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Ether derivatives of 3-piperidinopropan-1-ol as non-imidazole histamine H_3 receptor antagonists

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Abstract—A series of aliphatic and aromatic ether derivatives of 3-piperidinopropan-1-ol has been prepared by four different methods. The ethers obtained were evaluated for their affinities at recombinant human histamine H_3 receptor, stably expressed in CHO-K1 or HEK 293 cells. All compounds investigated show from moderate to high in vitro affinities in the nanomolar concentration range. Selected compounds were investigated under in vivo conditions after oral administration to mice. Some proved to be highly potent and orally available histamine H_3 receptor antagonists. The most potent antagonists in this series have been in vitro the 4-(1,1-dimethylpropyl)phenyl ether **19** (hH_3R $K_i = 8.4$ nM) and in vivo the simple ethyl ether **2** ($ED_{50} = 1.0$ mg/kg).

1. Introduction

Histamine is a biogenic amine with multiple physiological activities and since 1907, when it was first synthesized, is still in the centre of general interest.[1] Its important physiological role is attributed to four known receptor subtypes: H_1–H_4. The third histamine receptor (H_3R) acts as an autoreceptor inhibiting the synthesis and the release of histamine upon activation. The H_3R occurs also as heteroreceptor modulating the release of a number of neurotransmitters including acetylcholine, dopamine, glutamate, noradrenaline and others.[2] The molecular structure of this receptor was unknown until 1999 when it was published by Lovenberg et al.[3] The H_3R shows functional constitutive activity in vivo, polymorphisms and multiple splice variants that differ across species (for review, see[4,5]).

H_3R antagonists could be useful for the treatment of a wide range of central nervous system (CNS) disorders including attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, schizophrenia, epilepsy as well as sleep disorders (narcolepsy) or obesity.[6–9] Numerous histamine H_3R ligands have been preclinically evaluated and may be some, at least one, have even entered clinical stages, for example, GT-2331 (ciproxifan formerly perceptin; entered phase II clinical studies for ADHD).[9,10] So far, none of the H_3R antagonists has been brought into the market. Thus, much effort is focused on understanding H_3 receptor (patho)physiology and on the design of selective and potent H_3R ligands.

The first H_3R antagonists were 4(5)-substituted imidazoles (for review, see[9,11]). However, due to well-known unfavourable imidazole-based properties (CYP 450 binding,[12] potential lack of selectivity towards histamine H_3/H_4 receptors,[13] and lower affinity for cloned human H_3R than that for, e.g., rodent[14]) the actual focus is on the development of non-imidazole compounds (for review, see[11a,15]).

The aromatic imidazole moiety was successfully replaced among others by an aliphatic piperidine, pyrrolidine or piperazine ring (for review, see[11a,15]). Such compounds (different to endogenous ligand) may give

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Keywords: Histamine; H_3 receptor; Non-imidazole ligands; Binding; Antagonists.

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a chance for enhanced selectivity, that is, for low binding at H_4 receptors. This could be confirmed by other investigations and there are known non-imidazole H_3R ligands inactive at the H_4 receptor.[13,18a]

Some of the non-imidazole H_3R antagonists have entered clinical trials, for example, Abbott Laboratories ABT-239, which has been described as a promising agent for the treatment of a variety of CNS disorders (ADHD, Alzheimer's disease and schizophrenia)[16,17] (Fig. 1).

Among classical approaches industrial high-throughput screenings (HTS) led to the identification of new non-imidazole ligands possessing the 3-piperidinylpropyloxy motif.[18] This motif is also present in the compound chosen as the lead structure (FUB 637) for the work presented here (Fig. 2). In 2001, Meier et al. published the results of ring replacements in piperidine analogues of the known imidazole-based H_3R antagonists.[19] Compound FUB 637 was one of the most interesting ligands with comparable in vitro and in vivo potency to its imidazole analogue, FUB 153 (Fig. 2).

As an extension of our previous work in the non-imidazole field [20–22] we have prepared a series of ether derivatives of 3-piperidinopropan-1-ol with general structure presented in Figure 3. All compounds were screened for their affinities at the human histamine H_3 receptor stably expressed in CHO-K1 cells or HEK 293. The in vivo potencies of selected compounds were also investigated.

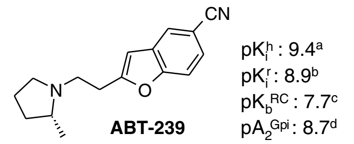


Figure 1. Structure and histamine H_3 potencies of ABT-239.[15,17] (a) Binding assay to recombinant human H_3 receptor versus $[^3H]N^\alpha$-methylhistamine. (b) Binding assay to recombinant rat H_3 receptor versus $[^3H]N^\alpha$-methylhistamine. (c) Functional assay on rat brain cortical synaptosomes. (d) Functional assay on guinea pig ileal segments.

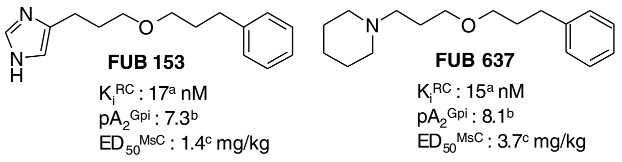


Figure 2. In vitro and in vivo histamine H_3 receptor antagonist potencies of FUB 153 and FUB 637.[19] (a) Functional assay on rat cerebral cortex. (b) Functional assay on guinea pig ileum. (c) Histamine H_3 receptor screening after po administration to mice.

