New Histamine H_3-Receptor Ligands of the Proxifan Series: Imoproxifan and Other Selective Antagonists with High Oral in Vivo Potency†

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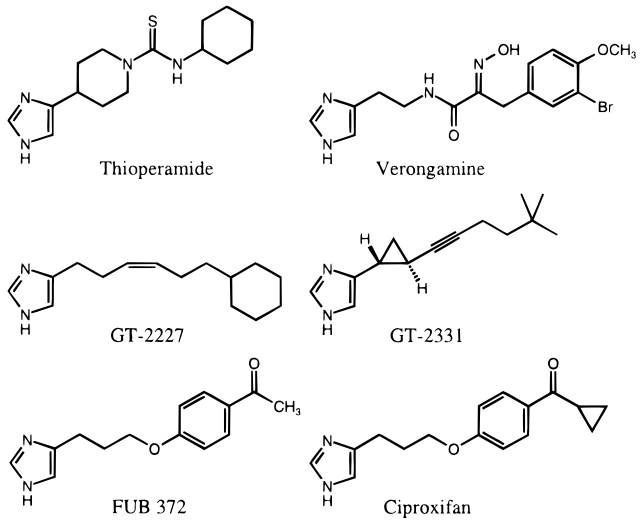
Histamine H_3-receptor antagonists of the proxifan series are described. The novel compounds possess a 4-(3-(phenoxy)propyl)-1*H*-imidazole structure and various functional groups, e.g., an oxime moiety, on the phenyl ring. Synthesis of the novel compounds and X-ray crystallography of one highly potent oxime derivative, named imoproxifan (4-(3-(1*H*-imidazol-4-yl)propyloxy)-phenylethanone oxime), are described. Most of the title compounds possess high antagonist potency in histamine H_3-receptor assays in vitro as well as in vivo in mouse CNS following po administration. Structure−activity relationships are discussed. Imoproxifan displays subnanomolar potency on a functional assay on synaptosomes of rat cerebral cortex (K_i = 0.26 nM). In vivo, imoproxifan increases the central N^{τ}-methylhistamine level with an ED_{50} of 0.034 mg/kg po. A receptor profile on several functional in vitro assays was determined for imoproxifan, demonstrating high selectivity toward the histamine H_3 receptor for this promising candidate for further development.

Introduction

Histamine mediates (patho)physiological processes by three receptors, termed histamine H_1, H_2, and H_3 receptors.[4] Whereas histamine H_1 and H_2 receptors are located postsynaptically, the histamine H_3 receptor is predominantly located presynaptically in the central nervous system (CNS) of various species including humans.[5,6] Histamine H_3 autoreceptors on histaminergic axon terminals modulate the synthesis and release of histamine by means of a negative feedback control.[7] The release of other neurotransmitters is also influenced by histamine H_3 heteroreceptors located on neurons thereof.[8] Several therapeutic applications have been proposed for histamine H_3-receptor antagonists,[9] which inhibit negative feedback loops at presynaptic and somatodendritic levels, thus increasing histamine release and histaminergic neuron activity, respectively. Most promising seems the use as cognition enhancers in diseases such as attention-deficit hyperactivity disorder (ADHD) and Alzheimer's disease. Thioperamide was the first potent, selective, and orally active histamine H_3-receptor antagonist.[10] Ciproxifan (Chart 1) has been described to possess high in vivo potency after oral administration to mice, to cause a quiet waking state in cats, and to increase attention in rats.[11] Ciproxifan as well as FUB 372 (Chart 1) belong to the proxifan class and are histamine H_3-receptor antagonists of high potency.[12]

Chart 1



Verongamine (Chart 1), a natural product from the marine sponge *Verongula gigantea*, displaying moderate affinity to histamine H_3 receptors (pK_i = 6.7),[13] has been used as a template for the development of histamine H_3-receptor antagonists, such as GT-2227 and GT-2331.[14] As illustrated in Chart 1, verongamine possesses an oxime moiety. In the present study, compounds derived from FUB 372 have been investigated for histamine H_3-receptor antagonist potency substituted with various functional groups, e.g., oxime, on the phenyl ring of the 4-(3-(phenoxy)propyl)-1*H*-imidazole

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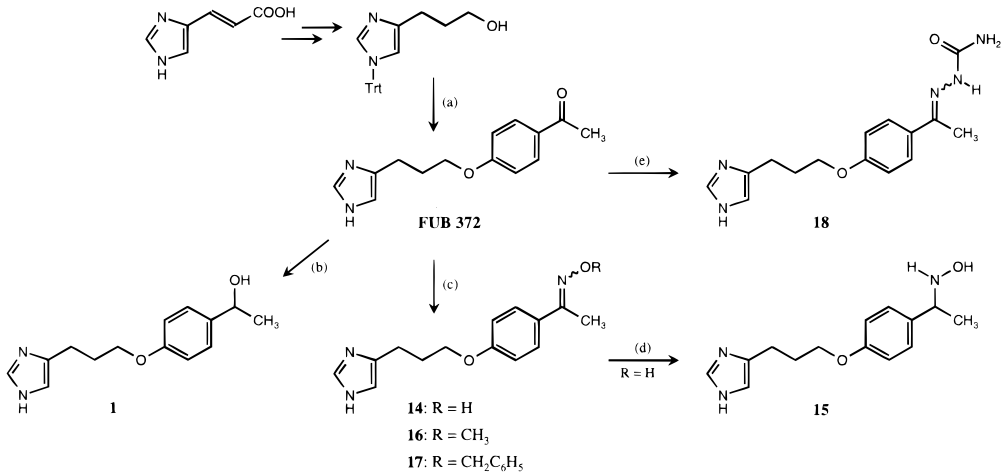
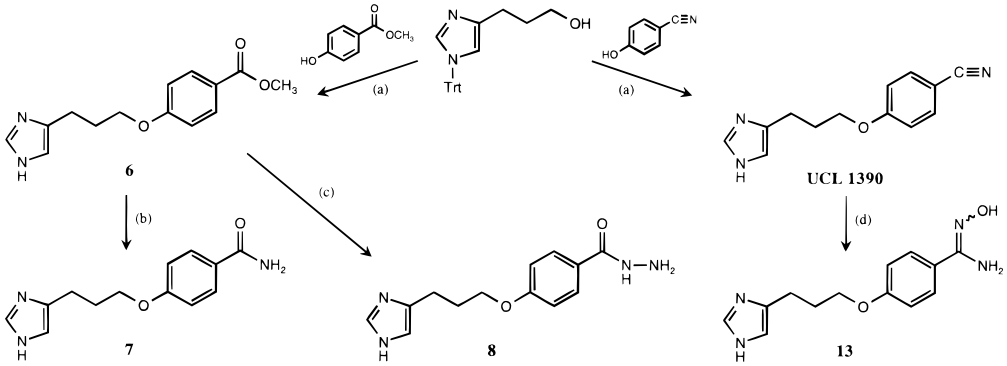
Scheme 1. Synthesis of Derivatives of FUB 372 (**1** and **14**−**18**)[a]



[a]Trt, trityl. Reagents: (a) (i) 4-hydroxyacetophenone, Ph_3P, DEAD, THF, ambient temperature, 3 days, (ii) 2 N HCl, THF, reflux, 90 min; (b) $LiAlH_4$, THF, reflux, 2 h; (c) $NH_2OR{\cdot}HCl$, Na_2CO_3, EtOH, reflux, 4 h; (d) $NaBH_3CN$, THF, ambient temperature, 10 min; (e) $NH_2CONHNH_2{\cdot}HCl$, NaOAc, EtOH, reflux, 4 h.

