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Diether derivatives of homo- or substituted piperidines as non-imidazole histamine H_3 receptor ligands

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ABSTRACT

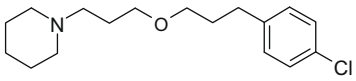
Synthesis and biological activities of a series of homo- or substituted piperidine unsymmetrical diethers are described. The novel compounds were evaluated for histamine H_3 receptor binding affinities at recombinant human H_3 receptor stably expressed in HEK-293 cells. All diethers showed in vitro affinities in nanomolar concentration range. The most potent compounds are 1-[3-(3-(4-chlorophenoxy)propoxy)propyl]-3-methylpiperidine **11** (K_i = 3.2 nM) and 1-[3-(3-(4-chlorophenoxy)propoxy)propyl]azepane **13** (K_i = 3.5 nM).

1. Introduction

Histamine H_3 receptors, as autoreceptors, control the histamine synthesis and the release from histaminergic neurons. Histamine as neurotransmitter in the mammalian brain regulates numerous brain functions and plays an important role in vigilance, attention, sleep/wake and feeding/weight regulation.[1–3] Histamine H_3 receptors act also as heteroreceptors modulating the release of various neurotransmitters such as acetylcholine, dopamine, norepinephrine, glutamate or serotonin.[4–10] These neurotransmitters are involved in cognition, mood and sensory gating.

So far, histamine H_3 receptor inverse agonists/antagonists are the preferred class for the development of potential therapeutic drugs for the treatment of sleep disorders (narcolepsy), obesity and cognition disorders (attention-deficit hyperactivity disorder, Alzheimer's disease, schizophrenia).[11–15]

Many pharmaceutical companies and academic research groups have synthesized a large variety of highly potent histamine H_3 receptor antagonists/inverse agonists (for review see Refs. 16–21). Within non-imidazole histamine H_3 receptor ligands, BF2.649 (tiprolisant) has been reported recently as a potent, selective and valuable drug candidate (Fig. 1).[21] BF2.649 showed significant inhibitory potency in several rodent models of schizophrenia and efficiency in treating excessive daytime sleepiness in narcoleptic patients as a first confirmation in proof-of-concept.[25,26] Presently, BF2.649 is under clinical investigation in Phase II trials for the treatment of schizophrenia and dementia among other drug candidates[24,26] (for review on clinical developments see Ref. 27).



BF2.649
K_i^{RC}: 17 nM[a]
pA_2^{Gp}: 8.25[b]
hK_i: 2.4 ± 0.5 nM[c]
EC_{50}: 1.5 ± 0.1 nM[d]
h$'K_i$: : 0.16 ± 0.03 nM[e]
h$''K_i$: : 2.7 ± 0.5 nM[f]
ED_{50}^{MsC}: 1.6 ± 0.9 mg/kg p.o.[g]

Figure 1. The structure and potency profile of BF2.649 (tiprolisant).[22–24] (a) Rat cerebral cortex; (b) isolated guinea pig ileum; (c) [^{125}I]iodoproxyfan binding assay at human H_3R stably expressed in CHO-K1 cells; (d) [^{35}S]GTPγS binding assay at human H_3R stably expressed in CHO-K1 cells; (e) [^{35}S]GTPγS binding assay at human H_3R stably expressed in HEK-293 cells; (f) [^{125}I]iodoproxyfan binding assay at human H_3R stably expressed in C6 cells; (g) central H_3R receptor assay in vivo after p.o. administration to mice.

This report is an extension of our previous work in the non-imidazole research area,[28,29] in which compound FUB 637, (1-[3-(phenylpropoxy)propyl]piperidine), the analogue of BF2.649, was taken as a

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lead structure. Recently we reported on the substitution of the piperidine moiety by different moieties mainly in 4-position (4-propyl, 4-butyl, 4-benzyl), replacement by other related nitrogen-containing bicycles (decahydroisoquinoline, 1,2,3,4-tetrahydroisoquinoline) or by the replacement of the 3-(piperidino)propyloxy fragment with bipiperidine.[29] Here, a second ether moiety has been introduced and a series of double-ether derivatives of substituted piperidines (3-methyl, 4-methyl) and azepanes has been prepared. The obtained ligands were screened for their binding affinities at recombinant human histamine H_3 receptor.

2. Results

2.1. Chemistry

The desired ethers **4–16** were prepared by Williamson type O-alkylation under solvent-free conditions using microwave irradiation according to the procedure described by Bogdał et al.[30] (Scheme 1). The alcohol (**1a**, **1b** or **1c**) was mixed with the appropriate (aryloxy)alkyl bromide (**2a**, **2**c, **3a**–**c**) 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 a domestic microwave oven.

