6**, Fig. **3**) was 2–5 times more potent than histaprodifen in different functional guinea-pig and rat assays [41]. In addition, functional selectivity experiments have shown that **5** and **6** did not stimulate H_2, H_3 and several other neurotransmitter receptors (M_3, α_{1D}, β_1, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, and 5-HT_4). Both compounds displayed only low to moderate affinity for these sites ($pA_2 < 6$) [41]. The *in vitro* effects of **5** and **6** are summarised in Table **1**. The high potency of **5** and **6** was also confirmed *in vivo*. Both compounds were potent H_1-receptor agonists in the pithed and in the anaesthetised rat where they elicited a significant vasodepressor effect [42].

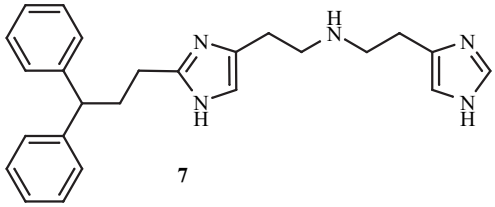
Based on molecular dynamics simulations, binding models for histamine (**1**), histaprodifen (**5**) and methylhistaprodifen (**6**) have been proposed. There are essential differences in the putative binding mode of the three agonists. Both phenyl rings of **5** and **6** fill out the space of the receptor pocket and affect the location of the protonated N^{α}-atom that is positioned more between TM 3 and TM 6 of the human H_1 receptor in contrast to **1** of which the protonated N^{α}-atom is closely located to TM 3. This orientation may explain both the increased potency and the decreased efficacy of histaprodifen and methylhistaprodifen compared to histamine [41].

HISTAPRODIFEN AS A LEAD FOR THE DEVELOPMENT OF NEW HISTAMINE H_1-RECEPTOR AGONISTS

Following the discovery of histaprodifen efforts were made to synthesise new derivatives of which high activity in different H_1-receptor assays could be expected. Unlike the observation in the 2-phenylhistamine series, the introduction of a substituent at the *meta* position of one phenyl ring of **5** did not improve activity (vide supra) [43]. An analogous modification of **6** with a *meta*-fluoro substituent led to the most potent compound in the original histaprodifen series (relative potency 522%, i.a. 1.00) [44]. With regard to the substitution pattern of the phenyl rings, several lines of evidence indicate that the structure-activity relationships in the histaprodifen series differ considerably from those in the 2-phenylhistamine series [43]. Furthermore, several attempts to increase potency by replacing one phenyl ring of **5** by a heterocyclic ring (e.g., pyridyl, thienyl), a benzyl or a cyclohexyl substituent failed. The racemate of the 3-pyridyl analogue of **5** was resolved by HPLC, and the enantiomers revealed virtually no discrimination vis-à-vis the guinea-pig ileal H_1 receptor (relative potency 7.6% vs. 5.2%, absolute configuration not determined) [45].

Based on an earlier finding that the introduction of a second imidazolylethyl substituent at the N^{α}-position of histamine resulted in an H_1-receptor agonist that was equipotent with histamine in guinea-pig ileum [46], the

structure of histaprodifen was modified using the same approach. Within a series of N^{α}-substituted histaprodifens, suprahistaprodifen (N^{α}-2-[(1*H*-imidazol-4-yl)ethyl]histaprodifen, **7**, (Fig. **4**) emerged as the most potent histamine H_1-receptor agonist described so far [47–49].



7

Fig. (4). Chemical structure of suprahistaprodifen (**7**).

The combination of the structures of histaprodifen and histamine in a single molecule was achieved by overlapping of both agonists and represents a strategy that resembles the so-called bivalent ligand approach. This approach predicts strong enhancement in potency and selectivity for a "dimer" of an agonist or antagonist compared to its monomeric counterpart [50–52]. Suprahistaprodifen displayed an i.a. of 0.81–0.96 and a relative potency of 3,600–5,600% compared to histamine in guinea-pig ileum [47–49]. In guinea-pig trachea **7** was even more potent (63,100%, i.a. 0.86) [48]. The high agonist potency of **7** found in these bioassays correlates well with the ability of **7** to activate GTPase and GTPγS binding in bovine aortic membranes. However, in this bioassay the order of agonist potency was **7** > **1** > **5** > **6** [53]. In endothelium-denuded rings of guinea-pig aorta moderately precontracted with $PGF_{2\alpha}$ compound **7** showed slightly lower agonist activity than in guinea-pig ileum (1,660%, i.a. 0.93). Recently, it has been shown that the agonist potency of **7** was 5-fold higher at recombinant guinea-pig H_1-receptors than at recombinant human H_1-receptors expressed in Sf9 insect cells [54]. In addition, in contrast to all other H_1-receptor agonists studied so far, **7** was considerably less potent at recombinant guinea-pig H_1-receptors expressed in insect cells than at native H_1-receptors in the guinea-pig ileum. An explanation for these striking differences could be that **7** stabilises a unique conformation of the guinea-pig H_1-receptor that is highly efficient in coupling to cognate mammalian G_q-proteins but less efficient in coupling to non-cognate insect cell G_q-like G-proteins [54].

In precontracted rings of rat aorta **7** induced an endothelium-dependent relaxation (rel. pot. 1,514%, i.a. 0.56). The effects of **7** in different H_1-receptor assays are summarised in Table **2**. Selectivity studies have shown that **7** lacked agonism at H_3, M_3, α_{1D}, β_1, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors and displayed low affinity for these sites [47]. Compound **7** contains a histamine fragment within its molecular structure. As expected, **7** displayed moderate agonist activity at H_2 receptors [47, 54].

