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Influence of imidazole replacement in different structural classes of histamine H_3-receptor antagonists

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Dedicated to Univ.-Prof. Dr. Dres. h.c.mult. H. Oelschläger, Jena, on occasion of his 80th Birthday

Abstract

The reference compounds for histamine H_3-receptor antagonists carry as a common feature an imidazole moiety substituted in the 4-position. Very recently novel ligands lacking an imidazole ring have been described possessing a N-containing non-aromatic heterocycle instead. In this study we investigated whether imidazole replacement, favourably by a piperidine moiety, is generally applicable to different structural classes of reference compounds, e.g., thioperamide, carboperamide, clobenpropit, FUB 181, ciproxifan, etc. While replacement led to a loss of affinity for many of the compounds, it was successfully applied to some ether derivatives. The piperidine analogues of FUB 181 and ciproxifan, 3-(4-chlorophenyl)propyl 3-piperidinopropyl ether hydrogen oxalate (**6**) and cyclopropyl 4-(3-piperidinopropyloxy)phenyl methanone hydrogen maleate (**7**), almost maintained in vitro affinities, pK_i values of 7.8 and 8.4, respectively, and showed high potency in vivo after p.o. administration (ED_{50} values of 1.6 and 0.18 mg/kg, respectively).

Keywords: Histamine; H_3 Receptor; Imidazole; Non-imidazole; Antagonist; Medicinal chemistry

1. Introduction

The third histamine receptor subtype (H_3) has been identified as a presynaptic autoreceptor located on histaminergic nerve endings inhibiting synthesis (Arrang et al., 1987a) and release (Arrang et al., 1985) of histamine upon activation. In addition, the histamine H_3 receptor also occurs as a heteroreceptor on non-histaminergic neurons thereby interacting with a variety of different neurotransmitter systems (Hill et al., 1997). Histamine plays an important role in the regulation of different physiological processes, e.g., arousal (Schwartz et al., 1991; Schwartz and Arrang, in press), and may be implicated in pathophysiological conditions and diseases affecting the central nervous system (Stark et al., 1996a). Histamine H_3-receptor antagonists have not been introduced to therapy, but potential therapeutic applications have been proposed, e.g., memory and learning deficits (Miyazaki et al., 1995; Blandina et al., 1996; Onodera et al., 1998), epilepsy (Yokoyama et al., 1993, 1994), schizophrenia (Schwarz and Arrang, in press), Alzheimer's disease (Panula et al., 1995; Morisset et al., 1996), and attention-deficit hyperactivity disorder (ADHD) (Leurs et al., 1998). In fact, compound GT 2331 (Ali et al., 1999) has entered phase II clinical trials for the treatment of ADHD (Gliatech Corporate Information).

The majority of histamine H_3-receptor antagonists reported in the literature to date contain a mono-substituted 4(5)-imidazole moiety. For potential therapeutic use, the design of histamine H_3-receptor ligands devoid of an imidazole ring is desirable, as a means of providing compounds with improved pharmacokinetic properties in

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vivo (Alves-Rodrigues et al., 1996). The development of non-imidazole histamine H_3-receptor antagonists has been pursued previously (Ganellin et al., 1991, 1998; Kiec-Kononowicz et al., 1995a,b; Menge et al., 1998; Walczynski et al., 1999a,b; Linney et al., 2000). Earlier investigations focused on imidazole replacement by other nitrogen-containing aromatic heterocycles within known histamine H_3-receptor antagonist structures. However, the non-imidazole compounds obtained were consistently substantially inferior to the parent imidazole containing antagonists (Ganellin et al., 1991; Kiec-Kononowicz et al., 1995a,b). One of the first successful replacements of the imidazole moiety of a known compound was reported in 1998 and resulted in the development of UCL 1972 (K_i= 39±11 nM; ED_{50}=1.1±0.6 mg/kg p.o.) (Ganellin et al., 1998). Very recent attempts were based on the structural development of new compounds using low-affinity non-imidazole histamine H_3-receptor ligands as leads (Menge et al., 1998; Walczynski et al., 1999a,b; Linney et al., 2000). This led to the discovery of potent non-imidazole histamine H_3-receptor antagonists (Fig. 1), e.g., the benzothiazole A (pA_2=7.76±0.13; pK_i=8.2±0.2) derived from sabeluzole (Menge et al., 1998; Walczynski et al., 1999a,b) and JB 98064 (pK_B=8.38±0.10; pK_i= 8.70±0.12) derived from dimaprit (Linney et al., 2000). All of these compounds possess a non-aromatic N-containing heterocycle as a common feature, linked from the nitrogen atom through an alkylene chain eventually to an aryl group.

In an effort to reveal general patterns underlying imidazole exchangeability, we revived the original idea of imidazole replacement within different structural classes of known histamine H_3-receptor antagonists. Compounds containing pyrrolidine or piperidine moieties have been shown to be potent non-imidazole histamine H_3-receptor antagonists (Ganellin et al., 1998; Linney et al., 2000). Based on these findings, the piperidino group was chosen as a general imidazole substitute for our investigation. In order to assess further moieties suitable for replacement, one piperidine-containing histamine H_3-receptor ligand (**5**, Table 1), found to be a potent antagonist in vitro and in vivo, was further derivatized by replacement of the piperidino group by azepane-, pyrrolidine-, or diethylamine moieties, respectively.

In an attempt to clarify principles and applicability of imidazole replacement, we investigated the change in pharmacological behaviour of known histamine H_3-receptor antagonists in vitro and in vivo, thereby covering various structural classes. In the present study we report the synthesis and pharmacological evaluation of novel non-imidazole histamine H_3-receptor ligands derived from already established histamine H_3-receptor antagonists (Schwartz et al., 2000). For progress in drug development, imidazole replacement seems to be of special interest since many related imidazole-containing compounds are known to interact with the cytochrome P_{450} system (Halpert et al., 1994) and other metabolic enzymes (Karjalainen et al., 2000).

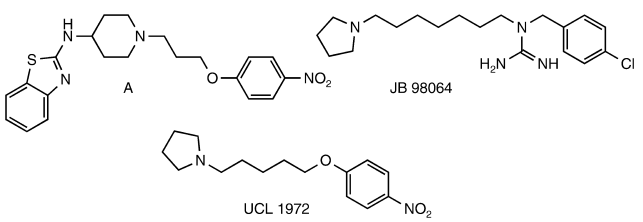


Fig. 1. Non-imidazole histamine H_3-receptor antagonists.

