Homologs of Histamine as Histamine H_3 Receptor Antagonists: A New Potent and Selective H_3 Antagonist, 4(5)-(5-Aminopentyl)-1*H*-imidazole

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The influence of alkyl chain length variation on the histamine H_3 receptor activity of histamine homologs **1** was investigated. A series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** was prepared with an alkyl chain length varying from one methylene group to 10 methylene groups. Besides the H_3 activity, the affinities of these compounds for the H_1 and H_2 receptors were determined. The ethylene chain of histamine is optimal for agonistic activity on all three histamine receptor subtypes. For the H_3 receptor, elongation of the alkyl chain from three methylene groups on leads to compounds with antagonistic properties. 4(5)-(5-Aminopentyl)-1*H*-imidazole (impentamine, **1e**) is the most potent and selective H_3 antagonist from this series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1**, with a pA_2 value of 8.4 (on guinea pig jejunum). A specific antagonistic binding site for this compound is proposed.

Introduction

The histamine H_3 receptor has been described to play a role as a general regulatory receptor system, regulating not only the release and synthesis of histamine but also the release of other neurotransmitters.[1] Therefore, this receptor can be regarded as a potential target for new therapeutics.[2-4] To characterize its role in physiology however, there is still a need for selective, preferably nontoxic ligands. The most potent H_3 ligands described so far are the H_3 agonist imetit (**3a**) and the H_3 antagonist clobenpropit (**3c**), both containing an isothiourea group. We directed part of our research to the development of non-isothiourea-containing selective histamine H_3 receptor ligands using the natural agonist histamine (**1b**) as a 'lead'.

A reasonable number of analogs of histamine and their effect on the histamine H_3 receptor have been described in literature. Most successful alterations of the structure of histamine have been performed by functionalization of the ethylene chain, resulting in, for instance, the potent and selective H_3 agonist (*R*)-α-methylhistamine (**2a**).[5] Alkylations of the amino group of histamine are tolerated when small alkyl groups are used. N^{α}-Methylhistamine (**2b**) and N^{α},N^{α}-dimethylhistamine (**2c**) are slightly more active than histamine (**1b**).[6] Replacement of the amino group with other polar cationic groups resulted in the potent and selective H_3 agonist imetit (**3a**).[7-10] Replacement of the imidazole ring of histamine and its analogs by other heterocycles or structural imidazole mimics resulted in less active (e.g., betahistine acts as a weak H_3 antagonist), but more frequently in inactive, compounds.[3,4] Substituents on the imidazole ring of histamine (**1b**) are also not allowed (e.g., *N*-methyl-, 2-methyl-, and 4(5)-methylhistamine are inactive).[6]

Recently, we reported a new potent and selective agonist for the H_3 receptor, which is not an ethylene chain analog of histamine (**1b**).[11] This compound, immepip (**4**), has an aminobutylene chain incorporated in a piperidine ring; yet in activity ($pD_2 = 8.0$ on guinea pig jejunum), it is comparable to (*R*)-α-methylhistamine

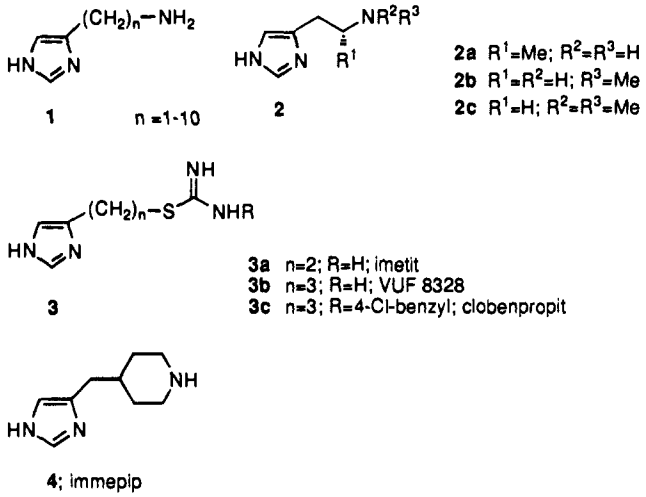

Figure 1. Discussed structures.

(**2a**) (pD_2 value of 7.8 on the same test system).[12] If we compare the structures of histamine (**1b**) and immepip (**4**), it is clear that the amino groups in both structures are separated by alkyl spacers different in length. The amino group of histamine (**1b**) is located at a distance of two methylene groups (≈4.5 Å) from the imidazole ring, compared to a distance of four methylene groups (≈7.5 Å) in immepip (**4**). Since immepip (**4**) is more potent than histamine (**1b**) on this receptor, we wanted to investigate the H_3 effect of chain length variation of the alkyl spacer in a series of histamine homologs. In literature, not much is known about the histamine H_3 activity of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1**. It has been reported that a histamine homolog with a chain length of only one methylene group (**1a**) is inactive on the H_3 receptor (guinea pig ileum).[3] Elongation of the alkyl chain to three methylene groups (**1c**) also has been described by Lipp[4] to result in a compound with no H_3 agonistic properties (rat cortex) and by Leurs[3] to result in a compound with weak H_3 antagonistic properties (pA_2 value of 6.0 on rat cortex).

