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Piperidine variations in search for non-imidazole histamine H_3 receptor ligands

Dorota Łażewska [a], Kamil Kuder [a], Xavier Ligneau [b], Jean-Charles Schwartz [b], Walter Schunack [c], Holger Stark [d], Katarzyna Kieć-Kononowicz [a,*]

[a] Jagiellonian University Medical College, Faculty of Pharmacy, Department of Technology and Biotechnology of Drugs, Medyczna 9, 30-688 Kraków, Poland
[b] Bioprojet-Biotech, 4 rue du Chesnay Beauregard, BP 96205, 35762 Saint-Grégoire, France
[c] Institut für Pharmazie, Freie Universität Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany
[d] Institut für Pharmazeutische Chemie, Biozentrum/ZAFES, Johann Wolfgang Goethe-Universität, Max-von-Laue-Strasse 9, 60438 Frankfurt/Main, Germany

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ABSTRACT

Synthesis and biological evaluation of the novel histamine H_3 receptor ligands is described. Two series of ethers (aliphatic and aromatic) have been prepared by four different methods. Compounds were evaluated for their affinities at recombinant human H_3 receptor stably expressed in CHO cells. The ethers show from low to moderate in vitro affinities in nanomolar concentration range. The most potent compound was the 1-[3-(4-*tert*-butylphenoxy)propyl]-4-piperidino-piperidine **16** (hH_3R K_i = 100 nM). Several members of the new series investigated under in vivo conditions, proved to be inactive.

1. Introduction

The histamine H_3 receptor (H_3R) has been known since 1983 when it was first characterized in rats by Arrang et al.[1] It has been identified in the central nervous system (CNS) and peripheral nervous system as a pre-synaptic receptor controlling the release of histamine and numerous other neurotransmitters (e.g. dopamine, acetylcholine, noradrenaline and GABA).[2,3]

The first histamine H_3R ligands (agonists, partial agonists and antagonists) were described in 1987, establishing the pharmacological identity of the receptor.[4] Since then a lot of potent histamine H_3R ligands have been prepared (for review see Refs. 5–10).

At the beginning, histamine H_3R antagonists were imidazole-containing compounds but due to the unwanted hepatic cytochrome P450 inhibition and potential drug–drug interactions, a new class of histamine H_3R antagonists (non-imidazole ones) was synthesized. In 1998 Ganellin et al. described active compounds with a piperidine and a pyrrolidine moiety as a good replacement of the imidazole ring.[11]

Now, this class of compounds is rapidly developing with unexpected large structural variations.[12–20] Some of the potent antagonists are presented on Figure 1.[5,21] Among them there is the new natural product, *conessine* (Fig. 1), a steroidal alkaloid with high potency and selectivity for both human and rat histamine H_3R.[22]

The first general construction pattern of H_3R non-imidazole antagonists was suggested in 2003 by Apodaca et al. containing: an amine group, a lipophilic core (an aromatic ring) and the second amine group.[23]

Recently, an updated pharmacophore model was suggested by Celanire et al.[5,10] generated from the numerous patent applications and medicinal chemistry papers. The model contains three main elements: a western part (with the amine moiety and a linker), a central core (the phenyl-like) and an eastern part (with a high chemical diversity) (Fig. 2).

Potential therapeutic indications for histamine H_3R antagonists include attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), narcolepsy, epilepsy, schizophrenia and obesity (for review see Refs. 24–28).

The histamine H_3R shows a high level of constitutive activity in both in vivo and in vitro studies, which might be critical for its regulatory function in the CNS.[29–31] This constitutive activity of histamine H_3R implies that inverse agonists (instead of neutral antagonists) may be useful in psychiatric disorders (e.g., AD).[32] However, the pharmacological effects of histamine H_3R ligands are complex as some compounds (e.g., Proxyfan, Fig. 3)[33,34] belong to all of the known classes of ligands (full agonist, partial agonist, neutral antagonist, partial inverse agonist or full inverse agonist, i.e., protean agonist) investigated in different systems or models.[35]

Some of the non-imidazole histamine H_3R antagonists have reached clinical studies (phases I and II): BF2.649 (Fig. 1; epilepsy), GSK-189254 (Fig. 1; dementia) and JNJ-17216498 (structure not

* Corresponding author. Tel.: +48 12 657 04 88; fax + 48 12 657 04 88.
E-mail address: mfkonono@cyf-kr.edu.pl (K. Kieć-Kononowicz).

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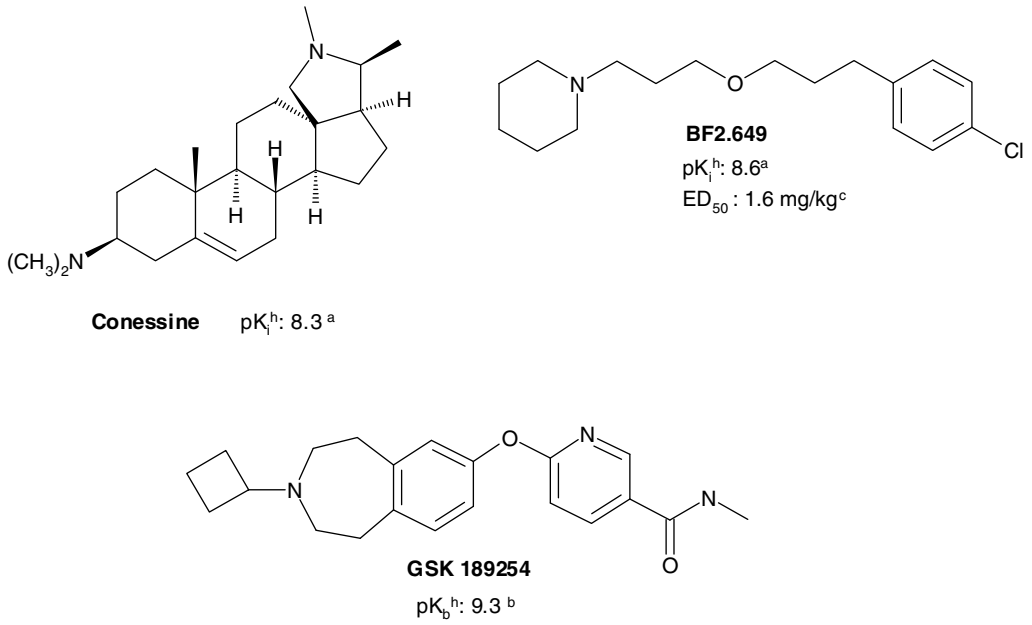


Figure 1. Structures of potent non-imidazole histamine H_3 antagonists.[5,21,22] (a) Binding assay to recombinant human histamine H_3 receptor. (b) GTPγS binding assay to recombinant human histamine H_3 receptor. (c) Histamine H_3 receptor screening after po administration to mice.