2. Materials and methods

2.1. Chemistry

2.1.1. General procedures

Melting points (mp) were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus and are uncorrected. For all compounds ^{1}H NMR spectra were recorded on a Bruker AC 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm downfield from internal trimethylsilane as reference. ^{1}H NMR signals are reported in order: Multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by D_2O; Cyhex, cyclohexyl; Ph, phenyl; Pip, piperidino; Pyr, pyrrolidinyl), number of protons, and approximate coupling constants in Hertz (Hz). Mass spectra were obtained on a Finnigan MAT CH7A (70 eV, EI spectra) or a Finnigan MAT CH5DF (FAB^+ spectra). All FAB^+ spectra were recorded in Me_2SO. Elemental analyses (C, H, N) were measured on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments and are within ±0.4% of the theoretical values. Preparative, centrifugally accelerated, rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4 mm layers of silica gel 60 F_{254} containing gypsum (Merck). Column chromatography was carried out using silica gel 63–200 μm (Macherey, Nagel) or silica gel 40–63 μm (Merck) for flash column chromatography. TLC was carried out on silica gel F_{254} plates (Merck).

2.1.2. Synthesis

Precursors **I** (Frankel et al., 1950), **III** (Doherty et al., 1957), and **IV** (Clinton et al., 1949) were prepared as described in the literature (Fig. 2). Precursor **II** was prepared from piperidine and methyl 3-bromopropionate in acetone with catalytic amounts of potassium iodide under basic conditions (Fig. 2).

Thiourea derivative **1** (Table 1) was obtained by reaction from both commercially available 1,4′-bipiperidine with cyclohexyl isothiocyanate. Amide **2** was synthesized under Schotten–Baumann conditions according to the procedure described by Stark et al. (1995) from commer-

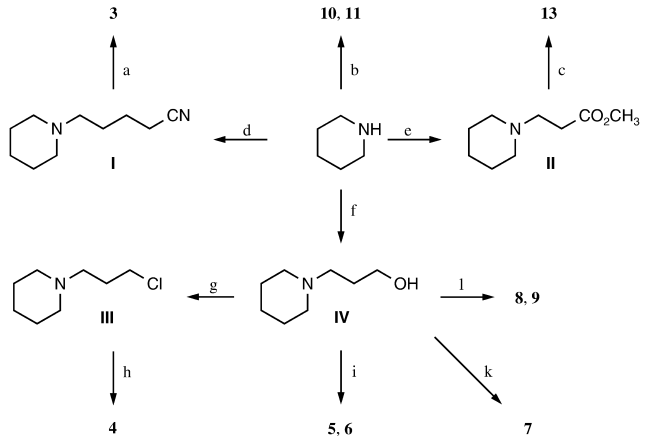


Fig. 2. Central building blocks and synthesis of compounds **3**–**11** and **13**. Footnotes: (a) $LiAlH_4$, THF, room temperature, 3 h; (b) arylalkyl halide, potassium carbonate, potassium iodide, EtOH, 60°C, 8 h; (c) *N*-hydroxy-4-chlorophenylacetamidine, sodium, MeOH, 0°C→room temperature, 1 h; reflux, 18 h; (d) Frankel et al. (1950); (e) methyl 3-bromopropionate, potassium iodide, potassium carbonate, acetone, reflux, 4 h; (f) Clinton et al. (1949); (g) Doherty et al. (1957); (h) 4-chlorobenzylthiourea, EtOH, potassium iodide, reflux, 6 days; (i) NaH, toluene, room temperature, 12 h; arylalkyl halide or methanesulfonate, 15-crown-5, tetrabutylammonium iodide, reflux, 4–17 h; (k) 4-cyclopropanecarbonylphenol, triphenylphosphine, diethylazodicarboxylate, THF, 0°C→room temperature, 16 h; (l) corresponding isocyanate, acetonitrile, reflux, 2–15 h.

cially available 1,4′-bipiperidine and *n*-heptanoyl chloride. Compound **3** was obtained by reduction of the cyano moiety of **I** (Frankel et al., 1950) with $LiAlH_4$ according to published procedures (Nystrom and Brown, 1948). The clobenpropit analogue **4** was prepared from **III** in an adapted preparation sequence described for the imidazole equivalent (Van der Goot et al., 1992). Ethers **5** and **6** were synthesized by Williamson reaction (Williamson, 1851) from intermediate **IV** (Clinton et al., 1949) and the corresponding commercially available arylalkyl halide or the freshly prepared methanesulfonate, respectively. The aromatic ether **7** was prepared from **IV** and commercially available 4-cyclopropanecarbonylphenol by Mitsunobu type reaction (Mitsunobu, 1981). Carbamates **8** and **9** were conveniently derived from **IV** (Clinton et al., 1949) and commercially available pentyl or phenyl isocyanate as described for the imidazole analogues (Sasse et al., 1999; Stark et al., 1996a,b). All reactants being commercially available, compounds **10** and **11** were obtained by alkylation of piperidine with the corresponding 1-chloro-ω-phenylalkanes under basic conditions. The benzothiazole derivative **12** was synthesized from both commercially available 2-piperidinoethanamine and 2-chlorobenzo-[*d*][1,3]thiazole by S_NAr reaction. Oxadiazole **13** was synthesized from **II** and *N*-hydroxy-4-chlorophenylacetamidine in alkaline solution in an adapted preparation sequence according to Clitherow et al. (1996). Ethers **14**, **15**, and **16** were obtained in three steps from both commercially available 1-bromo-3-phenylpropane and 1,3-propanediol to form 3-(3-phenylpropyloxy)propan-1-ol according to Williamson's protocol (Williamson, 1851), conversion of the alcohol to the chloroalkane with thionyl chloride and alkylation of the corresponding secondary amines under basic conditions as mentioned before. Synthetic procedures and analytical data for all final compounds are provided below.

2.1.2.1. N-Cyclohexyl-l,4′-bipiperidine-1′-yl-thiocarboxamide hydrogen oxalate ***(1)***

1,4′-Bipiperidine (0.84 g, 5 mmol) and cyclohexyl isothiocyanate (0.7 g, 5 mmol) were dissolved in dry Et_2O (30 ml). The solution was stirred at room temperature for 2 h. The precipitated product was filtered, washed with ether and crystallized with oxalic acid from Et_2O/EtOH: Yield 70%; mp 225°C; ^{1}H NMR (Me_2SO-d_6) δ 7.34 (d, J=7.7 Hz, 1H, NH), 4.76–4.79 (m, 2H, Pip′-2,6H$_e$), 4.16 (m, 1H, Cyhex-1H), 3.30–3.33 (m, 1H, Pip′-4H), 3.08 (m, 4H, Pip-2,6H$_2$), 2.84–2.90 (m, 2H, Pip′-2,6H$_a$), 1.97–2.00 (m, 2H, Pip′-3,5H$_e$), 1.84 (m, 2H, Cyhex-2,6H$_e$), 1.72 (m, 6H, Pip-3,5H$_2$, Cyhex-3,5H$_e$), 1.45–1.60 (m, 6H, Pip-4H$_2$, Cyhex-4H$_2$, Pip′-3,5H$_a$), 1.20–1.27 (m, 4H, Cyhex-2,3,5,6H$_a$); FAB$^+$-MS m/z (%) 310 (M+H$^+$, 100). Anal. ($C_{17}H_{31}N_3S\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