In order to investigate the effect of the chain length of the alkyl spacer of histamine homologs **1** on the histamine H_3 receptor activity, we have prepared a

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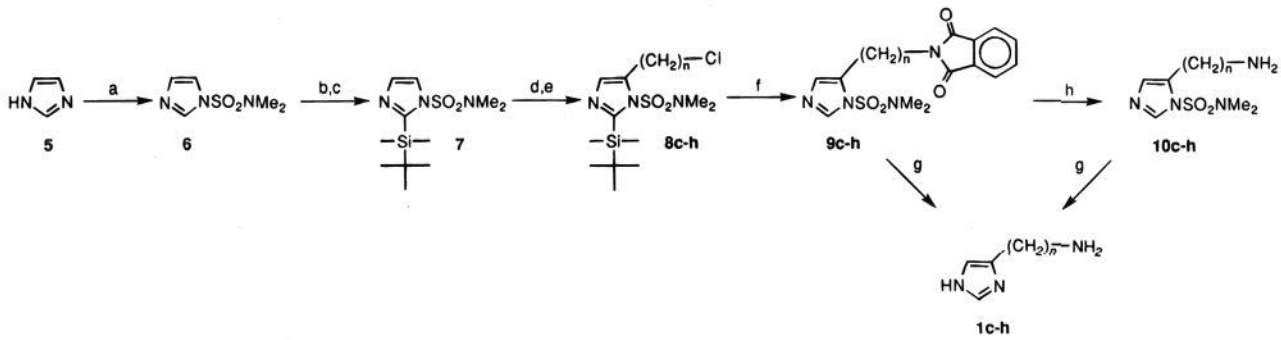
Scheme 1



[a] Reagents: (a) *N,N*-dimethylsulfamoyl chloride, Et_3N, toluene; (b) *n*-BuLi, THF, −70 °C; (c) *tert*-butyldimethylsilyl chloride; (d) *n*-BuLi, THF, −70 °C; (e) 1-chloro-ω-iodoalkane; (f) potassium phthalimide, DMF, 70 °C; (g) 30% HBr, reflux; (h) $H_2NNH_2 \cdot H_2O$, EtOH.

series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** with an alkyl chain length varying from one methylene group to 10 methylene groups. We determined the H_3 activity of these compounds functionally on an *in vitro* test system using guinea pig jejunum preparations. In order to establish the selectivity of these compounds for the H_3 receptor, we determined the affinities of the 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** on the H_1 and the H_2 receptor as well.

Chemistry

The 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1c–h** were prepared by a method described earlier by our group (Scheme 1).[13] This method is based on the direct coupling of an alkyl chain to the imidazole ring, by lithiation of a suitable 1,2-diprotected imidazole **7** and subsequent treatment with 1-chloro-ω-iodoalkanes. The ω-chloro group of the resulting products **8c–h** can be converted into an amino group via the Gabriel synthesis.[14] The protecting group on the 2-position of the imidazole ring (the *tert*-butyldimethylsilyl group) hydrolyzes under the basic conditions of the Gabriel synthesis. The free amino group can be obtained, either by hydrolysis of the phthalimide group under acidic conditions resulting directly in compounds **1c–h** or by reaction with hydrazine resulting in compounds **10c–h**. The advantage of hydrolysis of the phthalimide group under acidic conditions is that the N-protecting group on the imidazole ring can be removed in the same step. If however the protecting group is required in further reactions (like addition reactions on the amino group), hydrazine should be used because the protecting group is unaffected under these conditions.

After conversion of the chloro group into an amino group and removal of the protecting groups, the desired histamine analogs **1c–h** were obtained. Using this method we have prepared histamine analogs with an alkyl chain of up to 10 methylene groups. Some of the compounds were isolated as salts of oxalic acid because of better stability and isolation. We observed no problems using oxalates in our *in vitro* test system.

