Full Paper

New 1-Benzyl-4-hydroxypiperidine Derivatives as Non-imidazole Histamine H_3 Receptor Antagonists

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A series of 1-benzyl-4-(3-aminopropyloxy)piperidine and 1-benzyl-4-(5-aminopentyloxy)piperidine derivatives has been prepared. The 1-benzyl-4-hydroxypiperidine derivatives obtained were evaluated for their affinities at recombinant human histamine H_3 receptor, stably expressed in HEK 293T cells. All compounds investigated show moderate to pronounced *in-vitro* affinities. The most potent antagonists in this series **9b2** (hH_3R, pK_i = 7.09), **9b1** (hH_3R, pK_i = 6.78), **9b5** (hH_3R, pK_i = 6.99), and **9b6** (hH_3R, pK_i = 6.97) were also tested *in vitro* as H_3 receptor antagonists – the electrically evoked contraction of the guinea-pig jejunum. The histaminergic H_1 antagonism of selected compounds **9b1**, **9b2**, and **9b4**–**9b6** was established on the isolated guinea-pig ileum by conventional methods; the pA_2 values were compared with the potency of pyrilamine. The compounds did not show any H_1 antagonistic activity ($pA_2 < 4$; for pyrilamine pA_2 = 9.53).

Keywords: 1-Benzyl-4-(3-aminopropyloxy)piperidine / 1-Benzyl-4-(5-aminopentyloxy)piperidine derivatives / H_3 antagonists / Histamine H_3 receptor

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Introduction

The cloning [1] of the H_3 receptor has provided fresh impetus to the development of drug-like ligands of this receptor. Homology analysis of the H_3 receptor showed it to be significantly different from the previously cloned H_1 and H_2 receptors [1, 2]. The H_3 receptors are located presynaptically and, upon stimulation by histamine or another H_3 agonist, inhibit synthesis and release of histamine [3, 4]. They are also known to play an important role as heteroreceptors involved in the regulation of the release of several other important neurotransmitters such as acetylcholine [5], dopamine [6], noradrenaline [7], and serotonin [8]. Antagonists to the H_3 receptor are considered to be potential drugs for the treatment of Alzheimer's disease [9, 10], attention deficit-hyperactive disorder (ADHD) [11], memory and learning deficits [12–14], and epilepsy [15].

During the years, following number of H_3 antagonists belonging to different chemical classes, subsequently divided between classical imidazole-based [16–18] and non-imidazole series have been described [19, 20]; the imidazole derivatives were considered to be less attractive for pharmacokinetic as well as for toxicological reasons.

An early description of a systematic design of non-imidazoles was reported by Ganellin *et al*. [21]. Based on the SAR of a novel series of homologues *O*- and *S*-isosteric tertiary amines of *N*-ethyl-*N*-(4-phenylbutyl)amine, it was discovered that some activity was retained upon replacement of the imidazole moiety with cyclic amines. Selection of these amines as the preferred group, by optimizing the chain length, by replacing a chain methylene

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Abbreviations: formic acid-acetic anhydride (FAM); structure-activity relationship (SAR)

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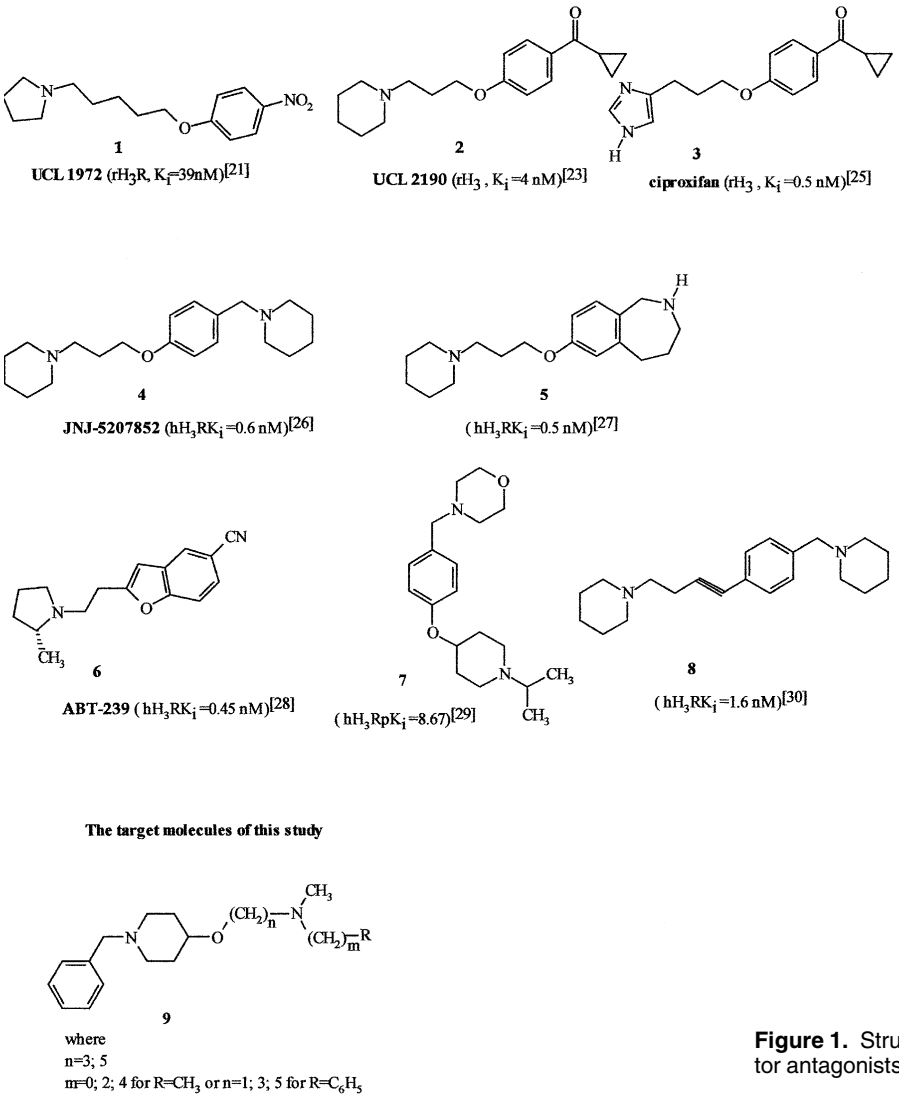
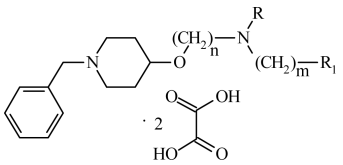


Figure 1. Structures of some known histamine H_3-receptor antagonists and target molecules of this study.

with oxygen, and by attaching a nitro group to the phenyl ring led to the **UCL 1972** (**1**; Fig. 1) – the most potent compound of this series.

Later on, the successful replacement of the imidazole moiety with piperidine and other basic tertiary amines was demonstrated with a variety of analogs [22 – 24]. As might have been expected, the effect of replacement of the imidazole by basic tertiary amines affected the H_3 inhibitor potency to different degrees, depending on the chemical series. Many compounds showed large losses in potency upon replacement of imidazole by piperidine. However, some of them such as ciproxifan analog **UCL 2190** [23] (**2**; Fig. 1) retained high potency, although not so much as the parent imidazole – ciproxifan [25] (**3**; Fig. 1). **UCL 2190** was one of the first representatives of piperidine-based ligands that contain the aminopropoxyphenyl group, which later appeared in several potent non-imidazole H_3-histamine receptor antagonists, for example compounds **4** [26] and **5** [27] (Fig. 1). Based on these results, it may be concluded that compounds carrying a piperidine ring are more likely to be successful in ethereal analogs than in the other series, especially in compounds, where the oxygen is directly connected to an aromatic group. With **ABT-239** [28] **6** and **7** [29] (Fig. 1), it has been shown that the highly flexible propyloxy link can be successfully replaced by the partially rigid 2-aminoethylbenzofuran substructure or the 4-phenoxypiperidine moiety. Another example of this theme (**8**; Fig. 1) [30] shows that not only rigidification of propyloxy link leads to active compounds, but also replacement of the oxygen and proximal methylene of **4** with an acetylene giving a more conformationally restricted analog, yields a derivative retaining the potency of the parent compound. This latter example suggests that the oxygen

Table 1. Antagonist potencies of 1-benzyl-4-hydroxypiperidine derivatives at histamine H_3 receptor.



