4-(ω-(Alkyloxy)alkyl)-1*H*-imidazole Derivatives as Histamine H_3 Receptor Antagonists/Agonists

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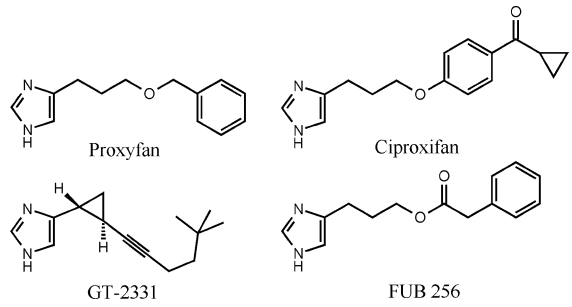
In an effort to develop new histamine H_3 receptor antagonists usable as pharmacological tools we present here novel unsymmetrical ether derivatives. Etherification of different ω-(1*H*-imidazol-4-yl)alkyl scaffolds led to compounds containing alkyl chains of increasing lengths either with or without unsaturated termini, cycloalkyl or arylalkyl moieties, or additional heteroatoms. When investigated in an in vitro assay on rat synaptosomes, the majority of compounds displayed potencies in the low nanomolar concentration range at the H_3 receptor, e.g., 4-(3-(3-cyclopentylpropyloxy)propyl)-1*H*-imidazole (**27**, $K_i = 7$ nM). FUB 465, 4-(3-(ethoxy)-propyl)-1*H*-imidazole (**14**), a useful tool for the characterization of constitutive activity of H_3 receptors in vivo in rodents, proved to be of high oral in vivo potency in mice ($ED_{50} = 0.26$ mg/kg). Further, the influence of chosen compounds on specific [^{35}S]GTPγS binding was assayed on HEK293 cell membranes expressing the human histamine H_3 receptor revealing partial agonism of the compounds in this particular model. These distinct responses are further hints for "protean agonism" in this class of compounds. Additionally, selected compounds were functionally investigated in vitro on isolated organs of the guinea-pig at H_3, H_1, and H_2 receptors.

Introduction

Constitutive activity of different receptor systems has been investigated within the past decade. For a long time it was not known whether this phenomenon existed in artifical overexpressed or mutated cell systems only or if it also applied to in vivo systems. Histaminergic neurotransmission in rodent brain was shown to be regulated by constitutively active histamine H_3 receptors in vitro as well as in vivo.[1] Presynaptically located,[2] histamine H_3 receptors mediate the inhibition of synthesis and release of histamine from histaminergic neurons via a negative feedback loop[3,4] but also exert modulatory effects on other neurotransmitter systems,[5] e.g., the dopaminergic[6] and serotonergic[7] systems. Due to complex neuronal interactions in the central nervous system (CNS) and its relatively high receptor density therein,[8] histamine H_3 receptors influence various physiological processes.[5] In addition, they have been associated with numerous pathological conditions affecting the CNS, e.g., food intake,[9] schizophrenia,[10] narcolepsy,[11] epilepsy and cognitive disorders, and attention-deficit hyperactivity disorder (ADHD).[12] Hence, the constitutively active histamine H_3 receptor system represents a promising therapeutic target for histamine H_3 receptor inverse agonists[13] and creates a demand for potent and selective ligands to serve as pharmacological tools.

Chart 1



At present, a large number of compounds representing various structural classes, e.g., carbamates, amides, isothioureas, esters, aliphatic and aromatic ethers, have been prepared in the search for novel histamine H_3 receptor ligands.[14] Ethers such as proxyfan[15] or ciproxifan[16] (Chart 1) are well-known and useful pharmacological tools, while the chiral alkyne derivative GT-2331[17] (cipralisant, Perceptin) has already entered Phase II clinical trials for the treatment of ADHD.[18] While GT-2331 was claimed to act as an antagonist, Fox et al. have recently reported partial agonist properties in another test assay.[19] The ethyl ether FUB 465 (**14**) served as a pharmacological tool in the study of the constitutively active histamine H_3 receptor, displaying inverse agonism, while proxyfan acted as a neutral antagonist in the same investigation.[1] Importantly, proxyfan has very recently been described as a "protean

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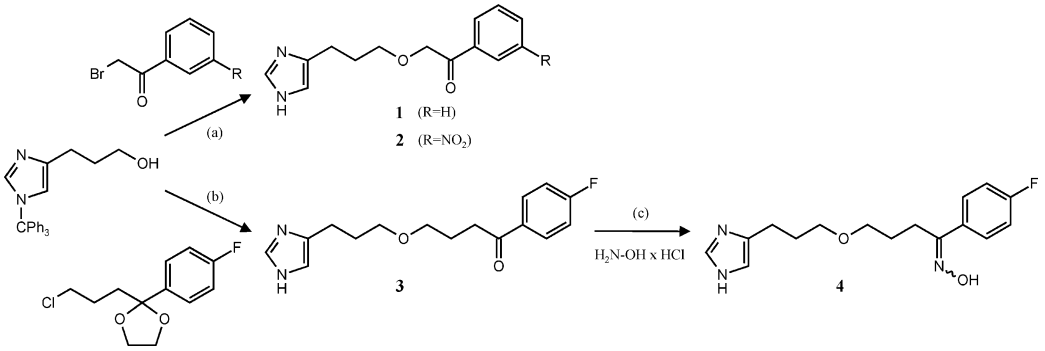
Scheme 1. Synthesis of Target Compounds **1**−**4**[a]



[a] (a) (i) CH_2Cl_2, 3 d, rt, (ii) HCl, EtOH, 1 h, reflux; (b) (i) NaH, toluene, 3 h, 60 °C → 48 h, 80 °C, (ii) HCl, H_2SO_4, THF, 12 h, reflux; (c) EtOH, Na_2CO_3, 12 h, reflux.

agonist" on histamine H_3 receptors.[20] On the basis of a theoretical ground of receptor theory and on the basis of experimental observations made with proxyfan on the paradoxical effects in different assays, one can assume one ligand possesses different responses depending on the receptor state and the measured functional reporting system. That is, it was reported that proxyfan can act as an agonist, neutral antagonist, or inverse agonist in vitro and in vivo on different responses in rodents and cats.[20]

On the basis of these observations, we investigated ethers derived from FUB 465 (**14**). In this study, variations in spacer lengths were performed and different aliphatic side-chains, either branched or unbranched, some of them with additional heteroatoms, or cyclic moieties were introduced. Furthermore, ethers were derived from esters such as FUB 256 (Chart 1) and derivatives thereof which have been described as potent histamine H_3 receptor antagonists in vitro.[21] However, these compounds displayed no detectable in vivo activity, likely due to rapid ester cleavage by unspecific esterases leading to inactive 3-(1*H*-imidazol-4-yl)propanol (ED_{50} > 10 mg/kg[26]).[21] To improve in vivo potency and oral availability of the compounds, differently substituted constitutional isomers were prepared, leading to ketone-containing ethers with increased metabolic stability as compared to esters. Many variations performed were inspired by the reports of successful optimizations in the class of imidazole-containing histamine H_3 receptor antagonists.[14] All novel compounds were investigated in vitro and in vivo for their histamine H_3 receptor antagonist/inverse agonist potencies in rodents. To evaluate possible protean agonism, selected compounds were assayed for effects on [^{35}S]-GTPγS binding on HEK293 cell membranes expressing the human histamine H_3 receptor. Selected ligands were additionally screened for their affinities at histamine H_1, H_2, and H_3 receptor subtypes on isolated organs of guinea-pig in order to confirm selectivity. In an attempt to discover new pharmacological tools, we present here structures and H_3 receptor potencies of novel dialkyl ethers.