Pharmacology

The H_3 activity of the compounds was determined on an *in vitro* test system, on the basis of the concentration-dependent inhibitory effect of histamine H_3 agonists on the electrically evoked contractile response of isolated guinea pig jejunum segments.[12] The binding affinity for the H_1 receptor was determined by the displacement of [^{3}H]mepyramine, bound to membranes of CHO cells expressing guinea pig H_1 receptors.[15] The binding affinity for the H_2 receptor was established by the displacement of [^{125}I]iodoaminopotentidine, bound to membranes of CHO cells expressing human H_2 receptors.[16]

Table 1. H_3 Antagonistic Activity of the Histamine Homologs **1** as Tested on the *in Vitro* Test System on the Guinea Pig Jejunum

compd	name or code[a]	n[b]	pA_2 H_3[c]	slope[d]	N[e]
1a	VUF 8319	1	<3		4
1b	histamine	2	$pD_2 = 6.2 \pm 0.3$		4
1c	VUF 8326	3	5.9 ± 0.3	0.9 ± 0.3	4
1d	VUF 4701	4	7.7 ± 0.2	0.8 ± 0.1	4
1e	VUF 4702	5	8.4 ± 0.2	1.1 ± 0.1	7
1f	VUF 4732	6	7.8 ± 0.2	1.2 ± 0.1	7
1g	VUF 4733	8	6.0 ± 0.2	1.2 ± 0.1	6
1h	VUF 4734	10	6.0 ± 0.3	0.9 ± 0.2	7

[a] Compound code number. [b] Alkyl chain length of **1** (number of methylene units). [c] Antagonistic parameter as determined on the described *in vitro* H_3 assay representing the negative logarithm of the abscissal intercept from the Schild plot ± SD. [d] Slope of Schild plot ± SD, not significantly different from unity. [e] Number of different animal preparations.

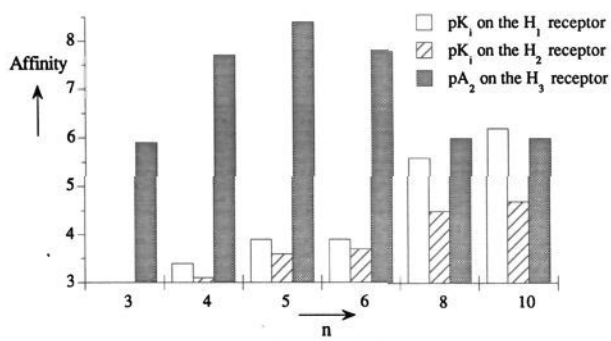


Figure 2. Influence of the alkyl chain length (n) of the histamine homologs **1** on the affinity of the H_1 and H_2 receptors and the antagonistic activity on the H_3 receptor.

Results and Discussion

All the compound have been tested for H_3 agonism and H_3 antagonism. From the results shown in Table 1 (see also Figure 2), it is clear that variation of the alkyl chain length in 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** has a drastic effect on the activity of these compounds on the histamine H_3 receptor. The histamine homolog with an alkyl chain shortened to one methylene group, VUF 8319 (**1a**), is inactive on this receptor. The ethylene chain of histamine (**1b**) is clearly optimal for activation

Figure 3. Graphical representation of a possible additional binding site for antagonists in the H_3 receptor, which can be occupied by either the protonated cationic nitrogen (triangle) or the imidazole ring (circle) of impentamine (**1e**) and VUF 8328 (**3b**). I: An H_3 agonist activates the receptor by binding to the 'active site'. II: An H_3 antagonist (like impentamine (**1e**) or VUF 8328 (**3b**)) binds with the protonated cationic nitrogen (IIa) or the imidazole ring (IIb) to an additional specific antagonistic binding site. No activation occurs.

of the H_3 receptor in the series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1**, since it is the only compound in this series with H_3 agonistic activity. Elongation of the alkyl chain results in compounds with a surprisingly high antagonistic activity on the histamine H_3 receptor. 4-(5)-(3-Aminopropyl)-1*H*-imidazole (VUF 8326, **1c**), for example, possesses moderate antagonistic activity, but the pentyl homolog of histamine, 4(5)-(5-aminopentyl)-1*H*-imidazole (impentamine or VUF 4702, **1e**), is a potent H_3 antagonist with a pA_2 value of 8.4 on the described *in vitro* test system. A further increase in the chain length to eight methylene groups results in a decrease of antagonistic activity to a pA_2 value of 6.0, which does not change on further lengthening (up to 10 methylene groups).

From these results it is clear that in a series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** the ethylene chain is essential for activation of the histamine H_3 receptor. The optimal chain length (through bonds) for antagonistic activity in this series seems to be five methylene groups (between the primary amino group and the imidazole ring). These results indicate that both the imidazole ring and the amino group play an important role in the activation mechanism of the H_3 receptor. It seems likely that there are specific binding sites for the imidazole ring and the protonated amine (at physiological pH) in the receptor. As soon as histamine binds to these sites, the receptor is activated. Apparently the higher alkyl analogs can not fulfill these requirements for activation (probably for steric reasons).

