Synthesis and in Vitro Pharmacology of a Series of New Chiral Histamine H_3-Receptor Ligands: 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Ether Derivatives

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To investigate stereospecificity and the mechanism of activation of the histamine H_3-receptor, a series of 2-(*R* and *S*)-amino-3-(1*H*-imidazol-4(5)-yl)propyl ether derivatives were synthesized. In these compounds, the structures of the well-known antagonist iodoproxyfan and the full agonists *R*- or *S*-(α)-methylhistamine were combined in one molecule. The obtained "hybrid" molecules were tested for H_3-receptor affinity on rat cerebral cortex. Some selected compounds were further screened for H_3-receptor functional activity with GTPγ[^{35}S] autoradiography studies using rat brain tissue sections. The affinity of all the synthesized compounds ($-\log K_i = 5.9-7.9$) was lower than that found for iodoproxyfan or two of its analogues; however, the compounds showed stereospecificity. The *S*-configuration of the series of 2-amino-3-(1*H*-imidazol-4(5)-yl)propyl ether derivatives, which resembles the stereochemistry of *R*-(α)-methylhistamine, was more favorable. Incorporation of an amino group in the propyl chain of iodoproxyfan and analogues did not alter the antagonistic behavior for compounds with an aromatic side chain. However, when also the aromatic moiety was replaced by a cyclohexyl group, the compounds behaved as agonists. This indicates that an interaction between the side chain amino group and the H_3-receptor protein is involved in H_3-receptor activation. The 2-(*S*)-amino-3-(1*H*-imidazol-4(5)-yl)propyl cyclohexylmethyl ether (**23**) has H_3-receptor agonistic properties with high affinity for the histamine H_3-receptor ($-\log K_i = 7.9 \pm 0.2$) and might serve as a useful tool for further studies concerning drug design and receptor−ligand interactions.

Introduction

The histamine H_3-receptor has been described as a presynaptically located autoreceptor which upon activation inhibits the release of histamine from histaminergic neurons.[1] The H_3-receptor also occurs on some non-histaminergic neurons of the central and autonomic nervous system where it acts as a heteroreceptor by controlling the release of other neurotransmitters.[2] So far there are no H_3-receptor ligands in therapeutic use but many possible therapeutic targets for H_3-receptor ligands have been suggested (i.e., asthma,[3] migraine,[3] learning and memory degenerative disorders[4−7] like Alzheimer's disease,[8] hypertension,[9] reperfusion arrhythmias,[10] septic shock, heart failure, and acute myocardial infarction[11]). The H_3-receptor regulates the release of pro-inflammatory mediators in inflammatory reactions.[12] Furthermore, it is also involved in the control of sleep variables,[13] inhibition of seizures,[14,15] and pain control mechanisms.[16]

The histamine H_3-receptor is known to be highly stereoselective.[17,18] H_3-Receptor agonists can be structurally divided into chiral and nonchiral compounds (Figure 1). The stereoselective action of the H_3-receptor ligands (α)-methylhistamine,[19] (α),(β)-dimethyl histamine,[20] immepyr,[21] and cyclopropylhistamine[22,23,24] (Figure 1) clearly demonstrate the stereospecificity of the H_3-receptor agonistic binding site.

The general structure of most of the H_3-receptor antagonists consists of an imidazole group linked via a spacer to a polar group which in turn is coupled via another spacer to a lipophilic moiety (Figure 2). Usually the lipophilic moiety is either an aromatic or saturated ring system, but it can also be a carbon chain. The polar group can be very heterogenic such as amine, amide, carbamate, ether, guanidine, isothiourea, 4-oxadiazole, 2-thioimidazole, or a thiourea moiety (see reviews in refs 17 and 18). Recently, it was even shown that the polar group is not essential for activity. Merely, an unsaturated carbon−carbon bond appropriately positioned in the molecule seems to be enough for H_3-receptor activity.[25]

Several chiral H_3-receptor antagonists (Figure 3) containing a cyclopropyl moiety and a chiral amino substituent five carbons away from the imidazole ring have been reported.[25] However, GT-2331 (Figure 3) revealed that this amine function is not essential for H_3-antagonistic activity.[26,27]

The preparation of analogues of iodoproxyfan that contain a chiral amino substituent two carbons away from the imidazole ring provides molecules that embody the general features of most H_3-receptor antagonists.

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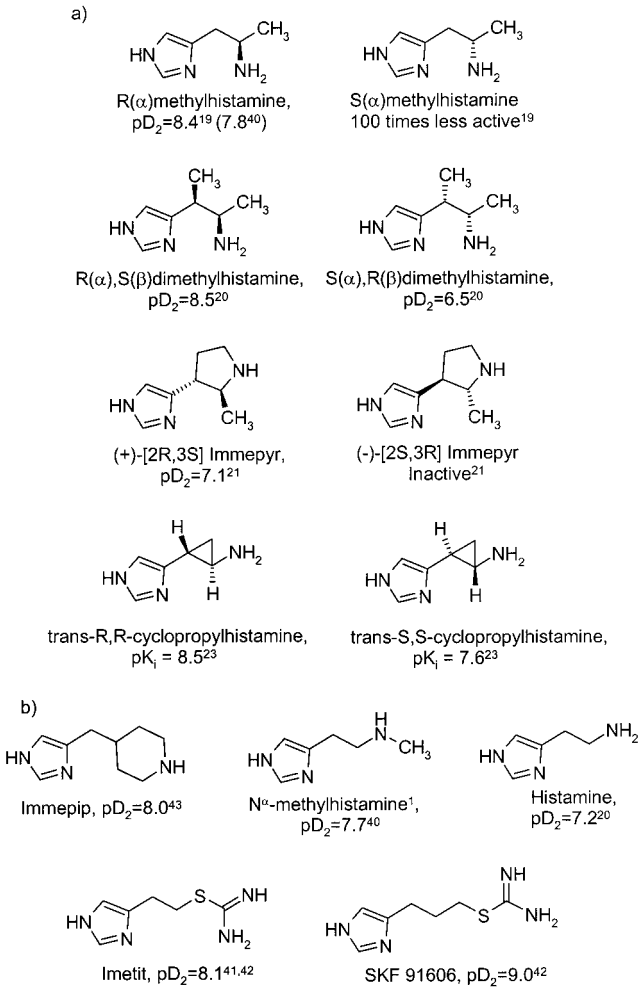


Figure 1. Structure and in vitro histamine H_3-receptor activity or affinity of some potent (a) chiral and (b) nonchiral H_3-receptor agonists.

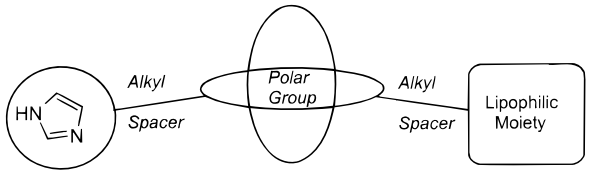


Figure 2. Schematic model of histamine H_3-receptor antagonists.

However, these molecules also contain a structural arrangement that can provide an internal hydrogen-bonding interaction between the distant nitrogen and the N^{π} imidazole ring nitrogen closest to the side chain. It is thought that this type of interaction is essential for compounds to behave as agonists. Thus, the aim of the present study was to investigate the effect of this particular chiral amino substitution on H_3-receptor affinity and functional response. Interestingly, the proposed molecules can also be regarded as substituted *R*-(α)-methylhistamine analogues (Figure 4).

Chemistry

D- or L-histidine or histidine methyl ester was used as a starting material for all chiral compounds. Tritylation of both primary and secondary amino groups of D- or L-histidine methyl ester was achieved with excess of trityl chloride in a one-step reaction (Scheme 1).

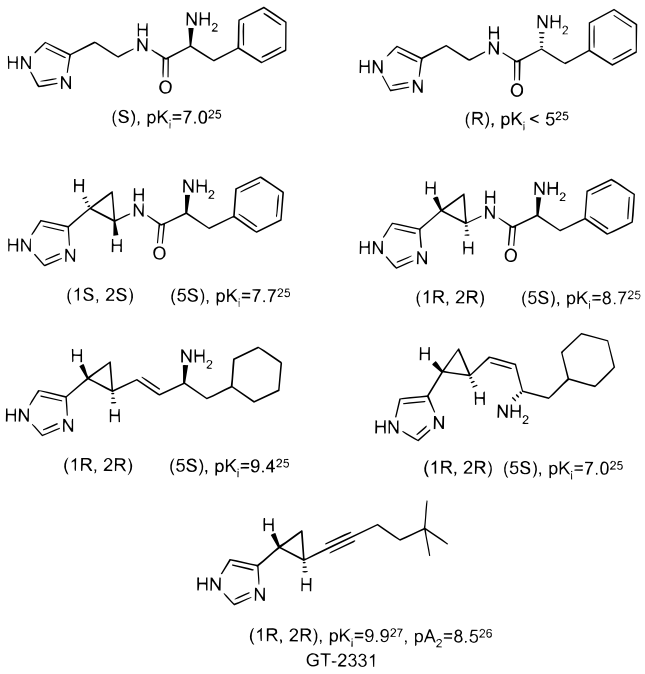


Figure 3. Structure and in vitro histamine H_3-receptor activity or affinity of some potent chiral H_3-receptor antagonists.