2.1.2.2. 1-(1,4′-Bipiperidine-1′-yl)heptane-1-one hydrogen oxalate ***(2)***

1,4′-Bipiperidine (1.68 g, 10 mmol) was dissolved in water (10 ml) and added dropwise to a solution of *n*-heptanoyl chloride (0.74 g, 5 mmol) in dioxane (20 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, NH_3-sat.; 95:5) and crystallized with oxalic acid from Et_2O/EtOH: Yield 55%; mp 131°C; ^{1}H NMR (Me_2SO-d_6) δ 4.49–4.52 (m, 1H, Pip′-2H$_e$), 3.97–4.00 (m, 1H, Pip′-6H$_e$), 3.29 (m, 1H, Pip′-4H), 2.95–3.07 (m, 5H, Pip′-6H$_a$, Pip-2,6H$_2$), 2.50 (m, 1H, Pip′-2H$_a$), 2.29 (t, J=7.6 Hz, 2H, OCCH$_2$), 1.97–1.99 (m, 2H, Pip′-3,5H$_e$), 1.72–1.74 (m, 4H, Pip-3,5H$_2$), 1.40–1.52 (m, 6H, Pip′-3,5H$_a$, Pip-4H$_2$, OCCH$_2$C*H*$_2$), 1.26 (m, 6H, OC(CH$_2$)$_2$(C*H*$_2$)$_3$), 0.86 (t, J=7.0 Hz, 3H, CH$_3$); EI-MS m/z (%) 280 (M$^+$, 10). Anal. ($C_{17}H_{32}N_2O\cdot C_2H_2O_4$) C, H, N.

2.1.2.3. 5-Piperidinopentanamine dihydrochloride ***(3)***

Precursor **I** (4.17 g, 25.1 mmol) was dissolved in dry THF (10 ml). A suspension of $LiAlH_4$ (1.5 eq) in dry THF (20 ml) was added at 0°C. The mixture was stirred at room temperature for 3 h and then carefully treated with EtOH. A saturated aqueous solution of potassium sodium tartrate (10 ml) and aqueous sodium hydroxide solution (2 M, 10 ml) were added consecutively. The precipitate was filtered and the organic layer separated, dried ($MgSO_4$), and

removed under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, NH_3-sat.; 90:10). The final product was crystallized with HCl (5–6 M solution in 2-propanol) from Et_2O/2-propanol: Yield 50%; mp 187–190°C; ^{1}H NMR (Me_2SO-d_6) δ 10.50 (s*, 1H, Pip-NH^+), 8.05 (s*, 3H, NH_3^+), 3.36–3.39 (m, 2H, Pip-2,6H_e), 2.91–2.97 (m, 2H, CH_2NH_2), 2.75–2.85 (m, 4H, Pip-2,6H_a, Pip-NCH_2), 1.68–1.87 (m, 7H, Pip-NCH_2CH_2, C$H_2CH_2NH_2$, Pip-3,4,5H_e), 1.55–1.62 (m, 2H, C$H_2(CH_2)_2NH_2$), 1.30–1.41 (m, 3H, Pip-3,4,5H_a), EI-MS *m*/*z* (%) 170 (M^+, 4). Anal. ($C_{10}H_{22}N_2$·2HCl·0.5H_2O) C, H, N.

2.1.2.4. N-(4-Chlorobenzyl)-S-(3-piperidinopropyl)isothiourea dihydrochloride ***(4)***

Precursor **III** (1.97 g, 10 mmol) and 4-chlorobenzylthiourea (Van der Goot et al., 1992) (1.98 g, 10 mmol) were dissolved in dry EtOH (30 ml). Catalytic amounts of potassium iodide were added. The mixture was then heated under reflux for 6 days. The solvent was removed under reduced pressure and the residue purified by column chromatography (eluent: CH_2Cl_2/MeOH; 95:5 to 90:10). The product was crystallized with HCl (5–6 M solution in 2-propanol) from Et_2O/2-propanol: Yield 8%; mp 104°C; ^{1}H NMR (Me_2SO-d_6) δ 11.03 (br*, 1H, NH), 10.31 (br*, 1H, NH), 9.57 (br*, 2H, NH_2^+), 7.46 (m, 4H, Ph-2,3,5,6H), 4.62 (s, 2H, $PhCH_2$), 3.38 (t, *J*=6.9 Hz, 2H, SCH_2), 3.35 (m, 2H, Pip-2,6H_e), 3.04 (m, 2H, Pip-NCH_2), 2.82 (m, 2H, Pip-2,6H_a), 2.06 (m, 2H, Pip-NCH_2CH_2), 1.68–1.77 (m, 5H, Pip-4H_e, Pip-3,5H_2), 1.09 (m, 1H, Pip-4H_a); FAB$^+$-MS *m*/*z* (%) 326 (M-H^+, 92). Anal. ($C_{16}H_{24}ClN_3S$·2HCl·H_2O) C, H, N.

2.1.2.5. 3-Phenylpropyl 3-piperidinopropyl ether hydrogen oxalate ***(5)***

Compound **IV** (2.86 g, 20 mmol) and NaH (suspended in mineral oil, ω=60%, 1.00 g, 25 mmol) in dry toluene (30 ml) were stirred overnight at ambient temperature under an argon atmosphere. 1-Bromo-3-phenylpropane (4.38 g, 22 mmol), catalytic amounts of 15-crown-5 and tetrabutylammonium iodide were added to the solution via argon counter-current. The reaction mixture was heated under reflux for 4 h, cooled, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, NH_3-sat.; 90:10) and crystallized with oxalic acid from Et_2O/EtOH: Yield 26%; mp 125°C; ^{1}H NMR (Me_2SO-d_6) δ 7.23–7.30 (m, 2H, Ph-3,5H), 7.15–7.20 (m, 3H, Ph-2,4,6H), 3.40 (t, *J*=5.9 Hz, 2H, N···CH_2O), 3.36 (t, *J*=6.4 Hz, 2H, OCH_2···Ph), 3.08 (br, 4H, Pip-2,6H_2), 2.98–3.02 (m, 2H, Pip-NCH_2), 2.61 (t, *J*=7.7 Hz, 2H, $PhCH_2$), 1.86–1.96 (m, 2H, Pip-NCH_2CH_2), 1.75–1.82 (m, 2H, $PhCH_2CH_2$), 1.71–1.73 (m, 4H, Pip-3,5H_2), 1.51 (br, 2H, Pip-4H_2); EI-MS *m*/*z* (%) 261 (M^+, 3). Anal. ($C_{17}H_{27}NO$·$C_2H_2O_4$) C, H, N.