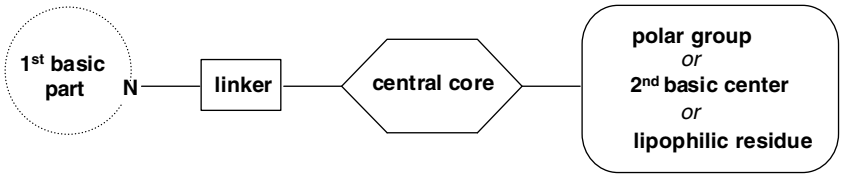


Figure 2. The modified pharmacophore model for non-imidazole histamine H_3 receptor antagonists.[5,10]

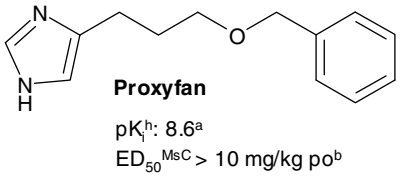


Figure 3. The structure and the activity of Proxyfan.[33,34] (a) Binding assay to recombinant human histamine H_3 receptor. (b) Histamine H_3 receptor screening after po administration to mice.

known, narcolepsy) and available results from these trials are referenced in http://clinicaltrials.gov/ct2/home.[10]

The present report provides an account of the synthesis and pharmacological evaluation of the new histamine H_3 receptor ligands. Compound FUB 637 (Fig. 4), a potent histamine H_3 receptor antagonist tested in vitro (hK_i: 3.1 nM) and in vivo (ED_{50}: 3.7 ± 1.0), was taken as a lead structure.[36]

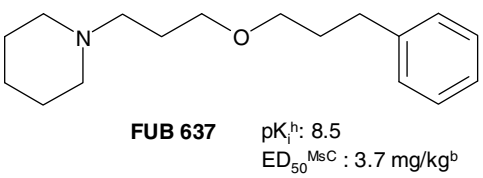


Figure 4. The structure and potencies of FUB 637.[36] (a) Binding assay to recombinant human histamine H_3 receptor. (b) Histamine H_3 receptor screening after po administration to mice.

In order to increase the collection of the structure–activity data of the piperidine-like compounds two series of FUB-type derivatives were synthesized and tested. In the first series, the piperidine ring has been replaced by the substituted piperidine ring (compounds **4**–**6**) or the other related nitrogen-containing heterocycles (compounds **4**–**8**) to investigate if it were possible to maintain their affinity for the histamine H_3 receptor.

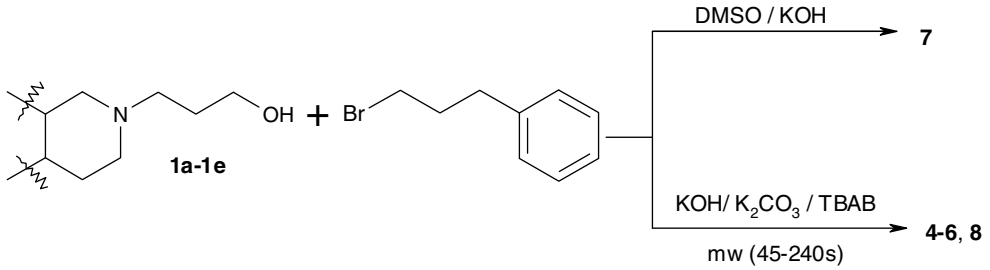
In the second series bipiperidine derivatives (compounds **9**–**16**) were analysed. The modification depended on the replacement of the strain propyloxy chain by a piperidine ring to reduce flexibility of this part of the molecule (a similar work was previously reported by Dvorak et al. with 4-hydroxypiperidine as a good replacement for the piperidinylpropyloxy fragment).[37] Also 3-phenylpropyl moiety was modulated and the compounds with two or three methylene linkers were prepared.

The compounds described herein were investigated in vitro for their histamine H_3 receptor potencies at human H_3 receptors stably expressed in CHO cells. Selected ligands were additionally screened in vivo for their antagonist potencies in the CNS after per os administration to mice.

2. Results

2.1. Chemistry

Two different strategies for the synthesis of the novel ethers **4**–**16** were employed. In the first approach aminoalcohols **1a**–**1e** were alkylated by Williamson-type O-alkylation with 1-bromo-3-phenylpropane (Scheme 1). This alkylation was conducted either in



Scheme 1. The synthesis of ethers **4**–**8**.

DMSO/KOH system at room temperature (compound **7**) or under microwave irradiation conditions in a domestic microwave oven (compounds **4**–**6** and **8**) as described previously.[13]

Aminoalkanols **1a**–**1e** were obtained from appropriate secondary amines and 3-chloropropan-1-ol by the method described earlier (with small excess of the amine; **1c**) or with small modifications (equal volume of reagents; **1a**, **1b**, **1d** and **1e**) (Scheme 2).[38]

In an alternative approach 4-piperidino-piperidine was N-alkylated with the appropriately substituted 2-phenoxyethyl bromides (**2a**–**2e**) or 3-phenoxypropyl bromides (**3b**, **3e** and **3f**) (Scheme 3). This type of coupling proceeded in two different conditions either in acetonitrile in the presence of anhydrous K_2CO_3 (15 h heating) or in the presence of $K_2CO_3$with KI in EtOH with water (8 h heating) (Scheme 3).

The aryloxyalkylbromides required (**2a**–**2e**, **3b**, **3e** and **3f**; Scheme 4) were prepared from suitable phenols and alpha, omega-alkylenedibromides in propan-1-ol. The desired products were free bases.