Cpd.	n	m	R	R_1	pK_i (s.e.m)	N	Cpd.	n	m	R	R_1	pK_i (s.e.m)	N	pA_2 (s.e.m)	N *caviae*)
12	3	0	H	H	6.42 (0.02)	3	**18**	5	0	H	H	5.66 (0.05)	3		
14	3	0	CH_3	H	6.47 (0.02)	3	**20**	5	0	CH_3	H	6.24 (0.06)	3		
9a1	3	0	CH_3	CH_3	6.01 (0.04)	3	**9b1**	5	0	CH_3	CH_3	6.78 (0.08)	3	7.06 (0.04)	10 (*3*)
9a2	3	2	CH_3	CH_3	6.73 (0.05)	3	**9b2**	5	2	CH_3	CH_3	7.09 (0.03)	3	7.79 (0.06)	12 (*4*)
9a3	3	4	CH_3	CH_3	6.25 (0.02)	3	**9b3**	5	4	CH_3	CH_3	6.59 (0.03)	3		
9a4	3	1	CH_3		6.02 (0.04)	3	**9b4**	5	1	CH_3		6.76 (0.13)	3		
9a5	3	3	CH_3		6.08 (0.02)	3	**9b5**	5	3	CH_3		6.99 (0.03)	3	7.45 (0.05)	11 (*4*)
9a6	3	5	CH_3		6.44 (0.02)	3	**9b6**	5	5	CH_3		6.97 (0.08)	3	7.32 (0.04)	11 (*4*)

Controls

Cpd	pK_i (s.e.m)	N	pA_2 (s.e.m)	N (*caviae*)
Histamine (*agonist*)	7.65 (0.01)	3		
Thioperamid (*antagonist or inverse agonist*)	7.29 (0.01)	3	8.61 (0.07)	12 (*4*)
Imetit (*agonist*)	8.89 (0.05)	3		
Clobenpropit (*antagonist or inverse agonist*)	8.85 (0.04)	3		

N – number of different animal preparation; *caviae* – number of animals.

atom in the link is not absolutely essential for high H_3-histamine receptor binding affinity.

In the present work, we report the synthesis and preliminary pharmacological investigation of a new series of 1-benzyl-4-hydroxypiperidine-based H_3-histamine receptor antagonists **9** (Fig. 1) in which two concepts – rigidification of aminopropyloxy link by incorporation it into 4-hydroxypiperidine ring and replacement of phenyl (present in aminopropyloxyphenyl archetypal H_3 pharmacophore) by aminoalkyl and aminophenylalkyl chain. In this series, we varied the length of the *N*-alkyl spacer from one to five methylene groups and, in addition, replaced the alkyl chain by phenylalkyl substituents. We also studied the influence of the replacement of the *N*-aminopropyloxy chain by a *N*-aminopentyloxy one on the H_3-receptor antagonist activity.

Results and discussion

In-vitro binding assay at cloned human histamine H_3 receptors

The affinities of all compounds were determined by measuring the displacement curves of [^{3}H]N^a-methylhistamine binding at human histamine H_3 receptor expressed in HEK 239T cell membranes.

The presented 1-benzyl-4-(3-aminopropyloxy)- and 1-benzyl-4-(5-amino)pentyloxypiperi-dine derivatives all possess, moderate to pronounced H_3-receptor antagonist potency (Table 1).

It appeared that by comparison of homologous pairs, the 1-benzyl-4-(5-aminopentyloxy)piperidines (**9b1**–**9b6**) have a slightly higher potency than their 1-benzyl-4-(3-aminopropyloxy)piperidines analogues **9a1**–**9a6**. The difference is observed for compounds **12**, **14** and **18**, **20** where the 1-benzyl-4-(3-aminopropyloxy)piperidine (**12**; pK_i = 6.42) and its *N*-methyl derivative (**14**; pK_i = 6.47) have a slightly higher activity than their 1-benzyl-4-(5-aminopentyloxy)piperidine analogous (**18**; pK_i = 5.66; **20**; pK_i = 6.24).

In the *N*-aminopropyloxy series (compounds **12**, **14** and **9a1**–**9a6**) there is no significant difference in hH_3R potencies among the aminopropyloksy derivative (**12**; pK_i = 6.42) and *N*-methylaminopropyloxy derivative (**14**; pK_i = 6.47). Replacement of hydrogen in the *N*-methyl group by a second methyl group results in a decrease of potency for compound **9a1** (pK_i = 6.01); a further increase in the alkyl chain length to three methylene groups results in

an increase of potency for compound **9a2** (pK_i = 6.73) reaching the maximum for this series. Elongation of alkyl chain to five methylene groups again results in a decrease of potency for compound **9a3** (pK_i = 6.25). Replacement of hydrogen by a phenyl group at the end of *N*-alkyl chain leads to compounds **9a4 – 9a6** (pK_i = 6.02; pK_i = 6.08; pK_i = 6.44, respectively) with moderate potency, with slightly higher potency for compound **9a6**.

In the *N*-aminopentyloxy series (compounds **18**, **20** and **9b1 – 9b6**) the highest activity is again seen in the compound with the *N*-methyl-*N*-propyl substituent **9b2** (pK_i = 7.09). In this series, similar results were observed, as in the *N*-methyl-*N*-alkylaminopropyloxy derivatives, independently on an increase in the alkyl chain length to five methylene groups **9b3** or a decrease in the alkyl chain length to one methyl group **9b1** results in an increase of potency (pK_i = 6.59) and (pK_i = 6.78), respectively.

In the *N*-phenylalkyl derivatives of 1-benzyl-4-[5-(*N*-methylaminopentyloxy)]piperidine there is no significant difference in hH_3R potencies, particularly among the compounds **9b5** and **9b6 (**pK_i = 6.99; pK_i = 6.97, respectively). This is in contrary to the *N*-phenylalkyl derivatives of 1-benzyl-4-[5-(*N*-methylamino-propyloxy)]piperidine **9a4-9a6** where the *N*-methyl-*N*-phenylpentylaminopropyloxy derivative **9a6** shows a slightly higher potency than its *N*-methyl-*N*-phenylalkyl analogues **9a4**, **9a5**.

Clearly, 1-benzyl-4-[5-(*N*-methyl-*N*-subsitutedaminopentyloxy)]-piperidine **9b1-9b6** display a higher potency than their *N*-methyl-*N*-propyloxy **9a1-9a6** analogues. The highest potency for both homologous series is seen in the compound with the *N*-methyl-*N*-propylaminopentyloxy substituent **9b2** (pK_i = 7.09) and with slightly lower potencies for compounds **9b5** (pK_i = 6.99) and **9b6** (pK_i = 6.97) carrying on *N*-methyl-*N*-phenylpropylaminopentyloxy- and *N*-methyl-*N*-phenylpentylaminopentyloxy-substituent, respectively.

H_3 histamine receptor antagonist potency in electrically-evoked contraction of the guinea-pig jejunum

The most potent antagonists in this series **9b2** (hH_3R pK_i = 7.09), **9b1** (hH_3R pK_i = 6.78), **9b5** (hH_3R pK_i = 6.99), and **9b6** (hH_3R pK_i = 6.97) were *in-vitro* tested as H_3-receptor antagonists by electrically-evoked contraction of the guinea-pig jejunum (Table 1). All compounds tested showed antagonist properties. The highest activity is seen, as *in-vitro* binding assay at cloned human histamine H_3 receptors, in the compound with the *N*-methyl-*N*-propyl substituent **9b2** (pA_2 = 7.79). Again, it appeared that compound **9b5** (pA_2 = 7.45) has a slightly higher potency than its *N*-methyl-*N*-phenylpentyl and *N,N*-dimethyl analogues **9b6** (pA_2 = 7.32) and **9b1** (pA_2 = 7.06), respectively.

H_1 histamine receptor antagonist potency in contraction of the guinea-pig ileum

Additionally, selected compounds **9b1**, **9b2** and **9b4 – 9b6** were also tested for H_1 antagonistic effects *in vitro*, following standard methods, using the guinea pig ileum. They did not show any H_1-antagonistic activity ($pA_2 < 4$; for pyrilamine pA_2 = 9.53).

Chemistry

The general synthetic procedures used in this study are illustrated in Scheme 1 and Scheme 2.

The 1-benzyl-4-[3-(*N*-methyl-*N*-propylamino)propyloxy]- and 1-benzyl-4-[3-(*N*-methyl-*N*-pentylamino)propyloxy]piperidines **9a2**, **9a3** (Scheme 1, *Procedure* A), were synthesized by standard methods. Compound **14** was acetylated with an appropriate acid anhydride and next, obtained amides **15a2** and **15a3** were reduced with $LiAlH_4$ in dry ethyl ether followed by purification with column chromatography.

