[^{125}I]Iodoproxyfan and Related Compounds: A Reversible Radioligand and Novel Classes of Antagonists with High Affinity and Selectivity for the Histamine H_3 Receptor†

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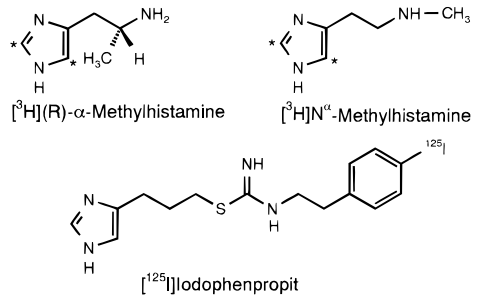
The synthesis and biological evaluation of new histamine H_3 receptor antagonists with an iodinated aryl partial structure are described as part of an extensive research program to find model compounds for the development of a new radioligand with high H_3 receptor affinity and specific activity. All compounds were tested for their H_3 receptor antagonist activity in a [^{3}H]-histamine-release assay with synaptosomes from rat cerebral cortex. The new leads with potent H_3 receptor antagonist activity belong to a series of derivatives of 3-(1*H*-imidazol-4-yl)propanol with carbamate (**4**−**7**), ester (**8**−**16**), and ether (**17**−**22**) as functional groups. Structure−activity relationships are discussed. The most active compound in the functional test ($-\log K_i = 8.3$) and in binding studies with [^{3}H]-(*R*)-α-methylhistamine on rat cerebral cortex ($-\log K_i = 9.0$) *in vitro* was 3-(1*H*-imidazol-4-yl)propyl (4-iodophenyl)methyl ether (iodoproxyfan, **19**) exhibiting no central H_3 receptor antagonist activity *in vivo*. The potency of iodoproxyfan is more than 300 times lower at H_1, H_2, α_1, α_2, β_1, 5-HT_{2A}, 5-HT_3, and M_3 receptors than at histamine H_3 receptors. Because of the high potency and selectivity of **19**, this compound has also been prepared in the [^{125}I]-iodinated form by a nucleophilic halogen exchange reaction using the corresponding bromo derivative **22** as a precursor. The newly prepared [^{125}I]iodoproxyfan (**23**) possesses advantageous pharmacological properties and fulfills all criteria of a useful radioligand.

With the discovery of the histamine H_3 receptor, the neurotransmitter function of histamine was strengthened.[1] This finding gave fresh impetus to an old field of research.[2] In histaminergic neurons, histamine is released from storage vesicles and acts at postsynaptically localized H_1 and H_2 receptors. At the presynaptic site, activation of H_3 receptors leads to an inhibition of histamine synthesis from L-histidine and an inhibition of histamine release *via* a negative feed-back mechanism.[3,4] H_3 receptor antagonists inhibit this mechanism and thus stimulate histamine release. Moreover, H_3 receptors have also been shown to act as heteroreceptors inhibiting the release of a number of different neurotransmitters.[5−9] Due to this interaction, H_3 receptor antagonists could influence a number of physiological and pathophysiological functions. Although histamine H_3 receptors are also found in peripheral tissues, the highest density, and therefore the main pharmacological target, is found in the brain. Antagonists of the named receptor may be indicated for different diseases or conditions like epilepsy,[10] stress,[11] memory and learning deficits,[12] and cognitive and sleep disorders[13] and influence a variety of physiological processes.[14] The therapeutic indications, however, are not totally clear at present. New pharmacological tools are highly recommended to clarify these problems. Radioligands are useful tools to localize and characterize the function of receptors. The currently available radioligands are either tritiated agonists like [^{3}H]-N^α-methylhistamine[15,16] and the more selective [^{3}H]-(*R*)-α-methylhistamine[2,17] or the [^{125}I]-iodinated antagonist iodophenpropit (Chart 1).[18,19] The agonists have been useful for demonstrating the G protein coupling of H_3 receptors and their distribution in brain. Despite these facts, agonistic tritiated radioligands have the problem that their binding is more complex than that of antagonists, and they are not allowing a sensitive receptor detection, two drawbacks which limit their use. Especially the low sensitivity of the tritium-labeled ligands is a critical point because the density of histamine H_3 receptors in the brain is lower than that of many other aminergic receptors. On the other hand, [^{125}I]iodophenpropit (K_D = 0.57 nM)[19] displays some limitations as discussed earlier.[20]

Chart 1. Radioligands of the Histamine H_3 Receptor



The aim of the present study was to design a new iodinated radioligand of the histamine H_3 receptor