2.1.2.6. 3-(4-Chlorophenyl)propyl 3-piperidinopropyl ether hydrogen oxalate ***(6)***

Synthetic procedure was performed as described for **5** starting with **IV** and 3-(4-chlorophenyl)propyl methanesulfonate, except the reaction mixture was heated under reflux for 17 h. For purification the reaction mixture was carefully poured into water (50 ml) and extracted with Et_2O. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product purified by column chromatography (first eluent: petroleum ether/ethyl acetate; 3:1; second eluent: CH_2Cl_2/MeOH, NH_3-sat.; 90:10). The final product was crystallized with oxalic acid from Et_2O/MeOH: Yield 56%; mp 148°C; ^{1}H NMR (Me_2SO-d_6) δ 7.32–7.34 (m, 2H, Ph-3,5H), 7.22–7.24 (m, 2H, Ph-2,6H), 3.40 (t, *J*=6.0 Hz, 2H, N···CH_2O), 3.35 (t, *J*=6.4 Hz, 2H, OCH_2···Ph), 3.08 (br, 4H, Pip-2,6H_2), 2.97–3.01 (m, 2H, Pip-NCH_2), 2.61 (t, *J*=7.6 Hz, 2H, $PhCH_2$), 1.85–1.92 (m, 2H, Pip-NCH_2CH_2), 1.74–1.81 (m, 2H, $PhCH_2CH_2$), 1.70–1.73 (m, 4H, Pip-3,5H_2), 1.52 (br, 2H, Pip-4H_2); EI-MS *m*/*z* (%) 295 (M^+, 4). Anal. ($C_{17}H_{26}ClNO$·$C_2H_2O_4$) C, H, N.

2.1.2.7. Cyclopropyl 4-(3-piperidinopropyloxy)phenyl methanone hydrogen maleate ***(7)***

A solution of 4-cyclopropanecarbonylphenol (0.25 g, 1.5 mmol), precursor **IV** (0.22 g, 1.5 mmol), and triphenylphosphine (0.45 g, 1.7 mmol) in dry THF (20 ml) was stirred and cooled to 0°C under nitrogen. A solution of diethylazodicarboxylate (0.3 g, 1.7 mmol) in dry THF (20 ml) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred under nitrogen for 16 h. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate. The product was extracted with HCl (2N solution) and the aqueous layer was neutralized with aqueous sodium hydroxide. The free base was extracted with CH_2Cl_2 and the organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (eluent: Et_2O containing 1% triethylamine). The final product was crystallized either with oxalic acid or maleic acid from EtOH (analytical data is given for the maleate): Yield 33%; mp 92°C; ^{1}H NMR (CF_3COOD) δ 8.12 (m, 2H, Phe-2,6H), 7.05 (m, 2H, Phe-3,5H), 6.38 (s, 2H, maleic acid), 4.36–4.39 (t, *J*=5.4 Hz, 2H, OCH_2), 3.83–3.90 (m, 2H, Pip-2,6H_e), 3.52–3.57 (Pip-NCH_2), 3.02–3.12 (m, 2H, Pip-2,6H_a), 2.80–2.86 (m, 1H, cyclopropyl-1H), 2.42–2.48 (m, 2H, Pip-NCH_2CH_2), 1.90–2.20 (m, 5H, Pip-3,5H_2, Pip-4H_a), 1.45–1.49 (m, 2H, cyclopropyl-CH_2), 1.34–1.38 (m, 2H, cyclopropyl-CH_2); EI-MS *m*/*z* (%) 287 (M^+, 3). Anal. ($C_{18}H_{25}NO_2$·$C_4H_4O_4$·0.75 H_2O) C, H, N.

*2.1.2.8. N-Pentyl-3-piperidinopropylcarbamate hydrochloride **(8)***

Compound **IV**·HCl (0.79 g, 4.4 mmol) and pentyl isocyanate (0.58 ml, 4.4 mmol) were heated under reflux in dry acetonitrile (30 ml) under argon atmosphere for 15 h. The mixture was brought to room temperature. After evaporation of the solvent, the residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH, NH_3-sat.; 90:10). The final product was crystallized with HCl (5–6 M solution in 2-propanol) from 2-propanol: Yield 26%; mp 89°C; ^{1}H NMR (Me_2SO-d_6) δ 10.53 (s*, 1H, Pip-NH^+), 7.13 (t, J=5.4 Hz, 1H, NH), 3.98 (t, J=6.3 Hz, OCH_2), 3.36–3.39 (m, 2H, Pip-2,6H_e), 2.93–3.03 (m, 4H, NCH_2, Pip-NCH_2), 2.78–2.87 (m, 2H, Pip-2,6H_a), 1.98–2.05 (m, 2H, CH_2CH$_2$O), 1.67–1.86 (m, 5H, Pip-3,5H_2, -4H_e), 1.36–1.42 (m, 3H, NHCH$_2$CH_2, Pip-4H_a), 1.21–1.32 (m, 4H, CH_2CH_2CH$_3$), 0.86 (t, J=7.0 Hz, 3H, CH_3); EI-MS m/z (%) 256 (M^+, 3). Anal. ($C_{14}H_{28}N_2O_2$·HCl·0.5H_2O) C, H, N.

*2.1.2.9. N-Phenyl-3-piperidinopropylcarbamate hydrochloride **(9)***

Synthetic procedure and purification as described for **8** starting with **IV**·HCl and phenyl isocyanate, except the reaction mixture was heated under reflux for 2 h. The final product was recrystallized from MeOH: Yield 65%; mp 170°C; ^{1}H NMR (Me_2SO-d_6) δ 10.47 (s*, 1H, Pip-NH^+), 9.69 (s, 1H, Ph-NH), 7.45–7.47 (m, 2H, Ph-2,6H), 7.26–7.30 (m, 2H, Ph-3,5H), 6.97–7.01 (m, 1H, Ph-4H), 4.15 (t, J=6.3 Hz, OCH_2), 3.39–3.42 (m, 2H, Pip-2,6H_e), 3.06–3.10 (m, 2H, Pip-NCH_2), 2.83–2.86 (m, 2H, Pip-2,6H_a), 2.07–2.14 (m, 2H, CH_2CH$_2$O), 1.68–1.82 (m, 5H, Pip-3,5H_2, -4H_e), 1.36–1.42 (m, 1H, Pip-4H_a); EI-MS m/z (%) 262 (M^+, 5). Anal. ($C_{15}H_{22}N_2O_2$·HCl·0.1H_2O) C, H, N.