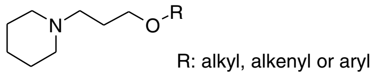


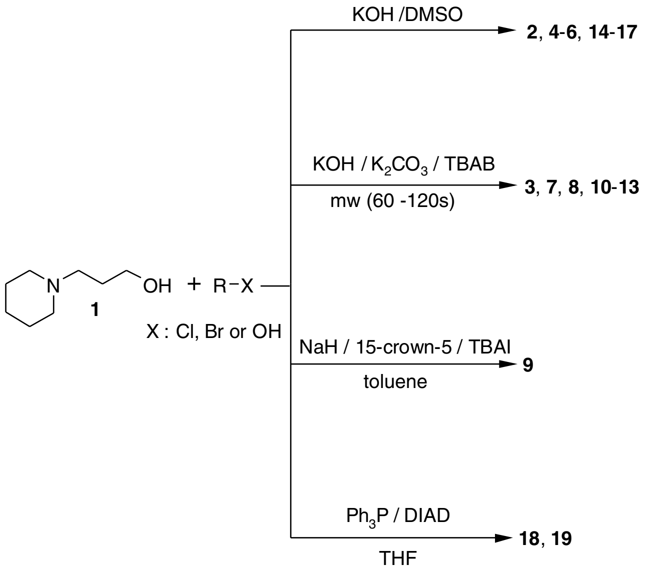
Figure 3. General structure of prepared ethers **2**–**19**.

2. Chemistry

The novel ether derivatives **2**–**19** were synthesized by four different methods as outlined in Scheme 1. 3-Piperidinopropan-1-ol (**1**) was obtained from piperidine and 3-chloropropan-1-ol by the method described previously.[20]

Ethers **2**, **4**–**6** and **14**–**17** were synthesized by the Johnstone and Rose procedure.[23] The alcohol **1** and appropriate alkyl halide were added to powdered KOH stirred in dimethylsulfoxide (DMSO) and usually heated in an oil bath (50 or 90 °C).

Ethers **3**, **7**, **8** and **10**–**13** were prepared under solvent-free conditions using microwave irradiation according to the procedure described by Bogdał et al.[24] (Table 1). Alcohol **1** was mixed with appropriate alkyl halide and a catalytic amount of tetrabutylammonium bromide (TBAB). The mixture was absorbed on a mixture of powdered potassium carbonate and potassium hydroxide and then irradiated in an open vessel in the domestic microwave oven.



Scheme 1. General methods of synthesis of ethers **2**–**19**.

Table 1. Conditions of the synthesis of ethers under microwave irradiation

Compound	Microwave oven power[a] [W]	Time [s]
3	100	2 × 60
7	300	60
8	100	2 × 60
10	300	60
11	300	60
12	300	60
13	100	60

[a] Domestic microwave oven Samsung M1618.

The target ether **9** was obtained by classical Williamson ether synthesis.[25] The alcohol **1** was transformed into its sodium alcoholate to which (bromomethyl)cyclopropane was added. Compounds **18** and **19** were synthesized by a Mitsunobu type ether formation from **1** and the appropriate phenol.[26]

Compounds were purified by column chromatography and isolated as salts of oxalic acid. Their purity was checked by TLC. Structures and purity of final compounds were confirmed by standard techniques (^{1}H NMR, MS, IR and elemental analysis) (cf. Section 5 and Table 2).

3. Pharmacological results and discussion

3.1. In vitro binding assay at cloned human histamine H_3 receptors

The affinities of compounds were determined by measuring the displacement curves of [^{125}I]iodoproxyfan binding at human histamine H_3 receptors expressed in CHO-K1 or HEK 293 cells stably transfected with the full-length coding sequence of the hH_3R, as described previously (Table 2).[27,28]

Tested compounds showed different affinities from high (**2** and **3**) to low (**19**) nanomolar concentration range. In the aliphatic series (compounds **2**–**4** and **8**) elongation of the carbon chain led to an increase in H_3R potencies from hK_i values of 743 nM (**3**) to 342 nM (**8**). The introduction of alkyl substituents (methyl or ethyl) in β-position within the butyl series **4**–**6** did not influence the activities ($hK_i > 700$ nM), whereas branching at the end of the chain showed a slight increase in affinity (**7**). In the cycloalkyl series (**9**–**12**) the size of the ring (cyclopropyl, cyclobutyl and cyclohexyl) did not change the potencies opposite to elongation of the carbon skeleton. Compound **12** (2-cyclohexylethyl derivative; K_i 40 nM) is about 8-fold more potent than the corresponding cycloalkylmethyl ethers **9**–**11** ($hK_i > 300$ nM). The unsaturated allyl ether **13** showed moderate histamine H_3 receptor affinity, whereas the aliphatic propyl derivative **3** is weak (hK_i 700 nM) one. Stiffening the end of the carbon chain seems to be advantageous, whereas in the different position (as in (*E*)-but-2-enyl (**14**)) led to a slight drop in H_3R affinity.

The aromatic derivatives showed at least one to two orders of magnitude higher affinities than those of the nonaromatic compounds. The compounds with the highest affinities in this series are **19** and **16**.

3.2. In vivo assay on Swiss mice

Selected compounds were screened for modulating N^{τ}-methylhistamine level in the brain cortex of Swiss mice after oral treatment (Table 2). All compounds tested showed antagonist properties. Compounds **11** and **14** enhanced N^{τ}-methylhistamine level with weak antagonist potency only if they do any at all. However, ether **2** showed antagonist behaviour equipotent to that of thioperamide, which is one of the reference imidazole-containing H_3R antagonists (ED_{50} = 1 mg/kg, po).[29] In contrast to this high in vivo potency, compound **2** showed moderate affinity in vitro only (Table 2). The observed discrepancy may be connected with species differences, improvement in absorption or formation of active metabolites. These astonishing divergent effects between in vivo and in vitro potencies were also noticed in the whole series of alkyl derivatives (compounds **2**, **3**, and **8**). The gradual loss of oral activity with elongation of the carbon chain was revealed, whereas in in vitro studies the opposite tendency was observed. In contrast to the comparable in vitro results of ethers **10** and **11**, compound **11** enhanced N^{τ}-methylhistamine level with only weak antagonist potency. Ether **12** did not retain good in vitro potency, was only moderately potent in vivo (ED_{50} = 7.7 mg/kg, po) and less potent than **10**. Remarkably, the aromatic derivatives tested showed high antagonist potencies, but did not reach the potency of compound **2**. Compounds **2**, **10**, **13** and **17**–**19** revealed in vivo potencies higher than that of the parent lead structure FUB 637 ($ED_{50} \leqslant 3.7$ mg/kg, po).

