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Research Article

Structure–Activity Relationships of New 1-substitutedmethyl-4-[5-(*N*-methyl-*N*-propylamino) pentyloxy]piperidines and Selected 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methy-l-*N*-propyl)-pentanediamines as H_3-Antagonists

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Novel, potent non-imidazole histamine H_3 receptor antagonists have been prepared and *in vitro* tested as H_3-receptor antagonists (the electrically evoked contraction of the guinea-pig jejunum). The present compounds contain a 4-hydroxypiperidine core, which behaves as a conformationally restricted version of the 3-amino-1-propanol moiety common to the many previously described non-imidazole H_3 ligands. Detailed structure-activity studies revealed that 1-(2-benzofuranylmethyl)- 5c (pA_2 = 8.47 ± 0.05) and 1-(3-benzofuranylmethyl)-4-[5-(N-methyl-N-propyl)pentyloxy]piperidine 5d (pA_2 = 8.15 ± 0.07) exhibit high potency for the H_3 histamine receptor. In addition, the potency of selected 1-[(N-substituted-N-methyl)-3-propyloxy]-5-(N-methyl-N-propyl)pentanediamines as antagonist of the H_3 histamine receptor was also evaluated. Replacement of the 4-hydroxypiperidine of the leads 7 and 5c by a highly flexible 3-(methylamino)propyloxy chain yields compounds 6a (pA_2 = 8.02) and 6b (pA_2 = 6.23) with higher and lower potency than their piperidine analogues (7, pA_2 = 7.79; 5c, pA_2 = 8.47), respectively. The histaminergic H_1 antagonism of selected compounds 5c, 5d and 6a has been established on the isolated guinea-pig ileum by conventional methods; the pA_2 values have compared with the potency of pyrilamine. None of them showed any H_1-antagonistic activity (pA_2 < 4; for pyrilamine pA_2 = 8.5).

Key words: histamine H_3-receptor, H_3 non-imidazole antagonists, 1-substitutedmethyl-4-[5-(*N*-methyl-*N*-propylamino)pentyloxy]piperidines, 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)pentanediamines

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Histamine is a biogenic amine involved in a large variety of physiological functions. It exerts its actions through four distinct G protein-coupled receptors, named H_1, H_2, H_3 and H_4 (1,2). H_1 and H_2 receptor antagonists are well-known therapeutic agents and are in use for the treatment of allergic disease (3) and peptic ulcer (4), respectively. H_4 receptor is involved in inflammatory processes and takes an immunomodulatory role. Ligands of these receptors could be effective in the regulation of the immune response (5).

The histamine H_3 receptor was discovered in 1983 by Arrang *et al.* (6) as a presynaptic autoreceptor, and the gene was successively cloned in 1999 by Lovenberg *et al.* (7). Based on tissue distribution analysis, it has been proved that the expression of the receptor is predominantly restricted to the brain (8). The H_3 receptor does not only mediate the inhibition of synthesis and release of histamine from histaminergic neurons via a negative feedback loop (9,10), but also exerts modulatory effects on other neurotransmitter systems, for example, the cholinergic (11,12), dopaminergic (13), noradrenergic (14) and serotoninergic (15) systems, in both the central and peripheral nervous system. A variety of potential therapeutic application for H_3 receptor antagonists/inverse agonists has been proposed to be potential drugs for the treatment of several CNS disorders, such as attention-deficit hyperactivity disorder (ADHD) (16,17), Alzheimer's disease (18), epilepsy (19), schizophrenia (20) and obesity (21). However, emerging novel therapeutic concepts have been introduced and some indication in the H_3 receptor field, for example, migraine, pain or allergic rhinitis, might take advantage of peripherally acting ligands. For example, kojic acid analogues of benzyl-1-(4-(3-(piperidine-1-yl)propoxy)phenyl)-methanamine derivatives might act peripherally (22). Another approach for the treatment of allergic rhinitis is the search of new dual H_1H_3 receptor antagonists (23). Recently, scientists at the GlaxoSmithKlein Medicines Research Centre have published dual H_1H_3 receptor antagonists based on phthalazinone core (24).

The physiological and pathophysiological implications of histamine H_3 receptors increase the need for potent and

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selective ligands as pharmacological tools and potential drugs development. The first generation of H_3 antagonists was characterized by the presence of an imidazole ring as in histamine, many of which have found utility as pharmacological tools (25,26). In contrast to the early work in the field, most chemical series of current interest appear to be non-imidazole compounds because of major disadvantages of 4-substituted imidazole moiety, including poor brain penetration and issue related to hepatic cytochrome P_{450} enzymes inhibition, such as drug–drug interactions, liver toxicity and inhibition of adrenal synthesis (27–30). Additionally, non-imidazoles H_3 antagonists/inverse agonists tend to be more selective versus H_1, H_2 and H_4 receptors (31).

Since 1994, when the marine natural product aplysamine-1 was patented as a weak H_3 histamine receptor antagonist (32), diamine-based ligands, containing the characteristic aminopropoxyphenyl structural pharmacophore, have become an important chemical class of H_3 histamine receptor antagonists. This motif has been repeated in a number of different series of compounds from several laboratories, for example, compounds **1** (33) and **2** (34) (Chart 1). Later on, the successful replacement of the highly flexible propyloxy link with 4-phenoxypiperidine moiety **3** (35) (Chart 1) or the partially rigid 2-aminoethylbenzofuran substructure **4** (36) (Chart 1) was demonstrated.

Previously, we reported the synthesis and preliminary pharmacological investigation of new series of 1-benzyl-4-(3-aminopropyloxy)- and 1-benzyl-4-(5-amino)pentyloxypiperidine derivatives (37). It appeared that by comparison of homologous pairs, the 1-benzyl-4-(5-aminopentyloxy)piperidines have slightly higher potency than their 1-benzyl-4-(3-aminopropyloxy)piperidines analogues. 1-Benzyl-4-[5-(*N*-methyl-*N*-propylaminopentyloxy)] piperidine was the most potent compound of theses series (pA_2 = 7.79) and was chosen as the lead compound for further structural modification. As the H_3 receptor antagonist potency could not be increased by modifying the N-substituent of 1-benzyl-4-[5-(*N*-methyl-*N*-substitutedaminopentyloxy)]piperidine, attention was paid to replacement benzene ring by various substituents consist of benzene fused six-, five-membered heterocycles containing carbonyl group and oxygen or only oxygen atom and benzene fused six-, five-membered hydrocarbons rings like 3,4-dihydro-4-oxo-2H-chromen-2-yl- and -3-yl-, 4-oxo-2H-chromen-2-yl- and -3-yl-, 2- and 3-benzofuranyl, 2-indenyl or 2-naphthyl one. With the aim of investigation the effect of increased flexibility of the central core on antagonistic potency, the 4-hydroxypiperidine was replaced by 3-(methylamino)propyloxy chain, and two of the most active analogues of both 4-hydroxypiperidine series, that is, benzyl (**6a**) and 2-benzofuranyl (**6b**) derivative were synthesized and pharmacological evaluated. In addition, structure–activity relationships (SAR) resulting from variation of the position of 4-[5-(*N*-methyl-*N*-propylaminopentyloxy)]piperidinyl moiety attached by methylene linker in benzene fused six-, five-membered heterocyclic and the presence or absence of double bond at heterocycle ring are discussed.