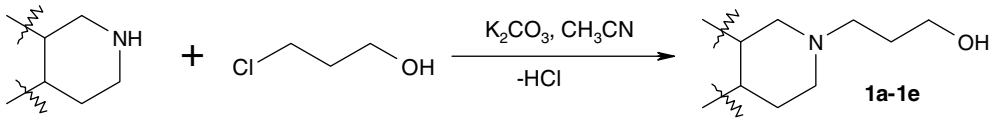
The final compounds **4**–**16** were isolated as salts of oxalic acid (hydrogen oxalates or dihydrogen oxalates). Their purity was checked by TLC, and their structures were confirmed by standard spectral techniques (^{1}H NMR, IR) and elemental analysis (cf. Section 5).

2.2. Pharmacology

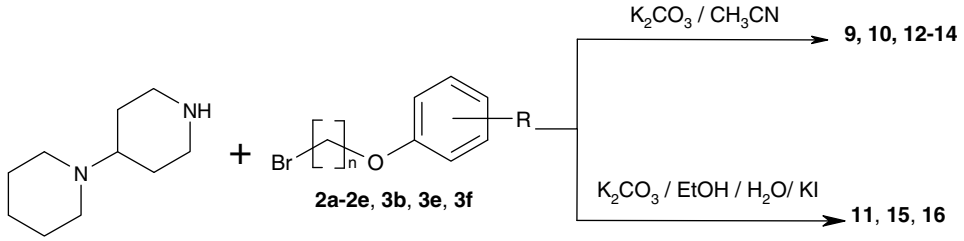
Histamine H_3 receptor affinities of the newly synthesized compounds were evaluated at the human receptor. The displacement curves of [^{125}I]iodoproxyfan binding at human histamine H_3R expressed in CHO-K1 cells stably transfected with the full-length coding sequence of the human H_3R, were measured as described previously.[34,39] Selected compounds were screened in an in vivo assay on the modulation of N^{τ}-methylhistamine levels in the brain cortex of Swiss mice after per os treatment. Results of the pharmacological screening are summarized in Table 1 (for **4**–**8**) and Table 2 (for **9**–**16**).

3. Discussion

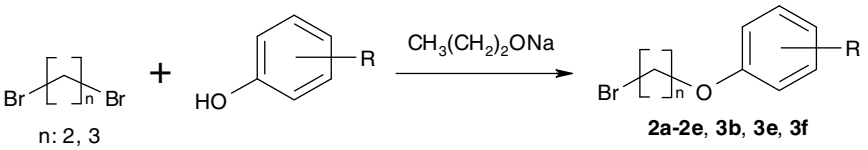
All investigated compounds, with the exception of **11** (K_i > 10,000 nM), exhibited a moderate level of H_3 receptor binding affinity in the nanomolar concentration range (K_i: 100–560 nM).



Scheme 2. The synthesis of aminoalkanols **1a**–**1e**.



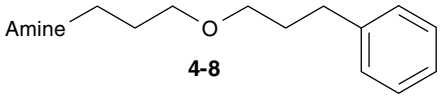
Scheme 3. The synthesis of ethers **9**–**16**.



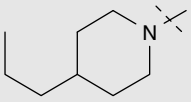
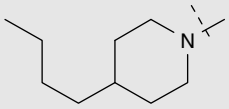
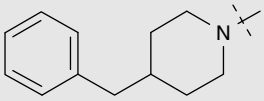
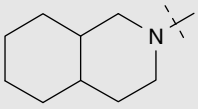
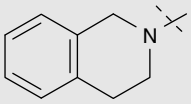
R: **a**: 3-Cl, **b**: 3-OCH_3, **c**: 3-CF_3, **d**: 4-CH_3, **e**: 4-Cl, **f**: 4-*tert*-butyl

Scheme 4. The synthesis of 2-phenoxyethyl bromides (**2a**–**2e**) and 3-phenoxypropyl bromides (**3b**, **3e** and **3f**).

Table 1
Binding affinities of compounds **4**–**8** at the human histamine H_3 receptor

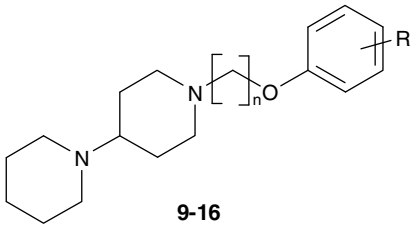


4-8

Compound	Amine	H_3 potency	
		In vitro hK_i[a] [nM] $x \pm$ SEM	In vivo ED_{50}[b] [mg/kg] po
4		249 ± 22	>10
5		274 ± 27	>10
6		326 ± 66	>10
7		393 ± 90	>10
8		560 ± 136	>10
FUB 637		3.1 ± 0.5[c,d]	3.7 ± 1.0[d]

[a] [^{125}I]Iodoproxyfan binding assay at human histamine H_3 receptors stably expressed in CHO-K1 cells.
[b] Central histamine H_3 receptor assay in vivo after po administration to mice.
[c] [^{3}H]-(*R*)-α-methylhistamine binding assay at human histamine H_3 receptors stably expressed in C6 cells.
[d] Ref. 36.

Table 2
Binding affinities of the compounds **9**–**16** at the human histamine H_3 receptor



9-16

Compound	*n*	R	H_3 potency	
			In vitro hK_i[a] [nM ± SEM]	In vivo ED_{50}[b] [mg/kg] po
9	2	3-Cl	235 ± 57	[c]
10	2	3-OCH_3	132 ± 30	[c]
11	3	3-OCH_3	> 10,000	>20
12	2	3-CF_3	164 ± 64	[c]
13	2	4-CH_3	300 ± 98	[c]
14	2	4-Cl	176 ± 45	[c]
15	3	4-Cl	165	>20
16	3	4-*tert*-butyl	100	>20
FUB 637			3.1 ± 0.5[d,e]	3.7 ± 1.0[e]

[a] [^{125}I]Iodoproxyfan binding assay at human histamine H_3 receptors stably expressed in CHO-K1 cells.
[b] Central histamine H_3 receptor assay in vivo after po administration to mice.
[c] Not tested.
[d] [^{3}H]-(*R*)-α-methylhistamine binding assay at human histamine H_3 receptors stably expressed in C6 cells.