4. Conclusions

In this study, we report on novel potent histamine H_3 receptor ligands. These compounds are ether derivatives of 3-piperidinopropan-1-ol. They proved to be histamine H_3 receptor ligands investigated in [^{125}I]iodoproxyfan binding studies on the human histamine H_3 receptor and showed affinities from high to low nanomolar concentration range. In vivo screening of selected compounds showed the highest antagonist potency for the ethyl ether derivative **2**.

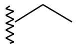
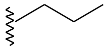
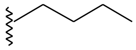
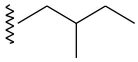
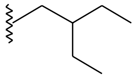
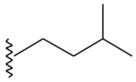
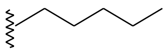
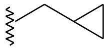
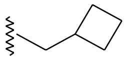
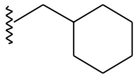
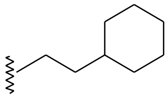
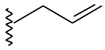
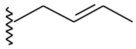
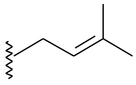
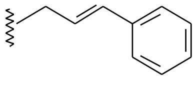
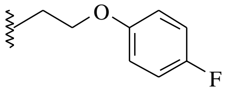
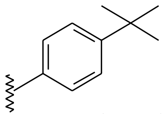
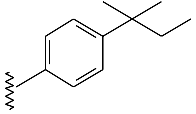
Ether derivatives **17**–**19** are highly potent both in vitro and in vivo studies and may be interesting subjects for further investigation and development.

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-Merkury 300 MHz spectrometer in DMSO-d_6. Chemical shifts are expressed in parts per million 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 ** (*, the centre of the chemical shift is given and **, the range of the whole signal is given); Cyclobut, cyclobutyl; Cycloprop, cyclopropyl; Cyclohex, cyclohexyl; Ph, phenyl; and Pip, piperidino), approximate coupling constants *J* in Hertz (Hz) and number of protons. Mass spectra (MS) were obtained on an EI-MS Finnigan MAT CH7A (70 eV, EI spectra). IR spectra were recorded with a Perkin-Elmer 297 spectral photometer or FT Jasco IR spectrometer from KBr discs (s, strong).

Table 2. Antagonist potencies of ether derivatives of 3-piperidinopropan-1-ol at histamine H_3 receptor (general structure cf. Fig. 3)

Compound	R	Formula	M_w (g/mol)	hK_i[a] (nM)	ED$_{50}$ ± SEM[c] (mg/kg) po
2		$C_{10}H_{21}NO{\cdot}C_2H_2O_4$	261.33	700 ± 95	1.0 ± 0.1
3		$C_{11}H_{23}NO{\cdot}C_2H_2O_4$	275.35	743 ± 50	5.3 ± 0.1
4		$C_{12}H_{25}NO{\cdot}C_2H_2O_4{\cdot}0.75H_2O$	302.90	719 ± 126[b]	[d]
5		$C_{13}H_{27}NO{\cdot}C_2H_2O_4{\cdot}0.10H_2O$	305.21	713 ± 44[b]	[d]
6		$C_{14}H_{29}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	321.94	728 ± 168[b]	[d]
7		$C_{13}H_{27}NO{\cdot}C_2H_2O_4{\cdot}H_2O$	321.41	557 ± 56	10 ± 1
8		$C_{13}H_{27}NO{\cdot}C_2H_2O_4$	303.41	342	6.1 ± 1.7
9		$C_{12}H_{23}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	291.87	341[b]	[d]
10		$C_{13}H_{25}NO{\cdot}C_2H_2O_4{\cdot}0.50H_2O$	310.40	309 ± 36	4.2 ± 0.4
11		$C_{15}H_{29}NO{\cdot}1.5C_2H_2O_4{\cdot}0.50H_2O$	383.46	376 ± 38	~15
12		$C_{16}H_{31}NO{\cdot}C_2H_2O_4$	343.47	40 ± 13	7.7 ± 0.2
13		$C_{11}H_{21}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	277.85	387 ± 57	3.1 ± 0.4
14		$C_{12}H_{23}NO{\cdot}C_2H_2O_4{\cdot}0.20H_2O$	290.96	521 ± 69	>10
15		$C_{13}H_{25}NO{\cdot}C_2H_2O_4$	301.39	339[b]	[d]
16		$C_{17}H_{25}NO{\cdot}C_2H_2O_4$	349.44	5.6 ± 1.0[b]	[d]
17		$C_{16}H_{24}NO_2F{\cdot}C_2H_2O_4{\cdot}0.50H_2O$	380.43	31 ± 5	2.8 ± 0.1
18		$C_{18}H_{29}NO{\cdot}C_2H_2O_4$	365.48	22 ± 3	2.8 ± 0.4
19		$C_{19}H_{31}NO{\cdot}C_2H_2O_4$	379.51	8.4 ± 1.3	2.1 ± 0.2
FUB 637				3.1 ± 0.5[e]	3.7 ± 1.0[f]
Thioperamide				60 ± 12[g]	1.0 ± 0.5[h]

[a] [^{125}I]Iodoproxyfan binding assay at human H_3 receptors stably expressed in CHO-K1 cells.

[b] [^{125}I]Iodoproxyfan binding assay at human H_3 receptors stably expressed in HEK 293 cells.

[c] Central histamine H_3 receptor assay in vivo after po administration to mice.

[d] Not tested.

[e] [^{3}H]-(*R*)-α-Methylhistamine binding assay at human H_3 receptors stably expressed in C6 cells.

[f] Ref. 19.

[g] Ref. 27.

[h] Ref. 29.