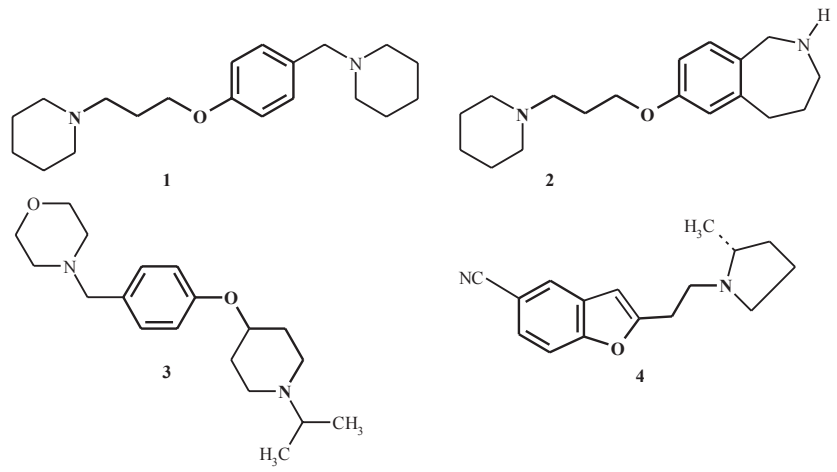


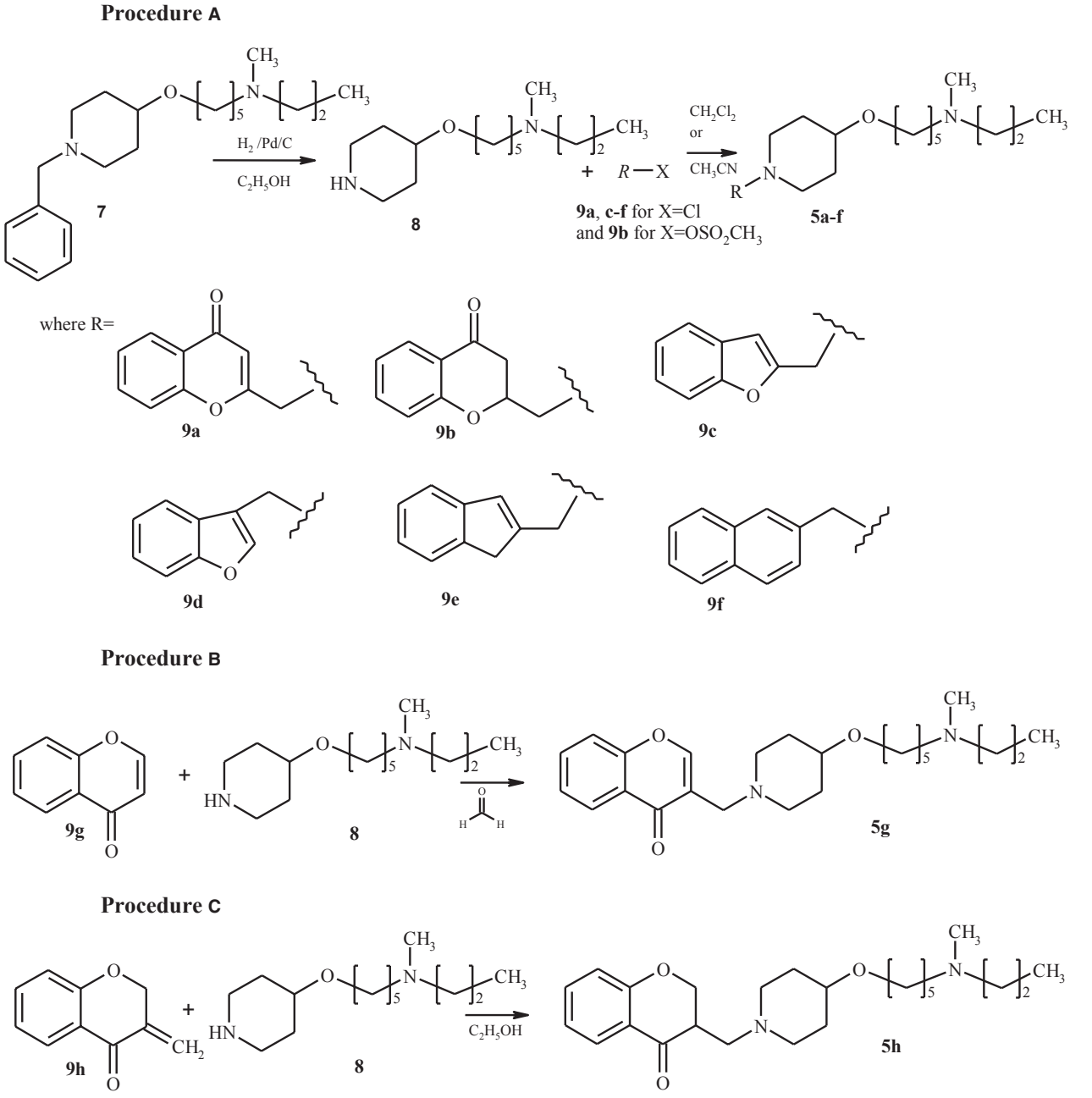
Chart 1: Representative non-imidazole H_3-histamine receptor antagonists containing the characteristic aminopropoxyphenyl structural pharmacophor, its rigid analogues and the target molecules of this study.

In the present work, we report the synthesis and preliminary pharmacological investigation [functionally on *in vitro* test system using guinea-pig jejunum preparations (38)] of new series of 1-[(substitutedmethyl)]-4-[5-(*N*-methyl-*N*-propyl)pentyloxy]piperidines and selected 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)pentandiamines as H_3 histamine receptor antagonists.

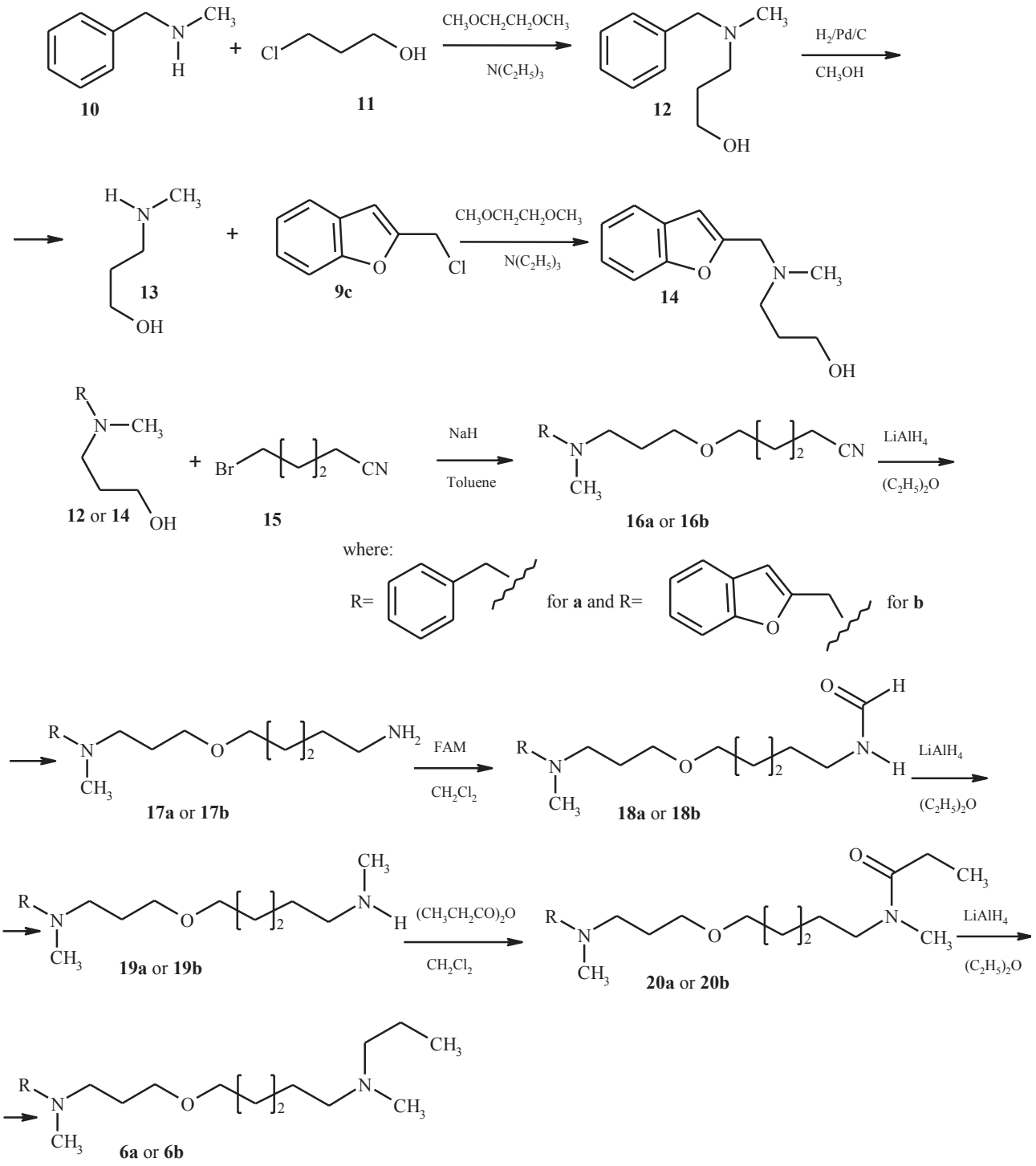
Furthermore, to determine whether the most active compounds of both series are or are not dual H_1H_3 receptor antagonists, compounds **5c**, **5d** and **6a** have been tested for H_1 antagonistic effects *in vitro*, following standard methods, using the guinea-pig ileum (39).

Chemistry

The general synthetic procedures used in this study are illustrated in Schemes 1 and 2. The key intermediate for all novel synthesized 4-hydroxypiperidines **5a**–**h** is 4-[5-(*N*-methyl-*N*-propyl)pentyloxy]piperidine **8,** which was prepared by hydrogenation of 1-benzyl4-[5-(*N*-methyl-*N*-pro-



Scheme 1: Synthesis of 1-substitutedmethyl-4-[5-*N*-methyl-*N*-propylamino]piperidines **5a**–**h**.



Scheme 2: Synthesis of 1-[*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)- pentanediamines **6a** and **6b**.

pyl)pentyloxy]piperidine **7** with a catalytic amount of palladium on charcoal in ethanol.

The 4-hydroxypiperidines **5a**–**f** (Scheme 1; Procedure A) were obtained from **8** by alkylation with the corresponding mesyl chloride **9b** and chlorides **9a**, **c**–**f** in dichloromethane or acetonitrile followed by purification with column chromatography. The product **5g** (Scheme 1; Procedure B) was synthesized by Mannich reaction involving the condensation of 1,4-benzopyrone **9g** with formaldehyde and **8** in ethanol. The compound **9h** in ethanol solution was treated with **8** to yield **5h**.