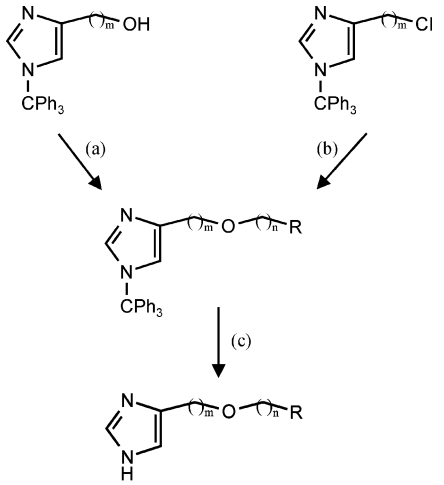
Chemistry

The precursor (1-triphenylmethyl-1*H*-imidazol-4-yl)-methanol was prepared from 1,3-dihydroxyacetone and formamidine acetate in liquid NH_3 under pressure[22,25] followed by introduction of the trityl protecting group as described.[23] The next higher homologue, trityl-protected 2-(1*H*-imidazol-4-yl)ethanol, was obtained from α-amino-γ-butyrolactone hydrobromide which was treated with sodium amalgam and ammonium isothiocyanate and then exposed to Raney nickel in alkaline solution as described by Turner,[24] followed by introduction of the protecting group by the method of Ganellin et al.[25] The key element 3-(1*H*-imidazol-4-yl)propanol hydrochloride was synthesized starting from urocanic acid in its trityl-protected and deprotected form as described by Stark et al.[26] The corresponding chlorides, i.e., 4-chloromethyl-1-triphenylmethyl-1*H*-imidazole[27] and 4-(3-chloropropyl)-1-triphenylmethyl-1*H*-imidazole,[28] were prepared as stated in the literature.

The majority of compounds was prepared via Williamson-type ether formation by reaction of the imidazole-containing alcoholates with the appropriate alkyl halide (**1**−**3**, **6**, **7**, **9**, **10**, **14**−**25**, **27**, **28**, and **31**).[29] Ethers **8** and **26** were obtained in an inverse manner from commercially available 2-(cyclohexyl)ethanol and the corresponding trityl-protected 4-(ω-chloroalkyl)-1*H*-imidazole,[27,28] since 2-(cyclohexyl)ethyl halides would have been subject to elimination reaction. Methyl ether **13** was prepared inversely using sodium methanolate as solvent resulting in a large excess of the nucleophile. The alcoholates were freshly prepared according to standard procedures using NaH in an aprotic solvent and were activated by catalytic amounts of 15-crown-5 and tetrabutylammonium iodide (Scheme 2). In general, reaction temperatures were increased after addition of the corresponding halides, except for the commercially available 2-bromo-1-phenylethanones (Scheme 1) which underwent ether formation with the alcohol at ambient temperature (**1**, **2**). Oxime **4** was readily available from **3** by reaction with hydroxylamine hydrochloride in the presence of Na_2CO_3 (Scheme 1).

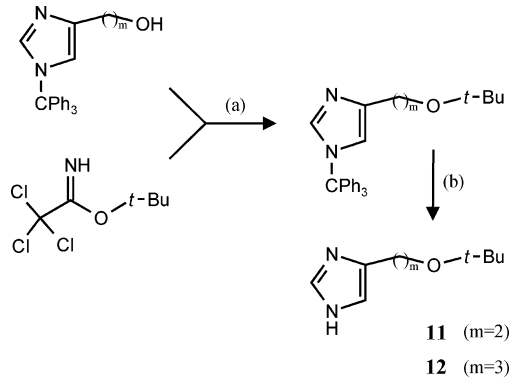
The *tert*-butyl ethers **11** and **12** were prepared from the appropriate trityl-protected 3-(1*H*-imidazol-4-yl)-alcohol and commercially available *tert*-butyl-2,2,2-trichloroacetimidate in the presence of the Lewis acid catalyst $BF_3 \cdot Et_2O$ (Scheme 3) according to Armstrong et al.[30] Trityl ether **5** was synthesized from unprotected 3-(1*H*-imidazol-4-yl)propanol hydrochloride[26] using a standard reaction protocol (Scheme 4). Final compounds **29** and **30** resulted from the addition of the respective α,β-unsaturated carbonyl derivative to 3-(1*H*-imidazol-4-yl)propanol hydrochloride[26] catalyzed by H_2SO_4.

Scheme 2. General Procedure for the Synthesis of Ethers **6**−**10**, **13**−**28**, **31**[a]



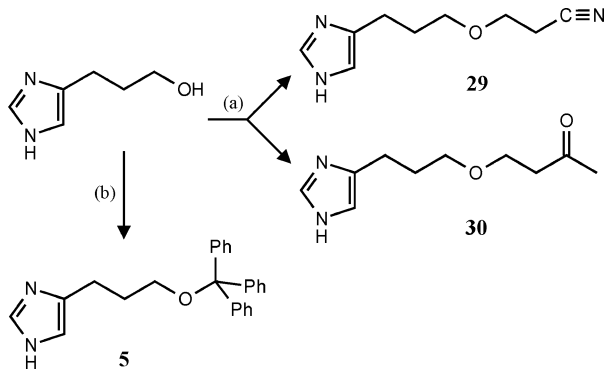
[a] Hal: Cl, Br; m: 1, 3; *n*: 0−3; R: alkenyl, alkynyl (**21**−**24**), alkyl (**13**−**20**, **31**), arylalkyl (**6**), cycloalkyl (**7**−**10** and **25**−**28**); (a) (i) NaH, toluene, 2 h, 60−70 °C (**14**, **15**, and **21**−**23**) or 12 h, rt (**6**, **7**, **9**, **10**, **16**−**20**, **24**, **25**, **27**, **28**, and **31**), (ii) R−Hal, 15-crown-5, tetrabutylammonium iodide, 24−48 h, 70−80 °C; (b) sodium 2-(cyclohexyl)ethanolate, toluene, 24 h, 60 °C (**8**, **26**) or MeONa, MeOH, 48 h, reflux (**13**); (c) HCl, EtOH, acetone, 1 h, 70−80 °C (**6**−**10**, **16**−**20**, and **24**−**28**) or 2 N HCl, 45 min, 70 °C (**13**−**15**, **21**−**23**, and **31**).

Scheme 3. Synthesis of *tert*-Butyl Ethers **11** and **12**[a]



[a] (a) $BF_3 \cdot Et_2O$, cyclohexane, CH_2Cl_2, Ar, 18 h, 60−70 °C; (b) H_2 5 bar, Pd/C, MeOH, 24 h, rt.

Scheme 4. Synthesis of Compounds **5**, **29**, and **30**[a]



[a] 3-(1*H*-imidazol-4-yl)propanol hydrochloride[26] was used; (a) acrylonitrile (**29**) or vinyl methyl ketone (**30**), acetonitrile, H_2SO_4, 24 h, 40 °C; (b) triphenylmethyl chloride, acetonitrile, 2 h, 40 °C.

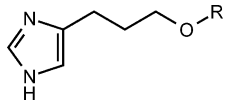
Trityl-protected ethers were transformed into the final compounds by detritylation under acidic conditions (cf. Schemes 1 and 2), either by refluxing in 2 N HCl[31] (**13**−**15**, **21**−**23**, and **31**) or with slight modifications (**1**, **2**, **6**−**10**, and **16**−**28**). Ketone derivative **3** was deprotected under conditions that ensured simultaneous cleavage of both the trityl and the acetal group (Scheme 1). *tert*-Butyl derivatives **11** and **12** were deprotected hydrogenolytically in order to avoid decomposition of the *tert*-butyl ethers under acidic conditions (Scheme 3).