Elemental analyses (C, H and N) were measured on a 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 by Dragendorff's reagent or by UV absorption at 254 nm. The following abbreviations are used: CH$_2$Cl$_2$, dichloromethane; 15-crown-5,1,4,7,10,13-pentaoxacyclopentadecane; DIAD, diisopropyl azodicarboxylate; DMSO, dimethyl sulfoxide; Et$_2$O, diethyl ether; EtOH, ethanol; MeOH, methanol; TBAB, tetrabutylammonium bromide; TBAI, tetrabutylammonium iodide; and THF, tetrahydrofuran.

5.1.2. General procedure for the preparation of ethers 2, 4–6 and 14–17. To 10 mL DMSO powdered KOH (1.1 g, 20 mmol) was added and stirred for 5 min in ambient temperature. Then 3-piperidinopropan-1-ol (**1**, 0.72 g, 5.0 mmol), TBAI (0.18 g, 0.5 mmol) and alkyl halide (6 mmol) were added. Stirring was continued for the proper time at ambient temperature or heated (50 or 90 °C). Then the mixture was poured into water (25 mL) and extracted with CH$_2$Cl$_2$ or Et$_2$O. The combined organic extracts were purified by further extraction and/or CC. The extracts were dried over anhydrous Na$_2$SO$_4$. The final products were crystallized as salts of oxalic acid from EtOH/Et$_2$O.

5.1.2.1. 1-(3-Ethoxypropyl)piperidine hydrogen oxalate (2). From 1-bromoethane (0.65 g, 6 mmol). Heated at 50 °C for 15 h. Extracted with Et$_2$O, followed by purification by CC (eluent: CH$_2$Cl$_2$–MeOH; 90:10). Yield: 24%. ^{1}H NMR: δ = 3.42–3.35 (m, 4H, CH_2OCH_2), 3.16–2.95 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.85 (m, 2H, PipCH$_2$-CH_2), 1.73–1.67 (m, 4H, Pip-3,5-*H*), 1.49 (br s, 2H, Pip-4-*H*), 1.08 (t, *J* = 7.2 Hz, 3H, CH_3); MS (70 eV): *m*/*z* (%) = 171 ([M·]$^+$, 4), 142 ([Pip-(CH$_2$)$_3$O$^+$], 15), 99 (15), 98 ([Pip-CH$_2^+$], 100), 84 [Pip$^+$], 6; IR (cm^{-1}): 1134s (ν [C–O–C]).

5.1.2.2. 1-(3-Butoxypropyl)piperidine hydrogen oxalate (4). From 1-bromobutane (0.82 g, 6 mmol). Heated at 90 °C for 47 h. Extracted with Et$_2$O, followed by purification by CC (eluent: CH$_2$Cl$_2$–MeOH; 90:10). Yield: 32%. ^{1}H NMR: δ = 3.41 (t, *J* = 5.8 Hz, 2H, CH_2–O), 3.37 (t, *J* = 6.6 Hz, 2H, O–CH_2), 3.18–3.05 (m, 6H, Pip-2,6-*H* + Pip-CH_2), 1.90 (m, 2H, PipCH$_2$-CH_2), 1.80–1.60 (s, 4H, Pip-3,5-*H*), 1.53–1.44 (m, 4H, Pip-4-*H* + CH_2C$_2$H$_5$), 1.38–1.26 (m, 2H, CH_2CH$_3$), 0.89 (t, *J* = 7.2 Hz, 3H, CH_3); MS (70 eV): *m*/*z* (%) = 199 ([M·]$^+$, 2), 142 ([Pip-(CH$_2$)$_3$O$^+$], 10), 99 (7), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 3); IR (cm^{-1}): 1113s (ν [C–O–C]).

5.1.2.3. 1-[3-(2-Methylbutoxy)propyl]piperidine hydrogen oxalate (5). From 1-chloro-2-methylbutane (0.64 g, 6 mmol). Heated at 90 °C for 48 h. Extracted with Et$_2$O, followed by purification by CC (eluent: CH$_2$Cl$_2$–MeOH; 90:10). Yield: 7%. ^{1}H NMR: δ = 3.42 (t, *J* = 6.1 Hz, 2H, Pip-(CH$_2$)$_2$CH_2-O), 3.27–2.98 (m, 8H, O-CH_2CH(CH$_3$) + Pip-CH_2 + Pip-2,6-*H*), 1.89 (m, 2H, PipCH$_2$-CH_2), 1.74–1.70 (m, 4H, Pip-3,5-*H*), 1.64–1.40 (m, 3H, Pip-4-H_e + CH_2CH$_3$), 1.38–1.33 (m, 1H, Pip-4-H_a), 1.15–1.06 (m, 1H, CH$_2$CH(CH$_3$)C$_2$H$_5$), 0.89–0.85 (m, 6H, 2CH_3); MS (70 eV): *m*/*z* (%) = 213 ([M·]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 10), 99 (7), 98 ([Pip-CH$_2^+$], 100).

5.1.2.4. 1-[3-(2-Ethylbutoxy)propyl]piperidine hydrogen oxalate (6). From 3-bromomethylpentane (0.99 g, 6 mmol). Heated at 50 °C for 48 h. Extracted with Et$_2$O, followed by purification by CC (eluent: CH$_2$Cl$_2$–MeOH; 90:10). Yield: 3%. ^{1}H NMR: δ = 3.42 (t, *J* = 5.8 Hz, 2H,CH_2-O), 3.27 (d, *J* = 5.5 Hz, 2H, O-CH_2CH(C$_2$H$_5$)$_2$), 3.20–3.04 (s, 2H, Pip-CH_2), 3.04–2.98 (m, 4H, Pip-2,6-*H*), 1.89 (m, 2H, PipCH$_2$-CH_2), 1.78–1.64 (m, 4H, Pip-3,5-*H*), 1.53 (br s, 2H, Pip-4-*H*), 1.42–1.27 (m, 5H, CH$_2$CH(CH_2CH$_3$)$_2$), 0.85 (t, *J* = 7.2 Hz, 6H, 2CH_3); MS (70 eV): *m*/*z* (%) = 227 ([M·]$^+$, 2), 142 ([Pip-(CH$_2$)$_3$O$^+$], 15), 99 (7), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 4).