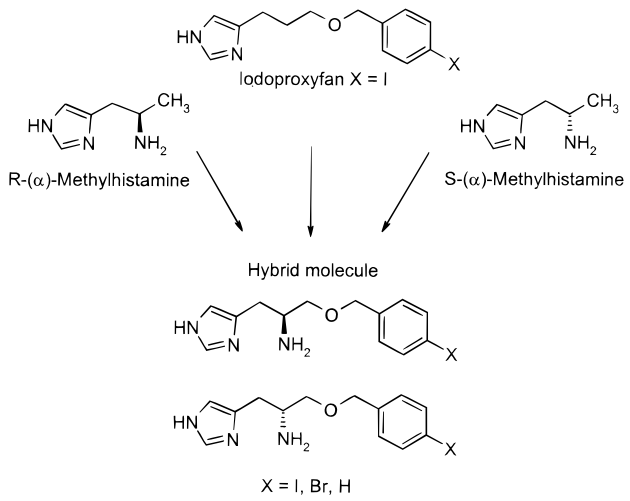


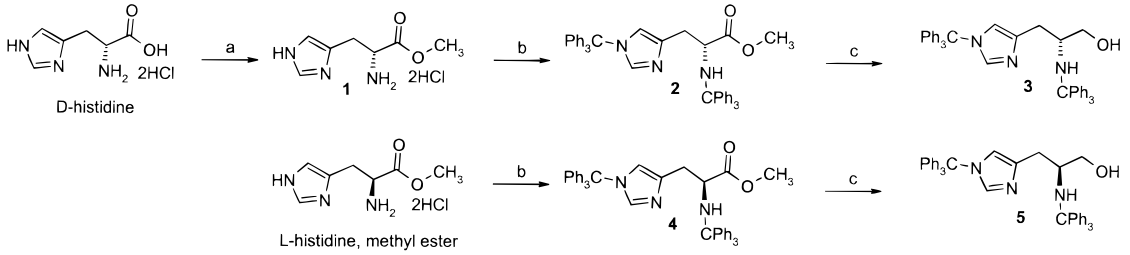
Figure 4. Hybrid molecules based on iodoproxyfan and (α)-methylhistamine.

Reduction of the ditritylated esters **2** and **4** with $LiAlH_4$ afforded the alcohols **3** and **5** which were used as starting materials in the ether syntheses (Scheme 2). Benzyl bromide, 4-bromobenzyl bromide, 4-iodobenzyl bromide, cyclohexylmethyl bromide, or methyl iodide were coupled with the alkoxides of **3**, **5**, and **6** affording the corresponding ether derivatives **7**−**10**, **11**−**15**, **16**−**18**. The trityl groups were hydrolyzed with THF/HCl, and the end products were obtained as dihydrochloride salts. Compounds **30**, **31**, and **32** were obtained by slightly modifying the synthesis method described by Stark et al.[28]

Pharmacology

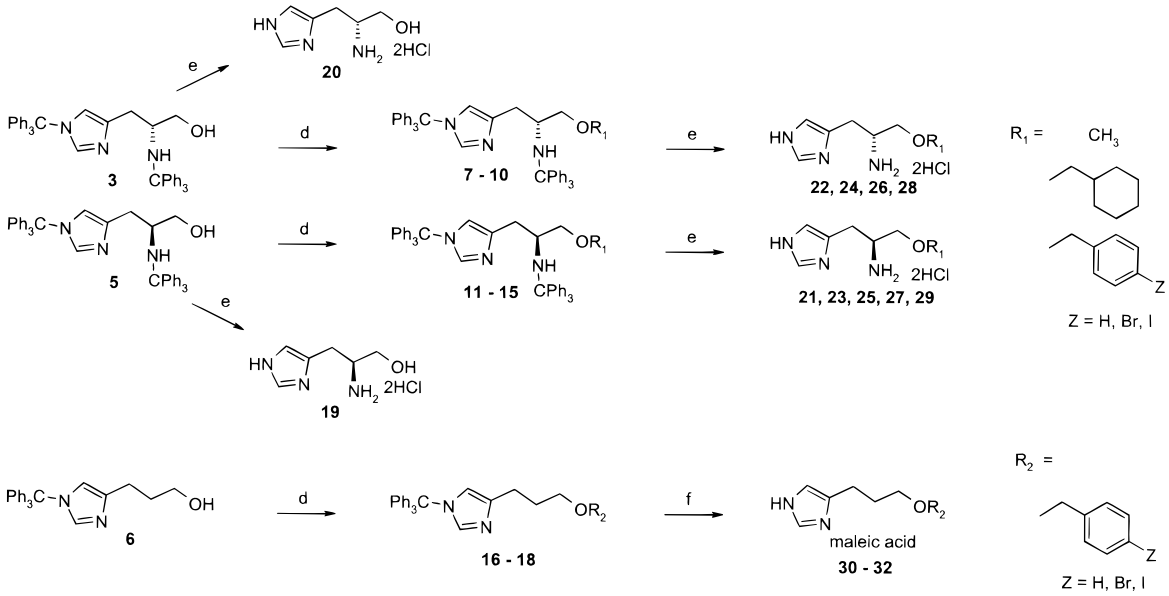
In Vitro Histamine H_3-Receptor Affinity. The affinity for the histamine H_3-receptor was determined by displacement of the radioligand [^{3}H]R-(α)-methylhistamine in an in vitro receptor binding assay using

Scheme 1. Synthesis of Trityl-Protected 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propanol (**3** and **5**)[a]



[a] Reagents and conditions: (a) $SOCl_2$, MeOH, 60 °C; (b) $ClCPh_3$, Et_3N, acetonitrile, rt; (c) $LiAlH_4$, THF, rt.

Scheme 2. Synthesis of 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Ether Derivatives and Iodoproxyfan Analogues[a]



[a] Reagents and conditions: (d) NaH, DMF, R-halide, 20−50 °C, 2−24 h; (e) 3 M HCl, THF, reflux, 3 h; (f) according to ref 28.

membrane homogenates of rat cerebral cortex according to West et al.[29]

In Vitro Histamine H_3-Receptor Activity in Rat Brain. Some selected compounds which exhibit high H_3-receptor affinity were screened for their in vitro activity in rat brain by detecting histamine H_3-receptor dependent activation of G-proteins with GTPγ[^{35}S] autoradiography on rat cortical and striatal brain sections according to Laitinen et al.[30]

Results and Discussion

Introduction of an amino group at the propylene chain of iodoproxyfan afforded a series of chiral molecules that incorporate the structure of (α)-methylhistamine (Figure 4).

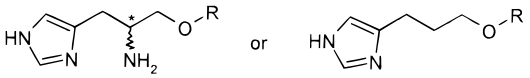
The Williamson ether synthesis of iodoproxyfan and two analogues was successfully carried out in the polar solvent DMF without the need of high temperature or a phase transfer catalyst as was described earlier.[28]

In Vitro Histamine H_3-Receptor Binding. Introduction of the amino group in the side chain reduced the affinity of all benzyl-containing compounds (**24**, **26**, **28**; **25**, **27**, **29**) by 1.2 to 2.6 log units compared to the parent compounds (**30**, **31**, **32**) (Table 1). The cyclohexylmethyl-containing compounds (**22** and **23**) could not be compared as the H_3-receptor affinity of the parent compound without a side chain amino group (cyclohexylmethyl 3-(1*H*-imidazol-4-yl)propyl ether) has not been published.

All synthesized compounds with an *S*-configuration at the chiral center, except compound **29**, showed higher H_3-receptor affinity than their corresponding *R*-enantiomers. The absolute configuration of the amino group in the more active *S*-enantiomer is the same as the configuration of the amino group in *R*-(α)-methylhistamine. The highest H_3-receptor affinity within the series of compounds with the *S*-configuration was observed for compound **23** that contains a cyclohexylmethyl moiety. Replacement of the cyclohexylmethyl group with a benzyl (**25**) or a 4-halo-benzyl moiety (**27**, **29**) reduced the affinity. The lowest affinity in the series of benzyl-substituted compounds was observed for the 4-I-benzyl-substituted compound (**29**).