Pharmacological Results and Discussion

In Vitro Assay on Synaptosomes of Rat Cerebral Cortex and Central in Vivo Testing in Mice. The new compounds were investigated in a functional in vitro assay on synaptosomes of rat cerebral cortex[36] and in vivo after oral administration to male *Swiss* mice.[36] In the series of compounds with 3-(1*H*-imidazol-4yl)-propyl partial structure and aromatic moiety (Table 1), the isomer of FUB 256[21] (**1**) and its *m*-nitro analogue (**2**) were inactive in vitro and in vivo (Table 1). Rearrangement of the carbonyl group changed electronic and steric parameters. This may be detrimental for ligand−receptor interaction. However, in the case of **3** rearrangement of the carbonyl group accompanied by an elongation of the alkyl chain was well tolerated, since **3** displayed nanomolar in vitro and high oral in vivo potency. Inspired by the improvement of acetoproxifan to imoproxifan,[32] the carbonyl group was replaced by an oxime moiety (**4**) which led to decreased, yet moderate in vivo potency. Sterically demanding moieties either neighboring the ether oxygen (**5**) or more distant from it, thereby branching out the spacer (**6**), were not beneficial for antagonist activities.

In the aliphatic series (**7**−**31**), cycloalkyl ethers with the (1*H*-imidazol-4-yl)methyl partial structure (**7**−**10**) generally had limited, if any, potency in vitro (Table 2). In agreement with this finding, **8** and **9** did not reveal in vivo potency. However, the cyclohexyl derivative **7** and its norbornyl analogue **10** displayed equally moderate in vivo activity. Among other reasons, this discrepancy may indicate an inverse agonist activity or may be due to pharmakokinetic, pharmakodynamic, or species differences. Unbranched alkyl ethers with 3-(1*H*-imidazol-4yl)propyl structure (**13**−**19**) were consistently found to be active as histamine H_3 receptor antagonists in vitro. Highest in vitro potency in this series was determined for the hexyl derivative **18** and its next higher homologue **19**. Compared to **18** and **19**, in vitro potency was found to decrease along with decreasing chain length (**13**−**17**). Results opposite to the in vitro data were obtained in vivo. The more lipophilic derivatives (**16**−**18** and **20**) did not influence the N^{τ}-methylhistamine level to a measurable extent, while the ethyl ether **14** (FUB 465) represented one of the most potent compound in this series, approaching the potency range of the reference antagonist/inverse agonist ciproxifan. Compound **14** (FUB 465) has been described to act as an inverse agonist at the constitutively active histamine H_3 receptor after oral administration to mice.[1] When coadministered, proxyfan acting as a neutral antagonist competitively blocked the increase in N^{τ}-methylhistamine level induced by FUB 465 without exerting a significant effect on histamine turnover when given alone. In another study it was shown that the pentyl ether **17** did not influence [^{35}S]GTPγS binding to mouse brain cortex, which may suggest neutral antagonist

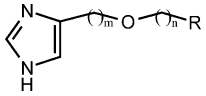
Table 1. Structures and Pharmacological Screening Results of 3-(1*H*-Imidazol-4-yl)propyl-type Ethers Containing Phenyl Moieties for Histamine H_3 Receptor Antagonist/Inverse Agonist Potency in Vitro and in Vivo in Rodents



no.	R	formula	M_r	mp (°C)	K_i (nM)[a] ± SEM	ED_{50} (mg/kg)[b] ± SEM
1	$CH_2C(=O)Ph$	$C_{14}H_{16}N_2O_2 \cdot C_4H_4O_4$	360.4	85	>500	>10
2	$CH_2C(=O)(3\text{-}NO_2\text{-}Ph)$	$C_{14}H_{15}N_3O_4 \cdot C_4H_4O_4 \cdot H_2O$	423.4	117	>500	>10
3	$(CH_2)_3C(=O)(4\text{-}F\text{-}Ph)$	$C_{16}H_{19}FN_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$	384.9	118	14 ± 4	0.28 ± 0.08
4	$(CH_2)_3C(=NOH)(4\text{-}F\text{-}Ph)$	$C_{16}H_{20}FN_3O_2 \cdot 1.3C_4H_4O_4$	456.3	116	nd[c]	4.0 ± 1.3
5	CPh_3	$C_{25}H_{24}N_2O$	368.5	153	>500	>10
6	$CH_2CHPhCH_2Ph$	$C_{21}H_{24}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	441.0	95	184 ± 4	nd

[a] Functional H_3 receptor in vitro assay on synaptosomes of rat cerebral cortex.[36] [b] Central H_3 receptor assay in vivo after oral administration to mice.[36] [c] nd, not determined.

Table 2. Structures and Pharmacological Screening Results of Aliphatic Ethers for Histamine H_3 Receptor Antagonist/Inverse Agonist Potency in Vitro and in Vivo in Rodents



no.	*m*	*n*	R	formula	M_r	mp (°C)	K_i (nM)[a] ± SEM	ED_{50} (mg/kg)[b] ± SEM
7	1	1	cycohexyl	$C_{11}H_{18}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$	319.4	102	>500	4.8 ± 2.1
8	1	2	cycohexyl	$C_{12}H_{20}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	328.9	90	>500	>10
9	1	3	cycohexyl	$C_{13}H_{22}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	342.9	94	≥500	>10
10	1	1	norbornyl	$C_{12}H_{18}N_2O \cdot C_4H_4O_4$	322.4	114	≈500	4.6 ± 2.2
11	2	0	tert.-butyl	$C_9H_{16}N_2O \cdot 0.8C_2H_2O_4$	240.2	168	>500	>10
12	3	0	tert.-butyl	$C_{10}H_{18}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	302.8	132	120 ± 20	1.3 ± 0.7
13	3	0	methyl	$C_7H_{12}N_2O \cdot C_2H_2O_4$	230.2	139	290 ± 140	≈10
14[c]	3	0	ethyl	$C_8H_{14}N_2O \cdot 0.75C_2H_2O_4$	221.7	167	580 ± 230[d]	0.26 ± 0.12
15	3	0	propyl	$C_9H_{16}N_2O \cdot 0.8C_2H_2O_4$	240.3	132	230 ± 70	1.8 ± 0.7
16	3	0	butyl	$C_{10}H_{18}N_2O \cdot C_4H_4O_4$	298.3	65	56 ± 19	>10
17	3	0	pentyl	$C_{11}H_{20}N_2O \cdot C_4H_4O_4$	312.4	70	33 ± 3	>30
18	3	0	hexyl	$C_{12}H_{22}N_2O \cdot C_4H_4O_4$	326.4	85	14 ± 2	>30
19	3	0	heptyl	$C_{13}H_{24}N_2O \cdot C_4H_4O_4$	340.4	88	16 ± 2	nd
20	3	0	octyl	$C_{14}H_{26}N_2O \cdot C_4H_4O_4$	354.5	79	nd[e]	>10
21	3	1	ethenyl	$C_9H_{14}N_2O \cdot 0.8C_2H_2O_4$	238.3	158	200 ± 80	0.33 ± 0.09
22	3	1	ethinyl	$C_9H_{12}N_2O \cdot 0.75C_2H_2O_4$	232.0	148	190 ± 100	0.57 ± 0.05
23	3	3	ethenyl	$C_{11}H_{18}N_2O \cdot C_2H_2O_4 \cdot 0.75H_2O$	297.8	156	27 ± 9	≥10
24	3	3	ethinyl	$C_{11}H_{16}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$	317.3	74	38 ± 5	0.93 ± 0.43
25	3	1	cyclopropyl	$C_{10}H_{16}N_2O \cdot C_4H_4O_4$	296.2	85	167 ± 23	3.8 ± 1.8
26	3	2	cyclohexyl	$C_{14}H_{24}N_2O \cdot C_4H_4O_4$	352.4	96	11 ± 1	2.5 ± 0.3
27	3	3	cyclopentyl	$C_{14}H_{24}N_2O \cdot C_4H_4O_4$	352.4	101	7 ± 1	0.28 ± 0.05
28	3	3	cyclohexyl	$C_{15}H_{26}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	371.0	115	20 ± 9	1.0 ± 0.2
29	3	2	cyano	$C_9H_{13}N_3O \cdot 0.8C_2H_2O_4$	251.3	136	674 ± 132	3.2 ± 1.3
30	3	2	acetyl	$C_{10}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	321.3	56	143 ± 47	4.2 ± 0.7
31	3	2	methoxy	$C_9H_{16}N_2O_2 \cdot C_4H_4O_4$	300.3	120	≈400	5.5 ± 1.8
ciproxifan							0.49 ± 0.09[f]	0.14 ± 0.03[f]
thioperamide							4 ± 1[g]	1.0 ± 0.5[h]

[a] Functional H_3 receptor in vitro assay on synaptosomes of rat cerebral cortex.[36] [b] Central H_3 receptor assay in vivo after oral administration to mice.[36] [c] FUB 465. [d] Reference 1. [e] nd, not determined. [f] Reference 16. [g] Reference 8. [h] Reference 34.

properties of the compound.[33] Hence, ethers **16**−**18** and **20** may act as neutral antagonists such as proxyfan while **14** and **15** may act as inverse agonists on this in vivo model displaying constitutive activity.[1] Based on ethyl ether **14**, disubstitution of the α-position (**12**) led to an approximately 5-fold increase in in vitro potency but lowered in vivo potency rendering **12** equally potent to thioperamide.[8,34] Potency was strongly diminished when the first spacer between imidazole nucleus and ether oxygen was shortened by one methylene group (**11**).