Since the dimerisation of histamine has proved to be a successful approach to increase agonist potency (vide supra) [46], dimers of histaprodifen have been synthesised of which dimer **8** (Fig. **5**) is the most potent H_1-receptor agonist reported so far in the rat aorta *in vitro* assay (rel. pot. 11,500%) [55]. Further compounds with high agonist activity are those derivatives of suprahistaprodifen in which the ethyl chain of the lead was elongated up to five CH_2 units and the hydrophilic basic imidazole ring was replaced by a lipophilic weakly basic pyridine ring. The exchange of the terminal imidazole ring for a pyridine ring resulted in compounds with high activity. An increase in agonist potency and efficacy was observed when the attachment of the alkyl spacer consecutively changed from the *para* to the *meta* and the *ortho* position of the pyridine ring. From the structure-activity-relationship study it could be concluded that those derivatives containing a butyl chain possessed the highest potency and affinity. N^{α}-4-(2-pyridylbutyl)histaprodifen (**9**, Fig. **5**) emerged as a high-efficacy partial agonist being almost equipotent with suprahistaprodifen (**7**) in different functional guinea-pig and rat bioassays (Table **2**) and displayed low to moderate antagonist affinity for histamine H_2 and H_3 receptors, respectively [47].

If the imidazolylethyl portion of suprahistaprodifen was replaced by various phenylalkyl- and thienylalkyl substituents, compounds with a butyl chain were the most potent H_1-receptor agonists again. Phenylbutylhistaprodifen, 2-thienylbutylhistaprodifen, and 3-thienylbutylhistaprodifen displayed 10-fold higher agonist potency than histamine in guinea-pig ileum but in contrast to **7** and **9**, their efficacy was diminished (i.a. 0.43–0.52) [56].

Table 2. Selectivity Profile of Suprahistaprodifen (7) and N^{α}-[4-(2-Pyridyl)butyl]histaprodifen (9) Obtained from Functional Studies[a]

Receptor	Tissue	Effect	7		9	
			pEC_{50}	pA_2	pEC_{50}	pA_2
H_1	gp ileum	contraction	8.3 (0.96)	7.7[b]	8.2 (0.89)	7.5[b]
H_1	gp aorta[c]	contraction	8.0 (0.93)	–	7.9 (0.89)	–
H_1	gp trachea	contraction	8.1 (0.86)	–	n.d.	n.d.
H_1	rat aorta	relaxation	6.5 (0.56)	–	6.7 (0.65)	–
H_2	gp right atrium	heart rate↑	5.0 (0.41)	–	n.a.	4.8
H_3	gp ileum[d]	relaxation	n.a.	<6.0	n.a.	6.1

[a]Data from [47, 48], [b]pK_P, [c]moderately precontracted with $PGF_{2\alpha}$, [d]myenteric plexus preparation, n.d. not determined, n.a. not active, gp guinea-pig, i.a. is given in parentheses.

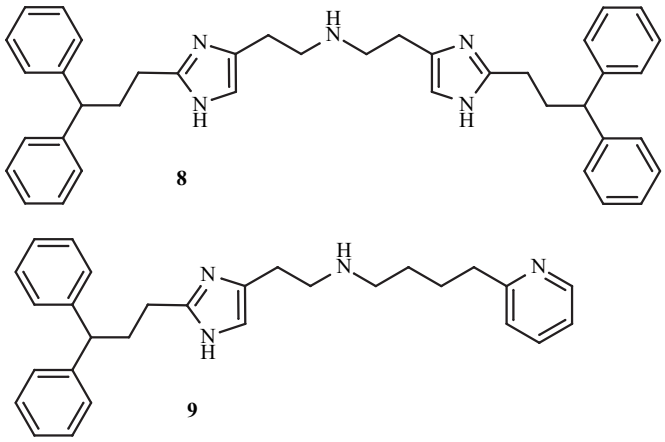


Fig. (5). Chemical structure of the histaprodifen "dimer" **8** and its 2-pyridylbutyl analog **9.**

COMPOUNDS WITHOUT AN IMIDAZOLE RING THAT SHOW H_1-RECEPTOR AGONIST POTENCY

Most surprisingly, the semi-synthetic ergot derivative lisuride (**10**, Fig. **6**), which is therapeutically used as a dopamine agonist in the treatment of Parkinson's disease and hyperprolactinaemia, has recently been found to possess high affinity for histamine H_1 receptors (pK_i 7.5) [57]. Further studies using R-SAT and NF-κB reporter-gene and inositol phosphate accumulation assays have shown that **10** is the most potent partial agonist for the human H_1 receptor reported to date [58]. At native H_1 receptors (guinea-pig ileum) lisuride behaved as a potent partial agonist of low efficacy (potency relative to histamine 1,160%, i.a. 0.27; potency relative to suprahistaprodifen 32%). Contractile responses to lisuride were susceptible to blockade by mepyramine (10 nM; unpublished results from the laboratory of H.H.P). It should be emphasised that lisuride is a "dirty" drug, since it shows high affinity for a variety of monoamine receptors that include not only dopamine and histamine but also serotonin and adrenergic receptors [59–68].

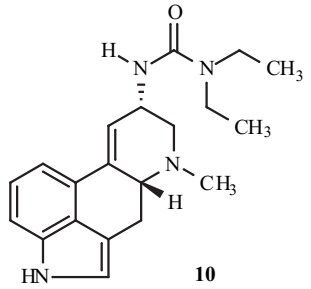


Fig. (6). Chemical structure of lisuride (**10**).

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