The difference in histamine H_3-receptor binding among the pair of enantiomers was the largest for the cyclohexylmethyl compounds (**22**, **23**). In the series of benzyl-substituted compounds (**24**, **25**; **26**, **27**; **28**, **29**) the difference in binding was reduced with increment of the bulky substituent at the 4-position of the phenyl ring. The smallest difference in binding among the enantiomers was observed for the 4-I-benzyl analogues (**28**, **29**). This effect is related either to the different electronic properties of the aromatic and cycloalkyl groups or to increased steric contributors on the molecules. It might be that a more rigid lipophilic tail forces the

Table 1. Structures and Histamine H_3-Receptor Affinity of 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Ether Derivatives



19 - 29 **30 - 32**

chirality[a]-no.	R	pK_i H_3[b] ± SD	n[c]
(*S*)-**19**	H	6.6 ± 0.4	3
(*R*)-**20**	H	5.9 ± 0.1	3
(*S*)-**21**	CH_3	5.9 ± 0.3	3
(*R*)-**22**	CH_2-cyclohexyl	6.8 ± 0.2	3
(*S*)-**23**	CH_2-cyclohexyl	7.9 ± 0.2	5
(*R*)-**24**	$CH_2C_6H_5$	6.5 ± 0.4	5
(*S*)-**25**	$CH_2C_6H_5$	7.3 ± 0.1	6
(*R*)-**26**	CH_2(4-BrC_6H_4)	6.7 ± 0.4	3
(*S*)-**27**	CH_2(4-BrC_6H_4)	7.1 ± 0.3	4
(*R*)-**28**	CH_2(4-IC_6H_4)	6.7 ± 0.5	3
(*S*)-**29**	CH_2(4-IC_6H_4)	6.6 ± 0.6	3
30	$CH_2C_6H_5$	8.5 ± 0.2[d]	4
31	CH_2(4-BrC_6H_4)	9.3 ± 0.2[e]	4
iodoproxyfan (**32**)	CH_2(4-IC_6H_4)	8.7 ± 0.6[f]	4
R-(α)-methylhistamine		8.6 ± 0.2	3
S-(α)-methylhistamine		6.8 ± 0.4	2
clobenpropit		8.8 ± 0.1[g]	4

[a] Absolute configuration at the chiral center. [b] H_3-Receptor binding assay (R-α-MeHA binding) on rat cerebral cortex[29] representing the negative logarithm of the K_i with standard deviation. [c] Number of independent experiments. [d] pK_i = 8.3 (*N*-α-MeHA binding in rat cortex[37]). [e] pK_i = 8.9 (*R*-(α)-MeHA binding in rat cortex[28]). [f] pK_i = 9.0 (*R*-(α)-MeHA binding in rat cortex[38]). [g] pK_i = 9.0 ([^{125}I]-iodophenpropit binding in rat cortex[39]).

carbon chain into a conformation where the interaction between the side chain amino group and the receptor is reduced, in contrast to the cyclohexylmethyl group which is more flexible. This could explain why the influence of the configuration at the chiral center is increased for cyclohexylmethyl compounds (**22**, **23**).

GTPγ[^{35}S] Autoradiography Screening for Histamine H_3-Receptor Functional Activity. Compounds with benzyl, substituted benzyl, and cyclohexyl methyl moieties as well as some reference compounds were selected for activity screening to assess histamine H_3-receptor dependent G-protein activation by GTPγ[^{35}S] autoradiography studies on rat brain tissue sections according to Laitinen et al.[30]

Responses were quantitated from the cerebral cortex and striatum (two H_3-receptor-enriched brain regions).[30−32] No differences were observed between the responses of the compounds in striatum and cerebral cortex (Table 2 and Table 3).

Figure 5 shows that histamine induced H_3-receptor dependent G-protein activation in cerebral cortex and striatum. This effect is blocked by the H_3-antagonist thioperamide. 2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-iodobenzyl ether (**29**) is also able to block the effect of histamine, however, to a lesser extent than thioperamide.

All compounds can be regarded as substituted *R*-(α)-methylhistamine analogues. Therefore, these compounds were screened for H_3-agonistic activity (Table 2). The screening assay does not distinguish between full or partial agonistic activity. Both enantiomers with a cyclohexyl methyl moiety (**22** and **23**) showed agonistic activity. Although the benzyl-containing compounds (**25**, **26**, and **27**) display some agonistic activity, the assay does not allow accurate determination of quantitative differences between these compounds.

Table 2. Histamine H_3-Agonistic Activity of Selected 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Ether Derivatives and Reference Compounds

		response of GTPγ[^{35}S] binding[a]	
no.	concn (M)	cortex	striatum
basal		−	−
histamine	10^{-6}	++	++
(*R*)-**22**	10^{-5}	++	++
(*S*)-**23**	10^{-5}	++	++
(*R*)-**24**	10^{-5}	−	−
(*S*)-**25**	10^{-5}	+/−	+
(*R*)-**26**	10^{-5}	+	+
(*S*)-**27**	10^{-5}	+	+
(*R*)-**28**	10^{-5}	−	−
(*S*)-**29**	10^{-5}	−	−
impentamine	10^{-5}	++	++

[a] H_3-Receptor dependent activation of G-proteins with GTPγ[^{35}S] autoradiography of rat cortical and striatal tissue sections.[30] Brain sections were incubated with the indicated concentrations of the compounds and the radioligand GTPγ[^{35}S]. ++ = maximal response; + = half-maximal response; +/− = weak response (between half-maximal and basal); − = no response above basal.

Table 3. Histamine H_3-Receptor Antagonistic Activity of Selected 2-(*R* and *S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Ether Derivatives and Reference Compounds

		response of GTPγ[^{35}S] binding[a]	
no.	concn (M)	cortex	striatum
basal		−	−
histamine (HA)	10^{-6}	++	++
HA + (*R*)-**22**	10^{-6}	++	++
	10^{-5}	++	++
HA + (*S*)-**23**	10^{-6}	++	++
	10^{-5}	++	++
HA + (*R*)-**24**	10^{-6}	++	++
	10^{-5}	++	++
HA + (*S*)-**25**	10^{-6}	++	++
	10^{-5}	++	++
HA + (*R*)-**26**	10^{-6}	++	++
	10^{-5}	+	+
HA + (*S*)-**27**	10^{-6}	++	++
	10^{-5}	+	+
HA + (*R*)-**28**	10^{-6}	++	++
	10^{-5}	+	+
HA + (*S*)-**29**	10^{-6}	+	+
	10^{-5}	+/−	+/−
HA + thioperamide	10^{-8}	−	−
HA + clobenpropit	10^{-8}	−	−
HA + iodoproxyfan (**32**)	10^{-8}	−	−

[a] H_3-Receptor dependent activation of G-proteins with GTPγ[^{35}S] autoradiography of rat cortical and striatal tissue sections.[30] Brain sections were first incubated with the indicated concentrations of the compounds and then incubated with 1 μM HA in the presence of the compounds and the radioligand GTPγ[^{35}S]. ++ = maximal response; + = half-maximal response; +/− = weak responce (between half-maximal and basal); − = no response above basal.

All compounds can also be regarded as substituted iodoproxyfan analogues and thus were screened for H_3-antagonistic activity (Table 3). Compounds with a 4-Br-benzyl (enantiomers **26** and **27**) or 4-I-benzyl moiety (enantiomers **28** and **29**) showed antagonistic activity. Compounds with a benzyl (enantiomers **24** and **25**) or cyclohexyl methyl moiety (enantiomers **22**, **23**) did not show any antagonistic activity. Remarkably, compound **24** with a benzyl moiety and the *R*-configuration did not show any antagonistic nor agonistic activity while having H_3-receptor affinity.

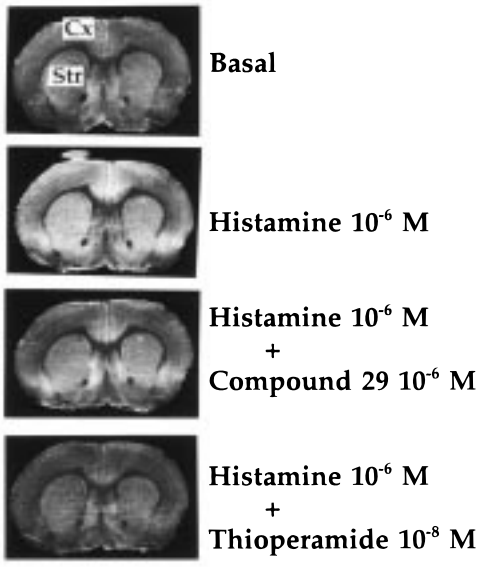


Figure 5. Visualization of histamine H_3-receptor dependent G-protein activity (appears as lighter images) using GTPγ[^{35}S] autoradiography of rat brain tissue sections.[30] For GTPγ[^{35}S] autoradiography, coronal sections covering the cerebral cortex (Cx) and the striatum (Str) were incubated in a three-step protocol.[30] DPCPX (10 μM), GDP (2 mM), and compound **29** (10^{-6} M) or thioperamide (10^{-8} M) were present throughout steps 2 and 3. In step 3, sections (except basal) were stimulated with histamine (10^{-6} M).