3-Amino substituted propan-1-ols (**1a**–**c**) were obtained from appropriate secondary amines and 3-chloropropan-1-ol by the method described earlier with small modifications (equal volume of reagents) (Scheme 2).[31]

The required (aryloxy)alkyl bromides (**2a**, **2c**, **3a**–**c**; Scheme 3) were prepared in propan-1-ol from suitable phenols and α,ω-dibromoalkanes. The desired products were obtained as free bases.

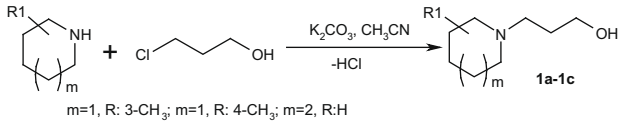
The final compounds **4–16** were isolated as salts of oxalic acid (hydrogen oxalates). Their purity was checked by TLC and their structures were confirmed by standard spectral techniques (^{1}H NMR, IR) and elemental analysis (Table 3). Some preparative and physicochemical properties of the ethers **4–16** are presented in Table 2.

2.2. Pharmacology

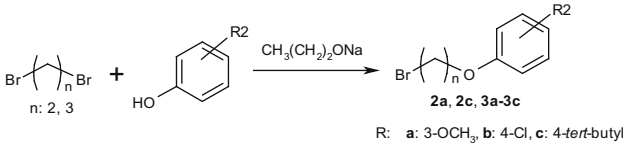
Histamine H_3 receptor affinities of the newly synthesized compounds were evaluated at the human receptor. Displacement of [^{125}I]iodoproxyfan from human histamine H_3 receptor expressed in HEK-293 cells, was measured as described previously.[32,33] Results of the pharmacological screening are summarized in Table 1.

3. Discussion

Two series of compounds were prepared with two or three methylene groups between both ether functionalities: (i) derivatives of substituted (2-bromoethoxy)benzenes (**4–7**) and (ii) derivatives of substituted (3-bromopropoxy)benzenes (**8–16**). Results of the displacement assay are shown in Table 1. All tested compounds exhibited pronounced to high affinities for human histamine H_3 receptor (K_i values from 3 to 62 nM).

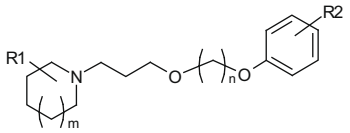


Scheme 2. The synthesis of 3-aminopropan-1-ols **1a**–**c**.



Scheme 3. The synthesis of 2-phenoxyethyl bromides (**2a**, **2c**) and 3-phenoxypropyl bromides (**3a**–**c**).

Table 1
Affinities of compounds **4–16** at human histamine H_3 receptor

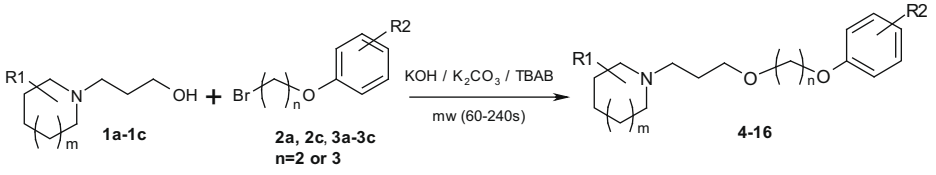


Compounds	R^1	*m*	*n*	R^2	$K_i \pm SE^a$ (nM)
4	3-CH_3	1	2	3-OCH_3	14.8 ± 2.8
5	4-CH_3	1	2	3-OCH_3	12.5 ± 1.6[b]
6	H	2	2	3-OCH_3	7.2 ± 1.1[b]
7	3-CH_3	1	2	4-$C(CH_3)_3$	62 ± 5
8	3-CH_3	1	3	3-OCH_3	27.3 ± 2.7
9	4-CH_3	1	3	3-OCH_3	49 ± 4
10	H	2	3	3-OCH_3	18.6 ± 2.3[b]
11	3-CH_3	1	3	4-Cl	3.2 ± 0.1
12	4-CH_3	1	3	4-Cl	27.9 ± 5.9
13	H	2	3	4-Cl	3.5 ± 0.5[b]
14	3-CH_3	1	3	4-$C(CH_3)_3$	12.8 ± 2.1[b]
15	4-CH_3	1	3	4-$C(CH_3)_3$	51 ± 5[b]
16	H	2	3	4-$C(CH_3)_3$	7.7 ± 0.6
BF2.649					2.40[c,d]

[a] [^{125}I]Iodoproxyfan binding assay at human H_3R stably expressed in HEK-293 cells.
[b] Ref. 40.
[c] Ref. 22.
[d] Ref. 28.

In the benzene ring three different substituents were introduced in the *para*-position: methoxy (compounds **4–6** and **8–10**), *tert*-butyl (compounds **7** and **14–16**) and chlorine (compounds **11–13**). In the methoxy series (**4–6**, **8–10**), elongation of the alkyl chain from two to three carbon atoms (Scheme 1) exhibited a decrease in H_3 receptor affinity. Compounds **8–10** (n = 3, K_i values of 27.3 nM, 49 nM and 18.6 nM, respectively) are about half as potent as the related compounds **4–6** (n = 2, K_i values of 14.8 nM, 12.5 nM and 7.2 nM, respectively).

