N^{α}-Imidazolylalkyl and Pyridylalkyl Derivatives of Histaprodifen: Synthesis and in Vitro Evaluation of Highly Potent Histamine H_1-Receptor Agonists

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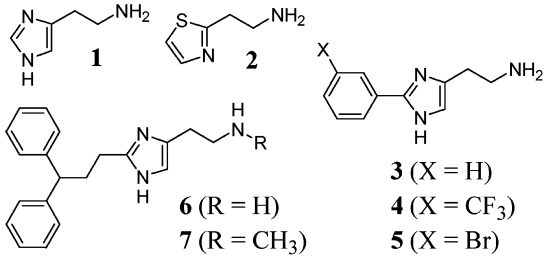
A novel series of N^{α}-imidazolylalkyl and pyridylalkyl derivatives of histaprodifen (**6**, 2-[2-(3,3-diphenylpropyl)imidazol-4-yl]ethanamine) was synthesized and evaluated as histamine H_1-receptor agonists. The title compounds displayed partial agonism at contractile H_1-receptors of guinea pig ileum and were at least equipotent with histamine. Agonist effects of the new derivatives were susceptible to blockade by the H_1-receptor antagonist mepyramine (2−100 nM). In the imidazole series, suprahistaprodifen (**51**, [2-[2-(3,3-diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-[2-(1*H*-imidazol-4-yl)ethyl]amine, N^{α}-2-[(1*H*-imidazol-4-yl)ethyl]histaprodifen) showed the highest H_1-receptor agonist potency ever reported in the literature (pEC_{50} 8.26, efficacy E_{max} 96%). Elongation of the alkyl spacer from ethyl to butyl decreased activity from 3630% (ethyl, **51**) to 163% (butyl, **53**) of histamine potency. The exchange of the terminal imidazole nucleus for a pyridine ring resulted in compounds with comparably high potency. A decrease in agonist potency and efficacy was observed when the attachment of the alkyl spacer was consecutively changed from the ortho to the meta and the para position, respectively, of the pyridine ring. The pyridine series that contained a butyl chain possessed the highest potency and affinity. N^{α}-[4-(2-pyridyl)butyl]histaprodifen (**56**) emerged as a strong partial agonist, being almost equipotent with **51** (pEC_{50} 8.16, E_{max} 89%). Compounds **51** and **56** also showed potent partial agonism at contractile H_1 receptors in guinea pig aorta and potently activated H_1-receptor-mediated endothelium-dependent relaxation in the rat aorta. Compounds **51**−**65** displayed low to moderate affinity at H_2, H_3, and M_3 receptors in functional models of guinea pig. Collectively, N^{α}-imidazolylalkyl- and N^{α}-pyridylalkyl-substituted histaprodifens represent a novel class of potent H_1-receptor agonists. These compounds may be useful to define the (patho)physiological role of the H_1-receptor and refine molecular models of H_1-receptor activation.

Introduction

There is an increasing understanding of the role of histamine (**1**, Chart 1) acting through histamine H_1 receptors in neurotransmission and various (patho)-physiological processes.[1] Histamine, acting through H_1 receptors, has been shown to operate as an endogenous anticonvulsant [2−5] and antidepressant.[6] In addition, histamine modulates pain[7,8] as well as food and water intake [9−11] and cognitive processes [12,13] by activation of H_1 receptors. Furthermore, histamine H_1 receptors are involved in the central thermoregulation,[14] the circadian rhythm of sleep and wakefulness,[15,16] and the regulation of the cardiovascular[17] and neuroendocrine system.[18] Histamine also induces migraine via the H_1 receptor.[19] Histamine produces dilation of meningeal blood vessels that could be blocked by H_1- and H_2-receptor antagonists. It could also be shown that H_1 receptors may be present on trigeminal neurones while H_2 receptors are not.[20]

Chart 1. Histamine (**1**) and Selective Histamine H_1-Receptor Agonists (**2**−**7**)



Since the discovery of the H_1 receptor, numerous derivatives have been synthesized to enhance agonist potency and selectivity.[1,21] At first the imidazole ring of histamine was replaced by other five-membered heterocyclic rings. Despite its moderate potency, the most prominent compound of this class, 2-(thiazol-2-yl)-ethanamine (**2**), is still used as a selective H_1-receptor agonist in numerous pharmacological studies. Another strategy focused on the ethanamine side chain. Shortening or elongation of this molecular fragment resulted in massive loss of potency.[21] An important step uncovering structural prerequisites for the development of H_1-receptor-selective compounds was the attachment of an alkyl group to the imidazole ring. Substitution at C-2

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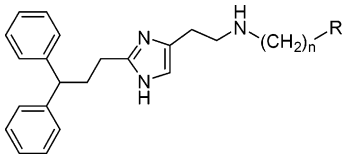
Table 1. Structures and Chemical Data of N^{α}-Substituted Derivatives of Histaprodifen



no.	n	R	formula	M_r	yield (%)	mp (°C)
51	2	1*H*-imidazol-4-yl	$C_{25}H_{29}N_5 \cdot 3C_2H_2O_4 \cdot 0.75H_2O$	683.2	17	195
52	3		$C_{26}H_{31}N_5 \cdot 3C_2H_2O_4$	683.6	7	183−185
53	4		$C_{27}H_{33}N_5 \cdot 3C_2H_2O_4 \cdot 1.25H_2O$	720.2	10	169
54	2	2-pyridyl	$C_{27}H_{30}N_4 \cdot 2C_2H_2O_4 \cdot H_2O$	608.6	10	169
55	3		$C_{28}H_{32}N_4 \cdot 2C_2H_2O_4$	604.6	16	203
56	4		$C_{29}H_{34}N_4 \cdot 2C_2H_2O_4$	618.6	14	192
57	5		$C_{30}H_{36}N_4 \cdot 2C_2H_2O_4$	632.6	21	191
58	2	3-pyridyl	$C_{27}H_{30}N_4 \cdot 2C_2H_2O_4 \cdot 1.5H_2O$	617.6	25	193
59	3		$C_{28}H_{32}N_4 \cdot 2C_2H_2O_4 \cdot H_2O$	622.6	6	190
60	4		$C_{29}H_{34}N_4 \cdot 2C_2H_2O_4$	618.6	32	180
61	5		$C_{30}H_{36}N_4 \cdot 2C_2H_2O_4$	632.6	21	164
62	2	4-pyridyl	$C_{27}H_{30}N_4 \cdot 2C_2H_2O_4 \cdot 0.75H_2O$	604.1	21	149−150
63	3		$C_{28}H_{32}N_4 \cdot 2C_2H_2O_4 \cdot H_2O$	622.6	38	182
64	4		$C_{29}H_{34}N_4 \cdot 2C_2H_2O_4 \cdot 0.25H_2O$	623.2	27	173
65	5		$C_{30}H_{36}N_4 \cdot 2C_2H_2O_4 \cdot 0.25H_2O$	637.2	12	163

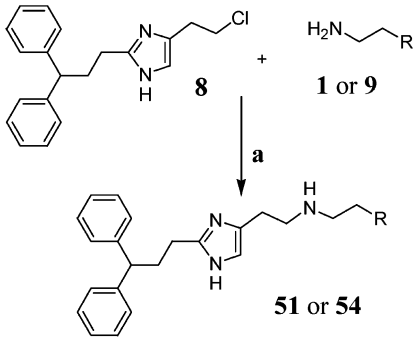
enhanced H_1-receptor selectivity, whereas substitution at C-5 resulted in H_2-receptor selectivity.[21,22] In accordance with these findings, the introduction of a small alkyl group (2-methylhistamine[22,23]) or a phenyl group (2-phenylhistamine[24] (**3**)) in the 2-position of the imidazole nucleus yielded agonists with moderate potency but increased selectivity for the histamine H_1 receptor. The potency of 2-phenyl derivatives was remarkably increased by introduction of various substituents at the meta position of the benzene ring, i.e. the potency of 2-(3-trifluoromethylphenyl)histamine (**4**) and 2-(3-bromophenyl)histamine (**5**) is in the range of the potency of **1**.[25] Furthermore, the H_1 histaminergic activity of **4** and **5** was slightly enhanced by N^{α}-methylation of these compounds.[26] Efforts to improve activity and selectivity by introduction of bulky groups with a flexible side chain at the 2-position resulted in H_1-receptor agonists with moderate potency.[27]

The serendipitous identification of histaprodifen (2-[2-(3,3-diphenylpropyl]imidazol-4-yl)ethanamine, **6**) as a potent H_1-receptor agonist from a series of potentially G-protein-stimulatory compounds, however, represented substantial progress in the design of histamine H_1-receptor agonists.[28] This compound, which combines a 2-substituted histamine and a 3,3-diphenylpropyl moiety typical of some histamine H_1-receptor antagonists, displays full agonism and a potency of 111% relative to histamine in guinea pig ileum. In accordance with earlier findings, potency was further enhanced by N^{α}-methylation of histaprodifen (methylhistaprodifen (**7**), 343% of histamine potency). Compounds **6** and **7** are potent H_1-receptor agonists in the pithed and in the anaesthetized rat.[29] Further modification of the new lead **6** (e.g., by elongation or shortening of the propyl spacer, or by introduction of larger N^{α}-alkyl substituents) resulted in decreased agonist potency or H_1-receptor antagonism.[28] Unlike our observation in the 2-phenylhistamine series, the introduction of a substituent at the meta position of the phenyl ring did not improve activity.[30] Based on the observation that the introduction of an N^{α}-[2-(1*H*-imidazol-4-yl)ethyl] substituent in the histamine molecule is well-tolerated with respect to H_1-receptor agonist potency,[31] we intended to modify the structure of **6** applying the same method. Preliminary studies have shown that N^{α}-[2-(1*H*-imidazol-4-yl)ethyl]histaprodifen (suprahistaprodifen, **51**) is the most potent histamine H_1-receptor agonist described so far. This compound displayed an intrinsic activity of 81% and a relative potency of 5600% compared to histamine in guinea pig ileum.[32] As suprahistaprodifen represents an amalgam of **6** and an additional histamine molecule, i.e., a hybrid molecule of two "monomeric" agonists, the combination of both structures in a single molecule represents a strategy that resembles the so-called bivalent ligand approach. This approach predicts strong enhancement in potency and selectivity for the "dimer" of an agonist or antagonist compared to its monomeric counterpart.[33−35] The discovery of **51** as a new lead prompted us to synthesize higher homologues (**52**, **53**) and to replace the hydrophilic, basic N^{α}-[2-(1*H*-imidazol-4-yl)ethyl] moiety by more lipophilic, weakly basic N^{α}-[ω-(pyridyl)alkyl] substituents, possessing an attachment of the alkyl spacer in the ortho, meta, or para position of the pyridine ring.

Chemistry

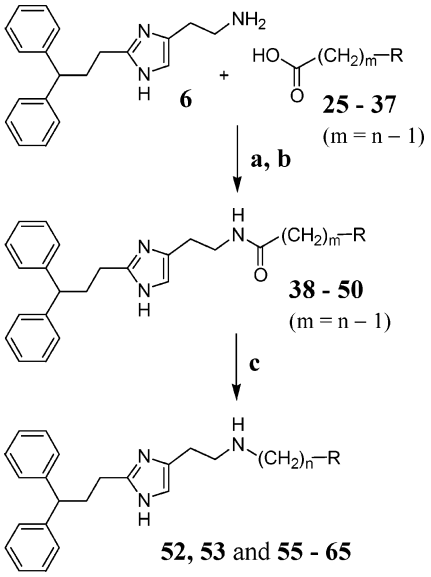
N^{α}-substituted histaprodifens (Table 1) were synthesized following two different synthetic pathways. Compounds **51** (suprahistaprodifen) and **54** were prepared by reaction of 4-(2-chloroethyl)-2-(3,3-diphenylpropyl)-1*H*-imidazole (**8**) with an excess of the respective amine (**1** or 2-(2-pyridyl)ethanamine (**9**)) in the presence of potassium carbonate and a catalytic amount of potassium iodide (Scheme 1) as described previously.[28] All other derivatives were obtained from N^{α}-acylation of **6** with carboxylic acids **25**−**37** activated by reaction with an excess of *N*,*N*'-carbonyldiimidazole (CDI).[36,37] The resulting amides **38**−**50** were subsequently reduced to secondary amines **52**, **53**, and **55**−**65** with diborane in THF (Scheme 2).[38] Appropriate carboxylic acids were commercially available (**27**, **30**, **31**, and **34**) or synthesized according to standard synthetic methods (Scheme 3). Compounds **26**, **32**, **35**, and **36** were prepared from

Scheme 1. General Procedure for the Synthesis of Histaprodifens **51** and **54** from **8**[a]



[a] (a) K_2CO_3, KI, EtOH/H_2O (1:1). For residue R please refer to Table 1.