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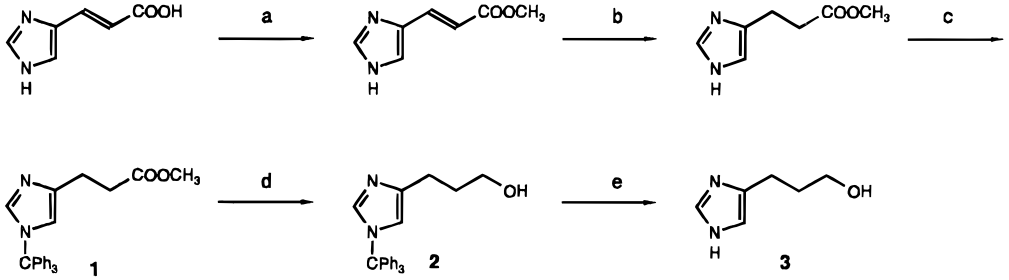
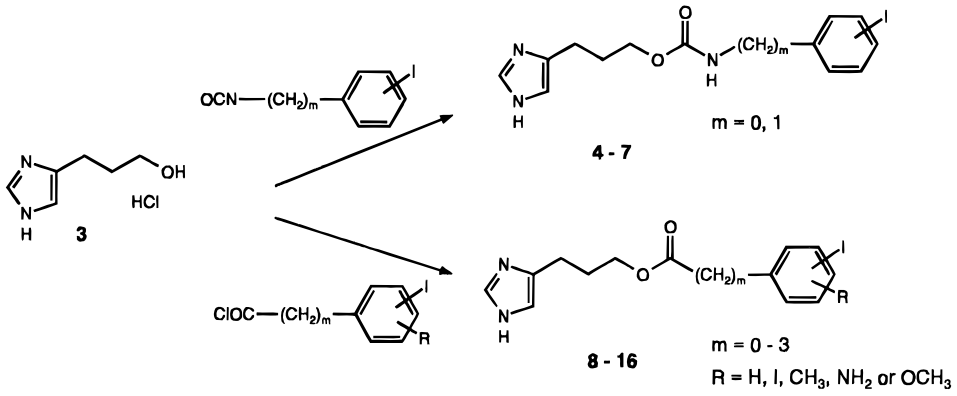
Scheme 1. Synthesis of 3-(1*H*-Imidazol-4-yl)propanol (**3**)[a]



[a] Reagents: (a) MeOH, HCl, 3−4 h reflux; (b) MeOH, Pd/C (10%), 2 bar of H_2, 24 h; (c) $ClCPhe_3$, Et_3N, acetonitrile, 12 h at ambient temperature; (d) $LiAlH_4$, THF, 3 h reflux; (e) 2 N HCl, EtOH, 1 h reflux.

Scheme 2. Synthesis of Carbamates and Esters



possessing antagonist binding and being more sensitive than the compounds mentioned before. Therefore, we have designed a [125I]-iodinated H_3 receptor antagonist displaying extremely high affinity and high selectivity, too. The developed radioligand [125I]iodoproxyfan (**23**) has been successfully used for binding assays as well as for autoradiographic studies.[20]

Our starting point was the observation that guanidino analogues of the combined H_2 receptor agonist/H_3 receptor antagonist impromidine are highly potent at H_3 receptors.[21] However, the iodinated compounds of this class failed to be potent radioligands due to their pronounced unspecific binding.[21] Most probably this is caused by the large number of possible hydrogen bonds of the polar guanidino group.

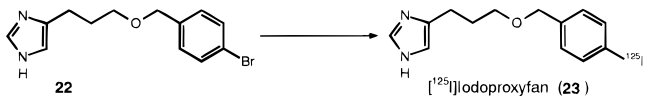
In an extensive research program, several different chemical classes of compounds all possessing high antagonist activity at histamine H_3 receptors could be found.[22] They all belong to a general construction pattern[23] having a nitrogen-containing heterocycle connected to a polar group by an alkyl chain. A lipophilic residue linked by an additional spacer to the polar group seems to enable the molecule to reach additional binding sites thereby increasing the antagonist activity. The polar group could frequently be varied while the H_3 receptor affinity was preserved. Therefore, step by step, we have simplified the polar group thereby minimizing the number of possible hydrogen bonds. New lead structures for H_3 receptor antagonists could be found by this procedure which were further optimized for drug development.[24,25] The present study focuses on the development of iodinated derivatives which could be used as radioligands of the H_3 receptor. The compounds belong to a carbamate, an ester, and an ether series. The number of heteroatoms of the polar moiety was consequently reduced. In each series the position of the iodine at the aromatic residue and the length of the spacer were varied. Additionally to the H_3 receptor activity of the compounds in functional tests on synaptosomes of rat cerebral cortex, they were also tested for their H_3 binding affinity on rat cerebral cortex and some selected compounds for their H_3 receptor antagonist activity *in vivo* after po administration to mouse. Finally, the activity at other histamine receptors in functional tests on isolated organs was also determined.

Chemistry

The key synthetic intermediate of all H_3 receptor antagonists of the new series is 3-(1*H*-imidazol-4-yl)-propanol (**3**). This compound could be prepared starting from urocanic acid by esterification, hydrogenation on Pd/C,[26] and protection of the imidazole ring by triphenylmethyl chloride, thus resulting in **1** (Scheme 1). The tritylation increases the lipophilicity which facilitates the isolation of **2** after reduction of **1** with complex hydrides, and it increases the yield of this reaction. The deprotection could be easily performed by refluxing in 2 N HCl for 2 h in almost quantitative yields.[27] In contrast to other synthetic approaches,[28,29] the alcohol **3** can thus be obtained in high yields and high purity, and it is available in the imidazole-protected (**2**) and unprotected (**3**) forms.