Scheme 2. Synthesis of Phenoxycarbonyl Derivatives **6**−**8** and **13**[a]



[a] Trt, trityl. Reagents: (a) (i) Ph_3P, DEAD, THF, ambient temperature, 3 days, (ii) 2 N HCl, THF, reflux, 90 min; (b) NH_3, MeOH, 100 °C/20 bar, 5 days; (c) $NH_2NH_2{\cdot}H_2O$, 120 °C, 2 h; (d) $NH_2OH{\cdot}HCl$, Na_2CO_3, EtOH, reflux, 24 h.

moiety. An X-ray crystallographic structure was determined for one compound, imoproxifan (**14**), which possesses high antagonist potency in test models of the histamine H_3 receptor in vitro as well as in vivo, to elucidate the conformation of the oxime moiety. Additionally, selectivity toward histamine H_3 receptors was determined for selected compounds.

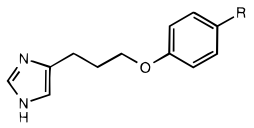
Chemistry

3-(1-(Triphenylmethyl)-1*H*-imidazol-4-yl)propanol, the key intermediate for all the compounds, was synthesized from urocanic acid in four steps as described previously.[15]

All title compounds or precursors thereof, with the exception of **9**, were synthesized by a Mitsunobu type ether formation[16] from 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[15] and the appropriate phenol, followed by deprotection of the imidazole ring (cf. Schemes 1 and 2; Table 1). FUB 372, which is an intermediate in the synthesis of **1** and **14**−**18**, was synthesized from 4-hydroxyacetophenone and 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol (Scheme 1).[12] On reduction of the ketone with $LiAlH_4$ under standard conditions, the secondary alcohol **1** was formed. Compound **2** was prepared analogously from the corresponding isopropyl phenyl ketone.[12] Compound **3** was prepared from ciproxifan,[12] which was reduced catalytically in pyrrolidine by simultaneous cleavage of the cyclopropyl ring to the corresponding secondary *n*-butyl alcohol derivative. The phenol precursor of **4** was prepared as described before.[17] Oximes **14**, **16**, and **17** are also derived from FUB 372 and were synthesized by reaction with the corresponding (substituted) hydroxylamine hydrochloride and Na_2CO_3 in EtOH (Scheme 1). Oximes **11**, **12**, and **19**−**30** were prepared analogously. With increasing steric hindrance of the ketone moiety (**20**−**24**, **26**−**30**), the molar excess of hydroxylamine hydrochloride and Na_2CO_3 as well as the reaction time were increased in order to maintain high yields. Compound **25** was prepared under mild reaction conditions with hydroxylamine hydrochloride in pyridine. Ketone precursors of the oximes have recently been described by Stark et al.[12] Reduction of the oxime moiety of **14** under mild reaction conditions ($NaBH_3CN$, pH 3−4)[18] afforded the corresponding hydroxylamine **15** (Scheme 1). Semicarbazone **18** was synthesized by reaction of FUB 372 with semicarbazide hydrochloride and sodium acetate in EtOH (Scheme 1).

Benzamide **7** and benzhydrazide **8** were prepared from the methyl benzoate **6** using standard procedures (Scheme 2). *N*-Hydroxybenzamidine **13** was synthesized from the corresponding benzonitrile (UCL 1390[19]) by reaction with hydroxylamine hydrochloride and Na_2CO_3 in EtOH (Scheme 2). *N*-Pyrrolidino amide **9** was pre-

Table 1. Structures, Physical Data, and Pharmacological Screening Results of *Para*-Substituted Proxifans for Histamine H_3-Receptor Antagonist Potency in Vitro and in Vivo in Rodents



no.	R	formula	M_r	yield (%)	mp[a] (°C)	K_i (nM)[b] ± SEM	ED_{50} (mg/kg)[c] ± SEM
1	$CH(OH)CH_3$	$C_{14}H_{18}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	366.9	55	95	5.8 ± 0.5	0.19 ± 0.06
2	$CH(OH)CH(CH_3)_2$	$C_{16}H_{22}N_2O_2 \cdot C_4H_4O_4$	390.4	85	139	29 ± 5	6.1 ± 3.8
3	$CH(OH)CH_2CH_2CH_3$	$C_{16}H_{22}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	399.5	50	97	5.1 ± 1.2	0.26 ± 0.07
4	$SO_2N(CH_3)_2$	$C_{14}H_{19}N_3O_3S \cdot 0.85C_2H_2O_4$	385.9	50	179[d]	77 ± 31	4.1 ± 1.6
5	NO_2	$C_{12}H_{13}N_3O_3 \cdot 0.8C_2H_2O_4$	319.3	20	198[e]	5.6 ± 1.2	~10
6	$COOCH_3$	$C_{14}H_{16}N_2O_3 \cdot 0.25H_2O$	264.8	50	140	2.8 ± 0.7	4.1 ± 1.9
7	$CONH_2$	$C_{13}H_{15}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	365.9	60	154	5.4 ± 1.6	>10
8	$CONHNH_2$	$C_{13}H_{16}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	385.4	85	143	1.5 ± 0.3	12 ± 5
9	CO-pyrrolidino	$C_{17}H_{21}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	424.5	35	130	31 ± 6	21 ± 7
10	CH_2CN	$C_{14}H_{15}N_3O \cdot 0.5H_2O$	250.3	35	126[f]	55 ± 12	3.4 ± 0.9
11	C(NOH)H	$C_{13}H_{15}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	370.4	85	154	0.44 ± 0.15	0.07 ± 0.02
12	$C(NOCH_3)H$	$C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	379.9	90	131	13 ± 3	0.18 ± 0.05
13	$C(NOH)NH_2$	$C_{13}H_{16}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	385.4	70	147	0.46 ± 0.17	>10
14	$C(NOH)CH_3$	$C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	384.4	85	145	0.26 ± 0.03	0.034 ± 0.009
15	$CH(NHOH)CH_3$	$C_{14}H_{19}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$	450.4	85	146	0.93 ± 0.08	0.88 ± 0.31
16	$C(NOCH_3)CH_3$	$C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4$	389.4	90	120	25 ± 5	0.097 ± 0.030
17	$C(NOCH_2C_6H_5)CH_3$	$C_{21}H_{23}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	470.0	80	137	24 ± 5	1.1 ± 0.4
18	$C(NNHCONH_2)CH_3$	$C_{15}H_{19}N_5O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	426.5	90	157	8.3 ± 0.7	0.27 ± 0.05
19	$C(NOH)CH_2CH_3$	$C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	398.4	80	114	2.2 ± 0.6	0.30 ± 0.12
20	$C(NOH)CH_2CH_2CH_3$	$C_{16}H_{21}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	408.0	80	129	4.5 ± 0.9	0.68 ± 0.28
21	$C(NOH)CH_2CH_2CH_2CH_3$	$C_{17}H_{23}N_3O_2 \cdot 0.25H_2O$	305.9	80	125	4.9 ± 2.0	0.51 ± 0.22
22	$C(NOH)CH_2CH_2CH_2CH_2CH_3$	$C_{18}H_{25}N_3O_2 \cdot 0.5H_2O$	324.4	80	138	12 ± 2	0.65 ± 0.24
23	C(NOH)-cyclopropyl	$C_{16}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	405.9	80	139	4.4 ± 1.4	0.21 ± 0.05
24	$C(NOH)CH_2C(CH_3)_3$	$C_{18}H_{25}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	436.0	84	133	260 ± 100	>10
25	$C(NOH)CH_2CH_2CH_2COOH$	$C_{17}H_{21}N_3O_4 \cdot 0.5H_2O$	340.4	85	170	~300	>10
ciproxifan	(R = CO-cyclopropyl)[g]					0.49 ± 0.09	0.14 ± 0.03
FUB 372	($R = COCH_3$)[g]					0.8 ± 0.16	0.24 ± 0.06
thioperamide[h]						4 ± 1	1.0 ± 0.5