Scheme 2. General Procedure for the Synthesis of Histaprodifens **52**, **53**, and **55**−**65** from **6**[a]



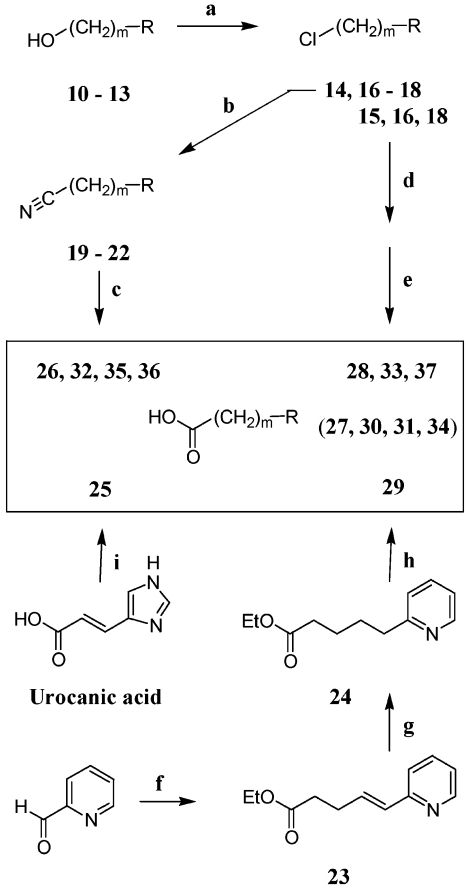
[a] (a) *N*,*N*′-Carbonyldiimidazole, THF, N_2; (b) THF, N_2; (c) diborane, THF, N_2. For residue R please refer to Table 1.

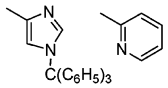
ω-heteroarylalkanols **10**−**13** by Kolbe nitrile synthesis via the chlorides **14**, **16**−**18**,[39] followed by hydrolysis of the nitriles **19**−**22**, compounds **28**, **33**, and **37** by alkylation of diethyl malonate,[40] subsequent hydrolysis of the diester, and decarboxylation. Compound **29** was prepared from pyridine-2-carboxaldehyde by Wittig synthesis,[41] followed by hydrogenation of the double bond and saponification of the ester moiety, while **25** was conveniently available by reduction of N^{τ}-trityl-protected urocanic acid.

Pharmacology

The interaction of the compounds with histamine H_1, H_2, and H_3 receptors was studied in various functional in vitro assays. Potency of the compounds at H_1 receptors was assessed by measuring the contraction of whole segments of guinea pig ileum. Selected compounds were additionally studied by measuring the contraction in rings of guinea pig aorta. The functional activity of selected compounds was further examined by measuring the relaxation in precontracted rings of rat aorta. Both responses are mediated by the H_1 receptor, too. In these models, (partial) agonist effects were antagonized by the

Scheme 3. General Procedures for the Synthesis of Carboxylic Acids[a]

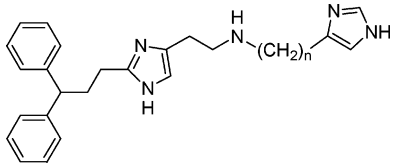


R =				
m = 1			**30**	**34**
m = 2	**25**	**15**, **27**	**31**	**12**, **17**, **21**, **35**
m = 3	**10**, **14**, **19**, **26**	**28**	**11**, **16**, **20**, **32**	**13**, **18**, **22**, **36**
m = 4		**29**	**33**	**37**

[a] (a) Thionyl chloride, THF, or CH_2Cl_2, respectively; (b) KCN/KI, DMSO; (c) KOH, EtOH/H_2O (1:1); (d) NaH, diethyl malonate, DMF, N_2; (e) KOH, EtOH/H_2O (1:1); 150 °C; (f) NaH, (3-(ethoxycarbonyl)propyl)triphenylphosphonium bromide, 1,2-dimethoxyethane; (g) Pd/C, H_2, EtOH; (h) 2 N NaOH, EtOH; (i) for details, see Experimental Section.

H_1-receptor antagonist mepyramine (2−100 nM). The ability of the compounds to interact with the H_2-receptor was studied in spontaneously beating guinea pig right atrium by measuring the inhibition of histamine-induced increase in heart rate. The effectiveness of selected compounds in blocking H_3 receptors was determined in field-stimulated guinea pig ileal longitudinal muscle preparations by measuring the inhibition of the relaxant response to (*R*)-α-methylhistamine. Only those concentrations of compounds were used that did not interfere with M_3 cholinoceptors. Affinities of compounds for M_3 receptors were studied in guinea pig

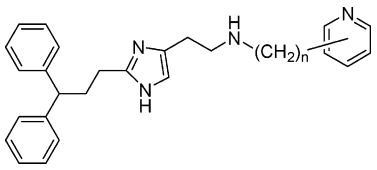
Table 2. Contractile Responses to **1**, **6**, **7**, and N^{α}-Imidazolylalkyl Derivatives of **6** (**51**−**53**) in GuineaPig Ileum



		agonism					antagonism vs histamine		
compd	n	pEC_{50}[a]	relative potency	95% cl	E_{max} (%)[a]	N[b]	pK_P[a,c]	c[d] (μM)	N[b]
1[e]		6.70 ± 0.02	100		100	>100			
6[e]		6.74 ± 0.02	111	99−124	100	34	6.04 ± 0.05	3−30	12
7[e]		7.24 ± 0.02	343	308−382	99 ± 1	19	6.45 ± 0.04	30	13
51	2	8.26 ± 0.06	3630	2930−4500	96 ± 1	22	7.67 ± 0.05[f]	0.1−10	27
52	3	7.87 ± 0.05	1468	1128−1911	95 ± 1	15	7.14 ± 0.06	0.1	7
53	4	6.91 ± 0.06	163	114−234	86 ± 4	8	6.17 ± 0.14	10	7

[a] Values ± SEM. [b] Number of experiments. [c] −log K_P, calculated according to the method of Marano and Kaumann.[56] [d] Concentration of the partial agonist. [e] For structure, see Chart 1. Data from ref 28. [f] See also Figure 2.

Table 3. Contractile Responses to **1**, **6**, **7**, and N^{α}-Pyridylalkyl Derivatives of **6** (**54**−**65**) in Guinea Pig Ileum



			agonism					antagonism vs histamine	
compd	n	pyridine substitution	pEC_{50}[a]	relative potency	95% cl	E_{max} (%)[a]	N[b]	pK_P[a,c]	c[d] (μM)	N[b]
1[e]			6.70 ± 0.02	100		100	>100			
6[e]			6.74 ± 0.02	111	99−124	100	34	6.04 ± 0.05	3−30	12
7[e]			7.24 ± 0.02	343	308−382	99 ± 1	19	6.45 ± 0.04	30	13
54	2	ortho	7.67 ± 0.05	923	619−1376	92 ± 1	12	7.15 ± 0.06	10	8
55	3	ortho	7.67 ± 0.04	930	715−1088	80 ± 2	6	7.13 ± 0.14	3	5
56	4	ortho	8.16 ± 0.06	2856	2103−3878	89 ± 1	14	7.45 ± 0.07	3	10
57	5	ortho	7.81 ± 0.02	1297	1177−1429	83 ± 1	10	6.74 ± 0.08	3	6
58	2	meta	7.11 ± 0.03	254	209−309	64 ± 3	8	6.52 ± 0.07	10	8
59	3	meta	6.93 ± 0.06	169	138−207	48 ± 4	8	6.18 ± 0.06	10	8
60	4	meta	7.87 ± 0.04	1479	1201−1821	88 ± 1	10	6.88 ± 0.12	3	5
61	5	meta	7.58 ± 0.04	761	567−1020	84 ± 2	9	6.61 ± 0.07	3−10	7
62	2	para	6.94 ± 0.09	174	115−267	78 ± 3	6	6.02 ± 0.06	10	6
63	3	para	6.57 ± 0.05	73	48−112	48 ± 6	6	5.69 ± 0.10	10	6
64	4	para	7.62 ± 0.06	832	610−1133	84 ± 1	10	6.56 ± 0.10	10	7
65	5	para	7.02 ± 0.05	207	136−316	57 ± 6	10	5.90 ± 0.05	10	6

[a] Values ± SEM. [b] Number of experiments. [c] −log K_P, calculated according to the method of Marano and Kaumann.[56] [d] Concentration of the partial agonist. [e] For structure, see Chart 1. Data from ref 28.

ileum by measuring the inhibitory effect of carbachol-induced contractions.

The contractile responses to N^{α}-imidazolylalkyl (**51**−**53**) and pyridylalkyl derivatives (**54**−**65**) of histaprodifen in guinea pig ileum are summarized in Tables 2 and 3, respectively. Antagonism by mepyramine (2−100 nM) of the contractile responses to **51**−**65** in guinea pig ileum is shown in Table 4. The contractile responses to selected derivatives of histaprodifen in guinea pig aorta are summarized in Table 5, while the relaxant responses in rat aorta are depicted in Table 6. The interaction of selected derivatives of histaprodifen with H_2, H_3, and M_3 receptors is summarized in Table 7.

Results and Discussion

H_1-Receptor Agonism in Guinea Pig Ileum. The data in Tables 2 and 3 show that N^{α}-imidazolylalkyl (**51**−**53**) and pyridylalkyl derivatives (**54**−**65**) of histaprodifen acted as partial agonists in guinea pig ileum with intrinsic activities ranging from 0.48 to 0.96 (histamine 1.00) and relative potencies ranging from 73 to 3630 (histamine 100). Table 4 shows the antagonism by mepyramine of the contractile responses to **51**−**65**.

Table 4. Antagonist Affinity Estimates of Mepyramine Against **1** and **51**−**65** in Guinea Pig Ileum

agonist	affinity[a]	c[b] (nM)	N[c]	agonist	affinity[a]	c[b] (nM)	N[c]
1	9.07 ± 0.03[d]	0.3−100	29	**58**	9.07 ± 0.11	3	4
51	8.83 ± 0.04[e]	2−100	16	**59**	8.74 ± 0.09	3	4
52	8.73 ± 0.08	3	6	**60**	8.77 ± 0.05	3	8
53	8.77 ± 0.05	3	6	**61**	8.83 ± 0.11	3	5
54	8.76 ± 0.06	3	6	**62**	8.83 ± 0.06	3	6
55	8.78 ± 0.05	3	6	**63**	8.49 ± 0.09[g]	3	4
56	9.18 ± 0.16[f]	3−30	19	**64**	8.95 ± 0.06	3	4
57	8.74 ± 0.05	3	7	**65**	8.63 ± 0.10[g]	3	4

[a] Apparent pA_2 ± SEM unless otherwise indicated. [b] Concentration of mepyramine. [c] Number of experiments. [d] Full pA_2, Schild plot slope 1 (0.97 ± 0.04, $P > 0.20$). Data from ref 28. [e] Full pA_2, Schild plot slope 1 (1.01 ± 0.06, $P > 0.50$). [f] Full pA_2, Schild plot slope 0.64 ± 0.08 ($P < 0.001$). [g] pD'_2 value.