In the aliphatic ether series (**4**–**8**, Table 1) introduction of a substituent in 4-position of the piperidine moiety decreased the affinity. The highest in vitro potency in this series was determined for the 4-propylpiperidine which decreased along with the introduction of larger substituents on the piperidine moiety or an additional ring system. The lowest potency was determined for a tetrahydro-isoquinoline derivative **8** (560 nM). All these compounds were inactive in vivo in a dosage of 10 mg/kg.

In the second aromatic series (Table 2), a 4-piperidino-piperidine moiety instead of the 3-piperidinopropyloxy template was introduced. However, apparently no improvement in H_3 receptor binding affinity was gained in comparison to that of FUB 637. The prepared compounds (**9**–**16**) are much less active than the lead structure (hH_3R $K_i \geqslant 100$ nM). The most potent is compound **16** (K_i: 100 nM), however, 33 times less active than FUB 637.

In addition, an elongation of the alkyl spacer from two to three carbon atoms did not cause a significant increase in H_3 receptor affinity (compound **14** vs compound **15**). The effects on the histamine hH_3R are only slightly influenced by substituents on the phenyl moiety. Substitution at the *para*-position showed slightly improved binding potency than that of the *meta*-substitution (compound **14** vs compound **9**). In the *meta*-substituted series (**9**–**12**), highest affinity (K_i: 132 nM) was observed for the compound incorporating the methoxy substituent (**10**). Unexpectedly, the lack of affinity was observed for compound **11** (homologue of **10**) which did not show any histamine H_3 receptor potency in vitro (K_i > 10,000 nM). In contrast to the other substitution patterns this variations led to a total loss of affinity. All compounds in this

series (**11**, **15** and **16**) were inactive in vivo in a dosage of 20 mg/kg po.

Compound **16** is the analogue of the compound 1-[3-(4-*tert*-butylphenoxy)propyl]piperidine (hK_i: 22 nM; ED_{50}: 2.8 mg/kg po) previously published.[13] Introduction of the additional piperidine ring caused diametrically opposed effect to our intention. Compound **16**, 4-piperidino-piperidine derivative, is about fivefold less potent in vitro and more than sevenfold potent in in vivo studies than the piperidine analogue.

4. Conclusion

The prepared compounds were less active than the lead structure FUB 637. The suggested changes both in the aliphatic ether series (larger basic moiety) and the aromatic ether series (piperidine linker) did not suit to histamine H_3 receptor. However, the examined compounds showed moderate affinities, the obtained results may contribute to the better understanding of the SAR of the non-imidazole histamine H_3 receptor ligands.

5. Experimental

5.1. Chemistry

5.1.1. General procedures

Melting points were determined on a MEL-TEMP II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian-Mercury 300 MHz spectrometer in DMSO-$d_6$or $CDCl_3$. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane as reference. Data are reported in the following order: multiplicity (br, broad; def, deformed; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet* or massif**; dHIQ, decahydro-isoquinoline; Ph, phenyl; Pip, piperidino; tHIQ, 1,2,3,4-tetrahydro-isoquinoline), approximate coupling constants *J* in hertz (Hz), number of protons. Mass spectra (MS) were obtained on an EI-MS Finnigan MAT CH7A (70EV, EI spectra). IR spectra were recorded with a Perkin-Elmer 297 spectral photometer or FT Jasco IR spectrometer from KBr discs (s, strong). Elemental analyses (C, H, N) were measured on Perkin-Elmer 240B or Elemental Vario-EL III instrument and are within ± 0.4% of the theoretical values. Column chromatography (CC) was performed using silica gel 60 (0.063–0.20 mm; Merck). TLC was carried out using silica gel F_{254} plates (Merck). The spots were visualized with Dragendorff's reagent or by UV absorption at 254 nm. The following abbreviations are used: CH_2Cl_2, dichloromethane; CH_3CN, acetonitrile; DMSO, dimethyl sulfoxide; Et_2O, diethyl ether; EtOH, ethanol; KI, potassium iodide; MeOH, methanol; TBAB, tetrabutylammonium bromide; W, watt; * the centre of the chemical shift is given; ** the range of the whole signal is given.

5.1.2. General procedure for the preparation of aminoalkanols (1a–1f)

Aminoalkanols were prepared according to Ref. 40, as described previously.[38]

5.1.3. General procedure for the synthesis of 2-phenoxyethyl bromides (2a–2e) and 3-phenoxypropyl bromides (3b, 3e and 3f)

To the solution of sodium (0.2 mol, 4.6 g) in 200 mL of propan-1-ol, a proper derivative of the phenol was added (0.2 mol) and 1, 2-dibromoethane or 1,3-dibromopropane (0.6 mol) was added dropwise for over 1 h. Then, the reaction mixture was heated at 60 °C for 3 h and refluxed for the next 3 h. The propan-1-ol was evaporated, and to the residue 50 mL of 10% NaOH was added and extracted with CH_2Cl_2 (50 mL) (for 4-chlorophenol **2e** after adding NaOH the mixture was left in the refrigerator for next day and the white solid was filtered). The organic solution was dried (Na_2SO_4) and evaporated to give a pure oil or further purified by CC.

5.1.3.1. 1-Bromo-2-(3-chlorophenoxy)ethane (2a). From 3-chlorophenol (0.2 mol, 25.7 g). Yield 47%.

5.1.3.2. 1-Bromo-2-(3-methoxyphenoxy)ethane (2b). From 3-me-thoxyphenol (0.1 mol, 12.4 g). Bp 95–96 °C (0.35 mm Hg) from Ref. 41. Yield 41%.

5.1.3.3. 1-Bromo-2-(3-trifluoromethylphenoxy)ethane (2c). From 3-trifluoromethylphenol (0.05 mol, 8.1 g). Yield: 41%.

5.1.3.4. 1-Bromo-2-(4-methylphenoxy)ethane (2d). From 4-methylphenyl (0.1 mol, 10.8 g). Yield 29%.

5.1.3.5. 1-Bromo-2-(4-chlorophenoxy)ethane (2e). From 4-chlorophenol (0.2 mol, 25.7 g). The white solid was crystallized from Et_2O/H_2O. Mp 36–38 °C (34–38 °C from Ref. 42). Yield: 31%.