Replacement of the 4-I-benzyl moiety with a sterically less bulkier group such as a 4-Br-benzyl, benzyl, or cyclohexyl group reduces antagonistic activity and gradually induces agonistic activity. Thus, bulkier groups diminish interactions essential for agonistic activity while sterically flexible groups allow those interactions. The side chain amino group of the cyclohexylmethyl agonists **22** and **23** has to be involved in histamine H_3-receptor activation as the reference compound cyclohexylmethyl 3-(1*H*-imidazol-4-yl)propyl ether is an antagonist.[33] This implies that internal hydrogen bond formation, which enables proton transfer across the imidazole group, might be responsible for H_3-agonistic activity. However, this possible internal hydrogen-bonding interaction may be disrupted by a possible internal hydrogen-bonding interaction between the distant nitrogen atom and the oxygen in the side chain (five- vs six-membered ring).

In the GTPγ[^{35}S] autoradiography screening assay no clear stereospecific effect was observed, neither for the agonists nor for the antagonists, at the concentrations studied.

Conclusions

The 2-(*R* and *S*)-amino-3-(1*H*-imidazol-4(5)-yl)propyl ether derivatives represent a new class of chiral histamine H_3-receptor ligands combining the structural units from the full agonists *R*- and *S*-(α)-methylhistamine and the antagonist iodoproxyfan.

Introduction of an amino group in the propyl chain reduces H_3-receptor affinity. Bulky and rigid lipophilic groups decrease H_3-receptor affinity, probably by altering the interaction between the side chain amino group and the H_3-receptor protein.

Stereoselectivity among the synthesized enantiomers was observed for histamine H_3-receptor binding. The enantiomers with the *S*-configuration exhibited higher affinity than the compounds with the *R*-configuration.

The H_3-receptor affinity and functional activity of the presented compounds reveals that the combination of a side chain amino group and a lipophilic tail does not prohibit H_3-receptor binding but directs H_3-receptor activation. For agonists, it seems that a side chain amino group and a cyclohexyl group as the lipophilic tail is preferred, as compounds with a planar and aromatic lipophilic tail possess weak or no agonistic activity at all. These findings suggest that histamine H_3-receptor activation is influenced by the interaction of the side chain amino group and the receptor protein. If this interaction is weak or absent, the compounds behave as antagonists. Although the results describe herein are interesting, a more complete structure−activity (SAR) study is needed to determine the effect of the lipophilic tail group in these unique H_3 ligands on receptor affinity and functional release.

The series of 2-(*R* and *S*)-amino-3-(1*H*-imidazol-4(5)-yl)propyl ether derivatives includes chiral compounds possessing either antagonistic or (partial) agonistic activity and provides interesting tools to investigate the mechanism of activation of the H_3-receptor.

Experimental Section

Chemistry. General Procedures. Melting points were determined with a Stuart Scientific SMP2 melting point apparatus (U.K.) and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 WB spectrometer operating at 100.6 and 400.1 MHz, respectively. Tetramethylsilane (TMS) was used as a reference for $CDCl_3$ and DMSO-d_6 and Na-(3-trimethylsilylpropionate) (TSP) for D_2O. Electrospray ionization mass spectra (ESI-MS) were acquired using a LCQ ion trap mass spectrometer equipped with an electrospray ionization source (Finnigan MAT, San Jose, CA). The spray needle voltage was 5.6 kV; the sheat gas (nitrogen) value was 95. The samples were diluted with methanol to 20 mg/mL and injected directly to the eluent flow via a 5 mL loop injector (the total amount of the sample is approximately 100 ng). The eluent was 90% methanol/water, and the flow rate was 10 mL/min. Full scan mass spectra (*m*/*z* 50−600) were recorded. The HR-MS spectra were recorded on a VG 70-250SE magnetic sector mass spectrometer (VG Analytical, Manchester, U.K.) with the following conditions: electron energy, 70 eV; ionization current, 500 μA; ion source temperature, 250 °C. Samples were introduced into the mass spectrometer in a glass sample holder using a direct insertion probe. The probe temperature was raised from 30 to 500 °C at a rate of 100 °C/min. Elemental analysis was carried out with a Carlo Erba EA 1110 CHNS-O elemental analyzer. Reactions were monitored by TLC on Kieselgel 60 F 254 (DC-Alufolien, Merck). Intermediates were purified by column chromatography on J. T. Bakers silica gel for flash chromatography (7024-02) using mixtures of ethyl acetate and dichloromethane as eluents. The optical rotation of the compounds was determined with a JASCO DIP-1000 polarimeter operating at 589.3 nm (D-line of sodium).

General Method 1. Ditritylation of D- and L-Histidine Methyl Esters (Preparation of Compounds 2 and 4). D- or L-histidine methyl ester hydrochloride (10.0 g, 41 mmol) was stirred with triethylamine (21.0 g, 208 mmol, 5 equiv) and acetonitrile (50 mL) for 0.5 h. Triphenylmethyl chloride (29.0 g, 104 mmol, 2.5 equiv) was dissolved in acetonitrile (900 mL) and added in small portions at 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The solvents were evaporated. The residual solid was grounded and stirred with water (200 mL) for 0.5 h. A light yellow solid material was filtered, washed with water, and then dried overnight in a vacuum oven. The products were used in the next step without further purification.

General Method 2. Reduction of Ditritylated D- and L-Histidine Methyl Esters (Preparation of Compounds 3 and 5). Glassware was dried at 180 °C overnight and cooled under Ar or N_2 flow. THF was refluxed with CaH and distilled just before use. $LiAlH_4$ (6.0 g, 158 mmol, 3.4 equiv) was put into the reaction flask under Ar. The flask was cooled in an ice bath, and THF (100 mL) was added dropwise. Compound **2** or **4** (30.0 g, 46 mmol) was dissolved in THF (200 mL), and the solution was added dropwise to the stirred reaction mixture. The ice bath was removed, and 6.5 g (163 mmol, 1.03 equiv to $LiAlH_4$) of NaOH in 65 mL of water was added dropwise. The mixture was stirred for 15 min, and the resulting precipitate was filtered off. The solvents were evaporated with a rotavapor, and traces of solvents were removed by oil pump vacuum. The crude materials were purified by column chromatography (ethyl acetate:CH_2Cl_2, 1:1) yielding a yellowish to white foamlike solid material.

General Method 3. Williamson Ether Synthesis (Preparation of Compounds 7−18). DMF was distilled and stored with 4 Å molecular sieves. NaH (80%) in white oil (0.5 g, 16.7 mmol, 5.2 equiv) was stirred with DMF (10 mL) for 1 h at room temperature. Compound **3** or **5** (2.0 g, 3.2 mmol) or **6** (2.0 g, 5.4 mmol) was added, and stirring was continued for 1 h. The suitable halide (1.2 equiv) was added, and stirring was continued for 1−5 h. Water (50 mL) was added, and stirring was continued for 0.5 h. The precipitated solid material was filtered, washed with water, and dried overnight in a vacuum oven. In those cases in which no solid material was obtained, the residue was extracted with CH_2Cl_2 which was then dried with Na_2SO_4 and evaporated. Crude products were purified by column chromatography (ethyl acetate:CH_2Cl_2, 1:10), yielding a white to light-yellow foamlike solid material.

General Method 4. Hydrolysis of Trityl Groups (Preparation of Compounds 19−29). The tritylated compound was dissolved in 40 mL of THF, and 35 mL of 3 M HCl was added. The mixture was stirred at 70−80 °C for at least 2 h. The solvents were evaporated, and 50−100 mL of H_2O was added. Triphenylmethanol was extracted with CH_2Cl_2. The water phase was evaporated, and the residue was coevaporated with absolute ethanol. Traces of solvents were removed under high vacuum (10^{-2} mbar) at 40−50 °C (overnight), yielding the pure product as a dihydrochloride salt.