Introduction of an unsaturated terminal moiety (**21**−**24**) was well tolerated in vitro especially with the more lipophilic derivatives (**23**, **24**) and resulted in comparable in vivo potencies with the exception of **23**. Likewise, cycloalkyl termini (**25**−**28**) led to compounds of high in vitro potency resulting in the cyclopentyl derivative **27**, the most potent compound in vitro in this investigation ($K_i = 7$ nM). The in vitro observations were confirmed in vivo, favoring a trimethylene chain as second spacer. Heteroatoms in the side chain provoked a drop of antagonist in vitro activity into the micromolar concentration range (**29**−**31**). Yet these compounds displayed moderate in vivo potency.

Screening of Selected Compounds in a [^{35}S]-GTPγS Binding Assay. To assess potential intrinsic activities, the ability of selected compounds to influence [^{35}S]GTPγS binding was investigated on a binding test to membranes of HEK293 cells expressing the human H_3 receptor (Table 3). Data are expressed as mean ± SEM for EC_{50} and intrinsic activities. Interestingly, the compounds investigated (**16**−**18**, **21**, and **22**) stimulated GTPγS binding in a concentration range from 336 to 40 nM thereby displaying partial agonist activities.

Table 3. Effects of Histamine H_3 Receptor Ligands on Specific [^{35}S]GTPγS Binding

no.	i.a.[a] ± SEM	EC_{50} (nM)[b] ± SEM
16	0.39 ± 0.02	311 ± 22
17	0.47 ± 0.02	97 ± 19
18	0.49 ± 0.03	40 ± 4
21	0.63 ± 0.05	336 ± 16
22	0.73 ± 0.10	135 ± 5

[a] i.a., intrinsic activity. [b] [^{35}S]GTPγS binding to HEK293 cell membranes expressing the human H_3 receptor.

Table 4. Activity of Selected Compounds at Histamine Receptor Subtypes

	H_3		H_2	H_1
no.	pK_i[a]	pA_2[b]	pA_2[c]	pA_2[d]
7	<6.0		<4.0	3.6
9	≈6.3		4.2	4.2
12	6.9		<4.5	<4.0
13	6.5		<4.5	<4.0
14	6.2		<4.5	<4.0
15	6.6		<4.5	<4.5
17	7.5	7.2	<4.5	4.7
18	7.9	7.4	5.0	5.1
19	7.8	7.8	5.7	<4.0
20		7.0	5.6	4.8
21	6.7		<4.5	<3.5
22	6.7		<4.5	<3.5
24	7.4	6.5	<4.0	<4.0
26	8.0	7.8	4.8	5.6
27	8.2	7.8	5.3	4.7
28	7.7		4.3	5.1

[a] Functional H_3 receptor in vitro assay on synaptosomes of rat cerebral cortex.[36] [b] Functional H_3 receptor assay on guinea-pig ileum (SEM ≤ 0.2).[39] [c] Functional H_2 receptor assay on guinea-pig atrium (SEM ≤ 0.2).[46] [d] Functional H_1 receptor assay on guinea-pig ileum (SEM ≤ 0.2).[46]

Intrinsic activities ranged from as low as 0.39 for compound **16** to as high as 0.73 for compound **22**. The partial agonist behavior of all compounds is in contrast to the results obtained in the in vitro and in vivo rodent models. Recently, Fox et al.[19] have reported the partial agonist behavior of GT-2331, so far presumed to be a histamine H_3 receptor antagonist.[17] Furthermore as mentioned before, Gbahou et al.[20] identified proxyfan as a protean H_3 receptor ligand with the ability to display agonism, neutral antagonism, and inverse agonism. Proxyfan also revealed protean agonist properties at the recombinant rat H_3 receptor expressed in the same cells.[20] Hence, the complex pharmacodynamic profile of the compounds discussed here may be caused not only by inter-assay and species differences. In addition to that, the distribution of distinct receptor active states or different coupling routes in different cells or tissues may have to be taken into consideration. These findings also stress the impact of the test setup and the measured response on the pharmacological quality that a compound exerts in different systems, which may yield seemingly opposing results.

Screening of Selected Compounds at Other Functional Histaminergic Receptor Assays. The potency of selected compounds was not only investigated on the synaptosomal [^{3}H]histamine release assay, but also on a peripheral model on the isolated guinea-pig ileum determining H_3 heteroreceptor function (Table 4). Here, functional antagonist potency was generally slightly lower than in the [^{3}H]histamine release assay with the exception of **19** for which consistent results could be obtained (pK_i and pA_2 = 7.8). Differences in antagonist activity between the two functional assays varied between 0.2 and 0.5 log units (**17**, **18**, **26**, and **27**) and were as high as 0.9 log units for **24**. These inconsistencies may be due to species differences,[35] varying accessibility of the H_3 receptor within preparations, or general differences in assay performance, e.g., different incubation conditions (duration, composition of media). Functional affinities at muscarinic M_3 receptors were low, which was a prerequisite for the measurement of H_3 receptor-mediated relaxant responses in guinea-pig ileum (results not shown).

Selected compounds were additionally investigated for their affinities at H_1 and H_2 receptors on isolated organs of the guinea-pig.[46] All compounds which were highly potent histamine H_3 receptor antagonists also displayed pronounced selectivity for the target receptor: The majority of pA_2 values at H_1 and H_2 receptors was determined to be ≤4.5, and all pA_2 values were below 5.7.

Conclusions

The development of new histamine H_3 receptor antagonists with different 3-(1*H*-imidazole-4-yl)alkyl scaffolds has been described. Etherification led to compounds with aliphatic or aromatic moiety. The novel ligands were pharmacologically investigated in vitro on synaptosomes of rat cerebral cortex and in vivo following oral administration to mice. In general, compounds possessing a 3-(1*H*-imidazole-4-yl)propyl element were of higher potency than related ones with monomethylene or dimethylene spacers, the majority displaying in vitro potencies in the nanomolar concentration range, e.g., compound **27**. In vivo, FUB 465, 4-(3-(ethoxy)-propyl)-1*H*-imidazole (**14**) showed the highest potency. However, comparably high oral availability and potency were also detected for a number of ligands with unsaturated termini (**21**, **22**, and **24**), cycloalkyl (**27**, **28**), or aryl moieties (**3**). When assayed in a [^{35}S]GTPγS binding test on HEK293 cell membranes expressing the human histamine H_3 receptor, all chosen compounds (**16**−**18**, **21**, and **22**) were found to act as partial agonists in this particular model. This underlines the impact of assay setup and moreover species differences when evaluating the behavior of ligands on histamine H_3 receptors but also the usefulness of the compounds as pharmacological tools. Finally, selected target compounds were functionally investigated in vitro on isolated organs of the guinea-pig for their potencies at H_3 vs H_1 and H_2 receptors, respectively. Proving high selectivity for the third histamine receptor subtype, the novel ethers may be potentially useful as pharmacological tools and as novel leads.