*2.1.2.10. 1-(6-Phenylhexyl)piperidine hydrogen oxalate **(10)***

Piperidine (4.7 g, 55 mmol), 1-chloro-6-phenylhexane (5.39 g, 27.5 mmol), potassium carbonate (7.7 g, 55 mmol) and catalytic amounts of potassium iodide were heated for 8 h at 60°C in a mixture of EtOH (25 ml) and water (5 ml). The solvent was evaporated. The residue was suspended in water and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH, NH_3-sat.; 90:10) and the final product crystallized with oxalic acid from Et_2O/EtOH: Yield 76%; mp 152°C; ^{1}H NMR (Me_2SO-d_6) δ 7.25–7.29 (m, 2H, Ph-3,5H), 7.19 (m, 3H, Ph-2,4,6H), 3.05 (m, 4H, Pip-NCH_2, Pip-2,6H_e), 2.92 (m, 2H, Pip-2,6H_a), 2.56 (t, J=7.6 Hz, 2H, $PhCH_2$), 1.70–1.72 (m, 4H, Pip-NCH$_2$CH_2, Pip-3,5H_e), 1.53–1.61 (m, 6H, PhCH$_2$CH_2, Pip-3,5H_a, Pip-4H_2), 1.29–1.30 (m, 4H, Ph(CH$_2$)$_2$(CH_2)$_2$); EI-MS m/z (%) 245 (M^+, 8). Anal. ($C_{17}H_{27}N$·$C_2H_2O_4$) C, H, N.

*2.1.2.11. 1-(4-Phenylbutyl)piperidine hydrogen oxalate **(11)***

Synthetic procedure and purification as described for **10** starting with piperidine and 1-chloro-4-phenylbutane. The desired product was crystallized with oxalic acid from 2-propanol: Yield 69%; mp 150°C; ^{1}H NMR (Me_2SO-d_6) δ 7.16–7.30 (m, 5H, Ph-2,3,4,5,6H), 2.92 (m, 6H, Pip-NCH_2, Pip-2,6H_2), 2.58–2.62 (t, J=7.3 Hz, 2H, $PhCH_2$), 1.51–1.72 (m, 10H, Pip-NCH$_2$(CH_2)$_2$, Pip-3,4,5H_2); EI-MS m/z (%) 217 (M^+, 6). Anal. ($C_{15}H_{23}$·$C_2H_2O_4$) C, H, N.

*2.1.2.12. N-(2-Piperidinoethyl)benzo[d][1,3]thiazole-2-amine dihydrochloride **(12)***

2-Piperidinoethanamine (1.29 g, 10 mmol) and 2-chlorobenzo[*d*][1,3]thiazole (1.87 g, 11 mmol) were dissolved in EtOH (50 ml). Triethylamine (3.04 g, 30 mmol) was added to the solution. The mixture was heated under reflux for 18 h. After cooling, the solvent was evaporated. HCl (5–6 M solution in 2-propanol) was added to the crude product. The resulting crystals were recrystallized from MeOH: Yield 88%; mp 225°C; ^{1}H NMR (Me_2SO-d_6) δ 10.54 (br*, 1H, benzothiazolyl-2-NH), 9.87 (br*, 1H, Pip-NH^+), 7.82 (d, J=7.8 Hz, 1H, benzothiazolyl-4H), 7.55 (d, J=8.0 Hz, 1H, benzothiazolyl-7H), 7.35–7.39 (m, 1H, benzothiazolyl-6H), 7.18–7.22 (m, 1H, benzothiazolyl-5H), 3.97 (br, 2H, thiazolyl-NHCH_2), 3.52 (br, 2H, Pip-2,6H_e), 3.37 (br, 2H, Pip-NCH_2), 2.97 (br, 2H, Pip-2,6H_a), 1.81 (br, 4H, Pip-3,5H_2), 1.70 (br, 1H, Pip-4H_e), 1.39 (br, 1H, Pip-4H_a); EI-MS m/z (%) 261 (M^+, 1). Anal. ($C_{14}H_{19}N_3S$·2HCl·0.25H_2O) C, H, N.

*2.1.2.13. 3-(4-Chlorobenzyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole hydrogen oxalate **(13)***

Intermediate **II** (1.0 g, 6 mmol) and *N*-hydroxy-4-chlorophenylacetamidine (0.74 g, 4 mmol) were dissolved in dry MeOH (15 ml) under argon atmosphere. The solution was cooled to 0°C. A freshly prepared solution of sodium (0.12 g, 5 mmol) in dry MeOH (20 ml) was slowly added to the reaction mixture. Stirring was continued for 1 h at ambient temperature after which time the solution was refluxed for 18 h. The mixture was cooled and the solvent removed under reduced pressure. The residue was suspended in DMF (40 ml) and the suspension stirred for 6 h at 80°C. The solvent was evaporated and the crude product suspended in water and extracted with CH_2Cl_2. The organic layers were combined, washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by rotatory chromatography (eluent: CH_2Cl_2, NH_3-atmosphere). The final product was crystallized with oxalic acid from Et_2O/EtOH: Yield 5%; mp 152°C; ^{1}H NMR (Me_2SO-d_6) δ 7.38–7.40

(m, 2H, Ph-3,5H), 7.31–7.34 (m, 2H, Ph-2,6H), 4.09 (s, 2H, $PhCH_2$), 3.29–3.34 (m, 4H, oxadiazolyl-CH_2, Pip-2,6H_e), 2.98 (br, 4H, Pip-NCH_2, Pip-2,6H_a), 1.65 (br, 4H, Pip-3,5H_2), 1.48 (br, 2H, Pip-4H_2); FAB$^+$-MS *m*/*z* (%) 306 ($M+H^+$, 68). Anal. ($C_{16}H_{20}ClN_3O\cdot C_2H_2O_4$) C, H, N.