[a] Crystallized from EtOH/Et_2O. [b] Functional H_3-receptor assay on synaptosomes of rat cerebral cortex.[26] [c] Central H_3-receptor screening after po administration to mice.[26] [d] Crystallized from 2-PrOH/Et_2O. [e] Formed in Et_2O. [f] Free base crystallized while drying in vacuo. [g] Ref 12. [h] Ref 10.

pared from 4-methoxybenzoyl chloride and pyrrolidine by a modified Einhorn reaction[20] and subsequent demethylation of the methoxyphenyl ether under mild reaction conditions with boron tribromide.[21] 1-(4-Hydroxybenzoyl)pyrrolidine reacted in low yields (5%) only in a standard Mitsunobu type ether formation; therefore, a modified Williamson synthesis[22] was used for the formation of **9**. 4-(3-Chloropropyl)-1-(triphenylmethyl)-1*H*-imidazole[23] was used as electrophilic reaction partner for classical Williamson ether formation resulting in moderate yields (35%) of **9**.

Structure Elucidation of Imoproxifan (14). Oxime **14** was chosen for further investigation because of its high potency in histamine H_3-receptor assays in vitro as well as in vivo. In this regard, the conformation of the oxime group was of special interest. *E*/*Z*-Configuration of oximes can be investigated by various chemical and physical methods. 4-Methoxyacetophenone was transformed to the corresponding oxime,[24] as a model compound, under the same reaction conditions as described for the synthesis of **14**. Chemical shifts of ^1H NMR spectra for the oxime hydroxyl function, phenyl and methyl protons, which are subject to shielding by the oxime hydroxyl group, were nearly identical for 4-methoxyacetophenone oxime indicating that the same isomer was present in **14** (results not shown). To assign *E*/*Z*-configuration for the oxime moiety, 4-methoxyacetophenone oxime was subjected to Beckmann rearrangement under standard conditions using PCl_5 in diethyl ether.[24] Only one product could be isolated, which proved to be *N*-(4-methoxyphenyl)acetamide by determination of ^1H NMR and MS spectra. These results indicated that the model oxime, 4-methoxyacetophenone oxime, was present in its *E*-configuration and, by analogy, so was **14**.

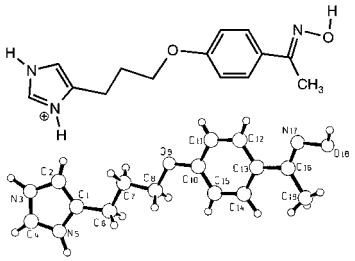
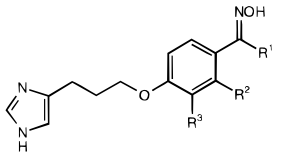


Figure 1. X-ray structure of protonated imoproxifan (14) in the crystal, generated with SCHAKAL.[25]

Since a rearrangement under the reaction conditions could not be totally excluded, X-ray crystallography was used to elucidate the question of *E*/*Z*-isomerism for the oxime moiety. The molecular structure of **14** as obtained from X-ray analysis is displayed in Figure 1 (SCHAKAL drawing[25]) together with the numbering scheme. The double bond character of the C(16)═N(17) bond in the oxime group was clearly confirmed by its length of 1.289(5) Å. It can also be seen that the group has an *E*-conformation, indicated, for example, by torsion angle C(13)−C(16)═N(17)−O(18) = −179.6(4)°. The oxime group is coplanar with the adjacent phenyl ring, and

Table 2. Structures, Physical Data, and Pharmacological Screening Results of Oxime Compounds for Histamine H_3-Receptor Antagonist Potency in Vitro and in Vivo in Rodents



no.	R^1	R^2	R^3	formula	M_r	yield (%)	mp[a] (°C)	K_i (nM)[b] ± SEM	ED_{50} (mg/kg)[c] ± SEM
26	H	OCH_3	H	$C_{14}H_{17}N_3O_3 \cdot C_4H_4O_4 \cdot 0.25H_2O$	395.9	80	137	nd[d]	12 ± 2
27	CH_3	OCH_3	H	$C_{15}H_{19}N_3O_3 \cdot C_4H_4O_4 \cdot 0.25H_2O$	409.9	80	129	371 ± 115	nc[e]
28	CH_3	CH_3	H	$C_{15}H_{19}N_3O_2$	273.3	80	177	1.4 ± 0.6	0.19 ± 0.09
29	CH_3	H	CH_3	$C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4$	389.4	80	182	1.5 ± 0.3	0.27 ± 0.05
30	CH_3	F	H	$C_{14}H_{16}FN_3O_2 \cdot C_4H_4O_4$	393.4	90	129	0.30 ± 0.08	0.032 ± 0.007

[a] Crystallized from EtOH/Et_2O. [b] Functional H_3-receptor assay on synaptosomes of rat cerebral cortex.[26] [c] Central H_3-receptor screening after po administration to mice.[26] [d] nd = not determined. [e] nc = not calculable.

the torsion along the bond C(13)−C(16) is very close to zero, C(12)−C(13)−C(16)═N(17) = 0.4(6)°. The linear chain connecting the phenyl and the terminal imidazole ring is in an *all-trans* arrangement, and the torsion angles along C(6)−C(7), C(7)−C(8), and C(8)−O(9) differ at most by 5° from 0° or 180°. All N−H and O−H groups of **14**, maleic acid, and methanol act as donors of hydrogen bonds, generating an extended network of four intermolecular and one intramolecular (within the maleic acid) hydrogen bonds in the crystal lattice (for hydrogen bonding, see Supporting Information).

Pharmacological Results and Discussion

Functional in Vitro Assay on Synaptosomes of Rat Cerebral Cortex. Histamine H_3-receptor antagonist potency was determined on a [^{3}H]histamine release test on synaptosomes of rat cerebral cortex.[26] All compounds investigated displayed nanomolar (**1**−**10**, **12**, **16**−**25**, **27**−**29**) or subnanomolar (**11**, **13**−**15**, **30**) potency in this functional test model (Tables 1 and 2). Moderate activity was observed for compounds with bulky groups in the *para*-position of the phenoxy moiety (**2**, **4**, **9**, **24**). Compounds with an alcohol functionality (**1**−**3**) showed high in vitro potency as long as the alkyl chain was not branched (**1**, **3**), and steric hindrance induced by an isopropyl moiety noticeably decreased antagonist potency (**1**, **3** → **2**). Benzoic acid derivatives **6**−**9** showed a similar activity pattern. Methyl benzoate **6**, benzamide **7**, and benzoic acid hydrazide **8** showed high potency, whereas the 1-benzoylpyrrolidine **9** displayed reduced H_3-receptor antagonist potency.