4-I-Benzyl Bromide was synthesized by reducing 4-I-ethylbenzoate with $LiBH_4$[34] to the corresponding alcohol and subsequently converted to the bromide with CBr_4 and PPh_3.[35]

D-Histidine Methyl Ester Dihydrochloride (1). $SOCl_2$ (10 mL, 137 mmol) was added dropwise to a stirred solution of 5.00 g (32.22 mmol) of D-histidine in 40 mL of methanol at 0 °C. The mixture was then stirred overnight at 60 °C. The solvent was evaporated, and the crude product was recrystallized from MeOH/ether (yield 7.7 g, 99%): mp 195−196 °C; ^{1}H NMR (D_2O) δ 3.50 (m (ABX), 2H, CH_2), 3.87 (s, 3H, CH_3), 4.55 (t, $J_{AX} = J_{BX} = 7$ Hz, 1H, NH$_2$CH), 7.49 (s, 1H, Im-*5*-*H*), 8.73 (d, $J = 1$ Hz, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propanoic Acid Methyl Ester, Dityrityl-D-histidine Methyl Ester (2). Compound **2** was made according to general method 1, and the product was used without purification (yield 34.4 g, 53.8 mmol, ∼100%): mp 78−80 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (d, $J = 10.5$ Hz, NH-trityl), 2.80 (q, $J_{AB} = 14.1$ Hz, $J_{AC} = 6.7$ Hz, 1H, Im-CH_AH), 2.97 (q, $J_{AB} = 14.1$ Hz, $J_{BC} = 6.0$ Hz, 1H, Im-CHH_B), 3.05 (s, 3H, CH_3), 3.68 (m, $J_{NH-trityl} = 10.1$ Hz, 1H, trityl-NH-CH_C), 6.64 (s, 1H, Im-*5*-*H*), 7.10−7.40 (m, more than 31H, phenyl-*H*, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propanol, Dityrityl-D-histidinol (3). Compound **3** was made according to general method 2 (yield 16.8 g, 26.8 mmol, 58%): mp 90−92.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.95 (q, $J_{AB} = 14.5$ Hz, $J_{AC} = 6.3$ Hz, 1H, Im-CH_AH), 2.39 (q, $J_{AB} = 14.5$ Hz, $J_{BC} = 2.9$ Hz, 1H, Im-CHH_B), 2.91 (m, 1H, H_2NCH_C), 2.99 (q, $J_{MN} = 11.3$ Hz, $J_{MC} = 6.3$ Hz, 1H, HO-CH_MH), 3.49 (q, $J_{MN} = 11.3$ Hz, $J_{NC} = 3.1$ Hz, 1H, HO-CHH_N), 6.29 (s, 1H, Im-*5*-*H*), 7.08−7.50 (m, 31H, phenyl-*H*, Im-*2*-*H*).

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propanoic Acid Methyl Ester, Dityrityl-L-histidine Methyl Ester (4). Compound **4** was made according to general method 1. The product was used without purification (yield 32.5 g, 49.7 mmol, ∼100%): mp 87−89 °C; ^{1}H NMR data are identical to those of compound **2**.

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propanol, Dityrityl-L-histidinol (5). Compound **5** was made according to general method 2. The amount of **4** was 28.7 g (43.9 mmol) (yield 22.6 g, 36.1 mmol, 82%): mp 85−86 °C; ^{1}H NMR data are identical to those of compound **3**.

3-[1-(Triphenylmethyl)imidazol-4(5)-yl]propanol (6). Compound **6** was made according to Stark et al.[28] The amount of 3-[1-(triphenylmethyl)imidazol-4(5)-yl]propanoic acid methylester was 14.3 g (36.1 mmol). White crystals were obtained (yield 11.3 g, 30.7 mmol, 85%): mp 132 °C (lit. 138 °C[28]); ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 2H, CH_2-CH_2-CH_2), 2.66 (t, $J = 6.8$ Hz, 2H, Im-CH_2), 3.70 (t, $J = 5.4$ Hz, 2H, HO-CH_2), 6.54 (s, 1H, Im-*5*-*H*), 7.11−7.34 (m, 16H, phenyl-*H*, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl Cyclohexylmethyl Ether (7). Compound **7** was made according to general method 3 with slight modifications. After the halide was added, the mixture was stirred at 50 °C until the reaction did not proceed anymore. More halide (2.4 equiv, 7.8 mmol) was added, and stirring was continued at 50 °C overnight. A yellowish oil was obtained (yield 270 mg, 0.37 mmol, 12%): ^{1}H NMR ($CDCl_3$) δ 0.70−0.90 (m, 11H, CH + CH_2 from cyclohexyl), 2.18 (q, $J_{AB} = 14.1$ Hz, $J_{AE} = 7.2$ Hz, 1H, Im-CH_AH), 2.51 (q, $J_{CD} = 9.0$ Hz, $J_{CE} = 5.9$ Hz, 1H, -O-CH_CH), 2.59 (q, $J_{AB} = 14.4$ Hz, $J_{BE} = 4.7$ Hz, 1H, Im-CHH_B), 2.75−2.84 (m, 3H, HNCH_E and O-CH_2-cyclohexyl), 2.98 (q, $J_{CD} = 9.1$ Hz, $J_{DE} = 3.9$ Hz, 1H, -O-CH_DH), 6.33 (s, 1H, Im-*5*-*H*), 6.99−7.50 (m, 31H, phenyl-*H*, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl Benzyl Ether (8). Compound **8** was made according to general method 3 (yield 2.00 g, 2.79 mmol, 87%): mp 65−68 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (q, $J_{AB} = 14.3$ Hz, $J_{AE} = 7.0$ Hz, 1H, Im-CH_AH), 2.63 (q, $J_{AB} = 14.3$ Hz, $J_{BE} = 4.8$ Hz, 1H, Im-CHH_B), 2.49 (broad s, NH), 2.71 (q, $J_{CD} = 9.1$ Hz, $J_{CE} = 6.1$ Hz, 1H, -O-CH_CH), 2.90 (m, 1H, HNCH_E), 3.14 (q, $J_{CD} = 9.1$ Hz, $J_{DE} = 3.7$ Hz, 1H, -O-CHH_D), 4.10 (d, 1H, $J_{MN} = 11.8$ Hz, -O-CH_MH-phenyl), 4.16 (d, 1H, $J_{MN} = 11.8$ Hz, -O-CHH_N-phenyl), 6.33 (s, 1H, Im-*5*-*H*), 7.05−7.52 (m, 36H, phenyl-*H*, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl 4-Bromobenzyl Ether (9). Compound **9** was made according to general method 3 (yield 1.92 g, 74%): mp 75−78 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (q, $J_{AB} = 14.3$ Hz, $J_{AE} = 7.0$ Hz, 1H, Im-CH_AH), 2.51 (broad s, 1H, NH), 2.61 (q, $J_{AB} = 14.3$ Hz, $J_{BE} = 4.7$ Hz, 1H, Im-CHH_B), 2.74 (q, $J_{CD} = 9.0$ Hz, $J_{CE} = 6.2$ Hz, 1H, -O-CH_CH), 2.89 (m, 1H, HNCH_E), 3.12 (q, $J_{CD} = 9.1$ Hz, $J_{DE} = 3.7$ Hz, 1H, -O-CHH_D), 4.05 (d, 1H, $J_{MN} = 12.2$ Hz, -O-CH_MH-(4-Br-phenyl)), 4.12 (d, $J_{MN} = 12.1$ Hz, 1H, -O-CHH_N-(4-Br-phenyl)), 6.32 (s, 1H, Im-*5*-*H*), 6.90−7.50 (m, 36H, phenyl-*H*, Im-*2*-*H*).

2-(*R*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl 4-Iodobenzyl Ether (10). Compound **10** was made according to general method 3 (yield 1.30 g, 48%): mp 75−76 °C; ^{1}H NMR data identical to those of compound **14.**

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl Cyclohexylmethyl Ether (11). Compound **11** was made according to Stark et al.[28] A yellowish solid foam was obtained (yield 960 mg, 1.3 mmol, 20%): mp 74 °C; ^{1}H NMR data identical to those of compound **7**.

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl Benzyl Ether (12). Compound **12** was made according to general method 3. The amount of **5** was 2.23 g (3.56 mmol) (yield 1.68 g, 2.35 mmol, 66%): mp 65−72 °C; ^{1}H NMR data identical to those of compound **8**.

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl 4-Bromobenzyl Ether (13). Compound **13** was made according to general method 3. The

amount of **5** was 1.50 g (2.40 mmol). A white hygroscopic foam was obtained (it is not possible to measure the melting point) (yield 1.55 g, 1.95 mmol, 81%): ^{1}H NMR data identical to those of compound **9**.

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl 4-Iodobenzyl Ether (14). Compound **14** was made according to general method 3 (yield 1.02 g, 1.21 mmol, 38%): mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (q, J_{AB} = 14.3 Hz, J_{AE} = 7.0 Hz, 1H, Im-CH_AH), 2.50 (broad s, 1H, N*H*), 2.61 (q, J_{AB} = 14.3 Hz, J_{BE} = 4.6 Hz, 1H, Im-CHH_B), 2.72 (q, J_{CD} = 9.0 Hz, J_{CE} = 6.2 Hz, 1H, -O-CH_CH), 2.88 (m, 1H, HNCH_E), 3.12 (q, J_{CD} = 9.0 Hz, J_{DE} = 3.7 Hz, 1H, -O-CHH_D), 4.04 (d, 1H, J_{MN} = 12.2 Hz, -O-CH_MH-(4-I-phenyl)), 4.10 (d, J_{MN} = 12.2 Hz, 1H, -O-CHH_N-(4-I-phenyl)), 6.32 (s, 1H, Im-*5-H*), 6.88 (d, $J_{2,3} = J_{5,6}$ = 8.3 Hz, 2H, 4-I-phenyl-*2,6-H*), 7.05−7.50 (m, 31H, phenyl-*H*, Im-*2-H*), 7.56 (d, $J_{2,3} = J_{5,6}$ = 8.3 Hz, 2H, 4-I-phenyl-*3,5-H*).