Experimental Section

Chemistry. General Procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 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, Perkin-Elmer 240 C, or Vario EL (Perkin-Elmer) 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 PF_{254} containing gypsum (Merck). Column chromatography was carried out using silica gel 63−200 μm (Merck). Thin-layer chromatography (TLC) was performed on silica gel PF_{254} plates (Merck), the spots were visualized with fast blue salt B or by UV absorption at 254 nm. Abbreviations for solvents used are Et_2O, diethyl ether; EtOH, ethanol; MeOH, methanol; THF, tetrahydrofuran.

General Procedure for the Synthesis of Acetophenone Derivatives 1 and 2. 3-(1-(Triphenylmethyl)-1*H*-imidazol-4-yl)propanol[26] (5 mmol, 1.84 g) and 5 mmol of the corresponding 2-bromo-1-phenylethanone were dissolved in dry CH_2Cl_2 (20 mL) and stirred for 3 d. The solvent was removed under reduced pressure, and the residue dissolved in EtOH (10 mL) and 2 N HCl (30 mL). The reaction mixture was refluxed for 1 h. EtOH was removed under reduced pressure, the resulting precipitate filtered, and the aqueous layer washed with Et_2O, alkalized with 2 N NaOH, and extracted with ethyl acetate. The organic layer was separated, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH/NH_3 25% (90/10/1)) to afford the pure product as a yellow oil which was crystallized from EtOH/Et_2O as a salt of maleic acid.

4-(3-(2-Phenyl-2-oxoethoxy)propyl)-1*H*-imidazole hydrogen maleate (1). Yield, 47%; M_r, 360.4; mp, 85 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 9.05 (s, 1H, Im-2-H), 8.01 (d, J = 8.0 Hz, 2H, Ph-2-H, Ph-6-H), 7.76 (t, J = 7.3 Hz, 1H, Ph-4-H), 7.65 (t, J = 7.6 Hz, 2H, Ph-3-H, Ph-5-H), 7.56 (s, 1H, Im-5-H), 6.11 (m, 4H, $OCH_2C(=O)$, Mal), 3.42 (t, J = 6.1 Hz, 2H, CH_2O), 2.59 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.72 (m, 2H, Im-CH_2 CH_2). Anal. ($C_{14}H_{16}N_2O_2 \cdot C_4H_4O_4$), C, H, N.

4-(3-(2-(3-Nitrophenyl)-2-oxoethoxy)propyl)-1*H*-imidazole Hydrogen Maleate (2). Yield, 12%; M_r, 423.4; mp, 117 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.79 (m, 2H, Ph-4-H, Im-2-H), 8.60 (d, J = 8.0 Hz, 1H, Ph-2-H), 8.50 (d, J = 8.0 Hz, 1H, Ph-6-H), 7.95 (t, J = 8.0 Hz, 1H, Ph-5-H), 7.49 (s, 1H, Im-5-H), 6.10 (m, 4H, $OCH_2C(=O)$, Mal), 3.43 (t, J = 5.8 Hz, 2H, CH_2O), 2.56 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.72 (m, 2H, Im-CH_2CH_2). Anal. ($C_{14}H_{15}N_3O_4 \cdot C_4H_4O_4 \cdot H_2O$), C, H, N.

4-(3-(4-(4-Fluorophenyl)-4-oxobutyloxy)propyl)-1*H*-imidazole Hydrogen Oxalate (3). A solution of 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[26] (5 mmol, 1.84 g) and NaH (60%, 7.5 mmol, 0.3 g) was stirred in toluene (20 mL) at 60 °C for 3 h. After addition of 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (5 mmol, 1.16 g), the reaction mixture was heated at 80 °C for 48 h. The solvent was removed in vacuo and the residue carefully suspended in H_2O. After addition of 2 N NaOH, the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and removed under reduced pressure. The oily residue was dissolved in a mixture of HCl (2 N, 20 mL), H_2SO_4 (2 N, 10 mL), and THF (30 mL) and refluxed for 12 h. After separation, the aqueous layer was washed extensively with Et_2O, basified with a saturated solution of potassium carbonate, and extracted with Et_2O. The organic layers were combined, dried ($MgSO_4$), and evaporated to afford **3** as a sticky oil which was crystallized from EtOH/Et_2O as a salt of oxalic acid. Yield, 30%; M_r, 384.9; mp, 118 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.57 (s, 1H, Im-2-H), 8.04 (d, J = 8.1 Hz, 2H, Ph-3-H, Ph-5-H), 7.35 (d, J = 8.0 Hz, 2H, Ph-2-H, Ph-6-H), 7.22 (s, 1H, Im-5-H), 3.39 (m, 4H, CH_2OCH_2), 3.05 (t, J = 7.0 Hz, 2H, $CH_2C(=O)$), 2.62 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.85 (m, 4H, Im-CH_2CH_2, OCH_2CH_2). Anal. ($C_{16}H_{19}FN_2O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$), C, H, N.

1-(4-Fluorophenyl)-4-(3-(1*H*-imidazole-4-yl)propyloxy)-butan-1-one Oxime Hydrogen Maleate (4). Compound **3** (0.26 mmol, 0.1 g) was dissolved in dry EtOH (5 mL). Na_2CO_3 (1.58 mmol, 0.17 g) and hydroxylamine hydrochloride (0.06 g, 0.8 mmol) were added, the mixture was refluxed for 12 h, filtered, and the solvent was removed. The crude product was suspended in H_2O and extracted with acetonitrile. The organic layers were combined, washed with H_2O and dried ($MgSO_4$). The final product was crystallized as a salt of maleic acid and recrystallized twice from EtOH/Et_2O. Yield, 25%; M_r, 456.3; mp, 116 °C; ^{1}H NMR, 400 MHz (Me_2SO-d_6) δ 11.19 (s*, 1H, OH), 8.78 (s, 1H, Im-2-H), 7.67 (d, J = 8.1 Hz, 2H, Ph-3-H, Ph-5-H), 7.34 (s, 1H, Im-5-H), 7.22 (d, J = 8.1 Hz, 2H, Ph-2-H, Ph-6-H), 6.03 (s, 2H, Mal), 3.22 (m, 4H, CH_2OCH_2), 2.64−2.76 (m, 4H, Im-CH_2, $CH_2C(=NOH)$), 1.83 (m, 2H, Im-CH_2CH_2), 1.68 (m, 2H, $CH_2CH_2C(=NOH)$). Anal. ($C_{16}H_{20}FN_3O_2 \cdot 1.3C_4H_4O_4$), C, H, N.

4-(3-(Triphenylmethoxy)propyl)-1*H*-imidazole (5). 3-(1*H*-Imidazol-4-yl)propanol hydrochloride[26] (5 mmol, 0.81 g) was dissolved in dry acetonitrile (10 mL). At 40 °C, a solution of triphenylmethyl chloride (5 mmol, 1.42 g) in dry acetonitrile (50 mL) was added and stirred for 2 h. The solvent was removed under reduced pressure, the residue suspended in Et_2O and stirred for 30 min at ambient temperature. The organic layer was separated and the residue dissolved in H_2O. Upon addition of 2 N NaOH, the final product precipitated as a white solid. The crystals were filtered, washed with H_2O, and dried. Yield, 85%; M_r, 368.5; mp, 153 °C; ^{1}H NMR, 300 MHz ($CDCl_3$) δ 7.92 (s, 1H, Im-2-H), 7.46−7.25 (m, 15H, 15 Ph-H), 6.66 (s, 1H, Im-5-H), 5.51 (s, 1H, N−H), 3.11 (t, J = 6.0 Hz, 2H, CH_2O), 2.76 (t, J = 7.4 Hz, 2H, Im-CH_2), 1.92 (m, 2H, Im-CH_2CH_2). Anal. ($C_{25}H_{24}N_2O$), C, H, N.