In most cases, oxime derivatives displayed different in vitro potency relative to the corresponding carbonyl derivatives (e.g., **7** → **13**, FUB 372 → **14**, ciproxifan → **23**) (cf. Table 1). Oxygen substitution of oximes derived from **11** and **14** with methyl (**12**, **16**) or benzyl (**17**) groups led to decreased in vitro potency. It is apparent that the hydroxy function of the oxime is important for an increased potency at the histamine H_3 receptor for compounds derived from FUB 372. This might be due to the possibility of additional hydrogen bonds to the receptor protein. Exchanging the oxime moiety with other hydrophilic groups, such as *N*-hydroxyamine (**15**) and semicarbazone (**18**), led to a decrease in in vitro potency (**14** (K_i = 0.26 nM) → **15** (K_i = 0.93 nM) → **18** (K_i = 8.3 nM)), but not to such an extent as *O*-alkylation of the oxime (**14** (K_i = 0.26 nM) → **16** (K_i = 25 nM), **17** (K_i = 24 nM)). Nevertheless, most of these compounds still maintain low-nanomolar affinity. Increasing the chain length of the alkyl chain of oximes **14** and **19**−**22** decreased potency, similar to the corresponding ketones,[12] with **14** being the most potent (K_i = 0.26 nM). Analogues of **14** with methyl, methoxy, or fluoro substitution of the phenyl ring (**27**−**30**) were also investigated (Table 2). Methyl substitution in *ortho*- or *meta*-positions in relation to the oxime moiety (**28**, **29**) led to a decrease in functional in vitro potency compared to **14**, but antagonist activity still remained in the low-nanomolar concentration range. The *ortho*-methoxy derivative **27** showed a dramatic decrease in histamine H_3-receptor antagonist potency. The only compound that was as effective as **14** was the *ortho*-fluoro-substituted derivative **30**. Histamine H_3-receptor potency in this series seems to be more influenced by steric demands than by electronic properties of the aromatic substituents.

In Vivo Screening in Mouse CNS. The novel compounds were also screened for their ability to increase N^τ-methylhistamine levels in mouse brain cortex after po administration as an index of increased histaminergic neuron activity.[26] Ciproxifan is an example of rational drug design and development leading to a compound highly potent in vivo with an ED_{50} value far below 1 mg/kg po, demonstrating much higher antagonist activity than was reached by the standard antagonist thioperamide in vivo as well as in vitro (Table 1).[11,12] The development of 4-phenoxy-substituted structures described here led to some compounds possessing even higher antagonist in vivo activity than ciproxifan. Only a few of these compounds showed low potency in modulating CNS N^τ-methylhistamine levels with an ED_{50} above 10 mg/kg po (**7**−**9**, **13**, **24**−**26**). As some of these compounds showed high in vitro H_3-receptor antagonist potency, but possess hydrophilic or labile functional groups (**7**, **8**, **13**), the low in vivo activity might be caused by pharmacokinetic parameters. Some compounds with various functional groups in the *para*-position of the phenoxy moiety, especially compounds with bulky groups (**2**, **17**) or electronegative substituents (**4**-**6**, **10**), show only moderate potency in the in vivo test system. Among the oximes, the increase in N^τ-methylhistamine level has in some cases been observed at extremely low doses, e.g., **11**, **14**, **16**, and **30** ($ED_{50} \leq$ 0.1 mg/kg po). Since it has extraordinarily high potency, compound **14** has been selected for further studies and for convenience is named imoproxifan. Some compounds

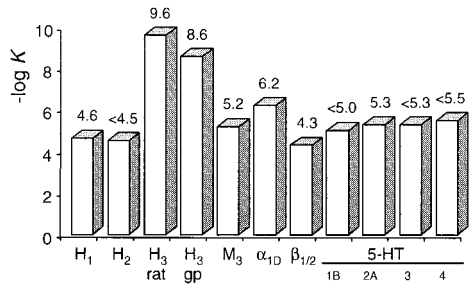


Figure 2. Functional receptor profile of imoproxifan (**14**): gp, histamine H_3-receptor test model on guinea pig ileum;[31,32] rat, determination of H_3-receptor antagonist potency on rat synaptosomes.[26]

with moderate in vitro antagonist potency showed comparable high activity in the in vivo test system, when compared to the in vitro/in vivo potency relationship of thioperamide, FUB 372, or ciproxifan (cf. Table 1). For example, **1**, **3**, **12**, **16**, **18**, **19**, **23**, **28**, and **29** were (almost) equipotent to ciproxifan or FUB 372 in vivo but far less active on the [^{3}H]histamine release model on rat synaptosomes in vitro. This might be due to different pharmacokinetic properties such as increased penetration of the blood−brain barrier due to high lipophilicity; nevertheless, it cannot be excluded that this was caused by unknown additional effects modulating the N^τ-methylhistamine level. In vivo potency was influenced noticeably by modulation of the alkyl chain length of oximes (**14**, **19**−**22**). Imoproxifan (**14**) is approximately 8−20 times more active than its higher homologues (**19**−**22**). Exchange of the methyl group by longer alkyl chains led to a dramatic reduction in in vivo and in vitro potency, but in vivo differences among ethyl to pentyl (**19**−**22**) substituted oximes were rather low (ED_{50} values from 0.3−0.65 mg/kg po) and in contrast to larger changes in potency observed in vitro (K_i values from 2.2−12 nM).

Screening of Selected Compounds at Other Functional Receptor Models. Imoproxifan (**14**) was selected for determining a receptor profile, including various functional serotoninergic[27−29] (5-HT_{1B}, 5-HT_{2A}, 5-HT_3, 5-HT_4), adrenergic[28,30] (α_{1D}, $\beta_{1/2}$), histaminergic[26,30−32] (H_3, H_2, H_1), and muscarinic[28] (M_3) receptor models (Figure 2). The high selectivity of imoproxifan (**14**) for the histamine H_3 receptor is clearly demonstrated in Figure 2. Only for adrenergic α_{1D} receptors moderate affinity was observed. But, the affinity for this receptor subtype was still 250 times lower than for histamine H_3 receptors. With regard to histamine H_1 and H_2 receptors, affinity was even 10 000 times lower.

For selected compounds, screening of histamine H_1- and H_2-receptor activity as well as histamine H_3-receptor potency was conducted in an additional test model on the guinea pig ileum (Table 3). Investigated compounds predominantly showed pA_2 values of below 5 for H_1 and H_2 receptors, with only one exception. Methyl ester **6** displayed moderate affinity for the histamine H_1 receptor, showing a pA_2 value of 6.8.

Another interesting effect was observed for some compounds having high potency on the histamine H_3-receptor model on rat synaptosomes but more than 1 log unit decreased antagonist affinity on the guinea pig ileum histamine H_3-receptor assay (Table 3: **1**, **7**−**9**, **11**, **13**, **14**, **18**, **28**, **30**). For amide **7**, hydrazide **8**, and amide oxime **13,** this discrepancy was very marked as the potency differed by 2.5 log units. These compounds have in common a second hydrophilic moiety, beside the carbonyl or oxime function, in this part of the molecule. This second hydrophilic moiety might disturb receptor−ligand interaction in the histamine H_3-receptor model on guinea pig ileum, which has been proposed to represent a histamine H_3-receptor subtype different from that in the CNS of rodents.[33−35] Chemical instability such as possible hydrolysis of the amide or hydrazide function under the assay conditions does not seem to be a reasonable explanation since the methyl ester **6**, which should be hydrolyzed more easily, shows high potency in this test system. The observed selectivity of **7**, **8**, and **13** for the central histamine H_3-receptor test model on rat synaptosomes suggests that these compounds might be useful for further investigation of the possible existence of distinct subtypes and species differences of histamine H_3 receptors.