It seems that steric hindrance limited histamine H_3 receptor affinity. The bulky *tert*-butyl residue in the *para*-position (com-



Scheme 1. The synthesis of ethers **4**–**16**.

Table 2
Physicochemical data of novel compounds **4–16**

No.	Formula	MW	Mp (°C)
4	$C_{18}H_{29}NO_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$	401.99	89–91
5	$C_{18}H_{29}NO_3 \cdot C_2H_2O_4$	397.45	99–101
6	$C_{18}H_{29}NO_3 \cdot C_2H_2O_4$	397.45	88–90
7	$C_{21}H_{35}NO_2 \cdot C_2H_2O_4$	423.53	145–148
8	$C_{19}H_{31}NO_3 \cdot C_2H_2O_4$	411.48	94–96
9	$C_{19}H_{31}NO_3 \cdot C_2H_2O_4$	411.48	88–90
10	$C_{19}H_{31}NO_3 \cdot C_2H_2O_4$	411.48	88–91
11	$C_{18}H_{28}NO_2Cl \cdot 0.9C_2H_2O_4$	406.92	132–134
12	$C_{18}H_{28}NO_2Cl \cdot C_2H_2O_4$	415.91	135–138
13	$C_{18}H_{28}NO_2Cl \cdot C_2H_2O_4$	415.91	126–129
14	$C_{22}H_{37}NO_2 \cdot 1.1C_2H_2O_4 \cdot 0.25H_2O$	451.09	101–104
15	$C_{22}H_{37}NO_2 \cdot C_2H_2O_4$	437.56	125–128
16	$C_{22}H_{37}NO_2 \cdot C_2H_2O_4$	437.56	120–122

Table 3
Data of elemental analysis for final compounds **4–16**

No.	% C		% H		% N	
	Calcd	Found	Calcd	Found	Calcd	Found
4	59.76	59.64	7.90	7.74	3.48	3.53
5	60.43	60.48	7.86	7.87	3.52	3.52
6	60.43	60.18	7.86	7.90	3.52	3.52
7	65.22	65.15	8.80	8.75	3.31	3.34
8	61.29	60.88	8.08	8.03	3.40	3.66
9	61.29	61.46	8.08	8.03	3.40	3.39
10	61.29	60.97	8.08	8.02	3.40	3.32
11	58.44	58.22	7.38	7.47	3.44	3.37
12	57.75	57.74	7.27	7.16	3.37	3.41
13	57.75	57.62	7.27	7.28	3.37	3.37
14	64.43	64.56	8.87	8.46	3.11	3.08
15	65.87	65.46	8.98	9.01	3.20	3.24
16	65.87	65.70	8.98	8.88	3.20	3.14

pounds **14–16**; K_i = 12.8 nM, 51 nM and 7.7 nM, respectively) caused a decrease in potency compared with that of the *para*-chlorinated compounds **11–13** (K_i = 3.2 nM, 27.9 nM and 3.5 nM, respectively). Compounds **11** and **13** showed the highest histamine H_3 receptor affinities with K_i values of 3.2 nM and 3.5 nM, respectively.

From these results for ethers **8–16**, the order of the most tolerable substituents in the phenyl ring (by the binding pocket of H_3 receptor) is concluded: 4-Cl > 4-*tert*-butyl > 3-OCH_3. In the ethoxybenzen series (**4–7**) the order of substituents seems to be different: 3-OCH_3 > 4-*tert*-butyl. However, the small number of compounds does not allow drawing of a final conclusion.

Introduction of a methyl group in the 4-position of the piperidine ring resulted in a decrease in binding affinities, compared with its constitutional 3-substituted isomers, as seen in compounds: **9** (K_i = 49 nM) versus **8** (K_i = 27.3 nM); **12** (K_i = 27.9 nM) versus **11** (K_i = 3.2 nM); **15** (K_i = 51 nM) versus **14** (K_i = 12.8 nM). Interestingly, the extent of this decrease depends on the substituent on the phenyl ring and the largest one is for the 4-chloro derivatives (**12** vs **11**). Replacement of the 3-methylpiperidine ring by a homopiperidine moiety results in derivatives with improved (**6** vs **4**; **10** vs **8**; **16** vs **14**) or comparable (**13** vs **11**) H_3 receptor affinities.

Compared to BF2.649 (K_i = 2.4 nM), compounds **11** (K_i = 3.2 nM) and **13** (K_i = 3.5 nM) showed affinities in the same concentration range.[22] Thus, introduction of the second ether moiety and the homo- or 3-methyl-piperidine ring resulted in a considerable histamine H_3 receptor affinity with presumed differences in pharmacokinetic behaviour.