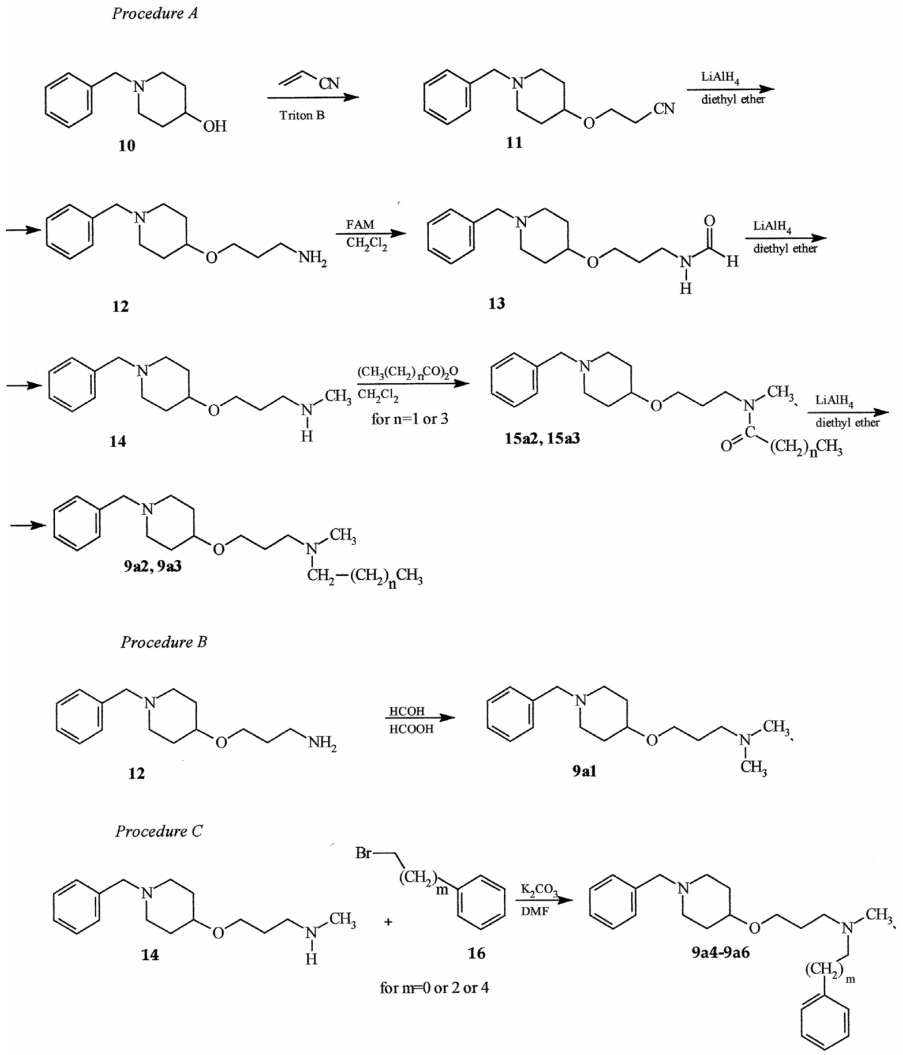
The 1-benzyl-4-[3-(*N*-methylamino)propyloxy]piperidine **14** was prepared from compound **10** by a four-step reaction (Scheme 1; *Procedure A*) including: O-alkylation with acrylonitrile in the presence of small amount of Triton B to compound **11**, reduction with $LiAlH_4$ in dry ethyl ether to compound **12** [31 – 33] (CAS RN 200868-41-3), formylation with formic acid-acetic anhydride (FAM) [34] to compound **13**, and, finally, reduction with $LiAlH_4$ in dry ethyl ether to compound **14**, each step was followed by purification with column chromatography.

The 1-benzyl-4-[3-(*N,N*-dimethylamino)propyloxy]piperidine **9a1** (Scheme 1, *Procedure B*) was synthesized by the reaction of 1-benzyl-4-(3-aminopropyloxy)piperidine **12** with formaldehyde in formic acid and separated by column chromatography.

The compounds **9a4 – 9a6** (Scheme 1, *Procedure C*) were synthesized from 1-benzyl-4-[3-(*N*-methylamino)propyloxy]piperidine **14** by alkylation with the corresponding primary phenylalkyl halides in the presence of K_2CO_3 in DMF followed by purification with column chromatography.

The 1-benzyl-4-[3-(*N*-methyl-*N*-phenylalkylamino)pentyloxy]-piperidines **9b4 – 9b6** (Scheme 2, *Procedure D*) were obtained from 1-benzyl-4-[3-(*N*-methylamino)pentyloxy]-piperidine **20** by alkylation with the corresponding primary phenylalkyl halides in the presence of potassium carbonate in DMF followed by purification with column chromatography.

The 1-benzyl-4-[3-(*N*-methylamino)pentyloxy]piperidine **20** was prepared from compound **10** by a four-step synthesis (Scheme 2; *Procedure D*) including: *O*-alkylation



Scheme 1. Synthesis of 1-benzyl-4-(3-aminopropyloxy)piperidine **12**, 1-benzyl-4-[3-(*N*-methylamino)propyloxy]piperidine **14**, 1-benzyl-4-[3-(*N*-methyl-alkylamino)-propyloxy]piperidines **9a1**–**9a3** and 1-benzyl-4-[3-(*N*-methyl-*N*-phenylamino)-propyloxy]piperidines **9a4**–**9a6**.

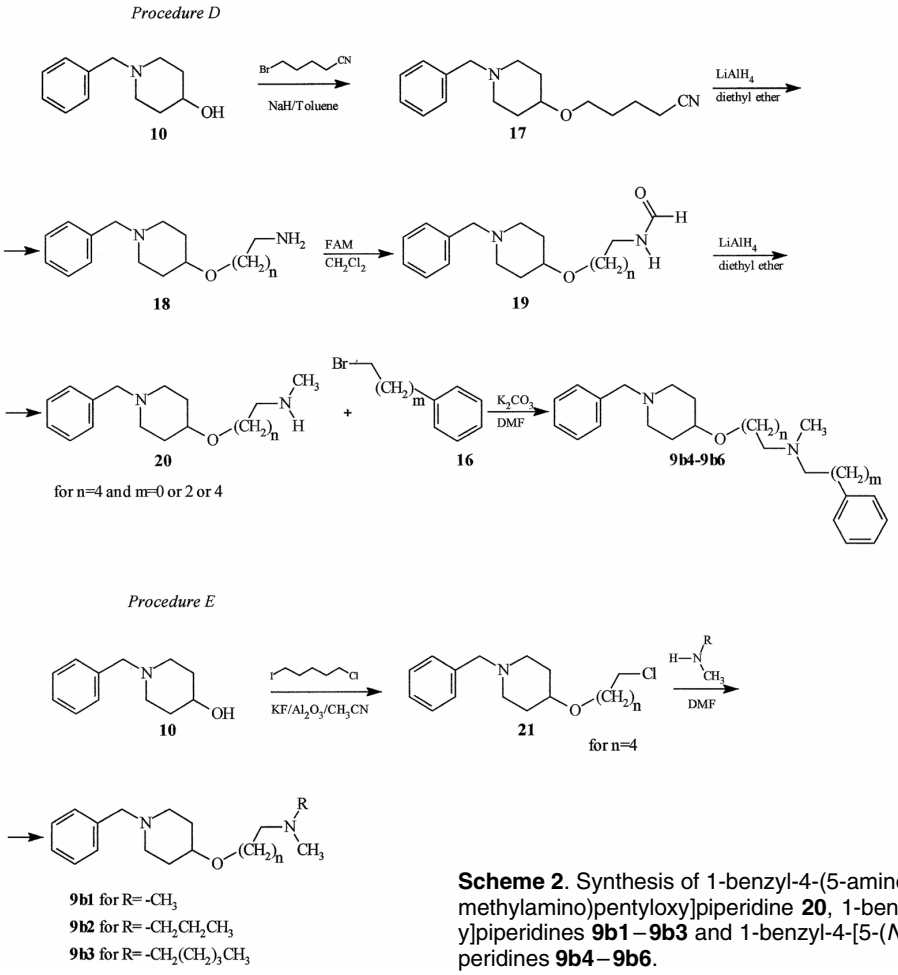
with 5-bromopentanenitrile in dry toluene in the presence of sodium hydride and 1,4,7,10,13-pentaoxycyclopentadecane (15-crown-5 ether) to compound **17**, reduction with $LiAlH_4$ in dry ethyl ether to compound **18,** formylation with formic acid-acetic anhydride (FAM) [34] to compound **19** and, finally, reduction with $LiAlH_4$ in dry ethyl ether to compound **20**, each step was followed by purification with column chromatography.