2.1.2.14. 3-(Azepane-1-yl)propyl 3-phenylpropyl ether hydrogen oxalate ***(14)***

Synthetic procedure was performed as described for **10** starting with 1-chloro-3-(3-phenylpropyloxy)propane and hexamethyleneimine. The crude product was purified by flash column chromatography (eluent: Et_2O/petroleum ether/triethylamine; 66:33:1) to afford the final product as a light yellow oil, which was crystallized with oxalic acid from Et_2O/EtOH: Yield 58%; mp 105°C; ^{1}H NMR (CF_3COOD) δ 7.30–7.34 (m, 2H, Ph-3,5H), 7.20–7.24 (m, 3H, Ph-2,4,6H), 3.87 (t, *J*=5.6 Hz, 2H, azepanyl-N···CH_2O), 3.74 (t, *J*=6.8 Hz, 2H, Ph···CH_2O), 3.59–3.65 (m, 2H, azepanyl-2,7H_e), 3.37–3.42 (m, 2H, azepanyl-NCH_2), 3.20–3.32 (m, 2H, azepanyl-2,7H_a), 2.77 (t, *J*=7.4 Hz, 2H, $PhCH_2$), 2.13–2.23 (m, 2H, azepanyl-NCH_2CH_2), 2.05–2.12 (m, 4H, azepanyl-3,6H_e, $PhCH_2CH_2$), 1.89–1.99 (m, 2H, azepanyl-3,6H_a), 1.84 (br, 4H, azepanyl-4,5H_2); EI-MS *m*/*z* (%) 275 (M^+, 3). Anal. ($C_{18}H_{29}NO\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

2.1.2.15. 3-Phenylpropyl 3-(pyrrolidine-1-yl)propyl ether hydrogen oxalate ***(15)***

Synthetic procedure was performed as described for **10** starting with 1-chloro-3-(3-phenylpropyloxy)propane and pyrrolidine. The crude product was purified by flash column chromatography (eluent: Et_2O/petroleum ether/triethylamine; 66:33:1) to afford the final product as a light yellow oil, which was crystallized with oxalic acid from Et_2O/EtOH: Yield 54%; mp 106°C; ^{1}H NMR (CF_3COOD) δ 7.30–7.34 (m, 2H, Ph-3,5H), 7.20–7.24 (m, 3H, Ph-2,4,6H), 3.84–3.86 (m, 4H, Pyr-N···CH_2O, Pyr-2,5H_e), 3.74 (t, *J*=6.7 Hz, 2H, Phe···CH_2O), 3.39–3.44 (m, 2H, Pyr-NCH_2), 3.10–3.16 (m, 2H, Pyr-2,5H_a), 2.75 (t, *J*=7.4 Hz, 2H, $PhCH_2$), 2.25–2.34 (m, 2H, Pyr-3,4H_e), 2.15–2.22 (m, 4H, Pyr-NCH_2CH_2, Pyr-3,4H_a), 2.03–2.10 (m, 2H, $PhCH_2CH_2$); EI-MS *m*/*z* (%) 247 (M^+, 3). Anal. ($C_{16}H_{25}NO\cdot C_2H_2O_4$) C, H, N.

2.1.2.16. 3-(Diethylamino)propyl 3-phenylpropyl ether hydrogen oxalate ***(16)***

Synthetic procedure was performed as described for **10** starting with 3-(3-phenylpropyloxy)-1-propylchloride and diethylamine. The crude product was purified by flash column chromatography (eluent: Et_2O/petroleum ether/triethylamine; 66:33:1) to afford the final product as a colourless oil, which was crystallized with oxalic acid from Et_2O/EtOH: Yield: 47%; mp 80°C; ^{1}H NMR (Me_2SO-d_6) δ 7.26–7.29 (m, 2H, Ph-3,5H), 7.15–7.20 (m, 3H, Ph-2,4,6H), 3.42 (t, *J*=5.9 Hz, 2H, N···CH_2O), 3.37 (t, *J*=6.4 Hz, 2H, Ph...CH_2O), 3.01–3.10 (m, 6H, $CH_2N(CH_2CH_3)_2$), 2.61 (t, *J*=7.7 Hz, 2H, $PhCH_2$), 1.77–1.87 (m, 4H, NCH_2CH_2, $PhCH_2CH_2$), 1.17 (t, *J*=7.2 Hz, 6H, $(CH_3)_2$); EI-MS *m*/*z* (%) 249 (M^+, 2). Anal. ($C_{16}H_{27}NO\cdot C_2H_2O_4$) C, H, N.

2.2. Pharmacology

2.2.1. General methods

2.2.1.1. Histamine H_3-receptor antagonist activity on guinea pig ileum

Histamine H_3-receptor antagonist potency was determined by concentration-dependent inhibition of (*R*)-α-methylhistamine-induced relaxation of field-stimulated isolated guinea pig ileum segments (longitudinal muscle with adhering plexus myentericus) in the presence of the antagonist according to Vollinga et al. (1992) and Ligneau et al. (1994). Each experiment was performed at least in triplicate. Data are presented as mean (S.E.M.≤0.15). 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 accompanied by 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, a cumulative concentration–response curve to (*R*)-α-methylhistamine was recorded. Subsequently the preparations were washed three times every 10 min without stimulation. The antagonist was incubated 20–30 min before redetermination of the concentration–response curve of (*R*)-α-methylhistamine (Schlicker et al., 1994). The new antagonists were tested at concentrations that did not block ileal muscarinic M_3 receptors (data not shown).

2.2.1.2. Histamine H_3-receptor assay on synaptosomes of rat cerebral cortex

Compounds were examined for their antagonist activity using an assay where K^+-evoked depolarization induces [^{3}H]histamine release from rat synaptosomes as described by Garbarg et al. (1992). Each experiment was performed at least in triplicate. Data are presented as mean (S.E.M. ≤0.2). Synaptosomal preparation was obtained by the method of Whittaker (1966) and preincubated with L-[^{3}H]histidine (0.4 μM) at 37°C for 30 min in a modified Krebs-Ringer buffer. The synaptosomes were washed thoroughly, transferred into a fresh 2 mM K^+ Krebs-Ringer solution supplemented with 2 mM or 30 mM K^+ (final concentration) and preconditioned for 2 min. Compounds and 1 μM histamine were added 5 min before depolarization was induced. Incubation was interrupted by

rapid centrifugation. [^{3}H]Histamine levels were measured by liquid scintillation spectrometry (Garbarg et al., 1992). pK_i values were calculated based on the Cheng–Prusoff equation (Cheng and Prusoff, 1973).

2.2.1.3. 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. (1992). Brain histaminergic neuronal activity was assessed by measuring the main metabolite of histamine, N^τ-methylhistamine. Mice were fasted for 24 h before p.o. treatment. Animals were decapitated 90 min after treatment, and the 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 (Garbarg et al., 1989). By treatment with 3 mg/kg ciproxifan the maximal increase in N^τ-methylhistamine level was obtained (Ligneau et al., 1998) and related to the level reached with the administered drug. The ED_{50} value was calculated as mean with S.E.M. (Parker and Waud, 1971; Waud and Parker, 1971).