The carbamates **4**−**7** could be obtained by reaction of the hydrochloride of **3** with the appropriate isocyanates (Scheme 2) which were obtained from the corresponding amines by reaction with trichloromethyl chloroformiate (diphosgene).[30] Due to the salt form the nucleophilicity of the imidazole ring is reduced, and the OH group of the molecule is the exclusive point of attack. The protection of the imidazole nucleus against nucleophilic attack by protonation to an imidazolium ring is preferred to a possible N-protection by tritylation, the conditions of an acidic detritylation after carbamate

Scheme 3. Synthesis of [^{125}I]Iodoproxyfan (**23**)[a]



[a] Reagents: [^{125}I]NaI, $Cu^{II}SO_4$, $Sn^{II}SO_4$, 2,5-dihydroxybenzoic acid, citric acid, H_2O.

formation also leading to hydrolysis of the carbamate moiety (results not shown).

The same hydrolysis took place when an ester derivative of **2** was detritylated under acidic conditions. The deprotection by hydrogenation was not successful either because in ethanol or other alcohols, which are the preferred solvents for this reaction, reesterification to a different extent took place. The synthesis of **8**−**16** could be done by Einhorn reaction[31] of carboxylic halides with **3** in pyridine and addition of 4-(dimethylamino)-pyridine (DMAP) as a hypernucleophilic acylating catalyst (Scheme 2). The diacylated byproduct could be monohydrolyzed at the amide bond by addition of water, and the esters could be separated by chromatography.

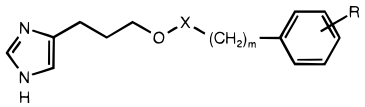
The phenolic ethers **17** and **18** were comfortably prepared by Mitsunobu reaction.[32] Compound **2** formed the intermediate alkoxy phosphonium salt which then reacted with *m*- or *p*-iodophenolates to the corresponding phenolic ethers and triphenylphosphine oxide. The cleavage of the protecting group was easily obtained under acidic conditions.

The other ethers, **19**−**22**, could be obtained by Williamson reaction.[33] The alcoholate of **2** was prepared with sodium hydride in an aprotic high-boiling solvent like toluene. Addition of the corresponding alkyl halide resulted in the tritylated ether derivative which could then be cleaved by standard methods mentioned before. The preparation of the radioiodinated compound **23** was performed by copper(I)-catalyzed nucleophilic halogen exchange reaction of the bromo precursor **22** with [^{125}I]-NaI (Scheme 3).[34] Before radiolabeling the method was optimized under nonlabeled conditions. Copper(I) is generated *in situ* by addition of tin(II) to a copper(II)-containing reaction mixture under nitrogen allowing high labeling yield (>97%).[35] After purification by semipreparative reversed-phase high-performance liquid chromatography, the separated radioligand obtained a specific activity of 2000 Ci/mmol.[20]

Pharmacological Results and Discussion

***In Vitro* Testing on Rat Cerebral Cortex Synaptosomes.** All newly designed compounds possess pronounced to high histamine H_3 receptor antagonist potency (Table 1). Concerning the polar group, a wide range of modifications were compatible with maintenance of antagonist activity. The different polar groups like carbamate, ester, or ether, though they have different electronic and steric parameters, were all well accepted. While there were no significant differences in activities between the carbamates and the esters, the ethers were slightly more potent than the two other groups. Substitution with iodine in *para*-position seems to have some advantage over the *meta*- or *ortho*-position in almost all series, but the differences were not significant. Disubstitution with iodine and a methyl group (**11**) or, in particular, a methoxy substituent (**15**) comparable to a modified Bolton−Hunter reagent decreased the *in vitro* activity. Likewise the trisubstitution with iodine and an amino group, shown in example **12**, also led to an evident decrease in H_3 receptor blocking activity. It can be speculated that the influence of the lipophilic residue on histamine H_3 receptor activity depends on a hydrophobic pocket. Too large substituents on the aryl moiety may block the binding in the hydrophobic pocket as a result of steric hindrance. The histamine H_3 receptor activity is not limited to an iodine substituent. The bromo precursor **22** for the synthesis of the labeled iodoproxyfan (**23**) also showed high activity in the nanomolar concentration range. In the carbamate series, compounds with one or two methylene groups between the polar group and phenyl

Table 1. Structures, Chemical Data, and Results of the Histamine H_3 Receptor Screening on Synaptosomes from Rat Cerebral Cortex