5.1.3.6. 1-Bromo-3-(3-methoxyphenoxy)propane (3b). From 3-methoxyphenol (0.1 mol, 12.4 g). The residue after the extraction was purified by CC (CH_2Cl_2). Yield: 12%.

5.1.3.7. 1-Bromo-3-(4-chlorophenoxy)propane (3e). From 4-chlorophenol (0.1 mol, 12.9 g). The residue after the extraction was purified by CC (CH_2Cl_2). Yield: 84%.

5.1.3.8. 1-Bromo-3-(4-*tert*-butylphenoxy)propane (3f). From 4-*tert*-butylphenol (0.1 mol, 15.0 g). The residue after the extraction was purified by CC (CH_2Cl_2). The crude product contaminated with 4-*tert*-butylphenol was used without further purification.

5.1.4. General procedure for the preparation of ethers 4–6 and 8

A mixture of appropriate 3-aminopropan-1-ol (**1a–1c**, 5.0 mmol), an alkyl halide (6.0 mmol), TBAB (0.17 g, 0.5 mmol), K_2CO_3 (4.8 g, 20 mmol) and KOH (1.1 g, 20 mmol) was heated in a domestic microwave oven (*M* = 100 W) in an open Erlenmeyer flask for the appropriate time. After cooling, the reaction mixture was extracted with CH_2Cl_2 (2× 20 mL). The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with 20 mL of 0.2% HCl and/or H_2O. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and after concentration, crystallized as salt of oxalic acid from EtOH/Et_2O.

5.1.4.1. 4-Propyl-1-[3-(phenylpropoxy)propyl]piperidine hydrogen oxalate (4). From 3-(4-propyl-piperidin-1-yl)-propan-1-ol (0.10 g, 0.5 mmol). Heated in the microwave oven for 60 s. Washed with 0.2% HCl and H_2O. Yield: 25%. Mp 106–108 °C. ^{1}H NMR [$CDCl_3$]: δ = 7.30–7.15 (m, 5H, Ph-2,3,4,5,6-*H*), 3.67 (def t, 2H, C*H*$_2$-Ph), 3.45–3.36 (m, 4H, C*H*$_2$-O-C*H*$_2$), 3.07 (t, *J* = 6.3 Hz, 2H, Pip-C*H*$_2$), 2.67–2.53 (m, 4H, Pip-2,6-*H*), 1.99–1.81 (m, 6H, PipCH$_2$-C*H*$_2$ + Pip-3,5-*H*), 1.73–1.61 (m, 2H, -C*H*$_2$-CH$_2$Ph), 1.44–1.28 (m, 5H, Pip-4-*H* + (C*H*$_2$)$_2$-4-Pip), 0.89 (t, *J* = 6.3 Hz, 3H, C*H*$_3$).

Anal. calcd for $C_{20}H_{33}NO \times C_2H_2O_4$ (M_r: 399.53).

5.1.4.2. 4-Butyl-1-[3-(phenylpropoxy)propyl]piperidine hydrogen oxalate (5). From 3-(4-butylpiperidin-1-yl)propan-1-ol(0.20 g, 1 mmol). Heated in the microwave oven for 60 s. Washed with 0.2% HCl and H_2O. Yield: 27%. Mp 117–119 °C. ^{1}H NMR [DMSO-d_6]: δ = 7.28–7.23 (m, 2H, Ph-3,5-*H*), 7.23–7.13 (m, 3H, Ph-2,4,6-*H*), 3.40–3.32 (m, 6H, C*H*$_2$-O-C*H*$_2$ + Pip-2,6-*H*$_e$), 2.99 (t, *J* = 7.7 Hz, 2H, C*H*$_2$-Ph), 2.83–2.76 (m, 2H, Pip-2,6-*H*$_a$), 2.59 (t, *J* = 7.4 Hz, 2H, Pip-C*H*$_2$), 1.90–1.72 (m, 6H, PipCH$_2$-C*H*$_2$ + Pip-3,5-

H), 1.39–1.21 (m, 9H, H_3C-(CH_2)$_3$-Pip + Pip-4-*H* + CH_2-CH_2Ph), 0.85 (t, *J* = 6.3 Hz, 3H, CH_3); MS (70 eV); *m/z* (%) = 317 ([M·]$^+$, 2), 198 (18), 154 (100), 91(27); IR (KBr) (cm^{-1}): 1114s (*ν* [C–O–C]).

Anal. calcd for $C_{21}H_{35}NO \times C_2H_2O_4$($M_r$: 407.56): C, 67.78; H, 9.15; N, 3.44. Found: C, 67.45; H, 9.23; N, 3.39.

5.1.4.3. 4-Benzyl-1-[3-phenylpropoxy)propyl]piperidine hydrogen oxalate (6). From 3-(4-benzylpiperidin-1-yl)propan-1-ol (1.17 g, 5 mmol). Heated in the microwave oven for 240 s (4× 60 s). After removing the solvent under reduced pressure, the residue was purified by CC [eluent $CHCl_3$/MeOH/MeOH saturated with gaseous NH_3; 98:2:2]. Yield: 19%. Mp 112–114 °C. ^{1}H NMR [$CDCl_3$]: *δ* = 7.32–7.21 (m, 6H, Ph-2,4,6-*H* + Ph-2′,4′,6′-*H*), 7.21–7.11 (m, 4H, Ph-3,5-*H* + Ph-3′,5′-*H*), 3.61 (br s, 2H, Ph′-CH_2-Pip), 3.42 (t, *J* = 5.6 Hz, 2H, O-CH_2), 3.38 (t, *J* = 6.6 Hz, 2H, CH_2-O), 3.06 (t, *J* = 7.7 Hz, 2H, CH_2-Ph), 2.67–2.58 (m, 6 H, Pip-2,6-*H* + Pip-CH_2), 2.01–1.90 (m, 3H, PipCH_2-CH_2 + Pip-4-*H*), 1.88–1.75 (m, 6H, Pip-3,5-*H* + CH_2-CH_2Ph); MS (70 eV); *m/z* (%) = 351 ([M·]$^+$, 5), 258 (20), 188 (100), 98 (16); IR (KBr) (cm^{-1}): 1114s (*ν* [C–O–C]).