5.1.2.5. 1-{3-[(*E*)-But-2-enyloxy]propyl}piperidine hydrogen oxalate (14). From (*E*)-1-bromobut-2-ene (0.81 g, 6 mmol). Heated at 50 °C for 15 h. Extracted with Et$_2$O, followed by purification by CC (eluent: CH$_2$Cl$_2$–MeOH; 90:10). Yield: 30%. ^{1}H NMR: δ = 5.71–5.59 (m, 1H, OCH$_2$CH=CH), 5.58–5.44 (m, 1H, OCH$_2$CH=CH), 3.83–3.81 (dd, J^2 = 6.1 Hz, J^2 = 2.3 Hz, 2H, OCH_2CH=CH), 3.36 (t, *J* = 6.1 Hz, 2H, Pip-(CH$_2$)$_2$CH_2-O), 3.07–2.96 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.85 (m, 2H, PipCH$_2$-CH_2), 1.71–1.67 (m, 4H, Pip-3,5-*H*), 1.65–1.63 (dd, J^2 = 5,0 Hz, J^2 = 1.4 Hz, 3H, CH_3), 1.49 (br s, 2H, Pip-4-*H*); MS (70 eV): *m*/*z* (%) = 197 ([M·]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 12), 99 (8), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 5); IR (cm^{-1}): 1106s (ν [C–O–C]), 976s (γ [=C–H]).

5.1.2.6. 1-{3-[3-Methylbut-2-enyloxy]propyl}piperidine hydrogen oxalate (15). From 1-bromo-3-methylbut-2-ene (0.89 g, 6 mmol). Heated at 50 °C for 18 h. Extracted with Et$_2$O, followed by further washing with water and 1% HCl. The acidic layer was alkalized by NaHCO$_3$ and extracted to CHCl$_3$. Organic layer was washed with water, dried (Na$_2$SO$_4$) and after removal of the solvent in vacuo crystallized. Yield: 22%. ^{1}H NMR: δ = 5.27 (t, *J* = 6.9 Hz, 1H, CH=C(CH$_3$)$_2$), 3.91 (d, *J* = 6.9 Hz, 2H, OCH_2), 3.41 (t, *J* = 6.1 Hz, 2H, CH_2O), 3.10 (br s, 4H, Pip-2,6-*H*), 3.05–2.99 (m, 2H, Pip-CH_2), 1.89 (m, 2H, Pip-CH$_2$CH_2), 1.74–1.71 (m, 4H, Pip-3,5-*H*), 1.64 (s, 6H, 2CH_3), 1.53 (br s, 2H, Pip-4-*H*); MS (70 eV): *m*/*z* (%) = 211 ([M·]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 14), 124 (5), 99 (9), 98 ([Pip-CH$_2^+$], 100), 96 (29), 84 ([Pip$^+$], 11), 69 ([(CH$_3$)$_2$C=CH–CH$_2^+$], 9); IR (cm^{-1}): 1102s (ν [C–O–C]).

5.1.2.7. 1-{3-{[(*E*)-3-Phenylprop-2-enyl]oxy}propyl}piperidine hydrogen oxalate (16). From (*E*)-1-bromo-3-phenylprop-2-ene (1.19 g, 6 mmol). Heated at 50 °C for 20 h. Extracted with Et$_2$O, followed by further washing with water and 1% HCl. The acidic layer was alkalized by NaHCO$_3$ and extracted to CHCl$_3$. Organic layer was washed with water, dried (Na$_2$SO$_4$) and after removal of the solvent in vacuo purified by CC (eluent: CH$_2$Cl$_2$–MeOH; 97:3). Yield: 15%. ^{1}H NMR: δ = 7.47 (d, *J* = 7.2 Hz, 2H, Ph-2,6-*H*), 7.36 (t, *J* = 6.9 Hz, 2H, Ph-3,5-*H*), 7.28 (d, $J = 7.4$ Hz, 1H, Ph-4-*H*), 6.63 (d, $J = 15.9$ Hz, 1H, CH=C*H*–Ph), 6.41–6.32 (dt, $J^2 = 16.2$ Hz, $J^3 = 5.8$ Hz, 1H, CH$_2$C*H*=CHPh), 4.11 (d, $J = 5.8$ Hz, 2H, CH_2–CH=CH), 3.50 (t, $J = 6.1$ Hz, 2H, CH_2O), 3.20–3.03 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.94 (m, 2H, Pip-CH$_2$CH_2), 1.80–1.60 (m, 4H, Pip-3,5-*H*), 1.53 (br s, 2H, Pip-4-*H*); MS (70 eV): *m/z* (%) = 259 ([M$^·$]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 11), 131 (6), 124 (10), 117 ([PhCH=CH–CH$_2^+$], 14), 115 (10), 99 (8), 98 ([Pip-CH$_2^+$], 100), 97 (11), 96 (50), 84 ([Pip$^+$], 7), 77 ([Ph$^+$], 6); IR (cm^{-1}): 1637s (*ν* [C=C]), 1227s (*ν* [C–O–C]).

5.1.2.8. 1-{3-[2-(4-Fluorophenoxy)ethoxy]propyl}piperidine hydrogen oxalate (17). From 1-bromo-2(4-fluorophenoxy)ethane (2.19 g, 10 mmol). Room temperature for 16 h. Extracted with CH$_2$Cl$_2$, followed by further washing with 1% HCl. The organic layer was dried (Na$_2$SO$_4$) and after removal of the solvent in vacuo purified by CC (eluent: CHCl$_3$: MeOH; 95: 5). Yield: 7%. ^{1}H NMR: $\delta = 7.13$–7.05 (m, 2H, Ph-2,6-*H*), 6.95–6.91 (m, 2H, Ph-3,5-*H*), 4.10–4.03 (m, 2H, CH_2-OPh), 4.02–3.66 (m, 2H, OCH_2CH$_2$Ph), 3.49 (t, $J = 6.1$ Hz, 2H, CH_2-O), 3.39–2.97 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.88 (m, 2H, PipCH$_2$-CH_2), 1.70–1.60 (m, 4H, Pip-3,5-*H*), 1.49 (br s, 2H, Pip-4-*H*); MS (70 eV): *m/z* (%) = 281 ([M$^·$]$^+$, 1), 150 (70), 142 ([Pip-(CH$_2$)$_3$O$^+$], 11), 135 (11), 133 (26), 105 (57), 99 (7), 98 ([Pip-CH$_2^+$], 100); IR (cm^{-1}): 1208s (*ν* [C–O–C]), 1124s (*ν* [C–O–C$_{\mathrm{Ar}}$]).