4. Conclusions

The described diethers are a new promising lead of potent histamine H_3 receptor ligands. The most active compounds **11** and **13** exhibit considerable affinities as that of BF2.649. Thus, it seems that the piperidine moiety can be successfully replaced by the 3-methylpiperidine or the homopiperidine ring while the second ether group is introduced to the structure. However, further investigations are proceeding to confirm these results and to check what kinds of structural variations are further acceptable for maintaining H_3 receptor affinity.

5. Experimental

5.1. Chemistry

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; t, triplet; m, multiplet; Azep, azepanyl; Ph, phenyl; Pip, piperidino), 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; Et_2O, diethyl ether; EtOH, ethanol; TBAB, tetrabutyl ammonium bromide; W, Watt.

5.1.1. General procedure for the preparation of 3-heterocyclic substituted propan-1-ols (1a–c)

ω-Aminoalkan-1-ols were prepared according to Ref. 34 as described previously.[31]

5.1.1.1. 3-(3-Methylpiperidin-1-yl)propan-1-ol (1a). From 3-methylpiperidine (0.2 mol, 19.84 g) and 3-chloropropan-1-ol (0.2 mol, 18.91 g). The reaction mixture was heated to reflux for 10 h and evaporated under Claisen column. Yield: 59%. [bp 114 °C (16 mm Hg) from Ref. 35].

5.1.1.2. 3-(4-Methylpiperidin-1-yl)propan-1-ol (1b). From 4-methylpiperidine (0.2 mol, 19.84 g) and 3-chloropropan-1-ol (0.2 mol, 18.91 g). The reaction mixture was heated to reflux for 10 h and evaporated under Claisen column. Yield: 59%. [bp 110 °C (13 mm Hg) from Ref. 35].

5.1.1.3. 3-(Azepan-1-yl)propan-1-ol) (1c). From homopiperidine (0.2 mol, 19.84 g) and 3-chloropropan-1-ol (0.2 mol, 18.91 g). The reaction mixture was heated to reflux for 10 h and evaporated under Claisen column. Yield: 60%. [bp 115–117 °C (12 mm Hg) from Ref. 36].

5.1.2. General procedure for the synthesis of 2-phenoxyethyl bromides (2a, 2c) and 3-phenoxypropyl bromides (3a–c)

To the solution of sodium (0.1 mol, 2.3 g) in 100 mL of propan-1-ol an appropriate derivative of the phenol was added (0.1 mol) and 1,2-dibromoethane or 1,3-dibromopropane (0.3 mol) was dropped 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 25 mL of 10% NaOH was added and extracted with CH_2Cl_2 25 mL. The organic solution was dried

(Na_2SO_4) and evaporated to give a pure oil or further purified by CC.

5.1.2.1. 2-Bromo-1-(3-methoxyphenoxy)ethane (2a). From 3-methoxyphenol (0.1 mol, 12.4 g). Yield 41%. [bp 95–96 °C (0.35 mm Hg) from Ref. 37].

5.1.2.2. 2-Bromo-1-(4-*tert*-butylphenoxy)ethane (2c). From 4-*tert*-butylphenol (0.1 mol, 15.0 g). Yield: 27%. [bp 117 °C (0.02 mm Hg) from Ref. 38].

5.1.2.3. 3-Bromo-1-(3-methoxyphenoxy)propane (3a). From 3-methoxyphenol (0.1 mol, 12.4 g). The residue after the extraction was purified by CC (CH_2Cl_2). Yield: 12%. [bp 113–114 °C (0.5 mm Hg) from Ref. 37].

5.1.2.4. 3-Bromo-1-(4-chlorophenoxy)propane (3b). From 4-chlorophenol (0.1 mol, 12.9 g). The residue after the extraction was purified by CC (CH_2Cl_2). Yield: 84%. [bp 110–111 °C (0.3 mm Hg) from Ref. 37].

5.1.2.5. 3-Bromo-1-(4-*tert*-butylphenoxy)propane (3c). 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. [bp 118–120 °C (0.4 mm Hg) from Ref. 37].

5.1.3. General procedure for the preparation of ethers 4–16

A mixture of appropriate 3-aminopropan-1-ol (**1a–c**, 2.5 mmol), an alkyl halide (3.0 mmol), TBAB (0.085 g, 0.25 mmol), K_2CO_3 (2.4 g, 10 mmol) and KOH (0.55 g, 10 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 dissolved in CH_2Cl_2 (20 mL) and washed with 20 mL of 3% HCl. The acidic layer was alkalized (10% NaOH) and extracted with Et_2O. The organic layer was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. A colourless oil was dissolved in 2 mL of dry EtOH and then 1.1 equiv of oxalic acid were added. The solution was stirred in the room temperature for 1 h. On addition of Et_2O precipitation took place and the white solid obtained was filtered. In some cases re-crystallisation in the same solvents was necessary for purification.