The 3-(methylamino)propyloxy derivatives **6a**, **b** were obtained from compound **12** or **14** by a six-step synthesis (Scheme 2) including the following: O-alkylation with 5-bromopentanenitrile in dry toluene in the presence of sodium hydride and 1,4,7,10,13-pentaoxycyclopentadecane (15-crown-5 ether) to compounds **16a** or **16b**, reduction with $LiAlH_4$ in dry ethyl ether to compound **17a** or **17b**, formylation with formic acid-acetic anhydride (FAM) to yield **18a**, **b**, reduction with $LiAlH_4$ in dry diethyl ether to obtain **19a** or **19b**, acetylated with propionic anhydride to amides **20a** or **20b** and reduction with $LiAlH_4$ in dry diethyl ether to the desired compounds **6a** or 6**b**, each step was followed by purification with column chromatography. 3-Benzylmethylamino-1-propanol **10** was N-alkylated with **11** in 1,2-dimethoxyethane (DME) in the presence of triethylamine (TEA) to 3-(*N*-benzyl-*N*-methylamino)-1-propanol **12** (40). Hydrogenation of (**12**) with a catalytic amount of palladium on charcoal in methanol yield to **13** (40). The compound **14** was prepared from 2-chloromethylbenzofuran **9c** through nucleophilic substitution of the chlorine atom by 3-methylamino-1-propanol **13** in DME in the presence of TEA. All obtained final free bases were treated with methanolic oxalic acid solution, and oxalic acid salts were precipitated with dry diethyl ether and crystallized twice from ethanol.

Experimental Section

General methods

All melting points (mp) were taken in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds, ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz, Varian Mercury VX 300 MHz. Chemical shifts are expressed in p.p.m. 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 was measured on Perkin Elmer Series II CHNS/O Analyzer 2400 (PerkinElmer, Inc., Waltham, MA, USA) and are within ±0.4% of the theoretical values. TLC was performed on silica gel 60 F_{254} plates (Merck, Darmstadt, Germany). Flash column chromatography was carried out using silica gel 60 Å 50 μm (J. T. Baker B. V.), employing the same eluent as was indicated by TLC. All obtained final free bases were treated with methanolic oxalic acid solution, and oxalic acid salts were precipitated with dry diethyl ether and crystallized twice from ethanol.

Description of the synthetic methods for preparing intermediates 9a–e and 9h has been given in Appendix S1 also graphic illustrations of synthetic pathways for these intermediates (Schemes 3 and 4) have been presented in supporting information section.

The 1,4-benzopyrone, 5-bromopentanonitrile, propionic anhydride, 3-benzylmethylamino-1-propanol, 3-chloro-1-propanol, 4-oxo-4H-1-benzopyran-2-carboxylic acid, 2-hydroxy-benzaldehyde, 3-bromo-1-propene, 2H-1-Benzopyran-2-one, 2-hydroxyacetophenone, ethyl chloroacetate and indan-1-one were all purchased from commercial source - (Sigma-Aldrich Corp, St. Louis, MO, USA).

Synthesis of 4-[5-(*N*-methyl-*N*-propyl)pentyloxy] piperidine 8

A mixture of **7** (0.007 mol) and Pd/C (10%; 70 mg) in 100 mL of ethanol was shaken in autoclave under 3 atm. of hydrogen at 50 °C temperature for 5 h. The catalyst was filtered off, and the solvent was removed in vacuo. The residue was purified by column chromatography with ethyl acetate:methanol:TEA: 9:4:1 to give **8** as colourless oil.

8. $C_{14}H_{30}N_2$, (M = 242.4); yield 98.0%; ^{1}H NMR($CDCl_3$) δ p.p.m.: 0.863–0.912 (t, 3H, CH_2CH_3, J = 7.33 Hz); 1.315–1.635 (m, 11H, $^{alif}CH_2$, $^{pip}CH_2$, NH); 1.84–1.88 (m, 2H, $^{pip}CH_2$); 2.077–2.17 (m, 2H, $^{pip}CH_2$); 2.2 (s, 3H, NCH_3); 2.246–2.335 (m, 4H, $^{alif}CH_2$); 2.722–2.759 (m, 2H, $^{pip}CH_2$); 3.223–3.306 (m, 1H, ^{pip}CHO); 3.394–3.438 (t, 2H, $^{alif}CH_2O$, J = 6.6 Hz); 3.485 (s, 2H, CH_2Ph); R_f = 0.17.

Elemental analysis for dioxalic acid salt $C_{14}H_{30}N_2 \cdot 2C_2H_2O_4$ (M = 422,48); $mp_{dioxalic\ acid\ salt}$ = 110–111 °C.

	C (%)	H (%)	N (%)
Calculated	51.17	8.11	6.63
Found	51.07	8.45	6.54

General method for the preparation of 1-substitutedmethyl-4-[5-(*N*-methyl-*N*-propylamino) pentyloxy]piperidines 5a–f

To a solution of 4-[5-(*N*-methyl-*N*-propyl)pentyloxy]piperidine **8** (0.0024 mol) in 60 mL of dichloromethane (for **5a**) or in 120 mL of acetonitrile (for **5b**) was added the corresponding chloride **9a** or mesyloxide **9b** (0.0012 mol). In case of compounds **5c**–**f** to solution of compound **8** (0.0011 mol) in 10 mL of acetonitrile, in the presence of potassium carbonate (0.0011 mol), was added the corresponding chloride **9c**–**f** (0.0011 mol). The mixture was stirred at room temperature for 72–96 h and next 24 h at 40 °C. The solvent was evaporated and residue was washed with saturated aqueous solution of potassium carbonate and extracted with ethyl acetate (3 × 50.0 mL). The organic extracts were dried (Na_2SO_4) and filtered. The solvent was evaporated to give the crude products as a sticky oil, which was purified by column chromatography.

5a. $C_{24}H_{36}N_2O_3$, (M = 400.52); yield 24%; ^{1}HNMR($CDCl_3$) δ p.p.m.: 0.87–0.89 (t, 3H, CH_2CH_3, J = 7.35 Hz); 1.31–1.36 (m, 2H, $^{alif}CH_2$); 1.46–1.54 (m, 4H, $^{alif}CH_2$); 1.55–1.59 (m, 2H, $^{alif}CH_2$); 1.61–1.67 (m, 2H, $^{pip}CH_2$); 1.86–1.89 (m, 2H, $^{pip}CH_2$); 2.23 (s, 3H, NCH_3); 2.31–2.37 (m, 6H, $^{alif}CH_2$, $^{pip}CH_2$); 2.79–2.82 (m, 2H, $^{pip}CH_2$); 3.28–3.31 (m, 1H,

^{pip}CHO); 3.39–3.42 (t, 2H, OCH_2, J = 6.6 Hz); 3.46 (s, 2H, NCH_2); 6.41 (s, 1H, CO-CH); 7.29–7.38 (m, 1H, ^{arom}CH); 7.4–7.45 (m, 1H, ^{arom}CH); 7.62–7.64 (m, 1H, ^{arom}CH); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 89:10:1) R_f = 0.37.

Elemental analysis for dioxalic acid salt $C_{24}H_{36}N_2O_3 \cdot 2C_2H_2O_4$ (M = 580.06); $mp_{dioxalic\ acid\ salt}$ = 155–158 °C.

	C (%)	H (%)	N (%)
Calculated	57.92	6.94	4.83
Found	58.10	7.06	4.85

5b. $C_{24}H_{38}N_2O_3$, (M = 402.57); yield 74%; ^{1}HNMR($CDCl_3$) δ p.p.m.: 0.88–0.90 (t, 3H, CH_2CH_3, J = 7.5 Hz); 1.32–1.38 (m, 2H, $^{alif}CH_2$); 1.46–1.52 (m, 4H, $^{alif}CH_2$); 1.56–1.63 (m, 4H, $^{alif}CH_2$, $^{pip}CH_2$); 1.84–1.86 (m, 2H, $^{pip}CH_2$); 2.22 (s, 3H, NCH_3); 2.27–2.35 (m, 6H, $^{alif}CH_2$, $^{pip}CH_2$); 2.72–2.77 (m, 2H, CO-CH_2); 2.78–2.83 (m, 4H, $^{alif}CH_2$, $^{pip}CH_2$); 3.26–3.29 (m, 1H, ^{pip}CHO); 3.41–3.43 (t, 2H, OCH_2, J = 6.6 Hz); 4.58–4.62 (m, 1H, $OCHCH_2$); 6.97–7.01 (m, 2H,^{arom}CH); 7.44–7.47 (m, 1H, ^{arom}CH); 7.87–7.88 (m, 1H, ^{arom}CH); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 39:10:1) R_f = 0.39.

Elemental analysis for dioxalic acid salt $C_{24}H_{38}N_2O_3 \cdot 2C_2H_2O_4$ (M = 582.65); $mp_{dioxalic\ acid\ salt}$ = 135–137 °C.

	C (%)	H (%)	N (%)
Calculated	57.72	7.27	4.81
Found	57.80	7.34	4.74

5c. $C_{23}H_{36}N_2O_2$, (M = 372.51); yield 41.48%; ^{1}H NMR, ($CDCl_3$), δ p.p.m.: 0.90–0.95 (t, 3H, J = 7.35, CH_2CH_3); 1.31–1.76 (m, 10H, $^{alif}CH_2$, $^{pip}CH_2$); 1.90–1.96 (m, 2H, $^{pip}CH_2$); 2.24 (s, 3H, NCH_3); 2.26–2.37 (m, 6H, $^{alif}CH_2$, $^{pip}CH_2$); 2.83–2.87 (m, 2H, $^{pip}CH_2$); 3.28–3.36 (m, 1H, ^{pip}CHO); 3.43–3.47 (t,2H, J = 6.6, OCH_2); 3.72 (s, 2H, NCH_2); 6.61 (s, 1H, 3-H); 7.21–7.32 (m, 2H, ^{arom}CH); 7.50–7.58 (m, 2H, ^{arom}CH); TLC (ethyl acetate:methanol:TEA: 9:1:4) R_f = 0.27.

Elemental analysis for dioxalic acid salt $C_{23}H_{36}N_2O_2 \cdot 2C_2H_2O_4$ (M = 554.64); $mp_{dioxalic\ acid\ salt}$ = 168–169 °C.