5.1.3. General procedure for the preparation of ethers 3, 7, 8 and 10–13. A mixture of 3-piperidinopropan-1-ol (**1**, 0.72 g, 5.0 mmol), an appropriate alkyl halide (6.0 mmol), TBAB (0.17 g, 0.5 mmol), K$_2$CO$_3$ (4.8 g, 20 mmol) and KOH (1.1 g, 20 mmol) was heated in a domestic microwave oven in an open Erlenmeyer flask for the appropriate time (Table 1). After cooling, the reaction mixture was extracted with CH$_2$Cl$_2$. The solvent was removed under reduced pressure, the residue dissolved in CH$_2$Cl$_2$ (or CHCl$_3$) and washed with H$_2$O. The organic layer was then dried over anhydrous Na$_2$SO$_4$, filtered and after concentration crystallized as a salt of oxalic acid from EtOH/Et$_2$O.

5.1.3.1. 1-(3-Propoxypropyl)piperidine hydrogen oxalate (3). From 1-bromopropane (0.74 g, 6 mmol). The extract after drying was further purified by CC (eluent: CHCl$_3$–MeOH; 90:10) and then crystallized. Yield: 4%. ^{1}H NMR: $\delta = 3.38$ (t, $J = 5.8$ Hz, 2H, O-CH_2), 3.29 (t, $J = 6.6$ Hz, 2H, CH_2O), 3.09–2.96 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.85 (m, 2H, PipCH$_2$-CH_2), 1.78–1.60 (m, 4H, Pip-3,5-*H*), 1.54–1.42 (m, 4H, Pip-4-*H* + CH_2CH$_3$), 0.84 (t, $J = 7.4$ Hz, 3H, CH_3); MS (70 eV): *m/z* (%) = 185 ([M$^·$]$^+$, 1), 142 ([Pip(CH$_2$)$_3$O$^+$], 23), 99 (13), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 6); IR (cm^{-1}): 1112s (*ν* [C–O–C]).

5.1.3.2. 1-[3-(3-Methylbutoxy)propyl]piperidine hydrogen oxalate (7). From 1-bromo-3-methylbutane (0.45 g, 3 mmol) and 3-piperidinopropan-1-ol (**1**, 0.36 g, 2.5 mmol). Yield: 8%. ^{1}H NMR: $\delta = 3.40$–3.33 (m, 4H, CH_2-O-CH_2), 3.07 (br s, 4H, Pip-2,6-*H*), 3.00–2.96 (m, 2H, Pip-CH_2) 1.85 (m, 2H, PipCH$_2$-CH_2) 1.70–1.55 (m, 5H, Pip-3,5-*H* + C*H*(CH$_3$)$_2$), 1.49 (br s, 2H, Pip-4-*H*), 1.36 (q, $J = 6.6$ Hz, 2H, CH_2-CH(CH$_3$)$_2$), 0.84 (d, $J = 6.6$ Hz, 6H, 2CH_3); MS (70 eV): *m/z* (%) = 213 ([M$^·$]$^+$, 1), 142 ([Pip(CH$_2$)$_3$O$^+$], 15), 99 (7), 98 ([Pip-CH$_2^+$], 100), 96 (10), 84 ([Pip$^+$], 6); IR (cm^{-1}): 1113s (*ν* [C–O–C]).

5.1.3.3. 1-(5-Pentyloxypropyl)piperidine hydrogen oxalate (8). From 5-bromopentane (0.91 g, 6 mmol). The extract after drying was further purified by CC (eluent: CHCl$_3$–MeOH; 70:30) and then crystallized. Yield: 13%. ^{1}H NMR: $\delta = 3.73$ (t, $J = 6.1$ Hz, 2H, CH_2-O), 3.32 (t, $J = 6.4$ Hz, 2H, O-CH_2), 3.06 (br s, 2H, Pip-CH_2), 3.00–2.94 (m, 4H, Pip-2,6-*H*), 1.89–1.80 (m, 2H, PipCH$_2$-CH_2), 1.75–1.60 (m, 4H, Pip-3,5-*H*), 1.49–1.42 (m, 4H, Pip-4-*H* + CH_2(CH$_2$)$_2$CH$_3$), 1.30–1.20 (m, 4H, (CH_2)$_2$CH$_3$), 0.84 (t, $J = 6.9$ Hz, 3H, CH_3); MS (70 eV): *m/z* (%) = 213 ([M$^·$]$^+$, 2), 142 ([Pip-(CH$_2$)$_3$O$^+$], 12), 99 (8), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 4); IR (cm^{-1}): 1117s (*ν* [C–O–C]).

5.1.3.4. 1-[3-(Cyclobutylmethoxy)propyl]piperidine hydrogen oxalate (10). From 1-bromomethylcyclobutane (0.23 g, 3 mmol) and 3-piperidinopropan-1-ol (**1**, 0.36 g, 2.5 mmol). Yield: 9%. ^{1}H NMR: $\delta = 3.38$ (t, $J = 5.8$ Hz, 2H, CH_2-O), 3.31 (d, $J = 6.6$ Hz, 2H, O-CH_2-Cyclobut), 3.24–2.94 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 2.51–2.39 (m, 1H, Cyclobut-1-*H*), 1.98–1.63 (m, 12H, PipCH$_2$-CH_2 + Pip-3,5-*H* + Cyclobut-2,3,4-*H*), 1.49 (br s, 2H, Pip-4-*H*); MS (70 eV): *m/z* (%) = 211 ([M$^·$]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 12), 99 (7), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 4); IR (cm^{-1}): 1110s (*ν* [C–O–C]).