Table 5. Contractile Responses to **1**, **6**, **7**, **51**, **54**, **56**, and **58** in Endothelium-Denuded Rings of Guinea Pig Aorta Moderately Precontracted with $PGF_{2\alpha}$

	agonism					antagonism by mepyramine[a]	
compd	pEC_{50}[b]	relative potency	95% cl	E_{max} (%)[b,c]	N[d]	pA_2[b]	N[d]
1	6.79 ± 0.05	100		100	10	9.00 ± 0.06[e]	8
6[e]	6.80 ± 0.04[f]	101	81−126	84 ± 2	11	9.01 ± 0.09	4
7[e]	7.40 ± 0.07[f]	410	296−569	89 ± 4	13	8.75 ± 0.07	4
51	8.01 ± 0.03	1660	1455−1892	93 ± 3	12	8.49 ± 0.10	6
54	7.09 ± 0.04	200	171−232	78 ± 1	6	8.36 ± 0.09	6
56	7.85 ± 0.10	1175	731−1890	89 ± 4	6	8.79 ± 0.15	4
58	7.08 ± 0.05	195	154−247	73 ± 4	4	8.49 ± 0.11	4

[a] Concentration of mepyramine: 10 nM except for **1** (30 nM) and **7** (100 nM). [b] Values ± SEM. [c] Maximum of histamine controls (relative to contraction evoked by 10 μM $PGF_{2\alpha}$) arbitrarily set to 100%. [d] Number of experiments. [e] Data from ref 28. [f] Values from ref 28 were corrected due to different mean value for histamine controls ($pEC_{50} = 6.50$).

Table 6. Endothelium-Dependent Relaxation of Rat Aorta by **1**, **6**, **7**, **51**, **54**, and **56**

	agonism					antagonism by mepyramine[a]	
compd	pEC_{50}[b]	relative potency	95% cl	E_{max} (%)[b,c]	N[d]	pA_2[b]	N[d]
1[e]	5.35 ± 0.04	100		100	>25	8.00 ± 0.07	8
6[e]	6.07 ± 0.08	528	330−847	50 ± 4	9	8.04 ± 0.06	6
7[e]	6.80 ± 0.07	2825	1854−4305	61 ± 6	10	8.02 ± 0.06	8
51	6.53 ± 0.07	1514	1045−2193	56 ± 4	10	8.02 ± 0.08	8
54	6.28 ± 0.07	843	582−1221	59 ± 3	11	7.98 ± 0.14	7
56	6.62 ± 0.04	1866	1510−2306	65 ± 5	11	8.21 ± 0.14	6

[a] Concentration of mepyramine: 50 nM except for **1**, **6**, **7** (100 nM). [b] Values ± SEM. [c] Relative to histamine controls. [d] Number of experiments. [e] Data from ref 28.

Table 7. Antagonist Affinity Estimates (Apparent pA_2, pD'_2 Values) of **51**−**65** at Histamine H_2 and H_3 Receptors, and at M_3 Cholinoceptors

compd	H_2[a] pD'_2 ± SEM	H_3[b,d] pA_2 ± SEM	M_3[c,d] pA_2 ± SEM
51	$pEC_{50} = 5.0$	<6.0 (4)	5.32 ± 0.11 (6)
52	3.92 ± 0.15 (2)	6.91 ± 0.07 (6)	6.11 ± 0.11 (4)
53	4.12 ± 0.02 (2)	7.99 ± 0.04 (6)	6.38 ± 0.06 (4)
54	4.37 ± 0.03 (2)	<6.3 (4)	5.30 ± 0.06 (6)[e]
55	4.96 ± 0.03 (2)	< 6.5 (6)	6.34 ± 0.03 (3)
56	4.78 ± 0.11 (2)	< 6.3 (6)	6.13 ± 0.05 (5)
57	5.02 ± 0.18 (3)	< 6.5 (4)	6.29 ± 0.04 (4)
58	4.62 ± 0.08 (2)	< 6.3 (4)	5.15 ± 0.15 (6)
59	4.05 ± 0.01 (2)	nd	nd
60	4.77 ± 0.18 (4)	nd	nd
61	5.25 ± 0.07 (2)	<6.5 (6)	6.25 ± 0.06 (4)
62	4.37 ± 0.08 (4)	<6.3 (6)	6.00 ± 0.08 (4)
63	4.36 ± 0.09 (3)	nd	nd
64	4.59 ± 0.03 (2)	nd	nd
65	4.12 ± 0.02 (2)	nd	nd

[a] Inhibition of histamine-induced rise in heart rate in guinea pig right atrium in the presence of mepyramine (0.3 μM). [b] Antagonism of the relaxant response to (*R*)-α-methylhistamine in field-stimulated guinea pig ileal longitudinal muscle. [c] Antagonism of carbachol-induced contractions in guinea pig ileum. [d] In the presence of mepyramine (1−3 μM). nd, not determined. Number of experiments in parentheses. When only two experiments were performed, the dispersion parameter represents half of the range observed. [e] pD'_2 value.

The interaction of mepyramine at different concentrations with the most potent agonist **51** is shown in Figure 1. The similarity of blocking potency of mepyramine (pA_2 8.5−9.2) is consistent with an interaction of **51**−**65** with the same receptor class (histamine H_1). As expected from partial agonists, compounds **51**−**65** (0.1−10 μM) antagonized the contractile response to histamine with pK_P values ranging from 5.7 to 7.7. The estimated pK_P values of **51**−**65** were up to 1 order of magnitude lower than the corresponding pEC_{50} values (see Tables 1 and 2 and Figure 2 for the histamine-blocking effect of **51**). The observation, which is consistent with recently published data on histaprodifens in guinea pig ileum,[28] indicates that pEC_{50} values, in contrast to pA_2, pK_I, or

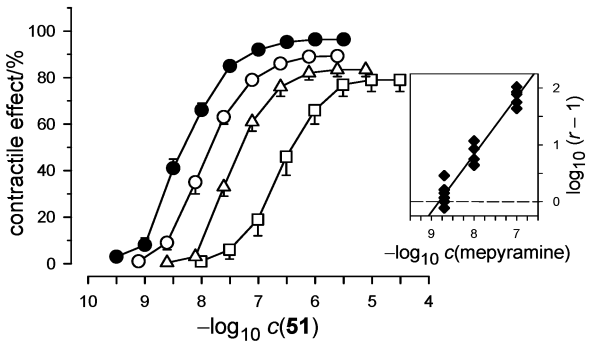


Figure 1. Contraction of guinea pig ileum by suprahistaprodifen (**51**) in the absence (●, $N = 16$, $E_{max} = 100\%$, $pEC_{50} = 8.26 \pm 0.06$) and presence of the competitive H_1-receptor antagonist mepyramine [nM]: 2 (○, $N = 6$, $E_{max} = 89 \pm 3\%$), 10 (△, $N = 5$, 83 ± 3%), and 100 (□, $N = 5$, 79 ± 5%). Inset: The Schild plot for mepyramine yielded a straight line of slope 1 (1.01 ± 0.06, $N = 16$, not significantly different from unity) and a full pA_2 value of 8.83 ± 0.04 (95% cl 8.73−8.92). Data is from four animals.

pK_P, do not necessarily reflect affinity values.[42] Histaprodifen (**6**) has recently been shown to be a potent full agonist in guinea pig ileum.[28] The corresponding N^{α}-monomethyl derivative of **6**, methylhistaprodifen (**7**), was even more potent.[28] Compounds **51** (suprahistaprodifen) and **56** were the most potent agonists derived from the present study with relative potencies that were 33- and 26-fold higher than that of **6** and 11- and 8-fold higher than that of **7**, respectively. It should be noted that the intrinsic activities of **51** and **56** were somewhat lower than the intrinsic activity (ia) of **6** (**51**, 0.96; **56**, 0.89). Further compounds of high potency and efficacy were **60** (rel pot. 1479, ia 0.88), **52** (rel pot. 1468, ia 0.95), **57** (rel pot. 1297, ia 0.83), **55** (rel pot. 930, ia 0.80), and **54** (rel pot. 923, ia 0.92).

Agonist potency (pEC_{50}) and partial agonist affinity (pK_P) decreased in the series of N^{α}-imidazolylalkyl derivatives of **6** when the length of the alkyl spacer linking the imidazole ring to the histaprodifen moiety

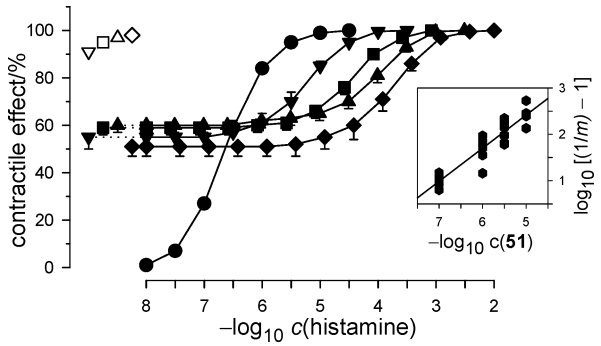


Figure 2. Contraction of guinea pig ileum by histamine (**1**) in the absence (●, $N = 27$, mean $pEC_{50} = 6.63$) and presence of suprahistaprodifen (**51**) [μM] ($E_{max} \pm$ SEM induced by **1**): 0.1 (▼, 99 ± 2%, $N = 6$), 1 (■, 99 ± 2%, $N = 7$), 3 (▲, 98 ± 2%, $N = 8$), and 10 (◆, 82 ± 4%, $N = 6$), respectively. All concentration−effect curves to **1** were normalized to 100% maximum effect prior to calculation of pK_P. Incubation time for **51** was 20 min. The initial response to **51** (*open* symbols) faded during the incubation period (*closed* symbols *below*). Inset: The plot of $\log[(1/m) - 1]$ vs $-\log c$(**51**)[56] gave a straight line with a slope significantly different from unity (0.72 ± 0.05, $P < 0.001$, $N = 27$). pK_P calculated as the corresponding abscissa intercept was 8.37 ± 0.20. The arithmetic mean of all 27 pK_P values was 7.67 ± 0.05 (see Table 2).

was increased (**51** vs **52** vs **53**; see Table 2). In the series of N^{α}-pyridylalkyl derivatives of **6**, agonist potency and partial agonist affinity were highest for **54**−**57**, in which the alkyl spacer was attached to the ortho position of the pyridine ring. Potency and affinity decreased when the substitution of the pyridine ring consecutively changed from the ortho to the meta and the para position, irrespective of the length of alkyl spacer (Table 3). The influence of the chain length of the alkyl spacer on the activity of the compounds justifies special mention. Irrespective of the substitution pattern of the pyridine ring, pEC_{50}, pK_P, and intrinsic activity dropped from compounds that had an ethyl chain to compounds that had a propyl chain, with the exception of one case, where pEC_{50} and pK_P values were equal (**54** vs **55**). Derivatives of the pyridine series that contained a butyl chain as an alkyl spacer showed the highest potency and efficacy, while compounds with a pentyl chain possessed somewhat lower activity than those with the butyl chain. The obviously different structure−activity relationships of the imidazole series **51**−**53** vs the pyridines **54**−**65** may reflect different binding properties of the "bisfunctional" imidazole nucleus (two nitrogen atoms) vs the "monofunctional" and more lipophilic pyridine moiety (one nitrogen atom) at the agonist binding site of the guinea pig H_1 receptor, but this has to be studied further.