no.	X	*m*	R	yield (%)	mp (°C)	formula	M_r	K_i (nM,[a] $\bar{X} \pm S_{\bar{x}}$)
4	(C=O)NH		4-I	81	139[b]	$C_{13}H_{14}IN_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	491.8	11 ± 4
5	(C=O)NH		3-I	83	132[b]	$C_{13}H_{14}IN_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	491.8	16 ± 4
6	(C=O)NH		2-I	79	114[b]	$C_{13}H_{14}IN_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	491.8	25 ± 5
7	(C=O)NH	1	4-I	75	111[b]	$C_{14}H_{16}IN_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	505.9	12 ± 2
8	C=O		4-I	60	148[c]	$C_{13}H_{13}IN_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	481.2	20 ± 7
9	C=O		3-I	70	105[c]	$C_{13}H_{13}IN_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	481.2	25 ± 5
10	C=O		2-I	60	96[c]	$C_{13}H_{13}IN_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	476.7	39 ± 9
11	C=O		3-I, 4-CH_3	70	112[c]	$C_{14}H_{15}IN_2O_2 \cdot C_4H_4O_4$	486.3	30 ± 10
12	C=O		4-NH_2, 3,5-I_2	75	155[c]	$C_{13}H_{13}I_2N_3O_2 \cdot C_4H_4O_4$	613.2	146 ± 28
13	C=O	1	4-I	60	88[c]	$C_{14}H_{15}IN_2O_2 \cdot C_4H_4O_4$	486.3	14 ± 5
14	C=O	2	4-I	80	147[c]	$C_{15}H_{17}IN_2O_2 \cdot C_4H_4O_4$	500.3	47 ± 14
15	C=O	2	3-I, 4-OCH_3	75	102[c]	$C_{16}H_{19}IN_2O_3 \cdot C_4H_4O_4$	530.3	232 ± 53
16	C=O	3	4-I	80	126[c]	$C_{16}H_{19}IN_2O_2 \cdot C_4H_4O_4$	514.3	41 ± 11
17			4-I	82	158−159[b]	$C_{12}H_{13}IN_2O \cdot C_4H_4O_4$	444.2	22 ± 6
18			3-I	79	116−117[b]	$C_{12}H_{13}IN_2O \cdot C_4H_4O_4$	444.2	17 ± 3
19		1	4-I	56	123−124[b]	$C_{13}H_{15}IN_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$	467.3	5 ± 1
20		1	3-I	58	92−95[b]	$C_{13}H_{15}IN_2O \cdot C_4H_4O_4$	458.3	7 ± 3
21		3	4-I	20	121−122[b]	$C_{15}H_{19}IN_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$	495.3	35 ± 9
22		1	4-Br	57	120[b]	$C_{13}H_{15}BrN_2O \cdot C_4H_4O_4$	411.3	14 ± 4
23		1	4-^{125}I					

[a] Functional H_3 receptor assay on synaptosomes from rat cerebral cortex.[37] [b] Recrystallization solvent: Et_2O/EtOH. [c] Recrystallization solvent: MeCN/EtOH.

Table 2. Activities of Compounds at Histamine Receptor Subtypes

no.	H_3 activity			H_2 activity	H_1 activity
	$-\log K_i$[a]	$-\log K_i$[b]	ED_{50} (mg/kg)[c]	$-\log K_B$[d,e]	$-\log K_B$[d,f]
3	6.4	6.2	>10		
4	8.0	8.1	>10	5.3	4.4
5	7.8	8.1		5.3	5.1
6	7.6	7.6		4.6	4.8
7	7.9	7.9		4.5	5.1
8	7.7	8.1		4.5	4.2
9	7.6	8.4		3.8	4.8
10	7.4	7.7		4.6	5.9
11	7.5	8.3		4.2	4.9
12	6.8	7.5		4.6	5.9
13	7.9	7.9		3.6	4.5
14	7.3	7.1		3.6	4.8
15	6.6	6.7		4.5	<4
16	7.4	7.5		4.0	4.8
17	7.7	8.5		5.2	6.2
18	7.8	8.6		5.6	6.2
19	8.3[g]	9.0[g]	>10	5.2[g]	5.8[g]
20	8.2	8.9	>10	5.8	5.8
21	7.5	8.1		5.1	5.2
22	7.9	8.9	>10	4.9	5.9
impromidine	7.2[h]	7.4[g]		6.3[h]	<5[h]
thioperamide	8.4[i]	8.7[i]	≈1	<5[i]	<4[i]

[a] Functional H_3 receptor assay on synaptosomes from rat cerebral cortex.[37] [b] H_3 receptor binding assay on rat cerebral cortex.[39] [c] H_3 receptor test *in vivo* after po administration to mouse.[37] [d] Different pharmacological behavior of compounds (competitive, noncompetitive, or partial agonist). [e] Functional H_2 receptor test on guinea pig atrium.[41] [f] Functional H_1 receptor test on guinea pig ileum.[41] [g] Values from ref 20. [h] Values from ref 1. [i] Values from ref 2.

ring (**4**−**7**) were nearly equipotent. In the ester series, the compound with one methylene spacer was the most active one (**13**). In the preferred ether family, the introduction of three methylene groups led to a decrease in activity (**21**). The most active compound is the *para*-substituted iodinated benzylic ether derivative **19**.

Binding Studies with [3H]-(*R*)-α-Methylhistamine on Rat Cerebral Cortex Membranes. The H_3 receptor activity of the novel compounds was also determined in binding studies (Table 2). The obtained K_i values in the binding study were in rather good agreement with the K_i values in the functional test on rat cerebral cortex synaptosomes. The limited differences between the two values could depend on the different conditions on the assays, e.g., the ionic composition of the incubation media, the incubation time, and the difference in tissue preparations. Compound **19**, with the highest activity in the functional test with a similar potency compared to the standard antagonist thioperamide (K_i = 4.3 nM),[2] also showed highest affinity in binding studies with a K_i value in the nanomolar concentration range. The obtained K_B of 1 nM for compound **19** in the H_3 receptor ileum assay in guinea pig[20] was in good agreement with its K_i value on the functional test on rat synaptosomes. Binding experiments using displacement of radiolabeled **23** showed for **19** the highest histamine H_3 receptor activity of all H_3 receptor antagonists known so far (K_i = 0.20 nM).[20] Iodoproxyfan (**19**) showed a similar K_i of about 0.3 nM in a standard H_3 receptor binding assay using [3H]-N^{α}-methylhistamine.[36] Although iodoproxyfan showed extremely high affinity in these binding assays, it should also be mentioned that clobenpropit, which showed lower affinity in inhibition of [125I]iodoproxyfan specific binding, demonstrated higher *in vitro* activity than iodoproxyfan in the functional test on synaptosomes of rat cerebral cortex.[20]