5.1.3.5. 1-[3-(Cyclohexylmethoxy)propyl]piperidine hydrogen oxalate (11). From 1-bromomethylcyclohexane (1.06 g, 6 mmol). Yield: 41%. ^{1}H NMR: $\delta = 3.43$ (t, $J = 5.5$ Hz, 2H, CH_2-O), 3.13 (d, $J = 6.6$ Hz, 2H, O-CH_2), 3.06–2.93 (m, 7H, Pip-CH_2 + Pip-2,6-*H* + Cyclohex-1-*H*), 1.87–1.49 (m, 14H, PipCH$_2$-CH_2 + Pip-3,4,5-*H* + Cyclohex-3,5-*H*), 1.29–1.13 (m, 2H, Cyclohex-2,6-H_e), 1.07–0.80 (m, 2H, Cyclohex-2,6-H_a); MS (70 eV): *m/z* (%) = 239 ([M$^·$]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 11), 99 (8), 98 ([Pip-CH$_2^+$], 100), 96 (6), 84 ([Pip$^+$], 5); IR (cm^{-1}): 1120s (*ν* [C–O–C]).

5.1.3.6. 1-[3-(2-Cyclohexylethoxy)propyl]piperidine hydrogen oxalate (12). From 2-bromoethylcyclohexane (1.15 g, 6 mmol). The extract after drying was further purified by CC (eluent: CHCl$_3$–MeOH; 97:3) and then crystallized. Yield: 7%. ^{1}H NMR: $\delta = 3.39$–3.34 (m, 4H, CH_2-O-CH_2), 3.04–2.93 (m, 6H, Pip-CH_2 + Pip-2,6-*H*), 1.83 (m, 2H, PipCH$_2$-CH_2), 1.75–1.55 (m, 10H, Pip-3,5-*H* + Cyclohex-3,4,5-*H*), 1.50 (br s, 2H, Pip-4-*H*), 1.37 (q, $J = 6.6$ Hz, 2H, CH_2-Cyclohex), 1.19 (m, 1H, Cyclohex-1-*H*), 1.15–1.05 (m, 2H, Cyclohex-2,6-H_e), 0.91–0.84 (m, 2H, Cyclohex-2,6-H_a); MS (70 eV): *m/z* (%) = 253 ([M$^·$]$^+$, 2), 142 ([Pip-(CH$_2$)$_3$O$^+$], 19), 99 (7), 98 ([Pip-CH$_2^+$], 100), 84 ([Pip$^+$], 5); IR (cm^{-1}): 1113s (*ν* [C–O–C]).

5.1.3.7. 1-[3-(Allyloxy)propyl]piperidine hydrogen oxalate (13). From 1-bromoprop-2-ene (0.73 g, 6 mmol). Yield: 12%. ^{1}H NMR: $\delta = 5.92$–5.79 (m, 1H,

–C*H*=CH$_2$), 5.23 (dd, J_E = 17.3 Hz, J^2 = 1.7 Hz, 1H, –CH=C*H*$_2$), 5.13 (dd, J_Z = 10.5 Hz, J^2 = 1.9 Hz, 1H, –CH=C*H*$_2$), 3.90 (d, *J* = 5.3 Hz, 2H, O–C*H*$_2$–CH=CH$_2$), 3.41 (t, *J* = 6.1 Hz, 2H, –C*H*$_2$O), 3.07–2.97 (m, 6H, Pip-2,6-*H* + Pip-C*H*$_2$), 1.87 (m, 2H, PipCH$_2$-C*H*$_2$), 1.71–1.67 (m, 4H, Pip-3,5-*H*), 1.49 (m, 2H, Pip-4-*H*); MS (70 eV): *m*/*z* (%) = 183 ([M$^\cdot$]$^+$, 1), 142 ([Pip(CH$_2$)$_3$O$^+$], 4), 99 (8), 98 ([Pip-CH$_2^+$], 100), 96 (11), 84 ([Pip$^+$], 7); IR (cm^{-1}): 1102s (*ν* [C–O–C]), 1626s (*ν* [C=C]).

5.1.4. Synthesis of 1-[3-(cyclopropylmethoxy)propyl]piperidine hydrogen oxalate (9). 15-Crown-5 (0.5 mmol, 0.1 mL) and 3-piperidinopropan-1-ol (**1**, 0.72 g, 5 mmol) were added to NaH (0.24 g, 6 mmol) (60% suspension in mineral oil) in dry toluene (10 mL). The reaction mixture was stirred at room temperature for 24 h. Then 1-bromomethylcyclopropane (0.68 g, 5 mmol) and a catalytic amount of TBAI were added and refluxed for 34 h. After cooling, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by CC (eluent: CH$_2$Cl$_2$–MeOH; 97:3). The pure fractions were crystallized as a salt of oxalic acid from EtOH/Et$_2$O. Yield: 5%. ^{1}H NMR: *δ* = 3.45 (t, *J* = 6.1 Hz, 2H, Pip-(CH$_2$)$_2$C*H*$_2$-O), 3.22 (d, *J* = 6.9 Hz, 2H, O-C*H*$_2$), 3.11–3.00 (m, 6H, Pip-2,6-*H* + Pip-C*H*$_2$), 1.90 (m, 2H, PipCH$_2$-C*H*$_2$), 1.80–1.60 (m, 4H, Pip-3,5-*H*), 1.53 (br s, 2H, Pip-4-*H*), 1.02–0.95 (m, 1H, Cycloprop-1-*H*), 0.47 (m, 2H, Cycloprop-2,3-H_e), 0.18 (m, 2H, Cycloprop-2,3-H_a); MS (70 eV): *m*/*z* (%) = 197 ([M$^\cdot$]$^+$, 1), 142 ([Pip-(CH$_2$)$_3$O$^+$], 14), 124 (2), 99 (8), 98 ([Pip-CH$_2^+$], 98), 84 ([Pip$^+$], 6).