H_1-Receptor Agonism on Guinea Pig Aorta. A modest degree of tone in endothelium-denuded rings of guinea pig aorta induced by a threshold concentration of $PGF_{2\alpha}$ resulted in a 10-fold increase in agonist potency of **1**, **6**, and **7**, respectively.[28] Compounds **51**, **54**, **56**, and **58** were potent partial agonists in precontracted rings of guinea pig aorta (Table 5). The pEC_{50} values were in the same concentration range as in the ileum bioassay. The findings are consistent with those recently obtained in both tissues with **1**, **6**, and **7**, respectively (Table 5).[28] Partial agonist responses to **51**, **54**, **56**, and **58** were susceptible to blockade by mepyramine, yielding pA_2 values around 8.5. A preliminary report has also shown the high partial agonist potency of **51** in another guinea pig tissue, viz. the isolated trachea, where the intrinsic activity reached 86%, and the pEC_{50} was 8.11.[32]

H_1-Receptor Agonism on Rat Aorta. The H_1 receptor mediates endothelium-dependent relaxation of precontracted rings of rat aorta.[43] If aortic rings were precontracted with U46619 (15.8 nM), then **51**, **54**, and **56** exerted a vasodilator response as recently described for **1**, **6**, and **7**, respectively (Table 6).[28] Compared to the guinea pig bioassays, pEC_{50} values were substantially lower in the rat bioassay. Lower efficiency of receptor-effector coupling or lower receptor density in the rat vs the guinea pig may be responsible for the decrease in agonist potency.[44] Additionally, lower affinity of the new compounds for the rat H_1 receptor per se may account for lower relaxant potency in this assay. Furthermore, the striking fact that **51** and **56**, which possess 10-fold potency compared with **7** in guinea pig tissues, were equipotent or slightly less potent than **7** in the rat bioassay hints at a substantially different structure−activity relationship of **51**-type compounds at the rat variant of the H_1 receptor. In accordance with these data, we have recently documented substantial differences in the pharmacological properties of agonists at human and guinea pig H_1 receptor.[48]

Interaction with Other Neurotransmitter Receptors. N^{α}-Imidazolylalkyl and pyridylalkyl derivatives of **6** did not stimulate atrial H_2 receptors (except the "histamine derivative" **51**), ileal H_3 heteroreceptors, and ileal M_3 cholinoceptors (Table 7). The antagonist affinities of **52**−**65** were very low at H_2 receptors ($pD'_2 \leq 5.0$). Some compounds showed micromolar affinity at M_3 receptors (pA_2 6.0−6.4). Such affinities prevented the use of higher antagonist concentrations when the antagonist profile of the compounds was studied at ileal H_3 heteroreceptors. It should be noted that the pA_2 values at H_3 receptors were generally lower than 6.5, with the exception of two cases. Suprahistaprodifen homologues **52** and **53** possessed appreciably high affinities at H_3 receptors (pA_2 values of 6.91 and 7.99). Compound **51** was found to stimulate atrial H_2 receptors as a partial agonist (intrinsic activity 0.41 ± 0.04, relative potency 10% compared with **1**). Similar effects of **51** were observed at recombinant human and guinea pig H_2 receptors.[48] The effect of **51** was abolished by the H_2-receptor antagonist cimetidine (30 μM). A functional evaluation of **51** vis-à-vis selected further neurotransmitter receptors revealed moderate antagonist affinity for α_{1D} ($pA_2 = 6.1 \pm 0.1$, rat aorta), β_1 ($pA_2 = 4.5 \pm 0.1$, guinea pig right atrium), 5-HT_{2A} ($pA_2 = 5.6 \pm 0.1$, rat tail artery), 5-HT_3 ($pA_2 < 6.0$, guinea pig ileum), and 5-HT_4 receptors ($pA_2 < 6.0$, rat esophagus).

Conclusions

N^{α}-Imidazolylalkyl and pyridylalkyl derivatives of histaprodifen (**6**) have been identified as potent histamine H_1-receptor agonists. Compound **51** (suprahistaprodifen) is the most potent compound in this series. In agreement with our present data, **51** has also been shown to act as a potent H_1-receptor agonist in the pithed and in the anaesthetized rat.[45] Compounds such as **51**, **54**, and **56** might substitute for histamine, which is used as a diagnostic tool to determine airway hyper-

responsiveness in asthmatic patients[46] or to elicit the wheal and flare response in the skin.[47] Derivatives of **6** as well as the new lead **51** have recently been used as tools to characterize differences in the agonist pharmacology of human and guinea pig histamine H_1 receptors.[48] Specifically, **51** is an ~5-fold more potent agonist at recombinant human H_1 receptor than recombinant guinea pig H_1 receptor expressed in Sf9 insect cells. Moreover, we observed that **51**, in contrast to all other H_1-receptor agonists studied so far, is considerably less potent at recombinant guinea pig H_1 receptor expressed in insect cells than at native H_1 receptor in the guinea pig ileum.[48] An explanation for these striking differences could be that **51** stabilizes a unique conformation in the guinea pig H_1 receptor that is highly potent at coupling to cognate mammalian G_q-proteins but much less potent at coupling to noncognate insect cell G_q-like G-proteins. Thus, analogues of **51** described in the present paper and related compounds that are currently undergoing functional characterization will help to increase the knowledge about species-dependent structure−activity relationships of H_1-receptor agonists and shed more light on the molecular mechanism of H_1-receptor activation.

Experimental Section

Chemistry. General Procedures. Melting points were determined on an Electrothermal Büchi 512 or 545 apparatus and are uncorrected. For all compounds ^{1}H NMR spectra were recorded on a Bruker DPX 400 (400 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from the internal standard Me_4Si. ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), approximate coupling constants in hertz, and the number of protons (Im, imidazole; Ph, phenyl; Pyr, pyridine). Mass spectra were recorded using a Finnigan MAT CH7A (70 eV, EI-spectra) or a Finnigan MAT CH5DF ($^+$FAB spectra). Elemental analyses (C, H, N) for all compounds were measured on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and are within ±0.4% of the theoretical values for all compounds. Column chromatography or flash column chromatography were carried out using silica gel 62−200 μm or 20−63 μm (Merck), respectively. TLC was performed on silica gel PF_{254} plates (Merck), and the spots were detected by UV light (wavelength 254 nm) and visualized with fast blue salt B reagent/NH_3. Abbreviations for solvents are the following: DMF, dimethylformamide; DMSO, dimethyl sulfoxide; Et_2O, diethyl ether; EtOH, ethanol; EtOAc, ethyl acetate; MeOH, methanol; PE, petroleum ether (bp 40−60 °C); TEA, triethylamine; THF, tetrahydrofuran.

Carboxylic Acids. General Procedure for the Synthesis of Nitriles 19 and 20. Following a slightly modified published procedure,[39] a solution of the respective propyl chloride (**14** and **16**, 15 mmol) in dry DMSO was slowly added to a dispersion of potassium cyanide (1.3 g, 20 mmol) and a catalytic amount of potassium iodide in DMSO heated to 80 °C. After being refluxed for 12 h, the mixture was poured into H_2O/NH_3 (pH 9) and extracted with CH_2Cl_2 (5 × 50 mL). The organic phase was dried over Na_2SO_4, evaporated, and purified by column chromatography (eluent: CH_2Cl_2/PE/TEA, 49:49:2).

4-(1-Trityl-1*H*-imidazol-4-yl)butyronitrile (19) was synthesized from 4-(3-chloropropyl)-1-trityl-1*H*-imidazole (**14**):[49] yield 53%; yellow oil ($C_{26}H_{23}N_3$); ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1H, Im-2-H), 7.41 (m, 3H, 3 *p*-Ph-H), 7.38 (m, 6H, 6 *m*-Ph-H) 7.10 (m, 6H, 6 *o*-Ph-H), 6.74 (s, 1H, Im-5-H), 2.87 (t, J = 7.3 Hz, 2H, Im-CH_2), 2,41 (t, J = 7.0 Hz, 2H, CH_2CN), 2.17 (m, 2H, $CH_2CH_2CH_2$); EI-MS *m*/*z* 377 (0.1), 243 (100).

4-(Pyridin-3-yl)butyronitrile (20) was synthesized from 3-(3-chloropropyl)pyridine (**16**):[50] yield 68%; colorless oil ($C_9H_{10}N_2$); ^{1}H NMR ($CDCl_3$) δ 8.79 (s, 1H, Pyr-2-H), 8.69 (d, J = 5.0 Hz, 1H, Pyr-6-H), 8.58 (d, J = 8.0 Hz, 1H, Pyr-4-H), 8.08 (m, 1H, Pyr-5-H), 3.07 (t, J = 7.8 Hz, 2H, Pyr-CH_2), 2.51 (t, J = 7.0 Hz, 2H, CH_2CN), 2.11 (m, 2H, $CH_2CH_2CH_2$); EI-MS *m*/*z* 146 (29), 106 (37), 92 (100).

Carboxylic Acids. General Procedure for the Synthesis of Compounds 26, 32, 35, and 36. The respective nitrile (**19**−**22**), dissolved in 40 mL of EtOH/H_2O (1:1), was treated with an excess of potassium hydroxide and refluxed for 3 h. After cooling, the mixture was diluted with H_2O, adjusted to pH 5 with 2 N HCl, and extracted with CH_2Cl_2 (3 × 50 mL), and the organic layer was evaporated. The substance was purified by column chromatography (eluent: CH_2Cl_2/MeOH, 9:1) and, if the product was an oil, crystallized as a hydrochloride.

4-(1-Trityl-1*H*-imidazol-4-yl)butyric Acid (26) was synthesized from **19**: yield 83%; white solid ($C_{26}H_{24}N_2O_2$); mp 174 °C; ^{1}H NMR (CD_3OD) δ 7.38−7.34 (m, 10H, Im-2-H, 6 *m*-Ph-H, 3 *p*-Ph-H), 7.13 (m, 6H, 6 *o*-Ph-H), 6.66 (s, 1H, Im-5-H), 2.55 (t, J = 7.4 Hz, 2H, Im-CH_2), 2,22 (t, J = 7.4 Hz, 2H, CH_2-CO), 1.87 (m, 2H, $CH_2CH_2CH_2$); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) *m*/*z* 397 ([M + H]$^+$, 7), 243 (100).

4-(Pyridin-3-yl)butyric Acid Hydrochloride (32) was synthesized from **20**: yield 36%; semisolid ($C_9H_{11}NO_2$·HCl); ^{1}H NMR (CF_3COOD) δ 8.82 (s, 1H, Pyr-2-H), 8.77 (d, J = 5.4 Hz, 1H, Pyr-6-H), 8.29 (d, J = 8.0 Hz, 1H, Pyr-4-H), 7.90 (m, 1H, Pyr-5-H), 3.04 (t, J = 7.8 Hz, 2H, Pyr-CH_2), 2,68 (t, J = 7.2 Hz, 2H, CH_2CO), 2.19 (m, 2H, $CH_2CH_2CH_2$); EI-MS *m*/*z* 165 (6), 106 (100), 92 (24).

3-(Pyridin-4-yl)propionic Acid Hydrochloride (35) was synthesized from 3-(pyridin-4-yl)propionitrile (**21**):[51] yield 79%; white solid ($C_8H_9NO_2$·HCl); mp 210 °C;^{1}H NMR (CD_3OD) δ 8.74 (d, J = 6.0 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.02 (d, J = 6.0 Hz, 2H, Pyr-3-H, Pyr-5-H), 3.23 (t, J = 7.1 Hz, 2H, Pyr-CH_2), 2,85 (t, J = 7.1 Hz, 2H, CH_2CO); EI-MS *m*/*z* 151 (100), 106 (77), 93 (24).

4-(Pyridin-4-yl)butyric Acid Hydrochloride (36) was synthesized from 4-(pyridin-4-yl)butyronitrile (**22**):[51] yield 98%; white solid ($C_9H_{11}NO_2$·HCl); mp 164 °C; ^{1}H NMR (CD_3OD) δ 8.75 (d, J = 6.2 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.00 (d, J = 6.2 Hz, 2H, Pyr-3-H, Pyr-5-H), 3.02 (t, J = 7.7 Hz, 2H, Pyr-CH_2), 2,42 (t, J = 7.2 Hz, 2H, CH_2CO), 2.04 (m, 2H, $CH_2CH_2CH_2$); EI-MS *m*/*z* 165 (20), 120 (1), 106 (79), 86 (100).