Anal. calcd for $C_{24}H_{33}NO \times C_2H_2O_4$($M_r$: 441.58): C, 70.72; H, 7.98; N, 3.17. Found: C, 70.46; H, 7.85; N, 3.25.

5.1.4.4. 2-[3-(3-Phenylpropoxy)propyl]-1,2,3,4-tetrahydro-isoquinoline hydrogen oxalate (8). From 3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-propan-1-ol (0.48 g, 2.5 mmol). Heated in the microwave oven for 45 s. Washed twice H_2O (20 mL). Yield: 10%. Mp. 101–103 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.28–7.12 (m, 9H, Ph-2,3,4,5,6-*H* + tHIQ-5,6,7,8-*H*), 4.22 (s, 2H, tHIQ-1-*H*), 3.43 (t, *J* = 6.1 Hz, 2H, CH_2-O), 3.38–3.25 (m, 4H, CH_2O-CH_2 + tHIQ-4-*H*), 3.07 (t, *J* = 8.0 Hz, 2H, tHIQ-3-*H*), 3.01 (t, *J* = 6.1 Hz, 2H, tHIQ-CH_2), 2.59 (t, *J* = 7.2 Hz, 2H, CH_2-Ph), 1.99–1.89 (m, 2H, tHIQ-CH_2-CH_2), 1.82–1.73 (m, 2H, CH_2-CH_2Ph); MS (70 eV); *m/z* (%) = 309 ([M·]$^+$, 2), 146 (100), 132 (87), 91(30); IR (KBr) (cm^{-1}): 1113s (*ν* [C–O–C]).

Anal. calcd for $C_{21}H_{27}NO \times C_2H_2O_4 \times 0.33\ H_2O$ (M_r: 405.36): C, 68.14; H, 7.36; N, 3.46. Found: C, 68.33; H, 7.23; N, 3.56.

5.1.5. The synthesis of 2-[3-(3-phenylpropoxy)propyl]decahydroisoquinoline hydrogen oxalate (7)

To 10 mL DMSO, powdered KOH (1.1 g, 20 mmol) was added and stirred for 5 min at ambient temperature. Then, 3-(octahydro-isoquinolin-2-yl)propan-1-ol (0.49 g, 2.5 mmol) and 1-bromo-3-phenylpropane (0.59 g, 3 mmol) were added and stirred for 1 h at the same temperature. Afterwards, the mixture was poured into H_2O (10 mL) and extracted with 10 mL CH_2Cl_2. The extracts were dried over anhydrous Na_2SO_4 and purified by CC (eluent: $CHCl_3$/MeOH; 85:15). The final product was crystallized as salt of oxalic acid from EtOH/Et_2O. Yield: 27%. Mp 112–116 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.33–7.23 (m, 2H, Ph-3,5-*H*), 7.23–7.10 (m, 3H, Ph-2,4,6-*H*), 3.41 (t, *J* = 5.8 Hz, 2H, CH_2-O), 3.36 (t, *J* = 6.4 Hz, 2H, CH_2O-CH_2), 3.27 (d, *J* = 11.1 Hz, 1H, dHIQ-1-H_e), 3.12–2.88 (m, 4H, dHIQ-3-*H* + dHIQ-CH_2), 2.83 (t, *J* = 11.4 Hz, 1H, dHIQ-1-H_a), 2.61 (t, *J* = 7.5 Hz, 2H, CH_2-Ph), 1.98–1.84 (m, 2H, dHIQCH_2-CH_2), 1.84–1.74 (m, 3H, CH_2-CH_2Ph + dHIQ-10-*H*), 1.74–0.85 (m, 11H, dHIQ-5,6,7,8,9-*H*); MS (70 eV); *m/z* (%) = 315.5 ([M·]$^+$, 4), 196 (18), 152 (100), 98 (6); IR (KBr) (cm^{-1}): 1117s (*ν* [C–O–C]).

Anal. calcd for $C_{21}H_{33}NO \times C_2H_2O_4 \times 0.25\ H_2O$ (M_r: 410.05): C, 67.37; H, 8.73; N, 3.42. Found: C, 67.42; H, 8.56; N, 3.40.

5.1.6. General procedure for the preparation of ethers 9, 10, 12–14

A mixture of 4-piperidino-piperidine (0.42 g, 2.5 mmol), phenoxyalkyl halide (2.5 mmol), K_2CO_3 (0.35 g, 2.5 mmol) in 15 ml of CH_3CN was heated to reflux for 15 h. After cooling, the solid was filtered and the solvent was evaporated under reduced pressure. The residue was purified by CC (eluent: CH_2Cl_2/MeOH; 90:10). The pure fractions were concentrated in vacuum and crystallized as hydrogen oxalate from EtOH/Et_2O.

5.1.6.1. 1-[2-(3-Chlorophenoxy)ethyl]-4-piperidino-piperidine dihydrogen oxalate (9). From 1-bromo-2-(3-chlorophenoxy) ethane **2a** (0.59 g, 2.5 mmol). Yield 16%. Mp. 223–225 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.29 (t, *J* = 8.2 Hz, 1H, Ph-5-*H*), 7.03–6.92 (m, 2H, Ph-2,4-*H*), 6.90 (d, *J* = 1.5 Hz, 1H, Ph-6-*H*), 4.16 (t, *J* = 4.9 Hz, 2H, CH_2-O), 3.30–2.90 (m, 9H, Pip-CH_2 + Pip-4-*H* + Pip′-2,6-*H* + Pip-2,6-H_e), 2.44–2.36 (m, 2H, Pip-2,6-H_a), 2.10–1.96 (m, 2H, Pip-3,5-H_e), 1.85–1.65 (m, 6H, Pip′-3,4,5-*H*), 1.51 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1227s (*ν* [C–O–C]).

Anal. calcd for $C_{18}H_{27}N_2OCl \times 2C_2H_2O_4$ (M_r: 502.95): C, 52.54; H, 6.21; N, 5.57. Found: C, 52.10; H, 6.40; N, 5.62.