The observation that the histamine homolog with an alkyl chain comprising five methylene groups (impentamine, **1e**) has a much higher affinity than for instance the propyl homolog (VUF 8326, **1c**) or the octyl homolog (VUF 4733, **1g**) seems to indicate an additional binding site, for specific antagonists, in the H_3 receptor. Occupation of this additional binding site by either the ammonium group (at physiological pH) or the imidazole ring of impentamine (**1e**) increases the affinity, but the receptor is not activated (as represented in Figure 3). In this respect it is interesting to note that similar observations can be made in the series of analogs of imetit (**3a**), described by Van der Goot.[7] Imetit (**3a**) is a potent agonist for the H_3 receptor (pD_2 value of 8.1 on guinea pig ileum), but when the ethylene chain between the imidazole ring and the isothiourea group is elongated to a propylene chain, a potent H_3 antagonist, VUF 8328 (**3b**), is obtained (pA_2 value of 8.0 on guinea pig ileum). The distance (through bonds) between the imidazole ring and the protonated nitrogen is comparable for both the elongated imetit analog VUF 8328 (**3b**) and impentamine (**1e**). This observation supports the idea of an extra binding site for antagonists to which either a protonated cationic nitrogen or the imidazole ring can bind, thereby enhancing the affinity but not activating the H_3 receptor.

Table 2. Binding Affinity of the Histamine Analogs **1** on the H_1 and H_2 Receptors

compd	name or code[a]	n[b]	pK_i H_1[c]	pK_i H_2[d]
1a	VUF 8319	1	<3	<3
1b	histamine	2	4.9	4.4
1c	VUF 8326	3	<3	<3
1d	VUF 4701	4	3.4 ± 0.1	3.1 ± 0.1
1e	VUF 4702	5	3.9 ± 0.1	3.6 ± 0.1
1f	VUF 4732	6	3.9 ± 0.1	3.7 ± 0.1
1g	VUF 4733	8	5.6 ± 0.1	4.5 ± 0.1
1h	VUF 4734	10	6.2 ± 0.1	4.7 ± 0.1

[a] Compound code number. [b] Alkyl chain length of **1** (number of methylene units). [c] Negative logarithm value of the binding affinity for the histamine H_1 receptor ± SEM. [d] Negative logarithm value of the binding affinity for the histamine H_2 receptor ± SEM.

Since introduction of substituents (aralkyl groups) on the isothiourea group of VUF 8328 (**3b**) resulted in even more potent antagonists, like clobenpropit (**3c**) (pA_2 value of 9.9 on guinea pig ileum), we are currently investigating the effect of introduction of these types of substituents on the amino group of the described 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** on their H_3 activity.

A rather striking observation can be made when comparing the butyl homolog of histamine VUF 4701 (**1d**) and immepip (**4**), which can be considered as its rigid analog. VUF 4701 (**1d**) is a rather potent antagonist, whereas immepip (**4**) is a potent and selective agonist on the H_3 receptor. The difference in activity may be due to specific steric and/or conformational effects.

Chain length variation in a series of 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** has a large effect on the affinity of these compounds for the H_1 and the H_2 receptor as well. It has been reported more than 60 years ago[17] that there is a marked decrease in the effect of the propylene (**1c**) and butylene (**1d**) homologs of histamine on the H_1 activity. For the H_2 receptor, both shortening to the methylene chain (**1a**) and elongation to the propylene chain (**1c**) have been reported to result in histamine analogs with an agonistic activity less than 0.5% of the activity of histamine (**1b**).[18] This is in agreement with the affinities for the H_1 and H_2 receptors of the 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** that we have determined. From Table 2 and Figure 2 it can be seen that variation in the length of the alkyl spacer of histamine results in compounds with a low affinity for the H_1 and H_2 receptors, although the affinity increases with increasing chain length. The histamine homolog with a decyl chain (**1h**) has a reasonable affinity for the H_1 receptor ($pK_i = 6.2$), which was confirmed to be a weak antagonist by a conventional *in vitro* assay on the guinea pig ileum (not shown).

We conclude that the ethylene chain is the optimal spacer in 4(5)-(ω-aminoalkyl)-1*H*-imidazoles **1** for agonistic activity on all three known histamine receptor subtypes. For the histamine H_1 and H_2 receptors, variation of the alkyl chain length only results in compounds with a low affinity, although the affinity

increases with increasing chain length. The histamine analog with a decyl chain (**1h**) is even a moderate H_1 antagonist, which is rather surprising for an imidazole-based structure.

For the H_3 receptor, the effect of chain elongation of histamine is most pronounced, resulting, e.g., in the potent and selective H_3 antagonist 4(5)-(5-aminopentyl)-1*H*-imidazole (impentamine, **1e**). This high activity suggests an additional specific antagonistic binding site in the H_3 receptor to which either the ammonium group or the imidazole ring can bind, leading to enhanced affinity but not to activation.