5.1.3.1. 1-[3-(2-(3-Methoxyphenoxy)ethoxy]propyl-3-methylpiperidine hydrogen oxalate (4). From 3-(3-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)ethane (**2a**) (0.69 g, 3 mmol). Heated in the microwave oven for 120 s (2 × 60 s). Yield of 70 mg (7%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.16 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.52–6.46 (m, 3H, Ph-2,4,6-*H*), 4.07–4.04 (m, 2H, CH_2-OPh), 3.71–3.67 (m, 5H, OCH_3 + O-CH_2···Ph), 3.50 (t, J = 6.2 Hz, 2H, Pip···CH_2-O), 3.40–3.25 (m, 2H, Pip-2,6-H_e), 3.05–2.90 (m, 2H, Pip-CH_2), 2.95–2.80 (m, 1H, Pip-6-H_a), 2.48–2.35 (m, 1H, Pip-2-H_a), 1.95–1.80 (m, 2H, PipCH$_2$-CH_2), 1.80–1.55 (m, 4H, Pip-4,5-H_2), 1.10–0.95 (m, 1H, Pip-3-*H*), 0.85 (d, J = 6.7 Hz, 3H, CH_3); IR (KBr) (cm^{-1}): 1201s (ν [C–O–C$_{arom}$]), 1156s (ν [C–O–C]).

5.1.3.2. 1-[3-(2-(3-Methoxyphenoxy)ethoxy]propyl-4-methylpiperidine hydrogen oxalate (5). From 3-(4-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)ethane (**2a**) (0.69 g, 3 mmol). Heated in the microwave oven for 300 s (5 × 60s). Yield of 50 mg (5%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.16 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.52–6.46 (m, 3H, Ph-2,4,6-*H*), 4.07–4.04 (m, 2H, CH_2-OPh), 3.71–3.67(m, 5H, OCH_3 + O-CH_2···Ph), 3.50 (t, J = 5.9 Hz, 2H, Pip···CH_2-O), 3.40–3.30 (m, 2H, Pip-2,6-H_e), 3.05–2.95 (m, 2H, Pip-CH_2), 2.90–2.80 (m, 2H, Pip-2,6-H_a) 1.95–1.85 (m, 2H, Pip-CH$_2$-CH_2), 1.80–1.67 (m, 2H, Pip-3,5-H_e), 1.56 (br s, 1H, Pip-4-*H*), 1.40–1.25 (m, 2H, Pip-3,5-H_a), 0.88 (d, J = 6.7 Hz, 3H, CH_3); IR (KBr) (cm^{-1}): 1204s (ν [C–O–C$_{arom}$]), 1155s (ν [C–O–C]).

5.1.3.3. 1–3-[2-(3-Methoxyphenoxy)ethoxy)propyl]azepane hydrogen oxalate (6). From 3-(azepan-1-yl)propan-1-ol (**1c**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)ethane (**2a**) (0.69 g, 3 mmol). Heated in the microwave oven for 120 s (2 × 60 s). Yield of 50 mg (5%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.16 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.52–6.46 (m, 3H, Ph-2,4,6-*H*), 4.5 (def t, 2H, CH_2-OPh), 3.75–3.67 (m, 5H, OCH_3 + Azep···O-CH_2), 3.50 (t, J = 5.9 Hz, 2H, Azep···CH_2-O), 3.25–3.10 (m, 4H, Azep-2-H_2 + Azep-7-H_2), 3.10–3.02 (m, 2H, Azep-CH_2), 1.98–1.85 (m, 2H, Azep-CH$_2$-CH_2), 1.80–1.70 (m, 4H, Azep-3-H_2 + Azep-6-H_2), 1.64–1.50 (m, 4H, Azep-4-H_2 + Azep-5-H_2); IR (KBr) (cm^{-1}): 1205s (ν [C–O–C$_{arom}$]), 1155s (ν [C–O–C]).

5.1.3.4. 1-[3-(2-(-4-*tert*-Butylphenoxy)ethoxy)propyl]-3-methylpiperidine hydrogen oxalate (7). From 3-(3-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 2-bromo-1-(4-*tert*-butylphenoxy)ethane (**2c**) (0.77 g, 3 mmol).Heated in the microwave oven for 240 s (4 × 60 s). Yield of 150 mg (14%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.27 (d, J = 8.9 Hz, 2H, Ph-3,5-*H*), 6.84 (d, J = 8.7 Hz, 2H, Ph-2,6-*H*), 4.04 (t, J = 5.4 Hz, 2H, CH_2-OPh), 3.68 (t, J = 5.4 Hz, 2H, O-CH_2···Ph), 3.50 (t, J = 6.2 Hz, 2H Pip···CH_2-O), 3.40–3.20 (m, 2H, Pip-2,6-H_e), 3.05–2.95 (m, 2H, Pip-CH_2), 2.72–2.60 (m, 1H, Pip-6-H_a), 2.45–2.35(m, 1H, Pip-2-H_a), 1.95–1.60 (m, 6H, PipCH$_2$-CH_2 + Pip-4,5-H_2), 1.23 (s, 9H, 3CH_3), 1.10–0.90 (m, 1H, Pip-3-*H*), 0.85 (d, J = 6.7 Hz, 3H, CH_3); IR (KBr) (cm^{-1}): 1248s (ν [C–O–C$_{arom}$]), 1127s (ν [C–O–C]).