Carboxylic Acids. General Procedure for the Synthesis of Compounds 28, 33, and 37. Following a slightly modified standard procedure,[40] a dispersion of sodium hydride (2.2 g, 45 mmol, 50% dispersion in mineral oil) and a catalytic amount of potassium iodide in 50 mL of dry DMF under argon atmosphere cooled in an ice bath was treated with diethyl malonate (7.5 g, 45 mmol). After 30 min the respective alkyl chloride (**15**, **16**, and **18**, 45 mmol), dissolved in 15 mL of dry DMF, was added and the mixture stirred for 2 d at 80 °C. The mixture was poured into 200 mL of H_2O/NH_3 (pH 9) and extracted with CH_2Cl_2 (5 × 50 mL). The organic layer was dried over Na_2SO_4 and evaporated. The oily intermediate was resolved in 40 mL of EtOH/H_2O (1:1) without further purification, treated with an excess of potassium hydroxide, and stirred under reflux for 3 h. The mixture was then adjusted to pH 4, and the solvents were removed under reduced pressure. Inorganic precipitates were removed by column chromatography (eluent: MeOH). The semisolid residue was heated to 150 °C for 3 h without further purification. After cooling the crude product was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH, 98:2) and crystallized as hydrochloride.

4-(Pyridin-2-yl)butyric Acid Hydrochloride (28) was synthesized from 2-(2-chloroethyl)pyridine (**15**):[52] yield 22%; white solid ($C_9H_{11}NO_2$·HCl); mp 114−116 °C; ^{1}H NMR (CD_3OD) δ 8.73 (d, J = 6.2 Hz, 1H, Pyr-6-H), 8.56 (m, 1H, Pyr-5-H), 8.02 (d, J = 6.2 Hz, 1H, Pyr-3-H), 7.95 (m, 1H, Pyr-4-H), 3.15 (t, J = 7.8 Hz, 2H, Pyr-CH_2), 2.46 (t, J = 7.1 Hz, 2H, CH_2CO), 2.11 (m, 2H, $CH_2CH_2CH_2$); EI-MS *m*/*z* 165 (1), 120 (33), 106 (35), 93 (100).

5-(Pyridin-3-yl)pentanoic Acid Hydrochloride (33) was synthesized from 3-(3-chloropropyl)pyridine (**16**):[50] yield 49%; white solid ($C_{10}H_{13}NO_2$·HCl); mp 131 °C; ^{1}H NMR (CD_3OD) δ 8.79 (s, 1H, Pyr-2-H), 8.73 (d, J = 5.8 Hz, 1H, Pyr-6-H), 8.56 (d, J = 8.0 Hz, 1H, Pyr-4-H), 7.90 (m, 1H, Pyr-5-H), 2.91 (t, J = 7.3 Hz, 2H, Pyr-CH_2), 2.39 (t, J = 7.3 Hz, 2H, CH_2CO), 1.76 (m, 2H, Pyr-CH$_2$CH_2), 1.68 (m, 2H, CH_2CH$_2$CO); EI-MS m/z 179 (0.2), 134 (3), 120 (25), 106 (14), 93 (100).

5-(Pyridin-4-yl)pentanoic Acid Hydrochloride (37) was synthesized from 4-(3-chloropropyl)pyridine (**18**):[51] yield 73%; white solid ($C_{10}H_{13}NO_2$·HCl); mp 168−170 °C; ^{1}H NMR (CD_3-OD) δ 8.75 (d, J = 6.2 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.00 (d, J = 6.2 Hz, 2H, Pyr-3-H, Pyr-5-H), 3.00 (t, J = 7.6 Hz, 2H, Pyr-CH_2), 2.37 (t, J = 7.3 Hz, 2H, CH_2CO), 1.81 (m, 2H, Pyr-CH$_2$CH_2), 1.70 (m, 2H, CH_2CH$_2$CO); EI-MS m/z 179 (1), 120 (2), 106 (11).

3-(1-Trityl-1*H*-imidazol-4-yl)acrylic Acid. 3-(1*H*-imidazol-4-yl)acrylic acid (urocanic acid) (3.0 g, 21.5 mmol), TEA (6.5 g, 65 mmol), and triphenylmethyl chloride (6.0 g, 21.5 mmol) were stirred in 50 mL of dry DMF overnight. The mixture was diluted with $CHCl_3$ and extracted with H_2O (3 × 50 mL) and afterward with citric acid solution pH 3 (3 × 50 mL). The organic phase was evaporated and purified by column chromatography (eluent: CH_2Cl_2/MeOH, 9:1): yield 42%; white solid ($C_{25}H_{20}N_2O_2$); mp 220 °C; ^{1}H NMR (CD_3OD) δ 7.54 (s, 1H, Im-2-H), 7.48 (d, J = 15.8 Hz, 1H, Im-CH), 7.41 (m, 3H, 3 *p*-Ph-H), 7.38 (m, 6H, 6 *m*-Ph-H), 7.29 (s, 1H, Im-5-H), 7.16 (m, 6H, 6 *o*-Ph-H), 6.42 (d, J = 15.8 Hz, 1H, CHCO), 6.40 (s, 1H, COOH); $^-$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) m/z 379 ([M − H]$^-$, 100), 305 (35), 137 (31).

3-(1-Trityl-1*H*-imidazol-4-yl)propionic Acid (25). The respective unsaturated precursor in 10 mL of dry ethanol was hydrogenated over 10% Pd/activated carbon. After filtration the product was purified via column chromatography (eluent: CH_2Cl_2/MeOH, 9:1): yield 76%; white solid ($C_{25}H_{22}N_2O_2$); mp 188−190 °C; ^{1}H NMR (CD_3OD) δ 7.42 (s, 1H, Im-2-H), 7.37 (m, 9H, 6 *m*-Ph-H, 3 *p*-Ph-H), 7.13 (m, 6H, 6 *o*-Ph-H), 6.71 (s, 1H, Im-5-H), 2.80 (t, J = 7.1 Hz, 2H, Im-CH_2), 2,57 (t, J = 7.1 Hz, 2H, CH_2CO); $^-$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) m/z 381 ([M − H]$^-$, 100), 306 (38), 153 (90), 138 (12).

5-(Pyridin-2-yl)pent-4-enoic Acid Ethyl Ester (23). Following a slightly modified published procedure,[41] (3-(ethoxycarbonyl)propyl)triphenylphosphonium bromide (4.48 g, 10 mmol) was added slowly to a suspension of sodium hydride (0.48 g, 10 mmol, dispersion in mineral oil) in 50 mL of dry 1,2-dimethoxyethane kept at room temperature. After stirring for 30 min, pyridine-2-carboxaldehyde (1.17 g, 10 mmol) was added and the mixture refluxed for 12 h. The mixture was poured into water and extracted with diethyl ether (3 × 50 mL). The organic phase was evaporated after drying over Na_2SO_4 and the residue purified by column chromatography (eluent: CH_2Cl_2/PE/TEA, 49:49:2): yield 38%; colorless oil ($C_{12}H_{15}NO_2$); ^{1}H NMR ($CDCl_3$) δ 8.60 (d, J = 4.4 Hz, 1H, Pyr-6-H), 7.64 (m, 1H, Pyr-5-H), 7.23 (t, J = 7.6 Hz, 1H, Pyr-3-H), 7.11 (m, 1H, Pyr-4-H), 6.47 (d, J = 11.7 Hz, 1H, Pyr-CH), 5.87 (m, 1H, Pyr-CHCH), 4.13 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.95 (m, 2H, CHCH_2), 2.49 (t, J = 7.5 Hz, 2H, CH_2CO), 1.23 (t, J = 7.1 Hz, 2H, OCH$_2$CH_3); EI-MS m/z 205 (28), 176 (5), 160 (20), 132 (100), 117 (32).

5-(Pyridin-2-yl)pentanoic Acid Ethyl Ester (24). Compound **23**, dissolved in 10 mL of dry ethanol, was hydrogenated over 10% Pd/activated carbon. After filtration the crude product was purified via column chromatography (eluent: CH_2Cl_2/PE/TEA, 49:49:2): yield 99%; colorless oil ($C_{12}H_{17}NO_2$); ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 5.0 Hz, 1H, Pyr-6-H), 7.62 (m, 1H, Pyr-5-H), 7.16 (d, J = 7.8 Hz, 1H, Pyr-3-H), 7.12 (m, 1H, Pyr-4-H), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH$_3$), 2.83 (t, J = 7.5 Hz, 2H, Pyr-CH_2), 2.36 (t, J = 7.5 Hz, 2H, CH_2CO), 1.78 (m, 2H, Pyr-CH$_2$CH_2), 1.72 (m, 2H, CH_2CH$_2$CO), 1.24 (t, J = 7.1 Hz, 2H, OCH$_2$CH_3); EI-MS m/z 207 (1), 178 (1), 162 (18), 134 (7), 120 (23), 106 (22), 93 (100).

5-(Pyridin-2-yl)pentanoic Acid (29). A solution of **24** in 20 mL of EtOH/H_2O (1:1) was treated with an excess of potassium hydroxide and refluxed for 3 h. After cooling the mixture was adjusted to pH 5 with 2 N HCl and evaporated. The crude product was purified by column chromatography (eluent: MeOH): yield 99%; white solid ($C_{10}H_{13}NO_2$); mp 86 °C; ^{1}H NMR (CD_3OD) δ 8.58 (d, J = 5.4 Hz, 1H, Pyr-6-H), 8.18 (m, 1H, Pyr-5-H), 7.69 (d, J = 8.0 Hz, 1H, Pyr-3-H), 7.61 (m, 1H, Pyr-4-H), 2.96 (t, J = 7.6 Hz, 2H, Pyr-CH_2), 2.35 (t, J = 7.1 Hz, 2H, CH_2CO), 1.81 (m, 2H, Pyr-CH$_2$CH_2), 1.67 (m, 2H, CH_2CH$_2$CO); EI-MS m/z 179 (0.2), 134 (3), 120 (25), 106 (14), 93 (100).