Experimental Section

Chemistry. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer with tetramethylsilane or sodium 3-(trimethylsilyl)propionate as an internal standard. Mass spectra were recorded on a Finnigan MAT-90. Melting points were measured on a Mettler FP-5 + FP-52 instrument and are uncorrected. THF was distilled from $LiAlH_4$, DMF was dried by passage through a column packed with Al_2O_3, and acetone was distilled from K_2CO_3. *n*-Butyllithium was purchased from Janssen Chimica as a 15% solution in hexane.

The 1-chloro-ω-iodoalkanes were prepared by refluxing the corresponding 1,ω-dichloroalkanes with 1 equiv of sodium iodide in acetone and purification of the product by distillation.[19] 1-(*N*,*N*-Dimethylsulfamoyl)imidazole (**6**) was synthesized by the method described by Chadwick and Ngochindo,[20] with the exception that toluene was used as a solvent instead of benzene. 4(5)-(1-Aminomethyl)-1*H*-imidazole (**1a**) was prepared according to literature procedure.[21] Histamine dihydrochloride (**1b**) was purchased from Janssen Chimica. 4(5)-(3-Aminopropyl)-1*H*-imidazole dihydrobromide (**1c**), 4(5)-(4-aminobutyl)-1*H*-imidazole dihydrobromide (**1d**), and 4(5)-(5-aminopentyl)-1*H*-imidazole dihydrobromide (**1e**) were prepared as described earlier by our group.[13]

2-(*tert*-Butyldimethylsilyl)-5-(6-chlorohexyl)-1-(*N*,*N*-dimethylsulfamoyl)imidazole (8f). 1-(*N*,*N*-Dimethylsulfamoyl)imidazole (**6**) (26.0 g, 0.15 mol) was dissolved in dry THF (500 mL) under an atmosphere of dry nitrogen and cooled to −70 °C. *n*-Butyllithium in hexane (100 mL, 0.16 mol) was added dropwise (internal temperature did not exceed −65 °C). After 15 min, a solution of *tert*-butyldimethylsilyl chloride (25.0 g, 0.17 mol) in dry THF (50 mL) was added (internal temperature did not exceed −65 °C) and the solution was allowed to warm to room temperature and stirred for an additional hour. The mixture was cooled to −70 °C again, and *n*-butyllithium in hexane (100 mL, 0.16 mol) was added dropwise (internal temperature did not exceed −65 °C). After 0.5 h, a solution of 1-chloro-6-iodohexane (44.3 g, 0.17 mol) in dry THF (50 mL) was added gradually and the mixture was allowed to (slowly) warm to room temperature overnight. The reaction mixture was poured into water (200 mL), and the THF was removed under reduced pressure. The product was extracted with $CHCl_3$ (3 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo; 73.2 g of a viscous orange-colored oil was obtained which was used without further purification. ^{1}H NMR analysis of the oil showed complete coupling of the 6-chlorohexyl chain to the 1,2-diprotected imidazole **7**. ^{1}H NMR ($CDCl_3$): δ 0.39 (s, 6H, $Si(CH_3)_2$), 1.01 (s, 9H, $C(CH_3)_3$), 1.38 (m, 4H, central CH_2's), 1.80 (m, 4H, 2*CH_2), 2.71 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.88 (s, 6H, $N(CH_3)_2$), 3.55 (t, 2H, J = 7 Hz, CH_2Cl), 6.93 (s, 1H, imidazole-4H).

2-(*tert*-Butyldimethylsilyl)-5-(8-chlorooctyl)-1-(*N*,*N*-dimethylsulfamoyl)imidazole (8g). The same procedure as for the preparation of **8f** was employed, using 9.64 g (55 mmol) of 1-(*N*,*N*-dimethylsulfamoyl)imidazole (**6**) in 100 mL of dry THF, 37.5 mL (60 mmol) of *n*-butyllithium solution, 9.0 g (60 mmol) of *tert*-butyldimethylsilyl chloride, and 18.0 g (65 mmol) of 1-chloro-8-iodooctane; 32.6 g of a viscous orange oil was obtained which was used without further purification. ^{1}H NMR analysis of the oil showed complete coupling of the 8-chlorooctyl chain to the 1,2-diprotected imidazole **7**. ^{1}H NMR ($CDCl_3$): δ 0.39 (s, 6H, $Si(CH_3)_2$), 1.01 (s, 9H, $C(CH_3)_3$), 1.37 (m, 8H, central CH_2's), 1.37 (m, 4H, 2*CH_2), 2.71 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.85 (s, 6H, $N(CH_3)_2$), 3.55 (t, 2H, J = 7 Hz, CH_2Cl), 6.95 (s, 1H, imidazole-4H).