5.1.3.5. 1-[3-(3-(3-Methoxyphenoxy)propoxy)propyl]-3-methylpiperidine hydrogen oxalate (8). From 3-(3-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)propane (**3a**) (0.74 g, 3 mmol). Heated in the microwave oven for 180 s (3 × 60 s). Yield of 330 mg (32%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.15 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.51–6.44 (m, 3H, Ph-2,4,6-*H*), 3.98 (t, J = 6.4 Hz, 2H, CH_2-OPh), 3.71 (s, 3H, OCH_3), 3.50 (t, J = 6.2 Hz, 2H, O-CH_2···Ph), 3.42 (t, J = 5.9 Hz, 2H Pip···CH_2-O), 3.36–3.20 (m, 2H, Pip-2,6-H_e), 3.05–2.90 (m, 2H, Pip-CH_2), 2.70–2.55 (m, 1H, Pip-6-H_a), 2.45–2.30(m, 1H, Pip-2-H_a), 1.96–1.60 (m, 8H, PipCH$_2$-CH_2 + CH_2-CH$_2$OPh + Pip-4,5-H_2), 1.10–0.90 (m, 1H, Pip-3-*H*), 0.85 (d, J = 6.7 Hz, 3H, CH_3); IR (KBr) (cm^{-1}): 1201s (ν [C–O–C$_{arom}$]), 1149s (ν [C–O–C]).

5.1.3.6. 1-[3-(3-(3-Methoxyphenoxy)propoxy)propyl]-4-methylpiperidine hydrogen oxalate (9). From 3-(4-Methylpiperidin-1-yl)propan-1-ol (**1b**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)propane (**3a**) (0.74 g, 3 mmol). Heated in the microwave oven for 240 s (4 × 60 s). Yield of 220 mg (21%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.15 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.51–6.45 (m, 3H, Ph-2,4,6-*H*), 3.98 (t, J = 6.4 Hz, 2H, CH_2-OPh), 3.70 (s, 3H, OCH_3), 3.49 (t, J = 6.2 Hz, 2H, O-CH_2···Ph), 3.42 (t, J = 5.6 Hz, 2H, Pip···CH_2-O), 3.35–3.25 (m, 2H, Pip-2,6-H_e), 3.03–2.90 (m, 2H, Pip-CH_2), 2.83–2.70 (m, 2H, Pip-2,6-H_a) 1.97–1.80 (m, 4H, PipCH$_2$-CH_2 + CH_2–CH$_2$OPh), 1.78–1.64 (m, 2H, Pip-3,5-H_e), 1.55 (br s, 1H, Pip-4-*H*), 1.40–1.20 (m, 2H, Pip-3,5-H_a), 0.88 (d, J = 6.4 Hz, 3H, CH_3); IR (KBr) (cm^{-1}): 1196s (ν [C–O–C$_{arom}$]), 1154s (ν [C–O–C]).

5.1.3.7. 1-[3-(3-(3-Methoxyphenoxy)propoxy)propyl]azepane hydrogen oxalate (10). From 3-(azepan-1-yl)propan-1-ol (**1c**) (0.39 g, 2.5 mmol) and 2-bromo-1-(3-methoxyphenoxy)propane

(**3a**) (0.74 g, 3 mmol). Heated in the microwave oven for 180 s (3 × 60 s). Yield of 280 mg (27%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.15 (t, J = 8.0 Hz, 1H, Ph-5-*H*), 6.51–6.44 (m, 3H, Ph-2,4,6-*H*), 3.98 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.71 (s, 3H, OC*H*$_3$), 3.50 (t, J = 6.2 Hz, 2H, Azep···O-C*H*$_2$), 3.42 (t, J = 6.2 Hz, 2H, Azep···C*H*$_2$-O), 3.20–3.08 (m, 4H, Azep-2-*H*$_2$ + Azep-7-*H*$_2$), 3.08–3.00 (m, 2H, Azep-C*H*$_2$), 1.96–1.80 (m, 4H, Azep-CH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh), 1.80–1.70 (m, 4H, Azep-3-*H*$_2$ + Azep-6-*H*$_2$), 1.70–1.65 (m, 4H, Azep-4-*H*$_2$ + Azep-5-*H*$_2$); IR (KBr) (cm^{-1}): 1201s (ν [C–O–C$_{arom}$]), 1162s (ν [C–O–C]).