2-(*S*)-(Triphenylmethylamino)-3-[1-(triphenylmethyl)-imidazol-4(5)-yl]propyl Methyl Ether (15). Compound **15** was made according to general method 3. A yellowish solid foam was obtained (yield 0.99 g, 1.55 mmol, 48%): mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (q, J_{AB} = 14.2 Hz, J_{AE} = 7.2 Hz, 1H, Im-CH_AH), 2.50 (broad s, 1H, N*H*), 2.60 (m, 2H, Im-CHH_B, -O-CH_CH), 2.82 (m, 1H, HNCH_E), 3.00 (s, 4H, CH_3 and -O-CHH_D), 6.33 (s, 1H, Im-*5-H*), 7.07−7.53 (m, 31H, phenyl-*H*, Im-*2-H*).

3-[1-(Triphenylmethyl)imidazol-4(5)-yl]propyl Benzyl Ether (16). Compound **16** was made according to general method 3. The amount of **6** was 2.00 g (5.43 mmol). The eluent for column chromatography was ethyl acetate:CH_2Cl_2 (1:1). Light-yellow crystals were obtained (yield 1.56 g, 3.40 mmol, 63%): mp 86 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 2H, CH_2-CH_2-CH_2), 2.64 (t, J = 7.6 Hz, 2H, Im-CH_2), 3.49 (t, J = 6.4 Hz, 2H, O-CH_2), 4.45 (s, 2H, phenyl-CH_2), 6.51 (s, 1H, Im-*5-H*), 7.11−7.34 (m, 21H, phenyl-*H*, Im-*2-H*).

3-[1-(Triphenylmethyl)imidazol-4(5)-yl]propyl 4-Bromobenzyl Ether (17). Compound **17** was made according to general method 3. The amount of **6** was 2.00 g (5.43 mmol). The eluent for column chromatography was ethyl acetate: CH_2Cl_2 (1:1). A light-yellow oil was obtained (yield 1.83 g, 3.40 mmol, 63%): ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 2H, CH_2-CH_2-CH_2), 2.63 (t, J = 7.5 Hz, 2H, Im-CH_2), 3.47 (t, J = 6.4 Hz, 2H, O-CH_2), 4.39 (s, 2H, 4-Br-phenyl-CH_2), 6.51 (s, 1H, Im-5-H), 7.11−7.34 (m, 18H, phenyl-*H*, Im-*2-H*), 7.42 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-Br-phenyl-*3,5-H*).

3-[1-(Triphenylmethyl)imidazol-4(5)-yl]propyl 4-Iodobenzyl Ether (18). Compound **18** was made according to general method 3. The amount of **6** was 6.0 g (16.3 mmol). The eluent for column chromatography was ethyl acetate: CH_2Cl_2 (1:1). A light yellow oil was obtained (yield 5.27 g, 9.02 mmol, 55%): ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 2H, CH_2-CH_2-CH_2), 2.63 (t, J = 7.5 Hz, 2H, Im-CH_2), 3.47 (t, J = 6.4 Hz, 2H, O-CH_2), 4.39 (s, 2H, 4-I-phenyl-CH_2), 6.51 (s, 1H, Im-*5-H*), 7.04 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-I-phenyl-*2,6-H*), 7.12−7.35 (m, 16H, phenyl-*H*, Im-*2-H*), 7.62 (d, $J_{2,3} = J_{5,6}$ = 8.3 Hz, 2H, 4-I-phenyl-*3,5-H*).

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propanol Dihydrochloride (19). Compound **19** was made according to general method 4. The amount of **5** was 2.00 g (3.20 mmol). White crystals were obtained after recrystallization from ethanol/ether (yield 560 mg, 2.62 mmol, 82%): mp 200 °C (lit. 196−198 °C[36]); ^{1}H and ^{13}C NMR data were identical to those of compound **20**; $[\alpha]_D$ −2.65 ± 0.04 (SD) (23.3 °C, H_2O, c = 1); $[\alpha]_D$ −2.9 (H_2O, c = 0.01).[36] HRMS: *m/z* 142.0969, calcd for $(M + H)^+$ $C_6H_{11}N_3O$ 142.0980. Anal. ($C_6H_{11}N_3O$·2 HCl·0.4H_2O) C: calcd, 32.56; found, 34.36; H, N.

2-(*R*)-Amino-3-(1*H*-imidazol-4(5)-yl)propanol Dihydrochloride (20). Compound **20** was made according to general method 4. The amount of starting material **3** was 2.51 g (4.01 mmol). White crystals were obtained (yield 720 mg, 3.36 mmol, 84%): mp 196−197 °C (lit. 196−198 °C[36]); ^{1}H NMR (D_2O) δ 3.20 (m, 2H, Im-CH_2), 3.72 (m, 2H, HO-CH_2), 3.84 (m, 1H, NH_2-C*H*), 7.46 (s, 1H, Im-*5-H*), 8.72 (s, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ 27.03 (t, HO-CH_2), 54.66 (d, H_2N-*C*H), 62.95 (t, Im-CH_2), 120.71 (d, Im-*5-C*H), 130.24 (s, Im-*4-C*), 137.06 (d, Im-*2-C*H); $[\alpha]_D$ 2.48 ± 0.03 (SD) (23.8 °C, H_2O, c = 1); $[\alpha]_D^{20}$ 2.9 (H_2O, c = 0.01).[36] HRMS: *m/z* 142.1061, calcd for $(M + H)^+$ $C_6H_{11}N_3O$ 142.0980. Anal. ($C_6H_{11}N_3O$·2HCl) C, H, N: calcd, 19.63; found, 18.62.

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Methyl Ether Dihydrochloride (21). Compound **21** was made according to general method 4. The amount of **15** was 1.95 g (3.05 mmol). White crystals were obtained after recrystallization from ethanol/ether (yield 560 mg, 2.45 mmol, 80%): mp 181 °C; ^{1}H NMR (D_2O) δ 3.10 (d, 2H, J = 6.9 Hz, Im-CH_2), 3.31 (s, 3H, CH_3), 3.46 (q, J_{AB} = 11.1 Hz, J_{AC} = 6.2 Hz, 1H, H_3C-O-CH_AH), 3.57 (q, J_{AB} = 11.1 Hz, J_{BC} = 3.4 Hz, 1H, H_3C-O-CHH_B), 3.71 (m, 1H, H_2NCH_C), 7.34 (s, 1H, Im-5-H), 8.61 (s, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ, 27.32 (t, Im-CH_2), 52.98 (d, H_2N-*C*H), 61.70 (t, O−CH_3), 73.07 (t, O-CH_2), 120.67 (d, Im-*5-C*H), 130.43 (s, Im-*4-C*), 137,14 (d, Im-*2-C*H); $[\alpha]_D$ 8.64 ± 0.06 (SD) (23.4 °C, H_2O, c = 1). HRMS: *m/z* 156.1175, calcd for $(M + H)^+$ $C_7H_{13}N_3O$ 156.1137. Anal. ($C_7H_{13}N_3O$·2HCl) C, H, N: calcd, 18.42; found, 17.73.

2-(*R*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Cyclohexylmethyl Ether Dihydrochloride (22). Compound **22** was made according to general method 4, starting from 840 mg (1.16 mmol) of **7**. White crystals were obtained after recrystallization from ethanol/ether (yield 230 mg, 0.74 mmol, 64%): mp 246 °C; ^{1}H NMR (D_2O) δ 0.88−0.97 (m, 2H, cyclohexyl-*H*), 1.10−1.28 (m, 3H, cyclohexyl-*H*), 1.60−1.70 (m, 6H, cyclohexyl-*H*), 3.20 (m, 2H, Im-CH_2), 3.32−3.39 (m, 2H, cyclohexyl-CH_2-O-), 3.59 (q, J_{AB} = 11.1 Hz, J_{AC} = 5.8 Hz, 1H, cyclohexylmethyl-O-CH_AH), 3.71 (q, J_{AB} = 11.1 Hz, J_{BC} = 3.7 Hz, 1H, cyclohexylmethyl-O-CHH_B), 3.81 (m, 1H, H_2NCH_C), 7.42 (s, 1H, Im-5-H), 8.69 (d, J = 1.2 Hz, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ 27.45 (t, cyclohexyl-*4-C*H_2), 28.19 (t, cyclohexyl-*3,5-C*H_2), 28.99 (t, Im-*C*H_2), 32.20 (t, cyclohexyl-*2,6-C*H_2), 39.91 (t, cyclohexyl-*1-C*H), 53.03 (d, H_2N-*C*H), 71.41 (t, cyclohexyl-*C*H_2-O), 80.19 (t, O-*C*H_2-CH), 120.62 (d, Im-*5-C*H), 130.33 (s, Im-*4-C*), 137.01 (d, Im-*2-C*H); $[\alpha]_D$ −11.77 ± 0.07 (SD) (23.3 °C, H_2O, c = 1), HRMS: *m/z* 238.1930, calcd for $(M + H)^+$ $C_{13}H_{23}N_3O$ 238.1919. Anal. ($C_{13}H_{23}N_3O$·2HCl·0.5H_2O) C, H, N.