Histaprodifens. General Procedure for the Synthesis of Amides 38−50. The respective carboxylic acid (**25**−**37**, 3 mmol) was dissolved in 10 mL of dry THF or, in case of carboxylic acid hydrochlorides, in 10 mL of dry THF and an equimolar amount of dry pyridine, and *N*,*N*′-carbonyldiimidazole (CDI, 0.65 g, 4 mmol) was added under a N_2 atmosphere. After stirring at room temperature for 1 h, histaprodifen (**6**, 0.91 g, 3 mmol)[28] in 10 mL of dry THF was added slowly, and the reaction mixture was stirred for 1−3 days at ambient temperature. THF was removed under reduced pressure. The residue was dissolved in 100 mL of CH_2Cl_2 and extracted with 0.1 N NaOH (3 × 50 mL). The organic layer was dried over Na_2SO_4, evaporated, and purified via flash column chromatography (eluent: CH_2Cl_2/MeOH/TEA, 97:2:1).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-3-(1-trityl-1*H*-imidazol-4-yl)propionamide (38)** was synthesized from **25**: yield 34%; white solid ($C_{45}H_{43}N_5O$); ^{1}H NMR ($CDCl_3$) δ 7.33−7.06 (m, 26H, 25 Ph-H, Im-2-H), 6.71 (s, 1H, Im-5-H), 6.36 (s, 1H, Im-5-H), 3.86 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.31 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.01 (t, J = 7.3 Hz, 2H, CH_2-Im), 2.77 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH_2CH$_2$N), 2.61 (t, J = 6.1 Hz, 2H, CH_2-Im$_{(C2)}$), 2.57−2.46 (m, 4H, COCH_2, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) m/z 670 ([M + H]$^+$, 11), 428 (3), 426 (3), 307 (9), 289 (7), 243 (100).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-4-(1-trityl-1*H*-imidazol-4-yl)butyramide (39)** was synthesized from **26**: yield 72%; white solid ($C_{46}H_{45}N_5O$); ^{1}H NMR ($CDCl_3$) δ 7.34−7.10 (m, 26H, 25 Ph-H, Im-2-H), 6.61 (s, 1H, Im-5-H), 6.53 (s, 1H, Im-5-H), 3.87 (t, J = 7.6 Hz, 1H, CHCH$_2$), 3.47 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 2.72 (t, J = 6.1 Hz, 2H, CH_2-Im), 2.57 (t, J = 7.2 Hz, 2H, CH_2-Im$_{(C2)}$), 2.47 (m, 4H, CHCH_2, Im$_{(C4)}$-CH_2CH$_2$N), 2.15 (t, J = 7.2 Hz, 2H, COCH_2), 1.86 (m, 2H, COCH$_2$CH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) m/z 684 ([M + H]$^+$, 2), 440 (2), 307 (1), 289 (2), 243 (100).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-3-(pyridin-2-yl)propionamide (40)** was synthesized from commercially available 3-(pyridin-2-yl)propionic acid (**27**): yield 28%; colorless oil ($C_{28}H_{30}N_4O$); ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 6.4 Hz, 1H, Pyr-6-H), 8.05 (d, J = 6.4 Hz, 1H, Pyr-5-H), 7.63 (d, J = 6.4 Hz, 1H, Pyr-3-H), 7.54 (t, J = 6.4 Hz, 1H, Pyr-4-H), 7.22−7.09 (m, 10H, 10 Ph-H), 6.71 (s, 1H, Im-5-H), 3.96 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.40 (m, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.28 (t, J = 7.0 Hz, 2H, CH_2-Pyr), 3.10 (m, 2H, COCH_2), 2.92 (m, 2H, Im$_{(C4)}$-CH_2), 2.83 (m, 2H, CH_2-Im$_{(C2)}$), 2.65 (q, J = 7.7 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) m/z 439 ([M + H]$^+$, 15), 289 (4).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-4-(pyridin-2-yl)butyramide (41)** was synthesized from **28**: yield 64%; colorless oil ($C_{29}H_{32}N_4O$); ^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 6.4 Hz, 1H, Pyr-6-H), 7.55 (t, J = 6.4 Hz, 1H, Pyr-5-H), 7.37 (d, J = 6.4 Hz, 1H, Pyr-3-H), 7.26−7.07 (m, 11H, 10 Ph-H, Pyr-4-H), 6.69 (s, 1H, Im-5-H), 3.89 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.51 (t, J = 7.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.08 (t, J = 7.1 Hz, 2H, CH_2-Pyr), 2.81 (t, J = 6.3 Hz, 2H, Im$_{(C4)}$-CH_2), 2.72 (m, 2H, CH_2-Im$_{(C2)}$), 2.52 (q, J = 7.7 Hz, 2H, CHCH_2), 2.22 (t, J = 7.1 Hz, 2H, COCH_2), 1.99 (m, 2H, CH_2CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/ *m*-NO_2-benzyl-OH) m/z 453 ([M + H]$^+$, 21), 307 (3), 289 (7).

5-(Pyridin-2-yl)pentanoic Acid [2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]amide (42) was synthesized from **29**: yield 60%; colorless oil ($C_{30}H_{34}N_4O$); ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J = 6.4 Hz, 1H, Pyr-6-H), 7.57 (d, J = 6.4 Hz, 1H, Pyr-5-H), 7.27−7.07 (m, 12H, 10 Ph-H, Pyr-3-H, Pyr-4-H), 6.63 (s, 1H, Im-5-H), 3.91 (t, J = 7.3 Hz, 1H, CHCH$_2$), 3.50 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 2.76−2.67 (m, 6H, CH_2-Pyr,

COCH_2, Im$_{(C4)}$-CH_2), 2.61 (t, J = 7.3 Hz, 2H, CH_2-Im$_{(C2)}$), 2.47 (q, J = 7.7 Hz, 2H, CHCH_2), 2.17 (m, 2H, CH_2CH$_2$-Pyr), 1.68 (m, 2H, COCH$_2$CH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 467 ([M + H]$^+$, 100), 306 (10), 289 (21).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-2-(pyridin-3-yl)acetamide (43)** was synthesized from commercially available 2-(pyridin-3-yl)acetic acid hydrochloride (**30**): yield 35%; colorless oil (C$_{27}$H$_{28}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.42 (m, 2H, Pyr-2-H, Pyr-6-H), 7.59 (d, J = 5.4 Hz, 1H, Pyr-4-H), 7.30−7.14 (m, 11H, 10 Ph-H, Pyr-5-H), 6.56 (s, 1H, Im-5-H), 3.92 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.48 (m, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.05 (t, J = 7.3 Hz, 2H, CH_2-Pyr), 2.70 (t, J = 6.3 Hz, 2H, Im$_{(C4)}$-CH_2), 2.61 (t, J = 6.4 Hz, 2H, CH_2-Im$_{(C2)}$), 2.46 (q, J = 7.7 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 425 ([M + H]$^+$, 70), 307 (7), 289 (38).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-3-(pyridin-3-yl)propionamide (44)** was synthesized from commercially available 3-(pyridin-3-yl)propionic acid (**31**): yield 34%; colorless oil (C$_{28}$H$_{30}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.55 (s, 1H, Pyr-2-H), 8.30 (d, J = 5.4 Hz, 1H, Pyr-6-H), 7.57 (m, 1H, Pyr-5-H), 7.30−7.09 (m, 11H, 10 Ph-H, Pyr-4-H), 6.79 (s, 1H, Im-5-H), 3.93 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.52 (t, J = 6.7 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.09 (t, J = 7.3 Hz, 2H, CH_2-Pyr), 2.89 (t, J = 7.3 Hz, 2H, COCH_2), 2.80 (t, J = 6.7 Hz, 2H, Im$_{(C4)}$-CH_2), 2.72 (m, 2H, CH_2-Im$_{(C2)}$), 2.60 (q, J = 7.7 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 439 ([M + H]$^+$, 20), 289 (5).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-4-(pyridin-3-yl)butyramide (45)** was synthesized from **32**: yield 29%; colorless oil (C$_{29}$H$_{32}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.55 (s, 1H, Pyr-2-H), 8.37 (d, J = 5.4 Hz, 1H, Pyr-6-H), 7.65 (m, 1H, Pyr-5-H), 7.30−7.10 (m, 11H, 10 Ph-H, Pyr-4-H), 6.81 (s, 1H, Im-5-H), 3.95 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.46 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.10 (t, J = 7.2 Hz, 2H, CH_2-Pyr), 2.89 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH_2), 2.81 (t, J = 7.2 Hz, 2H, CH_2-Im$_{(C2)}$), 2.62 (q, J = 7.7 Hz, 2H, CHCH_2), 2.30 (m, 2H, COCH_2), 1.93 (m, 2H, CH_2CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 453 ([M + H]$^+$, 48), 307 (6), 289 (13).

5-(Pyridin-3-yl)pentanoic Acid [2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]amide (46) was synthesized from **33**: yield 68%; colorless oil (C$_{30}$H$_{34}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.39 (s, 1H, Pyr-2-H), 8.36 (d, J = 5.4 Hz, 1H, Pyr-6-H), 7.43 (d, J = 5.4 Hz,1H, Pyr-5-H), 7.26−7.13 (m, 11H, 10 Ph-H, Pyr-4-H), 6.60 (s, 1H, Im-5-H), 3.91 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.47 (t, J = 6.3 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 2.86 (t, J = 7.0 Hz, 2H, CH_2-Pyr), 2.71 (t, J = 6.3 Hz, 2H, Im$_{(C4)}$-CH_2), 2.60 (m, 2H, CH_2-Im$_{(C2)}$), 2.54 (t, J = 7.0 Hz, 2H, COCH_2), 2.47 (q, J = 7.7 Hz, 2H, CHCH_2), 2.15 (t, J = 7.0 Hz, 2H, CH_2CH$_2$-Pyr), 1.59 (m, 2H, CO−CH$_2$CH_2); $^+$FAB-MS (Xe, DMSO/ *m*-NO$_2$-benzyl-OH) *m*/*z* 467 ([M + H]$^+$, 81), 307 (16), 289 (19).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-2-(pyridin-4-yl)acetamide (47)** was synthesized from commercially available 2-(pyridin-4-yl)acetic acid hydrochloride (**34**): yield 76%; colorless oil (C$_{27}$H$_{28}$N$_4$O); ^{1}H NMR (CF$_3$COOD) δ 8.77 (d, J = 5.3 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.12 (d, J = 5.3 Hz, 2H, Pyr-3-H, Pyr-5-H), 7.34−7.22 (m, 10H, 10 Ph-H), 7.08 (s, 1H, Im-5-H), 4.14 (s, 2H, CH_2-Pyr), 3.98 (t, J = 7.6 Hz, 1H, CHCH$_2$), 3.70 (t, J = 7.0 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.08 (t, J = 7.0 Hz, 2H, Im$_{(C4)}$-CH_2), 3.00 (t, J = 7.6 Hz, 2H, CH_2-Im$_{(C2)}$), 2.66 (q, J = 7.6 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/ *m*-NO$_2$-benzyl-OH) *m*/*z* 425 ([M + H]$^+$, 59), 307 (12), 289 (27).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-3-(pyridin-4-yl)propionamide (48)** was synthesized from **35**: yield 33%; colorless oil (C$_{28}$H$_{30}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.23 (d, J = 6.1 Hz, 2H, Pyr-2-H, Pyr-6-H), 7.66 (d, J = 6.1 Hz, 2H, Pyr-3-H, Pyr-5-H), 7.36−7.13 (m, 10H, 10 Ph-H), 6.62 (s, 1H, Im-5-H), 4.00 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.46 (t, J = 6.4 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.10 (t, J = 7.3 Hz, 2H, CH$_2$-Pyr), 2.89 (m, 4H, COCH_2, Im$_{(C4)}$-CH_2), 2.82 (t, J = 6.4 Hz, 2H, CH_2-Im$_{(C2)}$), 2.63 (t, J = 7.8 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/ *m*-NO$_2$-benzyl-OH) *m*/*z* 439 ([M + H]$^+$, 21), 289 (6).

***N*-[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]-4-(pyridin-4-yl)butyramide (49)** was synthesized from **36**: yield 66%; colorless oil (C$_{29}$H$_{32}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.44 (d, J = 6.1 Hz, 2H, Pyr-2-H, Pyr-6-H), 7.26−7.07 (m, 10H, 10 Ph-H), 7.05 (d, J = 6.1 Hz, 2H, Pyr-3-H, Pyr-5-H), 6.63 (s, 1H, Im-5-H), 3.91 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.50 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 2.72 (t, J = 6.1 Hz, 2H, Im$_{(C4)}$-CH_2), 2.66−2.56 (m, 4H, CH_2-Pyr, CH_2-Im$_{(C2)}$), 2.47 (q, J = 7.7 Hz, 2H, CHCH_2), 2.15 (m, 2H, COCH_2), 1.93 (m, 2H, CH_2CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 453 ([M + H]$^+$, 100), 307 (11), 289 (22).

5-(Pyridin-4-yl)pentanoic Acid [2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl]amide (50) was synthesized from **37**: yield 50%; colorless oil (C$_{30}$H$_{34}$N$_4$O); ^{1}H NMR (CDCl$_3$) δ 8.38 (d, J = 6.1 Hz, 2H, Pyr-2-H, Pyr-6-H), 7.23−7.10 (m, 10H, 10 Ph-H), 7.04 (d, J = 6.1 Hz, 2H, Pyr-3-H, Pyr-5-H), 6.66 (s, 1H, Im-5-H), 3.91 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.48 (t, J = 6.3 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.07 (t, J = 7.3 Hz, 2H, CH_2-Pyr), 2.82 (t, J = 6.2 Hz, 2H, Im$_{(C4)}$-CH_2), 2.77 (t, J = 7.7 Hz, 2H, CH_2-Im$_{(C2)}$), 2.55 (m, 4H, COCH_2, CHCH_2), 2.24 (m, 2H, CH_2CH$_2$-Pyr), 1.59 (m, 2H, COCH$_2$CH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 467 ([M + H]$^+$, 71), 307 (6), 289 (14).