The 1-benzyl-4-[3-(*N*-methyl-*N*-alkylamino)pentyloxy]piperidines **9b1-9b3** were obtained from compound **10** by a two-step synthesis (Scheme 2; *Procedure E*) including: O-alkylation with 1-chloro-5-iodopentane in the presence of KF/Al_2O_3 in acetonitrile to compound **21** and, finally, substituted with the appropriate secondary amines in DMF to compounds **9b1-9b3**, each step was followed by purification with column chromatography.

All obtained final free bases were treated with methanolic oxalic acid, and the oxalic acid salts were precipitated with dry diethyl ether.

The formic acid-acetic anhydride (FAM) was obtained according to van Es and Stewens [34] by the action of formic acid on acetic anhydride.

The 1-chloro-5-iodopentane was obtained according to Hass and Huffman [35] from 1,5-dichloropentane through nucleophilic mono-substitution of the chlorine atom by iodide in dry acetone with sodium iodide. The 5-phenylpentyl bromide was obtained according to Collins and Davis [36]. The 5-phenyl-1-pentanol was converted



Scheme 2. Synthesis of 1-benzyl-4-(5-aminopentyloxy)piperidine **18**, 1-benzyl-4-[5-(*N*-methylamino)pentyloxy]piperidine **20**, 1-benzyl-4-[5-(*N*-methyl-*N*-alkylamino)-pentyloxy]piperidines **9b1** – **9b3** and 1-benzyl-4-[5-(*N*-methyl-*N*-phenylalkylamino)-pentyloxy]piperidines **9b4** – **9b6**.

into the bromide by treatment with 50% aqueous hydrobromic acid and concentrated sulphuric acid. The 1-benzyl-4-hydroxypiperidine, acetonitrile, 5-bromopentanonitrile, propionic anhydride, pentanoic anhydride, benzyl bromide, 1-bromo-3-phenylpropane, 5-phenyl-1-pentanol, benzoyl chloride, dimethylamine, methylpropylamine, and methylpentylamine were all purchased from commercial sources.

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The authors have declared no conflict of interest.

Experimental

General methods

All melting points (m.p.) were taken in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds, ^{1}H-NMR spectra were recorded on a Varian EM 360 (60 MHz) spectrometer (Varian Inc., Palo Alto, CA, USA). Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^{1}H-NMR data are reported in order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by D_2O) number of protons, and approximate coupling constant in Hertz. Elemental analysis (C, H, N) for all compounds were measured on Heraeus EA 415-0 (Heraeus, Hanau, Germany) and are within ± 0.4% of the theoretical values. TLC was performed on silica gel PF_{254} plates (Merck, Germany). Flash column chromatography was carried out using silica gel 30 – 60 μm (J. T. Baker BV., Deventer, The Netherlands), employing the same eluent as was indicated by TLC. In each case, the final free base was treated with methanolic oxalic acid, and the oxalic acid salt were precipitated with dry diethyl ether.

*Synthesis of 1-benzyl-4-(3-cyanopropyloxy)piperidine **11***

To a solution of the 1-benzyl-4-hydroxypiperidine **10** (0.031 mol) dissolved in 90 mL of acetonitrile was added dropwise Triton B (2 mL). The mixture was heated at 80°C for 25 h. After cooling, the reaction mixture was poured out into 300 mL of ethyl ether. The resulting precipitate was filtered off and the solvent was evaporated to give the crude product as a sticky oil which was purified by column chromatography.

11: $C_{15}H_{20}N_2O$, (M = 244.3); yield 60.6%; ^{1}H-NMR ($CDCl_3$), δ: 1.57–1.68 (m, 2H, CH_2CHO), 1.83–1.91 (m, 2H, CH_2CHO), 2.11–2.19 (m, 2H, NCH_2), 2.56 (t, *J* = 6.3 Hz, 2H, CH_2CN), 2.68–2.75 (m, 2H, NCH_2), 3.35–3.43 (m, 1H, C*H*O), 3.48 (s, 2H, CH_2Ph), 3.64–3.68 (m, 2H, OCH_2), 7.21–7.34 (m, 5H, CH); TLC (dichloromethane / methanol / concentrated ammonium hydroxide: 394 : 5 : 1) R_f = 0.57.

Synthesis of 1-benzyl-4-(3-aminopropyloxy)piperidine ***12***

To a solution of 1-benzyl-4-(3-cyanopropyloxy)piperidine **11** (0.018 mol) in 50 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.06 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (2.3 mL), 10% of NaOH solution (2.3 mL), and water (2.3 mL). The suspension was stirred for 30 min and filtered. The filter cake was washed with ether (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and residue was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

12: $C_{15}H_{24}N_2O$, (M = 248.4); yield 60.0%; ^{1}H-NMR ($CDCl_3$), δ: ^{1}1.56–1.77 (m, 4H, CH_2CHO, NH_2^*), 1.67–1.75 (m, 2H, CH_2), 1.84–1.90 (m, 2H, CH_2CHO), 2.09–2.17 (m, 2H, NCH_2), 2.68–2.75 (m, 2H, NCH_2), 2.80 (t, *J* = 6.9 Hz, 2H, CH_2), 3,24–3,33 (m, 1H, *H*C-O-), 3.49 (s, 2H, PhCH_2), 3.46–3.3 (m, 2H, CH_2), 7.22–7.32 (m, 5H, C*H*); TLC (dichloromethane / methanol / concentrated ammonium hydroxide: 59 : 10 : 1) R_f = 0.43. Elemental analysis for dioxalic acid salt $C_{15}H_{24}N_2O$ 6 2 $C_2H_2O_4$ (M = 428.4); m.p.$_{\text{dioxalic acid salt}}$ = 166.5–167.2°C: calculated: C, 53.27; H, 6.59; N, 6.54. Found: C, 53.45; H, 6.72; N, 6.76.

Synthesis of 1-benzyl-4-[3-(N-formylamino)propyloxy]piperidine ***13***

To a solution of 1-benzyl-4-(3-aminopropyloxy)piperidine **12** (0.01 mol) in 60 mL of anhydrous dichloromethane was added FAM (18.0 mL). The mixture was stirred at 5–10°C for 0.5 h. Then, water (50.0 mL) and ethyl acetate (50.0 mL) were added and the mixture was neutralized with K_2CO_3. The water layer was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated; the residue was purified by column chromatography on silicagel to give compound **13** as a sticky oil.

13: $C_{16}H_{24}N_2O_2$; (M = 276.4); yield 89.0%; ^{1}H-NMR $CDCl_3$, δ: 1.58–1.69 (m, 2H, CH_2CHO), 1.72–1.82 (m, 2H, $CH_2CH_2CH_2$), 1.86–1.95 (m, 2H, CH_2CHO), 2.24–2.3 (m, 2H, NCH_2), 2.72–2.76 (m, 2H, NCH_2), 3.31–3.35 (m, 2H, CH_2, NCH_2), 3.35–3.45 (m, 1H, *H*C-O-), 3.57 (s, 2H, CH_2 Ph), 3.48–3.66 (m, 2H, OCH_2), 6.24 (s*, br 1H, N*H*), 7.23–7.35 (m, 5H, C*H*), 8.11 (s, 1H, C*H*O); TLC (dichloromethane / methanol / concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.51.

Synthesis of 1-benzyl-4-[3-(N-methylamino)propyloxy]piperidine ***14***

To a solution of 1-benzyl-4-[3-(*N*-formylamino)propyloxy]piperidine **13** (0.01 mol) in 30 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.037 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (1.4 mL), 10% of NaOH solution (1.4 mL), and water (1.4 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed with ether (2 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the residue was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

14: $C_{16}H_{26}N_2O$; (M = 262.4); yield 87.0%; ^{1}H-NMR, $CDCl_3$, δ: 1.53–1.65 (m, 2H, CH_2CHO), 1.7–1.79 (m, 2H, NCH_2), 1.82–1.89 (m, 3H, CH_2CHO, N*H**), 2.08–2.16 (m, 2H, •NCH_2), 2.41 (s, 3H, CH_3), 2.62–2.67 (t, *J* = 6.9 Hz, 2H, OCH_2), 2.69–2.76 (m, 2H, NCH_2), 3.23–3.32 (m, 1H, *H*C-O-), 3.47–3.51 (m, 2H, OCH_2), 3.48 (s, 2H, PhCH_2), 7.2–7.32 (m, 5H, C*H*); TLC (dichloromethane / methanol / concentrated ammonium hydroxide: 49 : 10 : 1) R_f = 0.45. Elemental analysis for dioxalic acid salt $C_{16}H_{26}N_2O \times 2\ C_2H_2O_4$ (M = 442.5); m.p.$_{\text{dioxalic acid salt}}$ = 149.4–150.7°C: calculated: C, 54.29; H, 6.83; N, 6.33. Found: C, 53.87; H, 6.72; N, 6.66.