3. Results and discussion

Compound structures and pharmacological results are shown in Tables 1 and 2. The affinities of the novel compounds were determined in vitro on isolated segments of the guinea pig ileum (Ligneau et al., 1994; Schlicker and Marr, 1996) and on synaptosomes of rat cerebral cortex (Garbarg et al., 1992). Results obtained on the two tests were generally in good agreement, slight differences for some compounds being potentially attributable to other experimental errors in two largely distinct settings of amino acid sequence differences between the guinea pig and the rat (Ligneau et al., 2000; Tardivel-Lacombe et al., 2000). In vivo testing was performed on mice brain after oral administration (Garbarg et al., 1992).

The starting point for this study was the standard reference antagonist thioperamide, a ligand of high in vitro affinity (pK_i=8.4, Arrang et al., 1987b; pA_2=8.3, Clitherow et al., 1996) as well as a potent antagonist in vivo (ED_{50}=1.0 mg/kg p.o., Ligneau et al., 1998). Replacement of the imidazole group by a piperidine moiety leading to **1** was not tolerated and led to a dramatic loss of potency in vitro and in vivo. The same observation was made for the carboperamide (Ligneau et al., 1994) analogue **2** and the impentamine (Vollinga et al., 1995) analogue **3**, with **2** still showing weak antagonist affinity in vitro.

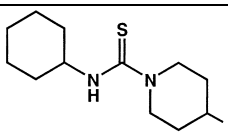
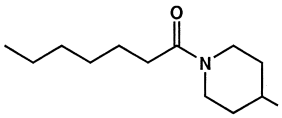
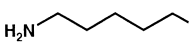
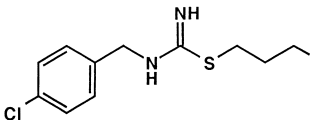
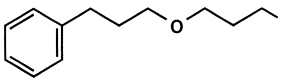
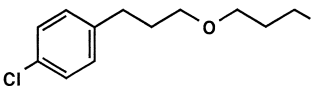
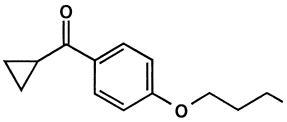
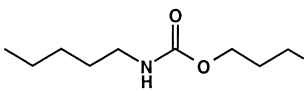
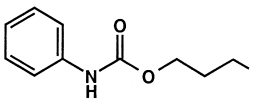
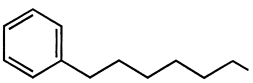
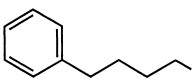
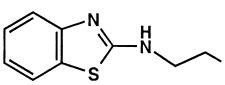
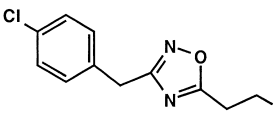
Another interesting candidate for imidazole replacement was the isothiourea derivative clobenpropit, a histamine H_3-receptor antagonist of high affinity in vitro (pK_B=9.9, Clitherow et al., 1996; pK_i=9.2, Ligneau et al., 1994). In vivo, however, clearly higher doses are required to enhance histamine release in the brain (ED_{50}=26 mg/kg p.o.) (Ligneau et al., 1998). As with the parent drug, **4** did not exhibit activity in vivo. In vitro, however, some of the affinity was maintained: **4** is a histamine H_3-receptor antagonist of moderate affinity on guinea pig ileum (pA_2=7.4).

Imidazole-containing aliphatic ethers of the 3-(phenylpropyloxy)propyl-type (Stark et al., 1998a,b), have proven to be potent and selective histamine H_3-receptor antagonists in vitro and in vivo. Previous efforts to develop non-imidazole histamine H_3-receptor antagonists for this structural type, e.g., by replacing the imidazole group with pyrazole, azine and diazine moieties (Kiec-Kononowicz et al., 1995a,b) were if any of limited success. In contrast to the previous replacements, compounds **5** (pA_2=8.1, pK_i=7.8) and **6** (pA_2=8.3, pK_i=7.8) displayed equipotent affinity in vitro with respect to the parent compounds FUB 153 and FUB 181 (Stark et al., 1998a,b). In accordance with this finding, **5** and **6** were also potent antagonists in vivo (Table 1). Schild analysis for the interaction of **6** and the histamine H_3-receptor agonist (*R*)-α-methylhistamine is shown in Fig. 3.

Potent non-imidazole histamine H_3-receptor antagonists of the aromatic ether type have been reported previously (Ganellin et al., 1998). Recently, ciproxifan was described as a highly potent and selective antagonist in vitro (pK_i=9.3) also displaying high efficacy in vivo (ED_{50}=0.14 mg/kg p.o.) (Ligneau et al., 1998; Stark et al., 2000). As with the aliphatic ethers **5** and **6,** the aromatic ether **7** also maintained high potency in vitro and in vivo (Table 1). The ciproxifan analogue **7** shows only slightly decreased affinity in vitro (pK_i=8.4) compared to ciproxifan (Ligneau et al., 1998; Stark et al., 2000) and is highly potent in vivo. These results need to be considered important, since the non-imidazole histamine H_3-receptor antagonist **7** in vitro resembles the activity of the reference antagonist thioperamide. In addition, the non-imidazole **7** surmounts the potency of thioperamide in vivo and is not significantly different from the efficacy of the parent imidazole-containing compound ciproxifan.

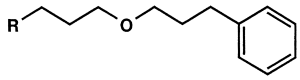
Whereas the aliphatic and aromatic ethers investigated led to a successful imidazole replacement, aliphatic and aromatic carbamates **8** and **9**, which were also derived from potent imidazole-containing antagonists (Sasse et al., 1999; Stark et al., 1996a,b), revealed only poor activity in vitro and no detectable potency in vivo. This is also true for the highly lipophilic phenylalkanes **10** and **11** as well as for the benzothiazole derivative **12**, although **11** still exhibits low potency in vivo. Recently, aromatase inhibition by the imidazole analogue of **11** has been described, emphasizing the importance of developing non-imidazole compounds (Karjalainen et al., 2000). The oxadiazole derivative **13** showed moderate affinity in vitro being another interesting lead for further optimization. Although imidazole replacement also led to a decrease in affinity when compared to the parent imidazole compound

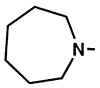
Table 1
Histamine H_3-receptor antagonist potencies in vitro and in vivo of known imidazole-containing ligands versus novel non-imidazole analogues: **Pip**, piperidino; **Im**, 1*H*-imidazol-4-yl