For most compounds the activity on histamine H_1 and H_2 receptors was measured in functional tests on isolated organs. All compounds showed very weak H_1 or H_2 receptor activity. The activities of all compounds were at least 2 orders of magnitude higher at H_3 receptors than at H_1 or H_2 receptors independent of the test system used. This means that all tested compounds are selective for histamine H_3 receptors in addition to their high potency. Like most of the iodinated derivatives, compound **19** showed a noncompetitive antagonist activity in these low-concentration ranges at H_1 and H_2 receptors. In addition, unlabeled iodoproxyfan (**19**) was at least 300 times less potent at α_1, α_2, and β_1 adrenergic, 5-HT_{2A} and 5-HT_3 serotonergic, and M_3 muscarinic receptors than at H_3 receptors,[20,36] further showing its selectivity.

This selectivity, together with the high affinity (K_D = 65 pM) and low nonspecific binding (∼35%), of [125I]-iodoproxyfan (**23**) probably accounts for the well-contrasted autoradiographic pictures the radioprobe allows to generate with short exposure times.[20] These advantages do not appear to be shared by any other radioprobe designed for the H_3 receptor so far.[2,15−19] Many of the described potent and selective compounds are useful pharmacological tools for histamine H_3 receptor investigations. But as they fail to have central *in vivo* activity after oral application in mice (ED_{50} > 10 mg/kg), their development to therapeutic drugs for humans seems unlikely.

Conclusions

The described imidazolylalkyl derivatives of the carbamate, ester, and ether series are potent leads for new histamine H_3 receptor antagonists. Although the compounds—due to their functionalities—have different physicochemical properties, they show high H_3 receptor antagonist activity and selectivity. The most potent series in functional tests and binding studies are the ethers **17**−**22**. The *para*-iodinated benzylic derivative **19**, named iodoproxyfan, has been selected for radiolabeling due to its potency and selectivity. This compound was also screened on different receptor systems where it showed high selectivity, too. The radiolabeling was successfully carried out by a nucleophilic halogen exchange using the bromo precursor **22**. [125I]Iodoproxyfan (**23**) has been effectively used for binding studies and autoradiographic localization studies of the histamine H_3 receptor as described by Ligneau et al.[20]

Experimental Section

Chemistry. General Procedures. Melting points were determined on an Electrothermal IA 9000 digital apparatus or a Büchi 512 instrument and are uncorrected. ^{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 order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by D_2O), number of protons, and approximate coupling constant in hertz. Mass spectra were obtained on an EI-MS Finnigan MAT CH7A and a Finnigan MAT 711 spectrometer. Elemental analyses (C, H, N) for all non-radioiodinated compounds were measured on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and are within ±0.4% of the theoretical values. TLC was performed on silica gel PF_{254} plates (Merck). Preparative, centrifugally

accelerated, radial thin layer chromatography was performed using a Chromatotron 7924T instrument (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 (Marchery & Nagel). Reversed-phase high-performance liquid chromatography (HPLC) was carried out on a Hibar prepacked RT 250-4 column (25 cm; Merck) for semipreparative work and a LiChrosorb RP-select B column (5 μm; Merck) for reaction control using a mixture of acetonitrile/H_2O/trimethylamine (45% aqueous)/acetic acid (100%) (360:640:2.6:2) containing 0.6 g of Na_2SO_4 L^{-1} as eluant to give carrier-free product. The flow rate was 1 mL min^{-1} and the resulting pressure 23 MPa. The compounds were detected by UV spectroscopy (wave length, 254 nm).

3-(1*H*-Imidazol-4-yl)propanol (3): Methyl-3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanoate (1). To a solution of methyl 3-(1*H*-imidazol-4-yl)propanoate hydrochloride[26] (9.5 g, 50 mmol) in 100 mL of acetonitrile and triethylamine (19.6 mL, 0.14 mol) was added dropwise a solution of triphenylmethyl chloride (15.5 g, 55 mmol) in acetonitrile under external cooling with ice. The mixture was allowed to warm up at ambient temperature and stirred for 12 h. The solvent was evaporated under reduced pressure, and the solid residue was suspended in 300 mL of water. After stirring for 1 h, the slightly yellow solid was isolated and crystallized from dry ethanol (yield, 16.1 g, 81%): mp 140.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 16H, Im-2-H, 15 Ph-H), 6.55 (s, 1H, Im-5-H), 3.62 (s, 3H, O-CH_3), 2.88 (t, J = 7.0, 2H, Im-CH_2), 2.66 (t, J = 7.0, 2H, CH_2-C=O). Anal. ($C_{26}H_{24}N_2O_2$) C, H, N.