General Procedure for the Synthesis of Aliphatic Ethers 6−10, 13−28, and 31. (1-Triphenylmethyl-1*H*-imidazol-4-yl)methanol[23] (5 mmol, 1.70 g) or 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[26] (5 mmol, 1.84 g), respectively, and NaH (60%, 6 mmol, 0.24 g) were stirred for 12 h at room temperature (**6**, **7**, **9**, **10**, **16**−**20**, **24**, **25**, **27**, **28**, and **31**) or 2 h at 60−70 °C (**14**, **15**, and **21**−**23**) in dry toluene (40 mL) in argon atmosphere. Upon addition of the appropriate alkyl halide (6 mmol), 15-crown-5 (0.5 mmol, 0.1 mL), and catalytic amounts of tetrabutylammonium iodide, the mixture was heated at 70−80 °C for 24−48 h. Target compounds **8**, **13**, and **26** were synthesized according to the procedure stated above but in an inverse manner starting from the corresponding trityl-protected 4-(ω-chloroalkyl)-1*H*-imidazole[27,28] and the appropriate freshly prepared alcoholate. The solvent was removed in vacuo and the residue treated with a mixture of 2 N HCl (35 mL), EtOH (10 mL), and acetone (5 mL) at 70−80 °C for 1 h (**6**−**10**, **16**−**20**, and **24**−**28**) or with 2 N HCl at 70 °C for 45 min (**13**−**15**, **21**−**23**, and **31**). The reaction mixture was filtered and washed with CH_2Cl_2. The aqueous layer was alkalized with NH_3 (25%) and extracted quantitatively with Et_2O. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness. The crude oily product was purified according to one of the following methods: The resulting oil was dried in vacuo and crystallized as a salt of maleic acid from EtOH/Et_2O (method A); the resulting oil was purified using rotary chromatography (eluent: CH_2Cl_2/MeOH (90/10), NH_3 atmosphere) followed by crystallization of the final product as a salt of either maleic or oxalic acid (as stated) from EtOH/Et_2O (method B); the resulting oil was purified using column chromatography (eluent: CH_2Cl_2/MeOH/NH_3 25% (95/4/1)) and the final product crystallized as a salt of maleic acid from EtOH/Et_2O (method C).

4-(3-(2,3-Diphenylpropyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (6). Purification, method C; yield, 34%; M_r, 441.0; mp, 95 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.82 (s, 1H, Im-2-H), 7.25−7.05 (m, 11H, 10 Ph-H, Im-5-H), 6.09 (s, 2H, Mal), 3.51 (d, J = 6.4 Hz, 2H, OCH_2CH), 3.36 (t, J = 6.1 Hz, 2H, CH_2O), 3.16 (m, 1H, CH), 3.01 (dd, ^2J = 13.5 Hz, ^3J = 6.3 Hz, 1H, H-*H′*(CH_2)-Ph), 2.82 (dd, ^2J = 13.4 Hz, ^3J = 8.7 Hz, 1H, H-*H′*(CH_2)-Ph), 2.60 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.79 (m, 2H, Im-CH_2CH_2). Anal. ($C_{21}H_{24}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$), C, H, N.

4-(Cyclohexylmethoxy)methyl-1*H*-imidazole Hydrogen Maleate (7). Purification, method A; yield, 50%; M_r, 319.4; mp, 102 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.84 (s, 1H, Im-2-H), 7.57 (s, 1H, Im-5-H), 6.01 (s, 2H, Mal), 4.45 (s,

2H, Im-CH_2), 3.22 (d, J = 5.5 Hz, 2H, OCH_2), 1.64−0.87 (m, 11H, cyclohexyl-H). Anal. ($C_{11}H_{18}N_2O\cdot C_4H_4O_4\cdot 0.5H_2O$), C, H, N.

4-(2-Cyclohexylethoxy)methyl-1*H*-imidazole Hydrogen Maleate (8). Purification, method A; yield, 88%; M_r, 328.9; mp, 90 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.83 (s, 1H, Im-2-H), 7.56 (s, 1H, Im-5-H), 6.07 (s, 2H, Mal), 4.45 (s, 2H, Im-CH_2), 3.43 (t, J = 6.6 Hz, 2H, OCH_2), 1.64−0.83 (m, 13H, CH_2-cyclohexyl, 11 cyclohexyl-H). Anal. ($C_{12}H_{20}N_2O\cdot C_4H_4O_4\cdot 0.25H_2O$), C, H, N.

4-(3-Cyclohexylpropyloxy)methyl-1*H*-imidazole Hydrogen Maleate (9). Purification, method A; yield, 55%; M_r, 342.9; mp, 94 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.84 (s, 1H, Im-2-H), 7.56 (s, 1H, Im-5-H), 6.07 (s, 2H, Mal), 4.45 (s, 2H, Im-CH_2), 3.38 (t, J = 6.5 Hz, 2H, OCH_2), 1.66−0.84 (m, 15H, CH_2CH_2-cyclohexyl, 11 cyclohexyl-H). Anal. ($C_{13}H_{22}N_2O\cdot C_4H_4O_4\cdot 0.25H_2O$), C, H, N.

4-(*exo*/*endo*-(Bicyclo[2.2.1]hept-2-yl)methoxy)methyl-1*H*-imidazole Hydrogen Maleate (10). Purification, method B; yield, 50%; M_r, 322.4; mp, 114 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.83 (s, 1H, Im-2-H), 7.56 (s, 1H, Im-5-H), 6.07 (s, 2H, Mal), 4.45 (s, 2H, Im-CH_2), 3.25 (m, 2H, OCH_2), 2.15 (s, 1H, norbornyl-2-H), 2.08 (s, 1H, norbornyl-5-H), 1.36−0.91 (m, 9H, 9 norbornyl-H). Anal. ($C_{12}H_{18}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(Methoxy)propyl)-1*H*-imidazole Hydrogen Oxalate (13). Purification, method B; yield, 40%; M_r, 230.2; mp, 139 °C; ^{1}H NMR, 400 MHz (Me_2SO-d_6) δ 8.62 (s, 1H, Im-2-H), 7.62 (s, 1H, Im-5-H), 3.33 (t, J = 6.3 Hz, 2H, OCH_2), 3.23 (s, 3H, CH_3), 2.65 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.83 (m, 2H, Im-CH_2CH_2). Anal. ($C_7H_{12}N_2O\cdot C_2H_2O_4$), C, H, N.

4-(3-(Ethoxy)propyl)-1*H*-imidazole Hydrogen Oxalate (14). Purification, method B; yield, 20%; M_r, 221.7; mp, 167 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.45 (s, 1H, Im-2-H), 7.17 (s, 1H, Im-5-H), 3.39 (m, 4H, CH_2OCH_2), 2.63 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.81 (m, 2H, Im-CH_2CH_2), 1.10 (t, J = 7.0 Hz, 3H, CH_3). Anal. ($C_8H_{14}N_2O\cdot 0.75C_2H_2O_4$), C, H, N.

4-(3-(Propyloxy)propyl)-1*H*-imidazole Hydrogen Oxalate (15). Purification, method B; yield, 20%; M_r, 240.3; mp, 132 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.48 (s, 1H, Im-2-H), 7.19 (s, 1H, Im-5-H), 3.37 (t, J = 6.3 Hz, 2H, CH_2O), 3.30 (t, J = 6.6 Hz, 2H, $OCH_2CH_2CH_3$), 2.64 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.50 (m, 2H, CH_2CH_3), 0.87 (t, J = 7.4 Hz, 3H, CH_3). Anal. ($C_9H_{16}N_2O\cdot 0.8C_2H_2O_4$), C, H, N.