5.1.6.2. 1-[2-(3-Methoxyphenoxy)ethyl]-4-piperidino-piperidine dihydrogen oxalate (10). From 1-bromo-2-(3-methoxyphe-n-oxy)ethane **2b** (0.58 g, 2.5 mmol). Yield 30%. Mp 224–226 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.16 (t, *J* = 8.0 Hz, 1H, Ph-5-*H*), 6.55–6.45 (m, 3H, Ph-2,4,6-*H*), 4.15 (t, *J* = 5.1 Hz, 2H, CH_2-O), 3.71 (s, 3H, OCH_3), 3.38–3.25 (m, 2H, Pip-CH_2), 3.25–3.02 (m, 7H, Pip-4-*H* + Pip′-2,6-*H* + Pip-2,6-H_e), 2.55–2.51 (m, 2H, Pip-2,6-H_a), 2.13–1.98 (m, 2H, Pip-3,5-H_e), 1.89–1.65 (m, 6H, Pip′-3,4,5-*H*), 1.50 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1202s (*ν* [C–O–C]), 1155s (*ν* [C–O–C]).

Anal. calcd for $C_{19}H_{30}N_2O_2 \times 2C_2H_2O_4$($M_r$: 498.51): C, 55.41; H, 6.87; N, 5.62. Found: C, 55.57; H, 7.04; N, 5.66.

5.1.6.3. 1-[2-(3-Trifluoromethylphenoxy)ethyl]-4-piperidino-piperidine dihydrogen oxalate (12). From 1-bromo-2-(3-trifluoromethylphenoxy)ethane **2c** (0.67 g, 2.5 mmol). Yield 19%. Mp 228–230 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.51 (t, *J* = 8.2 Hz, 1H, Ph-5-*H*), 7.30–7.24 (m, 3H, Ph-2,4,6-*H*), 4.24 (t, *J* = 4.9 Hz, 2H, CH_2-O), 3.36–2.90 (m, 9H, Pip-CH_2 + Pip-4-*H* + Pip′-2,6-*H* + Pip-2,6-H_e), 2.42–2.36 (m, 2H, Pip-2,6-H_a), 2.09–1.98 (m, 2H, Pip-3,5-H_e), 1.88–1.64 (m, 6H, Pip′-3,4,5-*H*), 1.50 (br s, 2H, Pip-3,5-H_a).

Anal. calcd for $C_{19}H_{27}N_2OF_3 \times 2C_2H_2O_4$($M_r$: 536.49): C, 51.48; H, 5.82; N, 5.22. Found: C, 51.45; H, 6.04; N, 5.25.

5.1.6.4. 1-[2-(4-Methylphenoxy)ethyl]-4-piperidino-piperidine dihydrogen oxalate (13). From 1-bromo-2-(4-methylphenoxy) ethane **2d** (0.54 g, 2.5 mmol). Yield 25%. Mp 202–205 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.06 (d, *J* = 8.2 Hz, 2H, Ph-3,5-*H*), 6.81 (d, *J* = 8.7 Hz, 2H, Ph-2,6-*H*), 4.07 (t, *J* = 5.6 Hz, 2H, CH_2-O),3.25–3.08 (m, 7H, Pip-CH_2 + Pip-4-*H* + Pip′-2,6-*H*), 2.90–2.85 (m, 2H, Pip-2,6-H_e), 2.35–2.28 (m, 2H, Pip-2,6-H_a), 2.21 (s, 3H, Ph-4-CH_3), 2.07–1.94 (m, 2H, Pip-3,5-H_e), 1.83–1.63 (m, 6H, Pip′-3,4,5-*H*), 1.50 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1243s (*ν* [C–O–C]).

Anal. calcd for $C_{19}H_{30}N_2O \times 2C_2H_2O_4$($M_r$: 482.51): C, 58.11; H, 7.78; N, 6.20. Found: C, 57.25; H, 7.10; N, 5.81.

5.1.6.5. 1-[2-(4-Chlorophenoxy)ethyl]-4-piperidino-piperidine dihydrogen oxalate (14). From 1-bromo-2-(4-chlorophenoxy) ethane **2e** (0.59 g, 2.5 mmol). Yield 35%. Mp 213–215 °C. ^{1}H NMR [DMSO-d_6]: *δ* = 7.30 (d, *J* = 8.7 Hz, 2H, Ph-3,5-*H*), 6.95 (d, *J* = 9.0 Hz, 2H, Ph-2,6-*H*), 4.10 (t, *J* = 4.9 Hz, 2H, CH_2-O),3.19–2.86 (m, 7H, Pip-CH_2 + Pip-4-*H* + Pip′-2,6-*H*), 2.90–2.80 (m, 2H, Pip-2,6-H_e), 2.32–2.24 (m, 2H, Pip-2,6-H_a), 2.06–1.97 (m, 2H, Pip-3,5-H_e), 1.80–1.60 (m, 6H, Pip′-3,4,5-*H*), 1.51 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1243s (*ν* [C–O–C]).

Anal. calcd for $C_{18}H_{27}N_2OCl \times 2C_2H_2O_4$($M_r$: 502.95): C, 52.54; H, 6.21; N, 5.57. Found: C, 53.08; H, 6.49; N, 5.73.

5.1.7. General procedure for the preparation of ethers 11, 15 and 16

A mixture of 4-piperidino-piperidine (0.67 g, 4 mmol), a phenoxyalkyl halide (2 mmol), K_2CO_3 (0.83 g, 6 mmol) in 42 mL of EtOH and 8 mL H_2O with catalytic KI was heated to reflux for 8 h. After cooling, the solid was filtered and the solvent was evaporated under reduced pressure to the half of the volume. Then, 20 mL 1% HCl

was added (neutral pH) and extracted with Et_2O (2 × 20 mL). After drying over Na_2SO_4, the organic layer was concentrated in vacuum and crystallized as dihydrogen oxalate from EtOH/Et_2O.