5.1.5. General procedure for Mitsunobu-type ether formation (18 and 19). Triphenylphosphine (1.31 g, 5 mmol) was dissolved in 15 mL of freshly distilled THF together with 3-piperidinopropan-1-ol (**1**, 0.72 g, 5 mmol) and 5 mmol of the phenol derivative and cooled in an ice bath. Then DIAD (1.01 g, 5 mmol) was added dropwise. The mixture was stirred for 72 h (for **18**) and 96 h (for **19**) at ambient temperature. Then, the solvent was removed under reduced pressure and the crude product purified by CC, eluent: CHCl$_3$–MeOH; 95:5. Pure fractions were crystallized as salts of oxalic acid from EtOH/Et$_2$O.

5.1.5.1. 1-[3-(4-*tert*-Butylphenoxy)propyl]piperidine hydrogen oxalate (18). From 4-*tert*-butylphenol (0.76 g, 5 mmol). Yield: 56%. ^{1}H NMR: *δ* = 7.28–7.25 (m, 2H, Ph-2,6-*H*), 6.84–6.81 (m, 2H, Ph-3,5-*H*), 3.97 (t, *J* = 6.1 Hz, 2H, C*H*$_2$-O), 3.11–3.06 (m, 6H, Pip-C*H*$_2$ + Pip-2,6-*H*), 2.11 (m, 2H, PipCH$_2$-C*H*$_2$), 1.75–1.65 (m, 4H, Pip-3,5-*H*), 1.50 (br s, 2H, Pip-4-*H*), 1.22 (s, 9H, C(C*H*$_3$)$_3$); MS (70 eV): *m*/*z* (%) = 275 ([M$^\cdot$]$^+$, 8), 126 ([Pip-(CH$_2$)$_3^+$], 4), 99 (8), 98 ([Pip-CH$_2^+$], 100); IR (cm^{-1}): 1514s (*ν* [C=C]); 1249s (*ν* [C–O–C]).

5.1.5.2. 1-[3-(4-(1,1-Dimethylpropyl)phenoxy)propyl]piperidine hydrogen oxalate (19). From 4-(1,1-dimethylpropyl)phenol (0.92 g, 5 mmol). Yield: 55%. ^{1}H NMR: *δ* = 7.20 (d, *J* = 8.8 Hz, 2H, Ph-2,6-*H*), 6.83 (d, *J* = 8.8 Hz, 2H, Ph-3,5-*H*), 3.97 (t, *J* = 6.1 Hz, 2H, C*H*$_2$-O), 3.12–3.06 (m, 6H, Pip-C*H*$_2$ + Pip-2,6-*H*), 2.07 (m, 2H, PipCH$_2$-C*H*$_2$), 1.72–1.62 (m, 4H, Pip-3,5-*H*), 1.60–1.45 (m, 4H, Pip-4-*H* + C*H*$_2$CH$_3$), 1.18 (s, 6H, C(C*H*$_3$)$_2$), 0.58 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$); MS (70 eV): *m*/*z* (%) = 289 ([M$^\cdot$]$^+$, 7), 124 (Pip-(CH$_2$)$_3$$^+$], 7), 99 (7), 98 ([Pip-CH$_2^+$], 100); IR (cm^{-1}): 1513s (*ν* [C=C]); 1248s (*ν* [C–O–C]).

5.2. Pharmacology

5.2.1. In vitro [^{125}I]iodoproxyfan binding assay. Affinities of the novel compounds **2**–**19** were investigated in a radioligand binding assay as described by Ligneau et al.[27] Stably transfected CHO-K1 (or HEK 293) cells were washed and harvested with a PBS medium. They were centrifuged (140*g*, 10 min, and +4 °C) and then homogenized with a Polytron in the ice-cold binding buffer (Na$_2$HPO$_4$/KH$_2$PO$_4$, *c* = 50 mmol/L, pH 7.5). The homogenate was centrifuged (23,000*g*, 30 min, and +4 °C) and the pellet obtained 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 H$_3$ receptor agonist.[28] The corresponding K_i values were determined according to the Cheng–Prusoff equation.[30] Data are presented as means of experiments performed at least in triplicate.

5.2.2. Histamine H$_3$ receptor antagonist potency in vivo in mice. In vivo testing was performed after oral administration to Swiss mice according to Garbarg et al.[31] 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.[32] By treatment with 3 mg/kg ciproxifan the maximal increase in N^τ-methylhistamine level was obtained[33] 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.[34]

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Appendix A. Data of elemental analysis for final compounds **2**–**19**

No.	% C		% H		% N	
	Calcd	Found	Calcd	Found	Calcd	Found
2	55.15	54.84	8.87	8.83	5.36	5.28
3	56.71	56.47	9.15	8.85	5.09	5.23
4	55.52	55.53	9.48	9.23	4.62	4.38
5	59.03	58.93	9.64	9.89	4.59	4.61
6	59.69	59.71	9.86	10.16	4.35	4.34
7	56.05	56.24	9.72	9.49	4.36	4.13
8	59.38	59.16	9.63	9.87	4.62	4.58
9	57.61	57.78	8.81	8.67	4.80	4.75
10	58.04	57.93	9.09	8.82	4.51	4.67
11	56.38	56.41	8.67	8.91	3.65	4.81
12	62.95	62.59	9.68	9.81	4.08	4.04
13	56.20	56.20	8.53	8.24	5.04	5.05
14	57.79	57.69	8.80	8.76	4.81	4.85
15	59.78	59.50	9.03	9.01	4.65	4.61
16	65.31	65.57	7.79	7.88	4.01	4.02
17	56.83	56.91	7.15	6.80	3.68	3.66
18	65.73	65.54	8.55	8.66	3.83	3.86
19	66.46	66.33	8.76	8.95	3.69	3.67

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