Table 3. Activity of Selected Compounds at Histamine Receptor Subtypes

	H_3		H_2	H_1		H_3		H_2	H_1
no.	pK_i[a]	pA_2[b]	pA_2[c]	pA_2[d]	no.	pK_i[a]	pA_2[b]	pA_2[c]	pA_2[d]
1	8.2	7.0	<4.0[e]	4.3	**16**	7.6	7.2	4.8	4.9[e]
2	7.5	6.7	nd[f]	nd	**18**	8.1	6.9	3.8[e]	3.6
6	8.6	7.9	4.3[e]	6.8	**19**	8.7	8.2	4.5[e]	4.6[e]
7	8.3	5.8	<4.3	3.8	**20**	8.3	7.9	4.7[e]	5.0[e]
8	8.8	6.2	<4.3	4.1	**21**	8.3	7.7	4.7[e]	nd
9	7.5	6.6	<4.3	4.9	**22**	7.9	8.0	5.0[e]	4.9[e]
11	9.4	8.0	3.8[e]	3.9[e]	**23**	8.4	7.6	4.7[e]	5.0[e]
12	7.9	7.3	4.7[e]	<4.5	**27**	6.4	6.2	<4.3	<5.0
13	9.3	6.8	4.0[e]	<4.0	**28**	8.9	7.5	4.4[e]	<4.1
14	9.6	8.6	<4.5[e]	4.6	**29**	8.8	8.3	4.7[e]	4.8
15	9.0	8.3	3.9[e]	<4.0	**30**	9.5	8.4	nd	nd

[a] Functional H_3-receptor assay on synaptosomes of rat cerebral cortex.[26] [b] Functional H_3-receptor assay on guinea pig ileum (SEM ≤ 0.2).[31,32] [c] Functional H_2-receptor assay on guinea pig atrium (SEM ≤ 0.2).[30] [d] Functional H_1-receptor assay on guinea pig ileum (SEM ≤ 0.2).[30] [e] pD'_2 value. [f] nd = not determined.

Conclusions

Further development of compounds belonging to the proxifan class possessing a *para*-substituted 4-(3-(phenoxy)propyl)-1*H*-imidazole as the general structural element has led to highly potent histamine H_3-receptor antagonists. The introduction of an oxime moiety proved to be very successful, as antagonist potency in vitro reached the subnanomolar concentration range in the [^{3}H]histamine release assay on synaptosomes of rat cerebral cortex. Extraordinarily high antagonist potency was also observed for some compounds under in vivo conditions on an index of histaminergic neuron activity in mouse brain cortex after po administration. Some compounds in this series displayed ED_{50} values below 0.1 mg/kg (**11**, **14**, **16**, **30**) for increasing N^τ-methylhistamine level in brain. The highly potent phenylethanone oxime **14**, imoproxifan, was selected for X-ray analysis in order to elucidate the conformation of the oxime moiety, which was determined to be exclusively in the *E*-configuration. Imoproxifan (**14**) also proved to be a selective histamine H_3-receptor antagonist, when examined in a functional receptor profile for other neurotransmitter receptors. Imoproxifan (**14**) might thus be a potential candidate for further development for the treatment of, e.g., ADHD or Alzheimer's disease.

Experimental Section

Chemistry. General Procedures. Melting points were determined on an Electrothermal IA 9000 digital or Büchi 512 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal Me_4Si as reference. ^{1}H NMR data are reported in the following order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet); approximate coupling constants in Hertz (Hz); number of protons, *, exchangeable by D_2O; Im, imidazole; Mal, maleic acid. NH signals of the imidazole were subject to rapid exchange due to traces of water in the solvent and are not indicated. Elemental analyses (C, H, N) were measured on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and were within ±0.4% of theoretical values for all compounds. Preparative, centrifugally accelerated, rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4-mm layers of silica gel 60 F_{254} containing gypsum (Merck). Column chromatography was carried out using silica gel 63−200 μm (Macherey, Nagel & Co.). Thin-layer chromatography (TLC) was performed on silica gel F_{254} plates (Merck); the spots were visualized with fast blue salt B or by UV absorption at 254 nm. Spectral data and elemental analyses are shown only for parent compounds which were obtained by different reactions or methods and additionally the most potent compounds (**1**, **3**, **5**−**9**, **11**, **13**−**16**, **18**, **25**, **30**).

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)ethanol (1). FUB 372[12] (free base, 2 mmol, 0.49 g) was dissolved in 20 mL of freshly distilled THF and slowly added to a suspension of $LiAlH_4$ (1 mmol, 0.04 g) in 20 mL of freshly distilled THF. The reaction mixture was heated to reflux for 2 h. After cooling to ambient temperature, 5 mL of 2 N NaOH was added dropwise. The organic phase was separated, washed with brine, dried (Na_2SO_4), and purified by column chromatography (eluent: CH_2Cl_2/MeOH (96/4), ammonia atmosphere). The colorless oil was crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.42 (s, 1H, Im-5-H), 7.23 (d, J = 8.2 Hz, 2H, Ph-2,6-H), 6.84 (d, J = 8.0 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 5.01 (s, 1H, OH*), 4.64 (m, 1H, CH), 3.98 (t, J = 6.2 Hz, 2H, CH_2O), 2.77 (t, J = 7.9 Hz, 2H, Im-CH_2), 2.05 (m, 2H, Im-CH_2CH_2), 1.28 (d, J = 6.5 Hz, 3H, CH_3). Anal. ($C_{14}H_{18}N_2O_2$·$C_4H_4O_4$·0.25H_2O) C, H, N.

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)butanol (3). Ciproxifan[12] (free base, 1.3 mmol, 0.35 g) was dissolved in 20 mL of pyrrolidine. After addition of Pd on activated carbon (10%) (0.1 g), the mixture was hydrogenated for 6 d at 1 bar. The solvent was removed under reduced pressure and the residue purified by rotatory chromatography (eluent: CH_2Cl_2/MeOH (90/10), ammonia atmosphere). The oil obtained was crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.42 (s, 1H, Im-5-H), 7.20 (d, J = 8.6 Hz, 2H, Ph-2,6-H), 6.84 (d, J = 8.5 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.95 (s, 1H, OH*), 4.44 (m, 1H, CH), 3.98 (t, J = 6.2 Hz, 2H, CH_2O), 2.79 (t, J = 7.6 Hz, 2H, Im-CH_2), 2.05 (m, 2H, Im-CH_2CH_2), 1.62−1.16 (m, 4H, CH_2CH_2-CH_3), 0.85 (t, J = 7.3 Hz, 3H, CH_3). Anal. ($C_{16}H_{22}N_2O_2$·$C_4H_4O_4$·0.5H_2O) C, H, N.

General Procedure for Mitsunobu Type Ether Formation. Method A. Triphenylphosphine (6 mmol, 1.57 g), 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[15] (5 mmol, 1.84 g), and 6 mmol of the corresponding phenol derivative were dissolved in 15 mL of freshly distilled THF under Ar atmosphere and cooled in an ice bath. Diethyl azodicarboxylate (DEAD) (6 mmol, 0.95 mL) was added dropwise. The mixture was stirred for 16−72 h at ambient temperature. Then, the solvent was removed under reduced pressure and the crude reaction product purified by column chromatography (eluent: EtOAc). Pure fractions were detritylated by heating to reflux in 20 mL of 2 N HCl and 40 mL of THF for 90 min. THF was evaporated under reduced pressure and the aqueous residue washed with Et_2O. The aqueous phase was basified with K_2CO_3 and extracted with Et_2O. The organic layer was separated and the solvent evaporated. The crude product was subjected to column chromatography (eluent: CH_2Cl_2/MeOH (90/10)). Pure fractions were crystallized as free base from EtOH, as hydrogen maleate, or as hydrogen oxalate from EtOH/Et_2O. Compounds **1**−**8**, **10**−**23**, and **25**−**30** or precursors of them were prepared by this method. A detailed description is given only for compounds with high antagonist potency.