	C (%)	H (%)	N (%)
Calculated	58.68	7.30	5.07
Found	58.46	7.33	5.04

5d. $C_{23}H_{36}N_2O_2$, (M = 372.51); yield 53.68%; ^{1}H NMR, ($CDCl_3$), δ p.p.m.: 0.86–0.91 (t, 3H, J = 7.5, CH_2CH_3); 1.24–1.65 (m, 10H, $^{alif}CH_2$, $^{pip}CH_2$); 1.86–1.90 (m, 2H, $^{pip}CH_2$); 2.13-2.17 (m, 2H, $^{pip}CH_2$); 2.21 (s, 3H, NCH_3); 2.26–2,35 (m, 4H, $^{alif}CH_2$); 2.79–2.83 (m, 2H, $^{pip}CH_2$); 3.22–3.29 (m, 1H, ^{pip}CHO); 3.39–3.43 (t, 2H, J = 6.6, OCH_2); 3.63 (s, 2H, NCH_2); 7.20–7.32 (m, 2H, ^{arom}CH); 7.44–7.48 (m, 1H, ^{arom}CH); 7.52 (s, 1H, 2-H); 7.70–7.73 (m, 1H, ^{arom}CH); TLC (ethyl acetate:methanol:concentrated ammonium hydroxide: 9:1:1) R_f = 0.29.

Elemental analysis for dioxalic acid salt $C_{23}H_{36}N_2O_2 \cdot 2C_2H_2O_4$ (M = 554.64); $mp_{dioxalic\ acid\ salt}$ = 155–157 °C.

	C (%)	H (%)	N (%)
Calculated	58.68	7.30	5.07
Found	58.53	7.42	4.93

5e. $C_{24}H_{38}N_2O$, (M = 370.54); yield 29%; H^{1}NMR, $CDCl_3$, δ p.p.m.: 0.88–0.93 (t, J = 7.2, 3H, CH_2CH_3); 1.30–1.40 (m, 2H, CH_2); 1.45–1.66 (m, 8H, CH_2); 1.86–1.91 (m, 2H, $CH_2^{pip.}$); 2.09–2.16 (m, 2H, $CH_2^{pip.}$); 2.25 (s, 3H, NCH_3); 2.31–2.40 (m, 4H, CH_2); 2.75–2.79 (m, 2H, $CH_2^{pip.}$); 3.24–3.33 (m, 1H, $CHO^{pip.}$); 3.37–3.45 (m, 6H, $OCH_2^{alif.}$, =C-CH_2-N, CH_2^{inden}); 6.67 (s, 1H, CH=C^{inden}); 7.11–7.16 (m, 1H, CH^{arom}); 7.21–7.31 (m, 2H, CH^{arom}); 7.4–7.42 (m, 1H, CH^{arom}); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 18:1:0.5) R_f = 0.31.

Elemental analysis for dioxalic acid salt $C_{24}H_{38}N_2O \cdot 2C_2H_2O_4$ (M = 554.58); $mp_{dioxalic\ acid\ salt}$ = 169–172 °C.

	C (%)	H (%)	N (%)
Calculated	60.64	7.65	5.05
Found	60.47	7.36	4.89

5f. $C_{25}H_{38}N_2O$, (M = 382.65); yield 21%;^{1}HNMR, $CDCl_3$, δ p.p.m.: 0.86–0.91 (t, 3H, J = 7.5, CH_2CH_3); 1.31–1.67 (m, 10H, $CH_2^{alif.}$, CH_2^{pip}); 1.85–1.92 (m, 2H, CH_2^{pip}); 2.13–2.17 (m, 2H, CH_2^{pip}); 2.21 (s, 3H, NCH_3); 2.26–2.35 (m, 4H, CH_2^{alif}); 2.75–2.82 (m, 2H, CH_2^{pip}); 3.27–3.30 (m, 1H, CHO-^{pip}); 3.40–3.44 (t, 2H, J = 6.6, OCH_2); 3.65 (s, 2H); 7.41–7.50 (m, 3H, CH^{arom}); 7.72 (s, 1H, CH^{arom}); 7.79–7.83 (m, 3H, CH^{arom}); TLC (eluents:dichloromethane:ethyl acetate and dichloromethane:methanol:concentrated ammonium hydroxide – gradient from 4:1 to 9:1:1) R_f = 0.47.

Elemental analysis for dioxalic acid salt $C_{24}H_{38}N_2O \cdot 2C_2H_2O_4$ (M = 562.73); $mp_{dioxalic\ acid\ salt}$ = 161–162 °C.

	C (%)	H (%)	N (%)
Calculated	61.9	7.53	4.98
Found	61.57	7.84	4.71

Synthesis of 1-(4-oxo-2H-chromen-3-ylmethyl)-4-[5-(*N*-methyl-*N*-propyl)pentyloxy]- piperidine 5g

A mixture of 1,4-benzopyrone **9g** (0.045 mol), 4-[5-(*N*-methyl-*N*-propyl)pentyloxy]piperidine **8** (0.05 mol), paraformaldehyde (0.09 mol) and 40 mL of absolute ethanol was refluxed for 24 h. The solvent was evaporated to give the crude product as a sticky oil, which was purified by column chromatography.

5g. $C_{24}H_{36}N_2O_3$, (M = 400.54); yield 27%; ^{1}H NMR ($CDCl_3$): δ p.p.m.: 0.87–0.92 (t, 3H, $-CH_2CH_3$, J = 7.35 Hz); δ = 1.26–1.45 (m, 2H^{pip}), δ = 1.46–1.67 (m, 4H, $-CH_2-^{alif}$); δ = 1.88–1.94 (m, 2H^{pip}); δ = 2.25 (s, 3H, N-CH_3), δ = 2.31–2.4 (m, 4H, $-CH_2-$), δ = 2.81–2.85 (m, 2H^{pip}); δ = 3.25–3.34 (m, 1H, -CHO), δ = 3.40–3.45 (t, $-CH_2-^{alif}$, J = 6.45); δ = 3.49 (s, 2H, $-CH_2-$); δ = 7.37–7.47 (m, 2H^{chromone}); δ = 7.63–7.69 (m, 1H^{chromone}); δ = 8.02 (s, 1H, OCH = ^{chromone}); δ = 8.21–8.24 (m, 1H^{chromon}); TLC (ethyl acetate:methanol:TEA: 9:1:4), R_f = 0.49.

Elemental analysis for dioxalic acid salt $C_{24}H_{36}N_2O_3 \cdot 2C_2H_2O_4$ (M = 580.64); $mp_{dioxalic\ acid\ salt}$ = 165–167 °C.

	C (%)	H (%)	N (%)
Calculated	57.91	6.93	4.82
Found	57.87	6.88	4.85

Synthesis of 1-(3,4-dihydro-4-oxo-2H-chromen-3-ylmethyl)-4-[5-(*N*-methyl-*N*-propyl)- pentyloxy] piperidine 5h

To a solution of 2,3-dihydro-3-methylene-4H-benzopyran-4-on **9h** (0.0033 mol) in 15 mL of ethanol was added **8** (0.0033 mol). The mixture was stirred for 168 h at room temperature. The solvent was evaporated, and residue was purified by column chromatography. The title products were obtained as sticky oil.

5h. $C_{24}H_{38}N_2O_3$, (M = 402.57); yield 30%; ^{1}HNMR δ p.p.m.: 0.83–0.98 (t, 3H, J = 7.35, CH_2CH_3); 1.29–1.65 (m, 8H, $^{pip}CH_2$, $^{alif}CH_2$); 1.85–1.99 (m, 2H, $^{pip}CH_2$); 2.03–2.15 (m, 2H, $^{pip}CH_2$); 2.22 (s, 3H, NCH_3); 2.27–2.47 (m, 4H, $^{alif}CH_2$, $^{pip}CH_2$); 2.4–2.96 (m, 6H, $^{alif}CH_2$,$^{pip}NCH_2$); 3.23–3.25 (m, 1H, ^{pip}CH); 3.4–3.45 (t, 2H, $^{alif}OCH_2$, J = 6.6 Hz); 4.36–4.43 (dd, 2H, J = 8.7 Hz, J = 2.7 Hz, $^{chrom}OCH_2$); 4.57–4.62 (dd, 1H, J = 4.5 Hz, J = 7.2 Hz, $^{chrom}CH$); 6.95–7.03 (m, 2H, ^{arom}CH); 7.44–7.51 (m, 1H, ^{arom}CH); 7.86–7.89 (dd, 1H, J = 1.8 Hz, J = 6 Hz, ^{arom}CH); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 19:1:0.5), R_f = 0.4.

Elemental analysis for dioxalic acid salt $C_{24}H_{38}N_2O_3 \cdot 2C_2H_2O_4$ (M = 582.65); $mp_{dioxalic\ acid\ salt}$ = 129–132 °C.

	C (%)	H (%)	N (%)
Calculated	57.72	7.27	4.81
Found	58.09	7.09	4.74

General method for the preparation of 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)pentanediamines 6a and 6b

Synthesis of 3-(*N*-benzyl-*N*-methylamino)-1-propanol 12. A mixture of 3-benzylmethylamine **10** (0.2 mol), 3-chloro-1-propanol **11** (0.2 mol), triethylamine (0.2 mol) and 1,2-dimethoxyethane (150 mL) was heated at 93 °C for 20 h. The reaction mixture was cooled, and the trimethylamine hydrochloride was filtered off. The solvent was evaporated, and the residue was distillated under reduced pressure to give **12** as colourless oil.