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Cyclohexylmethyl Ether Dihydrochloride (23). Compound **23** was made according to general method 4. The amount of **11** was 960 mg (1.33 mmol). White crystals were obtained after recrystallization from ethanol/ether (yield 170 mg, 0.55 mmol, 42%): mp 255 °C; ^{1}H and ^{13}C NMR data were identical to those of compound **22**; $[\alpha]_D$ 11.93 ± 0.03 (SD) (24.2 °C, H_2O, c = 1). HRMS: *m/z* 238.1947, calcd for $(M + H)^+$ $C_{13}H_{23}N_3O$ 238.1919. Anal. ($C_{13}H_{23}N_3O$·2HCl·0.13H_2O) C, H: calcd, 8.31; found, 7.60; N.

2-(*R*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Benzyl Ether Dihydrochloride (24). Compound **24** was made according to general method 4. The amount of **8** was 2.00 g (2.79 mmol). The product was recrystallized from 2-propanol/ether, yielding very hygroscopic crystals. The crystals were transferred into a flask with absolute ethanol, and the solvent was removed at first with a rotavapor and then with high vacuum, yielding a white, hygroscopic foam. The product was stored under Ar (yield 310 mg, 1.02 mmol, 37%): mp 74.5 °C; ^{1}H NMR (D_2O) δ 3.17 (m, 2H, Im-CH_2), 3.60 (q, J_{AB} = 11.0 Hz, J_{AC} = 5.4 Hz, 1H, benzyl-O-CH_AH), 3.73 (q, J_{AB} = 11.0 Hz, J_{BC} = 3.4 Hz, 1H, benzyl-O-CHH_B), 3.79 (m, 1H, H_2NCH_C), 4.57 (d, J_{MN} = 11.8 Hz, 1H, phenyl-CHH_N), 4.66 (d, J_{MN} = 11.7 Hz, 1H, phenyl-CHH_N), 7.28 (s, 1H, Im-5-H), 7.43 (m, 5H, phenyl-*H*), 8.63 (s, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ, 27.68 (t, Im-CH_2), 53.11 (d, H_2N-*C*H), 70.18 (t, benzyl-O-CH_2), 75.91 (t, phenyl-*C*H_2-O), 120.30 (d, Im-*5-C*H), 131.05 (s, Im-*4-C*), 131.38 (d, phenyl-*4-C*H), 131.48 (d, phenyl-*2,6-C*H), 131.65 (d, phenyl-*3,5-C*H), 137.27 (d, Im-*2-C*H), 139.80 (d, phenyl-*1-C*); $[\alpha]_D$ −16.43 ± 0.03 (SD) (24.4 °C, H_2O, c = 1). HRMS: *m/z* 232.1465, calcd for $(M + H)^+$ $C_{13}H_{17}N_3O$ 232.1450. Anal. ($C_{13}H_{17}N_3O$·2HCl·1.5H_2O) C, H, N.

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl Benzyl Ether Dihydrochloride (25). Compound **25** was made according to general method 4. The amount of **12** was 1.60 g (2.23 mmol).

The product was a white solid hygroscopic foam. It was stored under Ar (yield 570 mg, 1.87 mmol, 84%): mp 78 °C; ^{1}H and ^{13}C NMR data were identical to those of compound **24**; $[\alpha]_D$ 17.81 ± 0.04 (SD) (23.1 °C, H_2O, $c = 1$). HRMS: *m/z* 232.1496, calcd for $(M + H)^+$ $C_{13}H_{17}N_3O$ 232.1450. Anal. ($C_{13}H_{17}N_3O$·2HCl·1.26H_2O) C, H, N.

2-(*R*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-Bromobenzyl Ether Dihydrochloride (26). Compound **26** was made according to general method 4. The amount of **9** was 1.92 g (2.42 mmol) (yield 630 mg, 1.64 mmol, 68%): mp 181−183 °C; ^{1}H NMR (D_2O) δ 3.17 (d, 2H, J = 7.0 Hz, Im-CH_2), 3.60 (q, J_{AB} = 11.0 Hz, J_{AC} = 5.4 Hz, 1H, 4-Br-benzyl-O-CH_AH), 3.74 (q, J_{AB} = 11.0 Hz, J_{BC} = 3.3 Hz, 1H, 4-Br-benzyl-O-CHH_B), 3.80 (m, 1H, H_2NCH_C), 4.53 (d, J_{MN} = 12.0 Hz, 1H, 4-Br-phenyl-CH_MH), 4.62 (d, J_{MN} = 12.0 Hz, 1H, 4-Br-phenyl-CHH_N), 7.30 (s, 1H, Im-5-H) 7.32 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-Br-phenyl-*2,6-H*), 7.59 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-Br-phenyl-*3,5-H*), 8.60 (s, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ, 27.29 (t, Im-CH_2), 52.91 (d, H_2N-*C*H), 70.03 (t, O-*C*H_2-CH), 75.17 (t, 4-Br-phenyl-*C*H_2-O), 120.47 (d, Im-*5*-CH), 124.59 (s, phenyl-*4-C*-Br), 130.28 (s, Im-*4-C*), 133.28 (d, 4-Br-phenyl-*2,6-C*H), 134,52 (d, 4-Br-phenyl-*3,5-C*H), 136.90 (d, Im-*2-C*H), 138.95 (d, 4-Br-phenyl-*1-C*); $[\alpha]_D$ −21.72 ± 0.03 (SD) (24.6 °C, H_2O, c = 1). HRMS: *m/z* 310.0679, calcd for $(M + H)^+$ $C_{13}H_{16}BrN_3O$ 310.0555. Anal. ($C_{13}H_{16}BrN_3O$·2HCl·0.4H_2O) C, H, N.

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-Bromobenzyl Ether Dihydrochloride (27). Compound **27** was made according to general method 4. The amount of **13** was 1.55 g (1.95 mmol) (yield: 630 mg, 1.64 mmol, 84%): mp 183 °C; ^{1}H and ^{13}C NMR data were identical to those of compound **26**; $[\alpha]_D$ 20.26 ± 0.03 (SD) (23.9 °C, H_2O, c = 1). HRMS: *m/z* 310.0532, calcd for $(M + H)^+$ $C_{13}H_{16}BrN_3O$ 310.0555. Anal. ($C_{13}H_{16}BrN_3O$·2HCl·1.16H_2O) C, H, N.

2-(*R*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-Iodobenzyl Ether Dihydrochloride (28). Compound **28** was made according to general method 4. The amount of **10** was 1.30 g (1.54 mmol). White crystals were obtained after recrystallization from ethanol/ether (yield: 470 mg, 1.09 mmol, 71%): mp 192 °C; ^{1}H NMR (D_2O) δ 3.22 (d, 2H, J = 7.4 Hz, Im-CH_2), 3.64 (q, J_{AB} = 11.0 Hz, J_{AC} = 5.4 Hz, 1H, 4-I-benzyl-O-CH_AH), 3.78 (q, J_{AB} = 11.0 Hz, J_{BC} = 3.3 Hz, 1H, 4-I-benzyl-O-CHH_B), 3.87 (m, 1H, H_2NCH_C), 4.54 (d, J_{MN} = 12.1 Hz, 1H, 4-I-phenyl-CH_MH), 4.63 (d, J_{MN} = 12.1 Hz, 1H, 4-I-phenyl-CHH_N), 7.19 (d, $J_{2,3} = J_{5,6}$ = 8.1 Hz, 2H, 4-I-phenyl-*2,6-H*), 7.35 (s, 1H, Im-5-H), 7.75 (d, $J_{2,3} = J_{5,6}$ = 8.1 Hz, 2H, 4-I-phenyl-*3,5-H*), 8.69 (s, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ 27.16 (t, Im-CH_2), 52.75 (d, H_2N-*C*H), 70.02 (t, O-*C*H_2-CH), 75.09 (t, 4-I-phenyl-*C*H_2-O), 96.38 (s, phenyl-*4-C*-I), 120.35 (d, Im-*5*-CH), 130.01 (s, Im-*4-C*), 133.15 (d, 4-I-phenyl-*2,6-C*H), 136.71 (d, Im-*2-C*H), 139.38 (d, 4-I-phenyl-*1-C*), 140,34 (d, 4-I-phenyl-*3,5-C*H); $[\alpha]_D$ −22.04 ± 0.03 (SD) (23.6 °C, H_2O, c = 1). HRMS: *m/z* 358.0042, calcd for $(M + H)^+$ $C_{13}H_{16}IN_3O$ 358.0416. Anal. ($C_{13}H_{16}IN_3O$·2HCl) C, H, N.