General method for the preparation of 1-benzyl-4-[3-(N-methyl-N-alkylcarbonylamino)propyloxy]piperidine amides ***15a2, 15a3***

To a solution of 1-benzyl-4-[3-(N-methylamino)propyloxy]piperidine **14** (0.003 mol) in 20.0 mL of anhydrous dichloromethane was added the corresponding acid anhydride (0.009 mol). The mixture was stirred at room temperature for 1 h. Then, water (20 mL) was added, the mixture was neutralized with K_2CO_3, and water layer was extracted with dichlorometane (2 × 15 mL). The combined organic extracts were washed with water (3 × 30 mL), dried (Na_2SO_4), filtered, and evaporated to give compounds **15a2**, **15a3** as a sticky oil. In each case, the crude product was purified by column chromatography.

15a2

$C_{19}H_{30}N_2O_2$; (M = 318.5); yield 96.2%; ^{1}H-NMR, $CDCl_3$, δ: 1.1–1.17 (m, 3H, CH_2CH_3), 1.55–1.65 (m, 2H, CH_2CHO), 1.74–1.81 (m, 2H, CH_2), 1.83–1.90 (m, 2H, CH_2O), 2.15–2.21 (m, 2H, NH_2), 2.44–2.52 (m, 2H, CH_2), 2.72–2.75 (m, 2H, NCH_2), 2.90–2.98 (m, 3H, NCH_3), 3.26–3.32 (m, 1H, *H*C-O-), 3.35–3.46 (m, 4H, CH_2), 3.52–3.54 (s, 2H, PhCH_2), 7.21–7.31 (m, 5H, CH); TLC (dichloromethane / methanol / concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.69.

15a3

$C_{21}H_{34}N_2O_2$; (M = 346.5); yield 94%; ^{1}H-NMR, $CDCl_3$, δ: 0.9–0.95 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 1.29–1.42 (m, 2H, CH_2), 1.53–1.67 (m, 4H, CH_2CHO, CH_2), 1.74–1.88 (m, 4H, CH_2CHO, CH_2), 2.09–2.16 (m, 2H, NCH_2), 2.26–2.37 (m, 2H, CH_2), 2.71–2.75 (m, 2H, NCH_2), 2.95 (s, 3H, NCH_3), 3.26 (s, 1H, *H*C-O-), 3.37-3.47 (m, 4H, CH_2, CH_2), 3.49 (s, 2H, CH_2Ph), 7.23–7.32 (m, 5H, C*H*); TLC (dichloromethane / methanol / triethylamine: 89 : 10 : 1) R_f = 0.84.

General method for the preparation of 1-benzyl-4-[3-(N-methyl-N-alkylamino)propyloxy]piperidines ***9a2, 9a3***

To a solution of the appropriate 1-benzyl-4-[3-(*N*-methyl-*N*-alkylcarbonylamino)propyloxy]piperidine amides **15a2** and **15a3** (0.002 mol) in 10 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.0087 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (0.33 mL), 10% of NaOH solution (0.33 mL), and water (0.33 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed with ether (2 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and residue was purified by column chromatography on silicagel. The title products were obtained

as sticky oil. Free base was treated with methanolic oxalic acid and oxalic acid salt were precipitated with dry diethyl ether.

9a2

$C_{19}H_{32}N_2O$; (M = 304.5); yield 51.7%; ^{1}H-NMR, $CDCl_3$, δ: 0.86 – 0.91 (t, *J* = 3.9 Hz, 3H, CH_2CH_3), 1.41 – 1.51(m, 2H, CH_2), 1.53 – 1.65 (m, 2H, CH_2CHO), 1.68 – 1.77 (m, 2H, CH_2), 1.84 – 1.89 (m, 2H, CH_2CHO), 2.07 – 2.15 (m, 2H, NCH_2), 2.2 (s, 3H, NCH_3), 2.25 – 2.3 (m, 2H, CH_2), 2.37 – 2.42 (m, 2H, CH_2), 2.72 – 2.76 (m, 2H, NCH_2), 3.23 – 3.32 (m, 1H, *H*C-O-), 3.44 – 3.5 (m, 2H, CH_2), 3.48 (s, 2H, $PhCH_2$), 7.21 – 7.32 (m, 5H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.55. Elemental analysis for dioxalic acid salt $C_{19}H_{32}N_2O \times 2\ C_2H_2O_4$ (M = 484.55); m.p.$_{\text{dioxalic acid salt}}$ = 147.8 – 149.8°C: calculated: C, 57.01; H, 7.49; N, 5.78. Found: C, 57.23; H, 7.81; N, 5.69.

9a3

$C_{21}H_{36}N_2O$; (M = 332.5); yield 59.7%; ^{1}H-NMR, $CDCl_3$, δ: 0.87 – 0.91 (t, *J* = 6.9 Hz, 3H; CH_2CH_3), 1.23 – 1.36 (m, 4H, CH_2, CH_2), 1.40 – 1.50 (m, 2H, CH_2), 1.52-1.64 (m, 2H, CH_2CHO), 1.67 – 1.77 (m, 2H, CH_2), 1.83 – 1.89 (m, 2H, CH_2CHO), 2.07 – 2.14 (m, 2H, NCH_2), 2.20 (s, 3H, NCH_3), 2.28 – 2.33 (t, *J* = 7.6 Hz, 2H, CH_2), 2.37 – 2.41 (t, *J* = 7.3 Hz, 2H, CH_2), 2.71 – 2.75 (m, 2H, NCH_2), 3.23 – 3.32 (m, 1H, *H*C-O-), 3.44 – 3.48 (m, 4H, CH_2, CH_2Ph), 7.22 – 7.31 (m, 5H, C*H*); TLC (dichloromethane/methanol / concentrated ammonium hydroxide: 189 : 10 : 1) R_f = 0.34. Elemental analysis for dioxalic acid salt $C_{21}H_{36}N_2O \times 2\ C_2H_2O_4$ (M = 512.6); m.p.$_{\text{dioxalic acid salt}}$ = 146.8 – 148°C: calculated: C, 58.58; H, 7.86; N, 5.46. Found: C, 58.34; H, 7.71; N, 5.69.

Synthesis of 1-benzyl-4-[3-(N,N-dimethylamino)propyloxy]piperidine ***9a1***

The 1-benzyl-4-(3-aminopropyloxy)piperidine **12** (0.005 mol) was dissolved in 11.5 g of 100% formic acid and 0.9 g of 36% formaldehyde was added. The mixture was heated for 10 h at 100 – 105°C. After cooling, the mixture was alkalinized with sodium hydroxide to pH 12 and extracted with diethyl ether (3 × 50.0 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the crude product was purified by column chromatography on silicagel.

9a1: $C_{17}H_{29}N_2O$; (M = 277.4); yield 61.4%; ^{1}H-NMR, $CDCl_3$, δ: 1.56 – 1.77 (m, 4H, CH_2CHO), 1.86 – 1.90 (m, 2H, CH_2), 2.12 – 2.20 (m, 2H, NCH_2), 2.24 (s, 6H, CH_3), 2.36 (t, *J* = 6.9 Hz, 2H, CH_2N), 2.27 – 2.76 (m, 2H, NCH_2), 3.20 – 3.30 (m, 1H, *H*C-O-), 3.45 – 3.49 (m, 4H, OCH_2, CH_2Ph), 7.24 – 7.32 (m, 5H, CH); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 189 : 10 : 1) R_f = 0.37. Elemental analysis for dioxalic acid salt $C_{17}H_{29}N_2O \times 2\ C_2H_2O_4$ (M = 457.5); m.p.$_{\text{dioxalic acid salt}}$ = 160.0 – 162.0°C: calculated: C, 55.13; H, 7.27; N, 6.12. Found: C, 54.86; H, 6.80; N, 6.33.

General method for the preparation of 1-benzyl-4-[3-(N-methyl-N-phenylalkylamino)propyloxy]piperidines ***9a4 – 4a6***

To a solution of 1-benzyl-4-[3-(*N*-methylamino)propyloxy]piperidine **14** (0.0025 mol) with the presence of potassium carbonate (0.0025 mol) in 10 mL of anhydrous DMF was added corresponding phenylalkyl halide (0.0028 mol). The suspension was stirred for 24 h at room temperature and filtered. The solution was diluted with 20 mL of water and extracted with dichloromethane (3 × 25 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated to give the crude products which were purified by column chromatography. The title products were obtained as sticky oil. Free bases were treated with methanolic oxalic acid and oxalic acid salt were precipitated with dry diethyl ether.