No.	R-X		In vitro		In vivo
	R	X	pA_2 [a]	pK_i [b]	ED_{50}±S.E.M. (mg/kg) [c]
1		**Pip**	5.6		>10
		Im (Thioperamide)	8.3 [d]	8.4 [e]	1.0±0.5 [f]
2		**Pip**	6.4		>10
		Im (Carboperamide)		7.7 [g]	3.9±0.8 [g]
3		**Pip**	6.0	6.4	>10
		Im (Impentamine)	8.4 [h]		
4		**Pip**	7.4	6.3	>10
		Im (Clobenpropit)	9.9 [d]	9.2 [g]	26±7 [f]
5		**Pip**	8.1	7.8	3.7±1.0
		Im (FUB 153)	7.3	7.8 [i]	1.4±0.6 [i]
6		**Pip**	8.3	7.8	1.6±0.9
		Im (FUB 181)	8.2 [i]	7.9 [i]	0.8±0.2 [i]
7		**Pip**	7.9	8.4	0.18±0.06
		Im (Ciproxifan)	8.4 [j]	9.3 [j]	0.14±0.03 [j]
8		**Pip**	6.3		>10
		Im (FUB 305)	7.3 [k]	8.1 [k]	0.69±0.37 [k]
9		**Pip**	6.2	6.6	>10
		Im (FUB 138)	6.8	7.9 [f]	1.3±0.6 [f]
10		**Pip**	6.5	6.7	>10
		Im (FUB 427)	7.7 [l]	7.1 [m]	1.0±0.3 [m]
11		**Pip**	5.7		20
		Im (FUB 349)	7.5 [l]	7.3 [m]	2.2±0.7 [m]
12		**Pip**	6.6		>10
		Im		7.7 [n]	
13		**Pip**	7.2	6.9	~20
		Im	8.1 [d]	8.2 [d]	

[a] Functional H_3-receptor assay on guinea pig ileum (Ligneau et al., 1994; Schlicker et al., 1994). [b] Functional H_3-receptor assay on rat cerebral cortex (Garbarg et al., 1992). [c] H_3-receptor screening after p.o. administration to mice (Garbarg et al., 1992). [d] pK_B value (Clitherow et al., 1996). [e] Arrang et al. (1987a). [f] Stark et al. (1996a,b). [g] Ligneau et al. (1998). [h] Vollinga et al. (1995). [i] Stark et al. (1998a). [j] Ligneau et al. (1998); Stark et al. (2000). [k] Sasse et al. (1999). [l] De Esch et al. (1999). [m] Stark et al. (1998b). [n] Plazzi et al. (1995).

Table 2
In vitro and in vivo histamine H_3-receptor antagonist potencies of different amino groups in aliphatic ethers, related to **5**



No.	R	pA_2 [a]	ED_{50} ± S.E.M. [b] (mg/kg)
14		7.8	2.3±0.7
15		7.8	5.5±2.0
16		6.5	>10

[a] Functional H_3-receptor assay on guinea pig ileum (Ligneau et al., 1994; Schlicker et al., 1994).
[b] H_3-receptor screening after p.o. administration to mice (Garbarg et al., 1992).

(Clitherow et al., 1996), the principle investigated seems also applicable to this class of histamine H_3-receptor antagonists.

In an attempt to further elucidate moieties suitable for replacement in the case of **5** and **6**, other nitrogen-containing groups were attached to the 3-(phenylpropyloxy)propyl structure resulting in compounds **14**, **15**, and **16** (Table 2).

Enlargement from a six- to a more lipophilic and flexible seven-membered nitrogen containing ring system led to **14**. This structural change, however, hardly affected in vitro and in vivo activity compared to **5**. A smaller ring size was achieved by introduction of a pyrrolidine moiety (**15**). Although the five-membered ring system causes the compound to be both less lipophilic and less flexible than **5** and **14**, it was equipotent in vitro. Unfortunately, the in vivo potency of **15** was slightly diminished compared to **5** and **14**. When a lipophilic and flexible diethylamino moiety was introduced (**16**), in vitro and in vivo activity decreased significantly. Similar results were obtained before in a series of aromatic ethers (Ganellin et al., 1998).

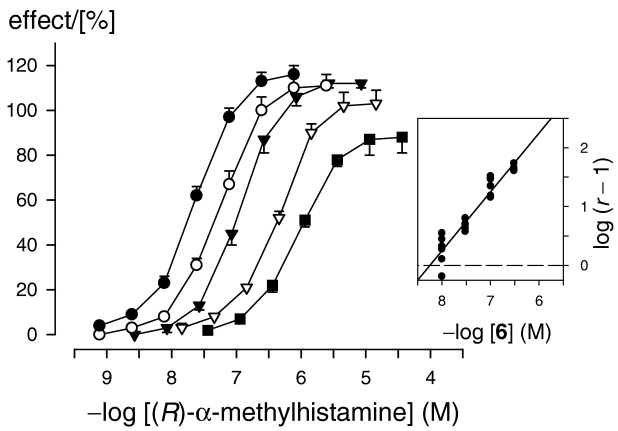


Fig. 3. Cumulative concentration–effect curves of *R*-(α)-methylhistamine on guinea pig ileum in the absence (●) and presence of **6**: (○) 10 nM, (▼) 30 nM, (▽) 100 nM, (■) 300 nM (left) and Schild Plot (right). Regression analysis yielded a slope of 0.99±0.07, which was found not to be significantly different from unity (competitive antagonism). The pA_2 value was 8.25±0.04 (95% conf. lim. 8.17–8.33).

4. Conclusion

In this study non-imidazole histamine H_3-receptor antagonists were developed from known H_3-receptor ligands of different structural classes by imidazole replacement. Exchange of the imidazole ring by a piperidine moiety was not generally feasible without loss of activity. Histamine H_3-receptor antagonists containing basic or hydrophilic connecting functionalities with carbonyl groups or related moieties were less suitable for imidazole replacement. Nevertheless, the known histamine H_3-receptor antagonists containing aliphatic and aromatic ether structures investigated in this study did tolerate imidazole replacement by piperidine, resulting in the development of the FUB 181 analogue **6** and the ciproxifan analogue **7**, two new potent non-imidazole histamine H_3-receptor antagonists with **7** being also highly potent in vivo. Imidazole exchange by an azepane or pyrrolidine ring also resulted in histamine H_3-receptor antagonists with high in vitro and in vivo potency in the case of **14** and **15**. Replacement of the imidazole moiety of other known histamine H_3-receptor antagonists was generally less successful. The inconsistencies of these findings point out distinct sensitivities of pharmacological properties of the individual compounds in this study towards imidazole replacement. However, with compounds **5**, **6**, **7**, and **14** potent non-imidazole histamine

H_3-receptor antagonists have been successfully designed from known antagonists. Moreover, in the light of a potential therapeutic use, the unparalleled in vivo potency of the ciproxifan analogue **7** in combination with possible pharmacokinetic advantages of this compound make it a promising subject for future investigations.

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