2-(*tert*-Butyldimethylsilyl)-5-(10-chlorodecyl)-1-(*N*,*N*-dimethylsulfamoyl)imidazole (8h). The same procedure as for the preparation of **8f** was employed, using 4.9 g (28 mmol) of 1-(*N*,*N*-dimethylsulfamoyl)imidazole (**6**) in 100 mL of dry THF, 20.0 mL (32 mmol) of *n*-butyllithium solution, 4.7 g (31 mmol) of *tert*-butyldimethylsilyl chloride, and 9.2 g (31 mmol), 1-chloro-10-iododecane; 18.3 g of a viscous orange oil was obtained which was used without further purification. ^{1}H NMR analysis of the oil showed complete coupling of the 10-chlorodecyl chain to the 1,2-diprotected imidazole **7**. ^{1}H NMR ($CDCl_3$): δ 0.38 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 1.32 (m, 12H, central CH_2's), 1.80 (m, 4H, 2*CH_2), 2.73 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.85 (s, 6H, $N(CH_3)_2$), 3.53 (t, 2H, J = 7 Hz, CH_2Cl), 6.94 (s, 1H, imidazole-4H).

1-(*N*,*N*-Dimethylsulfamoyl)-5-(6-phthalimidohexyl)-imidazole (9f). The crude product **8f** (73.2 g) was dissolved together with potassium phthalimide (40.3 g, 0.2 mol) in DMF (900 mL), and the mixture was heated at 70 °C. After 7 h, the mixture was filtered and the solvent was evaporated under reduced pressure. The residue (86.8 g) was stirred in 2-propanol (400 mL), and the precipitate (beige powder) was removed by filtration (1,6-diphthalimidohexane). The filtrate was concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (150 mL), washed with H_2O (3 × 150 mL), dried (Na_2SO_4), and concentrated in vacuo. A dark brown oil remained (47.6 g), which was pure enough for further use. A portion of this oil was purified by flash chromatography with ethyl acetate as eluent (R_f = 0.4). The ^{1}H NMR spectrum of the purified oil indicated complete removal of the protective group on the 2-position. ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 4H, central CH_2's), 1.69 (m, 4H, 2*CH_2), 2.72 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.90 (s, 6H, $N(CH_3)_2$), 3.70 (t, 2H, J = 7 Hz, CH_2-phthalimide), 6.82 (s, 1H, imidazole-4H), 7.72 (m, 5H, phthalimide-H + imidazole-2H).

1-(*N*,*N*-Dimethylsulfamoyl)-5-(8-phthalimidooctyl)imidazole (9g). The same procedure as for the preparation of **9f** was employed, using the crude product **8g** (32.6 g) in 150 mL of DMF and 13.6 g (73 mmol) of potassium phthalimide. After workup, a dark brown oil remained (23.8 g), which was pure enough for further use. A portion of this oil was purified by flash chromatography with ethyl acetate as eluent (R_f = 0.4). The ^{1}H NMR spectrum of the purified oil indicated complete removal of the protective group on the 2-position. ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 8H, central CH_2's), 1.66 (m, 4H, 2*CH_2), 2.71 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.88 (s, 6H, $N(CH_3)_2$), 3.68 (t, 2H, J = 7 Hz, CH_2-phthalimide), 6.82 (s, 1H, imidazole-4H), 7.75 (m, 5H, phthalimide-H + imidazole-2H).

1-(*N*,*N*-Dimethylsulfamoyl)-5-(10-phthalimidodecyl)-imidazole (9h). The same procedure as for the preparation of **9f** was employed, using the crude product **8h** (18.3 g) in 150 mL of DMF and 9.3 g (50 mmol) of potassium phthalimide. After workup, a dark brown oil remained (11.2 g), which was pure enough for further use. A portion of this oil was purified by flash chromatography with ethyl acetate as eluent (R_f = 0.4). The ^{1}H NMR spectrum of the purified oil indicated complete removal of the protective group on the 2-position. ^{1}H NMR ($CDCl_3$): δ 1.31 (m, 12H, central CH_2's), 1.68 (m, 4H, 2*CH_2), 2.71 (t, 2H, J = 8 Hz, imidazole-5-CH_2), 2.88 (s, 6H, $N(CH_3)_2$), 3.68 (t, 2H, J = 7 Hz, CH_2-phthalimide), 6.83 (s, 1H, imidazole-4H), 7.78 (m, 5H, phthalimide-H + imidazole-2H).

1-(*N*,*N*-Dimethylsulfamoyl)-5-(6-aminohexyl)imidazole (10f). **9f** (0.7 g, 1.7 mmol) was dissolved in 40 mL of warm ethanol; 0.3 mL (6.2 mmol) of hydrazine monohydrate was added, and this solution was heated under reflux for 4 h. After cooling of the solution to room temperature, a white precipitate formed and was removed by filtration. The filtrate was concentrated in vacuo, and 0.4 g (84%) of a light oil was isolated. ^{1}H NMR ($CDCl_3$): δ 1.33 (m, 6H, central CH_2's + NH_2), 1.60 (m, 4H, 2*CH_2), 2.64 (m, 4H, imidazole-5-CH_2 + CH_2NH_2), 2.83 (s, 6H, $N(CH_3)_2$), 6.75 (s, 1H, imidazole-4H), 7.78 (s, 1H, imidazole-2H).