9a4

$C_{23}H_{32}N_2O$ (M = 352.5); yield 27.8%; ^{1}H-NMR, $CDCl_3$, δ: 1.56 – 1.62 (m, 4H, CH_2CHO, CH_2), 1.73 – 1.82 (m, 4H, CH_2CHO, CH_2), 2.08 – 2.15 (m, 2H, NCH_2), 2.18 (s, 3H, NCH_3), 2.44 (t, *J* = 7Hz, 2H, CH_2), 2.70 – 2.75 (m, 2H, NCH_2), 3.25 – 3.32 (m, 1H, *H*C-O-), 3.45 – 3.47 (m, 4H, =N-CH_2Ph, CH_3-N-CH_2Ph), 7.19 – 7.37 (m, 10H, CH); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 189 : 10 : 1) R_f = 0.30. Elemental analysis for dioxalic acid salt $C_{23}H_{32}N_2O \times 2\ C_2H_2O_4$ (M = 532.6); m.p.$_{\text{dioxalic acid salt}}$ = 185 – 187°C: calculated: C, 60.89; H, 6.81; N, 5.26. Found: C, 60.55; H, 6.52; N, 4.96.

9a5

$C_{25}H_{36}N_2O$ (M = 380.6); yield 57.3%; ^{1}H-NMR, $CDCl_3$, δ: 1.52-1.64 (m, 2H, CH_2CHO), 1.67-1.88 (m, 6H, CH_2CHO, CH_2, CH_2), 2.06-2.13 (m, 2H, NCH_2), 2.21 (s, 3H, NCH_3), 2.24-2.42 (m, 4H, CH_2, CH_2), 2.62 (t, *J* = 7.8 Hz, 2H, CH_2), 2.71-2.75 (m, 2H, NCH_2), 3.23-3.29 (m, 1H, *H*C-O-), 3.44-3.48 (m, 4H, CH_2Ph, CH_2), 7.14-7.31 (m, 10H, C*H*); TLC (dichloromethane/methanol / concentrated ammonium hydroxide: 139 : 10 : 1) R_f = 0.25. Elemental analysis for dioxalic acid salt $C_{25}H_{36}N_2O \times 2\ C_2H_2O_4$ (M = 560.6); m.p.$_{\text{dioxalic acid salt}}$ = 178 – 182.2°C: calculated: C, 62.13; H, 7.19; N, 5.00. Found: C, 61.87; H, 6.91; N, 4.74.

9a6

$C_{27}H_{40}N_2O$ (M = 398.6); yield 35.9%; ^{1}H-NMR, $CDCl_3$, δ: 1.29 – 1.37 (m, 2H, CH_2), 1.44 – 1.76 (m, 8H, CH_2, CH_2, CH_2, CH_2CHO), 1.84 – 1.88 (m, 2H, CH_2CHO), 2.08 – 2.15 (m, 2H, NCH_2), 2.19 (s, 3H, NCH_3), 2.31 (t, *J* = 7.6 Hz, 2H, CH_2), 2.39 (t, *J* = 7.3 Hz, 2H, CH_2), 2.60 (t, *J* = 7.8 Hz, 2H, CH_2), 2.71 – 2.75 (m, 2H, NCH_2), 3.24 – 3.30 (m, 1H, *H*C-O-), 3.45 (t, *J* = 6.6 Hz, 2H, CH_2), 3.48 (s, 2H, CH_2Ph), 7.16 – 7.31 (m, 10H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.61. Elemental analysis for dioxalic acid salt $C_{27}H_{40}N_2O \times 2\ C_2H_2O_4$ (M = 560.6); m.p.$_{\text{dioxalic acid salt}}$ = 169 – 170°C: calculated: C, 66.42; H, 7.91; N, 5.00. Found: C, 66.07; H, 7.59; N, 4.68.

Synthesis of 1-benzyl-4-(4-nitrilopentyloxy)piperidine ***17***

To a solution of the 1-benzyl-4-hydroxypiperidine **10** (0.03 mol) in 80 mL of dry toluene was added sodium hydride (0.06 mol), and after stirred at room temperature for 1 h, to the suspension was added dropwise 15-crown-5 ether (0.036 mol) and then 5-bromopentanonitrile (0.036 mol). The reaction mixture was stirred at room temperature for 72 h, and excess of sodium hydride was quenched by dropwise addition of ethanol (10 mL). The solvent was evaporated under reduce pressure, and water (15 mL) was added. The mixture was extracted with dichlorometane (3 × 50.0 mL), organic layer dried (Na_2SO_4), and filtered. The solvent was evaporated and remaining material was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

17: $C_{17}H_{24}N_2O$ (M = 272.4); yield 32.4%; ^{1}H-NMR, $CDCl_3$, δ: 1.52 – 1.67 (m, 2H, CH_2CHO), 1.68-1.81 (m, 4H, CH_2CH_2), 1.82 – 1.90 (m, 2H, CH_2CHO), 2.09 – 2.17 (m, 2H, NCH_2), 2.37 (t, *J* = 6.9 Hz, 2H, CH_2), 2.68 – 2.74 (m, 2H, NCH_2), 3.23 – 3.32 (m, 1H, C*HO*), 3.46 (t, *J*

= 5.7 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2Ph), 7.21–7.33 (m, 5H, C*H*); TLC (dichloromethane/methanol/triethylamine: 289 : 10 : 1) R_f = 0.29.

Synthesis of 1-benzyl-4-(5-aminopentyloxy)piperidine ***18***

To a solution of 1-benzyl-4-(4-nitrilopentykoxy)piperidine **17** (0.01 mol) in 60 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.037 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (1.4 mL), 10% of NaOH solution (1.4 mL), and water (1.4 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed with ether (2 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the residue was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

18: $C_{17}H_{28}N_2O$ (M = 276.4); ^{1}H-NMR, $CDCl_3$, δ: 1.32–1.64 (m, 10H, CH_2, CH_2, CH_2, CH_2CHO, NH_2*), 1.82-1.90 (m, 2H, CH_2CHO), 2.07–2.15 (m, 2H, NCH_2), 2.68 (t, *J* = 6.9 Hz, 2H, CH_2), 2.72–2.77 (m, 2H, NCH_2), 3.22–3.31 (m, 1H, *HC*-O-), 3.42 (t, *J* = 6.6 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2Ph), 7.21–7.31 (m, 5H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 39 : 10 : 1) R_f = 0.45. Elemental analysis for dioxalic acid salt $C_{17}H_{28}N_2O \times 2\ C_2H_2O_4$ (M = 456.5); m.p.$_{\text{dioxalic acid salt}}$ = 136.2–138°C: calculated: C, 55.25; H, 7.06; N, 6.14. Found: C, 54.87; H, 6.89; N, 6.02.

Synthesis of 1-benzyl-4-[5-(N-formylamino)pentyloxy]piperidine ***19***

To a solution of 1-benzyl-4-(3-aminopropyloxy)piperidine **10** (0.004 mol) in 25 mL of anhydrous dichloromethane was added FAM (10 mL). The mixture was stirred at 5–10°C for 0.5 h. Then, water (50.0 mL) and ethyl acetate (50.0 mL) were added and the mixture was neutralized with K_2CO_3 and water layer was extracted with dichlorometane (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated, the residue was purified by column chromatography on silicagel to give compound **19** as a sticky oil.

19: $C_{18}H_{28}N_2O_2$ (M = 304.5); yield 85%; ^{1}H-NMR, $CDCl_3$, δ: 1.38–1.45 (m, 2H, CH_2), 1.51–1.64 (m, 6H, CH_2, CH_2, CH_2CHO), 1.84–1.89 (m, 2H, CH_2CHO), 2.12–2.17 (m, 2H, NCH_2), 2.72–2.76 (m, 2H, NCH_2), 3.21–3.34 (m, 3H, *HC*-O-, CH_2), 3.43 (t, *J* = 6.3 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2Ph), 5.69 (s, 1H, N*H**), 7.22–7.33 (m, 5H, C*H*), 8.16 (s, 1H, HN-C*H*O); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 189 : 10 : 1) R_f = 0.36.