2-(*S*)-Amino-3-(1*H*-imidazol-4(5)-yl)propyl 4-Iodobenzyl Ether Dihydrochloride (29). Compound **29** was made according to general method 4. The amount of **14** was 0.99 g (1.18 mmol) (yield 360 mg, 0.84 mmol, 71%): mp 191 °C; ^{1}H and ^{13}C NMR data were identical to those of compound **28**; $[\alpha]_D$ 22.32 ± 0.04 (SD) (23.7 °C, H_2O, c = 1), HRMS: *m/z* 358.0442, calcd for $(M + H)^+$ $C_{13}H_{16}IN_3O$ 358.0416. Anal. ($C_{13}H_{16}IN_3O$·2HCl) C, H, N.

3-(1*H*-Imidazol-4(5)-yl)propyl Benzyl Ether Maleate (30). Compound **30** was made according to Stark et al.[28] The amount of **16** was 1.50 g (3.27 mmol). White crystals were obtained (yield 610 mg, 1.84 mmol, 56%): mp 75 °C (lit. 61 °C[33]); ^{1}H NMR (D_2O) δ 1.96 (m, 2H, CH_2-CH_2-CH_2), 2.78 (t, J = 7.3 Hz, 2H, Im-CH_2), 3.58 (t, J = 6.2 Hz, 2H, O-CH_2), 4.52 (s, 2H, phenyl-CH_2), 6.29 (s, 2H, maleic acid), 7.10 (s, 1H, Im-*5-H*), 7.36-7.45 (m, 5H, phenyl-*H*), 8.51 (d, J = 1.3, 1H, Im-*2-H*); ^{13}C NMR (D_2O) δ 39.04 (t, CH_2-*C*H_2-CH_2), 44.46 (t, Im-*C*H_2), 77.32 (t, O-*C*H_2CH$_2$), 80.60 (t, O-*C*H_2-phenyl), 114.80 (d, Im-*5-C*H), 125.23 (d, phenyl-*4-C*), 125.46 (d, phenyl-*2,6-C*), 125.54 (d, phenyl-*3,5-C*), 128.69 (s, Im-*4-C*), 129.06 (s, phenyl-*1-C*), 130.10 (d, maleic acid-*2,3-C*H), 132,44 (d, Im-*2-C*H), 159.39 (s, maleic acid-*1,4-C*OOH). HRMS: *m/z* 216.1255, calcd for $(M)^+$ $C_{13}H_{16}N_2O$ 216.1262. Anal. ($C_{13}H_{16}N_2O$·2$C_2H_2O_2$) C, H, N.

3-(1*H*-Imidazol-4(5)-yl)propyl 4-Bromobenzyl Ether Maleate (31). Compound **31** was made according to Stark et al.[28] The amount of **17** was 1.83 g (3.40 mmol). White crystals were obtained (yield 230 mg, 0.56 mmol, 16%): mp 125 °C (lit. 120 °C[28]); ^{1}H NMR (D_2O) δ 1.94 (m, 2H, CH_2-CH_2-CH_2), 2.77 (t, J = 7.4 Hz, 2H, Im-CH_2), 3.56 (t, J = 6.2 Hz, 2H, O-CH_2), 4.48 (s, 2H, 4-I-phenyl-CH_2), 6.30 (s, 2H, maleic acid), 7.16 (s, 1H, Im-*5-H*), 7.28 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-Br-phenyl-*2,6-H*), 7.56 (d, $J_{2,3} = J_{5,6}$ = 8.4 Hz, 2H, 4-Br-phenyl-*3,5-H*), 8.55 (d, J = 1.3, 1H, Im-*2-H*); ^{13}C NMR (D_2O/DMSO-d_6) δ 23.16 (t, CH_2-*C*H_2-CH_2), 29.93 (t, Im-*C*H_2), 71.02 (t, O-*C*H_2CH$_2$), 74.17 (t, 4-Br-phenyl-*C*H_2-O), 117.81 (d, Im-*5-C*H), 124.00 (s, phenyl-*4-C*-Br), 132.85 (d, 4-Br-phenyl-*2,6-C*H), 134.13 (d, 4-Br-phenyl-*3,5-C*H), 135.23 (s, Im-*4-C*), 135.74 (s, 4-Br-phenyl-*1-C*), 137.56 (d, maleic acid-*2,3-C*H), 139.29 (d, Im-*2-C*H), 172.94 (s, maleic acid-*1,4-C*OOH). HRMS: *m/z* 294.0371, calcd for $(M)^+$ $C_{13}H_{15}BrN_2O$ 294.0368. Anal. ($C_{13}H_{15}BrN_2O$·2$C_2H_2O_2$) C, H, N.

3-(1*H*-Imidazol-4(5)-yl)propyl 4-Iodobenzyl Ether Maleate, Iodoproxyfan (32). Compound **32** was made according to Stark et al.[28] The amount of **18** was 5.2 g (8.90 mmol). White crystals were obtained (yield 2.18 g, 4.76 mmol, 53%): mp 130 °C (lit. 123−124 °C[28]); ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H, CH_2-CH_2-CH_2), 2.72 (t, J = 7.6 Hz, 2H, Im-CH_2), 3.46 (t, J = 6.1 Hz, 2H, O-CH_2), 4.42 (s, 2H, 4-I-phenyl-CH_2), 6.09 (s, 2H, maleic acid), 7.13 (d, $J_{2,3} = J_{5,6}$ = 8.1 Hz, 2H, 4-I-phenyl-*2,6-H*), 7.40 (s, 1H, Im-*5-H*), 7.71 (d, $J_{2,3} = J_{5,6}$ = 8.2 Hz, 2H, 4-I-phenyl-*3,5-H*), 8.92 (s, 1H, Im-*2-H*); ^{13}C NMR (DMSO-d_6) δ 20.95 (t, CH_2-*C*H_2-CH_2), 28.01 (t, Im-*C*H_2), 68.44 (t, O-*C*H_2CH$_2$), 71.06 (t, 4-I-phenyl-*C*H_2−O), 93.12 (s, phenyl-*4-C*-I), 115.52 (d, Im-*5-C*H), 129.54 (s, maleic acid-*1,4-C*OOH), 133.12 (s, Im-*4-C*), 133.67 (s, 4-I-phenyl-*1-C*), 135.70 (d, 4-I-phenyl-*2,6-C*H), 136.90 (d, 4-I-phenyl-*3,5-C*H), 138.26 (d, Im-*2-C*H), 167.29 (d, maleic acid-*2,3-C*H). HRMS: *m/z* 342.0266, calcd for $(M)^+$ $C_{13}H_{15}IN_2O$ 342.0229. Anal. ($C_{13}H_{15}IN_2O$·2$C_2H_2O_2$) C, H, N.

Pharmacology. In Vitro Screening for Histamine H_3-Receptor Agonistic and Antagonistic Activity. For GTPγ[^{35}S] autoradiography, 20 μm-thick brain sections from Wistar male rats (age 4 weeks) were incubated using a three-step protocol, as described by Laitinen et al.[30] GDP (2 mM) and the adenosine A_1-receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 10 μM) were present throughout steps 2 and 3. In step 3, brain sections were incubated with the indicated concentrations of the drugs in the presence of the radioligand GTPγ[^{35}S], followed by washing and drying. Autoradiograms were generated by apposing tissue sections to Hyperfilm-βmax (Amersham). Autoradiographs were digitized and images quantitated based on [^{14}C] standards. Responses were quantitated from the cerebral cortex and the striatum (two H_3-receptor-enriched brain regions). Cerebellum is devoid of H_3-receptors and H_3-receptor dependent GTPγ-[^{35}S] binding[30] and served as a control for possible nonspecific effects of the tested compounds. For the cortex and striatum, responses were quantitated from four individual animals.

In the antagonistic screening procedure, sections were first incubated with the indicated concentrations of the antagonists (present throughout steps 2 and 3) and then incubated in the presence of 1 μM HA plus the indicated concentrations of the antagonists (step 3). The established H_3-receptor antagonists thioperamide, clobenprobit, and iodoproxyfan, were included as controls.

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