12. $C_{11}H_{17}NO$, (M = 179.29); yield 51% bp = 152–156 °C/15 torr [lit. bp = 98–100 °C/0.25 torr [40]]; ^{1}HNMR ($CDCl_3$)δ p.p.m.: 1.74–1.77 (m, 2H, $CH_2CH_2CH_2$); 2.22 (s, 3H, NCH_3); 2.61–2.64 (t, J = 6 Hz, 2H, CH_2N); 3.51 (s, 2H, CH_2Ph); 3.74–3.78 (t, J = 6 Hz, 2H, CH_2OH); 4.50 (br, 1H, OH); 7.27–7.32 (m, 5H, $H_{aromat.}$).

Synthesis of 3-(methylamino)-1-propanol 13. A mixture of **12** (0.1 mol) and Pd/C (10%; 110 mg) in 100 mL of ethanol was shaken in autoclave under 20 atm. of hydrogen at 60 °C temperature for 4 h. The catalyst was filtered off, and the solvent was removed in vacuo. The residue was distillated under reduced pressure to give **13** as colourless oil.

13. $C_4H_{11}NO$, (M = 89.16); yield 61.0%; bp = 80–82 °C/13 torr [lit.^{0} bp = 74–76 °C/10 torr [40]] ^{1}HNMR($CDCl_3$) δ p.p.m.: 1.54–1.58 (m, 2H, $CH_2CH_2CH_2$); 2.27 (s, 3H, NCH_3); 2.61–2.63 (t, J = 6 Hz, 2H, CH_2N); 3.24 (br, 1H, OH); 3.56–3.58 (t, J = 6 Hz, 2H, CH_2OH).

Synthesis of 3-[[(benzofuran-2yl)methyl]amino]-1-propanol 14. To a solution of 3-(methylamino)-1-propanol **13** (0.022 mol) and TEA (0.022 mol) in 50 mL of DME was added 2-chloromethylbenzofuran **9c** (0.22 mol). The reaction mixture was heated at 80 °C for 24 h. After cooling, the resulting precipitate was filtered off and solvent was evaporated to give the crude product as a sticky oil, which was purified by column chromatography.

14. $C_{13}H_{17}NO_2$, (M = 219.31); yield 57%; ^{1}HNMR ($CDCl_3$) δ p.p.m.: 1.74–1.77 (m, 2H, $CH_2CH_2CH_2$); 2.34 (s, 3H, NCH_3); 2.66–2.70 (t, J = 6 Hz, 2H, CH_2N); 3.72 (s, 2H, $CH_2^{benzofurane}$); 3.76–3.0 (t, J = 6 Hz, 2H, CH_2OH); 4.77 (br, 1H, OH); 6.59 (s, 1H, H^{benzofurane}); 7.17–7.27.); 7.45–7.54 (m, 1H, H^{benzofurane}); TLC (ethyl acetate:methanol: TEA: 93:1:1), R_f = 0.22.

Synthesis of 1-[(*N*-substituted-*N*-methylamino)-3-propyloxy]-5-pentanenitriles 16a and **16b**. To a solution of the corresponding 3-(*N*-substituted-*N*-methylamino)-1-propanol **12** or **14** (0.009 mol) in 100 mL of dry toluene was added sodium hydride (0.018 mol). The resultant suspension was stirred at room temperature for 1 h and then was added dropwise 15-crown-5 ether (0.054 mol) and then treated in a single portion with 5-bromopentanonitrile (0.054 mol). The reaction mixture was stirred at room temperature for 72 h, and excess of sodium hydride was quenched by dropwise addition of ethanol (30 mL). The solvent was evaporated under reduce pressure, and water (50 mL) was added. The mixture was extracted with dichloromethane (3 × 50.0 mL), and organic layer was dried (Na_2SO_4) and filtered. The solvent was evaporated, and residue was purified by column chromatography. The title products were obtained as sticky oil.

16a. $C_{16}H_{24}N_2O$, (M = 260.42); yield 50%; ^{1}HNMR, $CDCl_3$,δ: 1.66–1.82 (m, 6H, CH_2^{alif}); 2.19 (s, 3H, NCH_3); 2.33–2.38 (t, 2H, J = 7.2, OCH_2); 2.41–2.46 (t, 2H, J = 7.2, OCH_2); 3.40–3.47 (m, 4H, CH_2^{alif}); 3.48 (s, 2H, $PhCH_2$); 7.22–7.34 (m, 5H, CH^{arom}); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 29:10:1), R_f = 0.29.

16b. $C_{18}H_{24}N_2O_2$, (M = 300.44); yield 42%; ^{1}HNMR, $CDCl_3$, δ: 1.61–1.71 (m, 4H, CH_2^{alif}); 1.76–1.85 (m, 2H, CH_2^{alif}); 2.27–2.32 (m, 2H, CH_2CN); 2.34 (s, 3H, NCH_3); 2.50–2.55 (t, 2H, J = 7.5, NCH_2); 3.36–3.40 (t, 2H, J = 5.7, OCH_2); 3.42–3.46 (t, 2H, J = 6.3, OCH_2); 3.71 (s, 2H, benzofuran-CH_2-N); 6.59 (s, 1H, 3-$H^{benzofurane}$); 7.17–7.28 (m, 2H, $CH^{benzofurane}$); 7.45–7.54 (m, 2H, $CH^{benzofurane}$); TLC (ethyl acetate:methanol:TEA: 39:1:1), R_f = 0.49.

Synthesis of 1-[(*N*-substituted-*N*-methylamino)-3-propyloxy]-5-pentanediamines 17a and **17b**. To a solution of the corresponding 1-[(*N*-substituted-*N*-methylamino)-3-propyloxy]-5-pentanenitrile **16a** or **16b** (0.0046 mol) in 40 mL of anhydrous ethyl ether $LiAlH_4$ (0.0092 mol) was added. The mixture was stirred at room temperature for 1 h and quenched by dropwise addition of water (0.35 mL), 10% of NaOH solution (0.35 mL) and water (0.35 mL). The suspension was stirred for 30 min and filtered. The filter cake was washed with ether (2 × 30 mL). The organic layers were combined, washed with water (3 × 30 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated, and residue was purified by column chromatography. The title products were obtained as sticky oil.

17a. $C_{16}H_{28}N_2O$, (M = 264.46); yield 87%; ^{1}HNMR, $CDCl_3$,δ: 1.32–1.61 (m, 8H, CH_2^{alif}, NH_2^*); 1.75–1.84 (q, 2H, J = 6.9, CH_2^{alif}); 2.18 (s, 3H, NCH_3); 2.42–2.47 (t, 2H, J = 7.5, CH_2^{alif}); 2.66–2.70 (t, 2H, J = 6.9, CH_2^{alif}); 3.37–3.41 (t, 2H, J = 6.6, OCH_2); 3.43–3.48 (t, 2H, J = 6.6, OCH_2); 3.48 (s, 2H, $PHCH_2$); 7.22–7.32 (m, 5H, CH^{arom}); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 29:10:1), R_f = 0.16.

17b. $C_{18}H_{28}N_2O_2$, (M = 304.48); yield 42%; ^{1}HNMR, $CDCl_3$, δ: 1.21–1.59 (m, 8H, CH_2^{alif}, NH_2^*); 1.76–1.86 (m, 2H, CH_2^{alif}); 2.32 (s, 3H, NCH_3); 2.50–2.55 (m, 2H, CH_2^{alif}); 2.64–2.67 (t, 2H, J = 6.9, CH_2^{alif}); 3.35–3.40 (t, 2H, J = 6.6, OCH_2); 3.43–3.47 (t, 2H, J = 6.6, OCH_2); 3.69 (s, 2H, benzofuran-CH_2-N); 6.57 (s, 1H, 3-$H^{benzofurane}$); 7.16–7.27 (m, 2H, $CH^{benzofurane}$); 7.44–7.53 (m, 2H, $CH^{benzofurane}$); TLC (dichloromethane:methanol: concentrated ammonium hydroxide: 9:1:1), R_f = 0.15.

Synthesis of 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-formylo)-pentanediamines 18a and **18b**. To a solution of the corresponding **17a** or **17b** (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 dichloromethane (2 × 50 mL). The organic layers were combined, washed with water (3 × 50 mL), dried (Na_2SO_4), filtered and evaporated, and residue was purified by column chromatography to give the desired compounds as sticky oil.

18a. $C_{17}H_{28}N_2O_2$, (M = 292.47); yield 99%; ^{1}HNMR, $CDCl_3$,δ: 1.32–1.41 (m, 2H, CH_2^{alif}); 1.42–1.62 (m, 4H, CH_2^{alif}); 1.74–1.83 (q, 2H, J = 6.9, CH_2^{alif}); 2.19 (s, 3H, NCH_3); 2.42–2.47 (t, 2H, J = 7.5, CH_2^{alif}); 3.25–3.32 (m, 2H, CH_2^{alif}); 3.37–3.41 (t, 2H, J = 6.6, OCH_2); 3.43–3.47 (t, 2H, J = 6.6, OCH_2); 3.48 (s, 2H, $PHCH_2$); 7.21–7.34 (m, 5H, CH^{arom}); 8.13–8.14 (s, 1H, COH); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 29:10:1), R_f = 0.42.