Synthesis of 1-benzyl-4-[5-(N-methylamino)pentyloxy]piperidine ***20***

To a solution of 1-benzyl-4-[5-(*N*-formylamino)pentyloxy]piperidine **19** (0.004 mol) in 25 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.013 mol). The mixture was stirred at room temperature for 1 h, and quenched by dropwise addition of water (0.5 mL), 10% of NaOH solution (0.5 mL), and water (0.5 mL). The suspension was stirred for 30 min, and filtered. The filter cake was washed with ether (2 × 25 mL). The combined organic extracts were washed with water (3 × 25 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the residue was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

20: $C_{18}H_{30}N_2O$ (M = 290.45); yield 76.2%; ^{1}H-NMR, $CDCl_3$, δ: 1.34–1.42 (m, 2H, CH_2), 1.48–1.64 (m, 6H, CH_2, CH_2, CH_2CHO), 1.83–1.89 (m, 2H, CH_2CHO), 2.07–2.15 (m, 2H, NCH_2), 2.2 (s, 1H, N*H**), 2.44 (s, 3H, NCH_3), 2.56–2.61 (t, *J* = 7.2 Hz, 2H, CH_2), 2.72–2.76 (m, 2H, NCH_2), 3.22–3.31 (m, 1H, *HC*-O-), 3.39-3.44 (t, *J* = 6.6 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2Ph), 7.22–7.31 (m, 5H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.28. Elemental analysis for dioxalic acid salt $C_{18}H_{30}N_2O$ x 2 $C_2H_2O_4$ (M = 470.5); m.p.$_{\text{dioxalic acid salt}}$ = 148.3–49.7°C: calculated: C, 56.16; H, 7.28; N, 5.95. Found: C, 55.84; H, 6.95; N, 5.83.

General method for the preparation of 1-benzyl-4-[5-(N-methyl-N-phenylalkylamino)pentyloxy]piperidines ***9b4–9b6***

To a solution of 1-benzyl-4-[5-(*N*-methylamino)pentyloxy]piperidine **20** (0.0007 mol) with the presence of potassium carbonate (0.0007 mol) in 5 mL of anhydrous DMF was added corresponding phenylalkyl halide (0.00083 mol). The suspension was stirred for 24 h at room temperature and filtered. The solution was diluted with 10 mL of water and extracted with dichloromethane (3 × 15 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated to give the crude products which were purified by column chromatography. The title products were obtained as sticky oil.

9b4

$C_{25}H_{36}N_2O$ (M = 380.8); yield 51.0%; ^{1}H-NMR δ: 1.25–1.40 (m, 2H, CH_2), 1.48–1.63 (m, 6H, CH_2CH_2CH_2), 1.84–1.89 (m, 2H, CH_2CH), 2.07–2.14 (m, 2H, CH_2N-), 2.17 (s, 3H, NCH_3), 2.33–2.38 (m, 2H, NCH_2), 2.72–2.76 (m, 2H, CH_2-N-CH$_3$), 3.23–3.29 (m, 1H, *HC*-O-), 3.41 (m, 2H, -O-CH_2), 3.47 (s, 2H, CH_2Ph), 3.49 (s, 2H, CH_2Ph), 7.21–7.32 (m, 10H); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 164 : 10 : 1) R_f = 0.47. Elemental analysis for dioxalic acid salt $C_{25}H_{36}N_2O \times 2\ C_2H_2O_4$ (M = 560.6); m.p.$_{\text{dioxalic acid salt}}$ = 192-193°C: calculated: C, 62.13; H, 7.19; N, 5.00. Found: C, 61.87; H, 7.01; N, 4.48.

9b5

$C_{27}H_{40}N_2O$ (M = 408.6); yield 35.0%; ^{1}H-NMR, $CDCl_3$, δ: 1.25–1.38 (m, 2H, CH_2), 1.44–1.64 (6H, CH_2, CH_2, CH_2CHO), 1.76–1.89 (m, 4H, CH_2, CH_2CHO), 2.09–2.15 (m, 2H, NCH_2), 2.23 (s, 3H, NCH_3), 2.32-2.41 (m, 4H, CH_2, CH_2), 2.63 (t, *J* = 7.8 Hz, 2H, CH_2), 2.72–2.76 (m, 2H, NCH_2), 3.22–3.31 (m, 1H, *HC*-O-), 3.41 (t, *J* = 6.6 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2Ph), 7.15–7.32 (m, 10H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.63. Elemental analysis for dioxalic acid salt $C_{27}H_{40}N_2O \times 2\ C_2H_2O_4$ (M = 588.7); m.p.$_{\text{dioxalic acid salt}}$ = 177.2–179°C: calculated: C, 63.25; H, 7.53; N, 4.76. Found: C, 63.09; H, 7.25; N, 4.37.

9b6

$C_{29}H_{44}N_2O$ (M = 436.7); yield 40.70%; ^{1}H-NMR, $CDCl_3$, δ: 1.25–1.37 (m, 4H, CH_2, CH_2), 1.42–1.68 (m, 10H, CH_2, CH_2, CH_2, CH_2, CH_2CHO), 1.83–1.89 (m, 2H, CH_2CHO), 2.06–2.14 (m, 2H, NCH_2), 2.19 (s, 3H, NCH_3), 2.27–2.32 (m, 4H, CH_2, CH_2), 2.61 (t, *J* = 7.8 Hz, 2H, CH_2), 2.72–2.76 (m, 2H, NCH_2), 3.22–3.29 (m, 1H, C*H*O), 3.41 (t, *J* = 6.6 Hz, 2H, CH_2), 3.48 (s, 2H, CH_2Ph), 7.14–7.31 (m, 10H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.65. Elemental analysis for dioxalic

acid salt $C_{29}H_{44}N_2O \times 2\ C_2H_2O_4$ (M = 616.75); m.p.$_{\text{dioxalic acid salt}}$ = 153.4 – 154.8°C: calculated: C, 64.27; H, 7.84; N, 4.54. Found: C, 63.96; H, 7.55; N, 4.32.

*Synthesis of 1-benzyl-4-(5-chloropentyloxy)piperidine **21***

To a solution of the 1-benzyl-4-hydroxypiperidine **10** (0.021 mol) in 30 mL of acetonitrile, with the presence of KF/Al_2O_3 (30 g/45) (0.14 mol) was added dropwise 1-chloro-5-iodopentane (0.26 mol). The suspension was heated at 26°C for 70 h, filtered, and the solvent was evaporated. The residue was dissolved in 100 mL of dichloromethane and washed with 10% of NaOH solution (3 × 10 mL). The organic layer was washed with water, dried (Na_2SO_4), and filtered. The solvent was evaporated and the residue was purified by column chromatography on silicagel. The title products were obtained as sticky oil.

21: $C_{17}H_{26}ClNO$ (M = 295.85); yield 24%; ^{1}H-NMR δ: 1.46 – 1.89 (m, 10H, CH_2CH, CH_2), 2.11 – 2.17 (m, 2H, NCH_2), 2.71 – 2.76 (m, 2H, NCH_2), 3.25 – 3.31 (m, 1H, OC*H*), 3.43 (m, 2H, OCH_2), 3.50 (s, 2H, CH_2Ph), 3.51 – 3.56 (m, 2H, ClCH_2), 7.22 – 7.32 (m, 5H); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 239: 10 : 1) R_f = 0.51.

*General method for the preparation of 1-benzyl-4-[5-(N-methyl-N-alkylamino)pentyloxy]piperidines **9b1 – 9b3***

To a solution of the 1-benzyl-4-(5-chloropentyloxy)piperidine **21** (0.001 mol) in 5 mL of anhydrous DMF was added corresponding methylalkylamine (0.01 mol). The reaction mixture was stirred for 24 h at 100°C. In the case of dimethylamine, the methanolic solution was used and the reaction was carried out in 35°C. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in 80 mL of dichloromethane, washed with 10% NaOH solution (3 × 10 mL). The organic layer was separated, washed with water, dried (Na_2SO_4), and filtered. The solvent was evaporated to give the crude products which were purified by column chromatography. The title products were obtained as sticky oil.

9b1

$C_{19}H_{32}N_2O$ (M = 304.5); yield 40%; ^{1}H-NMR, $CDCl_3$, δ: 1.29 – 1.40 (m, 2H, CH_2), 1.43 – 1.50 (m, 2H, CH_2), 1.52 – 1.64 (m, 4H, CH_2, CH_2CHO), 1.83 – 1.89 (m, 2H, CH_2CHO), 2.06 – 2.14 (m, 2H, NCH_2), 2.20 (s, 6H, NCH_3, NCH_3), 2.21 – 2.26 (m, 2H, CH_2), 2.72 – 2.75 (m, 2H, NCH_2), 3.22 – 3.30 (m, 1H, C*H*O), 3.39-3.44 (t, *J* = 6.6 Hz, 2H, CH_2), 3.48 (s, 2H, CH_2Ph), 7.21 – 7.31 (m, 5H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.35. Elemental analysis for dioxalic acid salt $C_{19}H_{32}N_2O \times 2\ C_2H_2O_4$ (M = 484.55); m.p.$_{\text{dioxalic acid salt}}$ = 97.5 – 100°C: calculated: C, 57.01; H, 7.49; N, 5.78. Found: C, 56.93; H, 7.55; N, 5.43.