1-(*N,N*-Dimethylsulfamoyl)-5-(8-aminooctyl)imidazole (10g). **9g** (7.6 g, 17.6 mmol) was dissolved in 100 mL of warm ethanol; 2.5 mL (51 mmol) of hydrazine monohydrate was added, and this solution was heated under reflux for 1 h. A white precipitate formed and was removed by filtration. The filtrate was concentrated in vacuo, and 5.2 g (98%) of a light oil was isolated. ^{1}H NMR ($CDCl_3$): δ 1.32 (m, 10H, central CH_2's + NH_2), 1.62 (m, 4H, 2*CH_2), 2.68 (m, 4H, imidazole-5-CH_2 + CH_2NH_2), 2.87 (s, 6H, $N(CH_3)_2$), 6.72 (s, 1H, imidazole-4H), 7.84 (s, 1H, imidazole-2H).

1-(*N,N*-Dimethylsulfamoyl)-5-(10-aminodecyl)imidazole (10h). The same procedure as for the preparation of **10g** was employed, using 2.0 g (4.4 mmol) of **9h** in 50 mL of ethanol and 0.6 mL (14 mmol) of hydrazine monohydrate; 1.2 g (84%) of a light oil was isolated. ^{1}H NMR ($CDCl_3$): δ 1.32 (m, 14H, central CH_2's + NH_2), 1.62 (m, 4H, 2*CH_2), 2.66 (m, 4H, imidazole-5-CH_2 + CH_2NH_2), 2.87 (s, 6H, $N(CH_3)_2$), 6.72 (s, 1H, imidazole-4H), 7.84 (s, 1H, imidazole-2H).

4(5)-(6-Aminohexyl)-1*H*-imidazole Dioxalate (1f). **9f** (44.9 g) was dissolved in 30% HBr (500 mL) and heated under reflux. After 16 h the mixture was cooled, filtered, and concentrated in vacuo. The residue was dissolved in absolute ethanol (300 mL), heated under reflux for 0.5 h, and concentrated under reduced pressure. The remaining dark oil was washed (under stirring) with 100 mL portions of acetone (removal of the formed ethyl *N,N*-dimethylsulfamoate group). After several washings, the oil crystallized. After filtration of the brown solid, 17.6 g (66% overall) of the product was obtained.

The dihydrobromide was converted in the dioxalate, using the following procedure: the dihydrobromide was dissolved in absolute EtOH, and 2 equiv of sodium ethanolate was added. This was refluxed for 0.5 h, and after filtration of sodium bromide, the filtrate was concentrated in vacuo. The residue was dissolved in 2-propanol and filtrated (removal of some remaining sodium bromide), and a saturable solution of oxalic acid in 2-propanol was added dropwise until a white precipitate was formed. The precipitate was collected by centrifugation, and the pellet was washed three times with 2-propanol, dried, and recrystallized from hot 2-propanol. A white powder was collected. Mp: 132.0 °C. ^{1}H NMR (D_2O): δ 1.33 (m, 4H, central CH_2's), 1.61 (m, 4H, 2*CH_2), 2.68 (t, 2H, J = 7 Hz, imidazole-4(5)-CH_2), 2.93 (t, 2H, J = 7 Hz, CH_2NH), 7.14 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H). ^{13}C NMR (D_2O): δ 25.0, 26.7, 28.0, 28.9, 40.9, 116.5, 134.0, 135.4, 166.7. MS (EI, rel. intensity) *m/z* 167 (M^+, 2), 151 ($M^+ - NH_2$, 6), 137 ($[ImC_5H_{10}]^+$, 4), 123 ($[ImC_4H_8]^+$, 3), 109 ($[ImC_3H_6]^+$, 5), 95 ($[ImC_2H_4]^+$, 39), 82 ($[ImCH_3^+$, 31), 81 ($[ImCH_2]^+$, 15), 45 ($[C_2H_7N]^+$, 100). HRMS: *m/z* 167.1426, calcd for $C_9H_{17}N_3$ 167.1422.