18b. $C_{19}H_{28}N_2O_3$, (M = 332.67); yield 42%; ^{1}HNMR, $CDCl_3$, δ: 1.26–1.40 (m, 2H, CH_2^{alif}); 1.43–1.59 (m, 4H, CH_2^{alif}); 1.70–1.85 (m, 2H, CH_2^{alif}); 2.33 (s, 3H, NCH_3); 2.50–2.55 (t, 2H, J = 7.5, NCH_2); 3.21–3.31 (m, 2H, CH_2NCOH); 3.34–3.39 (m, 2H, OCH_2);3.43–3.47 (t, 2H, J = 6.3, OCH_2); 3.70 (s, 2H, ^{benzofurane}-CH_2-N); 5.53 (br s, 1H, NH*); 6.58 (s, 1H, (s, 1H, 3-$H^{benzofurane}$); 7.17–7.28 (m, 2H, $CH^{benzofurane}$); 7.44–7.54 (m, 2H, $CH^{benzofurane}$); 8.14 (s, 1H, NCOH); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 9:1:1), R_f = 0.49.

Synthesis of 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl)pentanediamines 19a and **19b**. To a solution of the appropriate **19a** or **19b** (0.004 mol) in 50 mL of anhydrous ethyl ether was added $LiAlH_4$ (0.008 mol). The mixture was stirred at room temperature for 1 h and quenched by dropwise addition of water (0.3 mL), 10% of NaOH solution (0.3 mL) and water (0.3 mL). The suspension was stirred for 30 min and filtered. The filter cake was washed with ether (2 × 25 mL).

The organic layers were combined, washed with water (3 × 25 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated, and residue was purified by column chromatography. The title products were obtained as sticky oil.

19a. $C_{17}H_{30}N_2O$, (M = 279.49); yield 72%; ^{1}HNMR, $CDCl_3$,δ: 1.25–1.39 (m, 2H, CH_2^{alif}); 1.40–1.60 (m, 5H, CH_2^{alif}, NH*); 1.62–1.84 (m, 2H, CH_2^{alif}); 2.18 (s, 3H NCH_3); 2.42 (s, 3H NCH_3); 2.42–2.47 (t, 2H, J = 7.5, NCH_2); 2.54–2.58 (t, 2H, J = 7.2, NCH_2); 3.37-3.41 (t, 2H, J = 6.6, OCH_2); 3.43–3.47 (t, 2H, J = 6.6, OCH_2); 3.48 (s, 2H, $PhCH_2$); 7.20–7.34 (m, 5H, CH^{arom}); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 29:10:1), R_f = 0.22.

19b. $C_{19}H_{30}N_2O_2$, (M = 318.69); yield 89%; ^{1}HNMR, $CDCl_3$, δ: 1.31–1.39 (m, 2H, CH_2^{alif});1.43–160 (m, 5H, CH_2^{alif}, NH*); 1.76–1.86 (m, 2H, CH_2^{alif}); 2.32 (s, 3H, NCH_3); 2.42 (s, 3H, NCH_3); 2.50–2.57 (m, 4H, CH_2^{alif}); 3.35–3.40 (t, 2H, J = 6.6, OCH_2); 3.43–3.47 (t, 2H, J = 6.6, OCH_2); 3.70 (s, 2H, ^{benzofurane}-CH_2-N); 6.58 (s, 1H, 3-$H^{benzofurane}$); 7.17–7.27 (m, 2H, $CH^{benzofurane}$); 7.45–7.54 (m, 2H, $CH^{benzofurane}$); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 4:1:1), R_f = 0.22.

Synthesis of 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propionylcarbonyl)-pentanediamine amides 20a and **20b**. To an ice-cooled solution of the appropriate **19a** or **19b** in 70 mL of dichloromethane was slowly added propionic anhydride, and reaction mixture was stirred at room temperature for 2 h. Saturated aqueous solution of sodium bicarbonate was then added until pH 9, and the reaction mixture was stirred for 24 h. The organic layer was separated, dried (Na_2SO_4) and filtered. Dichloromethane was evaporated to give the crude products **20a** and **20b** as sticky oil, which was purified by column chromatography.

20a. $C_{20}H_{34}N_2O_2$, (M = 334.56); yield 93%; ^{1}HNMR, $CDCl_3$,δ: 1.11–1.18 (m, 3H, CH_2CH_3); 1.29–1.39 (m, 2H, CH_2^{alif}); 1.43–1.62 (m, 4H, CH_2^{alif}); 1.74–1.84 (m, 2H, CH_2^{alif}); 2.18–2.19 (d, 3H, J = 1.2, $PhCH_2NCH_3$); 2.27–2.36 (m, 2H, CH_2^{alif}); 2.42–2.47 (t, 2H, J = 7.5, CH_2^{alif}); 2.91–2.95 (d, 3H, J = 12.9, CH_3NCO); 3.33–3.47 (m, 6H, CH_2^{alif}); 3.48 (s, 2H, $PhCH_2$); 7.21–7.34 (m, 5H, CH^{arom}); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 139:10:1), R_f = 0.67.

20b. $C_{22}H_{34}N_2O_3$, (M = 374.58); yield 83%; ^{1}HNMR, $CDCl_3$, δ: 1.10–1.16 (m, 3H, CH_2CH_3); 1.24–1.34 (m, 2H, CH_2^{alif}); 1.43–1.59 (m, 4H, CH_2^{alif}); 2.23–2.35 (m, 5H, NCH_3, CH_2^{alif}); 2.49–2.54 (t, 2H, J = 7.5, CH_2^{alif}); 2.89–2.93 (d, 3H, J = 9.9, CH_3NCO); 3.31–3.38 (m, 4H, CH_2^{alif}); 3.42–3.47 (m, 2H, CH_2^{alif}); 3.69 (s, 2H, benzofuran-CH_2-N); 6.57 (s, 1H, 3-$H^{benzofurane}$); 7.16–7.30 (m, 2H, CH ^{benzofurane}); 7.44–7.53 (m, 2H, $CH^{benzofurane}$); TLC (dichloromethane:methanol:concentrated ammonium hydroxide: 9:1:1), R_f = 0.57.

Synthesis of 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)- pentanediamines 6a and **6b**. To a solution of the appropriate amides **20a** or **20b** (0.002 mol) in 50 mL of anhydrous ethyl ether $LiAlH_4$ (0.004 mol) was added. The mixture was stirred at room temperature for 2 h and quenched by dropwise addition of water (0.15 mL), 10% of NaOH solution (0.15 mL) and water (0.15 mL). The suspension was stirred for 30 min and filtered. The filter cake was washed with ether (2 × 25 mL). The combined organic layers were washed with water (3 × 25 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated, and residue was purified by column chromatography. The title products were obtained as sticky oil.

6a. $C_{20}H_{36}N_2O$, (M = 320.58); yield 51%; ^{1}HNMR, $CDCl_3$,δ: 0.86–0.91 (t, 3H, J = 7.5, CH_2CH_3); 1.30–1.37 (m, 2H, CH_2^{alif}); 1.41–1.62 (m, 6H, CH_2^{alif}); 1.77–1.84 (q, 2H, J = 6.9, CH_2^{alif}); 2.18 (s, 3H, NCH_3); 2.20 (s, 3H, NCH_3); 2.24–2.33 (m, 4H, CH_2^{alif}); 2.42–2.47 (t, 2H, J = 7.5, CH_2^{alif}); 3.36–3.41 (t, 2H, J = 6.6, OCH_2); 3.43–3.47 (t, 2H, J = 6.6, OCH_2); 3.48 (s, 2H, $PhCH_2$); 7.22–7.32 (m, 5H, CH^{arom}); TLC (dichloromethane: methanol:concentrated ammonium hydroxide: 139:10:1), R_f = 0.38.

Elemental analysis for dioxalic acid salt $C_{19}H_{36}N_2O \cdot 2C_2H_2O_4$ (M = 494.66); $mp_{dioxalic\ acid\ salt}$ = 123–125 °C.

	C (%)	H (%)	N (%)
Calculated	57.58	8.05	5.58
Found	57.42	7.91	5.66

6b. $C_{22}H_{36}N_2O_2$, (M = 360.58); yield 72%; ^{1}HNMR, $CDCl_3$, δ: 0.86–0.91 (t, 3H, J = 7.5, CH_2CH_3); 1.26–1.35 (m, 2H, CH_2^{alif}); 1.42–1.56 (m, 6H, CH_2^{alif}); 1.76–1.86 (q, 2H, J = 6.9, CH_2^{alif}); 2.12 (s, 3H, NCH_3); 2.26–2.34 (m, 4H, CH_2^{alif}); 2.32 (s, 3H, NCH_3); 2.50–2.55 (t, 2H, J = 7.5, CH_2^{alif}); 3.35–3.39 (t, 2H, J = 6.6, OCH_2); 3.42–3.47 (t, 2H, J = 6.6, OCH_2); 3.67 (s, 2H, ^{benzofurane}-CH_2-N); 6.57 (s, 1H, 3-$H^{benzofurane}$); 7.16–7.27 (m, 2H, $CH^{benzofurane}$); 7.44–7.53 (m, 2H, $CH^{benzofurane}$). TLC (dichloromethane: methanol:concentrated ammonium hydroxide: 9:1:1), R_f = 0.35.

Elemental analysis for dioxalic acid salt $C_{22}H_{36}N_2O_2 \cdot 2C_2H_2O_4$ (M = 520.66); $mp_{dioxalic\ acid\ salt}$ = 103–105 °C.

	C (%)	H (%)	N (%)
Calculated	59.97	7.76	5.38
Found	59.85	7.49	5.57

Pharmacology. The potency of all the obtained compounds was tested for H_3 antagonistic effects *in vitro* on the guinea-pig jejunum (38).