Histaprodifens. General Procedure for Compounds 51 and 54.[28] To a mixture of 4-(2-chlorethyl)-2-(3,3-diphenylpropyl)-1*H*-imidazole (**8**), K$_2$CO$_3$ (0.4 g, 3 mmol), an excess of the respective amine (**1** or **9**), and catalytic amounts of KI dissolved in EtOH (30 mL)was added H$_2$O until a clear solution was obtained. The mixture was then heated under reflux for 2−4 h. The solvents were removed in vacuo and the free bases extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and evaporated. After flash column chromatography (eluent: CH$_2$Cl$_2$/MeOH/TEA, 97:2:1) the purified free bases were obtained. Crystallization with oxalic acid from EtOH/Et$_2$O afforded **51** as tri- and **54** as dihydrogen oxalate, respectively.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][2-(1*H*-imidazol-4-yl)ethyl]amine Trihydrogen Oxalate (Suprahistaprodifen, 51) was synthesized from **8** (0.48 g, 1.5 mmol) and histamine (**1**) (1.45 g, 13 mmol): ^{1}H NMR (CF$_3$COOD) δ 8.76 (s, 1H, Im-2-H), 7.48 (s, 1H, Im-5-H), 7.34−7.25 (m, 10H, 10 Ph-H), 7.17 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.72 (s, 2H, CH_2-Im$_{(C4)}$), 3.65 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.41 (t, J = 7.3 Hz, 2H, NCH_2CH$_2$-Im), 3.28 (t, J = 7.3 Hz, 2H, CH_2-Im), 3.07 (t, J = 7.3 Hz, 2H, CH_2-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 400 ([M + H]$^+$, 18), 318 (6), 307 (13), 289 (18). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][2-(pyridin-2-yl)ethyl]amine Dihydrogen Oxalate (54) was synthesized from **8** (0.30 g, 1 mmol) and commercially available 2-(pyridin-2-yl)ethanamine (**9**, 0.57 g, 4.7 mmol): ^{1}H NMR (CF$_3$COOD) δ 8.70 (d, J = 5.8 Hz, 1H, Pyr-6-H), 8.62 (d, J = 8.0 Hz, 1H, Pyr-3-H), 8.01 (t, J = 7.6 Hz, 2H, Pyr-4-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, CHCH$_2$), 3.74 (t, J = 7.6 Hz, 2H, Im$_{(C4)}$-CH$_2$CH_2N), 3.67 (t, J = 7.3 Hz, 2H, NCH_2CH$_2$-Pyr), 3.55 (t, J = 7.3 Hz, 2H, CH_2-Pyr), 3.29 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH_2), 3.07 (t, J = 7.3 Hz, 2H, CH_2-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHCH_2); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 411 ([M + H]$^+$, 100), 318 (52), 307 (13), 289 (35). Anal. C, H, N.

Histaprodifens. General Procedure for the Synthesis of Amines 52, 53, and 55−65.[38] To a stirred, 1 M solution of diborane in THF (5−10 mL) cooled to 0 °C and maintained under nitrogen was added a solution of the respective amide (**38**−**50**, 0.6−1.7 mmol) in dry THF dropwise. The reaction mixture was then refluxed for 20 h. After cooling, 2.5−5 mL of 6 N HCl was added slowly until hydrogen was evolved. Afterward the mixture was heated to 50 °C for 6 h. THF was removed in vacuo, and NaOH pellets were added to the remaining, vigorously stirred aqueous layer. After dilution with H$_2$O, the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic residues were combined, washed with water, dried over Na$_2$SO$_4$, and evaporated. The crude product was purified via flash column chromatography (eluent: CH$_2$Cl$_2$/MeOH/TEA, 97:2:1) and the resulting colorless oil was crystallized as a salt of oxalic acid from EtOH/Et$_2$O (see also Table 1).

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][3-(1*H*-imidazol-4-yl)propyl]amine Trihydrogen Oxalate (52) was synthesized as described from **38**. The trityl-protected intermediate was dissolved in THF without further purification. After addition of 10 mL of 3 N HCl the solution was refluxed overnight. THF was removed under reduced pressure, and the residue was resolved in CH_2Cl_2 and extracted twice with 1 N HCl. The aqueous phase was alkalized with NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was evaporated and the crude product purified by flash column chromatography as described above: ^{1}H NMR (CF_3COOD) δ 8.59 (s, 1H, Im-2-H), 7.34−7.21 (m, 11H, 10 Ph-H, Im-5-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.60 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.37 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_2$-Im), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.99 (s, 2H, C*H*$_2$-Im), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 2.31 (m, 2H, NCH$_2$C*H*$_2$CH$_2$-Im); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 414 ([M + H]$^+$, 100), 318 (6), 307 (14), 289 (27). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][4-(1*H*-imidazol-4-yl)butyl]amine Trihydrogen Oxalate (53) was synthesized, deprotected, and purified as described for **52**, from **39**: ^{1}H NMR (CF_3COOD) δ 8.56 (s, 1H, Im-2-H), 7.54 (s, 1H, Im-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.59 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.37 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_3$-Im), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.90 (s, 2H, C*H*$_2$-Im), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 1.91 (m, 4H, NCH$_2$C*H*$_2$(CH$_2$)$_2$-Im, C*H*$_2$CH$_2$-Im); $^+$FAB-MS (Xe, DMSO/ *m*-NO$_2$-benzyl-OH) *m*/*z* 428 ([M + H]$^+$, 9), 307 (1), 289 (3). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][3-(pyridin-2-yl)propyl]amine Dihydrogen Oxalate (55) was synthesized as described from **40**: ^{1}H NMR (CF_3COOD) δ 8.70 (d, J = 5.8 Hz, 1H, Pyr-6-H), 8.62 (d, J = 8.0 Hz, 1H, Pyr-3-H), 8.01 (t, J = 7.5 Hz, 2H, Pyr-5-H, Pyr-4-H), 7.34−7.22 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.62 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.52 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_2$-Pyr), 3.35 (t, J = 7.9 Hz, 2H, C*H*$_2$-Pyr), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 2.45 (m, 2H, C*H*$_2$CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 425 ([M + H]$^+$, 2), 307 (16), 289 (9). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][4-(pyridin-2-yl)butyl]amine Dihydrogen Oxalate (56) was synthesized from **41**: ^{1}H NMR (CF_3COOD) δ 8.70 (d, J = 5.8 Hz, 1H, Pyr-6-H), 8.62 (d, J = 8.0 Hz, 1H, Pyr-3-H), 7.99 (t, J = 7.6 Hz, 2H, Pyr-4-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.59 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.38 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_3$-Pyr), 3.26 (m, 4H, C*H*$_2$-Pyr, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 2.02 (m, 4H, N−CH$_2$C*H*$_2$(CH$_2$)$_2$-Pyr, N(CH$_2$)$_2$C*H*$_2$CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 439 ([M + H]$^+$, 20), 307 (14), 289 (19). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][5-(pyridin-2-yl)pentyl]amine Dihydrogen Oxalate (57) was synthesized from **42**: ^{1}H NMR (CF_3COOD) δ 8.70 (d, J = 5.8 Hz, 1H, Pyr-6-H), 8.62 (d, J = 8.0 Hz, 1H, Pyr-3-H), 7.99 (t, J = 7.6 Hz, 2H, Pyr-4-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.57 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.32 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_4$-Pyr), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.20 (t, J = 7.9 Hz, 2H, C*H*$_2$-Pyr), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 1.96 (m, 4H, NCH$_2$C*H*$_2$(CH$_2$)$_3$-Pyr, N(CH$_2$)$_3$C*H*$_2$CH$_2$-Pyr), 1.64 (m, 2H, N(CH$_2$)$_2$C*H*$_2$(CH$_2$)$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 453 ([M + H]$^+$, 100), 307 (20), 289 (19). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][2-(pyridin-3-yl)ethyl]amine Dihydrogen Oxalate (58) was synthesized from **43**: ^{1}H NMR (CF_3COOD) δ 8.90 (s, 1H, Pyr-2-H), 8.81 (d, J = 6.1 Hz, 1H, Pyr-6-H), 8.68 (d, J = 7.9 Hz, 1H, Pyr-5-H), 8.15 (t, J = 7.0 Hz, 1H, Pyr-4-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.74 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.67 (t, J = 7.3 Hz, 2H, N−C*H*$_2$CH$_2$-Pyr), 3.55 (t, J = 7.3 Hz, 2H, C*H*$_2$-Pyr), 3.29 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 411 ([M + H]$^+$, 100), 318 (20), 306 (4), 289 (14). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][3-(pyridin-3-yl)propyl]amine Dihydrogen Oxalate (59) was synthesized from **44**: ^{1}H NMR (CF_3COOD) δ 8.79 (s, 1H, Pyr-2-H), 8.75 (d, J = 6.1 Hz, 1H, Pyr-6-H), 8.59 (d, J = 7.9 Hz, 1H, Pyr-5-H), 8.12 (t, J = 7.0 Hz, 1H, Pyr-4-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.62 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.48 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_2$-Pyr), 3.28 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.10 (m, 4H, C*H*$_2$-Pyr, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 2.32 (m, 2H, C*H*$_2$CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 425 ([M + H]$^+$, 2), 307 (17), 289 (10). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][4-(pyridin-3-yl)butyl]amine Dihydrogen Oxalate (60) was synthesized from **45**: ^{1}H NMR (CF_3COOD) δ 8.71 (d, J = 6.9 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.55 (d, J = 7.9 Hz, 1H, Pyr-5-H), 8.08 (t, J = 7.0 Hz, 1H, Pyr-4-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.59 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.37 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_3$-Pyr), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.09−3.01 (m, 4H, C*H*$_2$-Pyr, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 1.99 (m, 2H, NCH$_2$C*H*$_2$(CH$_2$)$_2$-Pyr), 1.91 (m, 2H, C*H*$_2$-CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 439 ([M + H]$^+$, 20), 307 (17), 289 (11). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][5-(pyridin-3-yl)pentyl]amine Dihydrogen Oxalate (61) was synthesized from **46**: ^{1}H NMR (CF_3COOD) δ 8.69 (d, J = 6.9 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.55(d, J = 8.0 Hz, 1H, Pyr-5-H), 8.08 (t, J = 7.0 Hz, 1H, Pyr-4-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.57 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.30 (m, 4H, NC*H*$_2$(CH$_2$)$_4$-Pyr, Im$_{(C4)}$-C*H*$_2$), 3.07 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.99 (t, J = 7.7 Hz, 2H, C*H*$_2$-Pyr), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 1.88 (m, 4H, NCH$_2$C*H*$_2$(CH$_2$)$_3$-Pyr, C*H*$_2$CH$_2$-Pyr), 1.60 (m, 2H, N(CH$_2$)$_2$C*H*$_2$(CH$_2$)$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 453 ([M + H]$^+$, 6), 307 (12), 289 (8). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][2-(pyridin-4-yl)ethyl]amine Dihydrogen Oxalate (62) was synthesized from **47**: ^{1}H NMR (CF_3COOD) δ 8.82 (d, J = 5.8 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.10 (d, J = 5.8 Hz, 2H, Pyr-3-H, Pyr-5-H), 7.34−7.23 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.78 (t, J = 7.6 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.70 (t, J = 7.3 Hz, 2H, NC*H*$_2$CH$_2$-Pyr), 3.62 (t, J = 7.3 Hz, 2H, C*H*$_2$-Pyr), 3.31 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.08 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 411 ([M + H]$^+$, 6), 318 (5), 307 (15), 289 (10). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][3-(pyridin-4-yl)propyl]amine Dihydrogen Oxalate (63) was synthesized from **48**: ^{1}H NMR (CF_3COOD) δ 8.77 (d, J = 6.0 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.02 (d, J = 6.0 Hz, 2H, Pyr-3-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.62 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.49 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_2$-Pyr), 3.28 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.18 (t, J = 7.9 Hz, 2H, C*H*$_2$-Pyr), 3.08 (t, J = 7.3 Hz, 2H, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 2.35 (m, 2H, C*H*$_2$CH$_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO$_2$-benzyl-OH) *m*/*z* 425 ([M + H]$^+$,6), 307 (14), 289 (9). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][4-(pyridyl-4-yl)butyl]amine Dihydrogen Oxalate (64) was synthesized from **49**; ^{1}H NMR (CF_3COOD) δ 8.77 (d, J = 5.8 Hz, 2H, Pyr-2-H, Pyr-6-H), 8.02 (d, J = 5.8 Hz, 2H, Pyr-3-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, J = 7.7 Hz, 1H, C*H*CH$_2$), 3.59 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-CH$_2$C*H*$_2$N), 3.37 (t, J = 7.3 Hz, 2H, NC*H*$_2$(CH$_2$)$_3$-Pyr), 3.27 (t, J = 7.3 Hz, 2H, Im$_{(C4)}$-C*H*$_2$), 3.09−3.01 (m, 4H, C*H*$_2$-Pyr, C*H*$_2$-Im$_{(C2)}$), 2.66 (q, J = 7.7 Hz, 2H, CHC*H*$_2$), 1.96 (m, 4H,

$NCH_2CH_2(CH_2)_2$-Pyr, CH_2CH_2Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) *m*/*z* 439 ($[M + H]^+$, 2), 307 (17), 289 (10). Anal. C, H, N.