3-[1-(Triphenylmethyl)-1*H*-imidazol-4-yl]propanol (2). To a suspension of $LiAlH_4$ (1.9 g, 50 mmol) in 75 mL of freshly distilled THF and 25 mL of dry Et_2O was added **1** (10.0 g, 25 mmol) in portions under cooling with ice. The reaction mixture was refluxed for 2 h. The $LiAlH_4$ was decomposed by dropwise addition of a 0.1 N NaOH. The solution was extracted with CH_2Cl_2, and the solvent was removed in vacuo. The product was crystallized from Et_2O (yield, 7.9 g, 86%): mp 138 °C; ^{1}NMR ($CDCl_3$) δ 7.34−7.10 (m, 16H, Im-2-H, 15 Ph-H), 6.55 (s, 1H, Im-5-H), 3.71 (t, J = 6.0, 2H, CH_2-O), 2.67 (t, J = 7.0, 2H, Im-CH_2), 1.85 (m, 2H, CH_2-CH_2-O). Anal. ($C_{25}H_{24}N_2O$) C, H, N.

3-(1*H*-Imidazol-4-yl)propanol (3). In a mixture of 50 mL of EtOH and 50 mL of 2 N HCl was suspended **2** (3.7 g, 10 mmol), and the mixture was refluxed for 1 h. EtOH was removed under reduced pressure, and triphenylmethanol was filtered off. The aqueous layer was extracted with Et_2O and then evaporated to dryness. The resulting **3**·HCl was pure enough for further reactions. An analytical sample was crystallized as hydrogen maleate from acetonitrile (yield, 2.4 g, 94%): mp 72−74 °C (138 °C, **3**·HCl; 146−147 °C, **3**·$C_2H_2O_4$[28]); ^{1}H NMR (**3**·HCl, Me_2SO-d_6) δ 14.3 (br*, 1H, NH), 9.04 (s, 1H, Im-2-H), 7.40 (s, 1H, Im-5-H), 3.44 (t, J = 6.0, 2H, CH_2-O), 2.67 (t, J = 7.0, 2H, Im-CH_2), 1.85 (m, 2H, CH_2-CH_2-O). Anal. ($C_6H_{10}N_2O$·$C_4H_4O_4$·0.5H_2O) C, H, N.

Carbamates 4−7. A solution of the corresponding amine (5 mmol) in dry ethyl acetate was added to a solution of trichloromethyl chloroformiate (0.8 mL, 6 mmol) in 20 mL of dry ethyl acetate with a catalytic amount of charcoal. The reaction mixture was stirred at ambient temperature for 5 min and then heated to reflux until the mixture was getting clear. The solution was cooled and filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in 40 mL of dry acetonitrile, and **3**·HCl (0.8 g, 5 mmol) was added. The reaction mixture was refluxed for 2−4 h and concentrated in vacuo, and the residue was purified by rotatory chromatography (eluent, $CHCl_3$/MeOH (95:5), ammonia atmosphere) to afford a colorless oil which was crystallized as hydrogen maleate from Et_2O/EtOH.

3-(1*H*-Imidazol-4-yl)propyl *N*-(4-iodophenyl)carbamate (4): ^{1}H NMR (Me_2SO-d_6) δ 9.79 (s*, 1H, CO-NH), 8.87 (s, 1H, Im-2-H), 7.61 (d, J = 7.3, 2H, Ph-3-H, Ph-5-H), 7.42 (s, 1H, Im-5-H), 7.30 (d, J = 7.7, 2H, Ph-2-H, Ph-6-H), 6.05 (s, 2H, Mal), 4.12 (t, J = 7.6, 2H, CH_2-O), 2.74 (t, J = 7.6, 2H, Im-CH_2), 1.97 (m, 2H, CH_2-CH_2-O); MS m/z 371 ($M^{\bullet+}$, free base, 14), 299 (47), 245 (37), 219 (98), 126 (10), 118 (10), 116 (16), 109 (25), 108 (11), 107 (10), 98 (12), 95 (47), 91 (17). Anal. ($C_{13}H_{14}IN_3O_2$·$C_4H_4O_4$·0.25H_2O) C, H, N.

Esters 8−16. The corresponding carboxylic acid (5 mmol) was stirred with 30 mL of thionyl chloride for 12 h at ambient temperature. The solvent was evaporated, and the acyl chloride was dissolved in dry pyridine. To this solution were added **3**·HCl (0.8 g, 5 mmol) and a catalytic amount of DMAP, and the reaction mixture was refluxed for 4−8 h. The solvent was evaporated under reduced pressure, and the oily residue was dissolved in 10 mL of water. The aqueous layer was alkalized with 2 N NaOH and extracted with ethyl acetate. The organic extract was washed with water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using $CHCl_3$/MeOH/NH_3 (25%) (80:19:1). This afforded a colorless oil which was crystallized as hydrogen maleate from acetonitrile and EtOH.