Selected compounds **5c**, **5d** and **6a** were also tested for H_1 antagonistic effects *in vitro*, following standard methods, using the guinea-pig ileum (39).

H3 antagonistic effects in vitro *on the guinea-pig jejunum for compounds 5a–h, 6a,b, 7 and 8*

Male guinea-pigs weighing 300–400 g were killed 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} M)]. 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 (TI-2)/HF-modem (Hugo Sachs Electronik, Hugstetten, Germany) connected to a pen recorder. After equilibration for 1 h 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 millisecond, with rectangular-wave electrical pulses, delivered by a Grass Stimulator S-88 (Grass Instruments Co., Quincy, MA, USA). After 30 min of stimulation, 5 min before adding (R)-α-methylhistamine, pyrilamine (1×10^{-5} M concentration in 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} M concentration in organ bath) was added, and after 20 min, 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 Student's *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 for 5c, 5d and 6a compounds

Selected compounds were tested for H_1 antagonistic effects *in vitro*, following standard methods, using the guinea-pig ileum (39).

Male guinea-pigs weighing 300–400 g were killed 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 contents, segments of about 2 cm long 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} M) 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 **5c**, **5d** and **6a,** 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.

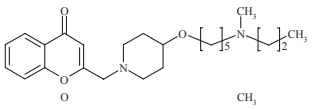
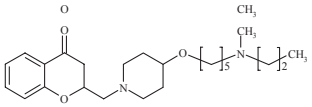
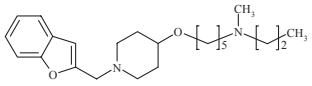
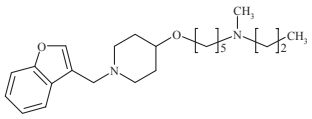
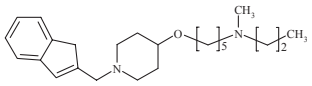
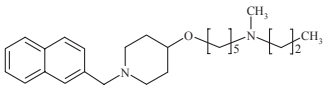
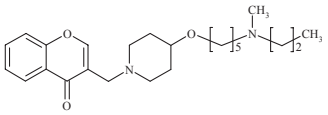
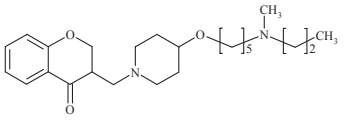
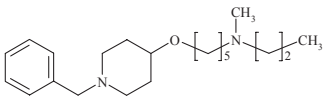
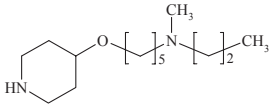
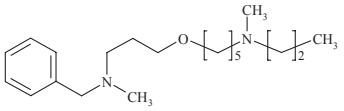
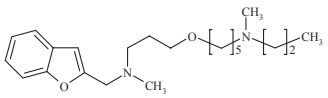
Results and Discussion

The potency of all synthesized compounds was preliminary *in vitro* tested as H_3 receptor antagonists – electrically evoked contraction of the guinea-pig jejunum. 1-Substitutedmethyl-4-[5-(*N*-methyl-*N*-propylamino)pentyloxy]piperidines (**5a**–**h**) and selected 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)pentanediamines (**6a**, **6b**) all showed moderate to high antagonist activity at H_3-receptor, except of derivative **6b** showing weak potency. Results are presented in Table 1.

The 1-benzyl-4-[5-(*N*-methyl-*N*-propylaminopentyloxy)] piperidine **7** has been selected as the lead structure from the previously examined compounds (37) to allow a direct comparison of the changes in activity of the newly designed compounds with the replacement of the benzyl group of the *N*-piperidine moiety.

It has appeared that by comparison of homologous pairs that **5g** and **5h** have higher potency than their analogous **5a** and **5b**. The differences are observed inside of each series. While it is quite a significant difference in H_3-receptor potency between derivative **5g** (pA_2 = 7.63) – with double bond – and **5h** (pA_2 = 7.1) – without double bond in 2,3-dihydro-4H-pyran-4-one ring – only very small difference in activity between the derivative **5a** (pA_2 = 7.2) and **5b** (pA_2 = 7.11) is observed. Moreover, comparing derivatives **5a** and **5b** with unsubstituted derivative **8** (pA_2 = 7.31), it is seen that H_3 antagonistic activity is almost on the same level, independently on the presence or absence of substituent **9a** or **9b**. These results suggest that in the chromones (**5a** and **5g**) and chromanones (**5b** and **5h**) series, the heterocyclic ring should contain a double bond and 4-[5-(*N*-methyl-*N*-propyl)pentyloxy]piperidi-

Table 1: H_3 antagonistic activity of 1-substituted-4-[5-(*N*-methyl-*N*-propylamino)pentyloxy]piperidines (**5a**–**h**, **7**, **8**) and 1-[(*N*-substituted-*N*-methyl)-3-propyloxy]-5-(*N*-methyl-*N*-propyl)pentanediamines (**6a**, **6b**) as tested on the *in vitro* test system on the guinea-pig jejunum

Cpd.	Structure	The concentrations of the tested compound c_i (M)	pA_2 (sem) H_3	*N* (*caviae*)
5a		1×10^{-7}; 3×10^{-7}; 1×10^{-6}	7.2 (0.1)	9 (3)
5b		1×10^{-7}; 3×10^{-7}; 1×10^{-6}	7.11 (0.14)	9 (3)
5c		3×10^{-9}; 1×10^{-8}; 3×10^{-8}	8.47 (0.05)	12 (4)
5d		1×10^{-8}; 3×10^{-8}; 1×10^{-7}	8.15 (0.07)	12 (4)
5e		3×10^{-8}; 1×10^{-7}; 3×10^{-7}	7.76 (0.09)	12 (4)
5f		1×10^{-7}; 3×10^{-7}; 1×10^{-6}	7.04 (0.11)	9 (3)
5g		3×10^{-8}; 1×10^{-7}; 3×10^{-7}	7.63 (0.08)	9 (3)
5h		1×10^{-7}; 3×10^{-7}; 1×10^{-6}	7.1 (0.15)	13 (4)
7		3×10^{-8}; 1×10^{-7}; 3×10^{-7}	7.79 (0.06)	12 (4)
8		1×10^{-7}; 3×10^{-7}; 1×10^{-6}	7.31 (0.1)	9 (3)
6a		1×10^{-8}; 3×10^{-8}; 1×10^{-7}	8.06 (0.05)	12 (4)
6b		3×10^{-7}; 1×10^{-6}; 3×10^{-6}	6.23 (0.12)	12 (4)
Thioperamide		3×10^{-9}; 1×10^{-8}; 3×10^{-8}	8.65 (0.07)	36 (12)

sem, standard error of the mean; *N*, number of different animal preparations; *cavie*, number of animals.

nyl substituent should be present at a favourable position 3.

To investigate the influence of the size of the heterocyclic ring and the presence of the carbonyl group, on the antagonistic activity on the histamine H_3 receptor, two methylbenzofuran derivatives containing 4-[5-(*N*-methyl-*N*-propylamino)pentyloxy]piperidinyl moiety at position 2 (**5c**) and 3 (**5d**) in benzofuran ring were synthesized. The reduction of a heterocyclic ring with a six-membered to five-membered ring and removal of the carbonyl group lead to compound **5c** ($pA_2 = 8.47$) and **5d** ($pA_2 = 8.15$) showing the highest potency for all presented 4-hydroxypiperidine derivatives. We observe that the 2-position of 4-[5-(*N*-methyl-*N*-propylamino)pentyloxy]piperidinyl moiety in the 2-methylbenzofuran ring (**5c**) is slightly favourable for histamine H_3-receptor antagonist activity than position 3. Replacement of the benzyl substituent by 2-methylindenyl

group **5e** (pA_2 = 7.76) reduced potency. Antagonistic activity was further reduced when the 2-methylindenyl substituent has been replaced by the most lipophilic 2-methylnaphthyl moiety **5f** (pA_2 = 7.04).

Surprisingly, replacement of the 4-hydroxypiperidine in the leads **7** and **5c** by a highly flexible 3-(methylamino)propyloxy chain yields compounds **6a** (pA_2 = 8.02) and **6b** (pA_2 = 6.23) with higher and lower affinity than their piperidine analogues (**7**, pA_2 = 7.79; **5c**, pA_2 = 8.47), respectively.

In conclusion, it may be noticed that the spatial configurations greatly decide on the activity of these series than the others physico-chemical parameters.

Additionally, selected compounds **5c**, **5d** and **6a** have also been tested for H_1 antagonistic effects *in vitro*, following standard methods, using the guinea-pig ileum. None of them showed any H_1-antagonistic activity ($pA_2 < 4$; for pyrilamine pA_2 = 8.5).

Due to the lack of antagonistic activity of selected compounds at H_1 receptor, we can conclude that the derivatives of **5c**, **5d** and **6a** are not double H_1H_3 receptor antagonists.

Conclusions and Future Directions

Novel, potent non-imidazole histamine H_3 receptor antagonists have been prepared possessing either a highly flexible 3-(methylamino)propyloxy chain or 4-hydroxypiperidine ring resulting in increased rigidity of these compounds. Investigation of the compounds in an *in vitro* functional assay on the guinea-pig ileum led to the identification of **5c** and **5d** as the most potent compounds *in vitro* in both series (pA_2 = 8.47 and pA_2 = 8.15, respectively). By comparing pairs of homologous compounds **5c**/**6b** versus **7**/**6a**, it was found that the **5c** (pA_2 = 8.47) has a higher activity than its 3-(methylamino)propyloxy analogue **6b** (pA_2 = 6.23), which is in contrast to a pair of homologues **7/6a**, where 3-(methylamine)propyloxy derivative **6a** (pA_2 = 8.02) has a higher activity than its 4-hydroxypiperidine analogue **7** (pA_2 = 7.79). For explanation of tentative interpretation of the different SAR for the compounds **5c**/**6b** versus **7**/**6a,** we will try to solve this problem by molecular modelling. However, further structural modifications, both in 4-hydroxypiperidine and 3-(methylamino)propyloxy series, are required to explain these unexpected results. At last, based on the SAR of all synthesized compounds, the most active derivatives will be chosen and investigated for their effects on central histaminergic neuron activity *in vivo*.