4(5)-(8-Aminooctyl)-1*H*-imidazole Dioxalate (1g). The same procedure as for the synthesis of **1f** was used with the exception that 2.3 g of **9g** was heated under reflux in 30% HBr (30 mL). After several washings with acetone, 1.14 g (67% overall) of a brown solid was collected. The dihydrobromide was converted into a dioxalate. A white powder was obtained. Mp: (95.0–97.0) °C. ^{1}H NMR (D_2O): δ 1.38 (m, 8H, central CH_2's), 1.60 (m, 4H, 2*CH_2), 2.66 (t, 2H, J = 7 Hz, imidazole-4(5)-CH_2), 2.93 (t, 2H, J = 7 Hz, CH_2NH), 7.13 (s, 1H, imidazole-5(4)H), 8.49 (s, 1H, imidazole-2H). ^{13}C NMR (D_2O): δ 25.1, 27.0, 28.1, 29.0, 29.3, 29.49, 29.51, 41.0, 116.4, 133.8, 135.7, 165.6. MS (EI, rel. intensity) *m/z* 195 (M^+, 0.6), 179 ($M^+ - NH_2$, 1), 165 ($[ImC_7H_{14}]^+$, 1), 151 ($[ImC_6H_{12}]^+$, 1), 137 ($[ImC_5H_{10}]^+$, 2), 123 ($[ImC_4H_8]^+$, 1), 109 ($[ImC_3H_6]^+$, 2), 95 ($[ImC_2H_4]^+$, 8), 82 ($[ImCH_3^+$, 9), 81 ($[ImCH_2]^+$, 5), 45 ($[C_2H_7N]^+$, 100). HRMS: *m/z* 195.1732, calcd for $C_{11}H_{21}N_3$ 195.1736. Anal. ($C_{11}H_{21}N_3 \cdot 2.15C_2H_2O_4$) C, H, N.

4(5)-(10-Aminodecyl)-1*H*-imidazole Dioxalate (1h). The same procedure as for the synthesis of **1f** was used with the exception that 2.2 g of **9h** was heated under reflux in 30% HBr (30 mL). After several washings with acetone, 0.6 g (27% overall) of a brown solid was collected. The dihydrobromide was converted into a dioxalate. A white powder was obtained. Mp: (154.5–155.0) °C. ^{1}H NMR (D_2O): δ 1.27 (m, 12H, central CH_2's), 1.62 (m, 4H, 2*CH_2), 2.67 (t, 2H, J = 7 Hz, imidazole-4(5)-CH_2), 2.94 (t, 2H, J = 7 Hz, CH_2NH), 7.14 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H). ^{13}C NMR (D_2O): δ 25.1, 27.0, 28.2, 29.1, 29.4, 29.6, 29.7, 29.88, 29.93, 41.0, 116.4, 133.8, 135.7, 167.3. MS (EI, rel. intensity) *m/z* 223 (M^+, 3), 207 ($M^+ - NH_2$, 4), 193 ($[ImC_9H_{18}]^+$, 5), 179 ($[ImC_8H_{16}]^+$, 6), 165 ($[ImC_7H_{14}]^+$, 5), 151 ($[ImC_6H_{12}]^+$, 6), 137 ($[ImC_5H_{10}]^+$, 6), 123 ($[ImC_4H_8]^+$, 3), 109 ($[ImC_3H_6]^+$, 6), 95 ($[ImC_2H_4]^+$, 27), 82 ($[ImCH_3^+$, 26), 81 ($[ImCH_2]^+$, 13), 45 ($[C_2H_7N]^+$, 100). HRMS: *m/z* 223.2049, calcd for $C_{13}H_{25}N_3$ 223.2048. Anal. ($C_{13}H_{25}N_3 \cdot 1.7C_2H_2O_4$) C, H, N.

Pharmacology. The histamine H_3 activity of the histamine homologs (**1**) was determined on an *in vitro* assay, on the basis of the inhibitory effect of histamine H_3 agonists on electrically evoked twitches (induced by endogenous acetylcholine release) of guinea pig jejunum preparations.[12] The addition of cumulative concentrations of an H_3 agonist results in a concentration-dependent inhibition of these evoked twitches, from which a concentration–response curve can be constructed. All histamine homologs (**1**) were tested for H_3 agonism and antagonism. H_3 antagonism was determined against (*R*)-α-methylhistamine. The potency of the antagonists was expressed by its pA_2 value, calculated from the Schild regression analysis, and at least three different concentrations were used. Statistical analysis was carried out with the Student's *t*-test, and $p < 0.05$ was considered statistically significant. Each compound was tested on tissue preparations of at least four different animals in triplicate. The binding affinity of the described compounds for the H_1 receptor was determined in at least three independent experiments, performed in triplicate, by the displacement of [^{3}H]mepyramine, bound to membranes of CHO cells expressing guinea pig H_1 receptors.[15] The binding affinity of the described compounds for the H_2 receptor was established in at least three independent experiments, performed in triplicate, by the displacement of [^{125}I]iodoaminopotentidine, bound to membranes of CHO cells expressing human H_2 receptors.[16]

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