3-(1*H*-Imidazol-4-yl)propyl (4-iodophenyl)methanoate (8): ^{1}H NMR (Me_2SO-d_6) δ 8.84 (s, 1H, Im-2-H), 7.93 (d, J = 8.4, 2H, Ph-3-H, Ph-5-H), 7.67 (d, J = 8.4, 2H, Ph-2-H, Ph-6-H), 7.42 (s, 1H, Im-5-H), 6.04 (s, 2H, Mal), 4.30 (t, J = 6.2, 2H, CH_2-O), 2.78 (t, J = 7.5, 2H, Im-CH_2), 2.06 (m, 2H, CH_2-CH_2-O); MS m/z 356 ($M^{\bullet+}$, free base, 11), 231 (24), 108 (54), 95 (100), 81 (13), 76 (13), 54 (11). Anal. ($C_{13}H_{13}IN_2O_2$·$C_4H_4O_4$·0.5H_2O) C, H, N.

3-(1*H*-Imidazol-4-yl)propyl 2-(4-iodophenyl)ethanoate (13): ^{1}H NMR (Me_2SO-d_6) δ 8.85 (s, 1H, Im-2-H), 7.68 (d, J = 8.2, 2H, Ph-3-H, Ph-5-H), 7.37 (s, 1H, Im-5-H), 7.08 (d, J = 8.3, 2H, Ph-2-H, Ph-6-H), 6.04 (s, 2H, Mal), 4.06 (t, J = 6.4, 2H, CH_2-O), 3.64 (s, 2H, Ph-CH_2), 2.66 (t, J = 7.6, 2H, Im-CH_2), 1.91 (m, 2H, CH_2-CH_2-O); MS m/z 370 ($M^{\bullet+}$, free base, 24), 244 (18), 217 (21), 127 (45), 108 (27), 98 (29), 95 (100), 90 (18), 81 (43), 54 (29). Anal. ($C_{14}H_{15}IN_2O_2$·$C_4H_4O_4$) C, H, N.

Phenyl Alkyl Ethers 17 and 18. A mixture of **2** (1.8 g, 5 mmol), triphenylphosphine (1.5 g, 6 mmol), and the corresponding iodophenol (1.2 g, 5 mmol) was dissolved in 20 mL of freshly distilled dry THF under nitrogen and cooling. A solution of diethyl azodicarboxylate (1.1 g, 6 mmol) in 4 mL of THF was added to this mixture and the reaction mixture stirred at ambient temperature for 48 h. After removal of the solvent under reduced pressure and silica gel column chromatography using ethyl acetate, the residue was dissolved in 10 mL of THF and 30 mL of 2 N HCl. The reaction mixture was heated at 70 °C for 2 h. The solvent was evaporated under reduced pressure, and triphenylmethanol was extracted with Et_2O. The aqueous layer was neutralized with K_2CO_3 and the product extracted with Et_2O and $CHCl_3$. The combined organic extracts were dried and evaporated to give an oil which was crystallized as hydrogen maleate from Et_2O/EtOH.

3-(1*H*-Imidazol-4-yl) 4-iodophenyl ether (17): ^{1}H NMR (Me_2SO-d_6) δ 8.86 (s, 1H, Im-2-H), 7.59 (d, J = 8.3, 2H, Ph-3-H, Ph-5-H), 7.41 (s, 1H, Im-5-H), 6.78 (d, J = 8.3, 2H, Ph-2-H, Ph-6-H), 6.04 (s, 2H, Mal), 3.98 (m, 2H, CH_2-O), 2.78 (t, J = 7.5, 2H, Im-CH_2), 2.05 (m, 2H, CH_2-CH_2-O); MS m/z 328 ($M^{\bullet+}$, free base, 13), 109 (100), 96 (15), 82 (68), 81 (43). Anal. ($C_{12}H_{13}IN_2O$·$C_4H_4O_4$) C, H, N.

Dialkyl Ethers 19−22. To a solution of the corresponding phenylalkyl chloride (5 mmol) and 15-crown-5 (0.1 g, 0.5 mmol) dissolved in 10 mL of dry toluene was added sodium 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanolate (5 mmol, freshly prepared by standard methods from **2** with NaH), and the mixture was refluxed for 24 h. The solvent was evaporated and the residue dissolved in 10 mL of THF and 30 mL of 2 N HCl. The reaction mixture was refluxed at 70 °C for 2 h. THF was evaporated under reduced pressure, and triphenylmethanol was extracted with Et_2O. The aqueous layer was neutralized with K_2CO_3 and the product extracted with Et_2O and $CHCl_3$. The combined organic extracts were dried and evaporated to give an oil which was crystallized as hydrogen maleate from Et_2O/EtOH.