5.1.3.8. 1-[3-(3-(4-Chlorophenoxy)propoxy)propyl]-3-methylpiperidine hydrogen oxalate (11). From 3-(3-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-chlorophenoxy)propane (**3b**) (3 mmol, 0.75 g). Heated in the microwave oven for 120 s (2 × 60 s). Yield of 220 mg (22%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.31 (d, J = 9.2 Hz, 2H, Ph-3,5-*H*), 6.94 (d, J = 8.9 Hz, 2H, Ph-2,6-*H*), 4.00 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.49 (t, J = 6.2 Hz, 2H, O-C*H*$_2$···Ph), 3.42 (t, J = 5.9 Hz, 2H, Pip···C*H*$_2$-O), 3.35–3.20 (m, 2H, Pip-2,6-*H*$_e$), 3.03–2.90 (m, 2H, Pip-C*H*$_2$), 2.74–2.55 (m, 1H, Pip-6-*H*$_a$), 2.48–2.30 (m, 1H, Pip-2-*H*$_a$), 1.98–1.55 (m, 8H, PipCH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh + pip-4,5-*H*$_2$), 1.10–0.90 (m, 1H, Pip-3-*H*), 0.86 (d, J = 6.4 Hz, 3H, C*H*$_3$); IR (KBr) (cm^{-1}): 1248s (ν [C–O–C$_{arom}$]), 1123s (ν [C–O–C]).

5.1.3.9. 1-[3-(3-(4-Chlorophenoxy)propoxy)propyl]-4-methylpiperidine hydrogen oxalate (12). From 3-(4-methylpiperidin-1-yl)propan-1-ol (**1b**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-chlorophenoxy)propane (**3b**) (3 mmol, 0.75 g). Heated in the microwave oven for 180 s (3 × 60 s). Yield of 180 mg (17%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.30 (d, J = 8.0 Hz, 2H, Ph-3,5-*H*), 6.94 (d, J = 9.0 Hz, 2H, Ph-2,6-*H*), 3.99 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.49 (t, J = 6.2 Hz, 2H, O-C*H*$_2$···Ph), 3.41 (t, J = 5.9 Hz, 2H, Pip···C*H*$_2$-O), 3.38–3.25 (m, 2H, Pip-2,6-*H*$_e$), 3.02–2.90 (m, 2H, Pip-C*H*$_2$), 2.85–2.70 (m, 2H, Pip-2,6-*H*$_a$) 1.96–1.80 (m, 4H, PipCH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh), 1.78–1.60 (m, 2H, Pip-3,5-*H*$_e$), 1.55 (br s, 1H, Pip-4-*H*), 1.36–1.25 (m, 2H, Pip-3,5-*H*$_a$), 0.88 (d, J = 6.4 Hz, 3H, C*H*$_3$); IR (KBr) (cm^{-1}): 1252s (ν [C–O–C$_{arom}$]), 1107s (ν [C–O–C]).

5.1.3.10. 1-[3-(3-(4-Chlorophenoxy)propoxy)propyl]azepane hydrogen oxalate (13). From 3-(azepan-1-yl)propan-1-ol (**1c**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-chlorophenoxy)propane (**3b**) (3 mmol, 0.75 g). Heated in the microwave oven for 180 s (3 × 60 s). Yield of 200 mg (19%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.30 (d, J = 9.2 Hz, 2H, Ph-3,5-*H*), 6.94 (d, J = 9.0 Hz, 2H, Ph-2,6-*H*), 3.99 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.49 (t, J = 6.2 Hz, 2H, O-C*H*$_2$···Ph), 3.41 (t, J = 5.9 Hz, 2H Azep···C*H*$_2$-O), 3.22–3.10 (m, 4H, Azep-2-*H*$_2$ + Azep-7-*H*$_2$), 3.10–2.96 (m, 2H, Azep-C*H*$_2$), 1.97–1.80 (m, 4H, Azep-CH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh), 1.80–1.68 (m, 4H, Azep-3-*H*$_2$ + Azep-6-*H*$_2$), 1.62–1.49 (m, 4H, Azep-4-*H*$_2$ + Azep-5-*H*$_2$); IR (KBr) (cm^{-1}): 1201s (ν [C–O–C$_{arom}$]), 1121s (ν [C–O–C]).