3-(1*H*-Imidazol-4-yl)propyl 4-Nitrophenyl Ether (5). Method A: ^{1}H NMR (D_2O) δ 8.56 (s, 1H, Im-2-H), 8.22 (d, J = 9.4 Hz, 2H, Ph-3,5-H), 7.23 (s, 1H, Im-5-H), 7.05 (d, J = 9.3 Hz, 2H, Ph-2,6-H), 4.24 (t, J = 6.0 Hz, 2H, CH_2O), 2.94 (t, J = 7.4 Hz, 2H, Im-CH_2), 2.20 (m, 2H, Im-CH_2CH_2). Anal. ($C_{12}H_{13}N_3O_3$·0.8$C_2H_2O_4$) C, H, N.

Methyl 4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzoate (6). Method A: ^{1}H NMR (Me_2SO-d_6) δ 7.87 (d, J = 8.0 Hz, 2H, Ph-2,6-H), 7.62 (s, 1H, Im-2-H), 6.99 (d, J = 7.9 Hz, 2H, Ph-3,5-H), 6.80 (s, 1H, Im-5-H), 4.05 (t, J = 6.0 Hz, 2H, CH_2O), 3.71 (s, 3H, OCH_3), 2.79 (t, J = 7.4 Hz, 2H, Im-CH_2), 2.05 (m, 2H, Im-CH_2CH_2). Anal. ($C_{14}H_{16}N_2O_3$·0.25H_2O) C, H, N.

4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzamide (7). Compound **6** (2 mmol, 0.5 g) was dissolved in 15 mL of dry MeOH. 40 mL of liquid ammonia was added at −78 °C and stirred in an autoclave at 100 °C/20 bar for 5 days. After evaporation of ammonia and solvent the crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)). Pure fractions were crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.83 (d, J = 8.7 Hz, 2H, Ph-2,6-H), 7.42 (s, 2H, NH_2*), 7.40 (s, 1H, Im-5-H), 6.95 (d, J = 8.7 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.07 (t, J = 6.1 Hz, 2H, CH_2O), 2.80 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2CH_2). Anal. ($C_{13}H_{15}N_3O_2$·$C_4H_4O_4$·0.25H_2O) C, H, N.

4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzoic Acid Hydrazide (8). Compound **6** (2 mmol, 0.5 g) was dissolved in 15 mL of hydrazine hydrate (99%) and heated to 120 °C for 2 h. After cooling to ambient temperature, the mixture was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)). Pure fractions were crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 9.56 (s, 1H, CONH*), 8.83 (s, 1H, Im-2-H), 7.79 (d, J = 8.6 Hz, 2H, Ph-2,6-H), 7.40 (s, 1H, Im-5-H), 6.96 (d, J = 8.7 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.27 (s, 2H, NH_2*), 4.06 (t, J = 6.1 Hz, 2H, CH_2O), 2.79 (t, J = 7.4 Hz, 2H, Im-CH_2), 2.07 (m, 2H, Im-CH_2CH_2). Anal. ($C_{13}H_{16}N_4O_2$·$C_4H_4O_4$·0.5H_2O) C, H, N.

1-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzoyl)pyrrolidine (9). 4-Methoxybenzoyl chloride (24 mmol, 4.20 g) and Et_3N (32 mL) were dissolved in 30 mL of THF. Pyrrolidine (24 mmol, 2 mL) dissolved in 5 mL of THF was added and the mixture refluxed for 1 h. After cooling to ambient temperature, it was filtered and the filtrate concentrated. The crude product was purified by column chromatography (eluent: CH_2Cl_2) to afford 1-(4-methoxybenzoyl)pyrrolidine[36] as an oil (yield: 75%): ^{1}H NMR (Me_2SO-d_6) δ 7.50 (d, J = 8.8 Hz, 2H, Ph-2,6-H), 6.96 (d, J = 8.7 Hz, 2H, Ph-3,5-H), 3.79 (s, 3H, OCH_3), 3.43 (m, 4H, pyrrolidine-2,5-H), 1.82 (m, 4H, pyrrolidine-3,4-H). 1-(4-Methoxybenzoyl)pyrrolidine (18 mmol, 3.68 g) was dissolved in 40 mL of dry CH_2Cl_2 and cooled to −80 °C under Ar atmosphere. BBr_3 (40 mL of a 1 M solution in CH_2Cl_2) (40 mmol, 10 g) was added slowly, maintaining the temperature below −60 °C. After complete addition of BBr_3, the mixture was stirred for 72 h at ambient temperature. The reaction was quenched after cooling to −80 °C by addition of dry MeOH (25 mL). The solvents were evaporated under reduced pressure, and the residue was taken up in water. On neutralization with K_2CO_3 the product crystallized and was recrystallized from EtOH to afford 1-(4-hydroxybenzoyl)pyrrolidine: yield 65%; mp 152 °C; ^{1}H NMR (Me_2SO-d_6) δ 9.82 (s, 1H, OH*), 7.39 (d, J = 8.1 Hz, 2H, Ph-2,6-H), 6.77 (d, J = 8.1 Hz, 2H, Ph-3,5-H), 3.44 (m, 4H, pyrrolidine-2,5-H), 1.81 (m, 4H, pyrrolidine-3,4-H). 1-(4-Hydroxybenzoyl)pyrrolidine (10 mmol, 1.91 g), Na_2CO_3 (15 mmol, 2.10 g), and tetrabutylammonium iodide (catalytic amount) were dissolved in 15 mL of dry DMF under Ar atmosphere and stirred for 1 h at ambient temperature.

4-(3-Chloropropyl)-1-(triphenylmethyl)-1*H*-imidazole[23] (10 mmol, 3.86 g) dissolved in 5 mL of dry DMF was added and the mixture heated to 75 °C for 3 days. The solvent was removed under reduced pressure and the product purified by column chromatography (eluent: EtOAc). Detritylation was achieved in 20 mL of 2 N HCl and 40 mL of THF by heating to reflux for 90 min. THF was evaporated under reduced pressure and the aqueous residue washed with Et_2O. The aqueous phase was basified with K_2CO_3 and extracted with Et_2O. The organic layer was separated and the solvent evaporated. The crude product was subjected to column chromatography (eluent: CH_2Cl_2/MeOH (90/10)). Pure fractions were crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.49 (d, J = 8.5 Hz, 2H, Ph-2,6-H), 7.42 (s, 1H, Im-5-H), 6.94 (d, J = 8.6 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.05 (t, J = 6.1 Hz, 2H, CH_2O), 3.43 (m, 4H, pyrrolidine-2,5-H), 2.80 (t, J = 7.6 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2CH_2), 1.84 (m, 4H, pyrrolidine-3,4-H). Anal. ($C_{17}H_{21}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

General Procedure for Oxime Formation. Method B. The corresponding free base of the aldehyde or ketone (2.5 mmol), 2−20 equiv of (substituted) hydroxylamine hydrochloride (5−50 mmol), and 2−20 equiv of Na_2CO_3 (5−50 mmol, 0.53−5.3 g) were dissolved in 20 mL of dry EtOH and heated to reflux for 4−18 h. After filtration of inorganic salts, the solvent was evaporated under reduced pressure. The product was purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)) and crystallized as free base from EtOH or as hydrogen maleate from EtOH/Et_2O. Compounds **11**, **12**, **14**, **16**, **17**, **19**−**24**, and **26**−**30** were prepared by this method.