3-(1*H*-Imidazol-4-yl)propyl (4-iodophenyl)methyl ether (19): ^{1}H NMR (Me_2SO-d_6) δ 8.80 (s, 1H, Im-2-H), 7.71 (d, J = 8.2, 2H, Ph-3-H, Ph-5-H), 7.35 (s, 1H, Im-5-H), 7.13 (d, J = 8.1, 2H, Ph-2-H, Ph-6-H), 6.10 (s, 2H, Mal), 4.41 (s, 2H, Ph-CH_2), 3.45 (t, J = 6.1, 2H, CH_2-O), 2.71 (t, J = 7.5, 2H, Im-CH_2), 1.88 (m, 2H, CH_2-CH_2-O); MS m/z 342 ($M^{\bullet+}$, free base,

5), 217 (44), 125 (61), 110 (44), 95 (39), 90 (22), 89 (13), 82 (100), 81 (37). Anal. ($C_{13}H_{15}IN_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

3-(1*H*-Imidazol-4-yl)propyl (4-bromophenyl)methyl ether (22): ^{1}H NMR (Me_2SO-d_6) δ 8.87 (s, 1H, Im-2-H), 7.55 (d, J = 7.7, 2H, Ph-3-H, Ph-5-H), 7.39 (s, 1H, Im-5-H), 7.27 (d, J = 8.0, 2H, Ph-2-H, Ph-6-H), 6.04 (s, 2H, Mal), 4.44 (s, 2H, Ph-CH_2), 3.46 (m, 2H, CH_2-O), 2.71 (t, J = 7.6, 2H, Im-CH_2), 1.89 (m, 2H, CH_2-CH_2-O); MS m/z 294 ($M^{\bullet+}$, free base, 2), 183 (14), 182 (98), 171 (18), 169 (19), 165 (10), 125 (46), 110 (35), 105 (11), 104 (41), 95 (48), 89 (10), 82 (100), 81 (53). Anal. ($C_{13}H_{15}BrN_2O \cdot C_4H_4O_4$) C, H, N.

Radiolabeled [125I]Iodopyroxyfan (23). The preparation of the radiolabeled compound was performed by Amersham (U.K.). To a mixture of 2,5-dihydroxybenzoic acid (20 μmol), citric acid (20 μmol), and tin(II) sulfate (1.5 μmol) was added **22** (1.5 μmol), and the mixture was dissolved under nitrogen in water. To this solution were added 15 μL of a 15 mM copper(II) sulfate solution and 1.5 mCi of [125I]NaI (specific activity, 2000 Ci/mmol). After 20 min under nitrogen and at ambient temperature, the mixture was heated at 120 °C for 45 min. The reaction was controlled by analytical HPLC. The solution was filtered through the Millipore 0.22 mm filter, and [125I]iodoproxyfan was separated by semipreparative HPLC. Compound **23** and the bromo precursor **22** had a retention time of 6.1 and 5.0 min, respectively.

Pharmacology. General Methods: Histamine H_3 Receptor Assay on Synaptosomes from Rat Cerebral Cortex. The new 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.[37] A synaptosomal fraction from rat cerebral cortex was preincubated for 30 min with L-[^{3}H]-histidine (0.4 μM) at 37 °C in a modified Krebs−Ringer solution. Then the synaptosomes were washed extensively, resuspended in fresh 2 mM K^+ Krebs−Ringer medium, and incubated for 2 min with 2 or 30 mM K^+ (final concentration). Drugs and 1 μM histamine were added 5 min before the depolarization stimulus. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels were determined by liquid scintillation spectrometry.[37] The K_i values were determined according to the Cheng−Prusoff equation.[38] The data presented are given as mean values with standard error of the mean for a minimum of three separate determinations each.

[^{3}H]-(*R*)-α-Methylhistamine Binding Assay. This assay was described by Arrang et al.[39] Rat cerebral cortex was homogenized with a Polytron homogenizer in 50 vol (w/v) of ice-cold 50 mM Na_2HPO_4/KH_2PO_4 buffer, pH = 7.5. After two differential centrifugations, the last pellet was washed and resuspended in fresh buffer. Aliquots of the membrane suspension were incubated for 60 min at 25 °C with [^{3}H]-(*R*)-α-methylhistamine and drugs at various concentrations. After stopping the incubation by dilution with ice-cold medium, the suspension was filtered through glass microfiber filters (Whatman, GF/B) under vacuum. Radioactivity retained on the filters was measured by liquid scintillation spectrometry. Specific binding was defined as that inhibited by 3 μM thioperamide, a specific H_3 receptor antagonist.

Histamine H_3 Receptor Antagonist Activity on the Guinea Pig Ileum. H_3 receptor activity was also measured by the concentration-dependent inhibition of electrically evoked twitches of isolated guinea pig ileum segments induced by (*R*)-α-methylhistamine in the presence of the antagonist according to Ligneau et al.[20] 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 at a frequency of 0.1 Hz. After 30 min of stimulation, cumulative concentration−response curves were recorded until no change in response was found. Subsequently the preparations were washed three times every 10 min without any stimulation. The antagonist was incubated 20−30 min before the redetermination of the concentration−response curve of (*R*)-α-methylhistamine.[40]

Histamine H_3 Receptor Antagonist Activity *in Vivo*. *In vivo* testing was performed for some selected compounds. It consisted in evaluating the increase in N^τ-methylhistamine levels in the brain after peroral application to Swiss mice as described by Garbarg et al.[37]

***In Vitro* Screening at H_1 and H_2 Receptors.** Selected compounds were screened for histamine H_2 receptor activity at the isolated spontaneously beating guinea pig right atrium as well as for H_1 receptor activity at the isolated guinea pig ileum by standard methods described by Hirschfeld et al.[41] Each pharmacological test was as least performed in triplicate, but the exact type of interaction has not been determined in each case. The given values represent the mean.

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