4-(3-(Butyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (16). Purification, method C; yield, 30%; M_r, 298.3; mp, 65 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.40 (s, 1H, Im-5-H), 6.05 (s, 2H, Mal), 3.36 (m, 4H, CH_2OCH_2), 2.67 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.84 (m, 2H, Im-CH_2CH_2), 1.45 (m, 2H, OCH_2CH_2), 1.30 (m, 2H, CH_2CH_3), 0.87 (t, J = 7.2 Hz, 3H, CH_3). Anal. ($C_{10}H_{18}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(Pentyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (17). Purification, method B; yield, 50%; M_r, 312.4; mp, 70 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.39 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.36 (m, 4H, CH_2OCH_2), 2.66 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.47 (m, 2H, OCH_2CH_2), 1.26 (m, 4H, $CH_2CH_2CH_3$), 0.85 (t, J = 6.8 Hz, 3H, CH_3). Anal. ($C_{11}H_{20}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(Hexyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (18). Purification, method C; yield, 45%; M_r, 326.4; mp, 85 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.88 (s, 1H, Im-2-H), 7.39 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.35 (m, 4H, CH_2OCH_2), 2.66 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.45 (m, 2H, OCH_2CH_2), 1.30 (m, 6H, $CH_2CH_2CH_2CH_3$), 0.85 (t, J = 6.8 Hz, 3H, CH_3). Anal. ($C_{12}H_{22}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(Heptyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (19). Purification, method B; yield, 55%; M_r, 340.4; mp, 88 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.93 (s, 1H, Im-2-H), 7.41 (s, 1H, Im-5-H), 6.05 (s, 2H, Mal), 3.36 (m, 4H, CH_2OCH_2), 2.67 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.45 (m, 2H, OCH_2CH_2), 1.24 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$), 0.85 (t, J = 6.4 Hz, 3H, CH_3). Anal. ($C_{13}H_{24}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(Octyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (20). Purification, method C; yield, 60%; M_r, 354.5; mp, 79 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.39 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.36 (m, 4H, CH_2OCH_2), 2.66 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.83 (m, 2H, Im-CH_2CH_2), 1.45 (m, 2H, OCH_2CH_2), 1.25 (m, 10H, $(CH_2)_5CH_3$), 0.85 (t, J = 6.5 Hz, 3H, CH_3). Anal. ($C_{14}H_{26}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(2-Propenyloxy)propyl)-1*H*-imidazole Hydrogen Oxalate (21). Purification, method B; yield, 16%; M_r, 238.3; mp, 158 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.50 (s, 1H, Im-2-H), 7.20 (s, 1H, Im-5-H), 5.87 (m, 1H, CH=CH_2), 5.23 (d, $J_{(E)}$ = 17.2 Hz, 1H, CH=CH_2), 5.13 (d, $J_{(Z)}$ = 10.3 Hz, 1H, CH=CH_2), 3.92 (d, J = 5.1 Hz, 2H, CH_2CH=CH_2), 3.40 (t, J = 6.2 Hz, 2H, CH_2O), 2.65 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.84 (m, 2H, Im-CH_2CH_2). Anal. ($C_9H_{14}N_2O\cdot 0.8C_2H_2O_4$), C, H, N.

4-(3-(2-Propinyloxy)propyl)-1*H*-imidazole Hydrogen Oxalate (22). Purification, method B; yield, 24%; M_r, 232.0; mp, 148 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.42 (s, 1H, Im-2-H), 7.17 (s, 1H, Im-5-H), 4.12 (s, 2H, CH_2C≡CH), 3.46 (t, J = 6.2 Hz, 2H, CH_2O), 3.41 (s, 1H, ≡CH), 2.63 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.83 (m, 2H, Im-CH_2CH_2). Anal. ($C_9H_{12}N_2O\cdot 0.75C_2H_2O_4$), C, H, N.

4-(3-(4-Pentenyloxy)propyl)-1*H*-imidazole Hydrogen Oxalate (23). Purification, method B; yield, 15%; M_r, 297.8; mp, 156 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.61 (s, 1H, Im-2-H), 7.25 (s, 1H, Im-5-H), 5.80 (m, 1H, CH=CH_2), 4.97 (m, 2H, CH=CH_2), 3.36 (m, 4H, CH_2OCH_2), 2.65 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.04 (m, 2H, CH_2CH=CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.57 (m, 2H, CH_2CH_2CH=CH_2). Anal. ($C_{11}H_{18}N_2O\cdot C_2H_2O_4\cdot 0.75H_2O$), C, H, N.

4-(3-(4-Pentinyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (24). Purification, method C; yield, 40%; M_r, 317.3; mp, 74 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.40 (s, 1H, Im-5-H), 6.05 (s, 2H, Mal), 3.40 (m, 4H, CH_2OCH_2), 2.77 (s, 1H, ≡CH), 2.67 (t, J = 7.6 Hz, 2H, Im-CH_2), 2.19 (m, 2H, CH_2C≡CH), 1.82 (m, 2H, Im-CH_2CH_2), 1.70−1.61 (m, 2H, OCH_2CH_2). Anal. ($C_{11}H_{16}N_2O\cdot C_4H_4O_4\cdot 0.5H_2O$), C, H, N.

4-(3-(Cyclopropylmethoxy)propyl)-1*H*-imidazole Hydrogen Maleate (25). Purification, method B; yield, 30%; M_r, 296.2; mp, 85 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.41 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.40 (t, J = 6.1 Hz, 2H, CH_2O), 3.20 (d, J = 6.8 Hz, 2H, OCH_2-cyclopropyl), 2.68 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.84 (m, 2H, Im-CH_2CH_2), 1.09−0.97 (m, 1H, cyclopropyl-1-H), 0.44 (m, 2H, cyclopropyl-2-H_e, cyclopropyl-3-H_e), 0.14 (m, 2H, cyclopropyl-2-H_a, cyclopropyl-3-H_a). Anal. ($C_{10}H_{16}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(2-Cyclohexylethoxy)propyl)-1*H*-imidazole Hydrogen Maleate (26). Purification, method B; yield, 30%; M_r, 352.4; mp, 96 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.87 (s, 1H, Im-2-H), 7.38 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.37 (m, 4H, CH_2OCH_2), 2.66 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.86 (q, J = 7.0 Hz, 2H, Im-CH_2CH_2), 1.66−0.45 (m, 13H, CH_2-cyclohexyl, 11 cyclohexyl-H). Anal. ($C_{14}H_{24}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(3-Cyclopentylpropyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (27). Purification, method A; yield, 70%; M_r, 352.4; mp, 101 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.88 (s, 1H, Im-2-H), 7.39 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.36 (m, 4H, CH_2OCH_2), 2.66 (t, J = 7.6 Hz, 2H, Im-CH_2), 1.82 (m, 2H, Im-CH_2CH_2), 1.56−1.04 (m, 13H, CH_2CH_2-cyclopentyl, 9 cyclopentyl-H). Anal. ($C_{14}H_{24}N_2O\cdot C_4H_4O_4$), C, H, N.

4-(3-(3-Cyclohexylpropyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (28). Purification, method B; yield, 60%; M_r, 371.0; mp, 115 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.90 (s, 1H, Im-2-H), 7.40 (s, 1H, Im-5-H), 6.05 (s, 2H, Mal), 3.37 (t, J = 6.2 Hz, 2H, CH_2O), 3.32 (m, 2H, OCH_2), 2.68 (t, J = 7.4 Hz, 2H, Im-CH_2), 1.83 (m, 2H, Im-CH_2CH_2), 1.68−0.82 (m, 15H, CH_2CH_2-cyclohexyl, 11 cyclohexyl-H). Anal. ($C_{15}H_{26}N_2O\cdot C_4H_4O_4\cdot 0.25H_2O$), C, H, N.

4-(3-(2-(Methoxy)ethoxy)propyl)-1*H*-imidazole Hydrogen Maleate (31). Purification, method B; yield, 11%; M_r, 300.3; mp, 120 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.43 (s, 1H, Im-2-H), 7.16 (s, 1H, Im-5-H), 6.05 (s, 2H, Mal), 3.48−3.38 (m, 6H, $CH_2OCH_2CH_2$), 3.25 (s, 3H, CH_3), 2.62 (t, J = 7.6

Hz, 2H, Im-CH_2), 1.86−1.77 (m, 2H, Im-CH_2CH_2). Anal. ($C_9H_{16}N_2O_2 \cdot C_4H_4O_4$), C, H, N.