[2-[2-(3,3-Diphenylpropyl)-1*H*-imidazol-4-yl]ethyl][5-(pyridin-4-yl)pentyl]amine Dihydrogen Oxalate (65) was synthesized from **50**: ^{1}H NMR (CF_3COOD) δ 8.68 (d, $J = 6.0$ Hz, 2H, Pyr-2-H, Pyr-6-H), 7.96 (d, $J = 6.0$ Hz, 2H, Pyr-3-H, Pyr-5-H), 7.34−7.21 (m, 10H, 10 Ph-H), 7.18 (s, 1H, Im-5-H), 3.99 (t, $J = 7.7$ Hz, 1H, $CHCH_2$), 3.57 (t, $J = 7.3$ Hz, 2H, $Im_{(C4)}$-CH_2CH_2N), 3.32 (t, $J = 7.3$ Hz, 2H, $NCH_2(CH_2)_4$-Pyr), 3.27 (t, $J = 7.3$ Hz, 2H, $Im_{(C4)}$-CH_2), 3.06 (m, 4H, CH_2-$Im_{(C2)}$, CH_2-Pyr), 2.66 (q, $J = 7.7$ Hz, 2H, $CHCH_2$), 1.90 (m, 4H, $NCH_2CH_2(CH_2)_3$-Pyr, CH_2CH_2-Pyr), 1.61 (m, 2H, $N(CH_2)_2CH_2(CH_2)_2$-Pyr); $^+$FAB-MS (Xe, DMSO/*m*-NO_2-benzyl-OH) *m*/*z* 453 ($[M + H]^+$, 5), 307 (18), 289 (10). Anal. C, H, N.

Pharmacology. Data Handling and Pharmacological Parameters. Data are presented as mean ± SEM or SE or with 95% confidence limits (cl). Agonist potencies were expressed as pEC_{50} values (negative decadic logarithm of the molar concentration of the agonist producing 50% of the maximal response). Maximal responses were expressed as E_{max} values (percentage of the maximal response to a reference compound). Antagonist affinities were expressed as either an apparent pA_2 or a full pA_2 value. The apparent pA_2 value was calculated from the following equation: $pA_2 = -\log c(B) + \log(r - 1)$, where $c(B)$ is the molar concentration of antagonist and r the ratio of agonist EC_{50} measured in the presence and absence of antagonist.[53] The full pA_2 value was determined according to the method of Arunlakshana and Schild[54] using antagonist concentrations over 1−2 log units. Noncompetitive antagonists were characterized by estimation of a pD'_2 value according to the equation: $pD'_2 = -\log c(B) + \log(100/E_{max} - 1)$.[55] Partial agonist affinity was estimated according to the method of Marano and Kaumann.[56] The equilibrium dissociation constant K_P for the partial agonist/receptor complex was estimated by comparing equiactive molar concentrations of the full agonist *A* (histamine) in the absence and presence of the partial agonist *P* (**51**−**65**) in the same tissue according to the equation $c(A) = m \cdot c(A)^* + b$ with $m = 1/[1 + (1 - \epsilon_P/\epsilon_A) \cdot c(P)/K_P]$, where $c(A)$ is the molar concentration of *A* in the absence of *P*, $c(A)^*$ the molar concentration of *A* in the presence of *P*, *m* the slope of a weighted regression line of $c(A)$ vs $c(A)^*$, *b* the ordinate intercept, and $c(P)$ the molar concentration of *P*. ϵ_A and ϵ_P represent the intrinsic efficacies of *A* and *P*, respectively. Weights were calculated according to ref 56. If $\epsilon_P \ll \epsilon_A$, $pK_P = -\log K_P$ can be calculated from $\log[(1/m) - 1] = \log c(P) - \log K_P$. Where appropriate, differences between means were determined by Student's *t*-test, after checking the homogeneity of the variances; *P* values < 0.05 were considered to indicate a significant difference between the mean values being compared.

Histamine H_1-Receptor Assay on Guinea Pig Ileum. Guinea pigs of either sex (300−400 g) were stunned by a blow on the neck and exsanguinated. The ileum was removed and cut into segments of 1.5 cm length. The tissues were mounted isotonically (preload of 5 mN) in a jacketed 20-mL organ bath that was filled with Tyrode's solution of the following composition (in mM): NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.0, NaH_2PO_4 0.4, $NaHCO_3$ 11.9, and glucose 5.0. The solution additionally contained atropine (0.1 μM) to block cholinergic M receptors. The solution was aerated with 95% O_2−5% CO_2 and warmed to a constant temperature of 37 °C. During an equilibration period of 80 min, the tissues were stimulated three times with **1** (1 μM, then 10 μM) followed by washout. Two or three cumulative concentration−response curves (CRC) were determined on each tissue: a first CRC to **1** (0.01−30 μM), a second CRC to **51**−**65** in the absence or presence of mepyramine (2−100 nM, incubation time 10−15 min), and a third CRC to **1** (0.01−1000 μM) without wash 3−15 min after the second CRC in the absence of mepyramine.

Histamine H_1-Receptor Assay on Guinea Pig Aorta. Guinea pigs were sacrificed and the thoracic aorta was removed and cleared of connective tissue. Rings of 2−4 mm length were cut and rolled with a pair of tweezers to destroy the endothelium. The rings were horizontally suspended between two L-shaped stainless steel holders (diameter 0.3 mm) and mounted isometrically in a jacketed 20-mL organ bath filled with modified Krebs−Henseleit solution of the following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2$ 1.80, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25.0, sodium pyruvate 2.0, and glucose 10.0. The solution was aerated with 95% O_2−5% CO_2 and warmed to a constant temperature of 37 °C. The applied resting force was 10 mN. After a stabilization period of 100 min with regular washings every 30 min, the preparations were challenged twice (duration 20 and 45 min) with $PGF_{2\alpha}$ (10 μM) followed by washout. Before a cumulative CRC to **1** (0.01−300 μM) or a test agonist in the absence and presence of mepyramine (10−100 nM) was established, the preparations were precontracted with a threshold concentration of $PGF_{2\alpha}$ (usually 0.4−1.5 μM) corresponding to 10−20% of the contraction induced by the second $PGF_{2\alpha}$ (10 μM) challenge. Mepyramine was incubated for 1 h. Cimetidine (30 μM), corticosterone (30 μM), cocaine (30 μM), prazosin (0.3 μM), yohimbine (0.3 μM), and propranolol (0.1 μM) were present in the bath fluid 30 min before the second challenge with $PGF_{2\alpha}$ (10 μM) until the end of the experiment.

Histamine H_1-Receptor Assay on Rat Aorta. Male Wistar rats (250−350 g) were killed within an atmosphere of CO_2. When cleared of connective tissue the thoracic aorta was cut into rings of 2−3 mm length. The rings were set up as described in the previous paragraph (Krebs−Henseleit solution with 1.25 mM $CaCl_2$ in the absence of sodium pyruvate). The bath fluid additionally contained prazosin (0.1 μM). After an equilibration period of 120 min with regular washings every 30 min, the rings were contracted with a submaximal concentration of the thromboxane A_2-mimetic compound U46619 (15.8 nM). When the contractile response to U46619 had reached a plateau (usually after 45 min), the rings were relaxed by establishing a cumulative CRC to **1** (0.1−1000 μM) or a test agonist in the absence or presence of mepyramine (50 nM). Mepyramine was incubated for 75 min. When the maximal relaxant response to **1** or the test agonist had been attained, relaxation was accomplished by addition of carbachol (300−1000 μM).

Histamine H_2-Receptor Assay on Guinea Pig Right Atrium (Spontaneously Beating). Hearts were removed from guinea pigs used for studies on the ileum (see above). The right atrium was quickly dissected and set up isometrically in Krebs−Henseleit solution under a resting force of 5 mN in a jacketed organ bath of 32.5 °C as previously described.[57] The bath fluid additionally contained propranolol (0.3 μM) and mepyramine (1 μM). After 30 min of continuous washing and an additional equilibration period of 15 min, two concentration−frequency curves to **1** (0.1−30 μM) were established in the presence and absence of the compound under study. Agonist **51** was used in the second CRC in the absence or presence of cimetidine (30 μM, 30 min) instead of **1**.

Histamine H_3-Receptor Assay on Electrically Stimulated Guinea Pig Ileum Longitudinal Muscle with Adhering Myenteric Plexus. Strips of guinea pig ileal longitudinal muscle, with adhering myenteric plexus of 2 cm length and proximal to the ileocaecal junction, were prepared as previously described.[58] The strips were mounted isometrically under a tension of approximately 7.5 mN in a jacketed 20-mL organ bath of filled with modified Krebs−Henseleit solution of the following composition (mM): NaCl 117.9, KCl 5.6, $CaCl_2$ 2.5, $MgSO_4$ 1.2, NaH_2PO_4 1.3, $NaHCO_3$ 25.0, glucose 5.5, and choline chloride 0.001. The solution was aerated with 95% O_2−5% CO_2 and warmed to a constant temperature of 37 °C. After an equilibration period of 1 h with washings every 10 min, the preparations were stimulated for 30 min with rectangular pulses of 15 V and 0.5 ms at a frequency of 0.1 Hz. Viability of the muscle strips was monitored by addition of the histamine H_3-receptor agonist (*R*)-α-methylhistamine (100 nM). The agonist caused a relaxation of the twitch response of more than 50% up to 100%. After washout, reequilibration and 30 min field-stimulation, a cumulative concentration−response curve to (*R*)-α-methylhistamine (1−

1000 nM) was constructed. Subsequently, the preparations were washed intensively and reequilibrated for 20−30 min. During the incubation period of the antagonist under study, the strips were stimulated continuously for 30 min. Finally, a second concentration−response curve to (*R*)-α-methylhistamine was obtained. The rightward displacement of the curve to the histamine H_3-receptor agonist evoked by the antagonist under study was corrected with the mean shift monitored by daily control preparations in the absence of antagonist. New antagonists were tested at concentrations that did not block ileal cholinergic M_3 receptors. Mepyramine (1−3 μM) was present throughout the experiments to block H_1 receptors.

M_3 Cholinoceptor Assay on Guinea Pig Ileum and Other Functional Receptor Assays. Experiments were performed as previously described. Mepyramine (1−3 μM) was present throughout the experiments to block H_1 receptors. Functional experiments on selected subtypes of adrenergic and serotonergic receptors were carried out as reported.[59]

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