4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzaldehyde Oxime (11). 4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzaldehyde[12] was treated with hydroxylamine hydrochloride (2 equiv) for 4 h as described in method B: ^{1}H NMR (Me_2SO-d_6) δ 10.96 (s, 1H, OH*), 8.86 (s, 1H, Im-2-H), 8.06 (s, 1H, CH), 7.94 (d, J = 8.7 Hz, 2H, Ph-2,6-H), 7.53 (s, 1H, Im-5-H), 6.94 (d, J = 8.5 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.04 (t, J = 6.0 Hz, 2H, CH_2O), 2.80 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2CH_2). Anal. ($C_{13}H_{15}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

***N*-Hydroxy-4-(3-(1*H*-imidazol-4-yl)propyloxy)benzamidine (13).** 4-(3-(1*H*-Imidazol-4-yl)propyloxy)benzonitrile[19] (1 mmol, 0.21 g), hydroxylamine hydrochloride (2 mmol, 0.14 g), and Na_2CO_3 (2 mmol, 0.21 g) were dissolved in 20 mL of EtOH and heated to reflux for 24 h. After filtration of inorganic salts, the solvent was evaporated under reduced pressure. The product was purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)) and crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 9.59 (s, 1H, OH*), 8.75 (s, 1H, Im-2-H), 7.60 (d, J = 8.6 Hz, 2H, Ph-2,6-H), 7.36 (s, 1H, Im-5-H), 6.92 (d, J = 8.7 Hz, 2H, Ph-3,5-H), 6.04 (br, 4H, Mal, NH_2*), 4.03 (t, J = 6.1 Hz, 2H, CH_2O), 2.78 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 2H, Im-CH_2CH_2). Anal. ($C_{13}H_{16}N_4O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenylethanone Oxime (14). FUB 372[12] was treated with hydroxylamine hydrochloride (2 equiv) for 4 h as described in method B: ^{1}H NMR (Me_2SO-d_6) δ 10.97 (s, 1H, OH*), 8.85 (s, 1H, Im-2-H), 7.57 (d, J = 8.7 Hz, 2H, Ph-2,6-H), 7.42 (s, 1H, Im-5-H), 6.91 (d, J = 8.9 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.03 (t, J = 6.2 Hz, 2H, CH_2O), 2.80 (t, J = 7.4 Hz, 2H, Im-CH_2), 2.10 (s, 3H, CH_3), 2.06 (m, 2H, Im-CH_2CH_2). Anal. ($C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

4-(3-(4-(1-(Hydroxyamino)ethyl)phenoxy)propyl)-1*H*-imidazole (15). Compound **14** (free base, 2 mmol, 0.52 g), methyl orange (pH indicator, 2 mg), and sodium cyanohydridoborate (6 mmol, 0.38 g) were dissolved in 20 mL of dry THF and stirred at ambient temperature for 5 min. After 5 min, a solution of 4 N HCl in dioxane was added dropwise in order to maintain the pH at 3−4. When a steady red color was obtained, the mixture was poured into 50 mL of water, basified with 1 N NaOH, and extracted with Et_2O. The organic layer was washed with water, dried (Na_2SO_4), purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)), and crystallized as hydrogen oxalate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 8.68 (s, 1H, Im-2-H), 7.36 (m, 3H, Im-5-H, Ph-2,6-H), 6.97 (m, 3H, OH*, Ph-3,5-H), 5.81 (s, 2H, NH_2*), 4.23 (m, 1H, CH), 4.06 (t, J = 6.1 Hz, 2H, CH_2O), 2.83 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.13 (m, 2H, Im-CH_2CH_2), 1.42 (d, J = 6.7 Hz, 3H, CH_3). Anal. ($C_{14}H_{19}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

***O*-Methyl (4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)-ethanone Oxime (16).** FUB 372[12] was treated with *O*-methylhydroxylamine hydrochloride (2 equiv) for 4 h as described in method B: ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.60 (d, J = 8.8 Hz, 2H, Ph-2,6-H), 7.42 (s, 1H, Im-5-H), 6.94 (d, J = 8.9 Hz, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.04 (t, J = 6.2 Hz, 2H, CH_2O), 3.88 (s, 3H, OCH_3), 2.80 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.14 (s, 3H, CH_3), 2.08 (m, 2H, Im-CH_2CH_2). Anal. ($C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4$) C, H, N.

(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)ethanone Semicarbazone (18). FUB 372[12] (2.5 mmol, 0.61 g), semicarbazide hydrochloride (5 mmol, 0.58 g), and NaOAc (5 mmol, 0.40 g) were dissolved in 20 mL of dry EtOH and heated to reflux for 4 h. The crude product was concentrated under reduced pressure, purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)), and crystallized as hydrogen maleate from EtOH/Et_2O: ^{1}H NMR (Me_2SO-d_6) δ 9.20 (s, 1H, CONH*), 8.86 (s, 1H, Im-2-H), 7.75 (d, J = 8.7 Hz, 2H, Ph-2,6-H), 7.42 (s, 1H, Im-5-H), 6.88 (d, J = 8.6 Hz, 2H, Ph-3,5-H), 6.43 (br, 2H, NH_2*), 6.04 (s, 2H, Mal), 4.03 (t, J = 6.1 Hz, 2H, CH_2O), 2.66 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.13 (s, 3H, CH_3), 2.07 (m, 2H, Im-CH_2CH_2). Anal. ($C_{15}H_{19}N_5O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

5-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)-5-(hydroxyimino)valeric Acid (25). 5-(4-(3-(1*H*-Imidazol-4-yl)propyloxy)phenyl)-5-oxovalerianic acid[12] (0.63 mmol, 0.20 g) and hydroxylamine hydrochloride (1.89 mmol, 0.13 g) were dissolved in 15 mL of dry pyridine and heated to reflux for 3 h. The solvent was removed under reduced pressure and the residue taken up in 10 mL of 2 N HCl. The pH was adjusted with K_2CO_3 to 5−6, then the mixture was stirred for 12 h at ambient temperature. The precipitate was filtered off and washed carefully with MeOH: ^{1}H NMR (Me_2SO-d_6) δ 10.98* (s, 1H, NOH*), 7.58 (d, J = 8.4 Hz, 2H, Ph-2,6-H), 7.52 (s, 1H, Im-2-H), 6.92 (d, J = 8.4 Hz, 2H, Ph-3,5-H), 6.77 (s, 1H, Im-5-H), 4.01 (t, J = 6.0 Hz, 2H, CH_2O), 2.68 (m, 4H, C(NOH)-CH_2, Im-CH_2), 2.26 (m, 2H, C(NOH)$CH_2CH_2CH_2$), 2.03 (m, 2H, Im-CH_2CH_2), 1.68 (m, 2H, C(NOH)CH_2CH_2). Anal. ($C_{17}H_{21}N_3O_4 \cdot 0.5H_2O$) C, H, N.