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Conflict of Interest

The authors have declared no conflict of interest.

References

1. Hough L.B. (2001) Genomics meets histamine receptors: new subtypes, new receptors. Mol Pharmacol;59:415–419.
2. Parsons M.E., Ganellin C.R. (2006) Histamine and its receptors. Br J Pharmacol;147(S1):S127–S135.
3. Leurs R., Church M.K., Taglialatela M. (2002) H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy;32:489–498.
4. Ganellin C.R. (1981) Medicinal chemistry and dynamic structure-activity analysis in discovery of drug acting at histamine H2 receptors. J Med Chem;24:913–920.
5. Zhang M., Thurmond R.L., Dunford P. (2007) The histamine H4 receptor: a novel modulator of inflammatory and immune disorders. Pharmacol Therap;113:594–606.
6. Arrang J.-M., Garbarg M., Schwartz J.-C. (1983) Autoinhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature;302:832–837.
7. Lovenberg T.W., Roland B.L., Wilson S.J., Jiang X., Pyati J., Huvar A., Jackson M.R., Erlander M.G. (1999) Cloning and functional expression of the human histamine H3 receptor. Mol Pharmacol;55:1101–1107.
8. Lovenberg T.W., Pyti J., Chang H., Wilson S.J., Erlander M.G. (2000) Cloning of rat histamine H3 receptor reveals distinct species pharmacological profiles. J Pharmacol Exp Therap;293:771–778.
9. Arrang J.-M., Garbarg M., Schwartz J.C. (1985) Autoregulation of histamine release in brain by presynaptic H3-receptors. Neuroscience;15:553–562.
10. Arrang J.-M., Garbarg M., Schwartz J.-C. (1987) Autoinhibition of histamine synthesis mediated by presynaptic H3-receptors. Neuroscience;23:149–157.
11. Clapham J., Kilpatrick G.J. (1992) Histamine H3 receptors modulate the release of [3H]-acetylcholine from slices of rat entorhinal cortex: evidence for the possible existence of H3 receptor subtypes. Br J Pharmacol;107:919–923.
12. Yokatoni K., Murakami Y., Okada S., Wang M., Nakamura K. (2000) Histamine H(3) receptor-mediated inhibition of endogenous acetylcholine release from the isolated, vascularly perfused rat stomach. Eur J Pharmacol;392:23–29.
13. Schlicker E., Fink K., Detzner M., Göthert M. (1993) Histamine inhibits dopamine release in the mouse striatum via presynaptic H3 receptors. J Neural Transm Gen Sect;93:1–10.
14. Schlicker E., Schunack W., Göthert M. (1990) Histamine H3 receptor-mediated inhibition of noradrenaline release in pig retina discs. Naunyn-Schmiedeberg's Arch Pharmacol;342:497–501.

15. Schlicker E., Betz R., Göthert M. (1988) Histamine H3 receptor-mediated inhibition of serotonin release in the rat brain cortex. Naunyn-Schmiedeberg's Arch Pharmacol;337:588–590.
16. Miyazaki S., Imaizumi M., Onodera K. (1995) Effects of thioperamide, a histamine H_3-receptor antagonist, on a scopolamine-induced learning deficit using an elevated plus-maze test in mice. Life Sci;57:2137–2144.
17. Onodera K., Miyazaki S., Imaizumi M., Stark H., Schunack W. (1998) Improvement by FUB 181, a novel histamine H_3-receptor antagonist, of learning and memory in the elevated plus-maze test in mice. Naunyn Schmiedebergs Arch Pharmacol;357:508–513.
18. Passani M.B., Cangioli I., Bocciottini L., Mannaioni P.F. (2000) Thioperamide and cimetidine modulate acetylcholine release from the amygdala of freely moving rats. Inflamm Res;49:S43–S44.
19. Yokoyama H., Onodera K., Maeyama K., Sakurai E., Iinuma K., Leurs R., Timmerman T., Watanabe H. (1994) Clobenpropit (VUF-9153), a new histamine H3 receptor antagonist, inhibits electrically induced convulsions in mice. Eur J Pharmacol;260:23–28.
20. Pillot C., Ortiz J., Héron A., Ridray S., Schwartz J.-C., Arrang J.-M. (2002) Ciproxifan, a histamine H3-receptor antagonist/inverse agonist, potentiates neurochemical and behavioral effects of haloperidol in the rat. J Neurosci;22:7272–7280.
21. Takahashi K., Suwa H., Ishikawa T., Kotani H. (2002) Targeted disruption of H3 receptors results in changes in brain histamine tone leading to an obese phenotype. J Clin Invest;110:1791–1799.
22. Sander K., Kottke T., Weizel L., Stark H. (2010) Kojic acid derivatives as histamine H_3 receptor ligands. Chem Pharm Bull;58:1353–1361.
23. Beaton G., Moree W.J. (2010) The expanding role of H_1 antihistamines: a potent survey of selective and dual activity compounds 2005–2010. Expert Opin Ther Pat;20:1197–1218.
24. Procopiou P.A., Browning C., Buckley J.M., Clark K.L., Fechner L., Gore P.M., Hancock A.P. *et al.* (2011) The discovery of phthalazinone-based human H_1 and H_3 single-ligand antagonists suitable for intranasal administration for the treatment of allergic rhinitis. J Med Chem;54:2183–2195.
25. Stark H., Schlicker E., Schunack W. (1996) Developments of histamine H3-receptor antagonists. Drugs Future;21:507–520.
26. Van der Goot H., Timmerman H. (2000) Selective ligands as tools to study histamine receptors. Eur J Med Chem;35:5–20.
27. Cowart M., Altenbach R., Black L., Faghih R., Zhao C., Hanckok A.A. (2004) Medicinal chemistry and biological properties of non-imidazole histamine H3 antagonists. Mini Rev Med Chem;4:979–992.
28. Celanire S., Wijtmans M., Talaga P., Leurs R., de Esch I.J.P. (2005) Keynote review: histamine H3 receptor antagonists reach out for the clinic. Drug Discovery Today;10:1613–1627.
29. Łażewska D., Kieć-Kononowicz K. (2010) Recent advances in histamine H_3 receptor antagonists/inverse agonists. Expert Opin Ther Pat;20:1147–1169.
30. Berlin M., Boyce C.W., De Lera Ruiz M. (2011) Histamine H3 receptor as a drug discovery target. J Med Chem;54:26–53.
31. Hancock A.A. (2006) The challenge of drug discovery of a GPCR target: analysis of preclinical pharmacology of histamine H_3 antagonists/inverse agonists. Biochem Pharmacol;71:1103–1113.
32. Pomponi S.A., Gullo V.P., Horan A.C., Patel M.G., Coval S. (1994) Method for treating airway congestion. U.S. Patent, 5,352,707 [Chem. Abstr. 1994, 121, 272,182n].
33. Apodaca R., Dvorak C.A., Xiao W., Barbier A.J., Boggs J.D., Wilson S.J., Lovenberg T.W., Carruthers N.I.A. (2003) A new class of diamine-based human histamine H3 receptor antagonists: 4-(aminoalkoxy) benzylamines. J Med Chem;46:3938–3944.
34. Gadski R.A., Hipskind P.A., Jesudason C.D., Pickard R.T., Beavers L.S. (Lilly Co. Eli) (2004) Substituted azepines as histamine H3 receptor antagonists, preparation and therapeutic uses. WO2004018432 [Chem. Abstr. 2004, 140, P235617e].
35. Dvorak C.A., Apodaca R., Barbier A.J., Berridge C.W., Wilson S.J., Boggs J.D., Xiao W., Lovenberg T.W., Carruthers N.I. (2005) 4-phenoxypiperidines: potent, conformationally restricted, non-imidazole histamine H3 antagonists. J Med Chem;48:2229–2238.
36. Cowart M.D., Bennani Y.L., Faghih R., Gfesser G. (2002) Novel amines as histamine-3 receptor ligands and their therapeutic applications, (Abbott Laboratories). WO 02074758. [Chem. Abstr. 137 (2002) P247602x].
37. Masłowska-Lipowicz I., Figlus M., Zuiderveld O.P., Walczyński K. (2008) New 1-benzyl-4-hydroxypiperidine derivatives as non-imidazole histamine H_3-antagonists. Arch Pharm;341:762–773.
38. Vollinga R.C., Zuiderveld O.P., Scheerens H., Bast A., Timmerman H. (1992) A simple and rapid in vitro test system for the screening of histamine H3 ligands. Methods Find Exp Clin Pharmacol;105:747–751.
39. Arunlakshana O., Schild H.O. (1959) Some quantitative uses of drug antagonists Br. J Pharmacol;14:48–55.
40. Parcell R.F., Hauck F.P. JR (1963) Preparation of tetrahydropyridines from enamines and imines. J Org Chem;28:3468–3473.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Description of the synthetic methods for preparing intermediates **9a**–**e** and **9h**.