5.1.3.11. 1-[3-(3-(4-*tert*-Butylphenoxy)propoxy)propyl]-3-methylpiperidine hydrogen oxalate (14). From 3-(3-methylpiperidin-1-yl)propan-1-ol (**1a**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-*tert*-butylphenoxy)propane (**3c**) (0.69 g, 3 mmol). Heated in the microwave oven for 120 s (2 × 60 s). Yield of 200 mg (18%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.26 (d, J = 8.7 Hz, 2H, Ph-3,5-*H*), 6.82 (d, J = 8.7 Hz, 2H, Ph-2,6-*H*), 3.97 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.50 (t, J = 6.4 Hz, 2H, O-C*H*$_2$···Ph), 3.42 (t, J = 5.9 Hz, 2H Pip···C*H*$_2$-O), 3.40–3.25 (m, 2H, Pip-2,6-*H*$_e$), 3.05–2.95 (m, 2H, Pip-C*H*$_2$), 2.75–2.60 (m, 1H, Pip-6-*H*$_a$), 2.46–2.30(m, 1H, Pip-2-*H*$_a$), 1.96–1.60 (m, 8H, PipCH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh + Pip-4,5-*H*$_2$), 1.05–0.93 (m, 1H, Pip-3-*H*), 0.85 (d, J = 6.7 Hz, 3H, C*H*$_3$); IR (KBr) (cm^{-1}): 1246s (ν [C–O–C$_{arom}$]), 1122s (ν [C–O–C]).

5.1.3.12. 1-[3-(3-(4-*tert*-Butylphenoxy)propoxy)propyl]-4-methylpiperidine hydrogen oxalate (15). From 3-(4-methylpiperidin-1-yl)propan-1-ol (**1b**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-*tert*-butylphenoxy)propane (**3c**) (0.81 g, 3 mmol). Heated in the microwave oven for 240 s (4 × 60 s). Yield of 150 mg (14%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.26 (d, J = 8.7 Hz, 2H, Ph-3,5-*H*), 6.82 (d, J = 8.7 Hz, 2H, Ph-2,6-*H*), 3.94 (t, J = 6.2 Hz, 2H, C*H*$_2$-OPh), 3.50 (t, J = 6.4 Hz, 2H, O-C*H*$_2$···Ph), 3.42 (t, J = 5.9 Hz, 2H, Pip···C*H*$_2$-O), 3.37–3.25 (m, 2H, Pip-2,6-*H*$_e$), 3.03–2.93 (m, 2H, Pip-C*H*$_2$), 2.85–2.70 (m, 2H, Pip-2,6-*H*$_a$) 1.95–1.78 (m, 4H, PipCH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh), 1.78–1.68 (m, 2H, Pip-3,5-*H*$_e$), 1.55 (br s, 1H, Pip-4-*H*), 1.40–1.27 (m, 2H, Pip-3,5-*H*$_a$), 1.23 (s, 9H, 3C*H*$_3$), 0.88 (d, J = 6.4 Hz, 3H, C*H*$_3$); IR (KBr) (cm^{-1}): 1243s (ν [C–O–C$_{arom}$]), 1124s (ν [C–O–C]).

5.1.3.13. 1-[3-(3-(4-*tert*-Butylphenoxy)propoxy)propyl]azepane hydrogen oxalate (16). From 3-(azepan-1-yl)propan-1-ol (**1c**) (0.39 g, 2.5 mmol) and 3-bromo-1-(4-*tert*-butylphenoxy)propane (**3c**) (0.81 g, 3 mmol). Heated in the microwave oven for 360 s (6 × 60 s). Yield of 280 mg (26%) of white solid. ^{1}H NMR [DMSO-d_6]: δ = 7.26 (d, J = 9.0 Hz, 2H, Ph-3,5-*H*), 6.82 (d, J = 9.0 Hz, 2H, Ph-2,6-*H*), 3.96 (t, J = 6.4 Hz, 2H, C*H*$_2$-OPh), 3.50 (t, J = 6.4 Hz, 2H, O-C*H*$_2$···Ph), 3.42 (t, J = 5.9 Hz, 2H Azep···C*H*$_2$-O), 3.20–3.10 (m, 4H, Azep-2-*H*$_2$ + Azep-7-*H*$_2$), 3.10–2.97 (m, 2H, Azep-C*H*$_2$), 1.95–1.84 (m, 4H, Azep-CH$_2$-C*H*$_2$ + C*H*$_2$-CH$_2$OPh), 1.78–1.68 (m, 4H, Azep-3-*H*$_2$ + Azep-6-*H*$_2$), 1.60–1.50 (m, 4H, Azep-4-*H*$_2$ + Azep-5-*H*$_2$), 1.22 (s, 9H, 3C*H*$_3$); IR (KBr) (cm^{-1}): 1185s (ν [C–O–C$_{arom}$]), 1131s (ν [C–O–C]).

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 displacement assay described by Ligneau et al.[32] Briefly, stably transfected 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 (23,000*g*, 30 min, +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 μg 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 microfiber 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.[33] The corresponding K_i values were determined according to the Cheng-Prusoff equation.[39] Data are presented as the mean of experiments performed at least in triplicate with standard error (SE).

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