(2-Fluoro-4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl)ethanone Oxime (30). (2-Fluoro-4-(3-(1*H*-imidazol-4-yl)propyloxy)phenyl)ethanone[12] was treated with hydroxylamine hydrochloride (5 equiv) for 4 h as described in method B: ^{1}H NMR (Me_2SO-d_6) δ 11.22 (s, 1H, OH*), 8.87 (s, 1H, Im-2-H), 7.39 (m, 2H, Im-5-H, Ph-6-H), 6.79 (m, 2H, Ph-3,5-H), 6.04 (s, 2H, Mal), 4.05 (t, J = 6.2 Hz, 2H, CH_2O), 2.79 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.08 (m, 5H, CH_3, Im-CH_2CH_2). Anal. ($C_{14}H_{16}FN_3O_2 \cdot C_4H_4O_4$) C, H, N.

Single-Crystal X-ray Analysis of 14. The X-ray diffraction experiments were executed on a Siemens four-circle diffractometer (AED) equipped with a N_2 gas stream cooling device. Precise lattice parameters and three-dimensional intensity data were collected at a low temperature of 193 °K using Nb-filtered Mo Kα radiation (λ = 0.71068 Å). The intensity data were corrected for Lorentz and polarization effects but not for absorption. Phase determination was made with direct methods (program SHELXS 97[37]), and refinement was done with the corresponding least-squares program of the SHELXL 97[37] program system. All hydrogens were located from difference syntheses. After convergence R-values of R_1 = 5.1% and wR_2 = 13.4% (based on F^2) were obtained. No significant peaks or holes were seen in a final difference Fourier map.

In the course of structure determination and refinement, it turned out that the present modification of the title molecule crystallizes with one molecule of maleic acid and in addition also with one molecule of methanol in the asymmetric unit (obtained from different methanol/diethyl ether mixtures).

During the crystallization experiments a second, methanol-free, crystalline modification was found (space group mono-

clinic, $P2_1/c$; $a = 7.823(1)$, $b = 21.949(2)$, $c = 10.842(2)$ Å; $\beta = 94.03(1)°$, $Z = 4$). Only an incomplete data set could be measured for this modification; however, the structure could be solved, yielding a molecular structure with the same conformation at the oxime group as in the present modification.

Crystal Data of 14. Single crystals of **14**, molecular formula $C_{14}H_{18}N_3O_2 \cdot C_4H_3O_4 \cdot CH_3OH$ ($M_r = 407.42$), were grown from MeOH/Et_2O: space group monoclinic $I2/a$; unit cell $a = 18.638(2)$, $b = 5.615(4)$, $c = 38.435(4)$ Å; $\beta = 90.63(3)°$, $V = 4022.1$ Å^3, $Z = 8$; $\rho_x = 1.346$ g·cm^{-3}, μ(Mo Kα) = 1.04 cm^{-1}. [The nonstandard I-centered lattice was chosen to have the monoclinic angle very close to 90°. The transformation to the standard C-centered monoclinic space group $C2/c$ is easily obtained by the matrix (line by line) (101), (010), (−100)]. A single crystal with dimensions of 0.21 × 0.17 × 0.04 mm^3 was used to collect the intensity data of 3980 reflections ($2\theta \leq 50°$) by using the $\omega-2\theta$ scan technique. No significant intensity variations, monitored via three check reflections, were observed. Merging gave 3557 unique reflections ($R_{int} = 4.7\%$, $R_\sigma = 2.0\%$) of which 1262 reflections had $F_o < 4\sigma(F_o)$.

Pharmacology. General Methods. Histamine H_3-receptor assay on synaptosomes of rat cerebral cortex: Compounds were tested for their H_3-receptor antagonist activity in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from rat synaptosomes according to Garbarg et al.[26] A synaptosomal fraction from rat cerebral cortex prepared according to the method of Whittaker[38] was preincubated for 30 min with L-[^{3}H]histidine (0.4 μM) at 37 °C in a modified Krebs-Ringer solution. The synaptosomes were washed extensively, resuspended in fresh 2 mM K^+ Krebs-Ringer's medium, and incubated for 2 min with 2 or 30 mM K^+ (final concentration). Drugs and 1 μM of histamine were added 5 min before the depolarization stimulus. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels were determined after purification by liquid scintillation spectrometry.[26] K_i values were determined according to the Cheng−Prussoff equation.[39] The data presented are given as mean values with standard error of the mean (SEM) each for a minimum of three separate determinations.

Histamine H_3-receptor antagonist activity on guinea pig ileum: For selected compounds H_3-receptor activity was measured by concentration-dependent inhibition of electrically evoked twitches of isolated guinea pig ileal segments induced by (*R*)-α-methylhistamine in the absence and presence of the antagonist according to Ligneau et al.[32] In brief, longitudinal muscle strips were prepared from the small intestine, 20−50 cm proximal to the ileocecal valve. The muscle strips were mounted between two platinum electrodes (4 mm apart) in 20 mL of Krebs buffer, containing 1 μM mepyramine, connected to an isometric transducer, continuously gassed with oxygen containing 5% CO_2 at 37 °C. After equilibration of the muscle segments for 1 h with washing every 10 min, they were stimulated continuously with rectangular pulses of 15 V and 0.5 ms duration at a frequency of 0.1 Hz. After 30 min of stimulation, a cumulative concentration−response curve was recorded. Subsequently the preparations were thoroughly washed twice every 10 min without stimulation. The antagonist was incubated 20−30 min before redetermination of the (*R*)-α-methylhistamine concentration−response curve.[31,32]

Histamine H_3-receptor antagonist potency in vivo in mice: In vivo testing was performed after peroral administration of the compounds as a methylcellulose suspension to Swiss mice as described by Garbarg et al.[26] Brain histamine turnover was assessed by measuring the level of the main metabolite of histamine, N^τ-methylhistamine. Mice were fasted for 24 h before po treatment. Animals were decapitated 90 min after treatment, and the brain was dissected out and homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^τ-methylhistamine level was measured by radioimmunoassay.[37] By treatment with 3 mg/kg of ciproxifan the maximal N^τ-methylhistamine level was obtained and related to the level reached with the administered drug, and the ED_{50} value was calculated as mean with SEM.[38]

In vitro screening at other histamine receptors: Selected compounds were screened for histamine H_2-receptor activity on the isolated spontaneously beating guinea pig right atrium as well as for H_1-receptor activity on the isolated guinea pig ileum by standard methods described by Hirschfeld et al.[30] Each pharmacological test was performed at least in triplicate, but the exact type of interaction has not been determined in each case. The values given represent the mean.

Muscarinic M_3-receptor assay on guinea pig ileum: The procedure used was that described by Pertz and Elz.[28]

Adrenergic α_{1D}-receptor assay on rat aorta: The procedure used was that described by Hirschfeld et al.[30]

Adrenergic $\beta_{1/2}$-receptor assay on guinea pig right atrium: The procedure used was that described by Pertz and Elz.[28]

Serotoninergic 5-HT_{1B}-receptor assay on guinea pig iliac artery: The procedure used was that described by Pertz.[27]

Serotoninergic 5-HT_{2A}-receptor assay on rat tail artery: The procedure used was that described by Pertz and Elz.[28]

Serotoninergic 5-HT_3-receptor assay on guinea pig ileum: The procedure used was that described by Elz and Keller.[29]

Serotoninergic 5-HT_4-receptor assay on rat esophagus: The procedure used was that described by Elz and Keller.[29]

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Supporting Information Available: Elemental analyses and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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