9b2

$C_{21}H_{36}N_2O$ (M = 460.5); yield 52%; ^{1}H-NMR δ: 0.88 (m, 3H, CH_2CH_3), 1.25 – 1.64 (m, 10H, CH_2CH, CH_2), 1.85 – 1.89 (m, 2H, CH_2CH), 2.07 – 2.14 (m, 2H, NCH_2), 2.20 (s, 3H, NCH_3), 2.21 – 2.33 (m, 4H, NCH_2), 2.72 – 2.76 (m, 2H, NCH_2), 3.23 – 3.29 (m, 1H, OC*H*), 3.42 (t, 2H, OCH_2), 3.49 (s, 2H, CH_2Ph), 7.22 – 7.32 (m, 5H, C*H*); TLC dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.44. Elemental analysis for dioxalic acid salt $C_{21}H_{36}N_2O \times 2\ C_2H_2O_4$ (M = 512.6); m.p.$_{\text{dioxalic acid salt}}$ = 163 – 164°C: calculated: C, 58.58; H, 7.86; N, 5.46. Found: C, 58.75; H, 8.06; N, 5.43.

9b3

$C_{23}H_{40}N_2O$ (M = 360.6); yield 47%; ^{1}H-NMR δ: 0.87 – 0.91 (m, 3H, CH_2CH_3), 1.22 – 1.67 (m, 14H, CH_2CH, CH_2), 1.84 – 1.89 (m, 2H, CH_2CH), 2.07 – 2.15 (m, 2H, NCH_2), 2.20 (s, 3H, NCH_3), 2.27 – 2.33 (m, 4H, NCH_2), 2.72 – 2.76 (m, 2H, NCH_2), 3.23 – 3.29 (m, 1H, OC*H*), 3.42 (m, 2H, OCH_2), 3.49 (s, 2H, CH_2Ph), 7.23 – 7.32 (m, 5H, C*H*); TLC (dichloromethane/methanol/concentrated ammonium hydroxide: 89 : 10 : 1) R_f = 0.55. Elemental analysis for dioxalic acid salt $C_{23}H_{40}N_2O \times 2\ C_2H_2O_4$ (M = 540.65); m.p.$_{\text{dioxalic acid salt}}$ = 145-146°C: calculated: C, 59.98; H, 8.20; N, 5.18. Found: C, 59.63; H, 8.01; N, 5.12.

Pharmacology

The affinities of all compounds were determined by measuring the displacement curves of [^{3}H]N^a-methylhistamine binding at human histamine H_3 receptor expressed in HEK 239T cell membranes [37]. Selected compounds **9b1**, **9b2**, **9b5**, and **9b6** were tested for H_3 antagonistic effects *in vitro* on the guinea pig jejunum [38]. Selected compounds **9b1**, **9b2** and **9b4 – 9b6**, were also tested for H_3-antagonist effects *in vitro*, following standard methods, using the guinea pig ileum [39].

In-vitro pharmacology

Radioligand displacement studies at the human H_3 receptor

Cell culture and transfection: HEK 293T cells were maintained in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 50 IU/mL penicillin, and 50 μg/mL streptomycin in 5% CO_2 humidified atmosphere at 37°C. Approximately 4×10^6 cells were seeded in a 10-cm dish and cultured overnight before transfection. The transfection mixture (for transfection of a dish of cells) containing 5 μg of human H_3R receptor cDNA [37] and 20 μL of 1 mg/mL 25 kDa linear polyethyleneimine (Polyscience, Inc., USA) was prepared in 0.5 mL serum-free DMEM with incubation for 10 – 15 minutes at room temperature before being added into the cell culture containing 6 mL fresh cell culture medium. Two days after transfection, the cells were scraped, collected as pellet by centrifugation, and stored at – 20°C until use.

[^{3}H]N^a-Methylhistamine binding assay

Displacement radioligand binding assay was performed in 50 mM Tris-HCl buffer (pH 7.4 at 25°C) containing homogenized human H_3R-transfected cells, with or without competing ligands (10^{-4} to 10^{-11} M), in the presence of 2.5 nM [^{3}H]N^a-Methylhistamine (70,4 Ci/mmol; Perkin Elmer, USA) in a total volume of 200 μL. The binding reaction was incubated for 60 min at 25°C, and terminated by rapid filtration over Unifilter GF/C 96-well filterplates (Perkin Elmer, USA) pretreated with 0.3% 750 kDa polyethylenimine, followed by three washes with ice cold 50 mM Tris-HCl (pH 7.4 at 4°C). Radioactivity retained on the filter was determined by liquid scintillation counting on the Microbeta Trilux with 25 μL Microscint"O"TM (Perkin Elmer, USA). The binding assay data were analyzed using Prism 4.0 (Graphpad Software, Inc., USA).

H_3 antagonistic effects in vitro on the guinea pig jejunum [38] for selected compounds ***9b1, 9b2, 9b5****, and* ***9b6***

Male guinea pigs weighing 300 – 400 g were sacrificed by a blow on the head. A portion of the small intestine, 20-50 cm proximal to the ileocaecal valve (jejunum), was removed and placed in Krebs buffer (composition (mM) NaCl 118; KCl 5.6; $MgSO_4$ 1.18; $CaCl_2$ 2.5; NaH_2PO_4 1.28; $NaHCO_3$ 25; glucose 5.5 and indomethacin (1×10^{-6} mol/L)). Whole jejunum segments (2 cm) were prepared and mounted between two platinum electrodes (4 mm apart) in 20 mL Krebs buffer, continuously gassed with 95% O_2/ 5% CO_2 and maintained at 37°C. Contractions were recorded isotonically under 1.0 g tension with Hugo – Sachs – Hebel-Messvorsatz (Tl-2)/HF-modem (Hugo Sachs Electronik, Hugstetten, Germany) connected to a pen recorder. After equilibration for one hour with washings every 10 min, the muscle segments were stimulated maximally between 15 and 20 Volt and continuously at a frequency of 0.1 Hz and a duration of 0.5 msec, with rectangular-wave electrical pulses, delivered by a Grass Stimulator S-88 (Grass Instruments Co., Quincy, MA, USA). After 30 min of stimulation, five minutes before adding (R)-α-methylhistamine, pyrilamine (1×10^{-5} mol/L concentration in an organ bath) was added, and then cumulative concentration-response curves (half-log increments) of (R)-α-methylhistamine, H_3 agonist, were recorded until no further change in response was found. Five minutes before adding the tested compounds, the pyrilamine (1×10^{-5} mol/L concentration in an organ bath) was added, and after 20 minutes cumulative concentration-response curves (half-log increments) of (R)-α-methylhistamine, H_3 agonist were recorded until no further change in response was found. Statistical analysis was carried out with the Students' t-test. In all test $p < 0.05$ was considered statistically significant. The potency of an antagonist is expressed by its pA_2 value, calculated from the Schild [39] regression analysis where at least three concentrations were used. The pA_2 values were compared with the potency of thioperamide.

H_1 antagonistic activity [39] for ***9a2, 9b2, 9b5****, and* ***9b6***

Selected compounds were tested for H_1 antagonist effects *in vitro*, following standard methods, using the guinea pig ileum [39]. Male guinea pigs weighing 300 – 400 g were sacrificed by a blow on the head. The ileum was excised and placed in phosphate buffer at room temperature (pH 7.4) containing (mM) NaCl (136.9); KCl (2.68); $NaHPO_4$ (7.19). After flushing the intraluminal contens, segments of about 2 cm long pieces were cut and mounted for isotonic contractions in water jacked 20 mL organ baths filled with oxygenated (O_2 : CO_2=95 : 5, v/v) Krebs buffer containing (mM) NaCl (117.5); KCl (5.6); $MgSO_4$ (1.18); $CaCl_2$ (2.5); NaH_2PO_4 (1.28); $NaHCO_3$ (25); glucose (5.5) and indomethacin (1×10^{-6} mol/L) at 37°C under a constant load of 0.5 g. After a 30 min equilibration period with washings every 10 min, a submaximal priming dose of histamine (1 μM) was given and washed out (standard washing procedure: three changes of buffer during 30 min). After washing out, the antagonistic activity of given compounds was measured by recording a Concentration Response Curve (CRC) for histamine in the presence of the testing compounds (**9a2**, **9b2**, **9b5,** and **9b6**) which was added 5 min before histamine. This procedure was repeated with higher concentrations of the compounds. The antagonism was of a competitive nature causing a parallel shift of the CRC. The pA_2-values were calculated according to Arunlakshana and Schild [39]. The pA_2 values were compared with the potency of pyrilamine.

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