5.1.7.1. 1-[3-(3-Methoxyphenoxy)propyl]-4-piperidino-piperidine dihydrogen oxalate (11). From 1-bromo-3-(3-methoxyphenoxy)propane**3b** (0.49 g, 2 mmol). Yield 19%. Mp 201–205 °C. ^{1}H NMR [DMSO-d_6]: δ = 7.14 (t, J = 8.2 Hz, 1H, Ph-5-H), 6.50–6.43 (m, J = 8.5 Hz, 3H, Ph-2,4,6-H), 3.95 (t, J = 5.9 Hz, 2H, CH_2-O),3.70 (s, 3H, OCH_3), 3.32–3.18 (m, 2H, Pip-CH_2), 3.18–2.94 (m, 5H, Pip-4-H + Pip′-2,6-H), 2.80–2.69 (m, 2H, Pip-2,6-H_e), 2.45–2.30 (m, 2H, Pip-2,6-H_a), 2.13–1.88 (m, 4H, Pip-CH$_2$-CH_2 + Pip-3,5-H_e), 1.88–1.60 (m, 6H, Pip′-3,4,5-H), 1.48 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1152s (ν [C–O–C]).

Anal. calcd for $C_{20}H_{32}N_2O_2 \times 1.5C_2H_2O_4 \times 0.5H_2O$ (M_r: 476.53): C, 57.97; H, 7.61; N, 5.88. Found: C, 58.14; H, 7.86; N, 5.93.

5.1.7.2. 1-[3-(4-Chlorophenoxy)propyl]-4-piperidino-piperidine dihydrogen oxalate (15). From 1-bromo-3-(4-chlorophenoxy)propane **3e** (0.50 g, 2 mmol). Yield 17%. Mp 233–236 °C. ^{1}H NMR [DMSO-d_6]: δ = 7.31 (d, J = 8.9 Hz, 2H, Ph-3,5-H), 6.93 (d, J = 8.9 Hz, 2H, Ph-2,6-H), 3.99 (t, J = 6.2 Hz, 2H, CH_2-O), 3.34–3.20 (m, 2H, Pip-CH_2), 3.20–3.00 (m, 5H, Pip-4-H + Pip′-2,6-H), 2.80–2.63 (m, 2H, Pip-2,6-H_e), 2.48–2.30 (m, 2H, Pip-2,6-H_a), 2.10–1.90 (m, 4H, Pip-CH$_2$-CH_2 + Pip-3,5-H_e), 1.84–1.64 (m, 6H, Pip′-3,4,5-H), 1.50 (br s, 2H, Pip-3,5-H_a); IR (KBr) (cm^{-1}): 1240s (ν [C–O–C]).

Anal. calcd for $C_{19}H_{29}N_2OCl \times 2C_2H_2O_4$($M_r$: 516.96): C, 53.43; H, 6.43; N, 5.42. Found: C, 53.32; H, 6.34; N, 5.46.

5.1.7.3. 1-[3-(4-*tert*-Butylphenoxy)propyl]-4-piperidino-piperidine hydrogen oxalate (16). From 1-bromo-3-(4-*tert*-butylphenoxy)propane **3f** (0.55 g, 2 mmol). Yield 35%. Mp 207–210 °C. ^{1}H NMR [DMSO-d_6]: δ = 7.25 (d, J = 8.5 Hz, 1H, Ph-3,5-H), 6.80 (d, 2H, J= 8.5 Hz, Ph-2,6-H), 3.94 (t, J = 5.9 Hz, 2H, CH_2-O), 3.34–3.24 (m, 2H, Pip-CH_2), 3.15–2.95 (m, 5H, Pip-4-H + Pip′-2,6-H), 2.84–2.72 (m, 2H, Pip-2,6-H_e), 2.47–2.35 (m, 2H, Pip-2,6-H_a), 2.10–1.90 (m, 4H, Pip-CH$_2$-CH_2 + Pip-3,5-H_e), 1.90–1.65 (m, 6H, Pip′-3,4,5-H), 1.48 (br s, 2H, Pip-3,5-H_a), 1.22 (s, 9H, 3CH_3); IR (KBr) (cm^{-1}): 1250s (ν [C–O–C]).

Anal. calcd for $C_{23}H_{38}N_2O \times C_2H_2O_4 \times 1.5\ H_2O$ (M_r: 475.61): C, 63.13; H, 9.11; N, 5.89. Found: C, 62.54; H, 8.70; N, 5.58.

5.2. Pharmacology

5.2.1. In vitro [^{125}I]iodoproxyfan binding assay

Potency of the novel compounds **4–16** was investigated in a radioligand binding assay described by Ligneau et al.[34] Stably transfected CHO-K1 (or HEK 293) cells were washed and harvested with a PBS medium. They were centrifuged (140 g, 10 min, +4 °C), and then homogenized with a Polytron in the ice-cold binding buffer (Na_2HPO_4/KH_2PO_4, c = 50 mmol/L, pH = 7.5). The homogenate was centrifuged (23,000g, 30 min, +4 °C) and the pellet obtained was resuspended in the binding buffer to constitute the membrane preparation used for the binding assay. Aliquots of the membrane suspension (5–15 g protein) were incubated for 60 min at 25 °C with [^{125}I]iodoproxyfan (c = 25 pmol/L) alone, or together with competing drugs dissolved in the same buffer to give a final volume of 200 μL. Incubations were performed in triplicate and stopped by four additions (5 mL) of ice-cold medium, followed by rapid filtration through glass microfibre filters (GF/B Whatman, Clifton, NJ) presoaked in polyethylene imine (ω = 0.3%). Radioactivity trapped on the filters was measured with a LKB (Rockville, MD) gamma counter (efficiency: 82%). Specific binding was defined as that inhibited by imetit (c = 1 mol/L), a specific histamine H_3 receptor agonist.[39] The corresponding K_i values were determined according to the Cheng-Prusoff equation.[43] Data are presented as the mean of experiments performed at least in triplicate.

5.2.2. Histamine H_3-receptor antagonist potency in vivo in the mouse

In vivo testing was performed after oral administration to Swiss mice according to Garbarg et al.[44] Brain histaminergic neuronal activity was assessed by measuring the main metabolite of histamine, N^τ-methylhistamine. Mice were fasted for 24 h before po treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was isolated. The cerebral cortex was homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^τ-methylhistamine level was measured by radioimmunoassay.[45] By treatment with 3 mg/kg ciproxifan the maximal increase in N^τ-methylhistamine level was obtained[46] and related to the level reached with the administered drug. Each experiment was performed at least in triplicate. The ED_{50} value was calculated as mean with SEM.[47]

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