Synthesis of *tert*-Butyl Ethers 11 and 12. 2-(1-(Triphenylmethyl)-1*H*-imidazol-4-yl)ethanol[20] (5 mmol, 1.77 g) or 3-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)propanol[26] (5 mmol, 1.84 g), respectively, and *tert*-butyl 2,2,2-trichloroacetimidate (10.5 mmol, 2.29 g) were dissolved in dry cyclohexane (10 mL) and CH_2Cl_2 (5 mL) in argon atmosphere. $BF_3 \cdot Et_2O$ (600 μL) was added, and the reaction mixture was stirred for 18 h at 60−70 °C. After filtration, the solvent was removed in vacuo. The resulting oil was dissolved in MeOH (20 mL) and exposed to H_2 (5 bar) for 24 h at room temperature in the presence of Pd/C in an autoclave. The mixture was filtered, the solvent removed under reduced pressure, and the crude product purified by column chromatography (eluent: CH_2Cl_2/MeOH (90/10)).

4-(2-(1,1-Dimethylethoxy)ethyl)-1*H*-imidazole Hydrogen Oxalate (11). The final product was crystallized as a salt of oxalic acid from EtOH/Et_2O. Yield, 15%; M_r, 240.3; mp, 168 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.39 (s, 1H, Im-2-H), 7.16 (s, 1H, Im-5-H), 3.52 (t, J = 6.8 Hz, 2H, CH_2O), 2.74 (t, J = 6.8 Hz, 2H, Im-CH_2), 1.11 (s, 9H, *tert*-butyl). Anal. ($C_9H_{16}N_2O \cdot 0.8C_2H_2O_4$), C, H, N.

4-(3-(1,1-Dimethylethoxy)propyl)-1*H*-imidazole Hydrogen Maleate (12). The final product was crystallized as a salt of maleic acid from EtOH/Et_2O. Yield, 1%; M_r, 302.8; mp, 132 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.88 (s, 1H, Im-2-H), 7.39 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 3.32 (t, J = 6.0 Hz, 2H, CH_2O), 2.66 (t, J = 7.7 Hz, 2H, Im-CH_2), 1.77 (m, 2H, Im-CH_2CH_2), 1.11 (s, 9H, *tert*-butyl). Anal. ($C_{10}H_{18}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$), C, H, N.

General Procedure for the Synthesis of Derivatives 29 and 30. 3-(1*H*-Imidazol-4-yl)propanol[26] hydrochloride (3 mmol, 0.5 g) and the appropriate α,β-unsaturated carbonyl derivative (20 mmol) were suspended in acetonitrile (50 mL) in the presence of concentrated H_2SO_4 (0.3 mL) and slowly warmed to 40 °C for 24 h. The mixture was neutralized with potassium carbonate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH/NH_3 25% (95/5/1)) to give the final product as a light yellow oil.

4-(3-(2-Cyanoethoxy)propyl)-1*H*-imidazole Hydrogen Oxalate (29). Crystallized as a salt of oxalic acid from EtOH/Et_2O and recrystallized from EtOH/petroleum ether/Et_2O. Yield, 9%; M_r, 251.3; mp, 136 °C; ^{1}H NMR, 400 MHz (Me_2SO-d_6) δ 8.36 (s, 1H, Im-2-H), 7.14 (s, 1H, Im-5-H), 3.56 (t, J = 5.9 Hz, 2H, OCH_2CH_2CN), 3.45 (t, J = 6.2 Hz, 2H, CH_2O), 2.74 (t, J = 5.9 Hz, 2H, OCH_2CH_2CN), 2.64 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.87−1.79 (m, 2H, Im-CH_2CH_2). Anal. ($C_9H_{13}N_3O \cdot 0.8C_2H_2O_4$), C, H, N.

4-(3-(3-Oxobutyloxy)propyl)-1*H*-imidazole Hydrogen Maleate (30). Crystallized as a salt of maleic acid and recrystallized as described for **29**. Yield, 25%; M_r, 321.3; mp, 56 °C; ^{1}H NMR, 300 MHz (Me_2SO-d_6) δ 8.81 (s, 1H, Im-2-H), 7.03 (s, 1H, Im-5-H), 6.41 (s, 2H, Mal), 3.45 (t, J = 6.2 Hz, 2H, OCH_2), 3.36 (t, J = 6.0 Hz, 2H, CH_2O), 2.81 (t, J = 7.2 Hz, 2H, Im-CH_2), 2.71 (t, J = 5.9 Hz, 2H, $CH_2C(=O)$), 2.20 (s, 3H, CH_3), 1.95 (m, 2H, Im-CH_2CH_2). Anal. ($C_{10}H_{16}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$), C, H, N.

Pharmacology. General Methods. Histamine H_3 Receptor Assay on Synaptosomes of Rat Cerebral Cortex. Compounds were tested for their H_3 receptor antagonist activities in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from rat synaptosomes according to Garbarg et al.[36] A synaptosomal fraction from rat cerebral cortex prepared according to the method of Whittaker[37] 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.[36] K_i values were determined according to the Cheng−Prussoff equation.[38] The data presented are given as mean values with standard error of the mean (SEM) each for a minimum of three separate experiments.

Histamine H_3 Receptor Antagonist Activity on Guinea-Pig Ileum.[39] Strips of guinea-pig ileal longitudinal muscle with adhering myenteric plexus, approximately 2 cm in length and proximal to the ileocaecal junction, were prepared as described previously.[40] The strips were mounted isometrically under a tension of approximately 7.5 ± 2.0 mN in 20 mL organ baths 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, D-glucose 5.5, and choline chloride 0.001, aerated with 95% O_2/5% CO_2 (V/V) and kept at 37 °C. Mepyramine (1 μM) was present throughout the experiment to block ileal H_1 receptors. 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 H_3 receptor agonist (*R*)-α-methylhistamine (100 nM), which 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 in the absence of the antagonist under study. During the incubation period, the strips were stimulated continuously for 30 min. Finally, a second concentration−response curve to (*R*)-α-methylhistamine was obtained.[39,41] The rightward displacement of the curve to the 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 the antagonist. All compounds were tested in concentrations that did not block ileal M_3 receptors.[47]

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.[36] 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 p.o. 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.[42] By oral 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.[43]

Human Histamine H_3-Receptor-Mediated [^{35}S]GTPγ[S] Binding. Some compounds were tested to determine their properties in a [^{35}S]GTPγ[S] binding assay to membrane of HEK293 cells stably transfected with the human H_3 receptor (hH_3R). Briefly, HEK293 cells were transfected with the recombinant expression vector pCIneo-hH_3R.[44] Stable transfectants were selected with 2 mg mL^{-1} of G418 and tested for [^{125}I]iodoproxyfan binding.[41] Selected clones were maintained in the presence of 1 mg ml^{-1} of G418. [^{35}S]GTPγ[S] binding assays were performed according to Rouleau et al.[45] with slight modifications. HEK293 (hH_3R) cells were homogenized in an ice-cold buffer (Tris/HCl 50 mM pH 7.5), and homogenates were centrifuged twice (20 000 × *g*, 20 min, +4 °C). The final pellet resuspended, membranes (10−20 μg protein) were incubated for 60 min in 96-well microplate (Millipore Multiscreen MAFCNOB050) at 20 °C with 0.1 nM [^{35}S]GTPγ[S] alone or together with the various drug tested in 200 μL of assay buffer (Tris/HCl 50 mM, NaCl 100 mM, $MgCl_2$ 10 mM, GDP 10 μM, pH 7.5). The nonspecific binding was determined using 10 μM GTPγ[S]. Incubations were stopped by rapid filtration under vacuum and followed by four washings (250 μL each) of filters using the ice-cold assay buffer. Radioactivity trapped on filters was measured by liquid scintillation spectrometry.

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.[46] Each pharmacological test was performed at least in triplicate, but the exact type of interaction was not 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.[47]

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Note Added in Proof

According to a recent study of Liu et al. (*J. Org. Chem.* **2004**, *69*, 192−194), a reconsideration of the absolute configuration of GT-2331 is suggested.

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